(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 June 2020 (11.06.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/118091 A1

(51) International Patent Classification:
A61K 9/70 (2006.01) *A61K 47/14* (2017.01)
A61K 31/4178 (2006.01) *A61K 47/20* (2006.01)
A61K 47/10 (2017.01) *A61P 1/08* (2006.01)
A61K 47/12 (2006.01)

(21) International Application Number:
PCT/US2019/064751

(22) International Filing Date:
05 December 2019 (05.12.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/775,551 05 December 2018 (05.12.2018) US
62/775,554 05 December 2018 (05.12.2018) US
62/775,543 05 December 2018 (05.12.2018) US

(71) Applicant: **STARTON THERAPEUTICS, INC.** [US/US]; 57 W. 57th Street, 4th Floor, New York, NY 10019 (US).

(72) Inventors: **BOROVINSKAYA, Marina**; 183 Windsong Circle, East Brunswick, NJ 08816 (US). **MODI, Nisarg**; 242 - 39 91st Avenue, 2nd Floor, Bellerose, NY 11426 (US). **PLAKOGIANNIS, Fotios**; 157 - 14 Cryders Lane, Whitestone, NY 11357 (US). **LATHER, Tamanna**; 27 Cedar Street, Jersey City, NJ 07305 (US).

(74) Agent: **DESJARDINS, Edward, J.** et al.; McDermott Will & Emery, The McDermott Building, 500 North Capitol Street, NW, Washington, DC 20001-1531 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

WO 2020/118091 A1

(54) Title: ONDANSETRON IN-ADHESIVE TRANSDERMAL PATCH

(57) Abstract: Drug-in-adhesive transdermal patches for the administration of the ondansetron are described. The patches find use, for example, to treat chemotherapy induced nausea and vomiting (CINV), which requires a high initial flux in the acute phase that is sustained over multiple days or weeks. Embodiments of the disclosure relate in part to formulations for manufacturing self-adhesive patches that include various combinations of a variety of advantageous components, which can be tailored to treat various patient groups or symptoms.

ONDANSETRON IN-ADHESIVE TRANSDERMAL PATCH

TECHNICAL FIELD

[0001] The present disclosure generally relates to transdermal patches for the delivery of the drug ondansetron to a subject to treat nausea and vomiting, in particular, after administration of chemotherapy, e.g., to treat chemotherapy induced nausea and vomiting (CINV). In particular, the disclosure relates to drug-in-adhesive transdermal patches. Embodiments of the present disclosurerelate to transdermal formulations for self-adhesive polyacrylic pressure sensitive adhesive (PSA) patches that include various specified preferred components, for example, an amphiphilic polymer and/or various preferred enhancers, such as DMSO, and/or a glycol, and/or an FD enhancer, and/or cross linkable polyacrylic adhesive. Embodiments of the disclosure allow adaptation of the formulation to provide more rapid onset and longer duration of steady state, and/or where the flux profile can be regulated to a preferred profile.

BACKGROUND

[0002] Ondansetron (ODS) is an antiemetic that is used to treat nausea and vomiting, in particular, after administration of chemotherapy to treat chemotherapy induced nausea and vomiting (CINV), which is particularly troublesome to patients. Oral and intravenous administration forms are available but suboptimal in their application, and many attempts have been made to develop more suitable dosage forms; specifically, patches for transdermal administration have been described.

[0003] However, such ODS transdermal patches suffer from various downsides that make them unsuitable for clinical application and/or inconvenient for the patient. For example, sufficient flux may be achieved in patches that have a large drug reservoir in a matrix separate from the adhesive, however, such patches are bulky and adhere to the skin poorly.

[0004] Drug-in-adhesive type patches that comprise ODS within an adhesive matrix are thinner, but many problems have been encountered. This is at least in part due to the specific characteristics of ODS, such as low solubility, a short half-life, a tendency to form crystals in the patch, and that a relatively high quantity of ODS is needed for its therapeutic effect. For example, the dose of ODS needs to be comparatively high, e.g., compared to granisetron, which makes ODS much more difficult to deliver transdermally, in particular in drug-in-adhesive type patches.

[0005] Flux data has been reported for different types of patches comprising ODS. However, flux will vary depending on the test used and in particular on the skin applied thereto. In particular, flux will differ depending on the general permeability characteristics of the skin that is tested, which substantially differs with the mammal that the skin is derived from. For example, rodent skin is known to have different barrier properties from humans, and displays a much higher flux for drugs.

Comparative skin permeability in different mammalian species is typically as follows, in order from highest to lowest: rabbit > rat > pig > human. Human skin is the least permeable of all mammals, and has a significantly lower permeability (and thus flux). For example, the permeability of rat skin is approximately 10 times higher than that of human skin. Further, skin permeability can be substantially affected by the water solubility of a given drug. In general, in case of poorly water soluble drugs, the in vitro flux for mouse skin can be 13 times higher compared to human skin. Thus a formulation that meets a target-flux in non-human skin does not indicate the same will be achievable for human skin.

[0006] Transdermal formulations of many drugs, in particular ODS, and in especially for drug-in-adhesive formulations/patches, often require the use of permeation or penetration enhancers to achieve a suitable flux or flux profile. Many hundreds of enhancers of different types or combinations thereof are known in various transdermal systems, but often it is impossible to predict which, or which type or in which combination, will provide a desired flux and flux profile for the drug of interest. Further, many such ingredients are irritants to the skin, especially when applied in the amount necessary for sufficient flux of ODS, and more so during application of an adhesive patch, particularly if applied for multiple days or weeks.

[0007] Various transdermal formulations, including those for ODS, make use of a large number of different fatty acids, alcohols, surfactants and other enhancers. Despite use of various enhancers and their combinations, known patches suffer from one or more shortcomings, among them insufficient flux or ODS loading, undesirable flux profile, incompatibility with adhesives of favorable characteristics, lack of adhesion, lack of comfort when worn, inflexibility, bulkiness, skin irritation, and other drawbacks.

[0008] Various polymers and their combinations have been used to make matrix patches, including ondansetron matrix patches. These include various hydrogel patches wherein the matrix contains significant amounts of water and is generally not self-adhesive. Among others, combinations of hydroxypropylcellulose (HPMC) with other polymers have been used. HPMC is typically used as a thickener in hydrogels. A particular HPMC (HPMC K4M) has been combined with polyvinylpyrrolidone (PVP) as described by Fathima *et al.* 2011, "Formulation and evaluation of matrix-type transdermal delivery system of ondansetron hydrochloride using solvent casting technique," *Research Journal Pharm and Tech.* 4(5)). However, the HPMC patches described are not self-adhesive patches and thus less practical in use, nor do they provide a sustained flux over multiple days. Another problem is that these patches require 5% menthol as a penetration enhancer which can cause skin irritation, especially when the patch is applied for multiple days. The formulation with menthol achieved a short term flux of about 12 hours as described, and during that time only achieved a low steady state flux (5.9 $\mu g/cm^2/h$ across rat skin; typically, the permeability

of rat skin is approximately 10 times higher than that of human skin, thus permeability across human skin would be expected to be much lower).

[0009] Various problems typically encountered in ODS transdermal patches include, among others, insufficient drug loading, insufficient drug release, unfavorable flux profile or duration, insufficient tackiness/skin adherence, and combinations of these. The maximally achieved flux across the skin may be insufficient, the flux may be fluctuating too much over time, the initial flow may be too high, with a risk of adverse effects appearing, or too low, resulting in breakthrough vomiting or nausea (especially in the acute CINV phase immediately after chemotherapy which tends to require a higher dosage); further the flux may taper off too abruptly thus causing nausea symptoms, or it may not be sufficiently prolonged, for example, it may not cover all of the delayed CINV phase; ideally a patch should provide sufficient flux for multiple days, which is difficult to achieve.

[0010] For drug-in-adhesive patches, the adhesive matrix may affect flux and typically needs additional ingredients (e.g., such as plasticizers to provide flexibility and strength to the polymer matrix). However, ingredients that affect the adhesive matrix may also affect the flux. Similarly, interactions between the drug and the adhesive matrix may occur and may be influenced by any of the ingredients present as well as the type and particulars of the matrix. Further, the chemical and physical nature of the adhesive matrix polymer or polymers (and any copolymers and cross- linkers, if present), and the multiple solvents, solubilizers and/or enhancers that are often necessary to increase skin permeation also have an effect on flux, flux profile, flexibility, tackiness and removability of the patch. Further, once sufficient flux of a favorable profile and tackiness, etc. is achieved, the combination of materials also needs to be non-irritant for the duration it is applied to the skin. However, many known solvents, solubilizers, plasticizers and enhancers are potential or known irritants when used in transdermals or patches in the necessary concentration, especially with regard to patches designed for multiple day use.

[0011] Drug-in-adhesive type patches, sometimes referred to as matrix patches, that have a sufficient and sustained flux may thus be particularly difficult to form. As discussed for example in U.S. 7,608,282, which provides patches for granisetron, the very nature of a matrix patch sets a limit on the amount of active material that can be carried by the patch, because the reservoir for the drug is provided by the adhesive matrix, rather than separately. The authors thus conclude that matrix patches (i.e., drug-in-adhesive patches) were simply not suitable for drugs that need to be administered in high amounts, such as ondansetron, as they cannot carry sufficient drug.

[0012] There remains a need in the art for a comfortable non-bulky transdermal adhesive patch with sufficient flux to deliver ODS across the human skin that can provide a rapid onset of sufficient flux within the first hours of use and/or that can sustain a sufficient flux to provide a rapid

sustained therapeutic effect over a prolonged time, in a favorable continuous flux profile that preferably extends over several days. In particular there remains a need for transdermal adhesive patches that rapidly reach a high steady state, e.g., within 1 hour or less, 2 hours or less, 3 hours or less, and so forth, and that provide this flux for an extended period of more than 24 hours and preferably for multiple days, to allow improved treatment of CINV. Further, there remains a need for an ODS patch with improved flexibility and/or adherence to the skin. Still further there is a need for an adhesive patch that is non-irritant for the duration of use. Also there remains a need for an adhesive patch that adheres well to skin yet is easy to remove. Yet further there is a need for non-irritant ODS patches that have an increased and/or prolonged flux. Also there is a need for ODS patches that have a favorable flux profile better suited to treat CINV. These and other features and advantages of the present disclosure will be explained and will become apparent to one skilled in the art through the summary that follows.

BRIEF SUMMARY

[0013] The present disclosure generally relates to transdermal patches of ondansetron, and in particular, to drug-in-adhesive patches. In particular, embodiments of the present disclosure relate to transdermal formulations for self-adhesive polyacrylic PSA patches that include an amphiphilic polymer. Preferably, formulations include one or more of lactic acid and DMSO, and may optionally include one or more fatty acid or fatty alcohol enhancer, or a derivative thereof. Embodiments of the disclsoure allow to adapt the formulation to provide an increased flux and an improved flux profile with a more rapid onset and longer duration of steady state. This allows a more tailored treatment of patient groups and symptoms, for example of chemotherapy induced nausea and vomiting (CINV), which requires a high initial flux in the acute phase that is sustained over multiple days or weeks. Also, embodiments relate to formulations that further comprise a solvent which may comprise one or more of diethylene glycol monoethyl ether (DEGEE, also known as Transcutol®), a Tween®-type or Span®-type surfactant, and hexylenegycol.

[0014] Surprisingly, it is shown herein, formulations for drug-in-adhesive patches can provide a sufficient loading and a sufficiently high flux over an extended duration of multiple days, *e.g.*; up to 2-7 days or up to 2-14 days, and the flux profile at the same time is adaptable to a rapid onset. In some embodiments, the rapid onset occurs within 30 minutes, within 1 hour, within 2 hours, within 3 hours, within 4 hours, within 5 hours, within 6 hours, within 10 hours, or within 1-12 hours or less. Thus, an early and high steady state ODS flux is provided which allows for an effective treatment of nausea and vomiting, benefiting in particular highly emetic patients, including, e.g., CINV patients. Accordingly, embodiments of the present disclosure provide improved ODS patches of the drug-in-adhesive type which are non-bulky, flexible, adhere well, are easily

removable and non-irritant, and achieve favorable flux profiles specifically adaptable for rapid onset of a high steady state flux.

[0015] In some embodiments, provided is a drug-in-adhesive patch for both rapid onset and sustained release transdermal administration of ondansetron to a human subject.

[0016] In other embodiments, provided is a patch comprising one or more polyacrylic adhesive, an amphiphilic polymer, one or more enhancer, and one or more solvent. In further embodiments, the amphiphilic polymer includes one or more of: a cellulose polymer, an acetyl- and succinoyl-substituted polymer, a hydroxypropylcellulose acetate succinate or hypromellose acetate succinate (HPMC-AS), AquaSolve™ HPMCAS-LF, AquaSolve™ HPMCAS-LG; AquaSolve™ HPMCAS-MF; AquaSolve™ HPMCAS-MG; AquaSolve™ HPMCAS-HF; AquaSolve™ HPMCAS-HG, substituted hydroxypropylcellulose (HPMC), hydroxypropylcellulose (HPMC), a Klucel™ polymer, Klucel™ HF, Klucel™ MF, Klucel™ GF, Klucel™ JF, Klucel™ EF, Klucel™ ELF, an HPMC derivative, a cellulose ether, a METHOCEL™ cellulose ether, METHOCEL™ E, METHOCEL™ F, METHOCEL™ J, METHOCEL™ K, Methocel™ 40-0101, METHOCEL™ 40-0202, METHOCEL™ E4M PRM, METHOCEL™ E50 PRM, METHOCEL™ 856N, METHOCEL™ K100M PRM, a carboxymethylcellulose (CMC), a WALOCEL™ polymer, WALOCEL™ CRT 1000, WALOCEL™ CRT 2000, WALOCEL™ CRT 10000, WALOCEL™ CRT 15000, WALOCEL™ CRT 30000, WALOCEL™ CRT 40000, WALOCEL™ CRT 50000, WALOCEL™ CRT 60000, polyvinylpyrrolidone (PVP), acrylic acid derivatives, a Plastoid® polymer, Plastoid®B, an Eudragit® polymer, Eudragit® L-100, Eudragit® L100-55; Eudragit® L30 D-55; Eudragit® L12,5; Eudragit® S100; Eudragit® S12,5; Eudragit® FS30D; Eudragit® E100; Eudragit® E12,5; Eudragit® EPO; Eudragit® S100; Eudragit® S12,5; Eudragit® FS30D; Eudragit® NE30D; Eudragit® NE40D; Eudragit® NM30D; Eudragit® RLPO; Eudragit® RL100; Eudragit® RL30D; Eudragit® RL12,5; Eudragit® RSPO; Eudragit® RS100; Eudragit® RS30D; Eudragit® RS12,5; PlasACRYL™ HTP20; PlasACRYL™ T20; and Acryl-EZE®.

[0017] In further embodiments, provided is a patch wherein the enhancer includes a FD enhancer that is selected from a fatty acid, a fatty alcohol, a fatty acid derivative, and a fatty alcohol derivative, and combinations thereof. In further embodiments, the FD enhancer is a fatty acid derivative or a fatty alcohol derivative, or combinations thereof, and further wherein the fatty acid derivative or fatty alcohol derivative consists of a substituted fatty acid moiety, or a substituted fatty alcohol moiety that comprises one or more additional group, wherein the additional group comprises one or more of hydroxyl, ethyl, methyl, propyl, butyl, and glyceryl, and wherein the fatty acid moiety or the fatty alcohol moiety of the FD enhancer has a carbon chain length from C4 to C26.

[0018] In further embodiments, provided is a patch wherein the solvent comprises one or more of: DMSO, lactic acid, diethylene glycol monoethyl ether (DEGEE), Span 20®, Span®40,

Span® 60, Span®80, Span®83, Span®85, Span®120, Tween 20®, Tween 21®, Tween 40®, Tween 60®, Tween 61®, Tween 65®, Tween 80®, and hexylengycol.

[0019] In further embodiments, provided is a patch wherein the enhancer further comprises one or more of: ethanol, propanol, decylmethyl sulfoxide, dimethylformamide, azone, urea, dimethylacetamide, a pyrrolidone derivative, 1-methyl-4-carboxy-2-pyrrolidone, 1-methyl-2-pyrrolidone, 1-lauryl-4-methoxycarbonyl-2-pyrrolidone, a polyol, propylene glycol, polyethylene glycol, a terpene, menthol, limonene, terpineol, pinene, carvol, a surfactant, a nonionic surfactant, a cationic surfactant, an anionic surfactant, Brij®, sodium lauryl sulfate, ethyl acetate, methyl acetate, octisalate, pentadecalactone, and acrylamide.

[0020] In further embodiments, provided is a patch wherein the enhancer comprises one or more of: butyric acid (C4:0), isobutyric acid (C4:0), valeric acid (C5:0), isovaleric acid (C5:0), levulinic acid (C5:0), caproic acid (C6:0), caprylic acid (C8:0), capric acid (C10:0), lauric acid (C12:0), myristic acid (C14:0), palmitic acid (C16:0), stearic acid (C18:0), and isostearic acid (C18:0), 5-dodecenoic acid (C12:1), 7-tetradecenoic acid (14:1), palmitoleic acid (16:1), oleic acid (C18:1), vaccenic acid (C18:1), elaidic acid (C18:1), paullinic acid (C20:1), gondoic acid (C20:1), erucic acid (C22:1), 15-docosenoic acid (C22:1), 17-tetracosenoic acid (24:1), nervonic acid (C24:1), and ximenic acid (C26:1), hexadecatrienoic acid (16:3), linoleic acid (C18:2), rumenic acid (C18:2), alpha-linolenic acid (C18:3), gamma-linolenic acid (C18:3), calendic acid (C18:3), stearidonic acid (C18:4) mead acid (C20:3), eicosadienoic acid (C20:3), eicosatrienoic acid (C20:3), dihomo-gamma-linolenic acid (C20:3), arachidonic acid (C20:4), docosadienoic acid (C22:2), adrenic acid (C22:4), osbond acid (C22:5), tetracosatetraenoic acid (C24:4), and tetracosapentaenoic acid (C24:5), butanol (C4), tert-butyl alcohol (C4), tert-amyl alcohol (C5), 3-methyl-3-pentanol (C6), capryl alcohol (C8), pelargonic alcohol (C9), capric alcohol (C10), undecyl alcohol (C11), lauryl alcohol (C12), pridecyl alcohol (C13), myristyl alcohol (C14), pentadecyl alcohol (C15), cetyl alcohol (C16), palmitoleyl alcohol (cis-9-hexadecen-1-ol, C16H32O), heptadecyl alcohol (1-n-heptadecanol, C17H36O), stearyl alcohol (C18), oleyl alcohol (C18H36O), linoleyl alcohol ($C_{18}H_{34}O$, cis,cis-9,12-octadecadien-1-ol), nonadecyl alcohol (C19), arachidyl alcohol (C20H42O), Heneicosyl alcohol (C21), behenyl alcohol (C22H46O), erucyl alcohol (cis-13-docosen-1-ol, C22H44O), Lignoceryl alcohol (C24), ceryl alcohol (C26), octyldodecanol (C20H42O, 2-Octyldodecan-1-ol), butyric acid (C4:0), isobutyric acid (C4:0), valeric acid (C5:0), isovaleric acid (C5:0), levulinic acid (C5:0), caproic acid (C6:0), caprylic acid (C8:0), capric acid (C10:0), lauric acid (C12:0), myristic acid (C14:0), palmitic acid (C16:0), stearic acid (C18:0), isostearic acid (C18:0), 5-dodecenoic acid (C12:1), 7- tetradecenoic acid (14:1), palmitoleic acid (16:1), oleic acid (C18:1), vaccenic acid (C18:1), elaidic acid (C18:1), paullinic acid (C20:1), gondoic acid (C20:1), erucic acid (C22:1), 15- docosenoic acid (C22:1), 17-tetracosenoic acid (24:1), nervonic acid

(C24:1), ximenic acid (C26:1), hexadecatrienoic acid (16:3), linoleic acid (C18:2), rumenic acid (C18:2), alpha- linolenic acid (C18:3), gamma-linolenic acid (C18:3), calendic acid (C18:3), stearidonic acid (C18:4) mead acid (C20:3), eicosadienoic acid (C20:3), eicosatrienoic acid (C20:3), dihomo- gamma-linolenic acid (C20:3), arachidonic acid (C20:4), docosadienoic acid (C22:2), adrenic acid (C22:4), osbond acid (C22:5), tetracosatetraenoic acid (C24:4), tetracosapentaenoic acid (C24:5), butanol (C4), tert-Butyl alcohol (C4), 2-butanol, isobutanol, tert-butanol, tert-Amyl alcohol (C5), 3-Methyl-3-pentanol (C6), capryl alcohol (C8), pelargonic alcohol (C9), capric alcohol (C10), Undecyl alcohol (C11), Lauryl alcohol (C12), Tridecyl alcohol (C13), Myristyl alcohol (C14), Pentadecyl alcohol (C15), Cetyl alcohol (C16), Palmitoleyl alcohol (cis-9- hexadecen-1-ol, C16H32O), Heptadecyl alcohol (1-n-heptadecanol, C17H36O), Stearyl alcohol (C18), Oleyl alcohol (C18H36O), linoleyl alcohol (C18H34O, cis,cis-9,12-Octadecadien-1-ol), Nonadecyl alcohol (C19), Arachidyl alcohol (C20H42O), Heneicosyl alcohol (C21), Behenyl alcohol (C22H46O), Erucyl alcohol (cis-13-docosen-1-ol, C22H44O), Lignoceryl alcohol (C24), Ceryl alcohol (C26), octyldodecanol (C20H42O, 2-Octyldodecan-1-ol), ethyl oleate, methyl oleate, decyloleate, oleyl oleate, glyceryl monooleate, isopropyl palmitate (ester of isopropyl alcohol and palmitic acid), isopropyl myristate, methyl laurate (lauric acid methyl ester), glyceryl laurate (lauric acid glyceryl ester, monolaurin, glycerol monolaurate), propylene glycol monolaurate type I, propylene glycol monolaurate type II (e.g. lauroglycol™90), lauryl lactate (ester of lauryl alcohol and lactic acid), butyl acetate.

[0021] In some embodiments, provided is a patch wherein the polyacrylic adhesive includes a self crosslinkable acrylic adhesive, the adhesive comprising one or more of: Duro-Tak® 387-2516, Duro-Tak® 87-9301, Duro-Tak® 387-2051, Duro-Tak® 87-2852, Duro-Tak® 87-2194, Duro-Tak® 87-2852, GELVA® 737, GELVA® 2655, and GELVA® 1753.

[0022] In some embodiments, provided is a formulation for a drug-in-adhesive patch for both rapid onset and sustained release transdermal administration of ondansetron to a human subject

[0023] In some embodiments, provided is a formulation comprising an amphiphilic polymer, one or more enhancer, and one or more solvent. In further embodiments, the amphiphilic polymer includes one or more of: a cellulose polymer, an acetyl- and succinoyl-substituted polymer, a hydroxypropylcellulose acetate succinate or hypromellose acetate succinate (HPMC-AS), AquaSolve™ HPMCAS-LF, AquaSolve™ HPMCAS-LG; AquaSolve™ HPMCAS-MF; AquaSolve™ HPMCAS-MG; AquaSolve™ HPMCAS-HF; AquaSolve™ HPMCAS-HG, substituted hydroxypropylcellulose (HPMC), hydroxypropylcellulose (HPMC), a Klucel™ polymer, Klucel™ HF, Klucel™ MF, Klucel™ GF, Klucel™ JF, Klucel™ EF, Klucel™ ELF, an HPMC derivative, a cellulose ether, a METHOCEL™ cellulose ether, METHOCEL™ E, METHOCEL™ F, METHOCEL™ J, METHOCEL™ K, Methocel™ 40-0101, METHOCEL™ 40-0202,

METHOCEL™ E4M PRM, METHOCEL™ E50 PRM, METHOCEL™ 856N, METHOCEL™ K100M PRM, a carboxymethylcellulose (CMC), a WALOCEL™ polymer, WALOCEL™ CRT 1000, WALOCEL™ CRT 2000, WALOCEL™ CRT 10000, WALOCEL™ CRT 15000, WALOCEL™ CRT 30000, WALOCEL™ CRT 40000, WALOCEL™ CRT 50000, WALOCEL™ CRT 60000, polyvinylpyrrolidone (PVP), acrylic acid derivatives, a Plastoid® polymer, Plastoid®B, an Eudragit® polymer, Eudragit® L-100, Eudragit® L100-55; Eudragit® L30 D-55; Eudragit® L12,5; Eudragit® S100; Eudragit® S12,5; Eudragit® FS30D; Eudragit® E100; Eudragit® E12,5; Eudragit® EPO; Eudragit® S100; Eudragit® S12,5; Eudragit® FS30D; Eudragit® NE30D; Eudragit® NE40D; Eudragit® NM30D; Eudragit® RLPO; Eudragit® RL100; Eudragit® RL30D; Eudragit® RL12,5; Eudragit® RSPO; Eudragit® RS100; Eudragit® RS30D; Eudragit® RS12,5; PlasACRYL™ HTP20; PlasACRYL™ T20; and Acryl-EZE®.

[0024] In some embodiments, provided is a formulation wherein the enhancer comprises an FD enhancer, wherein the FD enhancer is selected from a fatty acid, a fatty alcohol, a fatty acid derivative, and a fatty alcohol derivative, and combinations thereof. In further embodiments, the FD enhancer is a fatty acid derivative or a fatty alcohol derivative, or combinations thereof, and further wherein the fatty acid derivative or fatty alcohol derivative consists of a substituted fatty acid moiety, or a substituted fatty alcohol moiety that comprises one or more additional group, wherein the additional group comprises one or more of hydroxyl, ethyl, methyl, propyl, butyl, and glyceryl, and wherein the fatty acid moiety or the fatty alcohol moiety of the FD enhancer has a carbon chain length from C4 to C26.

[0025] In some embodiments, provided is a formulation wherein the solvent comprises one or more of: DMSO, lactic acid, diethylene glycol monoethyl ether (DEGEE), Span 20®, Span®40, Span® 60, Span®80, Span®83, Span®85, Span®120, Tween 20®, Tween 21®, Tween 40®, Tween 60®, Tween 61®, Tween 65®, Tween 80®, and hexylenegycol.

[0026] In some embodiments, provided is a formulation wherein the enhancer further comprises one or more of: ethanol, propanol, decylmethyl sulfoxide, dimethylformamide, azone, urea, dimethylacetamide, a pyrrolidone derivative, 1-methyl-4-carboxy-2-pyrrolidone, 1-methyl-2-pyrrolidone, 1-lauryl-4-methoxycarbonyl-2-pyrrolidone, a polyol, propylene glycol, polyethylene glycol, a terpene, menthol, limonene, terpineol, pinene, carvol, a surfactant, a nonionic surfactant, a cationic surfactant, an anionic surfactant, Brij®, sodium lauryl sulfate, ethyl acetate, methyl acetate, octisalate, pentadecalactone, and acrylamide.

[0027] In some embodiments, provided is a formulation wherein the enhancer comprises one or more of: butyric acid (C4:0), isobutyric acid (C4:0), valeric acid (C5:0), isovaleric acid (C5:0), levulinic acid (C5:0), caproic acid (C6:0), caprylic acid (C8:0), capric acid (C10:0), lauric acid (C12:0), myristic acid (C14:0), palmitic acid (C16:0), stearic acid (C18:0), and isostearic acid

(C18:0), 5-dodecenoic acid (C12:1), 7-tetradecenoic acid (14:1), palmitoleic acid (16:1), oleic acid (C18:1), vaccenic acid (C18:1), elaidic acid (C18:1), paullinic acid (C20:1), gondoic acid (C20:1), erucic acid (C22:1), 15-docosenoic acid (C22:1), 17-tetracosenoic acid (24:1), nervonic acid (C24:1), and ximenic acid (C26:1), hexadecatrienoic acid (16:3), linoleic acid (C18:2), rumenic acid (C18:2), alpha-linolenic acid (C18:3), gamma-linolenic acid (C18:3), calendic acid (C18:3), stearidonic acid (C18:4) mead acid (C20:3), eicosadienoic acid (C20:3), eicosatrienoic acid (C20:3), dihomo-gamma-linolenic acid (C20:3), arachidonic acid (C20:4), docosadienoic acid (C22:2), adrenic acid (C22:4), osbond acid (C22:5), tetracosatetraenoic acid (C24:4), and tetracosapentaenoic acid (C24:5), butanol (C4), tert-Butyl alcohol (C4), tert-Amyl alcohol (C5), 3-Methyl-3-pentanol (C6), capryl alcohol (C8), pelargonic alcohol (C9), capric alcohol (C10), Undecyl alcohol (C11), Lauryl alcohol (C12), Tridecyl alcohol (C13), Myristyl alcohol (C14), Pentadecyl alcohol (C15), Cetyl alcohol (C16), Palmitoleyl alcohol (cis-9-hexadecen-1-ol, C16H32O), Heptadecyl alcohol (1-n-heptadecanol, C17H36O), Stearyl alcohol (C18), Oleyl alcohol (C18H36O), linoleyl alcohol (C18H34O, cis,cis-9,12-Octadecadien-1-ol), Nonadecyl alcohol (C19), Arachidyl alcohol (C20H42O), Heneicosyl alcohol (C21), Behenyl alcohol (C22H46O), Erucyl alcohol (cis-13-docosen-1-ol, C22H44O), Lignoceryl alcohol (C24), Ceryl alcohol (C26), octyldodecanol (C20H42O, 2-Octyldodecan-1-ol), butyric acid (C4:0), isobutyric acid (C4:0), valeric acid (C5:0), isovaleric acid (C5:0), levulinic acid (C5:0), caproic acid (C6:0), caprylic acid (C8:0), capric acid (C10:0), lauric acid (C12:0), myristic acid (C14:0), palmitic acid (C16:0), stearic acid (C18:0), isostearic acid (C18:0), 5-dodecenoic acid (C12:1), 7- tetradecenoic acid (14:1), palmitoleic acid (16:1), oleic acid (C18:1), vaccenic acid (C18:1), elaidic acid (C18:1), paullinic acid (C20:1), gondoic acid (C20:1), erucic acid (C22:1), 15- docosenoic acid (C22:1), 17-tetracosenoic acid (24:1), nervonic acid (C24:1), ximenic acid (C26:1), hexadecatrienoic acid (16:3), linoleic acid (C18:2), rumenic acid (C18:2), alpha- linolenic acid (C18:3), gamma-linolenic acid (C18:3), calendic acid (C18:3), stearidonic acid (C18:4) mead acid (C20:3), eicosadienoic acid (C20:3), eicosatrienoic acid (C20:3), dihomo- gamma-linolenic acid (C20:3), arachidonic acid (C20:4), docosadienoic acid (C22:2), adrenic acid (C22:4), osbond acid (C22:5), tetracosatetraenoic acid (C24:4), tetracosapentaenoic acid (C24:5), butanol (C4), tert-Butyl alcohol (C4), 2-butanol, isobutanol, tert-butanol, tert-Amyl alcohol (C5), 3-Methyl-3-pentanol (C6), capryl alcohol (C8), pelargonic alcohol (C9), capric alcohol (C10), Undecyl alcohol (C11), Lauryl alcohol (C12), Tridecyl alcohol (C13), Myristyl alcohol (C14), Pentadecyl alcohol (C15), Cetyl alcohol (C16), Palmitoleyl alcohol (cis-9- hexadecen-1-ol, C16H32O), Heptadecyl alcohol (1-n-heptadecanol, C17H36O), Stearyl alcohol (C18), Oleyl alcohol (C18H36O), linoleyl alcohol (C18H34O, cis,cis-9,12-Octadecadien-1-ol), Nonadecyl alcohol (C19), Arachidyl alcohol (C20H42O), Heneicosyl alcohol (C21), Behenyl alcohol (C22H46O), Erucyl alcohol (cis-13-docosen-1-ol, C22H44O),

Lignoceryl alcohol (C24), Ceryl alcohol (C26), octyldodecanol (C20H42O, 2-Octyldodecan-1-ol), ethyl oleate, methyl oleate, decyloleate, oleyl oleate, glyceryl monooleate, isopropyl palmitate (ester of isopropyl alcohol and palmitic acid), isopropyl myristate, methyl laurate (lauric acid methyl ester), glyceryl laurate (lauric acid glyceryl ester, monolaurin, glycerol monolaurate), propylene glycol monolaurate type I, propylene glycol monolaurate type II (e.g. lauroglycol^{TM}90), lauryl lactate (ester of lauryl alcohol and lactic acid), butyl acetate.

[0028] In further embodiments, the patch provides a minimum predetermined flux within a first predetermined amount of time; provides a preferred predetermined flux within a second predetermined amount of time; and maintains the preferred flux within a predetermined range for a third predetermined amount of time. In further embodiments, the minimum predetermined flux is about 2.5 μg/cm^2/h. In yet further embodiments, the preferred predetermined flux is about 5 μg/cm^2/h. In further embodiments, the patch provides a minimum predetermined flux of about 1, 2.5, 5, 10, or 15 μg/cm^2/h. In other embodiments, the first predetermined amount of time is 90 minutes or less. In further embodiments, the second predetermined amount of time is within 12 hours. In other embodiments, wherein the third predetermined amount of time is at least two days. In further embodiments, the patch provides a predetermined range flux of about 30 μg/cm^2/h as measured in 12 hour time intervals for at least two days. In further embodiments, the patch delivers 4 mg or more of ondansetron per day to a human subject. In yet other embodiments, the patch delivers 4 mg or more of ondansetron per day to a human subject for at least 2 days.

[0029] In further embodiments provided herein, the formulation provides: a minimum predetermined flux within a first predetermined amount of time; provides a preferred predetermined flux within a second predetermined amount of time; and maintains the preferred flux within a predetermined range for a third predetermined amount of time. In yet further embodiments, the formulation provides a minimum predetermined flux of 30 μg/cm^2/h. In further embodiments, the first predetermined time is about 90 minutes or less. In yet other embodiments, the second predetermined amount of time is within 12 hours. In further embodiments, the third predetermined amount of time is at least 5 days. In yet further embodiments, the predetermined range flux is selected from: 30 μg/cm^2/h, 35 μg/cm^2/h, 40 μg/cm^2/h, 45 μg/cm^2/h, 50μg/cm^2/h, 55 μg/cm^2/h, 60μg/cm^2/h, 65 μg/cm^2/h, 70μg/cm^2/h, 75 μg/cm^2/h, 80 μg/cm^2/h, 85 μg/cm^2/h, 90 μg/cm^2/h and higher.

[0030] In some embodiments, provided is a method of forming a transdermal patch for treatment of nausea, vomiting, or chemotherapy induced nausea and vomiting, wherein a polyacrylic adhesive is added to a formulation in a sufficient amount to form one or more drug-in-adhesive layer after solvent-casting of the formulation mixed with the polyacrylic adhesive, wherein the formulation comprises ondansetron, one or more amphiphilic polymer, one or more enhancer, and

one or more solvent, and wherein in the resulting patch, the one or more drug-in-adhesive layer is are sandwiched between a backing layer, a release liner, and optionally one or more membrane between multiple drug-in-adhesive layers.

[0031] In some embodiments, provided is a method to treat nausea, vomiting, or chemotherapy induced nausea and vomiting, wherein a patch is applied to the skin of a subject in need thereof, wherein the patch comprises one or more drug-in-adhesive layer sandwiched between a backing layer and a release liner, and optionally one or more membrane between a plurality of drug-in-adhesive layers, and wherein each of the one or more drug-in-adhesive layer of the patch comprises: a polyacrylic adhesive, ondansetron, one or more enhancer, one or more solvent, and an amphiphilic polymer.

[0032] In still other aspects, the disclosure provides further emobdiments relating to patch formulations comprising ondansetron added to the formulation in form of its base, an enhancer combination of lactic acid with a fatty acid, fatty alcohol, or a derivative thereof, and DMSO, and patches formed therefrom. Certain of these embodiments allow a more tailored treatment of various patient groups and symptoms. Further embodiments relate to formulations for patches with a self-crosslinkable polyacrylic adhesive. Still further embodiments for patch formulations may include one or more amphiphilic polymers.

[0033] In some embdiments, the disclosure relates to formulations comprising ondansetron added to the formulation in form of a salt thereof, an enhancer combination of a glycol (e.g. propylene glycol, hexylene glycol, PEG) with a fatty acid, fatty alcohol, or a derivative thereof, and DMSO, and patches formed therefrom.

[0034] In some embodiments, provided are formulations to form both a rapid onset and a sustained release drug-in-adhesive patch for transdermal administration of ondansetron to a human subject.

[0035] In some embodiments, provided are rapid onset sustained release drug-in-adhesive patches for transdermal administration of ondansetron to a human subject, wherein the patch is adapted to provide a minimum flux of 2.5 $\mu g/cm^2$/hour or more which is reached within a rapid time period of 12 hours or less, and wherein a steady state flux of 30 $\mu g/cm^2$/hour or more is reached and maintained for 2 days or more, as determined in a Franz-diffusion cell test using human cadaver skin and phosphate buffered saline (PBS) of pH 4.5 with 0.01% sodium azide as a receiving medium and measuring in time intervals of 24 hours or less, or is able to deliver 4 mg or more ondansetron per day after application of the patch to human cadaver skin.

[0036] In other embodiments, provided are formulations which comprise: a polyacrylic adhesive, ondansetron, and a combination of enhancers, and wherein the enhancer combination comprises: i. DMSO; ii. a glycol; iii. an FD enhancer comprising one or more of a fatty acid, a fatty

alcohol, a fatty acid derivative, and a fatty alcohol derivative, and combinations thereof. In further embodiments of the formulation the ondansetron is present in the form of its hydrochloride.

[0037] In other embodiments, provided are patches, wherein an adhesive layer of the patch is formed as a matrix from a formulation comprising: a polyacrylic adhesive, ondansetron, and an enhancer combination; wherein ondansetron is added to the formulation in form of a salt thereof; and wherein the enhancer combination comprises: i. DMSO; ii. a glycol; iii. an FD enhancer comprising one or more of a fatty acid, a fatty alcohol, a fatty acid derivative, and a fatty alcohol derivative, and combinations thereof.

[0038] In other embodiments, provided are formulations wherein the FD enhancer comprises a fatty acid or fatty alcohol, the fatty acid or fatty alcohol comprising one or more of: butyric acid (C4:0), isobutyric acid (C4:0), valeric acid (C5:0), isovaleric acid (C5:0), levulinic acid (C5:0), caproic acid (C6:0), caprylic acid (C8:0), capric acid (C10:0), lauric acid (C12:0), myristic acid (C14:0), palmitic acid (C16:0), stearic acid (C18:0), and isostearic acid (C18:0), 5-dodecenoic acid (C12:1), 7-tetradecenoic acid (14:1), palmitoleic acid (16:1), oleic acid (C18:1), vaccenic acid (C18:1), elaidic acid (C18:1), paullinic acid (C20:1), gondoic acid (C20:1), erucic acid (C22:1), 15-docosenoic acid (C22:1), 17-tetracosenoic acid (24:1), nervonic acid (C24:1), and ximenic acid (C26:1), hexadecatrienoic acid (16:3), linoleic acid (C18:2), rumenic acid (C18:2), alpha-linolenic acid (C18:3), gamma-linolenic acid (C18:3), calendic acid (C18:3), stearidonic acid (C18:4) mead acid (C20:3), eicosadienoic acid (C20:3), eicosatrienoic acid (C20:3), dihomo-gamma-linolenic acid (C20:3), arachidonic acid (C20:4), docosadienoic acid (C22:2), adrenic acid (C22:4), osbond acid (C22:5), tetracosatetraenoic acid (C24:4), and tetracosapentaenoic acid (C24:5), butanol (C4), tert-Butyl alcohol (C4), tert-Amyl alcohol (C5), 3-Methyl-3-pentanol (C6), capryl alcohol (C8), pelargonic alcohol (C9), capric alcohol (C10), Undecyl alcohol (C11), Lauryl alcohol (C12), Tridecyl alcohol (C13), Myristyl alcohol (C14), Pentadecyl alcohol (C15), cetyl alcohol (C16), palmitoleyl alcohol (cis-9-hexadecen-1-ol, C16H32O), Heptadecyl alcohol (1-n-heptadecanol, C17H36O), Stearyl alcohol (C18), oleyl alcohol (C18H36O), linoleyl alcohol (C18H34O, cis,cis-9,12-Octadecadien-1-ol), Nonadecyl alcohol (C19), arachidyl alcohol (C20H42O), Heneicosyl alcohol (C21), Behenyl alcohol (C22H46O), Erucyl alcohol (cis-13-docosen-1-ol, C22H44O), Lignoceryl alcohol (C24), Ceryl alcohol (C26), and octyldodecanol (C20H42O, 2-Octyldodecan-1-ol).

[0039] In some embodiments, provided are formulations, wherein the FD enhancer comprises a saturated fatty acid, the saturated fatty acid comprising one or more of: butyric acid (C4:0), isobutyric acid (C4:0), valeric acid (C5:0), isovaleric acid (C5:0), levulinic acid (C5:0), caproic acid (C6:0), caprylic acid (C8:0), capric acid (C10:0), lauric acid (C12:0), myristic acid (C14:0), palmitic acid (C16:0), stearic acid (C18:0), and isostearic acid (C18:0).

[0040] In some embodiments, provided is a formulation wherein the FD enhancer comprises a monounsaturated fatty acid, the monounsaturated fatty acid comprising one or more of: 5-dodecenoic acid (C12:1), 7-tetradecenoic acid (14:1), palmitoleic acid (16:1), oleic acid (C18:1), vaccenic acid (C18:1), elaidic acid (C18:1), paullinic acid (C20:1), gondoic acid (C20:1), erucic acid (C22:1), 15-docosenoic acid (C22:1), 17-tetracosenoic acid (24:1), nervonic acid (C24:1), and ximenic acid (C26:1).

[0041] In some embodiments, provided is a formulation wherein the FD enhancer comprises a polyunsaturated fatty acid, the polyunsaturated fatty acid comprising one or more of: hexadecatrienoic acid (16:3), linoleic acid (C18:2), rumenic acid (C18:2), alpha-linolenic acid (C18:3), gamma-linolenic acid (C18:3), calendic acid (C18:3), stearidonic acid (C18:4) mead acid (C20:3), eicosadienoic acid (C20:3), eicosatrienoic acid (C20:3), dihomo-gamma-linolenic acid (C20:3), arachidonic acid (C20:4), docosadienoic acid (C22:2), adrenic acid (C22:4), osbond acid (C22:5), tetracosatetraenoic acid (C24:4), and tetracosapentaenoic acid (C24:5).

[0042] In some embodiments, provided is a formulation wherein the FD enhancer comprises a fatty alcohol, the fatty alcohol comprising one or more of: butanol (C4), tert-Butyl alcohol (C4), 2-butanol, isobutanol, tert-butanol, tert-Amyl alcohol (C5), 3-Methyl-3-pentanol (C6), capryl alcohol (C8), pelargonic alcohol (C9), capric alcohol (C10), Undecyl alcohol (C11), Lauryl alcohol (C12), Tridecyl alcohol (C13), Myristyl alcohol (C14), Pentadecyl alcohol (C15), Cetyl alcohol (C16), Palmitoleyl alcohol (cis-9-hexadecen-1-ol, C16H32O), Heptadecyl alcohol (1-n-heptadecanol, C17H36O), Stearyl alcohol (C18), Oleyl alcohol (C18H36O), linoleyl alcohol (C18H34O, cis,cis-9,12-Octadecadien-1-ol), Nonadecyl alcohol (C19), Arachidyl alcohol (C20H42O), Heneicosyl alcohol (C21), Behenyl alcohol (C22H46O), Erucyl alcohol (cis-13-docosen-1-ol, C22H44O), Lignoceryl alcohol (C24), Ceryl alcohol (C26), octyldodecanol (C20H42O, 2-Octyldodecan-1-ol).

[0043] In some embodiments, provided is a formulation wherein the FD enhancer comprises one or more fatty acid derivative, the fatty acid derivative comprising one or more of: ethyl oleate, methyl oleate, decyloleate, oleyl oleate, glyceryl monooleate, isopropyl palmitate (ester of isopropyl alcohol and palmitic acid), isopropyl myristate, methyl laurate (lauric acid methyl ester), glyceryl laurate (lauric acid glyceryl ester, monolaurin, glycerol monolaurate), propylene glycol monolaurate type I, propylene glycol monolaurate type II (e.g. lauroglycol^{TM}90), lauryl lactate (ester of lauryl alcohol and lactic acid), Hydramol^{TM} PGPL ester, PEG-PPG-8/3 laurate and butyl acetate.

[0044] In some embodiments, provided is a formulation further comprising a solvent, the solvent comprising one or more of: diethylene glycol monoethyl ether (DEGEE), Span 20®, Span®40, Span® 60, Span®80, Span®83, Span®85, Span®120, Tween 20®, Tween 21®, Tween 40®, Tween 60®, Tween 61®, Tween 65®, Tween 80®, and hexylenegycol.

[0045] In some embodiments, provided is a formulation further comprising one or more additional enhancer, the additional enhancer comprising one or more of: ethanol, propanol, decylmethyl sulfoxide, dimethylformamide, azone, urea, dimethylacetamide, a pyrrolidone derivative, 1-methyl-4-carboxy-2-pyrrolidone, 1-methyl-2-pyrrolidone, 1-lauryl-4-methoxycarbonyl-2-pyrrolidone, a polyol, propylene glycol, polyethylene glycol, a terpene, menthol, limonene, terpineol, pinene, carvol, a surfactant, a nonionic surfactant, a cationic surfactant, an anionic surfactant, Brij®, sodium lauryl sulfate, ethyl acetate, methyl acetate, octisalate, pentadecalactone, and acrylamide.

[0046] In some embodiments, provided is a formulation further comprising a polymer, the polymer comprising one or more of: a cellulose polymer, hydroxypropylcellulose (HPMC), a KlucelTM polymer, Klucel™ HF, Klucel™ MF, Klucel™ GF, Klucel™ JF, Klucel™ EF, Klucel™ ELF, an HPMC derivative, a cellulose ether, a METHOCEL™ cellulose ether, METHOCEL™ E, METHOCEL™ F, METHOCEL™ J, METHOCEL™ K, Methocel™ 400101, METHOCEL™ 40-0202, METHOCEL™ E4M PRM, METHOCEL™ E50 PRM, METHOCEL™ 856N, METHOCEL™ K100M PRM, a carboxymethylcellulose (CMC), a WALOCEL™ polymer, WALOCEL™ CRT 1000, WALOCEL™ CRT 2000, WALOCEL™ CRT 10000, WALOCEL™ CRT 15000, WALOCEL™ CRT 30000, WALOCEL™ CRT 40000, WALOCEL™ CRT 50000, WALOCEL™ CRT 60000, polyvinylpyrrolidone (PVP), acrylic acid derivatives, a Plastoid® polymer, Plastoid®B, , an Eudragit® polymer, Eudragit® L-100, Eudragit® L100-55; Eudragit® L30 D-55; Eudragit® L12,5; Eudragit® S100; Eudragit® S12,5; Eudragit® FS30D; Eudragit® E100; Eudragit® E12,5; Eudragit® EPO; Eudragit® S100; Eudragit® S12,5; Eudragit® FS30D; Eudragit® NE30D; Eudragit® NE40D; Eudragit® NM30D; Eudragit® RLPO; Eudragit® RL100; Eudragit® RL30D; Eudragit® RL12,5; Eudragit® RSPO; Eudragit® RS100; Eudragit® RS30D; Eudragit® RS12,5; PlasACRYL™ HTP20; PlasACRYL™ T20; Acryl-EZE®.

[0047] In some embodiments, provided is a formulation further comprising a polymer, wherein the polymer is an acetyl- and succinoyl-substituted amphiphilic polymer (AS-substituted polymer), wherein the AS-substituted polymer comprises one or more of: an acetyl- and succinoyl-substituted cellulosic polymer which is insoluble in acidic aqueous solutions and soluble in dilute caustic solution; an acetyl- and succinoyl-substituted cellulosic polymer which is insoluble in acidic aqueous solutions and soluble in both dilute caustic solution and acetone; an acetyl- and succinoyl-substituted cellulosic polymer which is insoluble in acidic aqueous solutions and soluble in both dilute caustic solution and methanol; an acetyl- and succinoyl-substituted cellulosic polymer which is insoluble in acidic aqueous solutions and soluble in each of dilute caustic solution, acetone and methanol; a hydroxypropylcellulose acetate succinate or hypromellose acetate succinate (HPMC-AS); a HPMC-AS wherein the acetyl, succinoyl, methoxyl, and hydroxypropoxy content in %(wt) is

within the following ranges: from about 4 to about 15% acetyl, about 2 to about 20% succinoyl, about 15 to about 30% methoxyl, and about 3 to about 12% hydroxypropoxy, from about 5 to about 13% acetyl, about 8 to about 16% succinoyl, about 19 to about 27% methoxyl, and about 3 to about 11% hydroxypropoxy, from about 5 to about 9% acetyl, about 14 to about 18% succinoyl, about 20 to about 24% methoxyl, and about 5 to about 9% hydroxypropoxy, or from about 7 to about 11% acetyl, about 10 to about 14% succinoyl, about 21 to about 25% methoxyl, and about 5 to about 9% hydroxypropoxy, or from about 10 to about 14% acetyl, about 4 to about 8% succinoyl, about 22 to about 26% methoxyl, and about 6 to about 10% hydroxypropoxy; AquaSolveTM HPMCAS-LF; AquaSolveTM HPMCAS-LG; AquaSolveTM HPMCAS-MF; AquaSolveTM HPMCAS-MG; AquaSolveTM HPMCAS-HF; AquaSolveTM HPMCAS-HG.

[0048] In some embodiments, provided is a formulation wherein the polyacrylic adhesive comprises a self crosslinkable acrylic adhesive, the adhesive comprising one or more of: Duro-Tak® 387-2516, Duro-Tak® 87-9301, Duro-Tak® 387-2051, Duro-Tak® 87-2852, Duro-Tak® 87-2194, Duro-Tak® 87-2852, GELVA® 737, GELVA® 2655, and GELVA® 1753.

[0049] In further embodiments provided herein, the formulation provides: a minimum predetermined flux within a first predetermined amount of time; provides a preferred predetermined flux within a second predetermined amount of time; and maintains the preferred flux within a predetermined range for a third predetermined amount of time. In yet further embodiments, the formulation provides a minimum predetermined flux of 30 $\mu g/cm^2$/hour. In further embodiments, the first predetermined time is about 90 minutes or less. In yet other embodiments, the second predetermined amount of time is within 12 hours. In further embodiments, the third predetermined amount of time is at least 2 days. In further embodiments, the third predetermined amount of time is at least 5 days. In yet further embodiments, the predetermined range flux is selected from: 35 μ/cm^2/h, 40 μ/cm^2/h, 45 μ/cm^2/h, 50 μ/cm^2/h, 55 μ/cm^2/h, 60 μ/cm^2/h, 65 μ/cm^2/h, 70 μ/cm^2/h, 75 μ/cm^2/h, 80 μ/cm^2/h, 85 μ/cm^2/h, 90 μ/cm^2/h, and higher.

[0050] In further embodiments of the patch, the ondansetron is present in form of its hydrochloride. In further embodiments, the patch provides a minimum predetermined flux within a first predetermined amount of time; provides a preferred predetermined flux within a second predetermined amount of time; and maintains the preferred flux within a predetermined range for a third predetermined amount of time. In further embodiments, the minimum predetermined flux is about 2.5 $\mu g/cm^2$/h. In yet further embodiments, the preferred predetermined flux is about 5 $\mu g/cm^2$/h. In other embodiments, the first predetermined amount of time is 90 minutes or less. In further embodiments, the second predetermined amount of time is within 12 hours. In other embodiments, wherein the third predetermined amount of time is at least two days. In further embodiments, the patch provides a preferred predetermined flux of about 30 $\mu g/cm^2$/h as measured

in 12 hour time intervals for at least two days. In further embodiments, the patch delivers 4 mg or more of ondansetron per day to human subject. In yet other embodiments, the patch delivers 4 mg or more of ondansetron per day to human subject for at least 2 days.

[0051] In some embodiments, provided is a formulation wherein the formulation or a patch formed therefrom provides a rapid time period to reach a minimum flux of 30 $\mu g/cm^2/h$ or more for the formulation and 2.5 $\mu g/cm^2/h$ or more for the patch, and wherein the rapid time period is selected from: 6, 5, 4, 3, 2, and 1 hour(s) or less, as determined in the Franz-diffusion cell test.

[0052] In other embodiments, provided is a formulation wherein the formulation or a patch formed therefrom provides a minimum steady state flux of 30 $\mu g/cm^2/h$ or more for the formulation and 2.5 $\mu g/cm^2/h$ or more for the patch, wherein the minimum steady state flux is substantially sustained for a sustained time period, wherein the sustained time period is selected from 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14 days or more as determined in the Franz-diffusion cell test.

[0053] In some embodiments, provided is a patch that provides a minimum steady state flux that is substantially maintained for 2 days or more, and wherein the minimum steady state flux is selected from: 1 $\mu g/cm^2/h$, 2.5 $\mu g/cm^2/h$, 3 $\mu g/cm^2/h$, 4 $\mu g/cm^2/h$, 5$\mu g/cm^2/h$, 6$\mu g/cm^2/h$, 7$\mu g/cm^2/h$, 8 $\mu g/cm^2/h$, and higher, as determined in the Franz-diffusion cell test.

[0054] In some embodiments, provided is a patch wherein ondansetron is present at least partially in form of its hydrochloride salt.

[0055] In some embodiments, provided is a method of forming a transdermal patch for treatment of nausea or vomiting from a formulation, wherein the formulation comprises a polyacrylic adhesive, ondansetron, and a combination of enhancers, wherein ondansetron is added to the formulation in form of a salt thereof, and wherein the enhancer combination comprises DMSO, a glycol, and an FD enhancer, and wherein the patch is formed from one or more drug-in-adhesive layers by solvent casting, and in the resulting patch, the one or more layers are sandwiched between a backing layer, a release liner, and optionally one or more membrane between multiple drug-in-adhesive layers. In further embodiments, the FD enhancer includes one or more of a fatty acid, a fatty alcohol, a fatty acid derivative, and a fatty alcohol derivative, wherein the fatty acid moiety or the fatty alcohol moiety of the FD enhancer has a carbon chain length from C4 to C26,

[0056] In some embodiments, provided is a method to treat nausea, vomiting, or chemotherapy induced nausea and vomiting, wherein a patch is applied to the skin of a subject in need thereof, and wherein one or more adhesive layer of the patch is formed as a matrix from a formulation comprising a polyacrylic adhesive, ondansetron, and a combination of enhancers, wherein ondansetron is added to the formulation in form of a salt thereof, and wherein the enhancer combination comprises DMSO, a glycol, and an FD enhancer, and wherein the patch comprises one or more drug-in-adhesive layers which are sandwiched between a backing layer and a release liner,

and optionally one or more membrane between a plurality of drug-in-adhesive layers. In further embodiments, the FD enhancer includes one or more of a fatty acid, a fatty alcohol, a fatty acid derivative, and a fatty alcohol derivative, wherein the fatty acid moiety or the fatty alcohol moiety of the FD enhancer has a carbon chain length from C4 to C26,

[0057] The foregoing summary with the preferred embodiments should not be construed tas limiting. It will become apparent to one of ordinary skill in the art that the embodiments of the disclosure described herein may be further modified without departing from the spirit and scope of the disclosure, and various illustrative modifications can be found in the detailed description that follows.

BRIEF DESCRIPTION OF THE DRAWINGS

[0058] Various features of illustrative embodiments of the disclosure are described below with reference to the drawings. The illustrated embodiments are intended to illustrate, but not to limit the full scope of possible embodiments. The drawings contain the following figures:

[0059] **FIG. 1** provides a graph showing individual plasma concentrations of ondansetron after topical administration (200 mg/patch) in female Yucatan Mini-pigs (Group 1).

[0060] **FIG. 2** provides a graph showing mean plasma concentrations of ondansetron after topical administration (200 mg/patch) in female Yucatan Mini-pigs (Group 1).

[0061] **FIG. 3** provides a graph showing individual plasma concentrations of ondansetron after topical administration (175 mg/patch) in female Yucatan Mini-pigs (Group 2).

[0062] **FIG. 4** provides a graph showing mean plasma concentrations of ondansetron after topical administration (175 mg/patch) in female Yucatan Mini-pigs (Group 2).

[0063] **FIG. 5** provides a graph showing in vitro flux data for human cadaver skin using formulation ONM9TP.

[0064] **FIG. 6** provides a graph showing in vitro flux data for human cadaver skin using formulation ONM95M.

[0065] **FIG. 7** provides a graph showing in vitro flux data for human cadaver skin using formulation ONM105.

[0066] **FIG. 8** provides a graph showing in vitro flux data for human cadaver skin using formulation ONM95PGML.

[0067] **FIG. 9A** provides a graph showing data from the ondansetron minipig study using formualtion ONM95M. Average plasma level for the time window 8-120 hours is shown.

[0068] **FIG. 9B** also provides a graph showing data from the ondansetron minipig study using formualtion ONM95M. Average plasma level for the time window 4-120 hours is shown.

DETAILED DESCRIPTION

[0069] It is understood that various configurations of the subject technology will become readily apparent to those skilled in the art from the disclosure, wherein various configurations of the subject technology are shown and described by way of illustration. As will be realized, the subject technology is capable of other and different configurations and its several details are capable of modification in various other respects, all without departing from the scope of the subject technology. Accordingly, the summary, drawings and detailed description are to be regarded as illustrative in nature and not as restrictive.

[0070] The detailed description set forth below is intended as a description of various configurations of the subject technology and is not intended to represent the only configurations in which the subject technology may be practiced. The appended drawings are incorporated herein and constitute a part of the detailed description. The detailed description includes specific details for the purpose of providing a thorough understanding of the subject technology. However, it will be apparent to those skilled in the art that the subject technology may be practiced without these specific details. In some instances, well-known structures and components are shown in block diagram form in order to avoid obscuring the concepts of the subject technology. Like components are labeled with identical element numbers for ease of understanding.

[0071] Unless otherwise defined, scientific and technical terms used in connection with the present teachings described herein shall have the meanings that are commonly understood by those of ordinary skill in the art. The terminology used in the description of the disclosure herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the disclosure. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. The techniques and procedures described herein are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the instant specification.

[0072] The nomenclatures utilized in connection with, and the laboratory procedures and techniques described herein are those well-known and commonly-used in the art.

DEFINITIONS

[0073] As used herein, the term “pharmaceutically acceptable salts” includes acid addition salts or addition salts of free bases. The term “pharmaceutically acceptable salts” within its scope include each of all the possible isomers and their mixtures, and any pharmaceutically acceptable metabolite, bioprecursor and/or pro-drug, such as, for example, a compound which has a structural formula different from the one of the compounds recited or described, yet is directly or indirectly

converted in vivo into such a compound upon administration to a subject, such as a mammal, and particularly a human being.

[0074] As used herein, the terms "subject" and "patient" are used interchangeably and include mammals; these may be non-primate mammals (e.g., without limitation, cows, pigs, horses, cats, dogs, and rats) and primate mammals (e.g., without limitation, monkeys and humans). Non-human animals include farm animals (e.g. horses, pigs, and cows) and pets (e.g. dogs and cats). In specific embodiments, the subject may be a human patient, or a non-human patient.

[0075] As used herein, the term "agent" refers to any molecule, compound, methodology and/or substance for use in the prevention, treatment, management and/or diagnosis of a disease or condition.

[0076] As used herein, the term "effective amount" refers to the amount of a therapy or agent that is sufficient to result in the prevention of the development, recurrence, or onset of a disease or condition, the prevention, treatment, reduction or amelioration of one or more symptoms thereof, the enhancement or improvement of the prophylactic effect(s) of another therapy, the reduction of the severity or the duration of a disease or condition, the amelioration of one or more symptoms of a disease or condition, the prevention of the advancement of a disease or condition, the regression of a disease or condition or one or more of its symptoms, and/or the enhancement or improvement of the therapeutic effect(s) of another therapy.

[0077] As used herein, the phrase "pharmaceutically acceptable" means approved by a regulatory agency of the federal or a state government, or listed in the U.S. Pharmacopeia, European Pharmacopeia, or other generally recognized pharmacopeia for use in animals, and more particularly, in humans.

[0078] As used herein, the term "therapeutic agent" refers to any molecule, compound, and/or substance that is used for treating and/or managing a disease or disorder.

[0079] As used herein, the terms "therapies" and "therapy" can refer to any method(s), composition(s), and/or agent(s) that can be used in the prevention, treatment and/or management of a disease or condition, or one or more symptoms thereof. In certain embodiments, the terms "therapy" and "therapies" refer to therapy by an ODS active, in particular in its transdermal application.

[0080] As used herein, the term "therapeutically effective amount" refers to an amount that provides some improvement or benefit to the subject. Alternatively stated, a "therapeutically effective" amount is an amount that will provide some alleviation, mitigation, or decrease in at least one clinical symptom in the subject.

[0081] As used herein, the term "inhibit" or "treat" refers to reduction in the amount, levels, density, turnover, association, dissociation, activity, signaling, pain or any other feature, symptom or pathology associated with an etiological agent or symptom associated with disease, disorder,

pathology or any other medical condition. For example, ondassetron can be used to "treat" or "inhibit" nausea and/or vomiting.

[0082] The term "derivative" or "derivatized" as used herein includes chemical modification of a compound, or pharmaceutically acceptable salts thereof or mixtures thereof. That is, a "derivative" may be a functional equivalent of a compound which is capable of inducing the functional activity of the compound in a given subject or application.

[0083] As used herein, the term "ODS" generally refers to ondansetron base, and the formulations and patches herein are specifically adapted for use with the base. However, instead of ondansetron base, use of an ondansetron salt, including, without limitation, ondansetron hydrochloride, and more preferably ondansetron lactate, may also be suitable in formulations and patches described herein.

[0084] As used herein, the terms "composition" and "formulation" may be used interchangeably, unless otherwise indicated. Generally, a formulation may be used as a stand- alone non-occlusive transdermal composition for application to the skin, or may be used in form of or to prepare a transdermal patch for application to the skin (patch formulation).

[0085] As used herein, the term "topical delivery" means delivery of drug into systemic circulation through the skin, which includes occlusive and non-occlusive delivery by a transdermal composition (typically non-occlusive) or patch (typically occlusive, depending on the backing layer of the patch).

[0086] As used in the description of the disclosure and the appended claims, the singular forms "a," "an," and "the" are intended to include the plural forms as well, unless the context clearly indicates otherwise. Also as used herein, "and/or" refers to and encompasses any and all possible combinations of one or more of the associated listed items, as well as the lack of combinations when interpreted in the alternative ("or"). For instance, the term "A and/or B" includes A, B, and (A and B).

[0087] Where a range of values is provided in this disclosure, it is intended that each intervening value between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the disclosure. For example, if a range of 1 μM to 8 μM is stated, it is intended that 2 μM, 3 μM, 4 μM, 5 μM, 6 μM, and 7 μM are also explicitly disclosed. Also for example, if a range of 1 $\mu g/cm^2/hr$ to 8 $\mu g/cm^2/hr$ is stated, it is intended that 2 $\mu g/cm^2/hr$, 3 $\mu g/cm^2/hr$, 4 $\mu g/cm^2/hr$, 5 $\mu g/cm^2/hr$, 6 $\mu g/cm^2/hr$, and 7 $\mu g/cm^2/hr$ are also explicitly disclosed.

[0088] The word "about" means a range of plus or minus 10% of that value, *e.g.*, "about 5" means 4.5 to 5.5, "about 100" means 90 to 100, *etc.*, unless the context of the disclosure indicates otherwise, or is inconsistent with such an interpretation. For example in a list of numerical values

such as "about 49, about 50, about 55, "about 50" means a range extending to less than half the interval(s) between the preceding and subsequent values, *e.g.*, more than 49.5 to less than 52.5. Furthermore, the phrases "less than about" a value or "greater than about" a value should be understood in view of the definition of the term "about" provided herein.

[0089] As used herein, "substantially" means sufficient to work for the intended purpose. The term "substantially" thus allows for minor, insignificant variations from an absolute or perfect state, dimension, measurement, result, or the like such as would be expected by a person of ordinary skill in the field but that do not appreciably affect overall performance. When used with respect to numerical values or parameters or characteristics that can be expressed as numerical values, "substantially" means within 10%, or within 5% or less, *e.g.*, with 2%.

[0090] As used herein, the term "plurality" can be 2, 3, 4, 5, 6, 7, 8, 9, 10, or more.

[0091] The various embodiments of the present disclosure are further described in detail in the paragraphs below.

DESCRIPTION

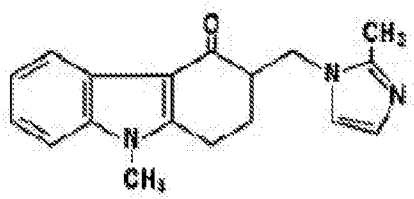
[0092] The present disclosure generally relates to transdermal patches of ondansetron. More specifically, embodiments described herein relate to transdermal formulations comprising ondansetron, in form of a salt thereof, an enhancer combination of lactic acid and/or a glycol with a FD enhancer (including e.g., fatty acids, fatty alcohols, fatty acid esters, or derivatives of any thereof), and DMSO. This combination together allows to provide a higher drug loading to deliver 4 mg or more daily, e.g., up to 16 mg per day, an increased flux, an extended duration of flux, and an improved flux profile in drug-in- adhesive type patches. For example, the improved flux profile may be adjusted to provide a more rapid onset of flux, e.g. within 30 minutes, within 1 hour, within 2 hours, within 3 hours, within 4 hours, or within up to 12 hours and/or a higher or more sustained flux for up to 2 days, or even for up to 14 days. This allows a more tailored treatment of patient groups and symptoms, for example of chemotherapy induced nausea and vomiting (CINV), which requires a rapid onset and high initial flux in the acute phase, followed by a sustained flux over multiple days. Further improvements, e.g., in flux, may be achieved by including one or more solvent, in particular one or more of diethylene glycol monoethyl ether (DEGEE), Transcutol® (TC), a Tween®-type surfactant, a Span®-type surfactant, and hexylengycol. Also, certain embodiments of the present disclosure relate to formulations for self-adhesive patches wherein the adhesive is a self crosslinkable polyacrylic adhesive. Further, formulations and patches of the present disclosure may optionally include one or more substituted amphiphilic polymer, and one or more optional excipients.

[0093] In the following, embodiments of formulations suitable for use in transdermal patches are described. In general, the ingredients of these formulations are indicated in % weight/weight (%

(w/w)); typically, the formulation is then mixed with one or more matrix component, including, without limitation, pressure sensitive acrylic adhesives, for example Duro-Tak® 387-2516. The resulting patch layer may be a single adhesive layer, or the patch may have multiple layers, optionally separated by one or more membrane. Unless indicated otherwise, ingredients indicated in % weight/weight (% (w/w)) refer to their weight percentages in the relevant matrix layer formed after drying to remove the solvent(s) and form a flexible matrix that may be self-adhesive, or may require an additional adhesive, e.g., in the form of an additional adhesive layer applied on top, or a layer or tape applied on all of its sides in sufficient breadth to provide adherence to the skin for the desired time.

ONDANSETRON

[0094] Ondansetron is chemically known as (±) 1, 2, 3, 9-tetrahydro-9-methy1-3-[(2-methyl-1H-imidazol-1-yl(methyl]-4H- carbazol-4-one (racemate; empirical formula: $C_{18}H_{19}N_3O$, molecular weight: 293.4). The chemical structure of ondansetron is shown below in Formula I (FI). Ondansetron hydrochloride is chemically known as (±) 1, 2, 3, 9-tetrahydro-9- methy1-3-[(2-methyl-1H-imidazol-1-y1)methyl]-4H- carbazol-4-one, monohydrochloride, dihydrate (empirical formula: $C_{18}H_{19}N_3O{\bullet}HCl{\bullet}2H_2O$, molecular weight: 365.9).



Formula I

[0095] Without wishing to be bound by theory, the addition of an amphiphilic polymer may be advantageous due to its effect on ODS, and in particular ODS base, and its flux over time, in particular its flux from an ODS-in-adhesive patch formed from such a formulation. Again without wishing to be bound by theory, the addition of an amphiphilic polymer may result in ODS, for example, ODS base, taking a particular form (e.g., fully or partially amorphous) that may result in or contribute to a desirable flux profile and/or improved flux, specifically a therapeutically effective flux over an extended period of time, more specifically a profile suitable to treat CINV with a high flux in the acute phase and a sustained flux for an extended period of multiple days. Again without wishing to be bound by theory, the advantageous combination of ODS with an amphiphilic polymer may apply in particular to drug-in-adhesive patches, and especially to those utilizing polyacrylic adhesives as described herein. In embodiments of the disclosure, increases in the maximum and the sustained flux by about 60% were determined in preliminary experiments.

[0096] The fully or partially amorphous form of ODS may be prepared by mixing ODS base or a salt with a solvent and the amphiphilic polymer in presence of the adhesive and the remaining ingredients of the formulation including any optional excipients. Suitable solvents for preparing amorphous ODS include, without limitation, organic solvents, e.g., methanol.

[0097] In embodiments of the formulations described herein may include, instead of or in addition to DMSO, one or more of: methanol, and isopropanol, in an amount e.g., as described for DMSO.

[0098] In formulations of the present disclosure, the addition of the active and in particular ondansetron in form of its base, rather than adding the active in form of a salt thereof, may be preferred. If a salt is added, it may be preferred that the salt is a lactate, in particular, ondansetron lactate. Without wishing to be bound by theory, it is believed that the ondansetron base added may at least partially (or substantially completely) be converted into the lactate of the active in the formulations and patches described herein, which may contribute to the favorable flux and flux profiles determined in the embodiments herein. Alternatively, a salt, e.g., without limitation, ondansetron hydrochloride may be used.

[0099] As used herein, ODS, "ondansetron". "ondansetron base" or "ondansetron lactate" refers to all pharmaceutically acceptable forms (including pharmaceutically acceptable salts thereof) of the aforementioned, either alone or in combinations, for example, without limitation, racemate, solvate, hydrate, hydrate of a racemate, isomer, amorphous form, crystalline form, cocrystals, solid solution, prodrug, analog, and derivative. One suitable form of ondansetron is ondansetron hydrochloride. Without wishing to be bound by theory, it is believed that ondansetron base may be suitable for use in certain embodiments, and similarly provide a rapid onset and/or sustained flux in transdermal patches and in particular in drug-in- adhesive patches, in particular if combined with lactic acid as a solvent, to form ondansetron lactate (partially or fully), salt or co-crystals with the ondansetron base (or combinations thereof) and may provide similar or better advantages; alternatively, ondansetron lactate may be used.

[0100] Acid addition salts of ondansetron that may be suitable to form part of the formulations described herein include, without limitation, hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, nitrate, phosphate, hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, succinate, saccharate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, p-toluenesulphonate and pamoate salts. Preferred salts of ODS include hydrochlorides, for example, ondansetron hydrochloride. The lactate salt may be a preferred salt. To form salts other than lactate, the relevant acid may be added, as will be apparent to a person of ordinary skill.

[0101] In embodiments of the formulations and patches described herein, use of ondansetron base (and/or its lactate, if formed) may be preferred for its better compatibility with all components; in particular, without limitation, in solid form, and more particularly in form of particles having a particle size range selected from 63μm and less, 38μm and less, or 20μm and less, e.g. 0-63 μm, 0-38 μm, 0-20 μm, 1-20 μm , 20-63 μm or 20-38 μm.

AMPHIPHILIC POLYMERS

[0102] In certain meobdiments, one or more amphiphilic polymer may be added t othe formuaotin. Amphiphilic polymers for use in embodiments described herein may include, without limitation, one or more of: a cellulose polymer, hydroxypropylcellulose (HPMC), a Klucel™ (e.g. Klucel™ HF, MF, GF, JF, EF, and ELF, all of Ashland, Covington, KY, U.S.A.), an HPMC derivative, a cellulose ether, METHOCEL™ cellulose ether (e.g. METHOCEL™ E, F, J, and K, Methocel™ 40-0101, 40-0202, E4M PRM, E50 PRM, 856N, and K100M PRM, all Dow Chemicals, Midland MI), a carboxymethylcellulose (CMC), WALOCEL™ (including, e.g., WALOCEL™ CRT 1000, 2000, 10000, 15000, 30000, 40000, 50000, and 60000, all Dow Chemicals, Midland MI). Alternatively or in addition, such optional polymers may further include, without limitation, one or more of polyvinylpyrrolidone (PVP), acrylic acid derivatives, Plastoid® (e.g. Plastoid®B, of Evonik, Darmstadt, Germany), Eudragit® (e.g., one or more of Eudragit® L-100, L100-55; L30 D-55; L12,5; S100; S12,5; FS30D; E100; E12,5; EPO; S100; S12,5; FS30D; NE30D; NE40D; NM30D; RLPO; RL100; RL30D; RL12,5; RSPO; RS100; RS30D; RS12,5; PlasACRYL™ HTP20; T20; Acryl-EZE®, all of Evonik, Darmstadt, Germany). Eudragits® may include two types of poly(meth)acrylates which include EUDRAGIT® L, S, FS and E polymers with acidic or alkaline groups, and less soluble EUDRAGIT® RL and RS polymers with cationic, and EUDRAGIT® NM polymer with neutral groups, and an acetyl- and/or succinoyl-substituted amphiphilic polymer, a acetyl- and/or succinoyl-substituted hydroxypropyl cellulose polymer, a mixture of acetic acid and monosuccinic acid esters of hydroxypropylmethyl cellulose, hydroxypropylcellulose acetate succinate (HPMC-AS, also known as hypromellose acetate succinate), AquaSolve™ HPMC-AS (Ashland, Covington, KY, U.S.A.), AquaSolve™ HPMCAS-LF, AquaSolve™ HPMCAS-LG, AquaSolve™ HPMCAS-MF, AquaSolve™ HPMCAS-MG, AquaSolve™ HPMCAS-HF, AquaSolve™ HPMCAS-HG.

[0103] A preferred amphiphilic polymer may be an acetyl- and/or succinoyl-substituted AS-amphiphilic polymer. Without wishing to be bound by theory, the addition of an AS-amphiphilic polymer having one or more functional groups to the patch formulation, in particular, without limitation, one or more functional groups selected from acetyl (-$COCH_3$), and succinoyl (-$COCH_2CH_2COOH$), may be particularly advantageous due to its effect on ODS and its flux over time, in particular its flux from an ODS-in-adhesive patch formed from such a formulation, e.g. due

to ODS taking a particular form (e.g. fully or partially amorphous) that may result in or contribute to a desirable flux profile and/or improved flux, as described herein. This effect may apply in particular to ODS in form of its base.

[0104] Suitable AS-amphiphilic polymer may comprise polymers which contain functional groups, in particular, one or more of acetyl- and succinoyl- groups. For example, without limitation, substituted cellulosic polymers with functional groups that render the polymer insoluble in acidic aqueous solutions, but soluble in dilute caustic solution, may be particularly suitable. Suitable cellulosic polymers may be soluble in acetone and/or methanol. Particularly useful examples include hydroxypropyl cellulose polymers, in particular hydroxypropylcellulose acetate succinate (HPMC-AS), as "Cellulose, 2-hydroxypropyl methyl ether, acetate hydrogen butanedioate" (CAS name), as 71138-97-1 (CASRN number), and in pharmaceutical applications also known as hypromellose acetate succinate.

[0105] To form a HPMC-AS, acetic anhydride and succinic anhydride may be reacted with hydroxypropylmethylcellulose (HPMC) under controlled conditions to produce HPMC-AS. Cellulose is a polymer chain composed of repeating β-1,4-anhydroglucose units, each of which contains three hydroxyl groups. The hydroxyl groups of HPMC used to make HPMC-AS are substituted with specific levels of methoxyl and hydroxypropoxy groups. The degree of substitution (DS) of methoxyl on HPMC may range e.g. from 1.78 to 2.02 (AquaSolve™ HPMC-AS), which influences the amount of free hydroxyl groups available for further substitution, while the molar substitution of hydroxypropoxy may be e.g. from 0.23 to 0.41 (AquaSolve™ HPMC-AS). Other synthetic polymers, in particular those made from cellulose or another hydroxyl-group containing polymer (e.g. hydroxyl-, 2-hydroxypropoxy-, and methoxy- group containing polymer such as HPMC) by addition or integration of further functional groups, e.g. one or more of acetyl-, and succinoyl- groups, to result in an AS-amphiphilic polymer of the characteristics herein-described, may also be suitable.

[0106] In certain embodiments, the content of acetyl and succinoyl groups may be, for example, form about 4 to about 15% acetyl and from about 2 to about 20% succinoyl. In particular, the content may be about 5 to about 13% acetyl and from about 8 to about 16% succinoyl. Alternatively, the content may be about 5 to about 9% acetyl and from about 14 to about 18% succinoyl. Still alternatively the content may be from about 7 to about 11% acetyl and from about 10 to about 14% succinoyl. In yet another alternative, the content may be from about 10 to about 14% acetyl and from about 4 to about 8% succinoyl.

[0107] In certain embodiments, the content of acetyl, succinoyl, methoxyl, and hydroxypropoxy groups may be, for example, form about 4 to about 15% acetyl, about 2 to about 20% succinoyl, about 15 to about 30% methoxyl, and about 3 to about 12% hydroxypropoxy. In

particular, the content may be about 5 to about 13% acetyl, about 8 to about 16% succinoyl, about 19 to about 27% methoxyl, and about 3 to about 11% hydroxypropoxy. Alternatively, the content may be about 5 to about 9% acetyl, about 14 to about 18% succinoyl, about 20 to about 24% methoxyl, and about 5 to about 9% hydroxypropoxy. Still alternatively the content may be about 7 to about 11% acetyl, about 10 to about 14% succinoyl, about 21 to about 25% methoxyl, and about 5 to about 9% hydroxypropoxy. In yet another alternative, the content may be about 10 to about 14% acetyl, about 4 to about 8% succinoyl, about 22 to about 26% methoxyl, and about 6 to about 10% hydroxypropoxy.

[0108] A particular example of HPMC-AS is AquaSolve™ HPMC-AS which is a mixture of acetic acid and monosuccinic acid esters of hydroxypropylmethyl cellulose that is commercially available in the form of a powder or granules (Ashland, Covington, KY, U.S.A.). AquaSolve™ HPMCAS is available in several grades (L, M and H) varying in extent of substitution of acetyl and succinoyl groups (i.e. content of acetyl and succinoyl groups (wt%) in the HPMCAS molecule), and each grade is available in particle size fine (F) or granular (G). The grades HPMCAS-LF, HPMCAS-LG, HPMCAS-MF, HPMCAS-MG, HPMCAS-HF, HPMCAS-HG may be suitable, and of these, the M particle size may be particularly suitable, and the fine grades are preferred, e.g., without limitation, HPMCAS-MF.

[0109] According to various embodiments described herein, a formulation may comprise an enhancer combination of solvents lactic acid and DMSO with an enhancer, in particular, one or more FD enhancer, in suitable concentrations to provide permeation enhancement for ODS in a transdermal patch, preferably in a drug-in-adhesive patch. This combination of components may provide an improved and easily adaptable flux profile in a transdermal patch, and particularly in drug-in-adhesive transdermal patches, which may be suitable for therapy of highly emetic patients, in particular patients suffering from CINV.

[0110] Without wishing to be bound by theory, it is believed that lactic acid significantly contributes to an improved flux profile, in particular if combined with an FD enhancer, and more particularly if combined with DMSO.

FD ENHANCERS

[0111] The term "FD enhancer" as used herein may be selected from one or more of fatty acids, fatty alcohols, and derivatives thereof, wherein the fatty acid or fatty alcohol derivative may consist of a substituted fatty acid moiety, or a substituted fatty alcohol moiety, in particular, without limitation, wherein the fatty acid moiety or the fatty alcohol moiety of the FD enhancer has a carbon chain length from C4 to C26. This may include, for example, without limitation, fatty acid esters, in particular those wherein the fatty acid or fatty acid moiety has a carbon chain length of C4 to C26, or longer, including in particular C4, C5, C6, C7, C8, C10, C11, C12, C14, C16, C18, C20, C22, C24

and C26, or combinations thereof. C18 fatty acids and alcohols and their derivatives including without limitation C18 fatty acids may be particularly useful in some embodiments; these when combined with a shorter chain fatty acid from C4 to C10 (e.g., without limitation, C4, C5, C6, C7, C8, C10) may be particularly preferred. Example derivatives include substituted fatty acids or fatty alcohols, for example as described herein, comprising one or more additional group selected from, without limitation, hydroxyl, ethyl, methyl, propyl, butyl, and glyceryl.

[0112] The FD enhancer may include, without limitation, saturated, unsaturated, monounsaturated and polyunsaturated fatty acids, e.g., without limitation, omega-3, omega-6, omega-7 and omega-9 fatty acids. The saturated, unsaturated, monounsaturated and polyunsaturated fatty acids may include, e.g., without limitation, fatty acids with a carbon chain of C12, C14, C16, C18, C20, C22, C24 and C26, in particular, without limitation, e.g. C14, C16, C18, and C20.

[0113] The FD enhancer may include, without limitation, branched-chain saturated fatty acids, including, without limitation, methyl-branched fatty acids, e.g. isostearic acid, and ethyl-branched fatty acids.

[0114] The FD enhancer may include, without limitation, one or more monounsaturated fatty acid, or a derivative thereof, including, without limitation, one or more of 5-dodecenoic acid (C12:1), 7- tetradecenoic acid (14:1), palmitoleic acid (16:1), oleic acid (C18:1), vaccenic acid (C18:1), elaidic acid (C18:1), paullinic acid (C20:1), gondoic acid (C20:1), erucic acid (C22:1), 15-docosenoic acid (C22:1), 17-tetracosenoic acid (24:1), nervonic acid (C24:1), and ximenic acid (C26:1), or one or more derivative thereof.

[0115] The FD enhancer may include, without limitation, one or more of oleic acid ("OA", C18:1) and oleic acid derivatives. Oleic acid derivatives may include, without limitation, one or more of ethyl oleate (OA ethyl ester), oleyl oleate (OA oleyl ester), glyceryl oleate (OA glyceryl ester), sorbitan monooleate (sorbitan oleate, Span 80), and oleyl alcohol (cis-9-octadecen-1-ol).

[0116] The FD enhancer may include, without limitation, one or more of polyunsaturated fatty acid, and a polyunsaturated fatty acid derivative; and the polyunsaturated acids may include, without limitation, one or more of: hexadecatrienoic acid (16:3), linoleic acid (C18:2), rumenic acid (C18:2), alpha-linolenic acid (C18:3), gamma-linolenic acid (C18:3), calendic acid (C18:3), stearidonic acid (C18:4) mead acid (C20:3), eicosadienoic acid (C20:3), eicosatrienoic acid (C20:3), dihomo-gamma-linolenic acid (C20:3), arachidonic acid (C20:4), docosadienoic acid (C22:2), adrenic acid (C22:4), osbond acid (C22:5), tetracosatetraenoic acid (C24:4), tetracosapentaenoic acid (C24:5), and derivatives thereof, including without limitation, one or more of alcohols and esters, e.g. linoleyl alcohol (the fatty alcohol of linoleic acid).

[0117] The FD enhancer may include, without limitation, one or more of saturated fatty acids, and saturated fatty acids derivatives; the saturated fatty acids may include, without limitation,

one or more of: stearic acid (C18:0), palmitic acid (C16:0), myristic acid (C14:0), and lauric acid (C12:0).

[0118] The FD enhancer may include, without limitation, one or more fatty acid ester, fatty acid ester derivative, and fatty acid derivative; these may include, without limitation, one or more of: ethyl oleate, methyl oleate, decyloleate, glyceryl monooleate, oleyl oleate, isopropyl palmitate (ester of isopropyl alcohol and palmitic acid), myristate, isopropyl myristate, methyl laurate (lauric acid methyl ester), glyceryl laurate (lauric acid glyceryl ester, monolaurin, glycerol monolaurate), propylene glycol monolaurate type I, propylene glycol monolaurate type II (e.g. lauroglycol^{TM}90, commercially available from Gattefosse, Lyon, France), lauryl lactate (ester of lauryl alcohol and lactic acid), Hydramol^{TM} PGPL ester, PEG-PPG-8/3 laurate and butyl acetate.

[0119] Alternatively or additionally, the FD enhancer may be provided in form of an oil, or an enriched part/fraction of an oil, e.g. a plant-derived oil, that is rich in one or more component of the FD enhancer. For example, the oil may contain, without limitation, one or more fatty acid, monounsaturated fatty acid, and polyunsaturated fatty acid. An enriched fraction of such an oil that contains an FD enhancer component of interest may be formed and used. Oils with suitable fatty acids include, without limitation, olive oil, macadamia oil, rapeseed oil, wall flower seed oil, mustard seed oil, nutmeg, palm oil, and coconut oil. Suitable oil fractions may include an "MCT oil" or "LCT" oil enriched e.g. in one or more of C8, C10, C12, C14, C16, C18 fatty acids.

[0120] The FD enhancer may include, without limitation, one or more saturated, monounsaturated or polyunsaturated fatty alcohol; which may include, without limitation, one or more of: butanol (C4), butyl alcohol (C4), tert-butyl alcohol (C4), tert-amyl alcohol (C5), 3- methyl-3-pentanol (C6), capryl alcohol (C8), pelargonic alcohol (C9), capric alcohol (C10), undecyl alcohol (C11), lauryl alcohol (C12), tridecyl alcohol (C13), myristyl alcohol (C14), pentadecyl alcohol (C15), cetyl alcohol (C16), palmitoleyl alcohol (cis-9-hexadecen-1-ol, $C_{16}H_{32}O$), heptadecyl alcohol (1-n-heptadecanol, $C_{17}H_{36}O$), stearyl alcohol (C18:0), oleyl alcohol ($C_{18}H_{36}O$, C18:1), linoleyl alcohol ($C_{18}H_{34}O$, cis,cis-9,12-octadecadien-1-ol), nonadecyl alcohol (C19), arachidyl alcohol ($C_{20}H_{42}O$), octyldodecanol ($C_{20}H_{42}O$, 2- octyldodecan-1-ol), heneicosyl alcohol (C21), behenyl alcohol ($C_{22}H_{46}O$), erucyl alcohol (cis-13-docosen-1-ol, $C_{22}H_{44}O$), lignoceryl alcohol (C24), and ceryl alcohol (C26).

[0121] The FD enhancer may include, without limitation, one or more saturated fatty alcohol; the saturated fatty alcohol may include, without limitation, one or more of: lauryl alcohol (C12), isolauryl alcohol (C12, 10-methyl-1-hendecanol), anteisolauryl alcohol (C12, 9- methyl-1-hendecanol), myristyl alcohol (C14), isomyristyl alcohol (C14, 12-methyl-1- tridecanol), anteisomyristyl alcohol (C14, 11-methyl-1-tridecanol), cetyl alcohol (C16), isopalmityl alcohol (C16, 14-methyl-1-pentadecanol), anteisopalmityl alcohol (C16, 13-methyl- 1-pentadecanol), stearyl

alcohol (C18), isostearyl alcohol (C18, 16-methyl-1-heptadecanol), and anteisostearyl alcohol (C18, 15-methyl-1-pentadecanol).

[0122] For use as FD enhancer, fatty alcohols or acids with a longer carbon chain length may be preferred for their non-irritant or skin protective effect when used in formulations as described herein; these include e.g., without limitation, C12-C26 fatty alcohols or acids as hereinabove described, preferably C12-C18 fatty alcohols or acids as hereinabove described, and may include saturated, monounsaturated or polyunsaturated alcohols or acids.

[0123] However, FD enhancers wherein the fatty acid/alcohol or fatty acid/alcohol moiety has a carbon chain length of C4 to C10, i.e., C4, C5, C6, C7, C8, C10, or combinations thereof, may also be used; for example, butyric acid (C4:0), isobutyric acid (C4:0), valeric acid (C5:0), isovaleric acid (C5:0), levulinic acid (C5:0), caproic acid (C6:0), caprylic acid (C8:0), capric acid (C10:0), butanol, butyl alcohol, 2-butanol, isobutanol, tert-butanol.

[0124] Optionally, if the one or more fatty acid/alcohol or fatty acid/alcohol derivative described above is not included in an amount and ratio indicated for the FD enhancer, it may be additionally included as to formulations described herein in an additional smaller amount as an optional ingredient, e.g. of up to 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1% or 0.5% of the patch formulation (% wt after drying). This may particularly apply to fatty acid/alcohol or fatty acid/alcohol derivative of a shorter chain length of C4-C10.

[0125] Preferred FD enhancers for the patches described herein may include, without limitation, one or more of: oleic acid, ethyl oleate (OA ethyl ester), oleyl oleate (OA oleyl ester, C36H68O2), glyceryl oleate (OA glyceryl ester), sorbitan monooleate (sorbitan oleate, Span 80), and oleyl alcohol (cis-9-octadecen-1-ol), elaidic acid (C18:1), gondoic acid (C20:1), erucic acid (C22:1), nervonic acid (C24:1), and ximenic acid (C26:1), or one or more derivative thereof. Polyunsaturated acids such as hexadecatrienoic acid (16:3), linoleic acid (C18:2), alpha- linolenic acid (C18:3), gamma-linolenic acid (C18:3), calendic acid (C18:3), stearidonic acid (C18:4) mead acid (C20:3), eicosadienoic acid (C20:3), eicosatrienoic acid (C20:3), dihomo- gamma-linolenic acid (C20:3), arachidonic acid (C20:4), docosadienoic acid (C22:2), and derivatives thereof, including without limitation, alcohols and esters, e.g. linoleyl alcohol (the fatty alcohol of linoleic acid).

[0126] It should be noted, according to some embodiments described herein, that the FD enhancer is not a lactic acid.

[0127] ODS formulations as described herein that include a FD enhancer, in particular in combination with lactic acid and DMSO, or alternatively in combination with a glycol (GLC) and DMSO, may allow to easily adapt the formulations and patches to provide a desirable flux profile, in particular in drug-in-adhesive patches. The provided flux and flux profile may be particularly

suitable to treat highly emetic patient groups, e.g. treating CINV symptoms. For example, the rapid onset of flux during the first hours may be particularly beneficial to treat symptoms in the acute phase of CINV, and the high sustained steady state flux may be particularly beneficial to treat the delayed phase.

[0128] In various embodiments, the amount of FD enhancer, lactic acid and DMSO, or alternatively FD enchancer, a glycol (GLC) and DMSO, in the enhancer formulation may vary and can be adapted as needed to achieve a suitable profile for the relevant patient group. Suitable amounts may include the following. DMSO may be added in a ratio of 0.25:1 to 3:1, for example 0.5:1, 1:1, 2:1, 4:1 (DMSO : total of LA and FD enhancer; or alternatively, DMSO : GLC and FD enhancer). Ratios of the FD enhancer and lactic acid (or alternatively the ratios of the FD enhancer and a glycol) may be about equal or may differ. If the FD enhancer and lactic acid (or FD enhancer and the glycol) are used in about equal amounts, then suitable ratios of FD:LA:DMSO (or FD:GLC:DMSO) may be from about 1:1:0.5 to about 1:1:8, e.g., 1:1:1, 1:1:2, 1:1:3, 1:1:4, 1:1:5, 1:1:6, or 1:1:7. Alternatively, suitable ratios (FD:LA:DMSO or FD:GLC:DMSO) may be from about 3:1:2 to about 3:1:32, e.g. 3:1:4, 3:1:6, 3:1:8, 3:1:10, 3:1:12, 3:1:14, 3:1:16, 3:1:18, 3:1:20, 3:1:22, 3:1:24, 3:1:26, 3:1:28, or 3:1:30. Still alternatively, suitable ratios (FD:LA:DMSO or FD:GLC:DMSO) may be from about 1:3:2 to about 1:3:32, e.g. 1:3::4, 1:3:6, 1:3:8, 1:3:10, 1:3:12, 1:3:14, 1:3:16, 1:3:18, 1:3:20, 1:3:22, 1:3:24, 1:3:26, 1:3:28, or 1:3:30.

[0129] To form a patch, to the enhancer formulation, first any optional polymer, and any optional excipients may be added; then the adhesive will be mixed in a ratio (wt/wt) from about 1:2 to about 2:1 (formulation:adhesive), e.g. for Duro-Tak® 387-2516 and other polyacrylic polymers, generally in a ratio of about 1:1; or in other words, typically, about 50% of an enhancer formulation, polymer and any excipients will be mixed with about 50% of an adhesive, wt/wt. The ratio may need to be adjusted depending on the polymer and desired adhesive characteristics such as cohesion, tack/stickiness etc., as will be apparent to a person of ordinary skill.

[0130] The ratios of lactic acid or glycol to DMSO and to the one or more FD enhancer typically may range from about 0.5:3:0.5 to about 1:1.5:1 (LA:DMSO:FD or GLC:DMSO:FD). The amount of lactic acid or a glycol may be equal to the amount of the FD enhancer, for example, the amount of lactic acid or glycol may be about equal to that of e.g., oleic acid. Depending on the FD enhancer, more or less lactic acid or glycol may be used. Generally, the amount of DMSO may be twice that of lactic acid or the glycol.

OTHER COMPONENTS

[0131] According to embodiments described herein, a formulation may additionally comprise a surfactant, including, without limitation, nonionic, cationic and anionic surfactants, which may comprise, without limitation, one or more of lactic acid, DMSO, a diethylene glycol

monoethyl ether (DEGEE), a Tween®-type surfactant, a Span®-type surfactant, a glycol, a Brij®-type surfactant, hexylengycol and sodium lauryl sulfate. DEGEE (also known as di(ethylene glycol) ethyl ether or 2-(2-ethoxyethoxy)ethanol)) is commercially available, for example, under the various trade names including Transcutol® (TC), Transcutol® P, Transcutol® CG, Transcutol® HP (Gattefosse, Lyon, France), and Carbitol™ (Dow Chemicals, Midland MI). Suitable surfactants include, without limitation, one or more of: a sorbitan ester (also known as Span®), and a polysorbate (a polyethoxylated sorbitan ester also known as Tween®).

[0132] The Span® or Tween® surfactant may, without limitation, be selected from one or more of: Span 20®, Span®40, Span® 60, Span®80, Span®83, Span®85, Span®120, Tween 20®, Tween 21®, Tween 40®, Tween 60®, Tween 61®, Tween 65®, and Tween 80®. Suitable percentages of a total amount of a surfactant to include into formulations described herein to perform a surfactant function may be less than 5% (wt/wt) of the patch formulation (based on the total after drying), typically e.g. less than 4%, 3%, 2%, 1%, or 0.5%. A suitable concentration of DEGEE in a patch formulation may generally be, for example, up to 50% in the formulation and up to 25% in the patch, e.g. from about 5 to about 15 % (wt), preferably about 8 to about 12 % (wt), more preferably about 10 % (wt) in the patch (after casting and evaporation of the solvent). Hexylengycol may be used in a sufficient amount, as will be apparent to a person of ordinary skill in the art. Surfactants other than DEGEE may be used in a similar amount, or the amount may be increased or decreased to achieve a suitable and sufficient amount, as will be apparent to a person of ordinary skill in the art.

[0133] Brij® is a group of nonionic surfactants commercially available from various sources (e.g. Sigma-Aldrich), and may be selected from one or more of Brij® 93 (average Mn ~357), Brij® S 100 (average Mn ~4,670), Brij® 58 (average Mn ~1124), Brij® O10 (average Mn ~709, also known as Brij 97, C18-1E10, Polyoxyethylene (10) oleyl ether, $C_{18}H_{35}(OCH_2CH_2)_nOH$, n~10), Brij® C10 (average Mn ~683), Brij® L4 (average Mn ~362, also known as polyethylene glycol dodecyl ether, polyoxyethylene (4) lauryl ether, (C20H42O5)n), Brig® O20 (average Mn ~1,150, Polyoxyethylene (20) oleyl ether, C18H35(OCH2CH2)nOH, n~20), Brij® S2 MBAL (also known as Brij® S2, polyethylene glycol octadecyl ether, polyoxyethylene (2) stearyl ether, main component: diethylene glycol octadecyl ether, $C_{18}H_{37}(OCH_2CH_2)_2OH$), Brij® S10 (average Mn ~711), Brij® S20, and Brij® 35 (also known as Brij® L23, C12E23, polyoxyethylene lauryl ether, $(C_2H_4O)_nC_{12}H_{26}O$).

[0134] A glycol is class of small organic compounds (e.g. MW typically below 150), or a polymer thereof, that belongs to the alcohol family, and wherein two hydroxyl (−OH) groups are attached to different carbon atoms. The simplest member of the glycol class is ethylene glycol (also known as 1,2-ethanediol), other members include, without limitation, propylene glycol (also called 1,2-propanediol), butylene glycol (1,3-butanediol), 1,4-butanediol, pentylene glycol, (1,2-

Pentanediol), hexylene glycol (2,4-pentanediol), 2-ethyl-1,3-hexanediol, and 2-methyl-2- propyl-1,3-propanediol. Similarly, higher molecular weight polymers of the above glycol diols, in particular of ethylene glycol, may be used; these include, without limitation, polyethyleneglycol (PEG). PEGs are available in different molecular weights, typically from about 300 g/mol to about 10,000,000 g/mol, e.g., PEG 300, 400, 600, 800, 1000, 1500, 6000, 8000, 10,000, 20,000, 35,000, etc. PEGs of different molecular weight have identical or similar surfactant properties but the higher molecular weight polymers may be preferred for their additional thickening function which may be desired in some patch formulations.

[0135] Without wishing to be bound by theory, any of the surfactants as described herein may also function as penetration enhancers in the formulations described herein, and may contribute further to the improved flux and/or profile in embodiments described herein, especially in drug-in-adhesive type patches, in particular in combination with the enhancer combination described herein. Suitable ratios (wt/wt) of surfactant (and in particular, DEGEE) to lactic acid (S:LA) may be from about 2:1 to about 1:6, for example about 1:1, 1:2, or 1:3, with ratios for DMSO and the FD enhancer in relation to LA as indicated herein above. Ratios that include a surfactant other than DEGEE, or in addition to DEGEE, may be adjusted accordingly, as will be apparent to a person of ordinary skill.

[0136] The adhesive matrix patches described herein may be formed from an adhesive formulation which comprises an adhesive, ODS, an enhancer combination as described herein, and a solvent. The adhesive formulation forms the patch formulation upon removal of the volatile solvent. All amounts of the formulations described herein are indicated in % (wt/wt) based on the patch formulation, i.e. without the solvent, unless apparent from the context or otherwise specified. The adhesive formulation may be solvent cast to form an adhesive layer, e.g. onto a backing layer and the adhesive layer may then be covered by a release liner upon removal of the solvent by evaporation (or alternatively the adhesive may be cast onto the release liner and covered by the backing layer). Optionally, the adhesive and the patch formulation may further comprise optional ingredients and excipients.

[0137] The amounts of the ingredients in the patch formulation may vary and may be adjusted to achieve a particular flux profile in the transdermal patch that is formed. The amounts will also depend on the characteristics of the patch, e.g. the desired patch size and thickness. For example, for larger or thicker patches the amount of ODS may be decreased, and for smaller or thinner patches it may be increased. Typically, the amount of ODS in a formulation (without accounting for the solvent which will be evaporated) may range from about 1% to about 50 % (wt) ODS, e.g., from about 1% to about 5% (wt), from about 5 to about 50% (wt), from about 10 to about 45% (wt), from about 15 to about 40% (wt), or from about 20 to 35% (wt), or from about 25 to 30%

(wt). Alternatively, the amount of ODS may be about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45% or 50% (wt). The total amount of the one or more FD enhancer depends on the enhancer(s) chosen and may range from about 0.1 to about 50 % (wt) of the formulation, e.g. from about 1 to about 40 % (wt), from about 2 to about 35% (wt), from about 5 to about 25% (wt), from about 10 to about 15% (wt), from about 5 to 45% (wt), from about 10 to 40% (wt), from about 15 to 35% (wt), or from about 20 to 30% (wt). Alternatively, the total amount of one or more FD enhancer may be about 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% (wt). The amount of the polymer may range for example from about 0.1 to about 15% (wt) of the formulation, e.g. from about 0.1 to about 10% (wt), from about 0.1 to about 5% (wt), from about 0.1 to about 2.5% (wt), or from about 0.1 to about 5% (wt). Alternatively, the total amount of one or more polymer may be about 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, or 15% (wt). The amount of the one or more additional enhancer or excipient may range from about 0.1 to about 10% (wt) of the formulation, e.g. about 0.1 to about 5 % (wt), about 0.1 to about 2.5 %, or about 0.1 to about 1%. Alternatively, the amount of the of the one or more additional enhancer or excipient may be about 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1%, 2%, 3%, 4%, or 5% (wt).

[0138] The amount of the adhesive in the patch formed from adding adhesive to the formulation may generally range from about 30 to about 70% (wt) of the formulation, e.g. about 40 to about 70% (wt), typically about 45 to about 50% (after evaporation of the solvent, with the ODS formulation making up the remaining about 50 to about 55% of the patch). Alternatively the amount of adhesive is about 30%, about 35%, about 40%, about 50%, about 55%, about 60%, about 65%, or about 70% (wt%).

[0139] According to an embodiment of the present disclosure, the ODS patch described herein may provide a release profile wherein the ODS flux increases gradually to achieve its maximum at about 4-6 hours, for example at about 5 hours, after patch application or as determined in vitro via Franz cells as described herein in example 1.

[0140] According to various embodiments of the present disclosure, the ODS formulations described herein may provide a maximum flux of at least about 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, or 90 $\mu g/cm^2/h$, or more, for formulations that provide a sustained steady state flux of up to 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 days, when measured with Franz diffusion cells as described herein in example 1. By "sustained steady state flux" is meant that the variance from the maximum flux is about +/-50%, +/-45%, +/-40%, +/-35%, +/-30%, +/-25%, +/-20%, +/-15%, +/-10%, or +/-5%.

[0141] According to some embodiments, the ODS patch described herein may provide a maximum flux of at least about 1, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, or 30

μg/cm^2/h, or more, for patches that provide a sustained steady state flux of up to 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 days, when measured with Franz diffusion cells as described herein in example 1.

[0142] According to some embodiments, the ODS patch described herein may provide a maximum flux of at least about 8, at least about 10, at least about 12, at least about 15, at least about 20 μg/cm^2/h, or at least about 25 μg/cm^2/hour, or at least about 30 μg/cm^2/hour or more for patches that provide a sustained release of up to 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 days, when measured with Franz diffusion cells as described herein in example 1.

[0143] According to some embodiments of the present disclosure, the patch described herein may achieve a maximum flux of about 2-30 μg/cm^2/hour, and preferably about 3-5 μg/cm^2/h during the first 5 hours. Without wishing to be bound by theory, this advantageous profile is provided to provide sufficient flux, especially during the acute phase, while avoiding side effects including drug-induced nausea, and at the same time provide a sustained-release for several days, e.g. at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 days, e.g., for about 2-3, 2-4, 2-5, 2-6, or 2-7 days, or even 5-7, 5-10, 5-12, 7-10, 7-12, or 7-14 days.

ADHESIVES

[0144] Suitable adhesives for the drug-in-adhesive patches and formulations therefore described herein include, without limitation, high molecular weight or highly crosslinked adhesives, typically available as self crosslinkable acrylic adhesives. Examples of such adhesives include, without limitation, Duro-Tak® 387-2516, Duro-Tak® 387-2051, Duro-Tak® 87-2852, Duro-Tak® 87-2194 and Duro-Tak® 87-2852 self crosslinkable acrylic adhesives (available from National Starch and Chemical Company, 10 Finderne Ave., P.O. Box 6500, Bridgewater, NJ 08807-0500), and GELVA® 737, GELVA® 2655, and GELVA® 1753 self crosslinkable acrylic adhesives (Monsanto's Chemical Group, 730 Worcester Street, Springfield, Mass. 01151).

[0145] Duro-Tak® 387-2516 is an acrylic copolymer adhesive containing EHA, vinyl acetate and hydroxyethyl acrylate and is commercially available from National Starch and Chemical Co, Bridgewater, N.J.). Alternatively, the adhesive may be an acrylic adhesive having one or more of hydroxyl functional groups and carboxyl functional groups. Still alternatively, the acrylic adhesive may be a "nonfunctional" adhesive which does not contain function groups (e.g. lacks –OH groups, -COOH groups, or both). Preferably the acrylic adhesive may be a pressure sensitive adhesive (PSA).

[0146] Other pressure sensitive adhesives that may be suitable to use in various embodiments include acrylic pressure sensitive adhesive (PSA), silicone PSA, rubber PSA, and combinations thereof.

[0147] Acrylic PSA may be selected from, without limitation, one or more of: Duro-Tak® 87-2196, Duro-Tak® 387-2051, Duro-Tak® 87-2194, Duro-Tak® 87-235A, Duro-Tak® 387-2054, Duro-Tak® 87-900A, Duro-Tak® 87-9301, Duro-Tak® 387-2516, Duro-Tak® 387-2510, Duro-Tak® 280-2516, Duro-Tak® 87-4098, GELVA GMS® 788, GELVA GMS® 9073, Duro-Tak® 387-2353, Duro-Tak® 87-2074, Duro-Tak® 387-2287, Duro-Tak® 87-2852, Duro-Tak® 87-2054, GELVA® 737, Duro-Tak® 80-1196, Duro-Tak® 87-2070, Duro-Tak® 87-2979, Duro-Tak® 87-2888, and Duro-Tak® 87-2296.

[0148] Suitable silicone PSA may be selected from, without limitation, one or more of: BIO-PSA® 7-4401, BIO-PSA® 7-4402, BIO-PSA® 7-4501, BIO-PSA® 7-4502, BIO-PSA® 7-4601, BIO-PSA® 7-4602, (Dow Corning®, Dow Chemicals, Midland MI), an amine compatible silicone PSA, a rubber PSA.

[0149] Amine compatible silicone PSA may be selected from, without limitation, one or more of BIO-PSA® 7-4101, BIO-PSA® 7-4102, BIO-PSA® 7-4201, BIO-PSA® 7-4202, BIO-PSA® 7-4301, BIO-PSA® 7-4302.

[0150] Rubber PSA may be selected from, without limitation, one or more of: polyisobutylene of low molecular weight, polyisobutylene of medium molecular weight, polyisobutylene of high molecular weight (including, e.g., polyisobutylene 1100000 MW, 35000 MW, 800000 MW, 55000 MW, 2300 MW, or mixtures thereof), Duro-Tak® 87-6908, and polyisobutylene/polybutene adhesive.

PATCH CONFIGURATIONS

[0151] As used herein, transdermal patch or patch refers to transdermal patches of the "drug-in-adhesive" type, also known as "in-adhesive" type. Drug-in-adhesive patches lack a separate reservoir and thus avoid leakage; the matrix material is an adhesive, preferably a pressure sensitive adhesive (PSA), and functions both for adhesion and as the reservoir, carrying the drug. Typically, an adhesive matrix material is mixed with a suitable liquid or solvent to form a solution or dispersion which is then applied to a physical support, e.g. a backing layer, to form a layer thereon which may then be dried to remove the liquid or solvent from the matrix. The liquid or solvent comprises ODS and further formulation ingredients (inclusing, e.g., one or more of, surfactant, solubilizer, enhancer, plasticizers, polymer, excipient, etc.). The other side of the matrix layer may then be covered with a release liner.

[0152] Drug-in-adhesive patches may take the form of a single-layer drug-in-adhesive patch, or a multi-layer drug-in-adhesive patch. In a drug-in-adhesive patch, the adhesive layer also contains the drug and not only serves to adhere the various layers together, along with the entire system to the skin, but is also responsible for the releasing of the drug. The adhesive layer is typically sandwiched between a temporary liner (taken off before application to the skin) and a backing (which supports

the adhesive matrix). A multi-layer drug-in-adhesive patch adds one or more layer of drug-in-adhesive layer, optionally separated by a membrane. One of the layers may be for rapid release of ondansetron, for example within the first 24 hours, e.g. within the first 12 hours, e.g. within 2 to 6 hours, within 90 minutes, within 1 hour, or within 30 minutes, or as desired, and the one or more further layers may be for sustained flux from a reservoir layer (this differs from a reservoir patch). The flux/release of ondansetron may thus be adjustable to better fit a particular desired flux profile over time.

[0153] The patch may alternatively comprise a non-adhesive or insufficiently adhesive matrix, and may then optionally comprise a release membrane comprising an adhesive polymer to provide sufficient tack to adhere to the skin for the desired duration. Still alternatively, the periphery of the patch may comprise an additional zone or layer of adhesive. For example, PatchProtect™ or tape may be used as an adhesive release membrane.

[0154] The size and thickness of a patch may depend on various factors, including drug loading and desired flux profile. Size will also depend on thickness, and vice versa: a thicker smaller patch can provide a similar drug loading as a thinner larger patch. It will be apparent to a person of ordinary skill how to adjust patch size and thickness to a desired degree of drug loading, delivery (e.g. about 4 to about 16 mg per day), and flux profile. With regard to patch size, in certain embodiments, the patch may have a surface area greater than 1 cm^2, and less than 110 cm^2, for example, the surface area may be, without limitation, from about 5 cm^2 to about 60 cm^2, e.g. from about 20 cm^2 to about 40 cm^2. With regard to patch thickness, in certain embodiments, the patch in use (i.e. one or more adhesive layer and backing/support layer, with the release liner removed) may have a thickness greater than 0.05 mm, and less than 0.5 mm, for example, the thickness may be, without limitation, from about 0.05 mm to about 0.4 mm, e.g. from about 0.1 mm to about 0.3 mm, from about 0.2 mm to about 0.3 mm. Alternatively, the thickness is about 0.05 mm, 0.06 mm, 0.07 mm, 0.08 mm, 0.09 mm, 0.1 mm, 0.15 mm, 0.2 mm, 0.25 mm, 0.3 mm, 0.35 mm, 0.4 mm, 0.45 mm, or 0.5 mm.

ONDANSETRON DELIVERY AND FLUX PROFILE

[0155] A delivery of about 4 mg to about 16 mg ondansetron per day may be determined by calculation based on the measured flux of the patch (or formulation, taking into account that the formulation will have a higher flux) as follows: the flux (i.e. µg per 1 hour and per 1 cm^2) is multiplied by a factor of 24 (24 hours in a day), and multiplied with a factor depending on the surface area of the patch measured in cm^2. Thus an illustrative formulation, without limitation, may achieve a flux of about 30-100 µg/cm^2/hour, or more, and may be incorporated into a patch which may achieve, e.g. a flux that may be about 6-12 times lower; if e.g. 10 times lower, a flux of 3-10 µg/cm^2/hour would result; thus a patch of a size of 20 cm^2 would deliver about 1,440-4,800 µg or

1.4-4.8 mg per day, a patch of a size of 40 cm^2 would deliver about 2,880-9,600 µg or 2.88-9.6 mg per day, a patch of 80 cm^2 would deliver about 5,760-19,200 µg or 5.8-19.2 mg, and a patch of a patch of 120 cm^2 would deliver about 8,640-28,800 µg or 8.6-28.8 mg. The advantageously high flux and sustained flux profile of the embodiments described herein allows to adapt patch adhesive materials and patch sizes accordingly, as will be apparent to a person of ordinary skill. This allows to provide comfortably small and flexible patches to patients.

[0156] The patches in the components and their amounts of the formulation, amount and concentration of ondansetron, patch size and thickness will be adapted to deliver a non-toxic dose of ondansetron at all times, in particular at the times when the maximum and steady state flux is achieved, e.g. they may be adjusted to deliver a maximum and steady state flux that results in an ondansetron concentration below 60 ng/mL in the blood of a patient.

[0157] The flux values described herein are measured in accordance with the Franz diffusion-cell test, which is well known in the art and can be performed as will be apparent to a person of ordinary skill, using human cadaver skin, a temperature of 32°C, i.e., body temperature, and phosphate buffered saline (PBS) of pH 4.5 with 0.01% sodium azide as a receiving medium and measuring in intervals of 12 hours or less. The permeation rate or flux will deviate from an average somewhat depending on the individual skin sample and other factors, thus for each measurement, averages of several samples should be performed, in particular, at least 3 samples should be tested. Additional samples, for example 6 or more, may have to be tested so that the deviation of the average flux in the steady state phase is a value of +/- 50% or less within one hour, preferably +/- 45%, +/- 35%, +/- 25%, +/- 15% or +/- 10 % within one hour, or less.

[0158] According some embodiments of the disclosure, the formulations/patches described herein may be adapted to provide for sustained delivery of ODS, a particular number of days or weeks, e.g. 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 days. A one-time administration of a patch for about 2, 3, 4, 5, 6, or 7 days generally will be convenient for a patient, e.g., after a chemotherapy regimen.

EXCIPIENTS and OTHER COMPONENTS

[0159] The patch formulations may comprise one or more optional excipient, some of which may have dual or multiple functionality, e.g. a particular excipient may function as a penetration enhancer or as a plasticizer, or both, depending on concentration and patch formulation ingredients. Optional excipients include, without limitation, optional penetration enhancers, plasticizers, pH adjusting agents, emulsifying agents, auxiliary emulsifying agents, surfactants, suspending agents, preservatives, antioxidants, chelating agents, emollients, humectants, demulcents, skin irritation reducing agents, tackifiers, and fillers.

[0160] Such optional excipients may be a second, a third, or a fourth additional FD enhancer, added to formulations as described herein-above, due to its dual functionality (e.g. as optional enhancer, plasticizer, pH adjusting agent, emulsifier, surfactant, plasticizer, etc.). For example, many fatty acids and fatty acid derivatives have functionality as surfactants or emulsifying agents, and butyric acid, levulinic acid may be added e.g. for their functionality as a plasticizer.

[0161] Alternatively or additionally, other additional excipients may be added, e.g., without limitation, as detailed below. Typically all optional and additional excipients are added in a smaller amount, e.g., without limitation, less than 5, 4, 3, 2, 1, 0.5 or 0.1% (% wt after drying). The total of all excipients preferably should be below 15, 10, 5%, or 1% (% wt after drying).

[0162] Further optional penetration enhancers may include: alcohols (e.g. ethanol, propanol, and isopropanol), sulfoxides (e.g. decylmethyl sulfoxide), amides (e.g. dimethylformamide, azone, urea, dimethylacetamide), pyrrolidone derivatives (e.g. 1-methyl-4-carboxy-2- pyrrolidone, 1-methyl-2-pyrrolidone, 1-lauryl-4-methoxycarbonyl-2-pyrrolidone), polyols (e.g. propylene glycol, polyethylene glycol), terpenes (e.g. menthol, limonene, terpineol, pinene, carvol), surfactants including nonionic, cationic and anionic surfactants (e.g. Brij®, sodium lauryl sulfate), ethyl acetate, methyl acetate, octisalate, pentadecalactone, and acrylamide.

[0163] It is preferred that the optional penetration enhancer (or combination thereof) be non-irritating to human skin for the duration of use, or be used in an amount that is non-irritating for the duration of use, in particular when the use is in form of a drug-in-adhesive patch over multiple days. Many known penetration enhancers are irritating to human skin, especially when used for a prolonged period and especially when used in form of an occlusive or semi-occlusive patch (rather than e.g. a topical application such as e.g. a lotion). As will be apparent to the skilled person that the amount of the optional penetration enhancer should be sufficiently low to avoid such irritation. In some formulations, it is preferred to exclude any skin-irritating penetration enhancers or other skin-irritating excipients, and if used, it is preferred to include them only in a low non-irritating amount.

[0164] The patch formulation may comprise one or more optional plasticizer to avoid brittleness and impart flexibility to the adhesive matrix layer. The necessity and choice of plasticizer will depend on the particular adhesive and formulation. Suitable plasticizers are well known in the art. For example, without limitation, the one or more optional plasticizer may be selected from, without limitation, one or more of: glycols (and/or glycol derivatives), in particular without limitation, e.g., polyethylene glycol 400, polyethylene glycol 600, propylene glycol, higher alcohols (e.g. dodecanol), surfactants, sebacic acid esters (e.g. dibutyl sebacate, diethyl sebacate), citric acid esters (e.g. tributyl citrate, triethyl citrate), phthalic acid esters (e.g. diethyl phthalate, dibutyl phthalate), glycerol or glycerol esters (e.g. glycerine triacetate, glycerin), sugar alcohols (e.g. sorbitol, sucrose), tartaric acid esters (e.g. diethyl tartrate), oil (e.g. silicone oil, mineral oil),

triacetin, and diisopropyl adipate. For inclusion into an adhesive patch formulation, and in particular an acrylic PSA patch formulation, preferred plasticizers include, without limitation, one or more of glycerol and glycerol esters.

[0165] Further optional excipients include for example, without limitation, one or more pH adjusting agents selected from, without limitation, buffers (e.g. citrate buffer, phosphate buffer, acetate buffer), acids (e.g. hydrochloric acid, acetic acid, succinic acid, citric acid, ascorbic acid, phosphoric acid), bases (e.g. sodium bicarbonate, triethanolamine, sodium hydroxide, calcium hydroxide, potassium hydroxide, ammonium hydroxide), and tromethamine. Preferred pH adjusting agents include, without limitation, one or more of sodium bicarbonate, sodium carbonate, acetic acid, and ascorbic acid.

[0166] Still further optional excipients include for example, without limitation, one or more of emulsifying agents, auxillary emulsifying agents, surfactants, suspending agents, preservatives, antioxidants, chelating agents, emollients, humectants, demulcents, skin irritation reducing agents, tackifiers, fillers, cross-linking agents, resins, crystallization inhibitors, and clays. For illustrative purposes, examples for various optional excipients that may be suitable additives in a patch formulation, in particular an acrylic PSA patch formulation, are given below.

[0167] Such optional emulsifying agents, auxillary emulsifying agents, surfactants and suspending agents may include, without limitation, one or more of monoglycerides, diglycerides, polyoxyl stearate, a mixture of tricetеareth-4 phosphate with ethylene glycol palmitostearate and with diethylene glycol palmitostearate, polyglyceryl-3 diisostearate, a mixture of PEG-6 stearate with ethylene glycol palmitostearate and with PEG-32 stearate, oleoylpolyoxyl-6 glycerides, lauroyl polyoxyl-6 glycerides, caprylocaproyl polyoxyl-8 glycerides, propylene glycol monocaprylate type I, propylene glycol monolaurate type II, propylene glycol monolaurate type I, propylene glycol monocaprylate type II, polyglyceryl-3 dioleate, a mixture of PEG-6 stearate with PEG-32 stearate, lecithin, cetyl alcohol, cholesterol, bentonite, veegum, magnesium hydroxide, dioctyl sodium sulfosuccinate, sodium lauryl sulfate, triethanolamine stearate, potassium laurate, polyoxyethylene fatty alcohol ethers, glyceryl monostearate, polyoxyethylenepoloxypropylene block copolymers (poloxamers), sorbitan monolaurate, lanolin alcohols and ethoxylated lanolin alcohols, sorbitan fatty acid esters, sucrose distearate, sodium alginate, alginic acid, hectorite, and aluminum silicate.

[0168] Emollients, demulcents and skin irritation reducing agents may be selected from, without limitation, one or more of glycerin, mineral oil, petrolatum, lanolin, zinc oxide, paraffin, cetyl alcohol, cetyl esters wax.

[0169] Preservatives and antioxidants may be selected from, without limitation, one or more of butylated hydroxyanisole, butylated toluene, alpha tocopherol, acorbyl palmitate, propionic acid, sodium bisulfate, propyl gallate, monothioglycerol, ascorbic acid, sodium ascorbate,

benzethoniumchloride, chlorhexidine, phenylethyl alcohol, chloroxylenol, cresol, hexetidine, phenoxyethanol, chlorobutanol, ascorbic acid, benzoic acid, sorbic acid, potassium sorbate, potassium metabisulfite, sodium metabisulfate, phenol, potassium benzoate, dehydroacetic acid, cetylpyridinium chloride, parabens, benzyl alcohol, benzalkonium chloride).

[0170] Chelating agents may be selected from, without limitation, one or more of sodium edetate, edetic acid, tartaric acid, fumaric acid, disodium edetate, trisodium edetate, dipotassium edetate).

[0171] Fillers may be selected from, without limitation, one or more of lactose, magnesium stearate, mannitol, titanium dioxide, talc, shellac, colloidal silicone dioxide, kaolin etc.).

[0172] Cross-linking agents may be selected from, without limitation, one or more of melamine formaldehyde (Aerotex® M3, Aerotex® 3730).

[0173] Resins may be selected from, without limitation, one or more of polyamide resin (Versamid® 100 P77.5, Versamid® 100 X-65).

BACKINGS

[0174] Many suitable methods and corresponding materials to make the patches described herein are known in the art. According to some embodiments, a patch may be formed, for example, without limitation, by solvent casting onto a backing layer or release liner, and sandwiching between both, as described herein.

[0175] Many suitable materials for the backing layer and release liner are known, and include polymer films, fabrics and non-woven materials, e.g. continuous films that prevent ingress of external moisture into the adhesive layer from activities such as showering or bathing. The backing and release liner should preferably be occlusive, or substantially occlusive. Such films include, without limitation, polypropylene, polyvinyl chloride, cellulose acetate, ethyl cellulose, polyurethane, polyethylene, and polyester. Optionally, the backing may be a layered composite that include a metal, such as, without limitation aluminum, e.g. polyethylene terephthalate-aluminum-polyethylene composites, or e.g. a polyester and an ethylene vinyl acetate copolymer heat seal layer (particularly as a backing), or e.g. a fluoropolymer coated polyester film (particularly as a release liner. Suitable backing layers include, without limitation, Scotchpak 1006, 1022, 1109, 9723, 9732, 9733 (3M company); suitable release liners include, without limitation, Scotchpak 1006, 9709, 9741, 9742, 9744, and 9755 (3M company). The thickness of the backing layer and of the release liner is generally more than 10 μm and less than 200 μm, typically about 20 μm to about 120 μm, e.g., about 40 μm to about 100 μm.

FORMULATIONS COMPRISING DMSO, A GLYCOL AND AN FD ENHANCER

[0176] In some aspects, the disclsore relates to transdermal patches of ondansetron, and in particular, to drug-in-adhesive patches. More specifically, embodiments described herein relate to

formulations comprising ondansetron added to the formulation in the form of a pharmaceutuically acceptable salt thereof, an enhancer combination of a glycol (e.g., propylene glycol, hexylene glycol, PEG) with a fatty acid, fatty alcohol, or a derivative thereof, and DMSO, and patches formed therefrom. In this manner, an increased flux and improved flux profile with a more rapid onset and longer duration of steady state may be provided. Certain embodiments allow a more tailored treatment of patient groups and symptoms, for example, to treat chemotherapy induced nausea and vomiting (CINV), which requires a high initial flux in the acute phase that is sustained over multiple days or weeks.

[0177] According to an embodiment of the present disclosure, a formulation may comprise an enhancer combination of a glycol, DMSO, and one or more FD enhancer in suitable concentrations to provide permeation enhancement for ODS in a transdermal patch, preferably in a drug-in-adhesive patch. This combination of components may provide an improved and easily adaptable flux profile in a transdermal patch, and particularly in drug-in-adhesive transdermal patches, which may be suitable for therapy of highly emetic patients, in particular patients suffering from CINV.

[0178] Without wishing to be bound by theory, it is believed that the combination of ondansetron, in particular in form a salt thereof, with a glycol, in particular if together with an FD enhancer and more particularly when further combined with DMSO significantly contributes to an improved flux profile.

[0179] A glycol suitable for use in embodiments of the present disclosure may be, without limitation, one or more of: propylene glycol (propane-1,2-diol), hexylen glycol (2-methyl-2,4-pentanediol), polyethylene glycol (PEG), PEG 300, PEG 400, and PEG 600. Other suitable glycols may include dipropylene glycol, butylene glycol, glycerine, and higher molecular weight polyethylene glycols (PEGs), e.g., without limitation, PEG 1000, and PEG 6000.

[0180] PEGs are oligomers or polymers of ethylene oxide of the general formula $H-(O-CH_2-CH_2)_n-OH$ and are typically prepared by polymerization of ethylene oxide. They are commercially available over a wide range of molecular weights from 300 g/mol to 10,000,000 g/mol (with PEG 300 including PEGs of up to 300 g/mol). PEGs of different geometries such as branched PEGs (typically 3-10 PEG chains emanating from a central core group), star PEGs (10-100 PEG chains emanating from a central core group), and comb PEGs having multiple PEG chains normally grafted onto a polymer backbone) are also available. In some embodiments, typically a low molecular weight PEG such as PEG-300 or PEG-400 will be used, although other PEGs such as, without limitation, PEG 1000 and PEG 6000, or of a higher molecular weight, may also be suitable, depending e.g., on the desired viscosity of the formulation, as will be apparent to a person of ordinary skill in the art.

[0181] In various embodiments, one or more amphiphilic polymer may be added to the formulation. Amphiphilic polymers may include, without limitation, one or more of: a cellulose polymer, hydroxypropylcellulose (HPMC), a Klucel™ (e.g., Klucel™ HF, MF, GF, JF, EF, and ELF, all of Ashland, Covington, KY, U.S.A.), an HPMC derivative, a cellulose ether, METHOCELTM cellulose ether (e.g. METHOCELTM E, F, J, and K, MethocelTM 40-0101, 40-0202, E4M PRM, E50 PRM, 856N, and K100M PRM, all Dow Chemicals, Midland MI), a carboxymethylcellulose (CMC), WALOCELTM (incl. e.g. WALOCELTM CRT 1000, 2000, 10000, 15000, 30000, 40000, 50000, and 60000, all Dow Chemicals, Midland MI). Alternatively or in addition, such optional polymers may further include, without limitation, one or more of polyvinylpyrrolidone (PVP), acrylic acid derivatives, Plastoid® (e.g. Plastoid®B, of Evonik, Darmstadt, Germany), Eudragit® (e.g. one or more of Eudragit® L-100, L100-55; L30 D-55; L12,5; S100; S12,5; FS30D; E100; E12,5; EPO; S100; S12,5; FS30D; NE30D; NE40D; NM30D; RLPO; RL100; RL30D; RL12,5; RSPO; RS100; RS30D; RS12,5; PlasACRYLTM HTP20; T20; Acryl-EZE®, all of Evonik, Darmstadt, Germany). Eudragits® may include two types of poly(meth)acrylates which include EUDRAGIT® L, S, FS and E polymers with acidic or alkaline groups, and less soluble EUDRAGIT® RL and RS polymers with cationic, and EUDRAGIT® NM polymer with neutral groups, and an acetyl- and/or succinoyl-substituted amphiphilic polymer, a acetyl- and/or succinoyl-substituted hydroxypropyl cellulose polymer, a mixture of acetic acid and monosuccinic acid esters of hydroxypropylmethyl cellulose, hydroxypropylcellulose acetate succinate (HPMC-AS, also known as hypromellose acetate succinate), AquaSolveTM HPMC-AS (Ashland, Covington, KY, U.S.A.), AquaSolveTM HPMCAS-LF, AquaSolveTM HPMCAS-LG, AquaSolveTM HPMCAS-MF, AquaSolveTM HPMCAS-MG, AquaSolveTM HPMCAS-HF, AquaSolveTM HPMCAS-HG.

[0182] Without wishing to be bound by theory, the addition of an amphiphilic polymer may be advantageous due to its effect on ODS and its flux over time, in particular its flux from an ODS-in-adhesive patch formed from such a formulation. Again without wishing to be bound by theory, the addition of an amphiphilic polymer may result in ODS base taking a particular form (e.g., fully or partially amorphous) that may result in or contribute to a desirable flux profile and/or improved flux, specifically a therapeutically effective flux over an extended period of time, more specifically a profile suitable to treat CINV with a high flux in the acute phase and a sustained flux for an extended period of multiple days. Again, without wishing to be bound by theory, the advantageous combination of ODS with an amphiphilic polymer may apply in particular to drug-in-adhesive patches, and especially to those utilizing polyacrylic adhesives as described herein. In some embodiments, increases in the maximum and the sustained flux by about 60% were determined in preliminary experiments.

[0183] The fully or partially amorphous form of ODS may be prepared by mixing with a solvent and the amphiphilic polymer in presence of the adhesive and the remaining ingredients of the formulation including any optional excipients. Suitable solvents for preparing amorphous ODS include, without limitation, organic solvents, e.g. methanol.

FORMULATIONS COMPRISING ONDANSETRON BASE

[0184] The present disclosure also relates to transdermal patches of ondansetron, and in particular, to drug-in-adhesive patches where the ondansetron is added to the formulation in the form of its base, an enhancer combination of lactic acid with a fatty acid, fatty alcohol, or a derivative thereof, and DMSO, and patches formed therefrom. Thus an increased flux and improved flux profile with a more rapid onset and longer duration of steady state may be provided. Certain embodiments allow a more tailored treatment of patient groups and symptoms, for example of chemotherapy induced nausea and vomiting (CINV), which requires a high initial flux in the acute phase that is sustained over multiple days or weeks. Also, embodiments relate to formulations that further comprise a surfactant. Certain embodiments include one or more of Transcutol®, Tween®, Span® and Brij® as a surfactant. Further, embodiments relate to formulations for patches with a self-crosslinkable polyacrylic adhesive. Still further embodiments may include one or more amphiphilic polymers.

[0185] In some embodiments, provided is a formulation to form both a rapid onset and a sustained release drug-in-adhesive patch for transdermal administration of ondansetron to a human subject. In some embodiments, the formulation includes a polyacrylic adhesive, ondansetron, and an enhancer component that includes lactic acid and a FD enhancer, wherein the FD enhancer is selected from a fatty acid, a fatty alcohol, a fatty acid derivative, and a fatty alcohol derivative, and combinations thereof. In further embodiments, the FD enhancer is a fatty acid derivative or a fatty alcohol derivative, or combinations thereof, and further wherein the fatty acid derivative or fatty alcohol derivative consists of a substituted fatty acid moiety, or a substituted fatty alcohol moiety that comprises one or more additional group, wherein the additional group comprises one or more of hydroxyl, ethyl, methyl, propyl, butyl, and glyceryl, and wherein the fatty acid moiety or the fatty alcohol moiety of the FD enhancer has a carbon chain length from C4 to C26. In yet further embodiments, the enhancer component further includes DMSO. In yet further embodiments, the formulation includes a surfactant. In other embodiments, the formulation includes an amphiphilic polymer.

[0186] In further embodiments, the formulation provides a minimum predetermined flux within a first predetermined amount of time; provides a preferred predetermined flux within a second predetermined amount of time; and maintains the preferred flux within a predetermined range for a third predetermined amount of time. In further embodiments, the formulation provides a minimum

predetermined flux of about 2.5 μg/cm^2/hour. In further embodiments, the formulation provides a minimum predetermined flux of about 2.5, 5, 7.5, 10, 12, 15, 20, 25, 30, 35, or 40 μg/cm^2/hour. In further embodiments, the first predetermined amount of time is 90 minutes or less, 60 minutes or less, 30 minutes or less, or 2 hours or less. In yet further embodiments, the second predetermined amount of time is within 12 hours, or within 18 hours, or within 24 hours. In other embodiments, the third predetermined amount of time is at least two days, or at least three days, or at least 4 days, or at least 5 days, or at least seven days or at least 14 days. In further embodiments, the predetermined range is a variance from the preferred flux of less than 50%, less than 45%, less than 40%, less than 35%, less than 30%, less than 25%, less than 20%, less than 15%, less than 10%, or less than 5%. In further embodiments, the preferred flux is about 30 μg/cm^2/h. In yet other embodiments, the formulation provides a preferred flux that is substantially maintained for 2 days or more, and wherein the preferred flux is between 30 μg/cm^2/hour and 90 μg/cm^2/hour.

[0187] In yet further embodiments, the composition further includes one or more of: ethanol, propanol, decylmethyl sulfoxide, dimethylformamide, azone, urea, dimethylacetamide, a pyrrolidone derivative, 1-methyl-4-carboxy-2-pyrrolidone, 1-methyl-2-pyrrolidone, 1-lauryl-4-methoxycarbonyl-2-pyrrolidone, a terpene, menthol, limonene, terpineol, pinene, carvol, ethyl acetate, methyl acetate, octisalate, pentadecalactone, and acrylamide.

[0188] In some embodiments, the formulation includes amphiphilic polymer. In some embodiments, the amphiphilic polymer is selected from a cellulose polymer, hydroxypropylcellulose (HPMC), an acetyl- and succinoyl-substituted cellulosic polymer, AquaSolve™ HPMCAS-LF; AquaSolve™ HPMCAS-LG; AquaSolve™ HPMCAS-MF; AquaSolve™ HPMCAS-MG; AquaSolve™ HPMCAS-HF; AquaSolve™ HPMCAS-HG, a Klucel™ polymer, Klucel™ HF, Klucel™ MF, Klucel™ GF, Klucel™ JF, Klucel™ EF, Klucel™ ELF, an HPMC derivative, a cellulose ether, a METHOCEL™ cellulose ether, METHOCEL™ E, METHOCEL™ F, METHOCEL™ J, METHOCEL™ K, Methocel™ 40-0101, METHOCEL™ 40-0202, METHOCEL™ E4M PRM, METHOCEL™ E50 PRM, METHOCEL™ 856N, METHOCEL™ K100M PRM, a carboxymethylcellulose (CMC), a WALOCEL™ polymer, WALOCEL™ CRT 1000, WALOCEL™ CRT 2000, WALOCEL™ CRT 10000, WALOCEL™ CRT 15000, WALOCEL™ CRT 30000, WALOCEL™ CRT 40000, WALOCEL™ CRT 50000, WALOCEL™ CRT 60000, polyvinylpyrrolidone (PVP), acrylic acid derivatives, a Plastoid® polymer, Plastoid®B, an Eudragit® polymer, Eudragit® L-100, Eudragit® L100-55; Eudragit® L30 D-55; Eudragit® L12,5; Eudragit® S100; Eudragit® S12,5; Eudragit® FS30D; Eudragit® E100; Eudragit® E12,5; Eudragit® EPO; Eudragit® S100; Eudragit® S12,5; Eudragit® FS30D; Eudragit® NE30D; Eudragit® NE40D; Eudragit® NM30D; Eudragit® RLPO; Eudragit® RL100; Eudragit® RL30D;

Eudragit® RL12,5; Eudragit® RSPO; Eudragit® RS100; Eudragit® RS30D; Eudragit® RS12,5; PlasACRYL™ HTP20; PlasACRYL™ T20; Acryl-EZE®.

[0189] In further embodiments, the amphiphilic polymer is an acetyl- and succinoyl-substituted amphiphilic polymer (AS-substituted polymer), and further wherein the AS-substituted polymer comprises one or more of: an acetyl- and succinoyl-substituted cellulosic polymer which is insoluble in acidic aqueous solutions and soluble in dilute caustic solution; an acetyl- and succinoyl-substituted cellulosic polymer which is insoluble in acidic aqueous solutions and soluble in both dilute caustic solution and acetone; an acetyl- and succinoyl-substituted cellulosic polymer which is insoluble in acidic aqueous solutions and soluble in both dilute caustic solution and methanol; an acetyl- and succinoyl-substituted cellulosic polymer which is insoluble in acidic aqueous solutions and soluble in each of dilute caustic solution, acetone and methanol; a hydroxypropylcellulose acetate succinate or hypromellose acetate succinate (HPMC-AS); a HPMC-AS wherein the acetyl, succinoyl, methoxyl, and hydroxypropoxy content in %(wt) is within the following ranges: from about 4 to about 15% acetyl, about 2 to about 20% succinoyl, about 15 to about 30% methoxyl, and about 3 to about 12% hydroxypropoxy, from about 5 to about 13% acetyl, about 8 to about 16% succinoyl, about 19 to about 27% methoxyl, and about 3 to about 11% hydroxypropoxy, from about 5 to about 9% acetyl, about 14 to about 18% succinoyl, about 20 to about 24% methoxyl, and about 5 to about 9% hydroxypropoxy, or from about 7 to about 11% acetyl, about 10 to about 14% succinoyl, about 21 to about 25% methoxyl, and about 5 to about 9% hydroxypropoxy, or from about 10 to about 14% acetyl, about 4 to about 8% succinoyl, about 22 to about 26% methoxyl, and about 6 to about 10% hydroxypropoxy; AquaSolve™ HPMCAS-LF; AquaSolve™ HPMCAS-LG; AquaSolve™ HPMCAS-MF; AquaSolve™ HPMCAS-MG; AquaSolve™ HPMCAS-HF; AquaSolve™ HPMCAS-HG..

[0190] In further embodiments of the formulation the polyacrylic adhesive includes a self crosslinkable acrylic adhesive, the adhesive comprising one or more of: Duro-Tak® 387-2516, Duro-Tak® 387-2051, Duro-Tak® 87-2852, Duro-Tak® 87-2194, Duro-Tak® 87-2852, GELVA® 737, GELVA® 2655, and GELVA® 1753.

[0191] In further embodiments, provided are rapid onset sustained release drug-in-adhesive patches for transdermal administration of ondansetron to a human subject comprising the formulation described herein. In some embodiments, the patch provides a minimum predetermined flux within a first predetermined amount of time; provides a preferred predetermined flux within a second predetermined amount of time; and maintains the preferred flux within a predetermined range for a third predetermined amount of time. In further embodiments, the predetermined range is a variance from the preferred flux of less than 50%, less than 45%, less than 40%, less than 35%, less than 30%, less than 25%, less than 20%, less than 15%, less than 10%, or less than 5%. In

further embodiments, the formulation provides a minimum predetermined flux of about 30 μg/cm^2/hour. In further embodiments, the patch provides a minimum predetermined flux of about 1, 2.5, 5, 10, or 15 μg/cm^2/houir. In further embodiments, the first predetermined amount of time is 90 minutes or less, 60 minutes or less, 30 minutes or less, or 2 hours or less. In yet further embodiments, the second predetermined amount of time is within 12 hours, or within 18 hours, or within 24 hours. In other embodiments, the third predetermined amount of time is at least two days, or at least three days, or at least 4 days, or at least 5 days, or at least seven days or at least 14 days. In further embodiments, the predetermined range is a variance from the preferred flux of less than 50%, less than 45%, less than 40%, less than 35%, less than 30%, less than 25%, less than 20%, less than 15%, less than 10%, or less than 5%. In further embodiments, the patch provides a steady state flux of about 30 μg/cm^2/h as measured in 12 hour time intervals for at least two days. In further embodiments, the patch delivers 4 mg or more of ondansetron per day after application of the patch to the skin of a human subject. In other embodiments, the patch delivers 4 mg or more of ondansetron per day after application of the patch to the skin of a human subject for at least 2 days. In some embodiments, the first predetermined time period is the time period required to reach at least a minimum predetermined flux of 2.5 μg/cm^2/hour, and further wherein the first predetermined time period is from about 30 minutes to about 6 hours. In yet further embodiments, the first predetermined time period is about 1 to about 3 hours. In other embodiments, wherein the first predetermined time period is the time period required to reach a minimum predetermined flux of 2.5 μg/cm^2/hour, and further wherein the first predetermined time period is from about 30 minutes to about 6 hours. In other embodiments, the first predetermined time period is about 1 to about 3 hours. In further embodiments, the preferred flux is about 30 μg/cm^2/hour. In further embodiments, the ondansetron is present at least partially in form of its lactate salt.

[0192] Other embodiments provided herein include a method of forming a transdermal patch for treatment of nausea or vomiting from a formulation, wherein the formulation includes a polyacrylic adhesive, ondansetron, and an enhancer component, wherein ondansetron is added to the formulation in form of its base, and wherein the enhancer component comprises DMSO, lactic acid, and an FD enhancer. In further embodiments, the FD enhancer is selected from a fatty acid, a fatty alcohol, a fatty acid derivative, and a fatty alcohol derivative, wherein the fatty acid derivative or fatty alcohol derivative consists of a substituted fatty acid moiety, or a substituted fatty alcohol moiety, and wherein the fatty acid moiety or the fatty alcohol moiety of the FD enhancer has a carbon chain length from C4 to C26, and wherein the patch is formed from one or more drug-in-adhesive layers by solvent casting, and in the resulting patch, the one or more layers are positioned between a backing layer, a release liner.

[0193] Other embodiments provided herein include a method to treat nausea, vomiting, or chemotherapy induced nausea and vomiting, wherein a patch is applied to the skin of a subject in need thereof, and wherein one or more adhesive layer of the patch is formed as a matrix from a formulation comprising a polyacrylic adhesive, ondansetron, and an enhancer component, and further wherein ondansetron is added to the formulation in form of its base. In further embodiments, the enhancer component comprises DMSO, lactic acid, and an FD enhancer. In further embodiments, the enhancer components is an FD enhancer that is selected from a fatty acid, a fatty alcohol, a fatty acid derivative, and a fatty alcohol derivative, wherein the fatty acid derivative or fatty alcohol derivative consists of a substituted fatty acid moiety, or a substituted fatty alcohol moiety, and wherein the fatty acid moiety or the fatty alcohol moiety of the FD enhancer has a carbon chain length from C4 to C26, and wherein the patch comprises one or more drug-in-adhesive layers which are positioned between a backing layer and a release liner.

[0194] In other embodiments, provided is a method of treating nausea or vomiting in a human subject, the method including the steps of: applying a patch of claim 14 to the human subject; within a first predetermined amount of time, achieving a minimum level of efficacy for treating nausea or vomiting in the human subject; within a second predetermined amount of time, achieving a preferred level of efficacy for treating nausea or vomiting in the human subject; and maintaining the preferred level of efficacy within a predetermined range for treating nausea or vomiting in the human subject for a third predetermined amount of time. In further embodiments, the first predetermined amount of time is less than about an hour, less than about thirty minutes, less than about 5 hours, or less than about 3 hours. In further embodiments, the third predetermined amount of time is at least 2 days, at least 5 days, at least 7 days, or at least 14 days. In further embodiments of the method, the minimum level of efficacy is achieved when at least 4 mg of ondansetron have been delivered to the human subject. In other embodiments of the method, the preferred level of efficacy is achieved when at least 8 mg of ondansetron have been delivered to the human subject.

[0195] Also provided are methods for delivering ondansetron from a formulation, or from a patch formed therefrom, to a human subject in need of ondansetron delivery, wherein ondansetron is present in amorphous form. In further embodiments, the formulation, or patch formed therefrom, includes an amphiphilic polymer. In yet further embodiments, the amphiphilic polymer is selected from one or more of: a cellulose polymer, hydroxypropylcellulose (HPMC), an acetyl- and succinoyl-substituted cellulosic polymer, AquaSolve™ HPMCAS-LF; AquaSolve™ HPMCAS-LG; AquaSolve™ HPMCAS-MF; AquaSolve™ HPMCAS-MG; AquaSolve™ HPMCAS-HF; AquaSolve™ HPMCAS-HG, a Klucel™ polymer, Klucel™ HF, Klucel™ MF, Klucel™ GF, Klucel™ JF, Klucel™ EF, Klucel™ ELF, an HPMC derivative, a cellulose ether, a METHOCEL™ cellulose ether, METHOCEL™ E, METHOCEL™ F, METHOCEL™ J, METHOCEL™ K,

Methocel™ 40-0101, METHOCEL™ 40-0202, METHOCEL™ E4M PRM, METHOCEL™ E50 PRM, METHOCEL™ 856N, METHOCEL™ K100M PRM, a carboxymethylcellulose (CMC), a WALOCEL™ polymer, WALOCEL™ CRT 1000, WALOCEL™ CRT 2000, WALOCEL™ CRT 10000, WALOCEL™ CRT 15000, WALOCEL™ CRT 30000, WALOCEL™ CRT 40000, WALOCEL™ CRT 50000, WALOCEL™ CRT 60000, polyvinylpyrrolidone (PVP), acrylic acid derivatives, a Plastoid® polymer, Plastoid®B, an Eudragit® polymer, Eudragit® L-100, Eudragit® L100-55; Eudragit® L30 D-55; Eudragit® L12,5; Eudragit® S100; Eudragit® S12,5; Eudragit® FS30D; Eudragit® E100; Eudragit® E12,5; Eudragit® EPO; Eudragit® S100; Eudragit® S12,5; Eudragit® FS30D; Eudragit® NE30D; Eudragit® NE40D; Eudragit® NM30D; Eudragit® RLPO; Eudragit® RL100; Eudragit® RL30D; Eudragit® RL12,5; Eudragit® RSPO; Eudragit® RS100; Eudragit® RS30D; Eudragit® RS12,5; PlasACRYL™ HTP20; PlasACRYL™ T20; Acryl-EZE®.

[0196] The present disclosure also relates to transdermal patches of ondansetron using transdermal formulations comprising ondansetron in form of its base, an enhancer combination of lactic acid with a FD enhancer (including *e.g.*, fatty acids, fatty alcohols, fatty acid esters, or derivatives of any thereof), and DMSO. This combination together allows to provide a higher drug loading that allows for the delivery of about 4 mg to about 16 mg ondansetron or more per day, an increased flux, an extended duration of flux, and an improved flux profile in drug-in-adhesive type patches. For example, the improved flux profile may be adjusted to provide a more rapid onset of flux, e.g. within 30 minutes, within 1 hour, within 2 hours, within 3 hours, within 4 hours, or within up to 12 hours, and/or a higher or more sustained flux for up to 2-7 days or more, and even for up to 14 days. This allows a more tailored treatment of patient groups and symptoms, for example of chemotherapy induced nausea and vomiting (CINV), which requires a rapid onset and high initial flux in the acute phase, followed by a sustained flux over multiple days. Further improvements, e.g. in flux, may be achieved by including one or more surfactant, including nonionic, cationic and anionic surfactants. In particular, surfactants may include one or more of diethylene glycol monoethyl ether (DEGEE), Transcutol® (TC), a Tween®-type surfactant, a Span®-type surfactant, a Brij® type surfactant, sodium lauryl sulfate, and a glycol. Also, certain embodiments relate to formulations for self-adhesive patches wherein the adhesive is a self crosslinkable polyacrylic adhesive. Further, formulations and patches as described herein may optionally include one or more substituted amphiphilic polymer, and one or more optional excipients.

[0197] According to some embodiments, a formulation may comprise an enhancer combination of lactic acid, DMSO, and one or more FD enhancer in suitable concentrations to provide permeation enhancement for ODS in a transdermal patch, preferably in a drug-in-adhesive patch. This combination of components may provide an improved and easily adaptable flux profile

in a transdermal patch, and particularly in drug-in-adhesive transdermal patches, which may be suitable for therapy of highly emetic patients, in particular patients suffering from CINV.

[0198] Without wishing to be bound by theory, it is believed that lactic acid significantly contributes to an improved flux profile, in particular if combined with an FD enhancer, and more particularly if combined with DMSO. In further embodiments, the lactic acid is believed to form a lactate salt with the ondansetron base, or forms a co-crystal with the ondansetron base, or forms combinations of both a lactate salt and co-crystals.

[0199] Further, without wishing to be bound by theory, it is believed that the addition of a surfactant, in particular one or more of diethylene glycol monoethyl ether (DEGEE), Transcutol® (TC), a Tween®-type surfactant, a Span®-type surfactant, a Brij® type surfactant, sodium lauryl sulfate, and a glycol, may allow the advantageous formulations to be formed and/or contribute to the improved flux profile.

[0200] In formulations of the disclosure, the addition of the active and in particular ondansetron in form of its base, rather than adding the active in form of a salt thereof, is preferred. If a salt is added, it is preferred that the salt is a lactate, in particular, ondansetron lactate. Without wishing to be bound by theory, it is believed that the ondansetron base added may at least partially (or substantially completely) be converted into the salt of the active in the formulations and patches described herein, which may contribute to the favorable flux and flux profiles determined in some embodiments. In further embodiments, the probability of salt conversion of the ondansetron is correlated to the molar ratio of acid to ondansetron base.

[0201] Without wishing to be bound by theory, it is believed that ondansetron base and/or its lactate that may be formed in certain formulations described herein are best suitable for use in methods of the disclosure, to provide a rapid onset and/or sustained flux in transdermal patches and in particular in drug-in-adhesive patches. However, other forms including pharmaceutically acceptable salts thereof, for example, without limitation, one or more of ondansetron lactate, and ondansetron hydrochloride, may also be suitable; these forms are collectively referred herein as "ODS", unless otherwise stated or apparent from the context. ODS in particular includes ondansetron isomers, racemic forms, amorphous forms, crystalline forms, co-crystals, a solid solution, a prodrugs, analogs or derivatives.

EXAMPLES

[0202] The structures, materials, compositions, and methods described herein are intended to be representative examples of the disclosure, and it will be understood that the scope of the disclosure is not limited by the scope of the examples. Those skilled in the art will recognize that the disclosure may be practiced with variations on the disclosed structures, materials, compositions and methods, and such variations are regarded as within the ambit of the disclosure.

Example 1
Transdermal Patch Compostion Example 1

[0203] Ondansetron hydrochloride (ODS-HCl) is weighed and dissolved in dimethyl sulfoxide (DMSO), lactic acid (LA), oleic acid (OA) and methanol. To the resulting solution the polymer Hydroxypropyl cellulose acetate (AquaSolve™ HPMCAS MF) is added and the mixture is homogenized to form a viscous gel. The gel is mixed with the adhesive Duro-Tak® 387-2516 and stirred for 1 hour or until it forms a uniform mixture. The resulting mixture is applied to a backing layer with 0.2 mm coating thickness using a doctor's knife, and dried at 70°C for 30 min to achieve 50 mg/cm^2 dried weight. The resulting patch layer has the composition listed below (all values in % w/w).

Transdermal Patch 1

Component	Weight %
ODS-HCl	10
DMSO	15
Lactic Acid	15
Oleic Acid	5
AquaSolve™ HPMCAS MF	5
Duro-Tak® 387-2516	50
Total	**100**

[0204] Transdermal Patch 1 is tested by *in vitro* skin permeability test using modified Franz-diffusion cells with membranes of human cadaver skin. Phosphate buffered saline (PBS) of pH 4.5 with 0.01% sodium azide is used as a receiving medium to determine skin flux. Samples are collected at predetermined time intervals and the drug is quantified by reversed phase HPLC analysis. The flux increases to about 4-4.5 µg/cm^2/h or more during the first 5 hours, is maintained at above 4 for at least 24 hours, and is maintained at above 3.5 for at least 48 hours.

Example 2
Transdermal Patch Compostion Example 2

[0205] The ODS-HCl Patch 2 is prepared as indicated in Example 1 except that Span 20 and sodium bicarbonate are added in the amounts indicated in the table below.

Transdermal Patch 2

Component	Weight %
ODS-HCl	10
DMSO	15
Lactic Acid	10
Oleic Acid	5
AquaSolve™ HPMCAS MF	5
Span 80	3
Sodium Bicarbonate	2
Duro-Tak® 387-2516	50
Total	**100**

[0206] Transdermal Patch 2 is tested as described above for Patch 1. The flux increases to about 3 μg/cm^2/h or more during the first 5 hours, is maintained at above 2.7 μg/cm^2/h for at least 24 hours, at above 1.9 μg/cm^2/h for at least 48 hours, and at above 1.6 μg/cm^2/h for at least 72 hours.

Example 3
Additional Sample Patches

[0207] Additional sample patches are produced as described above, having the formulations of Samples 1-3, as indicated below.

Component	Sample 1	Example 2	Example 3
Ondansetron HCl	10		
Ondansetron Base		10	
Amorphous Ondansetron			10
Lactic Acid	15	15	15
Oleic Acid	5	5	5
DMSO	15	15	15
HPMCAS MF	5	5	10
Durotak 2516	50	50	50
Flux (120 hours)	**2.5**	**5.88**	**5.75**

[0208] The transdermal patches described in Samples 1-3 are tested by in vitro skin permeability test using modified Franz-diffusion cells with membranes of human cadaver skin. Phosphate buffered saline (PBS) of pH 4.5 with 0.01% sodium azide is used as a receiving medium to determine skin flux. Samples are collected at predetermined time intervals and the drug is quantified by reversed phase HPLC analysis to determine a flux between 0-24 hours and at 120 hours after application of the patch.

Example 4
Formulations Comprising Ondansetron Hydrochloride, DMSO, a Glycol and an FD Enhancer

[0209] Ondansetron hydrochloride is weighed and dissolved in dimethyl sulfoxide (DMSO), a glycol (GLC), here propylene glycol, FD enhancer (oleic acid), and Transcutol P (TP) Solution;

any additional ingredients (e.g., an optional polymer such as HPMC-AS) are added. Each formulation is tested by in vitro skin permeability test using modified Franz-diffusion cells with human cadaver skin as a diffusion barrier. Phosphate buffered saline (PBS) of pH 4.5 with 0.01% sodium azide is used as a receiving medium to determine skin flux. Samples are collected at predetermined time intervals and the drug is quantified by reversed phase HPLC analysis.

[0210] The table below provides a summary of formulations X-1, X-2, X-3, X-4, and X-5, which are tested as described above. Formulations X-1 to X-5 (e.g., 1-1 to 1-5 for formulation 1 using oleic acid as FD enhancer) are mixed as indicated in the tables below.

[0211] In preliminary experiments, such formulations tend to show the following trend: the maximum flux for the formulations ranks highest for formulations 1 and lowest for formulation 4 (i.e., 1>2>3) with formulation 4 having a very late onset of flux (e.g., >24 hours), and formulation 5 having a low maximum flux. This may be particularly the case for fatty acids that are unsaturated or branched, and/or have a length of C12-C24. For example, e.g., for oleic acid, the flux increases to about 30-100 $\mu g/cm^2$/hour or more during the first 3-12 hours, achieving a peak flux, followed by a steady state phase wherein the peak flux is maintained, or a below-peak steady state flux, e.g. of about 50-90 $\mu g/cm^2/h$, for a duration of at least 96 hours or more. Instead of propylene glycol, alternatively or additionally, hexylen glycol, PEG (e.g., PEG-300, PEG-400), or mixtures thereof, may be used in the formulations as described and may display a similar trend.

Formulations	**X-1**	**X-2**	**X-3**	**X-4**	**X-5**
ODS hydrochloride	15	18	25	16	25
DMSO	31	31	--	--	31
GLC	31	31	38	19	--
FD enhancer (1-23)	10	--	--	25	10
TC	13	21	38	40	39
Total	**100**	**100**	**100**	**100**	**100**

Formulations	**1-1**	**1-2**	**1-3**	**1-4**	**1-5**
ODS hydrochloride	15	18	25	16	25
DMSO	31	31	--	--	31
GLC	31	31	38	19	--
Oleic Acid	10	--	--	25	10
TC	13	21	38	40	39
Total	**100**	**100**	**100**	**100**	**100**

Example 5
Additional Formulations with FD Enhancers

[0212] Formulations X-1, X-2, X-3, X-4, and X-5 are prepared as indicated above in Example 4 using the FD enhancer as indicated in the table below. The resulting formulations may show a similar trend as described in Example 4.

	FD Enhancer
1	Oleic acid (C18:1)
2	Isostearic acid (C18:0, methyl-branched)
3	Linoleic acid (C18:2)
4	Palmitoleic acid (C16:1)
5	Palmitic Acid (C16:0)
6	Lauric acid (C12:0)
7	Arachidonic acid (C20:4)
8	Ethyl oleate
9	Oleyl oleate
10	Glyceryl oleate
11	Glyceryl laurate
12	Methyl laurate
13	Lauryl lactate
14	Isopropyl palmitate
15	Octyldodecanol
16	Oleyl alcohol
17	Stearylalcohol
18	Cetyl alcohol
19	Myristyl alcohol
20	Butyl alcohol
21	Myristyl alcohol
22	Butyl alcohol

Example 6
Patches Comprising Ondansetron Hydrochloride, DMSO, a Glycol and an FD Enhancer

[0213] Ondansetron hydrochloride is weighed and dissolved in a formulation prepared as described in Examples 4 and 5 and using methanol as a solvent, to prepare transdermal patches 1-6. Before addition of the adhesive to patch formulations 2, 4, 5, and 6, the polymer HPMC-AS (hydroxypropyl cellulose acetate) is added, and the mixture is homogenized to form a viscous gel. A suitable form of this polymer is AquaSolve™ HPMCAS MF (Ashland, Covington, KY, U.S.A.). The gel is mixed with a suitable adhesive, in particular an acrylic adhesive (here: Duro-Tak® 387-2516), and stirred for one hour or until it forms a uniform mixture.

[0214] The following table provides an overview of patches 1-6 with formulations 1 or 2, with or without polymer, and with or without surfactant/sodium bicarbonate.

[0215] The patches are formed as follows. A formulation may be prepared as detailed in examples 1 and 2, optionally, for patches 5 and 6, surfactant and sodium bicarbonate are added. Optionally, for patches 2, 4, 5 and 6, to the resulting solution the polymer hydroxypropyl cellulose acetate (AquaSolve™ HPMCAS MF) is added and the mixture is homogenized to form a viscous gel. The gel is mixed with the adhesive Duro-Tak® 387-2516 and stirred for one hour or until it forms a uniform mixture. The resulting mixture is cast with a 0.2 mm coating thickness onto a

suitable support (typically directly onto a backing layer or release liner) using a scalpel. A suitable backing layer is Scotchpak 9733 (3M company), alternatively, for use as release liner, Scotchpak 9744 (3M company) can be employed. The patches are dried at 70°C for 30 min to achieve 50 mg/cm^2 dried weight.

Patch	Formulation	Polymer added	Surfactant/pH
1	1	-	-
2	1	Y	-
3	2	-	-
4	2	Y	-
5	1+	Y	Y
6	2+	Y	Y

[0216] After drying, the resulting patch layer has the composition listed below for each of the patches 1-6 (all values in % w/w).

Transdermal Patch 1:

	Patch 1 (% w/w)	
Formulation 1 (50% of total patch formulation):		50.0
15	ODS	7.5
31	DMSO	15.5
31	GLC	15.5
10	OA	5.0
13	Transcutol	6.5
-	**Adhesive**	**50.0**
	TOTAL	100

Transdermal Patch 2:

	Patch 2 (% w/w)	
Formulation 1 (45% of total patch formulation):		45.0
15	ODS	6.75
31	DMSO	13.95
31	GLC	13.95
10	OA	4.5
13	Transcutol	5.85
-	**Adhesive**	**50.0**
	Polymer (HPMC-AS)	**5.0**
	TOTAL	100

Transdermal Patch 3:

	Patch 3 (%w/w)	
Formulation 2 (50% of total patch formulation):		50.0
18	ODS	9.0
31	DMSO	15.5
31	GLC	15.5
21	Transcutol	10.5
-	**Adhesive**	**50.0**
	TOTAL	100.0

Transdermal Patch 4:

	Patch 4 (%w/w)	
Formulation 2 (45% of total patch formulation):		45.00
18	ODS	8.10
31	DMSO	13.95
31	GLC	13.95
21	Transcutol	9.45
-	**Adhesive**	**50.00**
	Polymer (HPMC-AS)	**5.00**
	TOTAL	100.00

Transdermal Patch 5:

	Patch 5 (%w/w)	
Formulation 1b (45% of total patch formulation):		45.00
15	ODS	6.75
31	DMSO	13.95
31	GLC	13.95
10	OA	4.50
8	Transcutol	3.60
3	**Span 80**	**1.35**
2	**Sodium Bicarbonate**	**0.90**
-	Adhesive	50.00
	Polymer (HPMC-AS)	5.00
	TOTAL	100

Transdermal Patch 6:

	Patch 6 (%w/w)	
Formulation 2b (45% of total patch formulation):		45.00
18	ODS	8.10
31	DMSO	13.95
31	GLC	13.95
16	Transcutol	7.20
3	**Span 80**	**1.35**
2	**Sodium Bicarbonate**	**0.90**
-	Adhesive	50.00
	Polymer (HPMC-AS)	5.00
	TOTAL	100.00

[0217] The transdermal patches are tested by in vitro skin permeability test using modified Franz-diffusion cells with membranes of human cadaver skin. Phosphate buffered saline (PBS) of pH 4.5 with 0.01% sodium azide is used as a receiving medium to determine skin flux. Samples are collected at predetermined time intervals and the drug is quantified by reversed phase HPLC analysis to determine a flux profile with rapid onset and/or sustained release.

Example 7

Additional Sample Patches Comprising OND-HCl, DMSO, a Glycol and an FD Enhancer

[0218] Additional sample patches are produced as described above, having the formulations in Samples 1-4, as indicated in the table below.

	Sample 1	**Sample 2**	**Sample 3**	**Sample 4**
Ondansetron HCl	10	10	2.85	10
DMSO	15	15	2.85	10
Lactic Acid	15	10	-	-
Oleic Acid	5	5	1.43	5
Span-20	-	3	-	-
Sodium Bicarbonate	-	2	-	-
HPMC AS-MF	5	5	-	-
Glycerin	-	-	4.29	10
Lg-90	-	-	2.85	10
Silicone Dioxide	-	-	1.43	-
Acrylamide	-	-	-	30
Gelatin	-	-	12.86	25
Duotak 2516	50	50	-	-
Water	-	-	71.42	-
Flux (0-4 Hr)	**6.75**	**4.72**	**6.72**	**5.0**
Flux (120 Hr)	**5.3**	**3.0**	**5.0**	**30.2**

[0219] The transdermal patches described in Samples 1-4 are tested by in vitro skin permeability test using modified Franz-diffusion cells with membranes of human cadaver skin.

Phosphate Buffer saline (PBS) of pH 4.5 with 0.01% sodium azide is used as a receiving medium to determine skin flux. Samples are collected at predetermined time intervals and the drug is quantified by reversed phase HPLC analysis to determine a flux between 0-24 hours and at 120 hours after application of the patch.

Example 8
Formulations Comprising Ondansetron Base, DMSO, a Glycol and an FD Enhancer

[0220] Ondansetron base is weighed and dissolved in dimethyl sulfoxide (DMSO), lactic acid (LA), FD enhancer (oleic acid), and Transcutol P (TP) Solution; any additional ingredients (e.g., an optional polymer such as HPMC-AS) are added. Each formulation is tested by in-vitro skin permeability test using modified Franz-diffusion cells with human cadaver skin as a diffusion barrier. Phosphate buffered saline (PBS) of pH 4.5 with 0.01% sodium azide is used as a receiving medium to determine skin flux. The experiments are performed at 32°C (body temperature). Samples are collected at predetermined time intervals and the drug is quantified by reversed phase HPLC analysis.

[0221] The table below provides a summary table of formulations X-1, X-2, X-3, X-4, and X-5, which are tested as described above. Formulations X-1 to X-5 (e.g. 1-1 to 1-5 for formulation 1 using oleic acid as FD enhancer) are mixed as indicated in the tables below. In preliminary experiments such formulations tend to show the following trend: the maximum flux for the formulations ranks highest for formulations 1 and lowest for formulation 4 (i.e. 1>2>3) with formulation 4 having a very late onset of flux (e.g., >24 hours), and formulation 5 having a low maximum flux. This may be particularly the case for fatty acids that are unsaturated or branched, and/or have a length of C12-C24. For example, e.g., for oleic acid, the flux increases to about 30-100 $\mu g/cm^2$/hour or more during the first 3-12 hours, achieving a peak flux, followed by a steady state phase wherein the peak flux is maintained, or a below-peak steady state flux, e.g,. of about 50-90 $\mu g/cm^2$/hour, for a duration of at least 96 hours or more.

Formulations	**X-1**	**X-2**	**X-3**	**X-4**	**X-5**
ODS base	15	18	25	16	25
DMSO	31	31	--	--	31
LA	31	31	38	19	--
FD enhancer (1-23)	10	--	--	25	10
TC	13	21	38	40	39
Total	**100**	**100**	**100**	**100**	**100**

Formulations	1-1	1-2	1-3	1-4	1-5
ODS base	15	18	25	16	25
DMSO	31	31	--	--	31
LA	31	31	38	19	--
Oleic Acid	10	--	--	25	10
TC	13	21	38	40	39
Total	**100**	**100**	**100**	**100**	**100**

Example 9
Additional Formulations with FD Enhancers

[0222] Formulations X-1, X-2, X-3, X-4, and X-5 are prepared as indicated above using the FD enhancer as indicated in the table below. The resulting formulations may show a similar trend as described in Example 8.

	FD Enhancer
1	Oleic acid (C18:1)
2	Isostearic acid (C18:0, methyl-branched)
3	Linoleic acid (C18:2)
4	Palmitoleic acid (C16:1)
5	Palmitic Acid (C16:0)
6	Lauric acid (C12:0)
7	Arachidonic acid (C20:4)
8	Ethyl oleate
9	Oleyl oleate
10	Glyceryl oleate
11	Glyceryl laurate
12	Methyl laurate
13	Lauryl lactate
14	Isopropyl palmitate
15	Octyldodecanol
16	Oleyl alcohol
17	Stearylalcohol
18	Cetyl alcohol
19	Myristyl alcohol
20	Butyl alcohol
21	Myristyl alcohol
22	Butyl alcohol

Example 10
Patches Comprising Ondansetron Base

[0223] Ondansetron base is weighed and dissolved in a formulation prepared as described in example 1 and 2 and using methanol as a solvent, to prepare transdermal patches 1-6. Before addition of the adhesive to patch formulations 2, 4, 5, and 6, the polymer HPMC-AS (hydroxypropyl cellulose acetate) is added, and the mixture is homogenized to form a viscous gel. A suitable form

of this polymer is AquaSolve™ HPMCAS MF (Ashland, Covington, KY, U.S.A.). The gel is mixed with a suitable adhesive, in particular an acrylic adhesive (here: Duro-Tak® 387-2516), and stirred for one hour or until it forms a uniform mixture.

[0224] The following table provides an overview of patches 1-6 with formulations 1 or 2, with or without polymer, and with or without surfactant/sodium bicarbonate. The patches are formed as follows. A formulation may be prepared as detailed in examples 1 and 2, optionally, for patches 5 and 6, surfactant and sodium bicarbonate are added. Optionally, for patches 2, 4, 5 and 6, to the resulting solution the polymer Hydroxypropyl cellulose acetate (AquaSolve™ HPMCAS MF) is added and the mixture is homogenized to form a viscous gel. The gel is mixed with the adhesive Duro-Tak® 387-2516 and stirred for one hour or until it forms a uniform mixture. The resulting mixture is cast with a 0.2 mm coating thickness onto a suitable support (typically directly onto a backing layer or release liner) using a scalpel. A suitable backing layer is Scotchpak 9733 (3M company), alternatively, for use as release liner, Scotchpak 9744 (3M company) can be employed. The patches are dried at 70°C for 30 min to achieve 50 mg/cm^2 dried weight.

Patch	Formulation	Polymer added	Surfactant/pH
1	1	-	-
2	1	Y	-
3	2	-	-
4	2	Y	-
5	1+	Y	Y
6	2+	Y	Y

[0225] After drying, the resulting patch layer has the composition listed below for each of the patches 1-6 (all values in % w/w).

Transdermal Patch 1:

	Patch 1 (% w/w)	
Formulation 1 (50% of total patch formulation):		50.0
15	ODS-Base	7.5
31	DMSO	15.5
31	LA	15.5
10	OA	5.0
13	Transcutol	6.5
-	**Adhesive**	**50.0**
	TOTAL	100

Transdermal Patch 2:

	Patch 2 (% w/w)	
Formulation 1 (45% of total patch formulation):		45.0
15	ODS Base	6.75
31	DMSO	13.95
31	LA	13.95
10	OA	4.5
13	Transcutol	5.85
-	**Adhesive**	**50.0**
	Polymer (HPMC-AS)	**5.0**
	TOTAL	100

Transdermal Patch 3:

	Patch 3 (%w/w)	
Formulation 2 (50% of total patch formulation):		50.0
18	ODS Base	9.0
31	DMSO	15.5
31	LA	15.5
21	Transcutol	10.5
-	**Adhesive**	**50.0**
	TOTAL	100.0

Transdermal Patch 4:

	Patch 4 (%w/w)	
Formulation 2 (45% of total patch formulation):		45.00
18	ODS Base	8.10
31	DMSO	13.95
31	LA	13.95
21	Transcutol	9.45
-	**Adhesive**	**50.00**
	Polymer (HPMC-AS)	**5.00**
	TOTAL	100.00

Transdermal Patch 5:

	Patch 5 (%w/w)	
Formulation 1b (45% of total patch formulation):		45.00
15	ODS Base	6.75
31	DMSO	13.95
31	LA	13.95
10	OA	4.50
8	Transcutol	3.60
3	**Span 80**	**1.35**
2	**Sodium Bicarbonate**	**0.90**
-	Adhesive	50.00
	Polymer (HPMC-AS)	5.00
	TOTAL	100

Transdermal Patch 6:

	Patch 6 (%w/w)	
Formulation 2b (45% of total patch formulation):		45.00
18	ODS Base	8.10
31	DMSO	13.95
31	LA	13.95
16	Transcutol	7.20
3	**Span 80**	**1.35**
2	**Sodium Bicarbonate**	**0.90**
-	Adhesive	50.00
	Polymer (HPMC-AS)	5.00
	TOTAL	100.00

[0226] The transdermal patches are tested by in vitro skin permeability test using modified Franz-diffusion cells with membranes of human cadaver skin. Phosphate buffered saline (PBS) of pH 4.5 with 0.01% sodium azide is used as a receiving medium to determine skin flux. Samples are collected at predetermined time intervals and the drug is quantified by reversed phase HPLC analysis to determine a flux profile with rapid onset and/or sustained release.

Example 11
Additional Sample Patches Comprising OND-Base

[0227] Additional sample patches are produced as described above, having the formulations in Samples 1-4, as indicated below.

	Sample 1	Sample 2	Sample 3	Sample 4
Ondansetron Base	9	5	7.5	9
DMSO	15	15	15	15
Lactic Acid	15	10	15	15
Oleic Acid	5	5		5
Transcutol P	6	-		6
GMO		5	5	
Hydramol ™ PGPL ester		5	5	
BHT		0.5	0.5	0.5
Duotak 9301	50	55	52	
Durotak 2516				50
Flux (0-24 Hr)	**9.1**	**7.92**	**28.4**	**5.0**
Flux (120 Hr)	**6.9**	**8.14**	**19.24**	**4.43**

[0228] The transdermal patches described in Samples 1-4 are tested by in vitro skin permeability test using modified Franz-diffusion cells with membranes of human cadaver skin. Phosphate buffered saline (PBS) of pH 4.5 with 0.01% sodium azide is used as a receiving medium to determine skin flux. Samples are collected at predetermined time intervals and the drug is quantified by reversed phase HPLC analysis to determine a flux between 0-24 hours and at 120 hours after application of the patch.

Example 12
Ondansetron Matrix Patch Formulation ONM9TP

[0229] Materials:

Chemical	Grade	Manufacturer	Supplier
Ondansetron Base	98-102%	Hikal Ltd.	Hikal Ltd., India
Transcutol P™		Gatteffose	Gatteffose, NJ, USA
Lactic Acid	85%-90% aq. Solution	Sigma Aldrich	Sigma Aldrich, St. Louis, USA
Oleic Acid	90%	Sigma Aldrich	Sigma Aldrich, St. Louis, USA
Dimethyl Sulfoxide (DMSO)	HRGC/HPLC trace grade	Pharmco-Aaper	Dawn Scientific, NJ, USA
Cithrol™ GMO (Glycerol Monooleate)	HP	Croda	Croda Inc., NJ, USA
Durotak™ 87-9301 (35.6% w/w Solution)		Henkel	Henkel Corporation, NJ, USA
Butylated Hydroxytoluene (BHT)		Sigma Aldrich	Sigma Aldrich, St. Louis, USA
Release Liner Scotchpack™ 3M 9744		3M Corp.	3M Corp. MN, USA
Backing Membrane Scotchpack™ 3M 9733		3M Corp.	3M Corp. MN, USA

Formulation ONM9TP (Final composition after drying):

Ingredient		Formulation ONM_009_TP (%W/W)
Active	Ondansetron Base	9
Solvent/Permeation Enhancers	DMSO	15
	Lactic Acid	15
	Oleic Acid	5
	Transcutol P™	6
Polymer/Adhesive	Duro-Tak™ 87-9301	49.5
Antioxidant	BHT	0.5

[0230] Rationale for the composition of the formulation:

[0231] General Principles. The rate of penetration of a substance through human skin is a function of its permeability and concentration gradient. The permeability is highest for molecules that are uncharged and lipophilic. For this reason, ondansetron base was chosen as the active agent and an adhesive matrix formulation was developed by trial and error that provided the highest concentration, facilitated release from the matrix and enhanced skin penetration.

[0232] The following excipients were chosen, not only because they solubilized the ondansetron, but also because they were compatible with Duro-Tak 87-9301, an acrylic adhesive, permitting a single-phase mixture that was uniform upon drying with optimal tak and release properties:

[0233] Transcutol P™ is a powerful solubilizing agent and skin penetration enhancer. It functions to create a single phase with the other ingredients which are otherwise immiscible.

[0234] A minimal amount of lactic acid was used to lower the pH as required for neutralizing and enhancing the solubility of ondansetron. Lower concentrations of lactic acid resulted in precipitation of ondansetron.

[0235] Oleic acid is a commonly used skin penetration enhancer.

[0236] Dimethyl Sulfoxide (DMSO) is a potent solvent and skin penetration enhancer. DMSO is thought to accelerate drug penetration during the first 24 hours providing a high early flux and reducing the lag time for initial drug delivery.

[0237] Butylated Hydroxytoluene (BHT) is used to reduce the rate of oxidation of ondansetron.

[0238] Procedure: (For preparing 10 gm of matrix):

Ingredient	Amount (g)
Ondansetron Base	0.9
DMSO	1.5
Lactic Acid	1.5
Oleic Acid	0.5
Transcutol P™	0.6
Methanol	0.5
BHT	0.5
Ethyl Acetate	5
DURO-TAK™ 87-9301	13.9

[0239] **Blend Preparation:** At ambient temperature, mix 1.5 gm DMSO, 1.5 gm Lactic Acid, 0.5 gm Oleic Acid, 0.6 gm Transcutol P, 0.5 gm of methanol and 0.05gm of BHT with slow stirring so as not to create air bubbles. Add 0.9 gm of Ondansetron base and mix it until it dissolves completely. Add 13.9 gm of Duro-Tak 87-9301 and 5.0 gm of ethyl acetate into above drug solution. Mix the dispersion for 60 min at a speed that does not create bubbles while stirring.

[0240] **Coating:** Coat the mixture blend on a sheet of release liner (3M 9744) using 4340 Motorized Film Applicator (Elcometer, MI, USA) at 25 C with the help of 3580 casting knife applicator. The wet coat thickness should be 0.2mm.

[0241] **Drying:** Dry the film for 10 min at room temperature to avoid blister formation during oven drying, then dry in the oven at 40 C for 60 min. Remove from the oven and carefully apply a sheet of the backing membrane (3M 9733 or 9730) in a manner that it does not create bubbles between backing membrane and dried coat.

[0242] **Die Cutting:** Circular patches with suitable surface area were cut from the sheet using swing arm sample die cutter (DC-500, Cheminstruments, OH, USA).

[0243] RESULTS: Collected data is shown in **FIG. 5**. In vitro studies have been conducted using the 9733 backing membrane on three days over a period of 1 month with three different cadaver skin donors and on a fourth day using the 9730 backing membrane. The flux of ondansetron through the skin increased rapidly to 10 µg/hr/sqcm within 24 hours and then gradually fell during the remainder of the dosing period. The average flux between 24 and 120 hours was 6.3 µg/hr/sqcm with a relative standard deviation of 142%. A major issue with this study is the large variability seen between cells in each of the 3 experiments. This variability seems to be related specifically to ondansetron since other patches prepared with different active agents, similar excipients and the same apparatus have significantly lower variability.

[0244] One experiment was done with the 3M 9730 backing membrane which has been associated with increased flux in other formulations. However, the flux in this case only averaged 1.7 µg/hr/sqcm (data not shown). Thus, the overall average for all experiments with this formulation is only 4.8 µg/hr/sqcm.

Example 13
Ondansetron Matrix Patch Formulation ONM95M

[0245] Materials:

Chemical	Grade	Manufacturer	Supplier
Ondansetron Base	98-102%	Hikal Ltd.	Hikal Ltd., India
Lactic Acid	85%-90% aq. Solution	Sigma Aldrich	Sigma Aldrich, St. Louis, USA
Dimethyl Sulfoxide (DMSO)	HRGC/HPLC trace grade	Pharmco-Aaper	Dawn Scientific, NJ, USA
Cithrol™ GMO (Glycerol Monooleate)	HP	Croda	Croda Inc., NJ, USA
Durotak™ 87-9301 (35.6% w/w Solution)		Henkel	Henkel Corporation, NJ, USA
Hydramol™ PGPL Ester		Lubrizol	Essential Ingredients, NJ, USA
Butylated Hydroxytoluene (BHT)		Sigma Aldrich	Sigma Aldrich, St. Louis, USA
Release Liner Scotchpack™ 3M 9744		3M Corp.	3M Corp. MN, USA
Backing Membrane Scotchpack™ 3M 9733		3M Corp.	3M Corp. MN, USA

[0246] Formulation ONM95M (Final composition after drying):

Ingredient		Formulation ONM_009_005_9301 (%W/W)
Active	Ondansetron HCl	7.5
Solvent/Permeation Enhancers	DMSO	15
	Lactic Acid	15
	Cithrol™ GMO	5
	Hydramol™ PGPL Ester	5
Polymer/Adhesive	Durotak™ 87-9301 (35.6% w/w Solution)	52
Antioxidant	BHT	0.5

[0247] Rationale for the composition of the formulation:

[0248] General Principles: The rate of penetration of a substance through human skin is a function of its permeability and concentration. The permeability is highest for molecules that are uncharged and lipophilic. For this reason, ondansetron base was chosen as the active agent and an adhesive matrix formulation was developed by trial and error that provided the highest concentration, facilitated release from the matrix and enhanced skin penetration.

[0249] The following excipients were chosen, not only because they solubilized the ondansetron, but also because they were compatible with Duro-Tak 387-9301, an acrylic adhesive, permitting a single-phase mixture that was uniform upon drying with optimal tak and release properties:

[0250] A minimal amount of Lactic acid was used to lower the pH as required for neutralizing and enhancing the solubility of ondansetron. Lower concentrations of lactic acid resulted in precipitation of ondansetron.

[0251] Dimethyl Sulfoxide (DMSO) is a potent solvent and skin penetration enhancer. DMSO is thought to accelerate drug diffusion during the first 24 hours providing a high early flux and reducing the lag time for initial drug delivery.

[0252] Cithrol™ GMO is a high purity glycerol monooleate commonly used in topical formulations to provide sustained release.

[0253] Hydramol™ PGPL is a poly ethylene/polypropylene glycol laurate ester. It is a solubilizer of both hydrophilic and hydrophobic agents widely used in cosmetic applications.

[0254] Butylated Hydroxytoluene (BHT) is used to reduce the rate of oxidation of ondansetron.

[0255] Procedure: (For preparing 10 gm of matrix patch):

[0256] **Blend Preparation:** At ambient temperature, mix 1.5 gm DMSO, 1.5 gm Lactic Acid, 0.5 gm Hydramol PGPL Ester, 0.5 gm GMO, 0.5 gm of Methanol and 0.05gm of BHT with slow stirring so as not to create air bubbles. Add 0.75 gm of Ondansetron base and mix it until it dissolves completely. Add 13.9 gm of Duro-tak 87-9301 and 5.0 gm of ethyl acetate into above drug solution. Mix the dispersion for 60 min at a speed that does not create bubbles while stirring.

[0257] **Coating:** Coat the mixture blend on a sheet of release liner (3M 9744) using 4340 Motorized Film Applicator (Elcometer, MI, USA) at 25 C with the help of 3580 casting knife applicator. The wet coat thickness should be 0.2mm.

[0258] **Drying:** Dry the film for 10 min at room temperature to avoid blister formation during oven drying, then dry in the oven at 40 C for 60 min. Remove from the oven and carefully apply a sheet of the backing membrane (3M 9733) in a manner that it does not create bubbles between backing membrane and dried coat.

[0259] **Die Cutting:** Circular patches with suitable surface area were cut from the sheet using a swing arm die cutter (DC-500, Cheminstruments, OH, USA).

[0260] **RESULTS**: In vitro studies have been conducted on three days over a period of 2 months with three different cadaver skin donors. The flux of ondansetron through the skin increased rapidly within the first 24 hours to 21 µg/hr/sqcm and then fell to about 13 µg/hr/sqcm by 48 hours. This level was maintained for the duration of dosing. The relative standard deviation is 68%. Results are shown in **FIG. 6**.

Example 14
Topical (Patch) Administration In Female Yucatan Mini-Pigs (non-GLP, Non-Crossover)

[0261] In this study, the exposure of ondansetron was evaluated in female Yucatan mini-pigs following topical (patch) administration. Blood samples were collected up to 168 hours with some animals having collections at 216 hours post-dose, and plasma concentrations of test article(s) were determined by LC-MS/MS. Pharmacokinetic parameters were determined using Phoenix WinNonlin (v8.0). Additional analysis was performed to determine the ondansetron concentrations on the animal's skin surface after patch removal and the residual concentration of ondansetron in the patches. Formulations 4 (ONM009TP) and Formulation 6 (ONM95M) were used in the minipig study.

[0262] A summary of the mean pharmacokinetic parameters for test article(s) are shown in the table below.

Summary of Mean Pharmacokinetic Parameters for Ondansetron after Topical (Patch) Administration in Female Yucatan Mini-pigs

	Group 1	Group 2
	Topical	Topical
Dose (mg/kg)	6.43	5.00
Animal Weight (kg)	31.5	35.6
C_{max} (ng/mL)	1.35	1.78
t_{max} (hr)	124	80.4
$t_{1/2}$ (hr)	14.4	16.7
MRT_{last} (hr)	125	77.8
AUC_{last}/D (hr·kg·ng /mL/mg)	13.2	21.2
AUC_{∞}/D (hr·kg·ng /mL/mg)	ND	25.1

C_{max}: maximum plasma concentration; t_{max}: time of maximum plasma concentration; $t_{1/2}$: half-life; MRT_{last}: mean residence time, calculated to the last observable time point; AUC_{last}/D: area under the curve, calculated to the last observable time point, which has been normalized by dose amount in mg/kg; AUC_{∞}/D: area under the curve extrapolated to infinity, which has been normalized by dose amount in mg/kg. ND: not determined.

RESULTS

[0263] Analytical Methodology LC-MS/MS: Plasma samples were extracted and analyzed as follows. Analytical stock solutions (1.00 mg/mL of the free drug) were prepared in DMSO. Standards were prepared in blank pig plasma containing sodium heparin as the anticoagulant. Working solutions were prepared in 50:50 acetonitrile:water. Working solutions were then added to plasma to make calibration standards to final concentrations of 500, 200, 100, 50, 25, 10, 5, 2.5, 1, 0.5, 0.25 and 0.1 ng/mL, and quality control samples to final concentrations 100, 10, 2.5 and 0.5

ng/mL. Standards and control samples were treated identically to the study samples. 125 µL supernatant was collected and analysis by LC-MS/MS.

[0264] Plasma samples were manually extracted via precipitation with acetonitrile in a 96-well plate. All operations were performed under yellow light due to the potential light sensitivity of the analytes.

[0265] Individual and mean concentrations and pharmacokinetic parameters are expressed as ng/mL of the free base. Samples that were below the limit of quantification (0.1 ng/mL) were not used in the calculation of mean values.

[0266] Swab Analysis for Swab Extraction: After the patch was removed the dose site was swabbed three times for any remaining test article. Swabs were analyzed by LC-MS/MS for test article concentration. Analytical stock solutions (1.00 mg/mL of the free drug) were prepared in DMSO. Working solutions were prepared in 50:50 acetonitrile:water. Working solutions were then added to 100% methanol to make calibration standards to final concentrations of 500, 200, 100, 50, 25, 10, 5, 2.5, 1, 0.5, 0.25 and 0.1 ng/mL, and quality control samples to final concentrations 100, 10, 2.5 and 0.5 ng/mL. Standards and control samples were treated identically to the swab extraction samples. Swab extraction samples were manually extracted in methanol.

[0267] Patch Analysis: The patches were removed at the 120 hour time point and individual patch weights were obtained. Six punches were cut from the 100 cm^2 original patch using an 8 mm biopsy punch in such a pattern as to obtain samples from multiple locations. The pieces cut from each original patch were treated as one sample and punch weights were obtained. All the pieces were extracted with methanol three times. All extracts were analyzed by LC-MS/MS for test article concentration.

[0268] Analytical stock solutions (1.00 mg/mL of the free drug) were prepared in DMSO.Working solutions were prepared in 50:50 acetonitrile:water. Working solutions were then added to 100% methanol to make calibration standards to final concentrations of 500, 200, 100, 50, 25, 10, 5, 2.5, 1, 0.5, 0.25 and 0.1 ng/mL, and quality control samples to final concentrations 100, 10, 2.5 and 0.5 ng/mL. Standards and control samples were treated identically to the swab extraction samples. Patch extraction samples were manually extracted in methanol. The LC-MS/MS conditions are identical as the ones for plasma samples.

[0269] Results: Concentrations versus time data are plotted in **FIGS 1 - 4**.

Example 15
Ondansetron Matrix Patch Formulation ONM105

[0270] Materials:

Chemical	Grade	Manufacturer	Supplier
Ondansetron Base	98-102%	Hikal Ltd.	Hikal Ltd., India
Lactic Acid	85%-90% aq. Solution	Sigma Aldrich	Sigma Aldrich, St. Louis, USA
Dimethyl Sulfoxide (DMSO)	HRGC/HPLC trace grade	Pharmco-Aaper	Dawn Scientific, NJ, USA
Cithrol™ GMO (Glycerol Monooleate)	HP	Croda	Croda Inc., NJ, USA
Durotak™ 87-9301 (35.6% w/w Solution)		Henkel	Henkel Corporation, NJ, USA
Propylene Glycol Monolaurate (PGML)			
Butylated Hydroxytoluene (BHT)		Sigma Aldrich	Sigma Aldrich, St. Louis, USA
Release Liner Scotchpack™ 3M 9744		3M Corp.	3M Corp. MN, USA
Backing Membrane Scotchpack™ 3M 9733		3M Corp.	3M Corp. MN, USA
Backing Membrane Scotchpack™ 3M 9730		3M Corp.	3M Corp. MN, USA

[0271] Formulation ONM105 (Final composition after drying):

Ingredient		Formulation ONM_009_005_9301 (%W/W)
Active	Ondansetron	8
Solvent/Permeation Enhancers	DMSO	30
	Lactic Acid	15
Polymer/Adhesive	Durotak™ 87-9301 (35.6% w/w)	47
Antioxidant	BHT	0.5

[0272] General Principles: The rate of penetration of a substance through human skin is a function of its permeability and concentration. The permeability is highest for molecules that are uncharged and lipophilic. For this reason, ondansetron base was chosen as the active agent and an adhesive matrix formulation was developed by trial and error that provided the highest concentration, facilitated release from the matrix and enhanced skin penetration.

[0273] The following excipients were chosen, not only because they solubilized the ondansetron, but also because they were compatible with Duro-Tak 387-9301, an acrylic adhesive,

permitting a single-phase mixture that was uniform upon drying with optimal tack and release properties:

[0274] A minimal amount of Lactic acid was used to lower the pH as required for neutralizing and enhancing the solubility of ondansetron. Lower concentrations of lactic acid resulted in precipitation of ondansetron.

[0275] Dimethyl Sulfoxide (DMSO) is a potent solvent and skin penetration enhancer. DMSO is thought to accelerate drug diffusion during the first 24 hours providing a high early flux and reducing the lag time for initial drug delivery. This formulation contains 30% by weight, which is the highest amount formulated for ondansetron so far. However, it possible that some DMSO evaporates during the drying process.

[0276] Butylated hydroxytoluene (BHT) is used to reduce the rate of oxidation of ondansetron.

[0277] Two different backing membrane films were used in studies with this formulation. The 3M 9730 membrane is much less permeable to moisture and atmospheric gases. This should reduce water transport from the skin and influx of oxygen to improve matrix stability.

[0278] Procedure: (For preparing 10 gm of matrix patch)

[0279] **Blend Preparation:** At ambient temperature, mix 1.5 gm DMSO, 1.5 gm lactic acid, 0.5 gm of methanol and 0.05gm of BHT with slow stirring so as not to create air bubbles. Add 0.75 gm of Ondansetron base and mix it until it dissolves completely. Add 13.9 gm of Duro-tak 87-9301 and 5.0 gm of ethyl acetate into above drug solution. Mix the dispersion for 60 min at a speed that does not create bubbles while stirring.

[0280] **Coating:** Coat the mixture blend on a sheet of release liner (3M 9744) using 4340 Motorized Film Applicator (Elcometer, MI, USA) at 25 C with the help of 3580 casting knife applicator. The wet coat thickness should be 0.2mm.

[0281] **Drying:** Dry the film for 10 min at room temperature to avoid blister formation during oven drying, then dry in the oven at 40°C for 60 min. Remove from the oven and carefully apply a sheet of the backing membrane (3M 9733) in a manner that it does not create bubbles between backing membrane and dried coat.

[0282] **Die Cutting:** Circular patches with suitable surface area were cut from the sheet using swing arm sample die cutter (DC-500, Cheminstruments, OH, USA).

[0283] RESULTS: Data is shown in **FIG. 7**. In vitro studies have been conducted on two days over a period of 2 weeks with two different cadaver skin donors. Two different backing membranes were used. BM9730 is the most impermeable to water vapor and atmospheric gases. Patches with this membrane consistently have higher flux values. Using the 9730 backing membrane, the flux of ondansetron through the skin on average increased rapidly to 5 μg/hr/sqcm

within 24 hours and then gradually fell to 2 µg/hr/sqcm during the remainder of the dosing period. The average flux between 24 and 120 hours was about 4 µg/hr/sqcm with a relative standard deviation of 160%. This is significant flux considering the simplicity of this formulation. One major issue with this study was the large degree of variability between cells. The source of the variability in not clear but appears to be related directly to ondansetron since studies with other active agents with similar excipients and the same apparatus show significantly less variability.

Example 16
Ondansetron Matrix Patch Formulation ONM95PGML

[0284] Materials:

Chemical	Grade	Manufacturer	Supplier
Ondansetron Base	98-102%	Hikal Ltd.	Hikal Ltd., India
Lactic Acid	85%-90% aq. Solution	Sigma Aldrich	Sigma Aldrich, St. Louis, USA
Dimethyl Sulfoxide (DMSO)	HRGC/HPLC trace grade	Pharmco-Aaper	Dawn Scientific, NJ, USA
Cithrol™ GMO (Glycerol Monooleate)	HP	Croda	Croda Inc., NJ, USA
Durotak™ 87-9301 (35.6% w/w Solution)		Henkel	Henkel Corporation, NJ, USA
Propylene Glycol Monolaurate (PGML)			
Butylated Hydroxytoluene (BHT)		Sigma Aldrich	Sigma Aldrich, St. Louis, USA
Release Liner Scotchpack™ 3M 9744		3M Corp.	3M Corp. MN, USA
Backing Membrane Scotchpack™ 3M 9733		3M Corp.	3M Corp. MN, USA
Backing Membrane Scotchpack™ 3M 9730		3M Corp.	3M Corp. MN, USA

[0285] Formulation ONM95PGML (Final composition after drying)

Ingredient		Formulation ONM_009_005_9301 (%W/W)
Active	Ondansetron	7.5
Solvent/Permeation Enhancers	DMSO	15
	Lactic Acid	15
	Cithrol™ GMO	5
	PGML	5
Polymer/Adhesive	Durotak™ 87-9301 (35.6% w/w Solution)	52
Antioxidant	BHT	0.5

[0286] General Principles: The rate of penetration of a substance through human skin is a function of its permeability and concentration. The permeability is highest for molecules that are uncharged and lipophilic. For this reason, ondansetron base was chosen as the active agent and an

adhesive matrix formulation was developed by trial and error that provided the highest concentration, facilitated release from the matrix and enhanced skin penetration.

[0287] The following excipients were chosen, not only because they solubilized the ondansetron, but also because they were compatible with Duro-Tak 387-9301, an acrylic adhesive, permitting a single-phase mixture that was uniform upon drying with optimal tak and release properties:

[0288] A minimal amount of lactic acid was used to lower the pH as required for neutralizing and enhancing the solubility of ondansetron. Lower concentrations of lactic acid resulted in precipitation of ondansetron.

[0289] Dimethyl Sulfoxide (DMSO) is a potent solvent and skin penetration enhancer. DMSO is thought to accelerate drug diffusion during the first 24 hours providing a high early flux and reducing the lag time for initial drug delivery.

[0290] Cithrol™ GMO is a high purity glycerol monooleate commonly used in topical formulations to provide sustained release.

[0291] PGML is propylene glycol monolaurate used as an excipient.

[0292] Butylated hydroxytoluene (BHT) is used to reduce the rate of oxidation of ondansetron.

[0293] Procedure: (For preparing 10 gm of matrix patch)

[0294] **Blend Preparation:** At ambient temperature, mix 1.5 gm DMSO, 1.5 gm lactic acid, PGML, 0.5 gm GMO, 0.5 gm of methanol and 0.05gm of BHT with slow stirring so as not to create air bubbles. Add 0.75 gm of Ondansetron base and mix it until it dissolves completely. Add 13.9 gm of Duro-tak 87-9301 and 5.0 gm of ethyl acetate into above drug solution. Mix the dispersion for 60 min at a speed that does not create bubbles while stirring.

[0295] **Coating:** Coat the mixture blend on a sheet of release liner (3M 9744) using 4340 Motorized Film Applicator (Elcometer, MI, USA) at 25°C with the help of 3580 casting knife applicator. The wet coat thickness should be 0.2 mm.

[0296] **Drying:** Dry the film for 10 min at room temperature to avoid blister formation during oven drying, then dry in the oven at 40 C for 60 min. Remove from the oven and carefully apply a sheet of the backing membrane (3M 9733) in a manner that it does not create bubbles between backing membrane and dried coat.

[0297] **Die Cutting:**Circular patches with suitable surface area were cut from the sheet using swing arm sample die cutter (DC-500, Cheminstruments, OH, USA).

[0298] RESULTS: Data is shown in **FIG. 8**. In vitro studies have been conducted on three days over a period of 4 weeks with three different cadaver skin donors. The highest flux was seen when using backing membrane 9730 which is less permeable to water vapor and atmospheric gases.

With this membrane, the flux of ondansetron through the skin on average increased rapidly to about 8 μg/cm^2/hour within 24 hours and then gradually to 2 μg/cm^2/hour over the remainder of the dosing period. The average flux between 24 and 120 hours was about 4.5 μg/cm^2/hour with a relative standard deviation of 75%.

Example 17
Flux Profile Analysis and Optimization for Different Ondansetron Patch Formulations

Table A. Conditions for the flux profile analysis:

Experimental Condition	
Franz-Diffusion Cell	Logan semi-automated Franz diffusion cells
Sampling Media mL	12
Receiving Media	PBS (pH =4.5) with 0.01% sodium azide
Membrane	Human cadaver skin
Skin Source	NY fire fighter skin bank
Loading in Donor	Matrix film
sample volume (mL)	12

Table B. Effects of different adhesives:

Formulation	OND_009_2074 (%W/W)	OND_009_2194 (%W/W)	OND_009_2287 (%W/W)	OND_009_2516 (%W/W)	OND_009_2852 (%W/W)	OND_009_9301 (%W/W)
OND	9	9	9	9	9	9
DMSO	15	15	15	15	15	15
Lactic Acid	15	15	15	15	15	15
Oleic Acid	5	5	5	5	5	5
Durotak-2074	50	-	-	-	-	-
Durotak-2194	-	50	-	-	-	-
Durotak-2287	-	-	50	-	-	-
Durotak-2516	-	-	-	50	-	-
Durotak-2852	-	-	-	-	50	-
Durotak-9301	-	-	-	-	-	50

[0299] Table C. Flux profile of ondansetron through human cadaver skin:

Time (Hr)	Flux (μg/cm^2/Hr) ± S.D.					
	OND_009_2074 (n=3)	**OND_009_2194 (n=3)**	**OND_009_2287 (n=3)**	**OND_009_2516 (n=4)**	**OND_009_2852 (n=4)**	**OND_009_9301 (n=4)**
0	0.00	0.00	0.00	0.00	0.00	0.0
24	1.35 ± 1.02	1.66 ± 1.38	11.01 ± 10.5	0.45 ± 0.50	0.15 ± 0.04	14.24 ± 9.96
48	1.45 ± 1.12	1.41 ± 2.26	12.76 ± 14.8	1.19 ± 0.95	0.68 ± 1.09	8.56 ± 6.96
72	1.41 ± 1.05	2.17 ± 3.01	12.23 ± 11.5	0.78 ± 0.11	1.16 ± 1.91	7.43 ± 4.01
96	1.72 ± 1.35	2.32 ± 2.98	10.34 ± 8.8	3.06 ± 3.97	1.88 ± 3.17	5.51 ± 2.37
120	1.21 ± 0.9	1.85 ± 2.26	6.35 ± 5.52	1.55 ± 2.79	0.19± 0.27	2.98 ± 1.27

[0300] Table D. Effect of different *in situ* salt on permeation

Excipient	Formulation 1 (%W/W)	Formulation 2 (%W/W)	Formulation 3 (%W/W)
Ondansetron	7.5	7.5	7.5
DMSO	15	15	15
Lactic Acid	15	-	7
Formic Acid	-	15	6
Transcutol P	6	-	-
GMO	5	5	5
Tween-80	-	5	5
BHT	0.5	0.5	0.5
Durotak 87-9301	51	52	54

[0301] Table E. Flux profile of ondansetron through human cadaver skin:

Time (Hr)	Flux (μg/cm²/hour) ± S.D.		
	Formulation 1 (n=3)	Formulation 2 (n=4)	Formulation 3 (n=4)
0	0.00	0	0.00
24	26.83 ± 22.6	0.23 ± 0.3	0.55 ± 0.6
48	16.73 ± 13.2	0.08 ± 0.02	0.32 ± 0.3
72	10.91 ± 11.1	0.06 ± 0.1	0.13 ± 0.1
96	6.01 ± 5.2		
120	5.06 ± 4.2		

[0302] Table F. Effect of different permeability enhancers on ondansetron permeability:

Excipient	Formulation 4 (%W/W)	Formulation 5 (%W/W)	Formulation 6 (%W/W)
Ondansetron	9	5	7.5
DMSO	15	15	15
Lactic Acid	15	10	15
Oleic Acid	5	5	-
Transcutol P	6	-	-
GMO	-	5	5
Hydramol	-	5	5
BHT	-	0.5	0.5
Durotak 87-9301	50	55	52

[0303] Table G. Flux profile of ondansetron through human cadaver skin:

Time (hours)	Flux (μg/cm²/hour) ± S.D.		
	Formulation 4 (n=8)	Formulation 5 (n=13)	Formulation 6 (n=7)
0	0.00	0	0.00
24	10.36 ± 19.12	4.61 ± 5.13	25.54 ± 21.68
48	8.14 ± 13.77	5.73 ± 4.15	16.73 ± 10.32
72	5.70 ± 7.46	5.86 ± 2.65	17.16 ± 8.65
96	3.66 ± 4.73	4.18 ± 1.87	15.32 ± 3.73
120	4.14 ± 5.55	3.37 ± 1.49	12.21 ± 3.08

DISCUSSION

[0304] Lactic acid salt of ondansetron showed higher permeability through human cadaver skin in vitro as compare to other salts (Tables C and D). Lactic acid salt was selected to use to evaluate different acrylate adhesives (Durotak). From among the acrylate adhesives, Durotak 9301 and Durotak 2287 showed very good permeability with average flux of 7.7 and 9.72 µg/cm^2/hour for 24-120 hours, respectively. Durotak 2287 showed very high variability in data with 93% RSD as compare to 9301, which showed only 58% RSD. For further study, Durotak 9301 was used (Table A and Table B). More than 100 formulations were formulated with different permeability enhancers and the best three formulations are shown in Table E with flux profiles in Table G. Formulation 4 (ONM009TP) and Formulation 6 (ONM 95M) were further applied in mini-pigs plasma concentration analysis.

[0305] Formulation 4 (ONM009TP) and Formulation 6 (ONM 95M) were used in the Mini Pig studies which provide the following data.

Table H: Pharmacokinetic profile of Formulation 6

PK parameter (N=5) Formulation 6 (ONM 95M)	**Range**	**Mean**	**SEM**
Cave (8-120 hr) ng/mL	0.2-1.9	0.9	0.2
Cmax (ng/mL)	0.4-3.3	1.4	0.6
AUC (nghr/mL)	37-259	123	44
Tmax (hr)	24-120	77	20
Clearance (L/hour/kg)	1.8-2.3	2.1	0.2
Jmax (µg/sqcm/hr)	0.3-2.4	1.3	0.4
Jave (8-120 hr) (µg/sqcm/hr)	0.1-1.5	0.6	0.2

Table I: *In Vivo* plasma data of Formulation 4 in mini-pigs

Animal #	**5561**	**5554**	**5565**	**5557**	**125**	**AVG**
Weight	**31.3**	**34.4**	**34.1**	**32.6**	**25.3**	**31.5**
Time (Hr)	**Plasma Concentration (ng/mL)**					
0	0	0	0	0	0	0
1	0	0.315	0.062	0	0	0.0754
2	0.024	0.758	0	0	0	0.1564
4	0.545	0.659	0.011	0	0	0.243
8	0.349	0.347	0	0	0.0822	0.15564
24	3.05	0.494	0.058	0.0765	0	0.7357
48	0.837	0.441	0	0	0	0.2556
72	1.13	1.97	0.052	0	0.036	0.6376
96	0.51	0.535	0.03	0	0	0.215
120	0.105	0.416	0.21	0.044	0	0.155
144	0.204	0.186	0.047	0.086	0	0.1046
168	0.254	0.536	0.057	20	0.208	4.211
216	0.248		0.087	0.138	0.269	0.1855

Table J: *In Vivo* plasma data of Formulation 6 (ONM 95M) in mini-pig

Animal #	5862	6434	5560	5119	4038	AVG
Weight	30.4	30	31.3	36.6	48.9	35.44
Time (Hr)	Plasma Concentration (ng/mL)					
0	0	0	0	0	0	0
1	0	0	0	0	0	0
2	0.926	0.343	0	0	0.133	0.2804
4	2.28	0.09	0	0	0	0.474
8	2.68	0.186	0	0	0	0.5732
24	3.28	1.81	0.314	0.055	0	1.0918
48	2.77	2.96	1.2	0.05	0.04	1.404
72	1.3	0.954	2.53	0.217	0.207	1.0416
96	1.31	0.321	1.32	0.256	0.375	0.7164
120	0.502	0.143	0.43	0.393	0.543	0.4022
144	0	0	0.143	0	0.114	0.0514
168	2.46	0.203	0	0	0.164	0.5654
216	0.481	0.195	0	0	0	0.1352

Data from the plasma profile is shown in **FIGS. 9A** and **9B**, and were drawn using an average of all five animals in the study and also by removing animal# 5119 and 4038.

* * *

[0306] It should be noted that the features illustrated in the drawings are not necessarily drawn to scale, and features of one embodiment may be employed with other embodiments as the skilled artisan would recognize, even if not explicitly stated herein. Descriptions of well-known components and processing techniques may be omitted so as to not unnecessarily obscure the embodiments.

[0307] While multiple embodiments are disclosed, still other embodiments of the present description will become apparent to those skilled in the art from this detailed description. The compostions and methods described herein are capable of myriad modifications in various obvious aspects, all without departing from the spirit and scope of the present disclosure. Accordingly, the drawings and descriptions are to be regarded as illustrative in nature rather than restrictive.

CLAIMS

WHAT IS CLAIMED IS:

1. A drug-in-adhesive patch for transdermal administration of ondansetron to a human subject, wherein said transdermal administration having ondansetron rapid onset and ondansetron sustained release.

2. The patch of claim 1 comprising:

(a) ondansetron,

(b) one or more polyacrylic adhesive,

(c) an amphiphilic polymer,

(d) one or more enhancer, and

(e) one or more solvent.

3. The patch of claim 2, wherein the amphiphilic polymer comprises one or more of: a cellulose polymer, an acetyl- and succinoyl-substituted polymer, a hydroxypropylcellulose acetate succinate or hypromellose acetate succinate (HPMC-AS), AquaSolve™ HPMCAS-LF, AquaSolve™ HPMCAS-LG; AquaSolve™ HPMCAS-MF; AquaSolve™ HPMCAS-MG; AquaSolve™ HPMCAS-HF; AquaSolve™ HPMCAS-HG, substituted hydroxypropylcellulose (HPMC), hydroxypropylcellulose (HPMC), a Klucel™ polymer, Klucel™ HF, Klucel™ MF, Klucel™ GF, Klucel™ JF, Klucel™ EF, Klucel™ ELF, an HPMC derivative, a cellulose ether, a METHOCEL™ cellulose ether, METHOCEL™ E, METHOCEL™ F, METHOCEL™ J, METHOCEL™ K, Methocel™ 40-0101, METHOCEL™ 40-0202, METHOCEL™ E4M PRM, METHOCEL™ E50 PRM, METHOCEL™ 856N, METHOCEL™ K100M PRM, a carboxymethylcellulose (CMC), a WALOCEL™ polymer, WALOCEL™ CRT 1000, WALOCEL™ CRT 2000, WALOCEL™ CRT 10000, WALOCEL™ CRT 15000, WALOCEL™ CRT 30000, WALOCEL™ CRT 40000, WALOCEL™ CRT 50000, WALOCEL™ CRT 60000, polyvinylpyrrolidone (PVP), acrylic acid derivatives, a Plastoid® polymer, Plastoid®B, an Eudragit® polymer, Eudragit® L-100, Eudragit® L100-55; Eudragit® L30 D-55; Eudragit® L12,5; Eudragit® S100; Eudragit® S12,5; Eudragit® FS30D; Eudragit® E100; Eudragit® E12,5; Eudragit® EPO; Eudragit® S100; Eudragit® S12,5; Eudragit® FS30D; Eudragit® NE30D; Eudragit® NE40D; Eudragit® NM30D; Eudragit® RLPO; Eudragit® RL100; Eudragit® RL30D; Eudragit® RL12,5; Eudragit® RSPO; Eudragit® RS100; Eudragit® RS30D; Eudragit® RS12,5; PlasACRYL™ HTP20; PlasACRYL™ T20; and Acryl-EZE®.

4. The patch of claim 2, wherein the enhancer comprises a FD enhancer that is selected from a

fatty acid, a fatty alcohol, a fatty acid derivative, and a fatty alcohol derivative, and combinations thereof.

5. The patch of claim 4, wherein the FD enhancer is a fatty acid derivative or a fatty alcohol derivative, or combinations thereof, and further wherein the fatty acid derivative or fatty alcohol derivative consists of a substituted fatty acid moiety, or a substituted fatty alcohol moiety that comprises one or more additional group, wherein the additional group comprises one or more of hydroxyl, ethyl, methyl, propyl, butyl, and glyceryl, and wherein the fatty acid moiety or the fatty alcohol moiety of the FD enhancer has a carbon chain length from C4 to C26.

6. The patch of claim 2, wherein the solvent comprises one or more of: DMSO, lactic acid, diethylene glycol monoethyl ether (DEGEE), Span 20®, Span®40, Span® 60, Span®80, Span®83, Span®85, Span®120, Tween 20®, Tween 21®, Tween 40®, Tween 60®, Tween 61®, Tween 65®, Tween 80®, and hexylengycol.

7. The patch of claim 4, wherein the solvent comprises one or more of: DMSO, lactic acid, diethylene glycol monoethyl ether (DEGEE), Span 20®, Span®40, Span® 60, Span®80, Span®83, Span®85, Span®120, Tween 20®, Tween 21®, Tween 40®, Tween 60®, Tween 61®, Tween 65®, Tween 80®, and hexylengycol.

8. The patch of claim 4, wherein the enhancer further comprises one or more of: ethanol, propanol, decylmethyl sulfoxide, dimethylformamide, azone, urea, dimethylacetamide, a pyrrolidone derivative, 1-methyl-4-carboxy-2-pyrrolidone, 1-methyl-2-pyrrolidone, 1- lauryl-4-methoxycarbonyl-2-pyrrolidone, a polyol, propylene glycol, polyethylene glycol, a terpene, menthol, limonene, terpineol, pinene, carvol, a surfactant, a nonionic surfactant, a cationic surfactant, an anionic surfactant, Brij®, sodium lauryl sulfate, ethyl acetate, methyl acetate, octisalate, pentadecalactone, Hydramol™ PGPL and acrylamide.

9. The patch of claim 4, wherein the enhancer comprises one or more of: butyric acid (C4:0), isobutyric acid (C4:0), valeric acid (C5:0), isovaleric acid (C5:0), levulinic acid (C5:0), caproic acid (C6:0), caprylic acid (C8:0), capric acid (C10:0), lauric acid (C12:0), myristic acid (C14:0), palmitic acid (C16:0), stearic acid (C18:0), and isostearic acid (C18:0), 5-dodecenoic acid (C12:1), 7-tetradecenoic acid (14:1), palmitoleic acid (16:1), oleic acid (C18:1), vaccenic acid (C18:1), elaidic acid (C18:1), paullinic acid (C20:1), gondoic acid (C20:1), erucic acid (C22:1), 15-docosenoic acid (C22:1), 17-tetracosenoic acid (24:1), nervonic acid (C24:1), and ximenic acid (C26:1), hexadecatrienoic acid (16:3), linoleic acid (C18:2), rumenic acid (C18:2), alpha-linolenic acid (C18:3), gamma-linolenic acid (C18:3), calendic acid (C18:3), stearidonic acid (C18:4) mead acid (C20:3), eicosadienoic acid (C20:3), eicosatrienoic acid (C20:3), dihomo-gamma- linolenic acid

(C20:3), arachidonic acid (C20:4), docosadienoic acid (C22:2), adrenic acid (C22:4), osbond acid (C22:5), tetracosatetraenoic acid (C24:4), and tetracosapentaenoic acid (C24:5), butanol (C4), tert-butyl alcohol (C4), tert-Amyl alcohol (C5), 3-Methyl-3-pentanol (C6), capryl alcohol (C8), pelargonic alcohol (C9), capric alcohol (C10), Undecyl alcohol (C11), Lauryl alcohol (C12), tridecyl alcohol (C13), Myristyl alcohol (C14), pentadecyl alcohol (C15), cetyl alcohol (C16), palmitoleyl alcohol (cis-9-hexadecen-1-ol, C16H32O), Heptadecyl alcohol (1-n- heptadecanol, $C_{17}H_{36}O$), Stearyl alcohol (C18), Oleyl alcohol ($C_{18}H_{36}O$), linoleyl alcohol ($C_{18}H_{34}O$, cis,cis-9,12-Octadecadien-1-ol), Nonadecyl alcohol (C19), Arachidyl alcohol ($C_{20}H_{42}O$), Heneicosyl alcohol (C21), Behenyl alcohol ($C_{22}H_{46}O$), Erucyl alcohol (cis-13-docosen-1-ol, $C_{22}H_{44}O$), Lignoceryl alcohol (C24), Ceryl alcohol (C26), octyldodecanol ($C_{20}H_{42}O$, 2-Octyldodecan-1-ol), butyric acid (C4:0), isobutyric acid (C4:0), valeric acid (C5:0), isovaleric acid (C5:0), levulinic acid (C5:0), caproic acid (C6:0), caprylic acid (C8:0), capric acid (C10:0), lauric acid (C12:0), myristic acid (C14:0), palmitic acid (C16:0), stearic acid (C18:0), isostearic acid (C18:0), 5-dodecenoic acid (C12:1), 7-tetradecenoic acid (14:1), palmitoleic acid (16:1), oleic acid (C18:1), vaccenic acid (C18:1), elaidic acid (C18:1), paullinic acid (C20:1), gondoic acid (C20:1), erucic acid (C22:1), 15-docosenoic acid (C22:1), 17-tetracosenoic acid (24:1), nervonic acid (C24:1), ximenic acid (C26:1), hexadecatrienoic acid (16:3), linoleic acid (C18:2), rumenic acid (C18:2), alpha-linolenic acid (C18:3), gamma-linolenic acid (C18:3), calendic acid (C18:3), stearidonic acid (C18:4) mead acid (C20:3), eicosadienoic acid (C20:3), eicosatrienoic acid (C20:3), dihomo-gamma-linolenic acid (C20:3), arachidonic acid (C20:4), docosadienoic acid (C22:2), adrenic acid (C22:4), osbond acid (C22:5), tetracosatetraenoic acid (C24:4), tetracosapentaenoic acid (C24:5), butanol (C4), tert- Butyl alcohol (C4), 2-butanol, isobutanol, tert-butanol, tert-Amyl alcohol (C5), 3-Methyl- 3-pentanol (C6), capryl alcohol (C8), pelargonic alcohol (C9), capric alcohol (C10), Undecyl alcohol (C11), Lauryl alcohol (C12), Tridecyl alcohol (C13), Myristyl alcohol (C14), Pentadecyl alcohol (C15), Cetyl alcohol (C16), Palmitoleyl alcohol (cis-9- hexadecen-1-ol, $C_{16}H_{32}O$), Heptadecyl alcohol (1-n-heptadecanol, C17H36O), Stearyl alcohol (C18), Oleyl alcohol ($C_{18}H_{36}O$), linoleyl alcohol ($C_{18}H_{34}O$, cis,cis-9,12- Octadecadien-1-ol), Nonadecyl alcohol (C19), Arachidyl alcohol ($C_{20}H_{42}O$), Heneicosyl alcohol (C21), behenyl alcohol ($C_{22}H_{46}O$), Erucyl alcohol (cis-13-docosen- 1-ol, $C_{22}H_{44}O$), Lignoceryl alcohol (C24), Ceryl alcohol (C26), octyldodecanol ($C_{20}H_{42}O$, 2-Octyldodecan-1-ol), ethyl oleate, methyl oleate, decyloleate, oleyl oleate, glyceryl monooleate, isopropyl palmitate (ester of isopropyl alcohol and palmitic acid), isopropyl myristate, methyl laurate (lauric acid methyl ester), glyceryl laurate (lauric acid glyceryl ester, monolaurin, glycerol monolaurate), propylene glycol monolaurate type I, propylene glycol monolaurate type II (e.g., lauroglycol^{TM}90), lauryl lactate (ester of lauryl alcohol and lactic acid), butyl acetate and Hydramol^{TM} PGPL ester.

10. The patch of claim 2, wherein the polyacrylic adhesive comprises a self crosslinkable acrylic adhesive, the adhesive comprising one or more of: Duro-Tak® 387-2516, Duro- Tak® 387-2051, Duro-Tak® 87-2852, Duro-Tak® 87-2194, Duro-Tak® 87-2852, GELVA® 737, GELVA® 2655, and GELVA® 1753.

11. The patch of claim 2, wherein the patch is characterized by:

(a) a minimum predetermined flux within a first predetermined amount of time;

(b) a preferred predetermined flux within a second predetermined amount of time; and

(c) maintenance of the preferred flux within a predetermined range for a third predetermined amount of time.

12. The patch of claim 11, wherein the minimum predetermined flux is about 2.5 $\mu g/cm^2$/hour.

13. The patch of claim 11, wherein the preferred predetermined flux is about 15 $\mu g/cm^2$/hour.

14. The patch of claim 11, wherein the first predetermined amount of time does not exceed 90 minutes.

15. The patch of claim 11, wherein the second predetermined amount of time does not exceed 12 hours.

16. The patch of claim 11, wherein the third predetermined amount of time is at least two days.

17. The patch of claim 11, wherein the patch provides a steady state flux of about 30 $\mu g/cm^2$/hour as measured in 12 hour time intervals for at least two days.

18. The patch of claim 11, where the patch delivers 4 mg or more of ondansetron per day to human subject.

19. The patch of claim 11, wherein the patch delivers at least 4 mg of ondansetron per day to human a subject for at least 2 days.

20. A formulation for a drug-in-adhesive patch for the transdermal administration of ondansetron to a human subject, wherein said transdermal administration having ondansetron rapid onset and ondansetron sustained release.

21. The formulation of claim 20 comprising:

(a) an amphiphilic polymer,

(b) one or more enhancer, and

(c) one or more solvent.

22. The formulation of claim 21, wherein the amphiphilic polymer comprises one or more of: a cellulose polymer, an acetyl- and succinoyl-substituted polymer, a hydroxypropylcellulose acetate succinate or hypromellose acetate succinate (HPMC-AS), AquaSolve™ HPMCAS-LF, AquaSolve™ HPMCAS-LG; AquaSolve™ HPMCAS-MF; AquaSolve™ HPMCAS-MG; AquaSolve™ HPMCAS-HF; AquaSolve™ HPMCAS-HG, substituted hydroxypropylcellulose (HPMC), hydroxypropylcellulose (HPMC), a Klucel™ polymer, Klucel™ HF, Klucel™ MF, Klucel™ GF, Klucel™ JF, Klucel™ EF, Klucel™ ELF, an HPMC derivative, a cellulose ether, a METHOCEL™ cellulose ether, METHOCEL™ E, METHOCEL™ F, METHOCEL™ J, METHOCEL™ K, Methocel™ 40-0101, METHOCEL™ 40-0202, METHOCEL™ E4M PRM, METHOCEL™ E50 PRM, METHOCEL™ 856N, METHOCEL™ K100M PRM, a carboxymethylcellulose (CMC), a WALOCEL™ polymer, WALOCEL™ CRT 1000, WALOCEL™ CRT 2000, WALOCEL™ CRT 10000, WALOCEL™ CRT 15000, WALOCEL™ CRT 30000, WALOCEL™ CRT 40000, WALOCEL™ CRT 50000, WALOCEL™ CRT 60000, polyvinylpyrrolidone (PVP), acrylic acid derivatives, a Plastoid® polymer, Plastoid®B, an Eudragit® polymer, Eudragit® L-100, Eudragit® L100-55; Eudragit® L30 D-55; Eudragit® L12,5; Eudragit® S100; Eudragit® S12,5; Eudragit® FS30D; Eudragit® E100; Eudragit® E12,5; Eudragit® EPO; Eudragit® S100; Eudragit® S12,5; Eudragit® FS30D; Eudragit® NE30D; Eudragit® NE40D; Eudragit® NM30D; Eudragit® RLPO; Eudragit® RL100; Eudragit® RL30D; Eudragit® RL12,5; Eudragit® RSPO; Eudragit® RS100; Eudragit® RS30D; Eudragit® RS12,5; PlasACRYL™ HTP20; PlasACRYL™ T20; and Acryl-EZE®.

23. The formulation of claim 21, wherein the enhancer comprises an FD enhancer, wherein the FD enhancer is selected from a fatty acid, a fatty alcohol, a fatty acid derivative, and a fatty alcohol derivative, and combinations thereof.

24. The formulation of claim 23, wherein the FD enhancer is a fatty acid derivative or a fatty alcohol derivative, or combinations thereof, and further wherein the fatty acid derivative or fatty alcohol derivative consists of a substituted fatty acid moiety, or a substituted fatty alcohol moiety that comprises one or more additional group, wherein the additional group comprises one or more of hydroxyl, ethyl, methyl, propyl, butyl, and glyceryl, and wherein the fatty acid moiety or the fatty alcohol moiety of the FD enhancer has a carbon chain length from C4 to C26.

25. The formulation of claim 21, wherein the solvent comprises one or more of: DMSO, lactic acid, diethylene glycol monoethyl ether (DEGEE), Span 20®, Span®40, Span® 60, Span®80, Span®83, Span®85, Span®120, Tween 20®, Tween 21®, Tween 40®, Tween 60®, Tween 61®, Tween 65®, Tween 80®, and hexylengycol.

26. The formulation of claim 21, wherein the enhancer further comprises one or more of: ethanol, propanol, decylmethyl sulfoxide, dimethylformamide, azone, urea, dimethylacetamide, a pyrrolidone derivative, 1-methyl-4-carboxy-2-pyrrolidone, 1- methyl-2-pyrrolidone, 1-lauryl-4-methoxycarbonyl-2-pyrrolidone, a polyol, propylene glycol, polyethylene glycol, a terpene, menthol, limonene, terpineol, pinene, carvol, a surfactant, a nonionic surfactant, a cationic surfactant, an anionic surfactant, Brij®, sodium lauryl sulfate, ethyl acetate, methyl acetate, octisalate, pentadecalactone, and acrylamide.

27. The formulation of claim 21, wherein the enhancer comprises one or more of: butyric acid (C4:0), isobutyric acid (C4:0), valeric acid (C5:0), isovaleric acid (C5:0), levulinic acid (C5:0), caproic acid (C6:0), caprylic acid (C8:0), capric acid (C10:0), lauric acid (C12:0), myristic acid (C14:0), palmitic acid (C16:0), stearic acid (C18:0), and isostearic acid (C18:0), 5-dodecenoic acid (C12:1), 7-tetradecenoic acid (14:1), palmitoleic acid (16:1), oleic acid (C18:1), vaccenic acid (C18:1), elaidic acid (C18:1), paullinic acid (C20:1), gondoic acid (C20:1), erucic acid (C22:1), 15-docosenoic acid (C22:1), 17-tetracosenoic acid (24:1), nervonic acid (C24:1), and ximenic acid (C26:1), hexadecatrienoic acid (16:3), linoleic acid (C18:2), rumenic acid (C18:2), alpha-linolenic acid (C18:3), gamma-linolenic acid (C18:3), calendic acid (C18:3), stearidonic acid (C18:4) mead acid (C20:3), eicosadienoic acid (C20:3), eicosatrienoic acid (C20:3), dihomo-gamma- linolenic acid (C20:3), arachidonic acid (C20:4), docosadienoic acid (C22:2), adrenic acid (C22:4), osbond acid (C22:5), tetracosatetraenoic acid (C24:4), and tetracosapentaenoic acid (C24:5), butanol (C4), tert-Butyl alcohol (C4), tert-Amyl alcohol (C5), 3-Methyl-3-pentanol (C6), capryl alcohol (C8), pelargonic alcohol (C9), capric alcohol (C10), Undecyl alcohol (C11), Lauryl alcohol (C12), Tridecyl alcohol (C13), Myristyl alcohol (C14), Pentadecyl alcohol (C15), Cetyl alcohol (C16), Palmitoleyl alcohol (cis-9-hexadecen-1-ol, $C_{16}H_{32}O$), Heptadecyl alcohol (1-n- heptadecanol, $C_{17}H_{36}O$), Stearyl alcohol (C18), Oleyl alcohol ($C_{18}H_{36}O$), linoleyl alcohol ($C_{18}H_{34}O$, cis,cis-9,12-Octadecadien-1-ol), Nonadecyl alcohol (C19), Arachidyl alcohol (C20H42O), Heneicosyl alcohol (C21), Behenyl alcohol ($C_{22}H_{46}O$), Erucyl alcohol (cis-13-docosen-1-ol, $C_{22}H_{44}O$), Lignoceryl alcohol (C24), Ceryl alcohol (C26), octyldodecanol ($C_{20}H_{42}O$, 2-Octyldodecan-1-ol), butyric acid (C4:0), isobutyric acid (C4:0), valeric acid (C5:0), isovaleric acid (C5:0), levulinic acid (C5:0), caproic acid (C6:0), caprylic acid (C8:0), capric acid (C10:0), lauric acid (C12:0), myristic acid (C14:0), palmitic acid (C16:0), stearic acid (C18:0), isostearic acid (C18:0), 5-dodecenoic acid (C12:1), 7-tetradecenoic acid (14:1), palmitoleic acid (16:1), oleic acid (C18:1), vaccenic acid (C18:1), elaidic acid (C18:1), paullinic acid (C20:1), gondoic acid (C20:1), erucic acid (C22:1), 15-docosenoic acid (C22:1), 17-tetracosenoic acid (24:1), nervonic acid (C24:1), ximenic acid (C26:1), hexadecatrienoic acid (16:3), linoleic acid (C18:2), rumenic acid (C18:2), alpha-linolenic acid (C18:3), gamma-linolenic acid (C18:3), calendic acid (C18:3), stearidonic acid (C18:4) mead acid

(C20:3), eicosadienoic acid (C20:3), eicosatrienoic acid (C20:3), dihomo-gamma-linolenic acid (C20:3), arachidonic acid (C20:4), docosadienoic acid (C22:2), adrenic acid (C22:4), osbond acid (C22:5), tetracosatetraenoic acid (C24:4), tetracosapentaenoic acid (C24:5), butanol (C4), tert- Butyl alcohol (C4), 2-butanol, isobutanol, tert-butanol, tert-Amyl alcohol (C5), 3-Methyl- 3-pentanol (C6), capryl alcohol (C8), pelargonic alcohol (C9), capric alcohol (C10), Undecyl alcohol (C11), Lauryl alcohol (C12), Tridecyl alcohol (C13), Myristyl alcohol (C14), Pentadecyl alcohol (C15), Cetyl alcohol (C16), Palmitoleyl alcohol (cis-9- hexadecen-1-ol, $C_{16}H_{32}O$), Heptadecyl alcohol (1-n-heptadecanol, C17H36O), Stearyl alcohol (C18), Oleyl alcohol ($C_{18}H_{36}O$), linoleyl alcohol ($C_{18}H_{34}O$, cis,cis-9,12- Octadecadien-1-ol), Nonadecyl alcohol (C19), Arachidyl alcohol ($C_{20}H_{42}O$), Heneicosyl alcohol (C21), Behenyl alcohol ($C_{22}H_{46}O$), Erucyl alcohol (cis-13-docosen- 1-ol, $C_{22}H_{44}O$), Lignoceryl alcohol (C24), Ceryl alcohol (C26), octyldodecanol ($C_{20}H_{42}O$, 2-Octyldodecan-1-ol), ethyl oleate, methyl oleate, decyloleate, oleyl oleate, glyceryl monooleate, isopropyl palmitate (ester of isopropyl alcohol and palmitic acid), isopropyl myristate, methyl laurate (lauric acid methyl ester), glyceryl laurate (lauric acid glyceryl ester, monolaurin, glycerol monolaurate), propylene glycol monolaurate type I, propylene glycol monolaurate type II (e.g., lauroglycol^{TM}90), lauryl lactate (ester of lauryl alcohol and lactic acid), butyl acetate and Hydramol^{TM} PGPL.

28. The formulation of claim 20, wherein the formulation provides:

(a) a minimum predetermined flux within a first predetermined amount of time;

(b) a preferred predetermined flux within a second predetermined amount of time;

(c) maintenance of the preferred flux within a predetermined range for a third predetermined amount of time.

29. The formulation of claim 28, wherein the formulation provides a minimum predetermined flux of at least 30 μg/cm^2/hour, and further wherein the first predetermined time is not greater than about 90 minutes.

30. The formulation of claim 29, wherein the second predetermined amount of time is not greater than 12 hours.

31. The formulation of claim 29, wherein the third predetermined amount of time is at least 5 days.

32. The formulation of claim 29, wherein the predetermined range flux is selected from: 30 μg/cm^2/h, 35 μg/cm^2/h, 40 μg/cm^2/h, 45 μg/cm^2/h, 50μg/cm^2/h, 55 μg/cm^2/h, 60μg/cm^2/h, 65 μg/cm^2/h, 70μg/cm^2/h, 75 μg/cm^2/h, 80 μg/cm^2/h, 85 μg/cm^2/h, 90 μg/cm^2/h and higher.

33. The formulation of claim 20 comprising:

(a) a polyacrylic adhesive;

(b) ondansetron or a pharmaceutically acceptable salt thereof;

(c) a combination of enhancers comprising:

(i) DMSO;

(ii) a glycol;

(iii) an FD enhancer comprising one or more of a fatty acid, a fatty alcohol, a fatty acid derivative, and a fatty alcohol derivative, and combinations thereof.

34. A drug-in-adhesive patch for transdermal administration of ondansetron to a human subject, wherein said transdermal administration having ondansetron rapid onset and ondansetron sustained release, said patch comprising the formulation of claim 33.

35. The patch of claim 34, wherein an adhesive layer of the patch is formed as a matrix from said formulation.

36. The formulation of claim 33, wherein the FD enhancer is a fatty acid derivative or a fatty alcohol derivative, or combinations thereof, and further wherein the fatty acid derivative or fatty alcohol derivative consists of a substituted fatty acid moiety, or a substituted fatty alcohol moiety that comprises one or more additional group, wherein the additional group comprises one or more of hydroxyl, ethyl, methyl, propyl, butyl, and glyceryl, and wherein the fatty acid moiety or the fatty alcohol moiety of the FD enhancer has a carbon chain length from C4 to C26.

37. The formulation of claim 33, wherein the FD enhancer comprises a fatty acid or fatty alcohol, the fatty acid or fatty alcohol comprising one or more of: butyric acid (C4:0), isobutyric acid (C4:0), valeric acid (C5:0), isovaleric acid (C5:0), levulinic acid (C5:0), caproic acid (C6:0), caprylic acid (C8:0), capric acid (C10:0), lauric acid (C12:0), myristic acid (C14:0), palmitic acid (C16:0), stearic acid (C18:0), and isostearic acid (C18:0), 5-dodecenoic acid (C12:1), 7-tetradecenoic acid (14:1), palmitoleic acid (16:1), oleic acid (C18:1), vaccenic acid (C18:1), elaidic acid (C18:1), paullinic acid (C20:1), gondoic acid (C20:1), erucic acid (C22:1), 15-docosenoic acid (C22:1), 17-tetracosenoic acid (24:1), nervonic acid (C24:1), and ximenic acid (C26:1), hexadecatrienoic acid (16:3), linoleic acid (C18:2), rumenic acid (C18:2), alpha-linolenic acid (C18:3), gamma-linolenic acid (C18:3), calendic acid (C18:3), stearidonic acid (C18:4) mead acid (C20:3), eicosadienoic acid (C20:3), eicosatrienoic acid (C20:3), dihomo-gamma-linolenic acid (C20:3), arachidonic acid (C20:4), docosadienoic acid (C22:2), adrenic acid (C22:4), osbond acid (C22:5), tetracosatetraenoic acid (C24:4), and tetracosapentaenoic acid (C24:5), butanol (C4), tert-

Butyl alcohol (C4), tert-Amyl alcohol (C5), 3-Methyl-3-pentanol (C6), capryl alcohol (C8), pelargonic alcohol (C9), capric alcohol (C10), Undecyl alcohol (C11), Lauryl alcohol (C12), Tridecyl alcohol (C13), Myristyl alcohol (C14), Pentadecyl alcohol (C15), Cetyl alcohol (C16), Palmitoleyl alcohol (cis-9-hexadecen-1-ol, $C_{16}H_{32}O$), Heptadecyl alcohol (1-n-heptadecanol, C17H36O), Stearyl alcohol (C18), Oleyl alcohol ($C_{18}H_{36}O$), linoleyl alcohol ($C_{18}H_{34}O$, cis,cis-9,12-Octadecadien-1-ol), Nonadecyl alcohol (C19), Arachidyl alcohol (C20H42O), Heneicosyl alcohol (C21), Behenyl alcohol ($C_{22}H_{46}O$), Erucyl alcohol (cis-13-docosen-1-ol, C22H44O), Lignoceryl alcohol (C24), Ceryl alcohol (C26), octyldodecanol ($C_{20}H_{42}O$, 2-Octyldodecan-1-ol).

38. The formulation of claim 33, wherein the FD enhancer comprises a saturated fatty acid, the saturated fatty acid comprising one or more of: butyric acid (C4:0), isobutyric acid (C4:0), valeric acid (C5:0), isovaleric acid (C5:0), levulinic acid (C5:0), caproic acid (C6:0), caprylic acid (C8:0), capric acid (C10:0), lauric acid (C12:0), myristic acid (C14:0), palmitic acid (C16:0), stearic acid (C18:0), and isostearic acid (C18:0).

39. The formulation of claim 33, wherein the FD enhancer comprises a monounsaturated fatty acid, the monounsaturated fatty acid comprising one or more of: 5-dodecenoic acid (C12:1), 7-tetradecenoic acid (14:1), palmitoleic acid (16:1), oleic acid (C18:1), vaccenic acid (C18:1), elaidic acid (C18:1), paullinic acid (C20:1), gondoic acid (C20:1), erucic acid (C22:1), 15-docosenoic acid (C22:1), 17-tetracosenoic acid (24:1), nervonic acid (C24:1), and ximenic acid (C26:1).

40. The formulation of claim 33, wherein the FD enhancer comprises a polyunsaturated fatty acid, the polyunsaturated fatty acid comprising one or more of: hexadecatrienoic acid (16:3), linoleic acid (C18:2), rumenic acid (C18:2), alpha-linolenic acid (C18:3), gamma-linolenic acid (C18:3), calendic acid (C18:3), stearidonic acid (C18:4) mead acid (C20:3), eicosadienoic acid (C20:3), eicosatrienoic acid (C20:3), dihomo-gamma-linolenic acid (C20:3), arachidonic acid (C20:4), docosadienoic acid (C22:2), adrenic acid (C22:4), osbond acid (C22:5), tetracosatetraenoic acid (C24:4), and tetracosapentaenoic acid (C24:5).

41. The formulation of claim 33, wherein the FD enhancer comprises a fatty alcohol, the fatty alcohol comprising one or more of: butanol (C4), tert-Butyl alcohol (C4), 2-butanol, isobutanol, tert-butanol, tert-Amyl alcohol (C5), 3-Methyl-3-pentanol (C6), capryl alcohol (C8), pelargonic alcohol (C9), capric alcohol (C10), Undecyl alcohol (C11), Lauryl alcohol (C12), Tridecyl alcohol (C13), Myristyl alcohol (C14), Pentadecyl alcohol (C15), Cetyl alcohol (C16), Palmitoleyl alcohol (cis-9-hexadecen-1-ol, $C_{16}H_{32}O$), Heptadecyl alcohol (1-n-heptadecanol, $C_{17}H_{36}O$), Stearyl alcohol (C18), Oleyl alcohol ($C_{18}H_{36}O$), linoleyl alcohol ($C_{18}H_{34}O$, cis,cis-9,12-Octadecadien-1-ol), Nonadecyl alcohol (C19), Arachidyl alcohol ($C_{20}H_{42}O$), Heneicosyl alcohol (C21), Behenyl alcohol ($C_{22}H_{46}O$),

Erucyl alcohol (cis-13-docosen-1-ol, $C_{22}H_{44}O$), Lignoceryl alcohol (C24), Ceryl alcohol (C26), octyldodecanol ($C_{20}H_{42}O$, 2-Octyldodecan-1-ol).

42. The formulation of claim 33, wherein the FD enhancer comprises one or more fatty acid derivative, the fatty acid derivative comprising one or more of: ethyl oleate, methyl oleate, decyloleate, oleyl oleate, glyceryl monooleate, isopropyl palmitate (ester of isopropyl alcohol and palmitic acid), isopropyl myristate, methyl laurate (lauric acid methyl ester), glyceryl laurate (lauric acid glyceryl ester, monolaurin, glycerol monolaurate), propylene glycol monolaurate type I, propylene glycol monolaurate type II (e.g. lauroglycol™90), lauryl lactate (ester of lauryl alcohol and lactic acid), and butyl acetate.

43. The formulation of claim 33, further comprising a solvent, the solvent comprising one or more of: diethylene glycol monoethyl ether (DEGEE), Span 20®, Span®40, Span® 60, Span®80, Span®83, Span®85, Span®120, Tween 20®, Tween 21®, Tween 40®, Tween 60®, Tween 61®, Tween 65®, Tween 80®, and hexylengycol.

44. The formulation of claim 33, further comprising one or more additional enhancer, the additional enhancer comprising one or more of: ethanol, propanol, decylmethyl sulfoxide, dimethylformamide, azone, urea, dimethylacetamide, a pyrrolidone derivative, 1-methyl-4-carboxy-2-pyrrolidone, 1-methyl-2-pyrrolidone, 1-lauryl-4-methoxycarbonyl-2-pyrrolidone, a polyol, propylene glycol, polyethylene glycol, a terpene, menthol, limonene, terpineol, pinene, carvol, a surfactant, a nonionic surfactant, a cationic surfactant, an anionic surfactant, Brij®, sodium lauryl sulfate, ethyl acetate, methyl acetate, octisalate, pentadecalactone, Hydramol™ PGPL and acrylamide.

45. The formulation of claim 33, further comprising a polymer, the polymer comprising one or more of: a cellulose polymer, hydroxypropylcellulose (HPMC), a Klucel™ polymer, Klucel™ HF, Klucel™ MF, Klucel™ GF, Klucel™ JF, Klucel™ EF, Klucel™ ELF, an HPMC derivative, a cellulose ether, a METHOCEL™ cellulose ether, METHOCEL™ E, METHOCEL™ F, METHOCEL™ J, METHOCEL™ K, Methocel™ 40-0101, METHOCEL™ 40-0202, METHOCEL™ E4M PRM, METHOCEL™ E50 PRM, METHOCEL™ 856N, METHOCEL™ K100M PRM, a carboxymethylcellulose (CMC), a WALOCEL™ polymer, WALOCEL™ CRT 1000, WALOCEL™ CRT 2000, WALOCEL™ CRT 10000, WALOCEL™ CRT 15000, WALOCEL™ CRT 30000, WALOCEL™ CRT 40000, WALOCEL™ CRT 50000, WALOCEL™ CRT 60000, polyvinylpyrrolidone (PVP), acrylic acid derivatives, a Plastoid® polymer, Plastoid®B, , an Eudragit® polymer, Eudragit® L-100, Eudragit® L100-55; Eudragit® L30 D-55; Eudragit® L12,5; Eudragit® S100; Eudragit® S12,5; Eudragit® FS30D; Eudragit® E100;

Eudragit® E12,5; Eudragit® EPO; Eudragit® S100; Eudragit® S12,5; Eudragit® FS30D; Eudragit® NE30D; Eudragit® NE40D; Eudragit® NM30D; Eudragit® RLPO; Eudragit® RL100; Eudragit® RL30D; Eudragit® RL12,5; Eudragit® RSPO; Eudragit® RS100; Eudragit® RS30D; Eudragit® RS12,5; PlasACRYL™ HTP20; PlasACRYL™ T20; Acryl-EZE®.

46. The formulation of claim 33, further comprising a polymer, wherein the polymer is an acetyl- and succinoyl-substituted amphiphilic polymer (AS-substituted polymer), wherein the AS-substituted polymer comprises one or more of: an acetyl- and succinoyl-substituted cellulosic polymer which is insoluble in acidic aqueous solutions and soluble in dilute caustic solution; an acetyl- and succinoyl-substituted cellulosic polymer which is insoluble in acidic aqueous solutions and soluble in both dilute caustic solution and acetone; an acetyl- and succinoyl-substituted cellulosic polymer which is insoluble in acidic aqueous solutions and soluble in both dilute caustic solution and methanol; an acetyl- and succinoyl-substituted cellulosic polymer which is insoluble in acidic aqueous solutions and soluble in each of dilute caustic solution, acetone and methanol; a hydroxypropylcellulose acetate succinate or hypromellose acetate succinate (HPMC-AS); a HPMC-AS wherein the acetyl, succinoyl, methoxyl, and hydroxypropoxy content in %(wt) is within the following ranges: from about 4 to about 15% acetyl, about 2 to about 20% succinoyl, about 15 to about 30% methoxyl, and about 3 to about 12% hydroxypropoxy, from about 5 to about 13% acetyl, about 8 to about 16% succinoyl, about 19 to about 27% methoxyl, and about 3 to about 11% hydroxypropoxy, from about 5 to about 9% acetyl, about 14 to about 18% succinoyl, about 20 to about 24% methoxyl, and about 5 to about 9% hydroxypropoxy, or from about 7 to about 11% acetyl, about 10 to about 14% succinoyl, about 21 to about 25% methoxyl, and about 5 to about 9% hydroxypropoxy, or from about 10 to about 14% acetyl, about 4 to about 8% succinoyl, about 22 to about 26% methoxyl, and about 6 to about 10% hydroxypropoxy; AquaSolve™ HPMCAS-LF; AquaSolve™ HPMCAS-LG; AquaSolve™ HPMCAS-MF; AquaSolve™ HPMCAS-MG; AquaSolve™ HPMCAS-HF; AquaSolve™ HPMCAS-HG.

47. The formulation of claim 33, wherein the polyacrylic adhesive comprises a self crosslinkable acrylic adhesive, the adhesive comprising one or more of: Duro-Tak® 3872516, Duro-Tak® 387-2051, Duro-Tak® 87-2852, Duro-Tak® 87-2194, Duro-Tak® 872852, GELVA® 737, GELVA® 2655, and GELVA® 1753.

48. The formulation of claim 33, wherein the formulation is characterized by:

(a) a minimum predetermined flux within a first predetermined amount of time;

(b) a preferred predetermined flux within a second predetermined amount of time; and

(c) maintenance of the preferred predetermined flux within a predetermined range for a third predetermined amount of time.

49. The formulation of claim 48, wherein the minimum predetermined flux is about 30 $\mu g/cm^2$/hour.

50. The formulation of claim 48, wherein the preferred predetermined flux is about 90 $\mu g/cm^2$/hour.

51. The formulation of claim 48, wherein the first predetermined amount of time is not greater than 90 minutes.

52. The formulation of claim 48, wherein the second predetermined amount of time is not greater than 12 hours.

53. The formulation of claim 48, wherein the third predetermined amount of time is at least two days.

54. The patch of claim 34, wherein ondansetron is present in the form of a hydrochloride salt.

55. The patch of claim 34, wherein the patch is characterized by:

(a) a minimum predetermined flux within a first predetermined amount of time;

(b) a preferred predetermined flux within a second predetermined amount of time; and

(c) maintenance of the preferred flux within a predetermined range for a third predetermined amount of time.

56. The patch of claim 34, wherein the minimum predetermined flux is about 2.5 $\mu g/cm^2$/hour.

57. The patch of claim 34, wherein the preferred predetermined flux is about 5 $\mu g/cm^2$/hour.

58. The patch of claim 34, wherein the first predetermined amount of time is not greater than 90 minutes.

59. The patch of claim 34, wherein the second predetermined amount of time is not greater than 12 hours.

60. The patch of claim 34, wherein the third predetermined amount of time is at least two days.

61. The patch of claim 34, wherein the patch provides a preferred predetermined flux of about 5 $\mu g/cm^2$/hour as measured in 12 hour time intervals for at least two days.

62. The patch of claim 34, where the patch delivers at least 4 mg of ondansetron per day after application of the patch to the skin of a human subject.

63. The patch of claim 34, wherein the patch delivers at least 4 mg or more of ondansetron per day after application of the patch to the skin of a human subject for at least 2 days.

64. The formulation of claim 20, comprising:

(a) a polyacrylic adhesive;

(b) ondansetron or a pharmaceutically acceptable salt thereof;

(c) an enhancer component comprising:

(i) lactic acid, and

(ii) an FD enhancer selected from a fatty acid, a fatty alcohol, a fatty acid derivative, and a fatty alcohol derivative, and combinations thereof.

65. The formulation of claim 64, wherein the FD enhancer is a fatty acid derivative or a fatty alcohol derivative, or combinations thereof, and further wherein the fatty acid derivative or fatty alcohol derivative consists of a substituted fatty acid moiety, or a substituted fatty alcohol moiety that comprises one or more additional group, wherein the additional group comprises one or more of hydroxyl, ethyl, methyl, propyl, butyl, and glyceryl, and wherein the fatty acid moiety or the fatty alcohol moiety of the FD enhancer has a carbon chain length from C4 to C26.

66. The formulation of claim 64, wherein the enhancer component further includes DMSO.

67. The formulation of claim 64, further comprising a surfactant.

68. The formulation of claim 64, further comprising an amphiphilic polymer.

69. The formulation of claim 20, wherein the formulation is characterized by:

(a) a minimum predetermined flux within a first predetermined amount of time;

(b) a preferred predetermined flux within a second predetermined amount of time;

(c) maintenance of the preferred flux within a predetermined range for a third predetermined amount of time.

70. The formulation of claim 69, wherein the minimum predetermined flux is about 2.5 $\mu g/cm^2$/hour.

71. The formulation of claim 69, wherein the preferred predetermined flux is about 90 $\mu g/cm^2$/hour.

72. The formulation of claim 69, wherein the first predetermined amount of time is not more than 90 minutes.

73. The formulation of claim 69, wherein the second predetermined amount of time not more

than 12 hours.

74. The formulation of claim 69, wherein the third predetermined amount of time is at least two days.

75. The formulation of claim 64, further comprising one or more of: ethanol, propanol, decylmethyl sulfoxide, dimethylformamide, azone, urea, dimethylacetamide, a pyrrolidone derivative, 1-methyl-4-carboxy-2-pyrrolidone, 1-methyl-2-pyrrolidone, 1-lauryl-4-methoxycarbonyl-2-pyrrolidone, a terpene, menthol, limonene, terpineol, pinene, carvol, ethyl acetate, methyl acetate, octisalate, pentadecalactone, and acrylamide.

76. The formulation of claim 64, further comprising an amphiphilic polymer.

77. The formulation of claim 76, wherein the amphiphilic polymer is selected from a cellulose polymer, hydroxypropylcellulose (HPMC), an acetyl- and succinoyl-substituted cellulosic polymer, AquaSolve™ HPMCAS-LF; AquaSolve™ HPMCAS-LG; AquaSolve™ HPMCAS-MF; AquaSolve™ HPMCAS-MG; AquaSolve™ HPMCAS-HF; AquaSolve™ HPMCAS-HG, a Klucel™ polymer, Klucel™ HF, Klucel™ MF, Klucel™ GF, Klucel™ JF, Klucel™ EF, Klucel™ ELF, an HPMC derivative, a cellulose ether, a METHOCEL™ cellulose ether, METHOCEL™ E, METHOCEL™ F, METHOCEL™ J, METHOCEL™ K, Methocel™ 40-0101, METHOCEL™ 40-0202, METHOCEL™ E4M PRM, METHOCEL™ E50 PRM, METHOCEL™ 856N, METHOCEL™ K100M PRM, a carboxymethylcellulose (CMC), a WALOCEL™ polymer, WALOCEL™ CRT 1000, WALOCEL™ CRT 2000, WALOCEL™ CRT 10000, WALOCEL™ CRT 15000, WALOCEL™ CRT 30000, WALOCEL™ CRT 40000, WALOCEL™ CRT 50000, WALOCEL™ CRT 60000, polyvinylpyrrolidone (PVP), acrylic acid derivatives, a Plastoid® polymer, Plastoid®B, an Eudragit® polymer, Eudragit® L-100, Eudragit® L100-55; Eudragit® L30 D-55; Eudragit® L12,5; Eudragit® S100; Eudragit® S12,5; Eudragit® FS30D; Eudragit® E100; Eudragit® E12,5; Eudragit® EPO; Eudragit® S100; Eudragit® S12,5; Eudragit® FS30D; Eudragit® NE30D; Eudragit® NE40D; Eudragit® NM30D; Eudragit® RLPO; Eudragit® RL100; Eudragit® RL30D; Eudragit® RL12,5; Eudragit® RSPO; Eudragit® RS100; Eudragit® RS30D; Eudragit® RS12,5; PlasACRYL™ HTP20; PlasACRYL™ T20; Acryl-EZE®.

78. The formulation of claim 76, wherein the amphiphilic polymer is an acetyl- and succinoyl-substituted amphiphilic polymer (AS-substituted polymer), and further wherein the AS-substituted polymer comprises one or more of: an acetyl- and succinoyl-substituted cellulosic polymer which is insoluble in acidic aqueous solutions and soluble in dilute caustic solution; an acetyl- and succinoyl-substituted cellulosic polymer which is insoluble in acidic aqueous solutions and soluble in both dilute caustic solution and acetone; an acetyl- and succinoyl-substituted cellulosic polymer which is

insoluble in acidic aqueous solutions and soluble in both dilute caustic solution and methanol; an acetyl- and succinoyl-substituted cellulosic polymer which is insoluble in acidic aqueous solutions and soluble in each of dilute caustic solution, acetone and methanol; a hydroxypropylcellulose acetate succinate or hypromellose acetate succinate (HPMC-AS); a HPMC-AS wherein the acetyl, succinoyl, methoxyl, and hydroxypropoxy content in %(wt) is within the following ranges: from about 4 to about 15% acetyl, about 2 to about 20% succinoyl, about 15 to about 30% methoxyl, and about 3 to about 12% hydroxypropoxy, from about 5 to about 13% acetyl, about 8 to about 16% succinoyl, about 19 to about 27% methoxyl, and about 3 to about 11% hydroxypropoxy, from about 5 to about 9% acetyl, about 14 to about 18% succinoyl, about 20 to about 24% methoxyl, and about 5 to about 9% hydroxypropoxy, or from about 7 to about 11% acetyl, about 10 to about 14% succinoyl, about 21 to about 25% methoxyl, and about 5 to about 9% hydroxypropoxy, or from about 10 to about 14% acetyl, about 4 to about 8% succinoyl, about 22 to about 26% methoxyl, and about 6 to about 10% hydroxypropoxy; AquaSolve™ HPMCAS-LF; AquaSolve™ HPMCAS-LG; AquaSolve™ HPMCAS-MF; AquaSolve™ HPMCAS-MG; AquaSolve™ HPMCAS-HF; AquaSolve™ HPMCAS-HG.

79. The formulation of claim 64, wherein the polyacrylic adhesive comprises a self crosslinkable acrylic adhesive, the adhesive comprising one or more of: Duro-Tak® 87-9301, Duro-Tak® 387-2516, Duro-Tak® 387-2051, Duro-Tak® 87-2852, Duro-Tak® 87-2194, Duro-Tak® 87-2852, GELVA® 737, GELVA® 2655, and GELVA® 1753.

80. The formulation of claim 64, wherein the first predetermined time period is the time period required to reach a minimum predetermined flux of 30 $\mu g/cm^2/h$, and further wherein the first predetermined time period is from about 30 minutes to about 6 hours.

81. The formulation of claim 80, wherein the first predetermined time period is about 1 to about 3 hours.

82. A drug-in-adhesive patch for transdermal administration of ondansetron to a human subject, wherein said transdermal administration having ondansetron rapid onset and ondansetron sustained release, said patch comprising the formulation of claim 64.

83. The patch of claim 82 wherein the patch is characterized by:

(a) a minimum predetermined flux within a first predetermined amount of time;

(b) provides a preferred predetermined flux within a second predetermined amount of time; and

(c) maintenance of the preferred flux within a predetermined range for a third predetermined amount of time.

84. The patch of claim 82, wherein the minimum predetermined flux is about 15 μg/cm^2/h.

85. The patch of claim 82, wherein the preferred predetermined flux is about 30 μg/cm^2/h.

86. The patch of claim 82, wherein the first predetermined amount of time is 90 minutes or less.

87. The patch of claim 82, wherein the second predetermined amount of time is within 12 hours.

88. The patch of claim 82, wherein the third predetermined amount of time is at least two days.

89. The patch of claim 82, wherein the patch provides a steady state flux of about 30 μg/cm^2/h as measured in 12 hour time intervals for at least two days.

90. The patch of claim 82, where the patch delivers 4 mg or more of ondansetron per day after application of the patch to the skin of a human subject.

91. The patch of claim 82, wherein the patch delivers 4 mg or more of ondansetron per day after application of the patch to the skin of a human subject for at least 2 days.

92. The patch of claim 83, wherein the first predetermined time period is the time period required to reach at least a minimum predetermined flux of 2.5 μg/cm^2/hour, and further wherein the first predetermined time period is from about 30 minutes to about 6 hours.

93. The patch of claim 92, wherein the first predetermined time period is about 1 to about 3 hours.

94. The patch of claim 83, wherein the preferred flux is about 2.5 μg/cm^2/hour.

95. The formulation of claim 83, wherein the preferred flux is about 30 μg/cm^2/hour.

96. The formulation of claim 83, wherein the formulation provides a preferred flux that is substantially maintained for at least 2 days, and wherein the preferred flux is between 3 μg/cm^2/hour and 8 μg/cm^2/hour.

97. The patch of claim 83, wherein ondansetron is present at least partially in the form of its lactate salt.

98. A method of forming a transdermal patch for treatment of nausea, vomiting, or chemotherapy induced nausea and vomiting, said method comprising

(a) providing a formulation comprising:

(i) ondansetron or a pharmaceutically accpetable salt thereof,

(ii) one or more amphiphilic polymer,

(iii) one or more enhancer, and

(iv) one or more solvent;

(b) adding a polyacrylic adhesive to the formulation to form an admixture;

(c) solvent-casting of a sufficient volume of the admixture to form one or more drug-in-adhesive layers in the resulting transdermal patch;

wherein the drug-in-adhesive layer in the transdermal patch is sandwiched between a backing layer, a release liner, and optionally one or more membrane between multiple drug-in-adhesive layers.

99. A method of forming a transdermal patch for treatment of nausea, vomiting, or chemotherapy induced nausea and vomiting, said method comprising

(a) providing a formulation comprising:

(i) a polyacrylic adhesive,

(i) ondansetron or a pharmaceutically acceptable salt thereof,

(iii) a plurality of enhancers comprising:

(A) DMSO,

(B) a glycol, and

(C) an FD enhancer, and

(iv) one or more solvent;

(b) adding a polyacrylic adhesive to the formulation to form an admixture;

(c) solvent-casting of a sufficient volume of the admixture to form one or more drug-in-adhesive layers in the resulting transdermal patch;

wherein the drug-in-adhesive layer in the transdermal patch is sandwiched between a backing layer, a release liner, and optionally one or more membrane between multiple drug-in-adhesive layers.

100. The method of claim 99, wherein the FD enhancer comprises one or more of a fatty acid, a fatty alcohol, a fatty acid derivative, and a fatty alcohol derivative, wherein the fatty acid moiety or the fatty alcohol moiety of the FD enhancer has a carbon chain length from C4 to C26.

101. A method of forming a transdermal patch for treatment of nausea and/or vomiting, said method comprising

(a) providing a formulation comprising:

(i) a polyacrylic adhesive,

(i) a base salt form of ondansetron,

(ii) an enhancer component comprising DMSO, lactic acid, and an FD enhancer,

and

(b) solvent-casting of the formulation to form one or more drug-in-adhesive layers in a resulting transdermal patch.

102. The method of claim 101, wherein the FD enhancer is selected from a fatty acid, a fatty alcohol, a fatty acid derivative, and a fatty alcohol derivative, wherein the fatty acid derivative or fatty alcohol derivative consists of a substituted fatty acid moiety, or a substituted fatty alcohol moiety, and wherein the fatty acid moiety or the fatty alcohol moiety of the FD enhancer has a carbon chain length from C4 to C26, and wherein the patch is formed from one or more drug-in-adhesive layers by solvent casting, and in the resulting patch, the one or more layers are positioned between a backing layer, a release liner.

103. A method to treat nausea, vomiting, or chemotherapy induced nausea and vomiting in a subject, the method comprising:

(a) providing a transdermal patch comprising one or more drug-in-adhesive layer situated between a backing layer and a release liner, and optionally one or more membrane between a plurality of drug-in- adhesive layers, and wherein each of the one or more drug-in-adhesive layer of the transdermal patch comprises:

(i) a polyacrylic adhesive,

(ii) ondansetron or a pharmaceutically acceptable salt thereof,

(iii) one or more enhancer,

(iv) one or more solvent, and

(v) an amphiphilic polymer; and

(b) applying the transdermal patch to the skin of a subject in need thereof.

104. A method to treat nausea, vomiting, or chemotherapy induced nausea and vomiting in a subject, the method comprising:

(a) providing a transdermal patch comprising one or more drug-in-adhesive layer situated between a backing layer and a release liner, and optionally one or more membrane between a plurality of drug-in-adhesive layers, and wherein each of the one or more drug-in-adhesive layer of the transdermal patch is formed from a matrix from a formulation comprising:

(i) a polyacrylic adhesive,

(ii) ondansetron or a pharmaceutically acceptable salt thereof,

(iii) a plurality of enhancers, which comprises:

(A) DMSO,

(B) a glycol, and

(C) an FD enhancer,

(iv) one or more solvent, and

(v) an amphiphilic polymer; and

(b) applying the transdermal patch to the skin of a subject in need thereof.

105. The method of claim 104, wherein the FD enhancer comprises one or more of a fatty acid, a fatty alcohol, a fatty acid derivative, and a fatty alcohol derivative, wherein the fatty acid moiety or the fatty alcohol moiety of the FD enhancer has a carbon chain length from C4 to C26.

106. A method to treat nausea, vomiting, and/or chemotherapy induced nausea and vomiting in a subject, the method comprising:

(a) providing a transdermal patch comprising one or more drug-in-adhesive layer of the transdermal patch is formed from a matrix from a formulation comprising:

(i) a polyacrylic adhesive,

(ii) ondansetron base salt, and

(iii) an enhancer component; and

(b) applying the transdermal patch to the skin of a subject in need thereof.

107. The method of claim 106, wherein the enhancer component comprises DMSO, lactic acid, and an FD enhancer.

108. The method of claim 107, wherein the FD enhancer is selected from a fatty acid, a fatty alcohol, a fatty acid derivative, and a fatty alcohol derivative, wherein the fatty acid derivative or fatty alcohol derivative consists of a substituted fatty acid moiety, or a substituted fatty alcohol moiety, and wherein the fatty acid moiety or the fatty alcohol moiety of the FD enhancer has a carbon chain length from C4 to C26, and wherein the patch comprises one or more drug-in-adhesive layers which are positioned between a backing layer and a release liner.

109. A method of treating nausea or vomiting in a human subject, the method comprising the steps of:

(a) applying a patch of claim 82 to the human subject;

(b) achieving a minimum level of efficacy for treating nausea or vomiting in the human subject within a first predetermined amount of time;

(c) achieving a preferred level of efficacy for treating nausea or vomiting in the human subject within a second predetermined amount of time; and

(d) maintaining the preferred level of efficacy within a predetermined range for treating nausea or vomiting in the human subject for a third predetermined amount of time.

110. The method of claim 109, further wherein the first predetermined amount of time is less than about an hour.

111. The method of claim 109, further wherein the first predetermined amount of time is less than about thirty minutes.

112. The method of claim 109, further wherein the second predetermined amount of time is less than about 5 hours.

113. 45. The method of claim 109, further wherein the second predetermined amount of time is less than about 3 hours.

114. The method of claim 109, further wherein the third predetermined amount of time is at least 2 days.

115. The method of claim 109, further wherein the third predetermined amount of time is at least 5 days.

116. The method of claim 109, further wherein the third predetermined amount of time is at least 7 days.

117. The method of claim 109, further wherein the third predetermined amount of time is at least 14 days.

118. The method claim 109, wherein the minimum level of efficacy is achieved when at least 4 mg of ondansetron have been delivered to the human subject.

119. The method claim 109, wherein the preferred level of efficacy is achieved when at least 8 mg of ondansetron have been delivered to the human subject.

120. A method of delivering ondansetron from a formulation, or from a patch formed therefrom, to a human subject in need of ondansetron delivery, wherein ondansetron is present in amorphous form.

121. The method of claim 120, wherein the formulation comprises an amphiphilic polymer.

122. The method of claim 121, wherein the amphiphilic polymer is selected from one or more of: a cellulose polymer, hydroxypropylcellulose (HPMC), an acetyl- and succinoyl-substituted cellulosic polymer, AquaSolve™ HPMCAS-LF; AquaSolve™ HPMCAS-LG; AquaSolve™ HPMCAS-MF; AquaSolve™ HPMCAS-MG; AquaSolve™ HPMCAS-HF; AquaSolve™

HPMCAS-HG, a Klucel™ polymer, Klucel™ HF, Klucel™ MF, Klucel™ GF, Klucel™ JF, Klucel™ EF, Klucel™ ELF, an HPMC derivative, a cellulose ether, a METHOCEL™ cellulose ether, METHOCEL™ E, METHOCEL™ F, METHOCEL™ J, METHOCEL™ K, Methocel™ 40-0101, METHOCEL™ 40-0202, METHOCEL™ E4M PRM, METHOCEL™ E50 PRM, METHOCEL™ 856N, METHOCEL™ K100M PRM, a carboxymethylcellulose (CMC), a WALOCEL™ polymer, WALOCEL™ CRT 1000, WALOCEL™ CRT 2000, WALOCEL™ CRT 10000, WALOCEL™ CRT 15000, WALOCEL™ CRT 30000, WALOCEL™ CRT 40000, WALOCEL™ CRT 50000, WALOCEL™ CRT 60000, polyvinylpyrrolidone (PVP), acrylic acid derivatives, a Plastoid® polymer, Plastoid®B, an Eudragit® polymer, Eudragit® L-100, Eudragit® L100-55; Eudragit® L30 D-55; Eudragit® L12,5; Eudragit® S100; Eudragit® S12,5; Eudragit® FS30D; Eudragit® E100; Eudragit® E12,5; Eudragit® EPO; Eudragit® S100; Eudragit® S12,5; Eudragit® FS30D; Eudragit® NE30D; Eudragit® NE40D; Eudragit® NM30D; Eudragit® RLPO; Eudragit® RL100; Eudragit® RL30D; Eudragit® RL12,5; Eudragit® RSPO; Eudragit® RS100; Eudragit® RS30D; Eudragit® RS12,5; PlasACRYL™ HTP20; PlasACRYL™ T20; Acryl-EZE®.

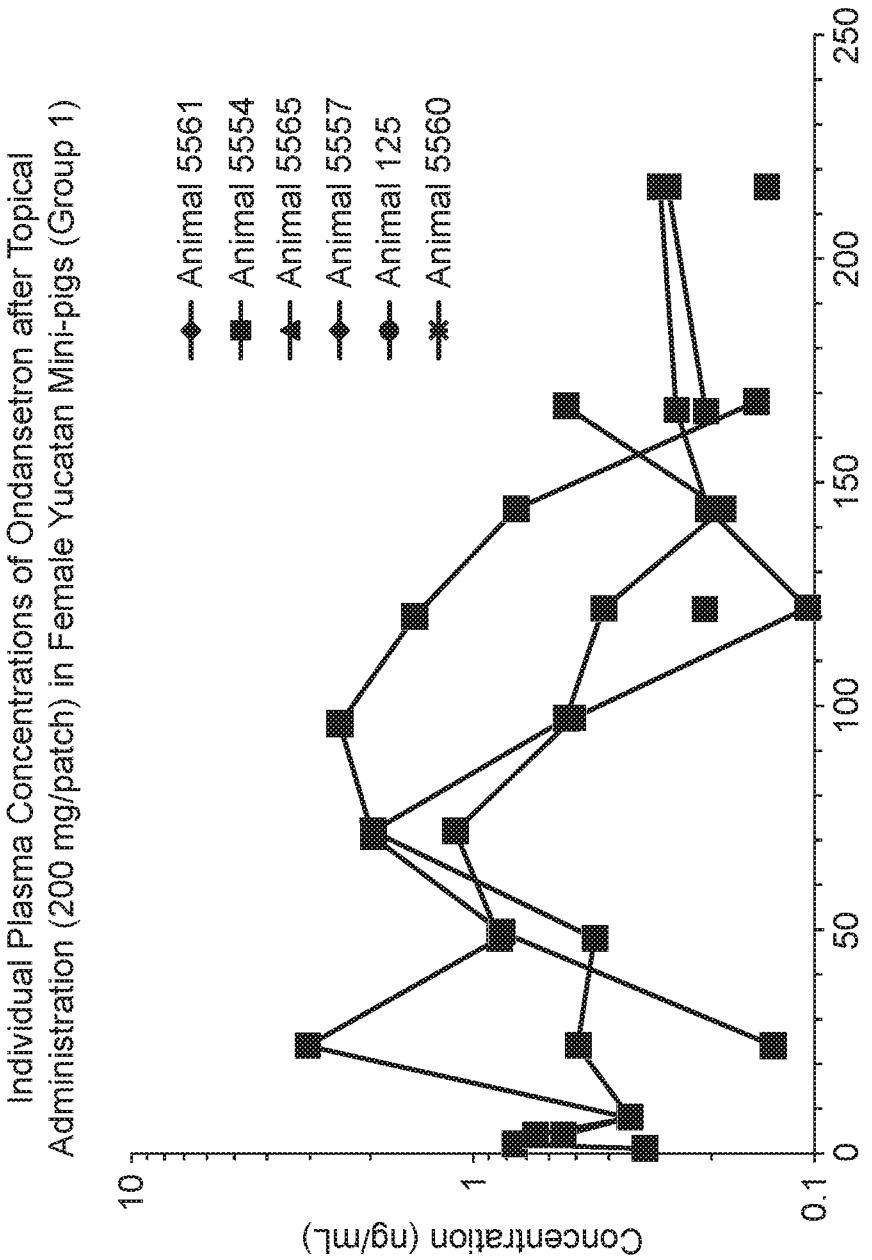

Individual Plasma Concentrations of Ondansetron after Topical Administration (200 mg/patch) in Female Yucatan Mini-pigs (Group 1)
Animal 5561
Animal 5554
Animal 5565
Animal 5557
Animal 125
Animal 5560
Concentration (ng/mL)
10
1
0.1
0
50
100
150
200
250
Time (hr)

FIG. 1

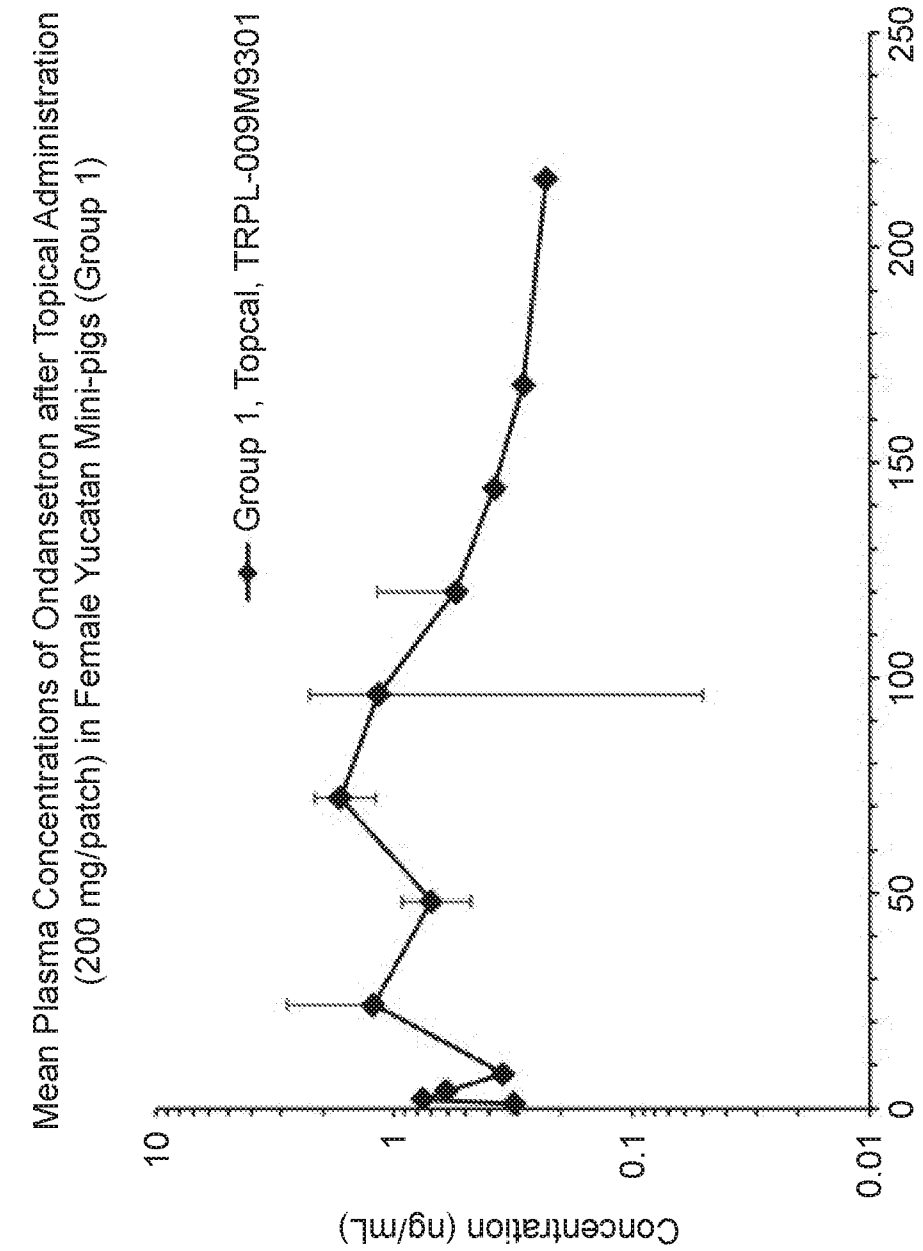

Mean Plasma Concentrations of Ondansetron after Topical Administration
(200 mg/patch) in Female Yucatan Mini-pigs (Group 1)
Group 1, Topcal, TRPL-009M9301
Concentration (ng/mL)
10
1
0.1
0.01
0
50
100
150
200
250
Time (hr)

FIG. 2

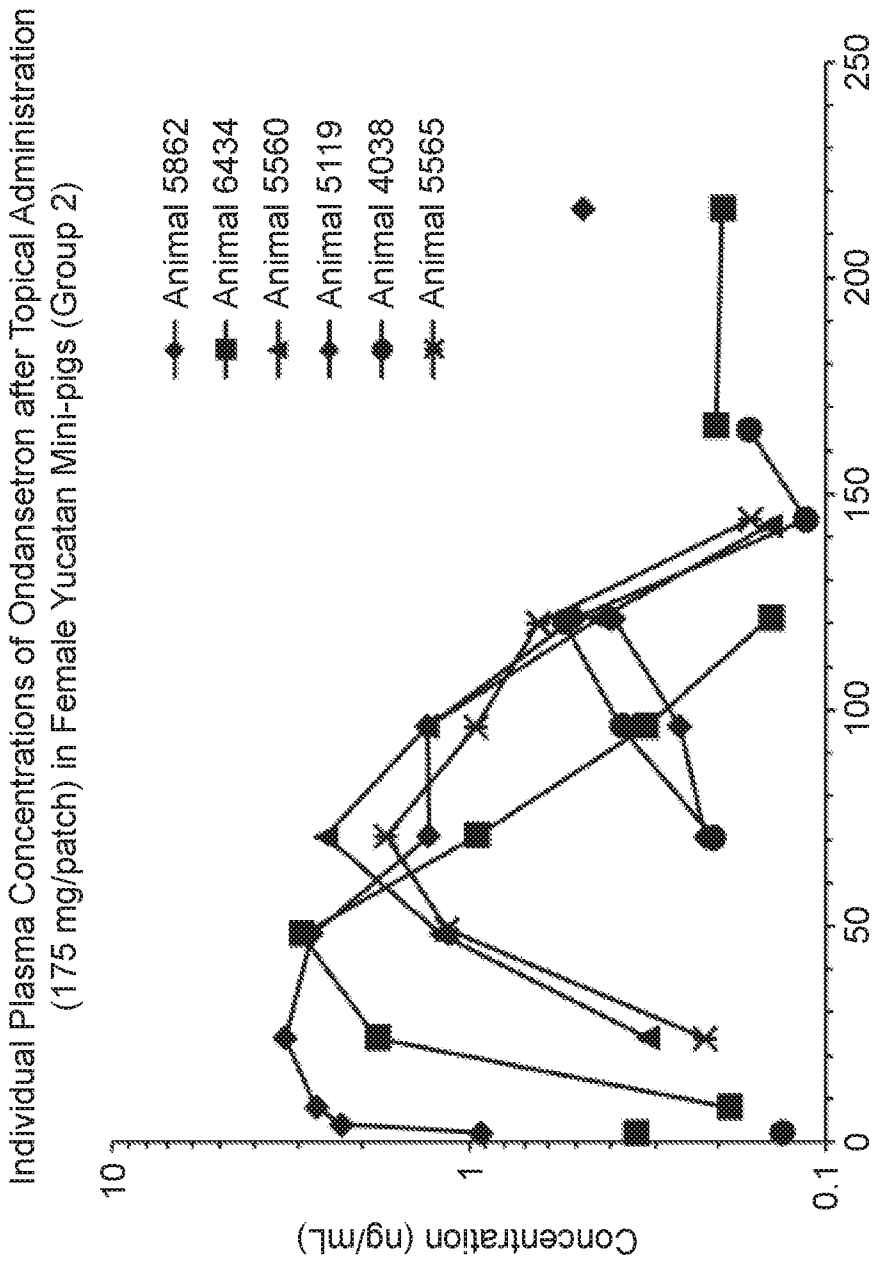

Individual Plasma Concentrations of Ondansetron after Topical Administration
(175 mg/patch) in Female Yucatan Mini-pigs (Group 2)
Animal 5862
Animal 6434
Animal 5560
Animal 5119
Animal 4038
Animal 5565
Concentration (ng/mL)
10
1
0.1
0
50
100
150
200
250
Time (hr)

FIG. 3

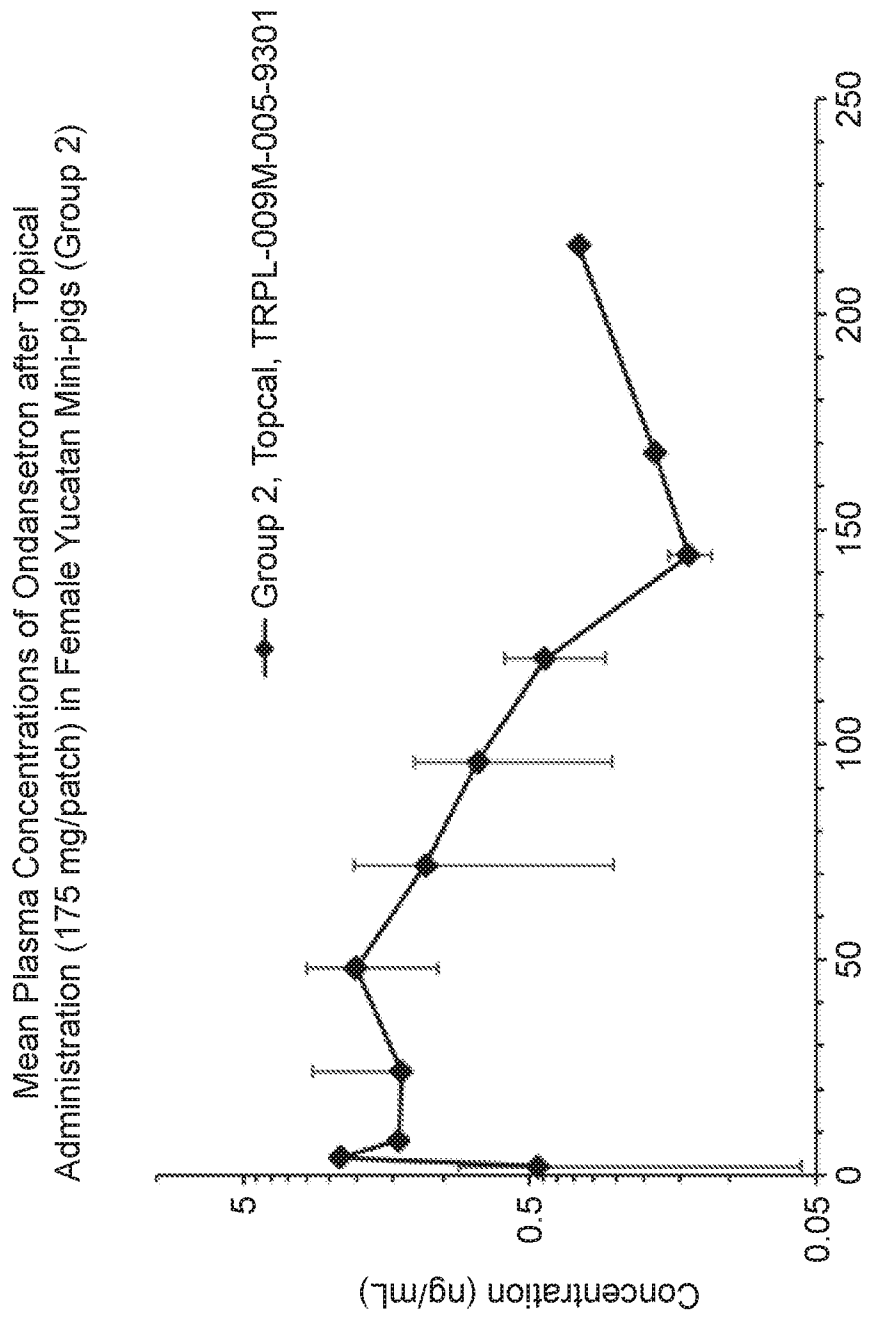

Mean Plasma Concentrations of Ondansetron after Topical Administration (175 mg/patch) in Female Yucatan Mini-pigs (Group 2)
Group 2, Topcal, TRPL-009M-005-9301
Concentration (ng/mL)
5
0.5
0.05
0
50
100
150
200
250
Time (hr)

FIG. 4

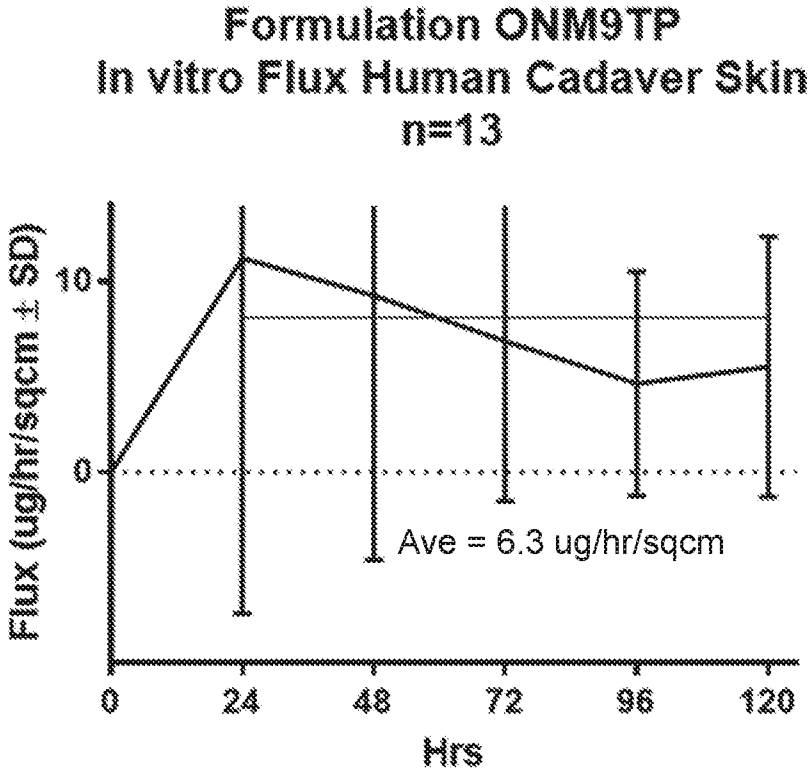

Formulation ONM9TP
In vitro Flux Human Cadaver Skin
n=13
Flux (ug/hr/sqcm ± SD)
10
0
Ave = 6.3 ug/hr/sqcm
0
24
48
72
96
120
Hrs

FIG. 5

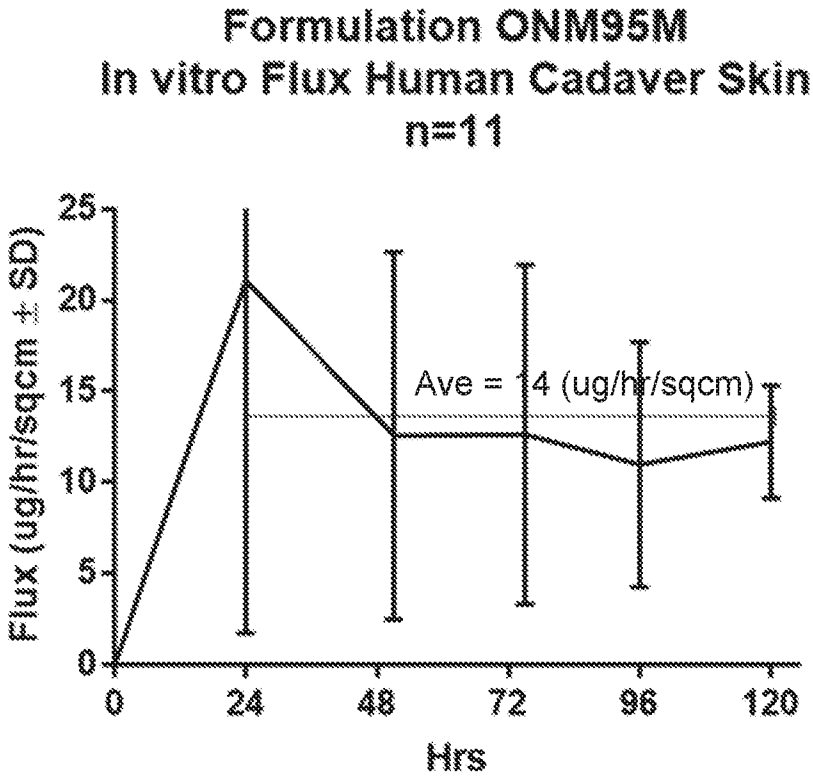

Formulation ONM95M
In vitro Flux Human Cadaver Skin
n=11
Flux (ug/hr/sqcm ± SD)
25
20
15
10
5
0
Ave = 14 (ug/hr/sqcm)
0
24
48
72
96
120
Hrs

FIG. 6

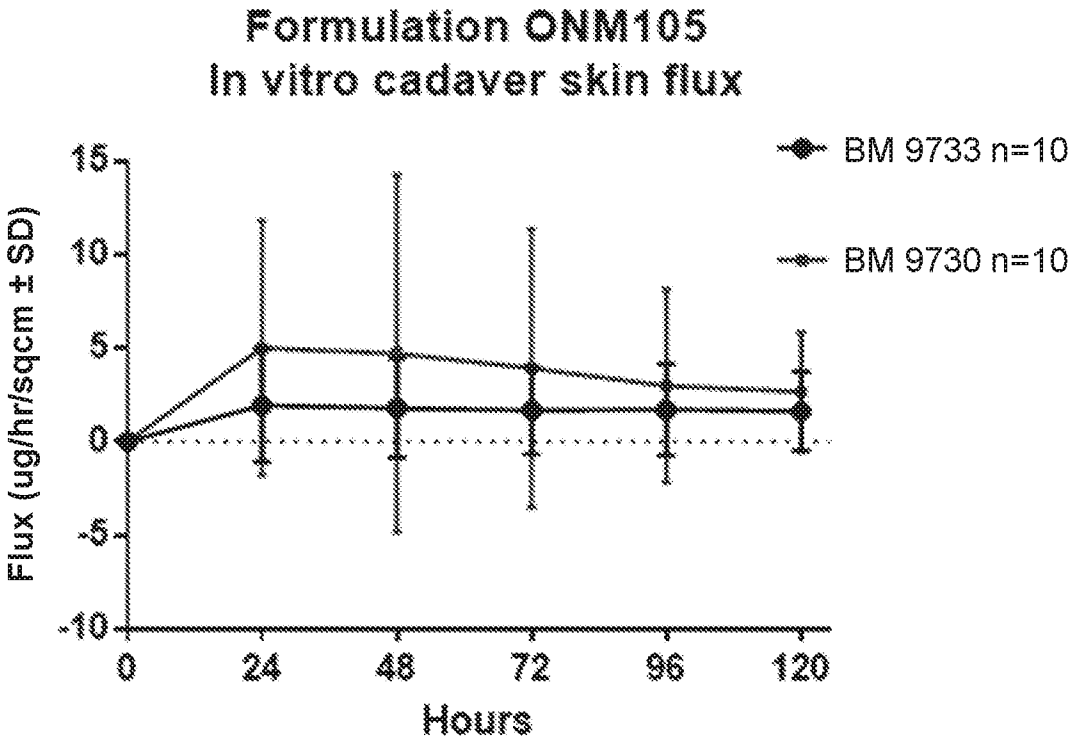

Formulation ONM105
In vitro cadaver skin flux
BM 9733 n=10
BM 9730 n=10
Flux (ug/hr/sqcm ± SD)
15
10
5
0
-5
-10
0
24
48
72
96
120
Hours

FIG. 7

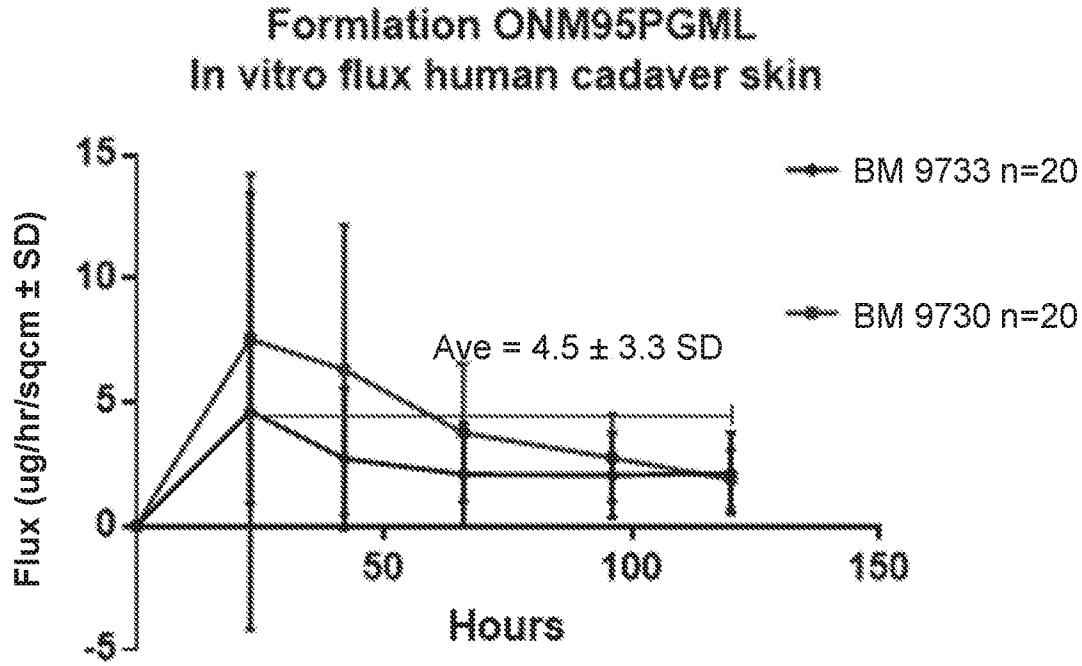

Formlation ONM95PGML
In vitro flux human cadaver skin
BM 9733 n=20
BM 9730 n=20
Ave = 4.5 ± 3.3 SD
Flux (ug/hr/sqcm ± SD)
15
10
5
0
-5
50
100
150
Hours

FIG. 8

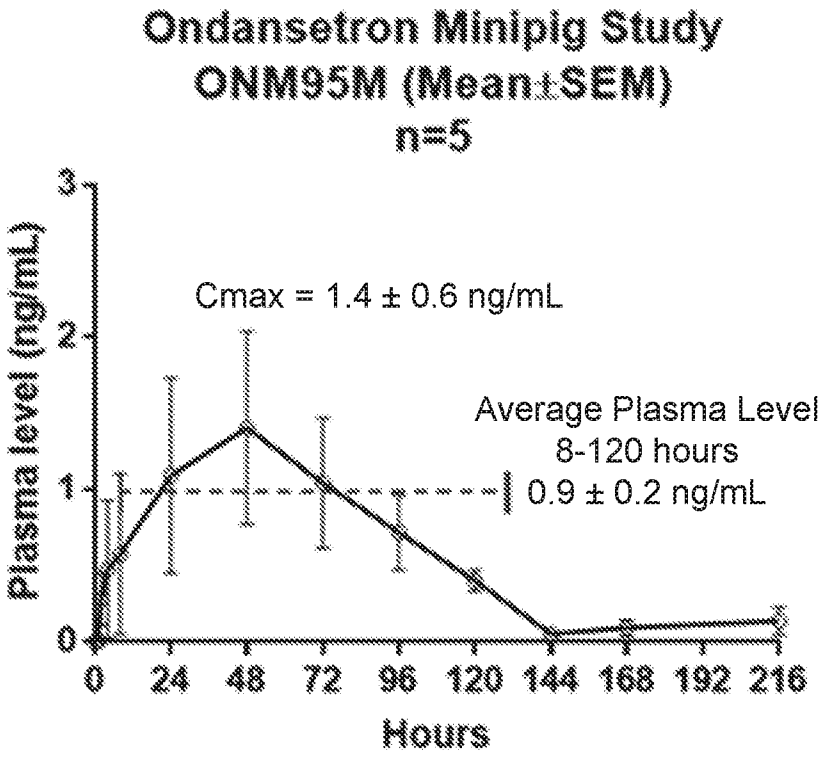

Ondansetron Minipig Study
ONM95M (Mean±SEM)
n=5
Plasma level (ng/mL)
Cmax = 1.4 ± 0.6 ng/mL
Average Plasma Level
8-120 hours
0.9 ± 0.2 ng/mL
0
1
2
3
0 24 48 72 96 120 144 168 192 216
Hours

FIG. 9A

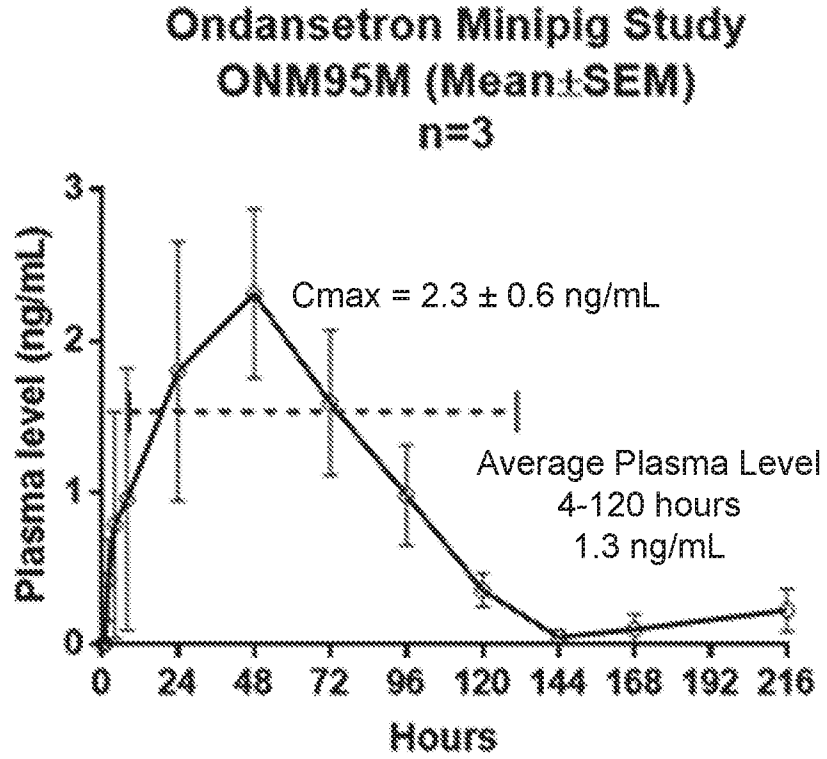

Ondansetron Minipig Study
ONM95M (Mean±SEM)
n=3
Plasma level (ng/mL)
Cmax = 2.3 ± 0.6 ng/mL
Average Plasma Level
4-120 hours
1.3 ng/mL
0
1
2
3
0 24 48 72 96 120 144 168 192 216
Hours

FIG. 9B

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/064751

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/70 A61K31/4178 A61K47/10 A61K47/12 A61K47/14
A61K47/20 A61P1/08
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 7 988 991 B2 (HISAMITSU PHARMACEUTICAL CO [JP]) 2 August 2011 (2011-08-02) example 9 example 10 -----	1-120
X	US 2008/004291 A1 (SINGH NIKHILESH N [US]) 3 January 2008 (2008-01-03) example 11 -----	1-120
X	WO 03/013482 A1 (STRAKAN GROUP LTD [GB]; KAMIYAMA FUMIO [JP] ET AL.) 20 February 2003 (2003-02-20) examples claims ----- -/--	1-120

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 January 2020	06/02/2020

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	S. von Eggelkraut-G.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/064751

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 163 902 A2 (PACIFIC CORP [KR]) 19 December 2001 (2001-12-19) examples figure 1 claims	1-120
X	WO 01/72282 A1 (CHONG KUN DANG PHARM CORP [KR]; HONG CHUNG IL [US] ET AL.) 4 October 2001 (2001-10-04) example 21	1-120
X	CHO JEONG-RAE ET AL: "Design of transdermal matrix patch containing ondansetron", JOURNAL OF KOREAN PHARMACEUTICAL SCIENCES, KOREAN SOCIETY OF PHARMACEUTICAL SCIENCES AND TECHNOLOGY, KOREA, vol. 46, no. 7, 18 August 2016 (2016-08-18), pages 677-684, XP036113091, ISSN: 2093-5552, DOI: 10.1007/S40005-016-0273-9 [retrieved on 2016-08-18] the whole document	1-120
X	Farsiya Fathima ET AL: "Formulation and Evaluation of Matrix-Type Transdermal Delivery System of Ondansetron Hydrochloride Using Solvent Casting Technique", Research J. Pharm. and Tech, 1 May 2011 (2011-05-01), XP055662557, Retrieved from the Internet: URL:https://www.researchgate.net/profile/Shashi_Ravi_Suman_Rudrangi/publication/271522356_Formulation_and_Evaluation_of_Matrix-Type_Transdermal_Delivery_System_of_Ondansetron_Hydrochloride_Using_Solvent_Casting_Technique/links/54cb559f0cf2c70ce525559a/Formulation-and-Evaluation-of-Matrix-Type-Transderma [retrieved on 2020-01-28] the whole document	1-120

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2019/064751

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 7988991 B2	02-08-2011	BR 0207955 A	25-02-2004
		CN 1499962 A	26-05-2004
		EP 1366762 A1	03-12-2003
		ES 2559666 T3	15-02-2016
		JP 4261911 B2	13-05-2009
		JP WO2002069942 A1	02-07-2004
		KR 20030080070 A	10-10-2003
		US 2004096491 A1	20-05-2004
		WO 02069942 A1	12-09-2002
US 2008004291 A1	03-01-2008	US 2008004260 A1	03-01-2008
		US 2008004291 A1	03-01-2008
		US 2010113427 A1	06-05-2010
		US 2010113483 A1	06-05-2010
		US 2011046117 A1	24-02-2011
		US 2011112116 A1	12-05-2011
		US 2012196877 A1	02-08-2012
		WO 2008005345 A2	10-01-2008
WO 03013482 A1	20-02-2003	NONE	
EP 1163902 A2	19-12-2001	CN 1329886 A	09-01-2002
		DE 60126017 T2	18-10-2007
		EP 1163902 A2	19-12-2001
		JP 2002029965 A	29-01-2002
		KR 20010113478 A	28-12-2001
		US 2002012695 A1	31-01-2002
WO 0172282 A1	04-10-2001	AU 4480401 A	08-10-2001
		KR 20010093728 A	29-10-2001
		US 2003129219 A1	10-07-2003
		WO 0172282 A1	04-10-2001