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(71) Applicant: **GLANIS PHARMACEUTICALS, INC.** [CA/CA]; Suite 1780-355 Burrard Street, Vancouver, BC V6C 2GB (CA).

(72) Inventors: **PLAKOGIANNIS, Fotios M.**; 157-14 Cryders Lane, Whitestone, NY 11357 (US). **MODI, Nisarg**; 32 Logan Avenue, 1st Floor, Jersey City, NJ 07306 (US).

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(54) Title: ORAL DELIVERY SYSTEM COMPRISING HYDROXYCHLOROQUINE AND/OR CHLOROQUINE

(57) Abstract: An Oral Delivery System (ODS) of the reservoir or plaster or adhesive type for administrating Hydroxychloroquine and/or Chloroquine for the treatment of rheumatoid arthritis, lupus erythematosus, SARS CoV-2, porphyria cutanea tarda for 1 day, 2 day, 3 day, 4 day, 5 day, 6 day and/or 7- day continuous application.

ORAL DELIVERY SYSTEM COMPRISING HYDROXYCHLOROQUINE AND/OR CHLOROQUINE.

This international application claims priority to U.S. Serial Number 63/012,443, filed April 20, 2020, the entirety of which is incorporated herein by reference.

SPECIFICATION

BACKGROUND OF THE INVENTION

The present disclosure relates to novel oral delivery system (ODS) of pharmaceutical compositions, which have a satisfactory in-vivo performance and good bioavailability. In particular, the oral pharmaceutical composition of Hydroxychloroquine/Chloroquine in the present disclosure includes either liquid or semi solid in a reservoir patch dosage form or matrix or adhesive in a plaster dosage form for treatment of rheumatoid arthritis, malaria, lupus erythematosus, SARS CoV-2 Infection, and porphyria Cutanea tarda for 1 Day, 2 Day, 3 Day, 4 Day, 5 Day, 6 Day and/or 7-day continuous application.

Rheumatoid arthritis (RA) is a chronic, inflammatory, autoimmune disorder. It is characterized by symmetric inflammation of synovial joints leading to progressive erosion of cartilage and bone. Upon untreated, the irreversible joint damage occurs within 2 years. During this disease, the body's own immune system attacks the lining of the membrane that surrounds the joints. 1-2% of world population is suffering from this disease. The occurrence of this disease is 3 times more in women than the men. This disease can occur at any age but the most patients are between 30 to 50 years of age. It can reduce the total life span of patient by 3 to 18 years. The average treatment cost in US is $6000/case/year[1].

Lupus erythematosus (LE) is another autoimmune disease which mainly targets women of childbearing age although it occurs at both extremes of age and in either sex. There are variable clinical presentation ranging from a skin rash uncomplaining by extra cutaneous stigmata to one comprising progressive multisystem disease[2].

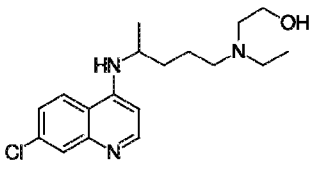
Porphyria Cutanea tarda (PCT) is a type of porphyria or blood disorder that affects the skin. PCT is one of the most common type of porphyria. It is sometimes referred as a Vampire Disease because people with this condition often experience symptoms following exposure to sunlight. It affects female more than males. The disorder usually develops after the age of 30. PCT is a rare disorder; the occurrence is estimated to be approximately 1 case in every 10,000 to 25,000 individuals in the general population[3].

Currently, American porphyria foundation (APF) recommends using 100 mg twice a week hydroxychloroquine. Which represents 28 mg/day. The APF recommendation dose can be developed orally. HCQ and/or CQ has been used off label due to unknown mechanism of

action of this drug. The other reasons are no availability of suitable dosage form, tablets are not scored for division and the 100 mg tablet is not available in the market[4].

Hydroxychloroquine (HCQ) is an immunomodulatory drug. Its sulfate salt, such as Plaquenil, is approved for the treatment of lupus erythematosus, rheumatoid arthritis, and malaria. Furthermore, HCQ and/or CQ gained interest as a potential therapeutic option for COVID-19 based on in vitro studies suggesting efficacy of HCQ and/or CQ against SARS-COv and SARS-COv-2[5]. Oral doses of the tablet range from 200 to 600 mg/day[6]. Pharmacokinetic studies reveal that the oral bioavailability is about 75% with rapid absorption kinetics. The drug is highly lipophilic and has a very large volume of distribution which results in a very long half-life (~50 Hrs). Plasma levels of the drug can be variable with variable absorption kinetics[7], but subsequent studies established that measurement of whole blood levels rather than plasma levels, and dosing based upon body weight considerably reduces this variability[8].

Hydroxychloroquine sulfate is a white, crystalline powder which is freely soluble in water and practically insoluble in alcohol, chloroform, and in ether. The molecular weight of hydroxychloroquine sulfate is 433.95[6].



H_2SO_4

The hydroxychloroquine base has a log P value of 3.6 with melting point of 90C. The water solubility of base is 0.026 mg/ml[9]. The base may have very good solubility in organic solvents as compare to its salt due to higher log P value.

HCQ is currently available as a 200 mg oral tablet of sulfate salt of API, which is equivalent to 155 mg of the base form of API. The numerous studies concluded that HCQ peak concentration in blood was around 129.6 ng/ml while the plasma concentration was around 50.3 ng/ml in around 3 hours following 200 mg oral dose administration. Furthermore, in randomized cross over study, the bioavailability of HCQ was found to be 0.74 based on the 155 mg dose administration through oral and IV infusion[10,11].

HCQ showed moderate protein binding (~40%) with albumin and apha1-acid glycoprotein. HCQ showed high volume of distribution because of deep tissue distribution[12,13]. Animal

study showed the high concentration of HCQ and/or CQ in the lungs, kidney, liver and spleen. In one of the animal studies, HCQ and/or CQ concentration was found to be 6-7 times higher in lung than the plasma[14].

Previous research reported HCQ clearance to be 15.5 L/Hr. Most research also have reported the terminal half-life of 30-60 days based on blood concentration and ~32 days based on the plasma concentration profile.[10]

Due to positive in-vitro studies on antiviral effect of HCQ and/or CQ, it gained interest as potential therapy against SARS-CoV-2. The anti-inflammatory action of HCQ and/or CQ is dependent on immunomodulation and the downstream production of cytokines. Furthermore, successful entry of SARS-CoV-2 into host cell is strongly dependent on angiotensin-converting enzymes-2 (ACE-2) interaction with the viral spike protein. HCQ and/or CQ reduces the glycosylation of ACE-2, which inhibits the binding of SARS-CoV-2 spike protein to the cell surface and cell integration. Recent study showed that HCQ and/or CQ binds with the gangliosides, which inhibits communication between spike protein and the cell membrane and thus inhibiting viral entry to the cell[15-18].

Rare but serious side effects have been reported, mostly with long term use. HCQ and/or CQ-induced acquired lysosomal storage disease causes some serious adverse effects, including myopathy and cardiomyopathy[19]. Most cases are caused by accumulation which can be augmented by CYP450 2C8 mutation[20]. Due to its higher log Ko/w value HCQ and/or CQ easily permeates myocytes, in which it binds lysosomal phospholipids, leading to lysosomal accumulation of phospholipids. Furthermore, HCQ and/or CQ inhibits lysosomal enzymes by increasing the pH, which leads to accumulation of glycogen and phospholipids. The abnormal accumulation of metabolic products in lysosomal results into lysosomal storage disease, leading to myofibrillar disorganization, atrophy, and fibrosis, which may lead to cardiomyopathy[21,22]. HCQ and/or CQ affect myocardial depolarization and repolarization through cardiac K+ channel blockage causing QT/QTc prolongation, which is an indicator of an increase risk of drug-induced torsade de pointes (TdP). TdP is usually self-limiting but can degenerate into lethal ventricular fibrillation and cause sudden cardiac death[20].

Currently, the recommended dose of less than 5mg/kg/day, HCQ and/or CQ is usually safe, although prolongation of the QT/QRS is rarely observed on a surface electrocardiogram[6].

In oral mucosal drug delivery, a oral mucosal patch or orally disintegrating composition is applied to the mucosal surface of oral cavity. Throughout the duration of oral mucosal application of a oral mucosal patch or oral disintegrating composition drug is continuously released and delivered through the intact mucosa (via transcellular, intercellular and transappendageal routes) to achieve systemic effect. Therefore, once applied oral disintegrating composition or oral mucosal patch can deliver drug into systemic circulation throughout the day or even for more than one day depending on the duration of its application which can be even up to a week.

Oral mucosal delivery can reduce the dosing frequency of chloroquine (CQ) and hydroxychloroquine (HCQ) which is currently administered orally 2-3 times a day. Through oral mucosal delivery, orally disintegrate compositions or oral thin film formulations or oral disintegrate tablet of CQ and/or HCQ can be applied to oral mucosa thereby delivering the drug throughout the duration of oral application. Depending on the requirement, duration of oral application and can be for one day, for two days, for three days, for four days, for five days, and/or for up to 15 days. Therefore, oral mucosal delivery can overcome the multiple dose regimen of oral delivery by reducing the dosing frequency.

Moreover, in oral mucosal drug delivery drug is delivered slowly and continuously throughout the duration of oral application hence there are no peaks and troughs in drug plasma concentration which are associated with multiple dose administration in a day. Therefore, by oral mucosal and/or oral disintegrating delivery of CQ and/or HCQ can have the therapeutic effect of the drug for extended period of time without drastic changes in drug plasma concentration. With respect to CQ and HCQ it is expected that adverse effects in patients will be less with the oral mucosal delivery as drug plasma concentration with oral mucosal delivery is less than peak plasma concentration associated with oral tablets.

It is typical for novel oral delivery system to achieve similar pharmacokinetic profiles as compared to an oral dose based on oral bioavailability and potentially reduce the overall exposure to the drug for very low oral bioavailable drugs. Oral mucosal drug products continuously deliver the active molecule in plasma at the steady state plasma concentration throughout the application period, which prevents peaks and valleys associated with typical oral drug delivery.

Oral mucosal drug delivery can be advantageous over conditional oral delivery because it avoids first-past effects, and variations in absorption rates due to intestinal activity and

content. However, unlike the intestinal tract, oral mucosal delivery is limited by the barrier function of the mucosa and a limited surface area for absorption. The best candidates for oral mucosal delivery are small molecular weight, lipophilic molecules that are extremely potent, requiring doses less than 25 mg/day. The half-life of the drug played a vital role during multiple dosing of oral mucosal system. The longer half-life eliminates the lag time during the consequence dosing due to availability of API from the previous dosing.

BRIEF SUMMARY OF THE INVENTION

The structure of reservoir ODS according to the disclosure comprises an active substance, Hydroxychloroquine and/or chloroquine in the form of liquid, or semisolid or suspension in the pouch system. The pouch system contains impermeable backing layer, which covers the ODS on the side averted from the mucosa and detachable protective layer containing release liner in contact with mucosa for controlled delivery of Hydroxychloroquine and/or chloroquine through the oral route.

The structure of matrix or plaster ODS according to the disclosure comprises an active substance, Hydroxychloroquine and/or chloroquine, suspended or solubilize in the polymer or adhesive matrix, cover between impermeable backing layer and release liner and/or detachable protective layer. According to the current disclosure, the active substance, Hydroxychloroquine and/or chloroquine itself is solubilized or suspended in the pressure-sensitive adhesive or polymer matrix, or an extra placebo pressure sensitive adhesive layer may be provided which enables fixation of the ODS on the mucosa.

The detachable and protective layer during storage covers the release liner in reservoir ODS and the pressure sensitive adhesive ODS surface facing the mucosa and is detached before application.

The disclosure provides comprises both ODS designed as matrix system and or ODS designed as reservoir membrane system.

The ODS according to the disclosure can be used both in the form of reservoir system as well as in the form of matrix system. According to the disclosure reservoir system comprises a pouch formed from an impermeable backing, a rate controlling membrane, an adhesive peripheral ring, covered by a strippable protective backing. The impermeable backing is configured to provide a central volume, which contains a drug reservoir in the form of a semisolid or liquid having dissolved and suspended drug, therein. Although preferred embodiments of the disclosure utilize an adhesive peripheral ring outside the path of drug from the system to the oral mucosa but other means for maintaining the system on the oral

mucosa can be employed. Such means include an in-line adhesive layer; adhesive overlays or other fastening means such as buckles, belts and elastic armbands is also contemplated.

The ODS according to the disclosure can be manufactured in such a manner that this active substance, Hydroxychloroquine and/or chloroquine containing mixture is coated onto a suitable support, for example to a thermoplastic film provided with a silicone layer, and possibly after evaporation of the solvent components-is covered with a further film which will later constitute the backing layer of ODS. The pharmaceutically acceptable substance suitable as auxiliaries such as plasticizer, tackifiers, solubilizers, stabilizers, fillers, carrier substances and permeation enhancers are in principle known to these skilled in the art.

The device of the present disclosure can release drug continuously by diffusion process. In this mode, the driving force is the difference in Hydroxychloroquine and/or chloroquine activity between the device reservoir and the oral mucosa and underlying tissue. The Hydroxychloroquine and/or chloroquine, which is entirely dissolved or disperse in the carrier and/or vehicle and/or polymer system in the case of present disclosure, permeates through the carrier to the oral mucosa. The reservoir or matrix system is in diffusion communication with the oral mucosa- which means that it either contacts the oral mucosa directly or contacts semipermeable material interposed between the reservoir or matrix system and the oral mucosa that provide permeation pathway for the Hydroxychloroquine and/or chloroquine and permeation enhancer to migrate from the reservoir or matrix to the oral mucosa. The interposed material may be homogenous, heterogeneous, or be composed of multiplicity of distinct layer.

Suitable base polymers for producing the active substance reservoir or matrix or the pressure sensitive adhesive layer of the ODS according to the disclosure are polymers based on cellulose and its derivatives (methylcellulose, ethyl cellulose, carboxymethyl cellulose, Hydroxypropyl cellulose, hydroxypropylmethyl cellulose etc.), natural polymers, polysaccharides and its derivatives such as but not limited to (agar, alginic acid and derivatives, cassia tora gum, collagen, gelatin, gellan gum, guar gum, pectin, potassium or sodium carrageenan, tragacanth, xanthan gum, copal, starch, chitosan, resin etc.), synthetic polymers and its derivatives such as without any limitation to carboxy vinyl polymers or carbomers (carbopol 940, carbopol 934, carbopol 971), polyethylene and its co-polymers etc. clays such as silicate etc. polyvinyl alcohol, polyacrylamide, polyvinyl pyrrolidone homopolymer and polyvinyl pyrrolidone copolymers (PVP, Poloxamer), acrylic acid its ester, polyacrylate copolymers, isobutylene, ethylene vinyl acetate copolymers, natural rubbers, synthetic rubbers such as styrene-diene copolymers, styrene-butadiene block copolymers, isoprene block copolymers, acrylonitrile butadiene rubber, butyl rubber or neoprene rubber, as well as pressure sensitive adhesive based on silicone, or “hot-melt adhesive”. The term

"hot-melt adhesive" comprises any adhesive which are not liquefied with solvent but by melting at elevated temperature, preferably in the range of from 60-200 °C. Suitable as hot-melt adhesive are in particular, mixture of esters of hydrogenated colophony with cellulose derivatives. The mentioned base polymers may also be used in form of suitable mixtures.

On top of the above-mentioned polymers other polymers known to the skilled artisan may also be used as a base polymers for producing polymer vehicle or the matrix or the pressure sensitive adhesive layer, provided they are compatible with Hydroxychloroquine and/or chloroquine. In theory, a variety of polymers, resins and additives known to the art can be taken into consideration for production of ODS. However, care must be take that these substances, in so far as coming into contact with the oral mucosa, are tolerated by the oral muosa, and that the formulation is suitable for delivering Hydroxychloroquine and/or chloroquine.

In another embodiment, the active substance, Hydroxychloroquine and/or chloroquine is in the simplest case dispersed, coarsely, colloidally or molecularly, in a solution or melt of base polymers. In the further ODS manufacturing techniques, the Hydroxychloroquine and/or chloroquine is in the form of supersaturated solution, nano-emulsion or nano-suspension, amorphous, crystalline, co-crystals, coated with base polymers or solubilize in polymers using hot melt extrusion process.

A preferred embodiment of the disclosure consists in that the active substance Hydroxychloroquine and/or chloroquine is present in the reservoir of ODS in dissolved condition; in this case the formulation should, if possible, contain a solubilizer. Selected examples for solubilizers are polysorbate such as but not limited to (polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80 etc), span such as but not limited to (span 80, span 20 etc), surfactants such as (anionic, cationic, nonionic and amphoteric), propylene glycol monocaprylate type I, propylene glycol monocaprylate type II, propylene glycol dicaprylate, medium chain triglycerides, propylene glycol monolaurate type II, linoleoyl polyoxyl-6 glycerides, Caprylic glyceride, oleoyl-polyoxyl-6-glycerides, lauroyl polyoxyl-6-gylcerides, polyglyceryl-3- dioleate, diethylene glycol monoethyl ether, propylene glycol monolaurate type I etc, cyclodextrins, polyhydric alcohol, especially 1,2-propanediol, butanediol, glycerine, polyethylene glycol (m.w. 200 and higher), Dimethyl Sulfoxide, Dimethyl Isosorbide, tetrahydrofurfuryl alcohol, diethyl tolumide, monoisopropylidene glycerine and others Solubilizers, surfactants, emulsifying agents, dispersing agents and similar compounds or chemicals known to those skilled in the art can be used either alone or in combination thereof. It has proved to be advantageous for the portion of the solubilizer to be 1 to 99% wt, especially preferred 5 to 75% wt. relative to the overall weight of the Hydroxychloroquine and/or chloroquine reservoir. It is to be taken into consideration that

some of the mentioned solubilizers, e.g. Dimethyl Sulfoxide, Dimethyl Isosorbide, diethylene glycol monoethyl ether, can simultaneously act as a permeation enhancing agents.

In another embodiment, solvents can be also used to make up the weight of the total reservoir or matrix or pressure sensitive adhesive matrix systems. Theses solvents can also be used to increase the solubility of Hydroxychloroquine and/or chloroquine in the reservoir or matrix systems. Such solvents known to those skilled in the art can be used either alone or in mixture thereof without any limitation to following like alcohol C_1-C_{20} such as but not limited to (methanol, ethanol, isopropyl alcohol, butanol, propanol etc.), polyhydric alcohols, isopropyl myristate, water, glycols such as but not limited (propylene glycol, polyethylene glycol, dipropylene glycol, hexylene glycol, glycerine etc.), pyrrolidone such as but not limited to (N-methyl 2-pyrrolidone, 2-pyrrolidone etc.), sulfoxides such as but not limited to (dimethyl Sulfoxide, decylmethylsulfoxide etc.), dimethyl Isosorbide, mineral oils, vegetable oils, volatile chemicals which can be used to make matrix patch such as but not limited to (ethanol, propanol, ethyl acetate, acetone, methanol, dichloromethane, chloroform, toluene, Isopropyl alcohol), acids such as but not limited to lactic acid, acetic acid, bases and others.

To achieve a high Hydroxychloroquine and/or chloroquine flux through the oral mucosa, it has proved particularly beneficial, especially in matrix or adhesive systems, for the Hydroxychloroquine and/or chloroquine reservoir or matrix or pressure sensitive adhesive to contain permeation enhancing excipients in an amount of 0.1 to 25%wt, preferably from 1 to 15%wt, in each case relative to the total weight of the Hydroxychloroquine and/or chloroquine reservoir or matrix or pressure sensitive adhesive. Preferred example for oral mucosal permeation-enhancing agents are water, sulfoxides, and similar chemicals such as but not limited to (dimethylsulfoxide, dimethylacetamide, dimethylformamide, decylmethylsulfoxide, dimethylisosorbide etc), azone, pyrrolidones such as but not limited to (N-methyl-2-pyrrolidone, 2-pyrrolidone etc), esters such as but not limited to (Propylene glycol monolaurate, butyl ethanoate, ethyl ethanoate, isopropyl myristate, isopropyl palmitate, methyl ethanoate, decyl oleate, glycerol monooleate, glycerol monolaurate, lauryl laurate etc), fatty acids such as but not limited to (capric acid, caprylic acid, lauric acid, oleic acid, myristic acid, linoleic acid, stearic acid , palmitic acid etc), alcohols, fatty alcohols and glycols such as but not limited to (oleyl alcohol, ethanol, dodecanol, propylene glycol, glycerol etc), ethers such as but not limited to (diethylene glycol monoethyl ether), urea, polyoxyethylene fatty alcohol ethers, polyoxyethylene fatty acid esters, esters of fatty alcohols, esters of long chain fatty acids with methyl, ethyl or isopropyl alcohol, esters of fatty alcohols with acetic acid, lactic acid, as well as oleic acid diethanolamine, essential oils, terpene and terpenoids such as but not limited to (terpineol, limonene, thymol, cineole etc), surfactant type enhancers (polysorbate 80, polysorbate 20 etc.), liposomes, niosomes, transferomes, ethanosomes, etc

and all penetration or permeation enhancers referred in the book "Percutaneous Penetration Enhancers" (Eric W. Smith, Howard I. Mailbach, 2005. Nov, CRC press). The permeation-enhancing substances mentioned above may be added either singly or as a mixture.

To achieve maximum release at constant release rate, the Hydroxychloroquine and/or chloroquine concentration in the active substance matrix or reservoir or pressure sensitive adhesive is preferably as optimized as possible. In this content, it has to be kept in mind, however, that the physical stability of the active substance may be adversely affected if the concentration is to high due to super-saturation, which causes precipitation. In the ODS of the disclosure, the Hydroxychloroquine and/or chloroquine concentrations employed are in the range 0.1 to 50%-wt, in particular from 1 to 25% wt, in each case relative to the total weight of the active substance reservoir or matrix or pressure sensitive adhesives.

Moreover, the Hydroxychloroquine and/or chloroquine matrix or pressure sensitive adhesive or individual layers of the matrix may contain plasticizers which are known to those skilled in the art either alone or in combination thereof without any limitation to following like glycerol and its esters, phosphate esters, glycol derivatives, sugar alcohols, sebacic acid esters, azelate, citric acid esters, tartaric acid esters, adipate, phthalic acid esters, triacetin, oleic acid esters and all the plasticizers which can be used in oral drug delivery system referred in the book "Handbook of Plasticizers" (George Wypych, 2004, Chem Tec Publishing). The concentration of these plasticizers may be up to 50% wt, and is preferably between 5 to 25% wt, in each case relative to the active substance matrix total weight.

The system and methods of the disclosure also comprise such embodiments where the Hydroxychloroquine and/or chloroquine matrix has a two or multi-layered structure, also called multi-laminate drug in adhesive patch. For example, the various matrix layers may contain polymer constitutes from the above-mentioned polymers. In this case, the matrix layers are differing from each other's in the term of polymer or pressure sensitive or hot melt polymers composition, Hydroxychloroquine and/or chloroquine concentration, different permeating enhancers or solubilizes. The layers can be separated using semi-permeable membrane between two distinct drug-in-adhesive layers or multiple drug-in-adhesive layers under a single backing film.

The system and methods of the disclosure provides a oral delivery system (ODS) for administration of Hydroxychloroquine and/or chloroquine comprising: an active substance area or reservoir comprises a pharmaceutical composition comprising Hydroxychloroquine and/or chloroquine and at least one excipient; an impermeable backing layer;

- optionally, a releasing membrane, which is covered by a detachable backing layer. The system and methods of the disclosure provides a ODS wherein the active substance area or

reservoir is configured as a polymer matrix system, a liquid system, a gel system, or a pressure sensitive adhesive system.

The system and methods of the disclosure provides a ODS, wherein the active substance reservoir is constructed in a pouch-shaped system. The system and methods of the disclosure provides a ODS, wherein the active substance reservoir is a preparation selected from the group consisting of flowable, viscous, semi-solid, gel-like, liquid preparation, solution, suspension, and emulsion. The system and methods of the disclosure provides a ODS, wherein the active substance reservoir is a preparation selected from the group consisting of film forming gel, film forming solution, and/or film forming spray. The system and methods of the disclosure provides a ODS wherein the active substance reservoir is confined on the oral mucosa facing side by an active substance permeable membrane and on the opposite side from the oral mucosa by an active substance impermeable layer.

The system and methods of the disclosure provides a ODS comprising an active substance permeable membrane which modifies or controls the rate of active substance release. The system and methods of the disclosure provides a ODS characterized in that the Hydroxychloroquine and/or chloroquine containing area is a single-, double-, or multilayered active substance matrix.

The system and methods of the disclosure provides a ODS further comprising an adhesive so that it may be applied as a plaster or bandage. The system and methods of the disclosure provides a ODS wherein the active substance is a matrix selected from the group consisting of a plastic or synthetic resin matrix, a pressure-sensitive adhesive matrix, wherein the basic polymer(s) of this matrix are selected from the group consisting of polymers based on acrylic acid and its esters, isobutylenes, ethylene-vinyl acetate copolymers, natural rubbers, synthetic rubbers, styrene-diene copolymers, styrene-butadiene block copolymers, isoprene block copolymers, acrylonitrile-butadiene rubber, butyl rubber and neoprene rubber, pressure sensitive adhesives based on silicone, hot-melt adhesive, mixtures of esters of hydrogenated colophony with cellulose derivatives, and combinations thereof. The system and methods of the disclosure provides a ODS wherein the active substance reservoir contains a fiber material, a woven fabric or a nonwoven, to which the active substance is adsorbed. The system and methods of the disclosure provides a ODS can deliver 1-40 mg/day Hydroxychloroquine and/or chloroquine through the oral mucosa to the blood in a subject, which can produce up to 2000 ng/ml plasma concentration. The system and methods of the disclosure provides a ODS wherein the Hydroxychloroquine and/or chloroquine is present in a concentration in the range of from 0.1-50 wt%, preferably from 1-30 wt%, more preferably 1 -20 wt%, in each case relative total mass of the active substance reservoir.

The system and methods of the disclosure provides a ODS wherein Hydroxychloroquine and/or chloroquine is present in the active substance reservoir either in dissolved or suspended state. The system and methods of the disclosure provides an ODS wherein the active substance reservoir contains at least one solubilizer, preferably in an amount of from 1 to 99 wt%, with particular preference from 5 to 70 wt%, in each case relative to the total weight of the active substance reservoir. The system and methods of the disclosure provides an ODS wherein the solubilizer is selected from the group consisting of polysorbate, span, surfactants (anionic, cationic, nonionic and amphoteric), propylene glycol monocaprylate and its derivatives, glycols and its derivatives, triglycerides and its derivatives, diethylene glycol monoethyl ether, cyclodextrins, polyhydric alcohol, polyethylene glycol (m.w. 200 and higher), tetrahydrofurfuryl alcohol, diethyl tolumide, monoisopropylidene glycerine, sulfoxides, and similar chemicals such as but not limited to dimethylsulfoxide, dimethylacetamide, dimethylformamide, decylmethylsulfoxide, dimethylisosorbide, Caprylocaproyl polyoxyl-8 glycerides, triacetine, and combinations thereof.

The system and methods of the disclosure provides an ODS wherein the active substance reservoir contains at least one permeation-enhancing agent, in an amount of from 0.1 to 50wt%, with particular reference from 1 to 25wt%, in each case relative to the total weight of the active substance reservoir. The system and methods of the disclosure provides an ODS where in the permeation-enhancing agent is selected from the group consisting of azone, pyrrolidones, N-methyl-2-pyrrolidone, 2-pyrrolidone, esters, Propylene glycol monolaurate, butyl ethanoate, ethyl ethanoate, isopropyl myristate, isopropyl palmitate, methyl ethanoate, decyl oleate, glycerol monooleate, glycerol monolaurate, lauryl laurate, fatty acids, alcohols, fatty alcohols and glycols, ethers, urea, polyoxyethylene fatty alcohol ethers, polyoxyethylene fatty acid esters, esters of fatty alcohols, esters of long chain fatty acids with methyl, ethyl or isopropyl alcohol, esters of fatty alcohols, acetic acid, lactic acid, diethanolamine, essential oils, propylene glycol monolaurate type I and type II, terpene and terpenoids, surfactant type enhancers, and combinations thereof.

The system and methods of the disclosure provides a method of treating and/or preventing rheumatoid arthritis comprising: selecting a patient in need of such treatment and/or prevention; applying to the oral mucosa of the patient an ODS of The system and methods of the disclosure ; thereby treating and/or preventing the rheumatoid arthritis. The disclosure provides a method of treating and/or preventing lupus erythematosus comprising: selecting a patient in need of such treatment and/or prevention; applying to the oral mucosa of the patient an ODS of the disclosure. The system and methods of the disclosure provides a method of treating and/or preventing malaria comprising: selecting a patient in need of such treatment and/or prevention; applying to the oral mucosa of the patient an ODS of the

disclosure. The system and methods of the disclosure provides a method of treating and/or preventing SARS CoV-2 infection comprising: selecting a patient in need of such treatment and/or prevention; applying to the oral mucosa of the patient an ODS of the disclosure. The system and methods of the disclosure provides a method of treating and/or preventing prophyra cutanea tarda comprising: selecting a patient in need of such treatment and/or prevention; applying to the oral mucosa of the patient an ODS of the disclosure.

The system and methods of the disclosure provides a method according characterized in that the application period of the ODS is at least 24 hr and maximally 7 days.

The system and methods of the disclosure provides a method of making an oral delivery system (ODS) for administration of Hydroxychloroquine and/or chloroquine comprising: providing an active substance area or reservoir;
providing an impermeable backing layer; optionally providing a releasing membrane, which is covered by a detachable backing layer, wherein the active substance area or reservoir comprises a pharmaceutical composition comprising Hydroxychloroquine and/or chloroquine and at least one excipient.

The system and methods of the disclosure provides a Hydroxychloroquine and/or chloroquine-containing ODS for use in the preparation of a medicament for use in treating and/or preventing rheumatoid arthritis or treating and/or preventing malaria or treating and/or preventing lupus erythematosus or treating and/or preventing SARS CoV-2 infection or treating and/or preventing porphyria cutanea tarda. A method for treating or preventing a disease or condition in a patient, wherein the disease or condition is selected from the group consisting of rheumatoid arthritis and/or lupus erythematosus and/or malaria and/or SARS CoV-2 infection and/or porphyria cutanea tarda, and combinations thereof, wherein said method comprises: selecting a patient in need of treating or preventing said disease or condition; administering to the patient the composition of the disclosure in a therapeutically effective amount, thereby treating or preventing said disease in said patient.

The disclosure provides for the use of the compounds and compositions of the disclosure for the production of a medicament for preventing and/or treating the indications as set forth herein.

In accordance with a further embodiment, the present disclosure provides for the use of the compounds and pharmaceutical compositions described herein, in an amount effective for use in a medicament, and most preferably for use as a medicament for treating a disease or disorder, for example, as set forth herein, in a subject.

In accordance with yet another embodiment, the present disclosure provides a use of the pharmaceutical compositions described herein, and at least one additional therapeutic

agent, in an amount effective for use in a medicament, and most preferably for use as a medicament for treating a disease or disorder associated with disease, for example, as set forth herein, in a subject.

The disclosure provides a method for treating and/or preventing a disease or condition as set forth herein in a patient, wherein said method comprises: selecting a patient in need of treating and/or preventing said disease or condition as set forth herein; administering to the patient a composition of the disclosure in a therapeutically effective amount, thereby treating and/or preventing said disease in said patient.

DETAILED DESCRIPTION OF THE INVENTION

Hydroxychloroquine and/or chloroquine refers to all pharmaceutically acceptable forms of Hydroxychloroquine and/or chloroquine either alone or in combinations thereof, for example in following forms but not limited to such as free base or salt or isomer or amorphous or crystalline or co crystalline or solid solution or prodrug or analog or derivatives or metabolites.

RA: Rheumatoid Arthritis

SARS CoV: Severe acute Respiratory Coronavirus

LE: Lupus Erythematosus

PCT: Prophyria Cutanea Tarda

ODS: Oral delivery system, which can bypass the first pass metabolism.

Range:

Terms Formulation and composition are used interchangeable.

Terms novel oral drug delivery system and oral delivery system are used Interchangeably.

Terms reservoir system and reservoir patch are used interchangeably.

Terms matrix system and matrix patch are used interchangeably.

Terms oral composition and pharmaceutical composition are used interchangeably.

Term liquid includes without any limitation solution, suspension, micro suspension, nano suspension, dispersion, sprays, aerosols, where solutions are preferred.

The term semisolid includes without any limitation such as gels, ointments, creams, emulsion, microemulsion, nanoemulsion, paste, balms, magma, lotions, mousses, waxes, where gels are preferred.

The term polymer film includes polymer without any limitation pressure sensitive adhesive and/or non-adhesive polymer.

Oral delivery system: Reservoir system and/or matrix system comprising Pharmaceutical composition.

All the pharmaceutical compositions are percent by weight.

Without any limitation enhancers used in liquid formulation can be used for semi solid and polymer formulation.

As used herein, the terms "subject" and "patient" are used interchangeably. As used herein, the term "patient" refers to an animal, preferably a mammal such as a non-primate (e.g., cows, pigs, horses, cats, dogs, rats etc.) and a primate (e.g., monkey and human), and most preferably a human. In some embodiments, the subject is a non-human animal such as a farm animal (e.g., a horse, pig, or cow) or a pet (e.g., a dog or cat). In a specific embodiment, the subject is an elderly human. In another embodiment, the subject is a human adult. In another embodiment, the subject is a human child. In yet another embodiment, the subject is a human infant.

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. As used herein, the term "effective amount" refers to the amount of a therapy that is sufficient to result in the prevention of the development, recurrence, or onset of a disease or condition, and one or more symptoms thereof, to enhance or improve the prophylactic effect(s) of another therapy, reduce the severity, the duration of a disease or condition, ameliorate one or more symptoms of a disease or condition, prevent the advancement of a disease or condition, cause regression of a disease or condition, and/or enhance or improve the therapeutic effect(s) of another therapy.

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.

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

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 small molecule therapy.

As used herein, the terms "treat," "treatment," and "treating" in the context of the administration of a therapy to a subject refer to the reduction or inhibition of the progression and/or duration of a disease or condition, the reduction or amelioration of the severity of a disease or condition, such as cancer, and/or the amelioration of one or more symptoms thereof resulting from the administration of one or more therapies.

The term "derivative" or "derivatized" as used herein includes chemical modification of a compound of the disclosure, or pharmaceutically acceptable salts thereof or mixtures

thereof. That is, a "derivative" may be a functional equivalent of a compound of the disclosure, which is capable of inducing the improved pharmacological functional activity in a given subject. Illustrative of such chemical modifications would be replacement of hydrogen by a halo group, an alkyl group, an acyl group or an amino group.

As used herein, the term "pharmaceutically acceptable salts" includes acid addition salts or addition salts of free bases. The term "pharmaceutically acceptable salts" of a compound of the disclosure is also meant to include within its scope 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 of the disclosure , and yet is directly or indirectly converted in vivo into a compound of the disclosure , upon administration to a subject, such as a mammal, particularly a human being.

The compound may be in the form of a pharmaceutically acceptable salt, such as an acid addition salt or a base salt, or a solvate thereof, including a hydrate thereof. Suitable acid addition salts are formed from acids which form non-toxic salts and examples are the 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. Suitable base salts are formed from bases which form non-toxic salts and examples are the sodium, potassium, aluminium, calcium, magnesium, zinc and diethanolamine salts.

The term "about" and the use of ranges in general, whether or not qualified by the term about, means that the number comprehended is not limited to the exact number set forth herein, and is intended to refer to ranges substantially within the quoted range while not departing from the scope of the disclosure. As used herein, "about" will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill in the art given the context in which it is used, "about" will mean up to plus or minus 10% of the particular term.

As used herein, the term "oral" refers to delivery, administration or application of a drug by means of direct contact with mucosa. Such delivery, administration or application is also known as dermal, percutaneous, transmucosal and buccal. As used herein, "Oral" includes mucosa and oral cavities, which includes oral, buccal, nasal, rectal and vaginal mucosa.

As used herein, "Oral delivery system" refers to a system (e.g., a device) comprising a composition that releases drug upon application to the mucosa (or any other surface noted above). A oral delivery system may comprise a drug-containing composition, and, optionally, a backing layer and/or a release liner layer. In some embodiments, the oral delivery system is

a substantially non-aqueous, solid form, capable of conforming to the surface with which it comes into contact, and capable of maintaining such contact so as to facilitate oral application without adverse physiological response, and without being appreciably decomposed by aqueous contact during oral application to a subject. Many such systems are known in the art and commercially available, such as transmucosal patches. Typically, oral delivery systems are classified into one of three categories: matrix-type systems, film forming systems and reservoir-type systems, as discussed in more detail below.

An oral drug delivery system also may include a drug impermeable backing layer or film. In some embodiments, the backing layer is adjacent the drug-containing composition. When present, the backing layer protects the polymer matrix layer (and any other layers present) from the environment and prevents loss of the drug and/or release of other components to the environment during use. Materials suitable for use as backing layers are well-known known in the art and can comprise films of polyester, polyethylene, vinyl acetate resins, ethylene/vinyl acetate copolymers, polyvinyl chloride, polyurethane, and the like, metal foils, non-woven fabric, cloth and commercially available laminates. A typical backing material has a thickness in the range of 2 to 1000 micrometers. For example, 3M's Scotch Pak® 1012 or 9732 (a polyester film with an ethylene vinyl acetate copolymer heat seal layer), 9723 (a laminate of polyethylene and polyester), or CoTran 9720 (a polyethylene film) are useful in the oral drug delivery systems described herein, as are Dow® backing layer films, such as Dow® BLF 2050 (a multi-layer backing comprising ethylene vinyl acetate layers and an internal SARAN® layer.

An oral drug delivery system also may include a release liner, typically located adjacent the opposite face of the system as compared to the backing layer. When present, the release liner is removed from the system prior to use to expose the polymer matrix layer and/or an adhesive layer prior to mucosal application. Materials suitable for use as release liners are well-known known in the art and include the commercially available products of Dow Corning Corporation designated Bio-Release® liner and Syl-off® 7610, Loparex's PET release liner (silicone-coated) and 3M's 1020, 1022, 9741, 9744, 9748, 9749 and 9755 Scotchpak.TM. (fluoropolymer-coated polyester films).

An oral delivery system may be packaged or provided in a package, such as a pouch stock material used in the prior art for oral drug delivery systems in general. For example, DuPont's Surlyn® can be used in a pouchstock material. Alternatively, a pouchstock comprising a coextruded ethylene acrylic acid/low-density polyethylene (EAA/LDPE) material, or Barex® from INEOS (acrylonitrile-methyl acrylate) may be used.

The disclosure provides pharmaceutical composition for oral delivery of Hydroxychloroquine and/or chloroquine up to 7 days.

In one embodiment, the disclosure provides pharmaceutical compositions as liquid formulation for oral delivery of Hydroxychloroquine and/or chloroquine. In one aspect the disclosure further provides liquid formulation comprising Hydroxychloroquine and/or chloroquine and vehicle system. The disclosure further provides the vehicle system, which comprises solvents (solubilizer), permeation enhancing agents, if required acid or base for pH adjustment mentioned should be use. The liquid formulation comprising Hydroxychloroquine and/or chloroquine and vehicle system is preferred.

In one aspect liquid formulation comprise Hydroxychloroquine and/or chloroquine and vehicle system wherein, Hydroxychloroquine and/or chloroquine is present in an amount between 0.1- 50 wt%, vehicle system is present in an amount between 5 – 99.9 wt%. More preferably, Hydroxychloroquine and/or chloroquine is present in an amount between 1- 25 wt%, vehicle system is present in an amount between 1 – 99 wt%. The disclosure further provides an exemplary composition comprising about 0.1-50 wt% Hydroxychloroquine and/or chloroquine, 0.1-99.9 wt% dimethylsulfoxide, 0.1-99.9 wt% dimethylisosorbide, 0.1-99.9 wt% dipropylene glycol, 0.1-99.9 wt% highly purified diethylene glycol monoethyl ether, 0.1-50 wt% fatty acid, 0.1-50 wt% Lactic acid, 0.1-99.9 %wt propylene glycol, 0.1-99.9 %wt polyethylene glycol-400, 0.1-50 %wt water, pH between 3.5-8. More Preferably, about 1-25 wt% Hydroxychloroquine and/or chloroquine, 5-50 wt% dimethylsulfoxide, 5-50 wt% dimethylisosorbide, 1- 25wt% dipropylene glycol, 1- 50 wt% highly purified diethylene glycol monoethyl ether, 0.1-20 wt%, fatty acid, 0.1-20 wt% Lactic acid, 1- 25 %wt propylene glycol, 1- 25 %wt polyethylene glycol-400, 1-25 %wt water, pH adjusted between 4 -7. Without limiting in scope an exemplary formulation in this range is illustrated in Example 1.

In another embodiment, the disclosure provides pharmaceutical compositions as semisolid formulation for oral delivery of Hydroxychloroquine and/or chloroquine for up to 7 days.

In one aspect the disclosure further provides semisolid formulation comprising Hydroxychloroquine and/or chloroquine and polymeric vehicle system. The disclosure further provides the vehicle system, which comprise solvents (Solubilizer), permeability enhancing excipients and polymer or gelling agent or thickening agent, if required acid or base for pH adjustment. The semisolid formulation comprising Hydroxychloroquine and/or chloroquine and a polymeric vehicle system is preferred.

One aspect of semisolid formulation comprises Hydroxychloroquine and/or chloroquine and a polymeric vehicle system wherein, Hydroxychloroquine and/or chloroquine is present in an amount between 0.1-50 wt%, and the polymeric vehicle system is present in an amount between 0.1 – 99.9 wt%. More preferably, Hydroxychloroquine and/or chloroquine

is present in an amount between 1-30 wt%, and the polymeric vehicle system is present in an amount between 25-99 wt% to make up to 100 wt%

The disclosure further provides an exemplary formulation comprising about 0.1-50 wt% Hydroxychloroquine and/or chloroquine, 0.5-99.9 wt% dimethylsulfoxide, 0.5-99.9 wt% polyethylene glycol-400, 0.5-99.9 wt% diethylene glycol monoethyl ether, 0.5- 99.9 %wt propylene glycol, 0.5-99.9 wt% dipropylene glycol, 0.1-50 wt% Lactic acid, 0.5-99.9 wt%, dimethyl isosorbide, 0.5-50 wt% fatty acid, 0.5-50 %wt water, 0.1- 50% wt polyvinyl pyrrolidone, pH between 3.5-8. More Preferably, about 0.1-25 wt% Hydroxychloroquine and/or chloroquine, 0.5-50 wt% dimethylsulfoxide, 0.5- 50 wt% polyethylene glycol-400, 0.5-50 wt% diethylene glycol monoethyl ether, 0.5- 50 %wt propylene glycol, 0.5-50 wt% dipropylene glycol, 0.1-20 wt% Lactic acid, 0.5-50 wt%, dimethyl isosorbide, 0.5-50 wt% fatty acid, 0.5-50 %wt water, 0.1- 30% wt polyvinyl pyrrolidone, pH adjusted between 4 -7.

The disclosure further provides another exemplary formulation comprising about 0.1-25 wt% Hydroxychloroquine and/or chloroquine, 0.5-50 wt% dimethylsulfoxide, 0.5- 50 wt% polyethylene glycol-400, 0.5-50 wt% highly purified diethylene glycol monoethyl ether, 0.5-50 %wt propylene glycol, 0.5-50 wt% dipropylene glycol, 0.1-20 wt% Lactic acid, 0.5-50 wt%, dimethyl isosorbide, 0.5-50 wt% fatty acid, 0.5-50 %wt water, 0.1- 30% wt polyvinyl pyrrolidone,0.1-15 wt% hydroxypropyl cellulose HF, pH adjusted between 4 -7.

The disclosure further provides yet another exemplary formulation comprising about 0.1-25 wt% Hydroxychloroquine and/or chloroquine, 0.5-50 wt% dimethylsulfoxide, 0.5- 50 wt% polyethylene glycol-400, 0.5-50 wt% highly purified diethylene glycol monoethyl ether, 0.5- 50 %wt propylene glycol, 0.5-50 wt% dipropylene glycol, 0.1-20 wt% Lactic acid, 0.5-50 wt%, dimethyl isosorbide, 0.5-30 wt% Caprylocaproyl polyoxyl-8 glycerides, 0.5-50 wt% Propylene glycol monolaurate type II, 0.5-30 %wt Tween-20, 0.1-15 wt% hydroxypropyl cellulose HF, pH adjusted between 4-7. Without limiting in scope exemplary formulations in this range is illustrated in examples.

The disclosure further provides yet another exemplary formulation comprising about 0.1-25 wt% Hydroxychloroquine and/or chloroquine, 0.5-50 wt% dimethylsulfoxide, 0.5- 50 wt% Hexylene Glycol, 0.5-50 wt% highly purified diethylene glycol monoethyl ether, 0.5-50 wt% Triacetine, 0.1-20 wt% Lactic acid, 0.5-50 wt%, dimethyl isosorbide, 0.5-30 wt% Caprylocaproyl polyoxyl-8 glycerides, 0.5-50 wt% fatty acid, 0.5-50 %wt water, 0.1- 30% wt polyvinyl pyrrolidone,0.1-15 wt% hydroxypropyl cellulose HF, pH adjusted between 4-7.

The disclosure further provides yet another exemplary formulation comprising about 0.1-25 wt% Hydroxychloroquine and/or chloroquine, 0.5-50 wt% dimethylsulfoxide, 0.5- 50 wt% Hexylene Glycol, 0.5-50 wt% highly purified diethylene glycol monoethyl ether, 0.5-50 wt% Triacetine, 0.1-20 wt% Lactic acid, 0.5-50 wt%, dimethyl isosorbide, 0.5-30 wt%

Caprylocaproyl polyoxyl-8 glycerides, 0.5-50 wt% fatty acid, 0.5-50 %wt water, 0.1- 30% wt polyvinyl pyrrolidone, 0.1-15 wt% hydroxypropyl cellulose HF, pH adjusted between 4-7.

The disclosure further provides yet another exemplary formulation comprising about 0.1-25 wt% Hydroxychloroquine and/or chloroquine, 0.5-99 wt% dimethylsulfoxide, 0.5- 99 wt% polyethyelene glycol-400, 0.5- 99 %wt propylene glycol, 0.5-99 wt% Propylene glycol monolaurate type II, 0.5-50 %wt water, 0.1-15 wt% hydroxypropyl cellulose HF, pH adjusted between 4-7. Without limiting in scope exemplary formulations in this range is illustrated in examples.

The disclosure pertains to the oral delivery of Hydroxychloroquine and/or chloroquine for the treatment of RA and/or Malaria and/or LE and/or PCT and/or SARS CoV. Another embodiment pertains to the use of acrylic or silicone pressure sensitive adhesive and/or polymer matrix which do not contain functional groups and which are not cross linked, but are able to absorb or solubilize large amount of Hydroxychloroquine and/or chloroquine and at the same time provide equal or better adhesion to mucosa and permeation through mucosa. More preferred examples of pressure sensitive adhesive (PSAs), that could be used but not limited to, include those based on pure acrylate monomers as well as acrylate copolymers and terpolymers using for example as the co-monomers vinyl acetate or hydrocarbon copolymers which may also include pacifiers and other pressure sensitive adhesive modifiers. Some examples of these PSAs are Durotak 87-900A, 87-901A, 87-2516, 87-9301, Bio PSA-4202, Bio-PSA 4302, Bio-PSA 4502, Bio PSA-4602 and etc.

Another embodiment of disclosure is to inhibit crystallization in matrix patches using solubilizer an/or solvents and/or permeability enhancing agents by providing stabilization of the patch through absorption and immobilization of the liquid in the patch. For example, of such excipients include but not limited to PVP, PVP/PVA, hydroxypropylcellulose, hydroxyethylcellulose, methyl cellulose, sodium carboxymethyl cellulose, colloidal silica, Xanthan gum, and etc.

Another embodiment is in matrix and/or drug-in-adhesive and/or drug-in-polymer with two kinds of enhancers, volatile and non-volatile. Volatile enhancers are the excipients that have a vapor pressure 0.2 mmHg and higher at 20°C such as dimethylsulfoxide, dimethylisosorbide, diethylene glycol monoethyl ether and etc., while, the non-volatile enhancers are the liquids that have a vapor pressure less than 0.2 mm Hg at 20°C such as urea, lauryl lactate and etc. Volatile enhancers are the enhancers that will evaporate during drying process of matrix and/or drug-in-adhesive and/or drug-in-polymer preparation.

In another embodiment of the disclosure is a formulation comprising about 0.1-99 wt% Hydroxychloroquine and/or chloroquine, 0.5-99 wt% dimethylsulfoxide, 0.5- 99 wt% Triacetine, 0.5-99 wt% highly purified diethylene glycol monoethyl ether, 0.5-99 wt%

propylene glycol monoluarate type II, 0.1-99 wt% adhesive. More preferably 0.1-50 wt% Hydroxychloroquine and/or chloroquine, 0.5-50wt% dimethylsulfoxide, 0.5- 50 wt% Triacetine, 0.5-50 wt% highly purified diethylene glycol monoethyl ether, 0.5-50 wt% propylene glycol monoluarate type II, 0.1-90 wt% adhesive.

The invention will be illustrated in more detail with reference to the following Examples, but it should be understood that the present invention is not deemed to be limited thereto.

EXAMPLES

Example 1

This Example describes the preparation of a patch or semisolid formulation, which must give a blood level (±20%) bioequivalent to 50 mg oral Hydroxychloroquine and/or chloroquine. Initially, a oral formulation will be prepared containing a dose of 50 mg Hydroxycholorquine based on the in-vitro permeability flux profile obtained from Franz-diffusion cells, the dose will be adjusted to obtain desired blood level (±20%) bioequivalent to oral 50 mg/day Hydroxychloroquine and/or chloroquine. Different approaches will be implemented (e.g. change in drug loading dose, combination of solvents/enhancers etc.) to prepare an oral formulation which can deliver target therapeutic blood level from day 1 to day 5 or day 7.

Example 2

Below is a description of the experimental procedure, utilized for development and optimization of oral matrix patch or oral semisolid formulation containing Hydroxychloroquine and/or chloroquine, or a combination of hydroxychloroquine and/or chloroquine. Exemplary formulations are set forth in Table 1:

Table 1

Excipients	HCQ 1 (%w/w)	HCQ 2 (%w/w)	HCQ 3 (%w/w)	HCQ 4 (%w/w)
Hydroxychloroquine/Chloroquine	0.1 – 20%	0.1 – 20%	0.1 – 20%	0.1 – 20%
Enhancers		0.1 – 20%		0.1 – 20%

Solvents			0.1 – 20%	0.1 – 20%
Adhesive/Polymers	80 – 99.9%	50 – 99.8%	50 – 99.8%	30 – 99.7%

The oral formulation of the disclosure may comprise **solvents** known to those skilled in the art either alone or in combinations thereof without any limitation to following like alcohol C_1-C_{20} such as but not limited to (methanol, ethanol, isopropyl alcohol, butanol, propanol etc.), polyhydric alcohols, glycols such as but not limited to (propylene glycol, polyethylene glycol, dipropylene glycol, hexylene glycol, butyene glycol, glycerine etc.), derivative of glycols, pyrrolidone such as but not limited to (N methyl 2- pyrrolidone, 2-pyrrolidone etc.), sulfoxides such as but not limited to (dimethyl sulfoxide, decymethylsulfoxide etc), dimethylisosorbide, mineral oils, vegetable oils, sesame oil water, polar solvents, semi polar solvents, non polar solvents, volatile chemicals which can be used to make matrix patch such as but not limited to (ethanol, propanol, ethyl acetate, acetone, methanol, dichloromethane, chloroform, toluene, IPA, hexane), acids such as but not limited to acetic acid, lactic acid, levulinic acid, bases and others, pentane, dimethylformamide, butane, lipids. More preferably in the range of 0.01% - 95% w/w or w/v. In exemplary embodiments, formulations of the disclosure may comprise **solvents** at a concentration of about 0.01%, about 0.02%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 75%, about 75%, and about 80%, and about 95% of the formulation. In exemplary embodiments, formulations of the disclosure may comprise **solvents** at a concentration of about 1 to 20%, of about 5% to 25%, about 10% to about 20%, or about 15% to about 18%, about 30% to about 70%, about 35% to about 65%, about 63.13%, and about 40% to about 64% w/w. In exemplary formulations of the disclosure, the solvents will represent approximately 1 wt % to 75 wt %, preferably 2 wt % to 30 wt %, more preferably 5 wt. % to 20 wt. % of the formulation.

The oral formulation of the disclosure may comprise **gelling agents and/or thickening and/or suspending agents and/or polymers and/or adhesive polymers and/or**

pressure sensitive adhesive polymers known to those skilled in the art either alone or in combinations thereof without any limitation to following like natural polymers, polysaccharides and its derivatives such as but not limited to (agar, alginic acid and derivatives, cassia tora, collagen, gelatin, gellum gum, guar gum, pectin, potassium, or sodium carageenan, tragacanth, xantham, gum copal, chitosan, resin etc.), semisynthetic polymers and its derivatives such as without any limitation to cellulose and its derivatives (methylcellulose, ethyl cellulose, carboxymethyl cellulose, hydroxylpropyl cellulose, hydroxylpropylmethyl cellulose etc.), synthetic polymers and its derivatives such as without any limitation to carboxyvinyl polymers or carbomers (carbopol 940, carbopol 934, carbopol 971p NF), polyethylene, and its copolymers etc, clays such as but not limited to (silicates, bentonite), silicon dioxide, polyvinyl alcohol, acrylic polymers (eudragit), acrylic acid esters, polyacrylate copolymers, polyacrylamide, polyvinyl pyrrolidone homopolymer and polyvinyl pyrrolidone copolymers such as but not limited to (PVP, Kollidon 30, poloxamer), isobutylene, ethyl vinyl acetate copolymers, natural rubber, synthetic rubber, pressure sensitive adhesives such as silicone polymers such as but not limited to (bio psa 4302, bio-psa 4202 etc.,), acrylic pressure sensitive adhesives such as but not limited to (duro –tak 87-2156, duro-tak 387-2287, duro-tak 87-9301, duro-tak 387-2051 etc.), polyisobutylene such as but not limited to (polyisobutylene low molecular weight, plyisobutylene medium molecular weight, polyisobutylene 35000 mw, etc), acrylic copolymers, rubber based adhesives, hot melt adhesives, styrene-butadiene copolymers, bentonite, all water and/or organic solvent swellable polymers, etc. In exemplary embodiments, formulations of the disclosure may comprise **gelling agents and/or thickening and/or suspending agents and/or polymers and/or adhesive polymers and/or pressure sensitive adhesive polymers** at a concentration of abount 0.01%, about 0.02%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 75%, about 75%, and about 80%, and about 85%, and about 90% of the formulation. In exemplary embodiments, formulations of the disclosure may comprise **gelling agents and/or thickening and/or suspending agents and/or polymers and/or adhesive polymers and/or pressure sensitive adhesive polymers** at a concentration of about 1 to 20%, of about 5% to 25%, about 10% to about 20%, or about 15% to about 18%, about 30% to about 70%, about 35% to about 65%,

about 63.13%, and about 40% to about 64% w/w. In exemplary formulations of the disclosure, the gelling agents and/or thickening and/or suspending agents and/or polymers and/or adhesive polymer and/or pressure sensitive adhesive polymers will represent approximately 1 wt % to 75 wt %, preferably 2 wt % to 30 wt %, more preferably 5 wt. % to 20 wt. % of the formulation, and more preferably in the range of 0.1% 80% w/w or w/v.

The oral formulation of the disclosure may comprise **permeation enhancers** known to those skilled in the art either alone or in combination thereof without any limitation to the following, such as sulfoxides, and similar chemicals such as but not limited to (dimethylsulfoxide, dimethylacetamide, dimethylformamide, decymethylsulfoxide, dimethylisosorbide etc), azone, pyrrolidones such as but not limited to (N-methyl-2-pyrrolidone, 2-pyrrolidon etc.), esters, fatty acid esters such as but not limited to (propylene glycol monolaurate, butyl ethanoate, ethyl ethanoate, isopropyl myristate, isopropyl palmitate, methyl ethanoate,lauryl lactate, ethyl oleate decyl oleate, glycerol monooleate, glycerol monolaurate, lauryl laurate etc.), fatty acids such as but not limited to (capric acid, caprylic acid, lauric acid, oleic acid, myristic acid, linoleic acid, stearic acid, palmitic acid etc.), alcohols, fatty alcohols and glycols such as but not limited to (oleyl alcohol, nathanol, dodecanol, propylene glycol, glycerol etc.), ethers alcohol such as but not limited to (diethylene glycol monoethyl ether), urea, triglycerides such as but not limited to triacetin, polyoxyethylene fatty alcohol ethers, polyoxyethylene fatty acid esters, esters of fatty alcohols, essential oils, surfactant type enhancers such as but not limited to (brij, sodium lauryl sulfate, tween, polysorbate), terpene, terpenoids and all penetration or permeation enhancers referred in the book "Percutaneous Penetration Enhancers" *(Eric W. Smith, Howard I. Maibach, 2005. Nov, CRC press).* In exemplary embodiments, formulations of the disclosure may comprise **permeation enhancers** at a concentration of abount 0.01%, about 0.02%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 75%, about 75%, and about 80% of the formulation. In exemplary embodiments, formulations of the disclosure may comprise **permeation enhancers** at a concentration of about 1 to 20%, of about 5% to 25%, about 10% to about 20%, or about 15% to about 18%, about 30% to about 70%, about 35% to about 65%, about

63.13%, and about 40% to about 64% w/w. In exemplary formulations of the disclosure, the **permeation enhancers** will represent approximately 1 wt % to 75 wt %, preferably 2 wt % to 30 wt %, more preferably 5 wt. % to 20 wt. % of the formulation, and more preferably in the range of 0.01% - 95% w/w or w/v.

All of the components from Table 1, with the exception of the Hydroxychloroquine and/or chloroquine, were mixed together with stirring for 18 hours. Next, the Hydroxychloroquine and/or chloroquine was added into the excipient mixture to prepare the final oral formulations.

Example 3

The following steps are provided using composition HCQ and/or CQ 1 as an example for preparing an oral patch. The above ingredients are blended by stirring for 18 hours and then, using a commercial benchtop spreader, the matrix is evenly spread onto an 8 x 14 inch sheet of release liner (such as 3M 9744) to a thickness of 0.5mm.

The sheet is then placed in an oven at 110°F for one hour to evaporate off the ethyl acetate adhesive solvent. An opaque backing membrane (such as 3M 9730 NR film) with low permeability to oxygen to inhibit photo and oxidative degradation is then carefully applied by hand to avoid formation of bubbles and voids. A circular die (1.5 inches diameter) is used to cut patches (7 sqcm) for subsequent studies. After drying, the drug adhesive matrix has a surface density of 5 – 30 mg/sqcm, containing hydroxychloroqyine in 0.1 – 20% w/w.

Example 4

The prepared oral formulations were then subjected to a flux measurement test as follows. Human cadaver memebrane, stored at -80°C, was thawed at room temperature in phosphate buffered saline (PBS), and visually inspected for defects before using in the study. The flux was then measured using standard Franz diffusion cells comprising a cylindrical donor compart and a separate water jacketed cylindrical receptor compartment with the volume of 13 mL. The cadaver membrane was clamped between the two compartments with the dermis side facing toward the receptor compartment. The donor compartment was filled with the Hydroxychloroquine and/or chloroquine formulations prepared as described above. The receptor compartment was filled with receptor medium, held at constant temperature, and constantly stirred to collect the Hydroxychloroquine and/or chloroquine as it diffuses through the membrane and into receptor compartment. It is important to confirm that the receptor fluid is always in contact with the membrane. The receptor compartment was emptied at 24 hr

intervals for assay of Hydroxychloroquine and/or chloroquine and replaced with fresh receptor solution. In order to maintain the sink condition in the receptor compartment, it is important to keep the Hydroxychloroquine and/or chloroquine concentration in the receptor compartment less than 10% of its solubility.

The oral formulation of the disclosure may comprise **plasticizers** known to those skilled in the art either alone or in combination thereof without any limitation to following like glycerol and its esters, phosphate esters, glycol derivatives, sugar alcohols, sebacic acid esters, citric acid esters, tartaric acid esters, adipate, phthalic acid esters, triacetin, oleic acid esters and all the plasticizers which can be used in oral drug delivery system referred in the book "Handbook of Plasticizers" *(George Wypych, 2004, Chem Tec Publishing).* In exemplary embodiments, formulations of the disclosure may comprise **plasticizers** at a concentration of abount 0.01%, about 0.02%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 75%, about 75%, and about 80% of the formulation. In exemplary embodiments, formulations of the disclosure may comprise **plasticizers** at a concentration of about 1 to 20%, of about 5% to 25%, about 10% to about 20%, or about 15% to about 18%, about 30% to about 70%, about 35% to about 65%, about 63.13%, and about 40% to about 64% w/w. In exemplary formulations of the disclosure, the **plasticizers** will represent approximately 1 wt % to 75 wt %, preferably 2 wt % to 30 wt %, more preferably 5 wt. % to 20 wt. % of the formulation. More preferably in the range of 0.01% - 95% w/w or w/v.

Example 5

The oral formulation of the disclosure may comprise **emollients, humectants, irritation reducing agents** and similar compounds or chemicals known to those skilled in the art either alone or in combinations thereof without any limitation to following like petrolatum, lanolin, mineral oil, dimethicone, zinc oxide, glycerin, propylene glycol and others. More preferably in the range of 0.01% - 95% w/w or w/v. In exemplary embodiments, formulations of the disclosure may comprise **emollients, humectants, irritation reducing agents** and similar compounds at a concentration of abount 0.01%, about 0.02%, about 0.05%, about

0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 75%, about 75%, and about 80% of the formulation. In exemplary embodiments, formulations of the disclosure may comprise **emollients, humectants, irritation reducing agents** and similar compounds at a concentration of about 1 to 20%, of about 5% to 25%, about 10% to about 20%, or about 15% to about 18%, about 30% to about 70%, about 35% to about 65%, about 63.13%, and about 40% to about 64% w/w. In exemplary formulations of the disclosure, the emollients, humectants, irritation reducing agents and similar compounds will represent approximately 1 wt % to 75 wt %, preferably 2 wt % to 30 wt %, more preferably 5 wt. % to 20 wt. % of the formulation, and more preferably in the range of 0.01% - 95% w/w or w/v.

Example 6

The oral formulation of the disclosure may comprise **solubilizers, surfactants, emulsifying agents, dispersing agents** and similar compounds or chemicals known to those skilled in the art either alone or in combination thereof without any limitation to following like polysorbate such as but not limited to (polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80 etc.), span such as but not limited to (span 80, span 20 etc.), surfactants such as (anionic, cationic, nonionic and amphoteric), propylene glycol monocaprylate type I, propylene glycol monocaprylate type II, propylene glycol dicaprylate, medium chain triglycerides, propylene glycol monolaurate type II, linoleoyl polyoxyl-6 glycerides, oleoyl-polyoxy1-6-glycerides, lauroyl polyoxyl-6-gylcerides, polyglycery1-3- dioleate, diethylene glycol monoethyl ether, propylene glycol monolaurate type I, polyglyceryl-3-dioleate, caprylocaproyl polyoxyl — 8 glycerides etc, cyclodextrins and others. More preferably in the range of 0.01% 95% w/w or w/v. In exemplary embodiments, formulations of the disclosure may comprise **solubilizers, surfactants, emulsifying agents, dispersing agents and similar compounds** at a concentration of abount 0.01%, about 0.02%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about

17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 75%, about 75%, and about 80% of the formulation. In exemplary embodiments, formulations of the disclosure may comprise **solubilizers, surfactants, emulsifying agents, dispersing agents and similar compounds** at a concentration of about 1 to 20%, of about 5% to 25%, about 10% to about 20%, or about 15% to about 18%, about 30% to about 70%, about 35% to about 65%, about 63.13%, and about 40% to about 64% w/w. In exemplary formulations of the disclosure, the solubilizers, surfactants, emulsifying agents, dispersing agents and similar compounds will represent approximately 1 wt % to 75 wt %, preferably 2 wt % to 30 wt %, more preferably 5 wt. % to 20 wt. % of the formulation, and more preferably in the range of 0.01% 95% w/w or w/v.

Example 7

Different techniques and ingredients can be used to increase the stability and/or solubility of the active agents in formulation such as without any limitation to coating, encapsulation, microencapsulation, nanoencapsulation, lyophilization, chelating agents, complexing agents, etc.

Example 8

The oral formulation of the disclosure may comprise auxiliary **pH buffering agents and pH stabilizers** and similar compounds known to those skilled in the art which helps to maintain the appropriate pH of formulation preferably in the range of 4.0-8.0 either alone or in combination thereof without any limitation to following such as phosphate buffer, acetate buffer, citrate buffer, etc., acids such as but not limited to (carboxylic acids, inorganic acids, sulfonic acids, vinylogous carboxylic acids and others), base such as but not limited to (sodium hydroxide, potassium hydroxide, ammonium hydroxide, triethylamine, sodium carbonate, sodium bicarbonate) etc. More preferably in the range of 0.01% - 30% w/w or w/v. In exemplary embodiments, formulations of the disclosure may comprise **pH buffering agents and pH stabilizers** and similar compounds at a concentration of abount 0.01%, about 0.02%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%,

about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 75%, about 75%, and about 80% of the formulation. In exemplary embodiments, formulations of the disclosure may comprise **pH buffering agents and pH stabilizers** and similar compounds at a concentration of about 1 to 20%, of about 5% to 25%, about 10% to about 20%, or about 15% to about 18%, about 30% to about 70%, about 35% to about 65%, about 63.13%, and about 40% to about 64% w/w. In exemplary formulations of the disclosure, the **pH buffering agents and pH stabilizers** and similar compounds will represent approximately 1 wt % to 75 wt %, preferably 2 wt % to 30 wt %, more preferably 5 wt. % to 20 wt. % of the formulation, and more preferably in the range of 0.01% - 30% w/w or w/v.

Example 9

The oral formulation of the disclosure may comprise **antioxidants** such as but not limited to (sodium metabisulfite, citric acid, ascorbic acid, BHA, BHT), oxidizing agents, stabilizers, discoloring agents, preservatives and similar compounds or chemicals known to those skilled in the art which helps to get a stable formulation can be used either alone or in combination thereof without any limitation. More preferably in the range of 0.01% - 50% w/w or w/v. In exemplary embodiments, formulations of the disclosure may comprise **antioxidants** at a concentration of abount 0.01%, about 0.02%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 75%, about 75%, and about 80% of the formulation. In exemplary embodiments, formulations of the disclosure may comprise **antioxidants** at a concentration of about 1 to 20%, of about 5% to 25%, about 10% to about 20%, or about 15% to about 18%, about 30% to about 70%, about 35% to about 65%, about 63.13%, and about 40% to about 64% w/w. In exemplary formulations of the disclosure, the **antioxidants** will represent approximately 1 wt % to 75 wt %, preferably 2 wt % to 30 wt %, more preferably 5 wt. % to 20 wt. % of the formulation, and more preferably in the range of 0.01% - 50% w/w or w/v.

Example 10

The oral formulation of the disclosure may be formulated in ointment and/or cream base and/or gel and/or film forming formulation and/or oral matrix formulation and/or drug-in-adhesive matrix patch and/or matrix patch known to those skilled in the art.

Example 11

Materials to make the oral delivery system of the disclosure in patch form known to those skilled in the art, for example, such as but not limited to reservoir patch, matrix patch, drug in adhesives, film forming formulation, micro-dosing oral patch, oral films and may include, such as but are not limited to polymers, copolymers, derivatives, backing film, release membranes, release liners, etc. either alone or in combinations thereof. Pressure sensitive adhesives (such as but not limited to silicone polymers, rubber based adhesives, acrylic polymers, acrylic copolymers, polyisobutylene, acrylic acid – isooctyl acrylate copolymer, hot melt adhesives, polybutylene etc.), backing film (such as but not limited to ethylene vinyl acetate copolymers, vinyl acetate resins, polyurethane, polyvinyl chloride, metal foils, polyester, aluminized films, polyethylene, etc.), release membrane (such as but not limited to microporous polyethylene membrane, microporous polypropylene membrane, rate controlling ethylene vinyl acetate copolymer membrane etc.), release liners (such as but not limited to siliconized polyester films, fluoropolymer coated polyester film, polyester film, siliconized polyethylene terephthalate film, etc.) , tapes, etc.

The oral formulation and/or oral delivery system of the disclosure may deliver at least therapeutic effective dose of active agent, Hydroxychloroquine and/or chloroquine, and its derivatives, alone or in combinations thereof in human plasma required for treating and/or preventing rheumatoid arthritis and/or malaria and/or lupus erythematosus and/or SARS CoV infection and/or prophyra cutanea tarda. Therapeutically effective active agent Hydroxychloroquine and/or chloroquine, and/or its derivatives dosages refers to the therapeutic concentration of in human plasma required for treating and/or preventing rheumatoid arthritis and/or malaria and/or lupus erythematosus and/or SARS CoV infection and/or prophyra cutanea tarda. Furthermore, the precise therapeutic effective dose of Hydroxychloroquine and/or chloroquine, and its derivatives in the oral formulation or oral delivery system can be determined by those skilled in the art based on factors such as but not limited to the patient's condition etc. The oral formulation or oral delivery system will be available in different dosage strengths and patch sizes in order to achieve optimum therapeutic outcome based on patient's requirement.

In yet another embodiment, the oral formulation and/or oral delivery system of the disclosure may deliver at least therapeutic effective dose of Hydroxychloroquine and/or chloroquine and derivatives thereof, and pharmaceutically available salts thereof. Therapeutically effective doses of active agent Hydroxychloroquine and/or chloroquine, and its derivatives refers to the therapeutic concentration of active agent in human plasma required for the treatment and/or prevention and/or control of rheumatoid arthritis and/or malaria and/or lupus erythematosus and/or SARS CoV infection and/or prophyra cutanea tarda.

The oral formulation or oral patch of active agent Hydroxychloroquine and/or chloroquine and its derivatives can be applied to the mucosal surface in any of the following dosage regimens such as once in a day, once in two days, once in three days, once in four days, once in five days, once in six days, once in a week, once in a range of from about 8 to about 13 days, once in two weeks, or once in 15 days.

Example 12

Pressure sensitive adhesive Formulation:

Ingredients	%W/W
Active component	0.1% - 30%
Solvent	1%-40%
Permeation Enhancers	1%-40%
Pressure sensitive adhesive	20%-90%
Polymers	2%-50%

The present formulation is not deemed to be limited thereto.

While the disclosure has been described in detail and with reference to specific examples thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

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While the invention has been described in detail and with reference to specific examples thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

5

CLAIMS

WHAT IS CLAIMED IS:

1. An Oral delivery system (ODS) for administration of Hydroxychloroquine and/or Chloroquine comprising:

- an active substance area or reservoir which comprises a pharmaceutical composition comprising Hydroxychloroquine and/or Chloroquine and at least one excipient;

- an impermeable backing layer;

- optionally, a releasing membrane, which is covered by a detachable backing layer;

wherein the ODS, will bypass first pass metabolism.

2. The ODS according to claim 1, wherein the active substance area or reservoir is configured as a polymer matrix system, a liquid system, a gel system, or a pressure sensitive adhesive system.

3. The ODS according to any one of claims 1-2, wherein the active substance reservoir is constructed in a pouch-shaped system

4. The ODS according to any one of claims 1-3, wherein the active substance reservoir is a preparation selected from the group consisting of flowable, viscous, semi-solid, gel-like, liquid preparation, solution, dispersion, suspension, and emulsion.

5. The TDDS according to any one of claims 1-4 wherein the active substance reservoir is confined on the mucosa facing side by an active substance permeable membrane and on the opposite side from the mucosa by an active substance impermeable layer.

6. The ODS according to any one of claims 1-5, comprising an active substance permeable membrane which modifies or controls the rate of active substance release.

7. The ODS according to any one of claims 1-6, characterized in that the Hydroxychloroquine and/or chloroquine containing area is a single-, double-, or multilayered active substance matrix.

8. The ODS according to any one of claims 1-7 further comprising an adhesive which may be applied as a plaster or bandage.

9. The ODS according to any one of claims 1-8 wherein the active substance is a matrix selected from the group consisting of natural polymers, polysaccharides. agar, alginic acid and derivatives, cassia tora, collagen, gelatin, gellum gum, guar gum, pectin, potassium cargeenan, sodium carageenan, tragacanth, xantham, gum copal, chitosan, resin, semisynthetic polymers, cellulose, methylcellulose, ethyl cellulose, carboxymethyl cellulose, hydroxylpropyl cellulose, hydroxylpropylmethyl cellulose, synthetic polymers, carboxyvinyl polymers, carbomers, carbopol 940, carbopol 934, carbopol 971p NF, polyethylene, clays, silicates, bentonite, silicon dioxide, polyvinyl alcohol, acrylic polymers (eudragit), acrylic acid esters, polyacrylate copolymers, polyacrylamide, polyvinyl pyrrolidone homopolymer, polyvinyl

pyrrolidone copolymers, PVP, Kollidon 30, poloxamer, isobutylene, ethyl vinyl acetate copolymers, natural rubber, synthetic rubber, pressure sensitive adhesives, silicone polymers, bio psa 4302, bio-psa 4202, acrylic pressure sensitive adhesives, duro –tak 87-2156, duro-tak 387-2287, duro-tak 87-9301, duro-tak 387-2051, polyisobutylene, polyisobutylene low molecular weight, polyisobutylene medium molecular weight, polyisobutylene 35000 mw, acrylic copolymers, rubber based adhesives, hot melt adhesives, styrene-butadiene copolymers, bentonite, all water and/or organic solvent swellable polymers and combinations thereof.

10. The ODS according to any one of claims 1-9, wherein the active substance reservoir contains a fiber material, a woven fabric, or a nonwoven fabric, to which the active substance is adsorbed.

11. The ODS according to any one of claims 1-10, can deliver 1-40 mg/day Hydroxychloroquine and/or chloroquine through the oral mucosa to the blood in a subject, wherein the ODSproduces up to 2000 ng/ml plasma concentration.

12. The ODS according to any one of claims 1-11, wherein the Hydroxychloroquine and/or chloroquine is present in a concentration in the range of from 0.1-50 wt% relative total mass of the active substance reservoir.

13. The ODS according to any one of claims 1-12, wherein the Hydroxychloroquine and/or chloroquine is present in a concentration in the range of from 1-30 wt% relative total mass of the active substance reservoir.

14. The ODS according to any one of claims 1-13, wherein the Hydroxychloroquine and/or chloroquine is present in a concentration in the range of from 1 -20 wt% relative total mass of the active substance reservoir.

15. The ODS according to any one of claims 1-14, wherein Hydroxychloroquine and/or chloroquine is present in the active substance reservoir either in dissolved or suspended state.

16. The ODS according to any one of claims 1-15, wherein the active substance reservoir contains at least one solubilizer, in an amount of from 1 to 99 wt% relative to the total weight of the active substance reservoir.

17. , The ODS according to any one of claims 1-16, wherein the active substance reservoir contains at least one solubilizer in an amount of from 5 to 70 wt% relative to the total weight of the active substance reservoir.

18. The ODS according to any one of claims 1-17, wherein the solubilizer is selected from the group consisting of methanol, ethanol, isopropyl alcohol, butanol, propanol, polyhydric alcohols, glycols, propylene glycol, polyethylene glycol, dipropylene glycol, hexylene glycol, butyene glycol, glycerine, derivative of glycols, pyrrolidone, N methyl 2- pyrrolidone, 2 pyrrolidone, sulfoxides, dimethyl sulfoxide, decymethylsulfoxide, dimethylisosorbide, mineral oils, vegetable oils, sesame oil water, polar solvents, semi polar solvents, non polar solvents, volatile chemicals, ethanol, propanol, ethyl acetate, acetone, methanol,

dichloromethane, chloroform, toluene, IPA, hexane, acids, acetic acid, lactic acid, levulinic acid, bases, pentane, dimethylformamide, butane, lipids, and combinations thereof.

19. The ODS according to any one of claims 1-18, wherein the active substance reservoir contains at least one permeation-enhancing agent in an amount of from 0.1 to 50wt% relative to the total weight of the active substance reservoir.

20. The ODS according to any one of claims 1-19, wherein the active substance reservoir contains at least one permeation-enhancing agent, in an amount of from 1 to 25wt% relative to the total weight of the active substance reservoir.

21. The ODS according to any one of claims 1-20 where in the permeation-enhancing agent is selected from the group consisting of dimethylsulfoxide, dimethylacetamide, dimethylformamide, decymethylsulfoxide, dimethylisosorbide, azone, pyrrolidones, N-methyl-2-pyrrolidone, 2-pyrrolidon, esters, fatty acid esters, propylene glycol monolaurate, butyl ethanoate, ethyl ethanoate, isopropyl myristate, isopropyl palmitate, methyl ethanoate, lauryl lactate, ethyl oleate decyl oleate, glycerol monooleate, glycerol monolaurate, lauryl laurate, fatty acids, capric acid, caprylic acid, lauric acid, oleic acid, myristic acid, linoleic acid, stearic acid, palmitic acid, alcohols, fatty alcohols, glycols, oleyl alcohol, nathanol, dodecanol, propylene glycol, glycerol, ethers, alcohol, diethylene glycol monoethyl ether, urea, triglycerides, triacetin, polyoxyethylene fatty alcohol ethers, polyoxyethylene fatty acid esters, esters of fatty alcohols, essential oils, surfactant type enhancers, brij, sodium lauryl sulfate, tween, polysorbate, terpene, terpenoids, and combinations thereof.

22. The pharmaceutical composition of any one of claims 1 to 21 formulated as oral liquid formulation, oral semisolid formulation, oral polymer matrix formulation, oral adhesive matrix formulation, film forming gel formulation, film forming spray formulation, Oral liquid spray, or Oral Spray

23. Use of a Hydroxychloroquine and/or chloroquine- containing ODS according to any one of claims 1 to 22 for treating rheumatoid arthritis, malaria, lupus erythematosus, SARS CoV-2 Infection, and porphyria Cutanea tarda.

24. A method of treating and/or preventing rheumatoid arthritis comprising:

- selecting a patient in need of such treatment and/or prevention;
- applying to the oral mucosa of the patient an ODS as set forth in any one of claims 1-22;

thereby treating and/or preventing the rheumatoid arthritis.

25. A method of treating and/or preventing lupus erythematosus comprising:

- selecting a patient in need of such treatment and/or prevention;
- applying to the oral mucosa of the patient an ODS as set forth in any one of claims 1-22;

thereby treating and/or preventing the lupus erythematosus.

26. A method of treating and/or preventing malaria comprising:

- selecting a patient in need of such treatment and/or prevention;

- applying to the oral mucosa of the patient an ODS as set forth in any one of claims 1-22;

thereby treating and/or preventing the malaria.

27. A method of treating and/or preventing SARS CoV-2 comprising:

- selecting a patient in need of such treatment and/or prevention;

- applying to the oral mucosa of the patient an ODS as set forth in any one of claims 1-22;

thereby treating and/or preventing the SARS CoV-2.

28. A method of treating and/or preventing Prophyria Cutanea Tarda comprising:

- selecting a patient in need of such treatment and/or prevention;

- applying to the oral mucosa of the patient an ODS as set forth in any one of claims 1-22;

thereby treating and/or preventing the Prophyria Cutanea Tarda.

29. The method according to any of the preceding claims, characterized in that the application period of the ODS is at least 24 Hr and maximally 7 days.

30. A method of making a Oral delivery system (ODS) for administration of Hydroxychloroquine and/or chloroquine comprising:

- providing an active substance area or reservoir;

- providing an impermeable backing layer;

- optionally providing a releasing membrane, which is covered by a detachable backing layer,

wherein the active substance area or reservoir comprises a pharmaceutical composition comprising Hydroxychloroquine and/or chloroquine and at least one excipient.

31. The ODS according to any one of claims 1-22 where the oral delivery system can bypass first pass metabolism effect of the hydroxychloroquine and/or chloroquine.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2021/000249

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***A61K 31/4706*** (2006.01) , ***A61K 9/00*** (2006.01) , ***A61P 19/02*** (2006.01) , ***A61P 3/00*** (2006.01) , ***A61P 31/14*** (2006.01) , ***A61P 33/06*** (2006.01) (more IPCs on the last page)

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 (2006.01), A61P (2006.01), C07D (2006.01)

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

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Questel Orbit, Scopus (hydroxychloroquine, chloroquine, drug delivery, patch, oral patch, backing layer)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AHADIAN et al., "*Micro and nanoscale technologies in oral drug delivery*". Advanced Drug Delivery Reviews, January 2020 (2020), Vol. 157, pp. 37 - 62,	1, 23, 27, 31
Y	*section 4.4, page 16 last paragraph, page 21 second full paragraph*	2-7, 9, 11-21
Y	SHINKAR et al., "*Drug Delivery from the Oral Cavity: A Focus on Mucoadhesive Buccal Drug Delivery Systems*". PDA J Pharm Sci and Tech, 2012, Vol. 66, pp. 466-500, *abstract, page 467, page 483 section 2 – page 484	2-7, 9, 11-21, 24-26, 28-30
Y	CUI et al., "*Nanoparticles Incorporated in Bilaminated Films: A Smart Drug Delivery System for Oral Formulations*". Biomacromolecules, 2007, Vol. 8, pp. 2845-2850, *page 2845-2846*	2-7, 9, 11-21, 24-26, 28-30
Y	CA 2,104,903 A1 (STECHER et al.) 16 March 1994 (16-03-1994) *whole document*	24-26, 28-30

☒ Further documents are listed in the continuation of Box C. ☒ 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	
"D" document cited by the applicant in the international application	
"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 22 July 2021 (22-07-2021)	Date of mailing of the international search report 23 July 2021 (23-07-2021)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 819-953-2476	Authorized officer Orysia Zaporozan (819) 639-9424

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2021/000249

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SINGAL et al., "*Low-Dose Hydroxychloroquine is as Effective as Phlebotomy in Treatment of Patients with Porphyria Cutanea Tarda*". Clin Gastroenterol Hepatol, December 2012 (12-2012), Vol. 10(12), pp. 1402–1409, *page 1, 2*	24-26, 28-30
A, D	TETT et al., "*Bioavailability of hydroxychloroquine tablets in healthy volunteers*". Br. J. clin. Pharmac., 1989, Vol. 27, pp. 771-779,	1-31

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2021/000249

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claim Nos.: 8, 10, 22
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims 8, 10, 22 encompass a product that is not defined in clear and concise terms as required under PCT Article 6. The application provides support within the meaning of PCT Article 6 for specifically an oral drug delivery system. In the present case, the claims so lack clarity and/or support, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been established for the parts of the application which appear to be clear and/or supported, namely an oral drug delivery system intended for oral mucosal delivery.

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

A61P 37/06 (2006.01) , ***C07D 215/46*** (2006.01)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2021/000249

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
CA2104903A1	16 March 1994 (16-03-1994)	AT166646T	15 June 1998 (15-06-1998)
		AU4732693A	24 March 1994 (24-03-1994)
		AU7549496A	10 April 1997 (10-04-1997)
		CZ192393A3	16 March 1994 (16-03-1994)
		DE69318783D1	02 July 1998 (02-07-1998)
		EP0588430A1	23 March 1994 (23-03-1994)
		EP0588430B1	27 May 1998 (27-05-1998)
		FI934051A	16 March 1994 (16-03-1994)
		HU9302613D0	28 December 1993 (28-12-1993)
		HUT70025A	28 September 1995 (28-09-1995)
		IL107004D0	28 December 1993 (28-12-1993)
		JPH06199801A	19 July 1994 (19-07-1994)
		KR940007002A	26 April 1994 (26-04-1994)
		MX9305621A	31 March 1994 (31-03-1994)
		NO933293D0	15 September 1993 (15-09-1993)
		NO933293L	16 March 1994 (16-03-1994)
		NO180677B	17 February 1997 (17-02-1997)
		NO180677C	28 May 1997 (28-05-1997)
		NZ248671A	27 April 1995 (27-04-1995)
		PH30153A	21 January 1997 (21-01-1997)
		SK98793A3	07 September 1994 (07-09-1994)
		US5314894A	24 May 1994 (24-05-1994)