Abstract: The present invention relates to compositions and methods for rapid delivery of a pharmaceutical ingredient across the oral mucosa by administering a liquid composition comprising a pharmaceutical ingredient, Methylsulfonylmethane (MSM) and a carrier to oral mucous membranes of a subject in need thereof.
COMPOSITIONS AND METHODS FOR RAPID TRANSMUCOSAL DELIVERY OF PHARMACEUTICAL INGREDIENTS

FIELD OF THE INVENTION

The present invention relates to compositions and method for rapid delivery of a pharmaceutical ingredient across the oral mucosa by administering a liquid composition comprising a pharmaceutical ingredient, methylsulfonylmethane (MSM) and a carrier to oral mucous membranes of a subject in need thereof.

BACKGROUND OF THE INVENTION

The pharmaceutical industry is actively seeking to develop new and improved modes of drug delivery to enhance the effectiveness of particular drugs, including, targeting the drug to the intended site, reducing dosage, decreasing toxicity, and the like.

Transmucosal drug delivery has been explored intensively during the last decade to overcome the disadvantages of oral drug delivery via the gastrointestinal (GI) tract. Advantages of the former include the bypass of first-pass metabolism and the avoidance of pre-systemic elimination within the GI tract. In contrast, substances which are delivered by the traditional oral route (i.e., swallowing) are subjected to an environment that includes hydrochloric acid, enzymes such as pepsin in the stomach, bile acids and bile juices, pancreatic enzymes, the alkaline pH of the small intestine, and the bacterial content of the large intestine. Namely, the avoidance of the first pass effect provides rationale for the use of mucous formulations.

Mucous membranes are the moist linings of the orifices and internal parts of the body that are in continuity with the external surface. They cover, protect, and provide secretory and absorptive functions in the channels and extended pockets of the outside world that are incorporated in the body. The mucous membranes function as a barrier essential in preventing viruses and bacteria from entering into tissues. Of the various mucous membranes (e.g., oral, rectal, vaginal, ocular, nasal), drug delivery via the mucous membranes in the oral cavity seems to be the most easily tolerated by patients.

In general, the mucous membranes of the oral cavity can be divided into five main regions: the floor of the mouth (sublingual), the cheeks (buccal), the gums (gingival), the roof of the mouth (palatal), and the lining of the lips. These regions differ from each other with
respect to their anatomy, drug permeability, and physiological response to drugs. Sublingual
delivery gives rapid absorption and good bioavailability for some small permeants, although
this site is not well suited to sustained-delivery systems. The buccal mucosa, by comparison,
is considerably less permeable, but is probably better suited to the development of sustained-
delivery systems.

In addition to the differences in permeability of the various mucous membranes, the
extent of drug delivery is also affected by the properties of the drug to be delivered. The
ability of a molecule to pass through any mucous membrane is dependent upon its size, its
lipid solubility, and the extent to which it is ionized, among other factors. However, the
relatively small surface area of the oral mucosa and the significant loss of drug due to
uncontrolled swallowing and salivary flow are the main limitations of this route.

US Patent No. 6,676,959 discloses nicotine containing pharmaceutical compositions
for transmucosal absorption of nicotine.

composition for the treatment of sexual disorders. The compositions may be administered by
buccal or sublingual routes.

U.S. Patent No. 4,572,832 discloses a soft buccal dosage form containing a
medicament to be absorbed through the oral mucosa, a water-soluble protein, a polyhydric
alcohol, and a fatty acid ester or/and a carboxyvinyl polymer, which can be used for
administration to the mucous membranes of the mouth.

U.S. Patent No. 4,764,378 discloses buccal dosage forms for transmucosal
administration of drugs comprising a pharmaceutical compound dispersed in an erodible
matrix comprising a low molecular weight polyethylene glycol component, a medium or high
molecular weight polyethylene glycol component, and as an auxiliary a high molecular
weight polymer.

U.S. Patent No. 5,346,701 discloses a system for mucosal administration of a
macromolecular drug, comprising an inner drug/enhancer/polymer layer having one surface
adapted to contact the mucosal tissue of the oral cavity and adhere thereto, said inner layer
containing a bile salt enhancer, a hydrophilic polymer and a macromolecular drug having a
molecular weight of at least 500 daltons *inter alia* calcitonin or heparin.

U.S. Patent No. 4,713,243 discloses a thin film capable of adhering to a wet mucous
surface which comprises a bioadhesive layer consisting of hydroxypropyl cellulose,
polyethylene oxide, a plasticizer, a medicament, and optionally a water-insoluble polymer. The film is useful for controlled release of a medicament such as anesthetics, anti-inflammatories, antihistamines, antibiotics, and antibacterials.

U.S. Patent Nos. 5,948,430, 6,177,096, 6,284,264, 6,592,887, and 6,709,671 disclose mucoadhesive films capable of rapidly dissolving and adhering to the oral cavity comprising a water-soluble polymer and a pharmaceutically or cosmetically active ingredient and methods of use thereof.

**Methylsulfonylmethane**

Methylsulfonylmethane (MSM), also known as dimethyl sulfone or organic sulfur, is a naturally occurring sulfur-containing compound found in a variety of fruits, vegetables, grains, mammal's milk and animals including humans. MSM is the primary oxidative metabolite product of dimethyl sulfoxide in humans.

The toxicity of methylsulfonylmethane was evaluated in rats at a dose five to seven times the maximum recommended dose in humans and was found to be well tolerated in rats at dosages of up to 2 g/kg (Horvath et al, 2002, Food Chem Toxicol. 40(10): 1459-1462).

MSM is sold as a dietary supplement and is commonly used (often in combination with glucosamine and/or chondroitin) for treatment or prevention of osteoarthritis.

Published patents relating to the use of methylsulfonylmethane to prevent, treat or relieve various conditions include: U.S. Patent Nos. 6,440,391 and 5,569,679 (management of snoring), U.S. Patent No. 4,973,605 (relief of pain and nocturnal cramps and reduction of stress-induced death in animals), U.S. Patent No. 4,559,329 (reduction of gastric upset and allergic reactions), U.S. Patent No. 4,447,469 and U.S. Patent No. 6,541,045 (softener of skin, nails and other tissues), and International Patent Application Publication No. WO 1994/05293 (improving the condition of the skin).

U.S. Patent No. 4,568,547 discloses use of methylsulfonylmethane as a tableting and granulating excipient for pharmaceutical ingredients which are unstable in the presence of moisture.


U.S. Patent No. 6,444,234 discloses a liquid carrier composition effective for the transdermal delivery of a medicament having a given polarity, the composition comprising methylsulfonylmethane as a solvent modifier.
U.S. Patent No. 6,416,772 discloses a composition applied transdermally for relief of pain comprising alcohol, glycerin, an analgesic agent, the analgesic agent comprising a derivative of salicylic acid, methylsulfonylmethane, and emu oil.


U.S. Patent Application Publication No. 2004/0247669 discloses long lasting flavored dosage forms for sustained release of beneficial agents within the mouth. The composition potentially comprises MSM.


Despite the enormous efforts made in developing buccal and sublingual drug delivery systems only a few formulations have made a successful transition to the market. There is thus an ongoing need for improved methods and dosage forms for oral transmucosal delivery of medicaments that will facilitate effective and rapid penetration into the blood circulation and will thus further expand the utility of oral mucosa route of administration. Such methods and dosage forms would induce faster action of the medicaments and reduce the dosage required to achieve a therapeutic effect.

SUMMARY OF THE INVENTION

The present invention provides compositions, methods and a dosage form that achieve rapid onset of a beneficial agent by delivery across the oral mucous membranes. The methods comprise administering a liquid composition comprising a beneficial agent, methylsulfonylmethane (MSM) and a carrier to the oral mucosa. The methods achieve rapid and/or enhanced penetration of the beneficial agent into the blood circulation and allow lower therapeutic dosages of administration.

A prominent advantage of an oral mucosal delivery system is the bypass of the first-pass metabolism and the avoidance of the pre-systemic elimination within the GI tract.

The inventor of the present invention has found that the presence of MSM in a liquid composition provides an unexpected rapid absorption and enhanced penetration into the
blood circulation of pharmaceutical agents. Oral absorption and penetration of a pharmaceutical ingredient into the blood circulation according to the present invention occurs within a few minutes (e.g., 5-15 minutes or less). Furthermore, in some embodiments, the invention provides lower amounts of administration of an active ingredient in order to achieve a therapeutic effect.

In some embodiments, oral mucosal delivery by the composition of the present invention, wherein the active ingredient is the erectile dysfunction medicament, sildenafil citrate, facilitates a faster absorption and shorter time to maximal activity with a lower dose requirement when compared to oral delivery by swallowing of a tablet of sildenafil citrate. In some embodiments, oral mucosal delivery by the composition of the present invention, wherein the active ingredient is the non-steroid anti-inflammatory drug ibuprofen, results with higher levels of ibuprofen in the blood circulation, as compared to oral swallowing of ibuprofen.

According to some embodiments, the amount of MSM that was found to induce a rapid and efficient delivery of a pharmaceutical ingredient does not exceed 10% w/w. This upper limit of MSM is of significant advantage in compositions for oral mucosal applications as this amount is devoid of the unpleasant smell and taste associated with compositions comprising amounts of above 10% w/w MSM which are thus less tolerable to patients.

In one aspect, the present invention provides a pharmaceutical composition suitable for application to the oral mucosa, the composition comprising a pharmaceutical ingredient, methylsulfonylmethane and a carrier, wherein the composition is in the form of a liquid and wherein the methylsulfonylmethane is in an amount sufficient to induce rapid delivery of the pharmaceutical ingredient across the oral mucosa.

In another aspect, the present invention provides a method for rapid delivery of a pharmaceutical ingredient across the oral mucosa, the method comprising administering to the oral mucosa of a subject in need thereof a liquid composition comprising a pharmaceutical ingredient, methylsulfonylmethane and a carrier, wherein the methylsulfonylmethane is in an amount sufficient to induce rapid delivery of the pharmaceutical ingredient across the oral mucosa.

In some embodiments, rapid delivery of the pharmaceutical ingredient is delivery that occurs within 5 to 15 minutes or less from administration of the pharmaceutical ingredient. Each possibility represents a separate embodiment of the invention.
In some embodiments, the liquid composition utilized in the present invention is in the form selected from the group consisting of: a solution, a suspension and an emulsion. Each possibility represents a separate embodiment of the invention. In some embodiments, the emulsion is an oil-in-water emulsion or a water-in-oil emulsion. Each possibility represents a separate embodiment of the invention. In a particular embodiment, the emulsion is an oil-in-water emulsion.

The compositions utilized in the present invention comprise a carrier. In some embodiments, the carrier comprises an edible oil, purified water, and lecithin. In some embodiments, the edible oil is a vegetable oil. In a particular embodiment, the vegetable oil is selected from the group consisting of: cottonseed oil, peanut oil, poppy seed oil, sunflower oil, sesame oil, soybean oil, corn oil, olive oil, canola oil, and combinations thereof. Each possibility represents a separate embodiment of the invention.

The compositions utilized in the present invention further comprise at least one excipient selected from the group consisting of: a sweetening agent, a flavoring agent, a plasticizer, an elastomeric solvent, a filler material, a preservative, a lubricating agent, a wetting agent, an emulsifying agent, solubilizing agent, a suspending agent, a coloring agent, a disintegrating agent and combinations thereof. Each possibility represents a separate embodiment of the invention. In some embodiments, the compositions further comprise at least one excipient selected from the group consisting of: sucralose, sucrose, calcium salt, polysorbate 80, glycine, glycerin, tocopherol, sodium benzoate, and combinations thereof. Each possibility represents a separate embodiment of the invention.

In some embodiments, the compositions utilized in the present invention comprise a pharmaceutical ingredient in an amount of between 0.1% to 15% w/w, methylsulfonylmethane in an amount that does not exceed 10% w/w, a vegetable oil in an amount of between 1% to 20% w/w, purified water in an amount of between 50% to 85% w/w, sucrose in an amount sufficient to serve as a sweetener, and lecithin in an amount of between 1% to 20% w/w.

In some embodiments, the compositions utilized in the present invention comprise a pharmaceutical ingredient in an amount of between 0.1% to 15% w/w, methylsulfonylmethane in an amount that does not exceed 10% w/w, a vegetable oil in an amount of between 1% to 20% w/w, purified water in an amount of between 50% to 85% w/w, sucrose in an amount sufficient to serve as a sweetener, lecithin in an amount of between 1% to 20% w/w, polysorbate 80 in an amount of between 1% to 15% w/w, glycine
in an amount of between 1% to 15% w/w, at least one flavoring agent in an amount of between 1% to 10% w/w, and sodium benzoate in an amount of between 1% to 10% w/w. The compositions may further comprise glycerin in an amount of between 1% to 10% w/w.

5 In some embodiments, the pharmaceutical ingredient to be administered within the composition utilized in the present invention is selected from the group consisting of: an erectile dysfunction medication, a non-steroid anti-inflammatory drug (NSAID), a phytochemical agent, an analgesic, a migraine medication, a menopause medication, a sleep disorder medication, an erectile dysfunction medication, and an appetite suppressant. Each possibility represents a separate embodiment of the invention. In some embodiments, the pharmaceutical ingredient is selected from the group consisting of: a non-steroid anti-inflammatory drug (NSAID), and. Each possibility represents a separate embodiment of the invention.

In some embodiments, the pharmaceutical ingredient has a molecular weight of at least about 100 Daltons (Da) and up to about 5000 Da. In some embodiments, the pharmaceutical ingredient has a molecular weight of at least about 200 Daltons (Da) and up to about 5000 Da. In yet another embodiment, the pharmaceutical ingredient of the present invention is selected from the group consisting of: vitamin B12, an antibiotic, a peptide, calcitonin, vasopressin and oxytocin. In a particular embodiment, the pharmaceutical ingredient is vitamin B12.

In one embodiment, the NSAID is selected from the group consisting of ibuprofen (2-(isobutylphenyl)-propionic acid); methotrexate (N-[4-(2, 4 diaminomethylsulfinyl)phenyl]methylene]-L-glutamic acid); aspirin (acetylsalicylic acid); salicylic acid; diphenhydramine (2-(diphenylmethoxy)-NN-dimethylethylamine hydrochloride); naproxen (2-naphthaleneacetic acid, 6-methoxy-9-methyl-, sodium salt, (-)); phenylbutazone (4-butylnaphthalene-3,5-pyrazolidinedione); sulindac (2)-5-fuoro-2-methyl-l-[p-(methylsulfinyl)phenyl]methylen]-l-H-indene-3 -acetic acid; diflunisal (2',4', -difluoro-4-hydroxy-3-biphenylcarboxylic acid; piroxicam (4-hydroxy-2-methyl-N-2-pyridinyl-2H-l,2-benzothiazine-2-carboxamide 1,1-dioxide, meloxicam (4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-l,2-benzothiazine-3-carboxamide 1,1-dioxide); another oxicam; indomethacin (1-(4-chlorobenzoyl)-5-methoxy-2-methyl-H-indole-3-acetic acid); meclofenamate sodium (N-(2,6-dichloro-m-tolyl) anthranilic acid, sodium salt, monohydrate); nabumetone (4-(6-methoxy-2-naphthalenyl)-2-butanone); ketoprofen (2-(3-benzoylephenyl)-propionic acid;
tolmetin sodium (sodium 1-methyl-5-(4-methylbenzoyl-lH-pyrrole-2-acetate dihydrate); diclofenac sodium (2-[(2,6-dichlorophenyl)amino]benzenecic acid, monosodium salt; hydroxychloroquine sulphate (2-{4-[[7-chloro-4-quinylo] amino]penty]ethylamino}ethanol sulfate (1:1); penicillamine (3-mercaptop-D-valine); flurbiprofen (|l,|l-biphenyl]-4-acetic acid, 2-fluoro-4-ethyl-1,3,4,9-tetrahydropyrano-[3-4-13]indole-1-acetic acid; mefenamic acid (N-(2,3-xylyl)anthranilic acid; and diphenhydramine hydrochloride (2-diphenyl methoxy-N,N-di-methylethamine hydrochloride). Each possibility represents a separate embodiment of the invention. In one embodiment, the analgesic is selected from the group consisting of: acetaminophen and dipyridone (4-methylamino-l,5-dimethyl-2-phenyl-3-pyrazolone sodium methanesulfonate). Each possibility represents a separate embodiment of the invention.

In one embodiment, the phytochemical agent is selected from the group consisting of: parthenolide, theanine, resveratrol, elagic acid.

In another embodiment, the migraine medication is selected from the group consisting of: a triptan, sumatriptan (3-(2-(dimethylamino)ethyl)-N-methyl-lH-indole-5-methanesulfonamide), almogptan (1-(((3-(2(dimethylamino)ethyl)indol-5-yl)methyl)sulfonyl)pyrrolidine), and amitriptyline (3-(10,11-dihydro-5H-dibenzo (a,d)cyclohepten-5-ylidene)-N,N-dimethyl-l-propanamine). Each possibility represents a separate embodiment of the invention.

In yet another embodiment, the menopause medication is selected from the group consisting of: venlafaxine, paroxetine, a phytoestrogen; and a plant extract. In one embodiment, the plant extract is derived from a plant selected from the group consisting of black cohosh and maca. Each possibility represents a separate embodiment of the invention.

In yet another embodiment, the sleep disorder medication is selected from the group consisting of diphenhydramine (2-(benzhydryloxy)-N,N-dimethylethylamine), valerian and melatonin (5-methoxy-N-acetyltryptamine). Each possibility represents a separate embodiment of the invention.

In yet another embodiment, the erectile dysfunction medication is selected from the group consisting of: sildenafil citrate, a prostataglandin, a testosterone, yohimbine, pentoxifylline, trazodone, apomorphine, minoxidil, misoprostol, papaverine, nitroglycerin, phentolamine, moxisylyte, linsidomine, and a pyridylguanidine compound. Each possibility
represents a separate embodiment of the invention. In a particular embodiment, the erectile dysfunction medication is sildenafil citrate.

In yet another embodiment, the appetite suppressant is selected from the group consisting of: D-phenylalanine, L-phenylalanine and combination thereof.

The liquid composition utilized in the present invention may be in any dosage form known in the art. In one embodiment, the liquid composition is in the form of a spray. In accordance with this embodiment, the composition is administered onto the oral cavity or surfaces by spraying the composition onto the oral cavity or surfaces. In another embodiment, the composition is administered in a container in the form of a dropper. In accordance with this embodiment, the composition is administered onto the oral cavity or surfaces by dripping a few drops of the composition onto the oral cavity or surfaces. Alternatively, the composition may be contained in a bottle and the composition may be administered by absorbing the composition onto a swab, a sponge, a cotton wool and the like.

In some embodiments, the oral mucosa is selected from the group consisting of the sublingual mucosa, the buccal mucosa, gingival mucosa, palatal mucosa and a combination thereof.

In another aspect, the present invention provides a method for treating erectile dysfunction in a subject in need thereof, the method comprising, administering to the oral mucosa of a subject in need thereof a liquid composition comprising a therapeutic effective amount of an erectile dysfunction medication, methylsulfonylmethane, and a carrier, wherein said methylsulfonylmethane is in an amount sufficient to induce rapid delivery of said erectile dysfunction medication across the oral mucosa.

In yet another aspect, the present invention provides a pharmaceutical composition for use in treating erectile dysfunction in a subject in need thereof, the composition comprising a therapeutic effective amount of an erectile dysfunction medication, methylsulfonylmethane, and a carrier, wherein said composition is in the form of a liquid and wherein said methylsulfonylmethane is in an amount sufficient to induce rapid delivery of said erectile dysfunction medication across the oral mucosa.

In some embodiments, the erectile dysfunction medication is selected from the group consisting of: sildenafil citrate, a prostaglandin, a testosterone, yohimbine, pentoxifylline, trazodone, apomorphine, tadalafil, minoxidil, misoprostol, papaverine, nitroglycerin, phenolamine, moxisylyte, linsidomine, and a pyridylguanidine compound flibanserin. Each
possibility represents a separate embodiment of the invention. In a particular embodiment, the erectile dysfunction medication is sildenafil citrate. In one embodiment, the sildenafil citrate is in an amount of between 1% to 3% w/w.

In yet another aspect, the present invention provides a method for treating a condition that would benefit from administration of an NSAID in a subject in need thereof, the method comprising administering to the oral mucosa of a subject in need thereof a liquid composition comprising a therapeutic effective amount of an NSAID, methylsulfonylmethane, and a carrier, wherein said methylsulfonylmethane is in an amount sufficient to induce rapid delivery of said NSAID across the oral mucosa.

In yet another aspect, the present invention provides a pharmaceutical composition for use in treating a condition that would benefit from administration of an NSAID in a subject in need thereof, the composition comprising a therapeutic effective amount of an NSAID, methylsulfonylmethane, and a carrier, wherein said composition is in the form of a liquid and wherein said methylsulfonylmethane is in an amount sufficient to induce rapid delivery of said erectile dysfunction medication across the oral mucosa.

In one embodiment, the NSAID is selected from the group consisting of: ibuprofen (2-(isobutylphenyl)-propionic acid); methotrexate (N-[4-(2, 4 diamino 6-pteridinylmethyl]methylamino]benzoyl]-L-glutamic acid); aspirin (acetylsalicylic acid); salicylic acid; diphenhydramine (2-(diphenylmethoxy)-NN-dimethylethylamine hydrochloride); naproxen (2-naphthaleacetic acid, 6-methoxy-9-methyl-, sodium salt, (-)); phenylbutazone (4-butyl-1,2-diphenyl-3,5-pyrazolidinedione); sulindac-(2)-5-fluoro-2-methyl- l-[[p-(methylsulfinyl)phenyl]methylene]-l-H-indene-3 -acetic acid; diflunisal (2',4'-difluoro-4-hydroxy-3-biphenylcarboxylic acid; piroxicam (4-hydroxy-2-methyl-N-2-pyridinyl-2H-1,2-benzothiazine-2-carboxamide 1,1-dioxide, meloxicam (4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide); anoxicam; indomethacin (l-(4-chlorobenzoyl)-5-methoxy-2-methyl-H-indole-3-acetic acid); meclofenamate sodium (N-(2,6-dichloro-m-tolyl) anthranilic acid, sodium salt, monohydrate); nabumetone (4-(6-methoxy-2-naphthalenyl)-2-butanone); ketoprofen (2-(3-benzoylphenyl)-propionic acid; tolmetin sodium (sodium l-methyl-5-(4-methylbenzoyl-H-pyrrole-2-acetate dihydrate); diclofenac sodium (2-[2,6-dichlorophenyl]amino]benzeneacetic acid, monosodium salt); hydroxychloroquine sulphate (2-[4-[7-chloro-4-quinolyl] amino]pentyl]ethylamino]ethanol sulfate (1:1); penicillamine (3-mercaptop-D-valine); flurbiprofen ([l,1-biphenyl]-4-acetic acid, 2-fluoro-aphamethyl-, (+)); etodolac (1-8-diethyl-13,4,9,tetra hydropyrano-[3-4,13]indole-l-
acetic acid; mefenamic acid (N-(2,3-xylyl)anthranilic acid; and diphenhydramine hydrochloride (2-diphenylmethoxy-N,N-di-methylethamine hydrochloride).

In a particular embodiment, the NSAID is ibuprofen (2-(isobutylphenyl)-propionic acid). In a particular embodiment, the ibuprofen is in an amount of between

In some embodiments, the condition that would benefit from administration of an NSAID is at least one condition selected from the group consisting of: inflammation, mild to moderate pain, fever and arterial thrombosis. In some embodiments, the condition is at least one condition selected from the group consisting of: headaches or migraines, rheumatoid arthritis, osteoarthritis, psoriatic arthritis, Reiter's syndrome, acute gout, dysmenorrhea, and renal colic.

Further embodiments and the full scope of applicability of the present invention will become apparent from the detailed description given hereinafter. However, it should be understood that the detailed description and specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

**BRIEF DESCRIPTION OF THE FIGURES**

*Figure 1* is a plot demonstrating the pharmacokinetic profile of sildenafil citrate administered either by Trans Mucosal Oral Delivery (TMOD) or by oral delivery using gavage. Presented are the average plasma concentrations at the indicated time points of sildenafil citrate ± SEM in rabbits administered with either 10 mg/kg sildenafil citrate by gavage or with 5 mg/kg sildenafil citrate by the TMOD.

*Figure 2* is a plot demonstrating the accumulated concentrations of sildenafil citrate in the plasma of rabbits administered with either 10 mg/kg sildenafil citrate by oral delivery using gavage or with 5 mg/kg of sildenafil citrate by TMOD.

*Figure 3* is a plot demonstrating ibuprofen concentrations in swine plasma following TMOD and PO administration of the composition of the present invention comprising ibuprofen or commercially available ibuprofen solution (all pigs received a total of 8 mg/kg of ibuprofen).
DETAILED DESCRIPTION OF THE INVENTION

The present invention provides methods and compositions for accelerating transmucosal delivery of pharmaceutical ingredients, inter alia, Non-Steroid Anti-Inflammatory Drugs (NSAIDs), and erectile dysfunction medications. The composition of the invention is particularly suitable for transmucosal delivery of molecules having molecular weight of at least 100 Daltons (Da) and up to about 5000 Da, and is advantageous over prior art transmucosal delivery formulations which are suitable only for smaller sized molecules, for example up to about 200 Da. The present invention further provides methods of treating an erectile dysfunction and conditions or symptoms which would benefit from administration of an NSAID. Accordingly, the methods of the present invention comprise administering liquid compositions comprising MSM and a carrier to the oral mucosa to effectively and rapidly treat an erectile dysfunction or conditions treated with NSAIDs.

Medicaments taken by mouth and swallowed are absorbed first into the blood perfusing the gastrointestinal tract. The venous drainage from the GI tract is drained into the blood perfusing the liver. This means that medicaments absorbed from the lumen of gastrointestinal tract are immediately presented to the liver, the major detoxifying organ of the body. In addition to protecting the organism from ingested toxins, the liver also metabolizes medicaments, which are treated in the same way. Blood from the liver then returns to the left side of the heart via the hepatic portal vein and reaches the rest of the systemic circulation. This first pass through the liver may result in the removal of a substantial proportion of an ingested medicament. The first pass effect is more pronounced for some drugs than others.

Certain areas of the alimentary canal have a venous drainage, which does not involve a first pass through the liver. These areas (the mucous membrane of the buccal cavity, under the tongue and the nasopharynx, and also the distal rectum) drain directly into the left side of the heart. The avoidance of this first pass effect is the rationale for the use of buccal, and sublingual formations.

Both sublingual and buccal formulations depend on the efficient transfer of medicament from a hydrophilic vehicle to the mucous membrane of the sublingual or buccal mucosa. Transfer of medicament through the interstices between or through epithelial cells is governed principally by the lipid solubility of the medicament. Where a drug is water insoluble this is a further barrier to absorption from the sublingual area.
The present invention relates to formulations which are particularly suitable for use in administration of pharmaceutical ingredients or medicaments via a mucosal surface such as, for example, the sublingual mucosa or the buccal mucosa.

The composition of the invention is particularly suitable for transmucosal delivery of macromolecules having molecular weight of up to about 5000 Da and is advantageous over prior art transmucosal delivery formulations which are suitable only for smaller sized molecules, for example up to about 200 Da. According to a particular embodiment of the invention, the liquid composition is effective for oral transmucosal delivery of high molecular weight active agents, especially medicaments and other active agents having molecular weights of at least about 200, 250, 350, 450, 550 or 650 Daltons (Da) and up to about 5000 Da. Each possibility represents a separate embodiment of the invention.

In one aspect, the present invention provides a method for rapid delivery of a pharmaceutical ingredient across the oral mucosa, the method comprises administering to the oral mucosa of a subject in need thereof a liquid composition comprising a pharmaceutical ingredient and methylsulfonylmethane (MSM) in a carrier, wherein the methylsulfonylmethane is in an amount sufficient to induce rapid delivery of said pharmaceutical ingredient across the oral mucosa.

According to the present invention, methylsulfonylmethane improves and accelerates the oral mucosal absorption of a pharmaceutical ingredient such as sildenafil citrate and ibuprofen. The present invention discloses that the provision of methylsulfonylmethane in a liquid composition unexpectedly accelerates delivery of active ingredients across the oral mucosa. As a consequence, the active ingredient appears in the blood circulation within a few minutes from administration.

In some embodiments, the MSM is provided in an amount sufficient to induce rapid delivery of a pharmaceutical ingredient across the oral mucosa. The amount of MSM that is sufficient to induce a rapid delivery of the pharmaceutical ingredient is an amount that does not exceed 10% w/w. In some embodiments, the amount of MSM does not exceed 9% w/w, 8% w/w, 7% w/w, 6% w/w, 5% w/w, 4% w/w, 3% w/w, 2% w/w, 1% w/w, or 0.5% w/w of the total weight of the composition. Each possibility represents a separate embodiment of the present invention. In one embodiment, the amount of MSM is 5% w/w of the total weight of the composition.
As used herein the term "amount sufficient to induce rapid delivery" refers to an amount of methylsulfonylmethane which upon formulation with a pharmaceutical ingredient, and following transmucosal administration to a subject, substantially increases the rate of appearance of the pharmaceutical ingredient in the blood circulation of the subject, as compared to a formulation of the same pharmaceutical ingredient which lacks methylsulfonylmethane.

By "delivery" it is meant that the pharmaceutical ingredient is released from the composition in which it is formulated, absorbed onto the oral mucosal site and penetrates to the mucous membranes and thereafter to the blood circulation. Such deliveries of drugs may be measured by conventional pharmacokinetics methods known in the art and utilized in the Examples section that follows.

The compositions utilized in the present invention are very rapidly absorbed onto the mucous membranes of the mouth. For example, the compositions are absorbed onto the mucous membranes within a few to several seconds after application and with a high percentage of the active agent being transmigrated and made bio-available. In some embodiments, the rapid delivery occurs immediately following administration of the compositions utilized in the present invention. In some embodiments, the delivery occurs within 1 to 30, 1 to 25, 1 to 20, 1 to 15, 1 to 10, 1 to 8, 1 to 6, 1 to 5, 1 to 4, 1 to 3, or 1 to 2 minutes from administration of the composition. In some embodiments, the delivery occurs within 5 to 30, 5 to 25, 5 to 20, 5 to 15, or 5 to 10 minutes from administration of the composition. Each possibility represents a separate embodiment of the invention. In one embodiment, the delivery occurs within 5 minutes from administration.

The compositions utilized in the present invention are liquid. Liquid dosage forms include aqueous or non-aqueous solutions, lotions or suspensions, or oil-in-water or water-in-oil emulsions. Solutions or suspensions may be syrups or elixirs. In a particular embodiment, the transmucosal oral delivery system of this invention is in the form of an oil-in-water emulsion.

In one embodiment, the means for storing or containing the dosage form, include, but are not limited to, a container suitable for long storage and blister packaging for pharmaceuticals, among others.

In a particular embodiment, the compositions are liquid aerosol formulations adapted as mouth-sprays or as droppers. Spray containers may comprise a pump and metered dosing device to assist correct dosing. In general, from about 0.05 to about 3 ml, for example, about
0.14 ml of the compositions utilized in the present invention are administered in each spraying. In some embodiments, the container is a bottle.

As used herein, the term “administering” refers to administration of the composition of the present invention to the mucous membranes of the oral cavity (i.e., oral mucosa).

Examples of suitable sites of administration within the oral mucosa include, without limitation, the mucous membranes of the floor of the mouth (sublingual mucosa), the cheeks (buccal mucosa), the gums (gingival mucosa), the roof of the mouth (palatal mucosa), the lining of the lips, and combinations thereof.

Pharmaceutical compositions

The effectiveness of MSM is not limited by the type of carrier used and suitable excipients may be selected as is well known in the art to impart to the compositions the desired consistency and other characteristics.

The present invention provides a composition for rapid delivery across the oral mucosa, the composition comprising a pharmaceutical ingredient, methylsulfonylmethane, an edible oil, purified water, and lecithin.

In one embodiment, the edible oil is a vegetable oil. Exemplary vegetable oils include, but are not limited to cottonseed oil, peanut oil, poppyseed oil, sunflower oil, sesame oil, soybean oil, corn oil, olive oil, canola oil and combinations thereof.

The composition may further comprise at least one excipient, such as a sweetening agent, a flavoring agent, a plasticizer, an elastomeric solvent, a filler material, a preservative, a lubricating agent, a wetting agent, an emulsifying agent, solubilizing agent, a suspending agent, a coloring agent, a disintegrating agent, or combinations thereof. It is to be understood that some excipients may fall within more than one class of the aforementioned excipients.

In some embodiments, the composition comprises at least one excipient selected from the group consisting of: sucralose, sucrose, calcium salt, polysorbate 80, glycine, tocopherol, glycerin, sodium benzoate, and combinations thereof. One example of a calcium salt is calcium carbonate.

The term "glycerin" interchangeably refers to glycerine or glycerol. In some embodiments, the glycerin used for the preparation of the compositions of the present invention is glycerin USP.

The term "% (percent) weight/weight" or ("% w/w") denotes the fraction of: the mass of a substance divided by the total mass of all substances and multiplied by 100%.
In some embodiments, the compositions utilized in the present invention comprise: a pharmaceutical or nutraceutical ingredient in an amount that does not exceed about 5%, MSM in an amount that does not exceed about 10%, vegetable oil in an amount that does not exceed about 40%, sucrose in an amount that does not exceed about 20%, lecithin in an amount that does not exceed about 20%, and purified water in an amount of at least about 50%, wherein the percentages are weight per weight percent calculated as the weight of each substance divided by the total weight of the composition and multiplied by 100.

In some embodiments, the compositions utilized in the present invention comprise a pharmaceutical ingredient in an amount of between 0.1% to 15% w/w, methylsulfonylmethane in an amount that does not exceed 10% w/w, a vegetable oil in an amount of between 1% to 20% w/w, purified water in an amount of between 50% to 85% w/w, sucrose in an amount sufficient to serve as a sweetener, and lecithin in an amount of between 1% to 20% w/w.

In some embodiments, the compositions utilized in the present invention comprise a pharmaceutical ingredient in an amount of between 0.1% to 15% w/w, methylsulfonylmethane in an amount that does not exceed 10% w/w, a vegetable oil in an amount of between 1% to 20% w/w, purified water in an amount of between 50% to 85% w/w, sucrose in an amount sufficient to serve as a sweetener, lecithin in an amount of between 1% to 20% w/w, polysorbate 80 in an amount of between 1% to 15% w/w, glycine in an amount of between 1% to 15% w/w, at least one flavoring agent in an amount of between 1% to 10% w/w, at least one tocopherol in an amount of between 1% to 10% w/w, and sodium benzoate in an amount of between 1% to 10% w/w.

In one embodiment, the composition comprises a pharmaceutical ingredient in an amount of between 1% to 10% w/w, between 1% to 5% w/w, or between 2% to 4% w/w of the total weight of the composition. In one embodiment, the pharmaceutical ingredient is in an amount of between 2% to 4% w/w of the total weight of the composition.

In one embodiment, the methylsulfonylmethane is in an amount that does not exceed 10% w/w of the total weight of the composition. In some embodiments, the methylsulfonylmethane is present in an amount of between 2% to 7% w/w of the total weight of the composition.

In another embodiment, the vegetable oil is in an amount of between 1% to 20% w/w, between 1% to 15% w/w, or between 1% to 10% w/w of the total weight of the composition. Each possibility represents a separate embodiment of the invention. In a particular
embodiment, the vegetable oil is in an amount of between 1% to 5% w/w of the total weight of the composition.

In a further embodiment, the purified water is in an amount of between 50% to 85% w/w, between 50% to 80% w/w, between 50% to 70% w/w, or between 50% to 60% w/w of the total weight of the composition. Each possibility represents a separate embodiment of the invention. In a particular embodiment, the purified water is in an amount of between 50% to 60% w/w of the total weight of the composition.

In still a further embodiment, the sucrose is in an amount of between 1% to 20% w/w, between 1% to 15% w/w, between 5% to 15% w/w, or between 5% to 10% w/w, of the total weight of the composition. Each possibility represents a separate embodiment of the invention. In a particular embodiment, the sucrose is in an amount of between 5% to 10% w/w of the total weight composition.

In yet another embodiment, the polysorbate 80 is in an amount of between 1% to 15% w/w, between 1% to 10% w/w, or between 1% to 5% w/w, of the total weight of the composition. Each possibility represents a separate embodiment of the invention. In a particular embodiment, the polysorbate 80 is in an amount of between 1% to 5% w/w of the total weight composition.

In yet another embodiment, the glycine is in an amount of between 1% to 15% w/w, between 1% to 10% w/w, or between 1% to 5% w/w, of the total weight of the composition. Each possibility represents a separate embodiment of the invention. In a certain embodiments, the glycine is in an amount of between 1% to 5% w/w of the total weight of the composition.

In yet another embodiment, the at least one flavoring agent is in an amount of between 1% to 10% w/w, between 1% to 5% w/w, or between 1% to 3% w/w of the total weight of the composition. Each possibility represents a separate embodiment of the invention. In a particular embodiment, the at least one flavoring agent is in an amount of between 1% to 3% w/w of the total weight of the composition.

In yet another embodiment, the at least one tocopherol is in an amount of between 0.1% to 10% w/w, between 0.1% to 5% w/w, or between 0.1% to 3% w/w, of the total weight of the composition. Each possibility represents a separate embodiment of the invention. In a particular embodiment, the tocopherol is in an amount of between 0.1% to 3% w/w of the total weight of the composition.
In yet another embodiment, the sodium benzoate is in an amount of between 0.1% to 10% w/w, between 0.1% to 5% w/w, between 0.1% to 3% w/w, or between 0.1% to 1% w/w of the total weight of the composition. Each possibility represents a separate embodiment of the invention. In a particular embodiment, the sodium benzoate is in an amount of between 0.1% to 2% w/w of the total weight of the composition.

In some embodiments, the compositions utilized in the present invention are devoid of a polymer. Particularly the compositions of the present invention are devoid of a lactic acid polymer.

Production of the composition utilized in the present invention

The compositions utilized in the present invention are in a liquid form. Exemplary liquid forms for oral mucosal (e.g. sublingual and buccal) administration include, but are not limited to a solution or a suspension in an aqueous liquid or non-aqueous liquid, or in the form of an oil-in-water emulsion or a water-in-oil emulsion. Solution or a suspension form may be of syrups or elixirs. Liquid dosage forms include droppers or sprayers useful for dispersion in the oral cavity. These liquid compositions can include pharmaceutically acceptable inert ingredients such as diluents (e.g. calcium carbonate, sodium chloride, lactose, calcium phosphate, sodium phosphate, and the like); granulating and disintegrating agents (e.g. potato starch, alginic acid and the like); binding agents (e.g. starch, gelatin, acacia and the like); lubricating agents (e.g. magnesium stearate, stearic acid, talc and the like). Other inert ingredients that can be used in the invention include colorants, flavoring agents, plasticizers, humectants and the like. The liquid compositions provided in accordance with the present invention can be contained in any package known in the art.

The composition utilized in the present invention can be produced by various methods. In a typical process for the production of the composition, the water, methylsulfonylmethane, the pharmaceutical active ingredient, lecithin, and an edible oil are mixed at a temperature of between 40 °C to 70°C, the mixture is kneaded uniformly or homogenized, cooled, and inserted into a desirable container.

Liposomes can be incorporated into the tablet by adding lecithin and vegetable oil in solution to form liposomes as the pharmaceutical solution, and then gently vortexing to prevent damage to the liposomes before introduction into molds where gelling occurs.
The steps in these production processes may be combined in an adequate manner other than the manners mentioned above. In producing the composition according to the present invention, the components are used in the amounts prescribed above.

In addition to the above components, there may also be incorporated other additives selected from among the various pharmaceutically acceptable additives available to those skilled in the art for the purpose of assisting in the development of characteristics of the composition of the present invention, by improving the processability, and quality of the preparation, and by enhancing the dispersability and stability of the composition. Such additives are other than those mentioned as the essential components and include the following substances. Flavors (menthol, cherry flavor, saccharin sodium, glycyrrhizin, malt syrup, citric acid, tartaric acid, menthol, lemon oil, citrus flavor, common salt, etc.), Stabilizers/preservatives (parahydroxybenzoic acid alkyl esters, antioxidants, antifungal agents, etc.), Colors (water-soluble tar colors, natural colors, titanium oxide, etc.); Excipients/disintegration adjusting agents (magnesium silicate, light silicic acid anhydride, synthetic aluminum silicate, precipitated calcium carbonate, magnesium aluminum metasilicate, calcium hydrogen phosphate, etc.), Water-soluble polymers other than water-soluble proteins (natural polymers, synthetic polymers, etc.) and Stearic acid and its salts, talc, palmitic acid, and other substances known as emulsifiers, dispersants, binders, thickeners, etc.

The present oral dosage form can be used to deliver any active or therapeutic agent where absorption across the oral mucosa is desired. While according to an exemplary embodiment, the present invention will hereinafter be discussed with reference to administration of sildenafil citrate or ibuprofen, it should be understood that other active agents, pharmaceutical ingredients, nutraceutical ingredients, medicaments, or drugs may be adjunctively or alternatively employed.

Non-limiting examples include non-steroid anti-inflammatory drugs other than ibuprofen, analgesics, migraine medications, menopause medications, sleep disorder medications, erectile dysfunction medications other then sildenafil citrate, appetite suppressants, cough/cold/throat agents, vitamins, zinc, menthol, eucalyptus, hexyl resorcinol, caffeine, tooth whitening agents, anti-plaque agents, breath freshening agents, demulcents and the like.
Pharmaceutical ingredients

NSAIDs which may be incorporated into the composition of the invention include ibuprofen (2-(isobutylphenyl)-propionic acid); methotrexate (N-[4-(2, 4 diamino 6-pteridinylmethyl)methylamino]benzoyl)-L-glutamic acid); aspirin (acetylsalicylic acid); salicylic acid; diphenhydramine (2-(diphenylmethoxy)-NN-dimethylethylamine hydrochloride); naproxen (2-naphthaleneacetic acid, 6-methoxy-9-methyl-, sodium salt, (-)); phenylbutazone (4-butyl-1,2-diphenyl-3,5-pyrazolidinediedinede); sulindac-(2)-5-fuoro-2-methyl-1-[[p-(methylsulfiny)phenyl]methylene]-l-H-indene-3 -acetic acid; diflunisal (4-hydroxy-2-methyl-N-2-pyridinyl-2H-1,2-benzothiazine-2-carboxamide 1,1-dioxide, meloxicam (4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide); an oxicam; indomethacin (1-(4-chlorobenzoyl)-5-methoxy-2-methyl-H-indole-3 -acetic acid); meclofenamate sodium (N-(2,6-dichloro-m-tolyl) anthranilic acid, sodium salt, monohydrate); nabumetone (4-(6-methoxy-2-naphthalenyl)-2-butano); ketoprofen (2-(3-benzoylphenyl)-propionic acid; tolmetin sodium (sodium 1-methyl-5-(4-methylbenzoyl-1H-pyrrole-2-acetate dihydrate); diclofenac sodium (2-[(2,6-dichlorophenyl)amino]benzeneacetic acid, monosodium salt); hydroxychloroquine sulphate (2-[[4-[(7-chloro-4-quinolyl) amino]pentyl]ethylamino]ethanol sulfate (1:1); penicillamine (3-mercapto-D-valine); flurbiprofen ([l,l-biphenyl]-4-acetic acid, 2-fluoro-apamethyln-, (+-)); etodolac (l-8-diethyl-13,4,9,tetra hydropryro-[3-4-13]indole-1-acetic acid; mefenamic acid (N-(2,3-xylylanthranilic acid; and diphenhydramine hydrochloride (2-diphenyl methoxy-N,N-di-methylthamine hydrochloride).

Analgesic compounds which may be incorporated into the composition of the invention include acetaminophen and dipyrone (4-methylamino-1,5-dimethyl-2-phenyl-3-pyrazolone sodium methanesulfonate).

Migraine medications which may be incorporated into the composition of the invention include triptans, such as sumatriptan ( 3-(2-(Dimethylamino)ethyl)-N-methyl-H-indole-5-methanesulfonamide) and almotriptan l-((3-(2(dimethylamino)ethyl)indol-5-yl)methyl)sulfonyl)pyrrolidine and amitriptyline 3-(10,ll-dihydro-5H-dibeno (a,d)cyclohepten-5-ylidene)-N,N-dimethyl- l-propanamine.

Erectile dysfunction medications which may be incorporated into the composition of the invention include a steroid hormone such as testosterone, a peptide hormone, an amine hormone, and a hormone-like eicosanoid such as a prostaglandin, a leukotriene, flibanserin and a thromboxane.
Phytochemical agents which may be incorporated into the composition of the invention include but are not limited to parthenolide, theanine, resveratrol, and elagic acid.

The term "phytochemical agent" refers to chemical compounds that occur naturally in plants which have the potential to affect diseases.

The term "prostaglandin" refers to a family of compounds originally discovered in seminal fluid and found to cause vasodilation, and contraction or relaxation of uterine smooth muscle. The prostaglandins, leukotrienes, and related compounds are called eicosanoids because they are synthesized by microsomal enzymes from 20-carbon essential fatty acids, e.g., arachidonic acid (Hardman, J. 1996, in Goodman and Gilman's: The Pharmacological Basis of Therapeutics, Ch. 26, 9th ed., McGraw Hill).

Other pharmaceutical ingredients which may be used as erectile dysfunction medications include testosterone, yohimbine, pentoxifylline, trazodone, apomorphine, phentolamine, tadalafl, sildenafil and other pyrazolopyrimidone derivatives. Other agents include minoxidil, misoprostol, papaverine, nitroglycerin, phentolamine, moxisylyte, linsidomine, linear or cyclic peptides, pyridylguanidine compounds, and renin-angiotensin system inhibitors. These agents may be incorporated into the transmucosal composition at an effective dose to correct erectile dysfunction.

Menopause medications which may be incorporated into the composition of the invention include phytoestrogens, venlafaxine, paroxetine and plant extracts, such as those derived from black cohosh and maca.

Sleep disorder medications which may be incorporated into the composition of the invention include diphenhydramine (2-(benzhydryloxy)-N,N-dimethylethylamine), valerian and melatonin (5-methoxy-N-acetyltryptamine).

An appetite suppressant which may be incorporated into the composition of the invention is phenylalanine. The phenylalanine may be D-phenylalanine, L-phenylalanine or a mixture thereof.

Macromolecules which may be incorporated into the composition of the invention include vitamin B12, antibiotics, peptides, polypeptides, calcitonin, vasopressin and oxytocin. In a particular embodiment, the macromolecule is vitamin B12.

Method for treating an erectile dysfunction medication

In another aspect, the present invention provides a method for treating an erectile dysfunction in a subject in need thereof, the method comprising, administering to the oral mucosa of a subject in need thereof a liquid composition comprising a therapeutic effective
amount of an erectile dysfunction medicament, methylsulfonylmethane, and a carrier, wherein said methylsulfonylmethane is in an amount sufficient to induce rapid delivery of said erectile dysfunction medicament across the oral mucosa.

In a particular embodiment, the erectile dysfunction medicament utilized in the present invention is sildenafil citrate. Sildenafil citrate, sold as VIAGRA®, is a drug used to treat erectile dysfunction and pulmonary arterial hypertension (PAH). Currently, sildenafil is administered by oral swallowing of pills.

The compositions utilized in the present invention are preferably formulated as an orally administrable dosage form, such as a spray or a dropper, which thus enable convenient oral mucosal administration. The methylsulfonylmethane is present in the composition in an amount sufficient to enhance transmucosal delivery of the erectile dysfunction medicament (i.e., sildenafil citrate). That is, the amount of methylsulfonylmethane in the composition is sufficient to rapidly induce or accelerate the appearance of an erectile dysfunction medicament in the blood of a subject following transmucosal administration thereto, and/or to enhance the appearance of the erectile dysfunction medicament in the blood, as compared to a formulation of the same pharmaceutical ingredient which lacks methylsulfonylmethane. Advantageously, transmucosal delivery of an erectile dysfunction medicament offers a rapid therapeutic effect. According to one embodiment, the subject to be treated is a mammal. In another embodiment, the mammal is a human.

Method for treating symptoms that would benefit from administration of non-steroid anti-inflammatory drugs (NSAIDs)

In a further aspect, the present invention provides a method for treating symptoms that would benefit from administration of an NSAID in a subject in need thereof, the method comprises administering to the oral mucosa of a subject in need thereof a liquid composition comprising a therapeutic effective amount of an NSAID, methylsulfonylmethane, and a carrier, wherein said methylsulfonylmethane is in an amount sufficient to induce rapid delivery of said NSAID across the oral mucosa.

NSAIDs are used primarily to treat inflammation, mild to moderate pain, and fever. In some embodiments, the symptom or condition that would benefit from administration of an NSAID medicament is at least one symptom or condition selected from the group consisting of: inflammation, mild to moderate pain, and fever. In a particular embodiment, the symptoms are caused by indications selected from the group consisting of: headaches and
migraines, rheumatoid arthritis, osteoarthritis, inflammatory arthropathies, such as ankylosing spondylitis, psoriatic arthritis, and reiter's syndrome, acute gout, dysmenorrhoea (menstrual pain), ileus, renal colic and arterial thrombosis.

NSAIDs are associated with several side effects. The frequency of side effects varies among NSAIDs. The most common side effects are nausea, vomiting, diarrhea, constipation, decreased appetite, rash, dizziness, headache, and drowsiness. NSAIDs may also cause fluid retention, leading to edema. The most serious side effects are kidney failure, liver failure, ulcers and prolonged bleeding after an injury or surgery.

In a particular embodiment, the NSAID utilized in the present invention is ibuprofen. The NSAID ibuprofen, sold under the trade names ADVIL®, NUROFEN® and others is a non-steroidal anti-inflammatory drug (NSAID) and a member of the World Health Organization "Essential Drugs List". Due to its mechanism of non-selective COX inhibition, when taken orally ibuprofen can result in gastric damages, such as ulcers.

There is thus a rational for developing delivery systems that may bypass the GI track and/or reduce the dosage of administration. The methods of the present invention now demonstrate utility of pharmaceutical compositions and dosage forms that facilitate efficient delivery of pharmaceutical ingredients such as ibuprofen which may also be administered in lower dosages.

In addition to the exemplary aspects and embodiments described above, further aspects and embodiments will become apparent by reference to the figures and by study of the following examples. The materials, methods and examples discussed below are illustrative and are not intended to limit the scope of the invention.

EXAMPLES

Example 1: Preparation of Trans Oral Mucosal Sildenafil citrate (TOMSIL) composition

An aqueous composition comprising sildenafil citrate was prepared as specified in table 1. The resulting composition is a light brown colored emulsion. The density of the emulsion for transmucosal administration is: lmg/ml.
Table 1 - Trans oral mucosal sildenafil citrate composition.

<table>
<thead>
<tr>
<th>Name</th>
<th>CAS number</th>
<th>Weight (mg)</th>
<th>% (W/W)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purified Water</td>
<td>653</td>
<td>65.3</td>
<td></td>
</tr>
<tr>
<td>M.S.M 67-68-5</td>
<td></td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Sucrose 57-50-1</td>
<td></td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Sildenafil Citrate</td>
<td>15</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Leicithin</td>
<td>70</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Sunflower Oil</td>
<td>40</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Polysorbate 80 9005-65-6</td>
<td>30</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Glycine 56-40-6</td>
<td>30</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Menthol Crystals 2216-51-6</td>
<td>2.5</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Cherry flavor 2.5</td>
<td></td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Tocopherols 0191-41-0</td>
<td>6</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Sodium Benzoate 532-32-1</td>
<td>2</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1000</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Characteristics of the composition:

Organoleptic characters: Fine brown to off white liquid, menthol odor, with a bitter sweet after taste.

Storage instructions: Keep in a cool dry place at ambient temperature.

Directions for use: Shake well before use. Spray 7 times inside the month and hold for 60 seconds before swallowing.

Dosage: 14.91 mg. (7 sprays) - 1 time daily as needed.

Content: 14.91 mg. sildenafil citrate per gr. solution

The preparation of 500 gr of the TQMSIL solution is carried out according to the following procedure:

1. Purified double distilled water (326.5 g) are poured into a 1000 ml beaker, stirred and heated to a temperature of 65°C - 70°C (for 1 hour).
2. Dissolve 25 g of MSM in the water. Stir thoroughly at 60°C for 10 minutes.
3. Add 1 g sodium benzoate to the warm solution (60°C), heat and stir thoroughly for 10 minutes.
4. Add 7.5 g sildenafil citrate and stir thoroughly for 10 minutes.
5. Add Glycine (15 g), flavors, such as menthol and fruits (2.5 g), and sucrose (50 g) to the warm solution, heat and mix thoroughly for 30 minutes.

6. Add polysorbate 80 (15 g) to the warm solution. Continue to heat and mix thoroughly for 15 minutes.

7. Add lecithin (35 g) and stir thoroughly for 30 minutes. Homogenize with Silversohn L4R at RPM 6000 for 2 minutes. The obtained solution has a yellowish color. Weigh the contents and check the pH (about 6.2).

8. Into a separate 100 ml beaker add sunflower oil (20 g) and tocopherol Acetate (Microvit E) (1 g). Stir for 15 minutes.

9. Add the mix of 100 mL beaker of step 8 to the 1000 ml beaker. Continue to homogenize 2 minutes.

10. Heat at about 50°C and stir the obtained emulsion for an additional 30 minutes. Check the pH (about 6.3). The obtained emulsion has an orange-light color.

11. Check the pH in the next day.

Example 2: An in-vivo pharmacokinetic study of the Trans Oral Mucosal Sildenafil Citrate composition (TOMSIL)

The aim of the present study was to evaluate the pharmacokinetic and safety of transmucosal sildenafil citrate administration in liquid composition comprising methylsulfonylmethane (MSM) vs. oral administration of a commercial tablet of sildenafil. As presented herein below, the inventors of the present invention have now established that lower doses achieve a faster onset of sildenafil plasma concentrations.

An oil-in-water emulsion comprising sildenafil citrate (1.5% w/w), methylsulfonylmethane (MSM) (5% w/w), lecithin (7% w/w), and sunflower oil (5% w/w) was prepared for the TMOD administration. A pharmacokinetic study was performed on male rabbits aged 11-12 weeks and weighing no less than 2 kg. Rabbits were administered with either 10 mg/kg in the form of a crushed tablet of sildenafil citrate by a gavage tube inserted directly into the stomach or with half dose (5 mg/kg) of sildenafil citrate oil-in-water emulsion by the TMOD administration by spraying the latter into the oral cavity. Figure 1 demonstrates the obtained results for oral delivery using gavage vs. transmucosal oral delivery of sildenafil citrate composition of the present invention.
Table 2: The pharmacokinetic parameters for Oral delivery vs. TMOD of Sildenafil Citrate.

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Oral delivery of Sildenafil Citrate (Viagra, Pfizer) - 10 mg/kg</th>
<th>TMOD of Sildenafil Citrate - 5 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_{\text{max}} ) (ng/ml)</td>
<td>100</td>
<td>135</td>
</tr>
<tr>
<td>( T_{\text{max}} ) (min)</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>( \text{AUC}_{0-\infty} ) (ng min/ml)</td>
<td>12,368</td>
<td>10,166</td>
</tr>
<tr>
<td>( T_{1/2} ) (min)</td>
<td>88</td>
<td>65</td>
</tr>
</tbody>
</table>

The results point out the following findings:

- The maximal concentration by the TMOD administration is greater and is achieved much faster than by oral tablet administration (10 minutes for TMOD administration, vs. 30 minutes for oral tablet gavage).
- The AUC (calculated according to the amount administered) achieved for sildenafil transmucosal formulation is substantially higher than the sildenafil AUC achieved following oral administration to rabbits, therefore the bioavailability of sildenafil citrate administered by the transmucosal administration is higher.

It is thus concluded that the transmucosal administration of sildenafil to male human beings would supply the user with two important qualities (i) a faster absorption and shorter time to maximal activity and (ii) reduced therapeutic dosage.

Example 3: An in-vivo pharmacokinetic study of the Transmucosal oral delivery of Ibuprofen.

The pharmacokinetic profile of ibuprofen formulated within the composition of the present invention in the plasma following a single oral trans-mucosal (TM) injection and following an oral (PO) administration of ibuprofen in pigs was evaluated. White Landrace pigs (n=4 pigs, each pig weighed 12-14 Kg) were administered with either 8 mg/kg of ibuprofen formulated within the composition of the present invention or with 8 mg/kg of ibuprofen via conventional oral administration. TMOD administration was performed using an injector inserting 2 ml (8 mg/kg) of the formulated composition directly onto the open mouth surfaces. Oral (PO) administration was performed using a 10 ml syringe by oral gavage inserting 5 ml (8 mg/kg) of commercial solution of ibuprofen directly into the esophagus.
Blood Sampling

Blood samples from each pig were collected prior and post dosing. Ten blood samples (approx. 1.5-2ml) for TM dosing and following PO administration were collected from each animal via the jugular vein, at the following time points: Immediately prior to dosing (t=0), and at 5min., 10min., 20min., 30min., 1hr., 2hr., 3hr, and 5hr. post administrations. Blood samples were prepared to measure ibuprofen in swine plasma as follows: (i) add 200 µl plasma into an Eppendorf tube containing 1000 µl acetonitrile into; (ii) add ketoprofen as an internal standard solution (5 ppm concentration) and vortex for 20 s (ibuprofen standard solution of 18.4 ppm was used as a calibration); (iii) evaporate 800 µl; (iv) reconstitute the dry residue in 200µl chromatographic mobile phase v; (v) inject a 2 µl sample into the chromatographic system.

HPLC/MS parameters

Chromatograph: Waters 2695 separation Module HPLC.
Chromatographic column: Symmetry C18: 150x 2.1 mm, 5 um.
Injected volume: 2 µl
Mobile phase: acetonitrile /NH4- acetate 10 mM (pH 5) = 475: 525 vol/vol.
Row rate: 300 µl/min

Clinical monitoring

Pigs were clinically observed before and during the study for any signs of vomiting, diarrhea, depression, pupil constriction, salivation, agitation, faeces present, a change in appetite or any other abnormal symptoms. During each sampling time point, each animal was observed with regard to their sensory function and behavior, body orifices and for their general health status. The local safety was evaluated as evaluation of erythema and oedema grades totaled separately for each individual following macroscopic observation on the oral cavity.

Results

No mortality occurred during the study. No abnormal side effects or abnormal signs were observed in any of the treated animals. As can be seen in Figure 3, plasma ibuprofen concentration reached a peak, 30 min post administration. The blood concentrations of ibuprofen were higher throughout the experiment for the TMOD delivery as compared to the oral delivery (PO).
Table 3: Ibuprofen concentration (ng/ml) in swine plasma following transmucosal administration

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Pig No. 1</th>
<th>Pig No. 2</th>
<th>Pig No. 3</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
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Table 2: Ibuprofen concentration in swine plasma (ng/ml) following oral administration (PO)

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The foregoing description of the specific embodiments will so fully reveal the general nature of the invention that others can, by applying current knowledge, readily modify and/or adapt for various applications such specific embodiments without undue experimentation and without departing from the generic concept, and, therefore, such adaptations and modifications should and are intended to be comprehended within the meaning and range of equivalents of
the disclosed embodiments. It is to be understood that the phraseology or terminology employed herein is for the purpose of description and not of limitation. The means, materials, and steps for carrying out various disclosed functions may take a variety of alternative forms without departing from the invention.
CLAIMS

1. A pharmaceutical composition for rapid delivery of a pharmaceutical ingredient across the oral mucosa, the composition comprising a pharmaceutical ingredient, methylsulfonylmethane and a carrier, wherein said composition is in the form of a liquid and wherein said methylsulfonylmethane is in an amount sufficient to induce rapid delivery of said pharmaceutical ingredient across the oral mucosa.

2. The pharmaceutical composition of claim 1, wherein said methylsulfonylmethane is in an amount that does not exceed 10 % w/w.

3. The pharmaceutical composition of claim 1, wherein said rapid delivery is delivery that occurs within 5 to 15 minutes or less from administration of said pharmaceutical ingredient.

4. The pharmaceutical composition of claim 1, wherein said liquid is selected from the group consisting of: a solution, a suspension and an emulsion.

5. The pharmaceutical composition of claim 4, wherein said emulsion is an oil-in-water emulsion or a water-in-oil emulsion.

6. The pharmaceutical composition of claim 5, wherein said emulsion is an oil-in-water emulsion.

7. The pharmaceutical composition of claim 1, wherein said carrier comprises an edible oil, purified water, and lecithin.

8. The pharmaceutical composition of claim 7, wherein said edible oil is a vegetable oil.

9. The pharmaceutical composition of claim 8, wherein said vegetable oil is selected from the group consisting of: sunflower oil, cottonseed oil, peanut oil, poppy seed oil, sesame oil, soybean oil, corn oil, olive oil, canola oil, and combinations thereof.

10. The pharmaceutical composition of claim 1, wherein said composition further comprises an excipient selected from the group consisting of: a sweetening agent, a flavoring agent, a plasticizer, an elastomeric solvent, a filler material, a preservative, a lubricating agent, a wetting agent, an emulsifying agent, a solubilizing agent, a suspending agent, a coloring agent, a disintegrating agent and combinations thereof.
11. The pharmaceutical composition of claim 10, wherein said composition further comprises at least one excipient selected from the group consisting of: sucralose, sucrose, calcium salt, polysorbate 80, glycine, glycerin, tocopherol, sodium benzoate, and combinations thereof.

12. The pharmaceutical composition of claim 10, wherein said composition comprises:

- a pharmaceutical ingredient in an amount of between 0.1% to 15% w/w;
- methylsulfonylmethane in an amount that does not exceed 10% w/w;
- a vegetable oil in an amount of between 1% to 20% w/w;
- purified water in an amount of between 50% to 85% w/w;
- sucrose in an amount sufficient to serve as a sweetener; and
- lecithin in an amount of between 1% to 20% w/w.

13. The pharmaceutical composition of claim 11, wherein said composition comprises:

- a pharmaceutical ingredient in an amount of between 0.1% to 15% w/w;
- methylsulfonylmethane in an amount that does not exceed 10% w/w;
- a vegetable oil in an amount of between 1% to 20% w/w;
- purified water in an amount of between 50% to 85% w/w;
- sucrose in an amount sufficient to serve as a sweetener;
- lecithin in an amount of between 1% to 20% w/w;
- polysorbate 80 in an amount of between 1% to 15% w/w;
- glycine in an amount of between 1% to 15% w/w;
- at least one flavoring agent in an amount of between 1% to 10% w/w;
- tocopherol in an amount of between 1% to 10% w/w;
- sodium benzoate in an amount of between 1% to 10% w/w; and
- glycerin in an amount of between 1% to 10% w/w.

14. The pharmaceutical composition of claim 1, wherein said pharmaceutical
ingredient is selected from the group consisting of: an erectile dysfunction medication, a non-steroid anti-inflammatory drug (NSAID), a phytochemical agent, an analgesic, a migraine medication, a menopause medication, a sleep disorder medication, and an appetite suppressant.

15. The pharmaceutical composition of claim 14, wherein said pharmaceutical ingredient is selected from the group consisting of: a non-steroid anti-inflammatory drug (NSAID), and an erectile dysfunction medication.

16. The pharmaceutical composition of claim 15, wherein said NSAID is selected from the group consisting of: ibuprofen (2-(isobutylphenyl)-propionic acid); methotrexate (N-[4-(2, 4 diamino 6-pteridinyl-methyl)methylamino]benzoyl)-L-glutamic acid); aspirin (acetyl salicylic acid); salicylic acid; diphenhydramine (2-(diphenylmethoxy)-NN-dimethyl ethylamine hydrochloride); naproxen (2-naphthaleneacetic acid, 6-methoxy-9-methyl- sodium salt, (->); phenylbutazone (4-butyll ,2-diphenyl-3,5-pyrazolidinedione); sulindac-(2)-5-fluoro-2-methyl- 1\{[(p-(methylsulfinyl)phenyl)methylene]- 1-H-indene-3-acetic acid; diflunisal (2',4'-difluoro-4-hydroxy-3-biphenylcarboxylic acid; piroxicam (4-hydroxy-2-methyl-N-2-pyridinyl-2H-1 ,2-benzothiazine-2-carboxamide 1,1-dioxide, meloxicam (4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1 ,2-benzothiazine-3-carboxamide 1,1-dioxide); an oxicam; indomethacin (1-(4-chlorobenzoyl)-5-methoxy-2-methyl-H-indole-3-acetic acid); meclofenamate sodium (N-(2,6-dichloro-m-toly) anthranilic acid, sodium salt, monohydrate); nabumetone (4-(6-methoxy-2-naphthalenyl)-2-butanol); ketoprofen (2-(3-benzylophenyl)-propionic acid; tolmelin sodium (sodium l-methyl-5-(4-methylbenzoyl-H-pyrrole-2-acetate dihydrate); diclofenac sodium (2-[(2,6-dichlorophenyl)amino]benzeneatic acid, monosodium salt); hydroxychloroquine sulphate (2-[(4-[(7-chloro-4-quinolyl) amino]pentyl)ethylamino]ethanol sulfate (1:1); penicillamine (3-mercapto-D-valine); flurbiprofen ([1,1-biphenyl]-4-acetic acid, 2-fluoro-aphenylmethy-, (->)); etodolac (l-8-diethyl-13,4,9-tetra hydropyran-3,4-13]indole-l-acetic acid; mefenamic acid (N(2,3-xylyl)anthranilic acid; and diphenhydramine hydrochloride (2-diphenyl methoxy-N,N-di-methylethamine hydrochloride).

17. The pharmaceutical composition of claim 16, wherein said NSAID is ibuprofen (2-(isobutylphenyl)-propionic acid).
18. The pharmaceutical composition of claim 15, wherein said erectile dysfunction medication is selected from the group consisting of: sildenafil citrate, a prostaglandin, a testosterone, yohimbine, pentoxifylline, trazodone, apomorphine, tadalafil, minoxidil, misoprostol, papaverine, nitroglycerin, phentolamine, moxisylyte, linsidomine, flibanserin and a pyridylguanidine compound.

19. The pharmaceutical composition of claim 18, wherein said erectile dysfunction medication is sildenafil citrate.

20. The pharmaceutical composition of claim 1, wherein said oral mucosa is selected from the group consisting of: sublingual mucosa, buccal mucosa, gingival mucosa, palatal mucosa and a combination thereof.

21. A method for rapid delivery of a pharmaceutical ingredient across the oral mucosa, the method comprising administering to the oral mucosa of a subject in need thereof the composition according to any one of claims 1 to 20.

22. A method for treating erectile dysfunction in a subject in need thereof, the method comprising, administering to the oral mucosa of a subject in need thereof, the pharmaceutical composition according to any one of claims 1 to 13, wherein said pharmaceutical ingredient is an erectile dysfunction medication.

23. The method of claim 22, wherein said erectile dysfunction medication is selected from the group consisting of: sildenafil citrate, a prostaglandin, a testosterone, yohimbine, pentoxifylline, trazodone, apomorphine, tadalafil, minoxidil, misoprostol, papaverine, nitroglycerin, phentolamine, moxisylyte, linsidomine, and a pyridylguanidine compound flibanserin.

24. The method of claim 23, wherein said erectile dysfunction medication is sildenafil citrate.

25. The method of claim 24, wherein said sildenafil citrate is in an amount of between 1% to 3% w/w.

26. A method for treating a condition that would benefit from administration of an NSAID in a subject in need thereof, the method comprising administering to the oral mucosa of a subject in need thereof the pharmaceutical composition according to any one of claims 1 to 13, wherein said pharmaceutical ingredient is
The method of claim 26, wherein said NSAID is selected from the group consisting of: ibuprofen (2-(isobutylphenyl)-propionic acid); methotrexate (N-[4-(2, 4 diamino 6-pteridinyl-methyl)methylamino]benzoyl]-L-glutamic acid); aspirin (acetylsalicylic acid); salicylic acid; diphenhydramine (2-(diphenylmethoxy)-NN-dimethylethylamine hydrochloride); naproxen (2-naphthaleneacetic acid, 6-methoxy-9-methyl-, sodium salt, (-)); phenylbutazone (4-butyln,2-diphenyl-3,5-pyrazolidinedione); sulindac-(2)-5-fluoro-2-methyl-1-[[p-(methylsulfinyl)phenyl]methylene]- 1-H-indene-3-acetic acid; diflunisal (2',4'-difluoro-4-hydroxy-3-biphenylcarboxylic acid; piroxicam (4-hydroxy-2-methyl-N-2-pyridinyl-2H-I ,2-benzothiazine-2-carboxamide 1,1-dioxide, meloxicam (4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-I ,2-benzothiazine-3-carboxamide 1,1-dioxide); an oxican; indomethacin (1-(4-chlorobenzoyl)-5-methoxy-2-methyl-H-indole-3-acetic acid); meclofenamate sodium (N-(2,6-dichloro-m-tolyl) anthranilic acid, sodium salt, monohydrate); nabumetone (4-(6-methoxy-2-naphthalenyl)-2-butanon); ketoprofen (2-(3-benzoylphenyl)-propionic acid; tolfmetin sodium (sodium 1-methyl-5-(4-methylbenzoyl)-H-pyrrole-2-acetate dihydrate); diclofenac sodium (2-[(2,6-dichlorophenyl)amino]benzeneacetic acid, monosodium salt); hydroxychloroquine sulphate (2-[(4-[(7-chloro-4-quinolyl) amino]pentyl]ethylamino)ethanol sulfate (1:1); penicillamine (3-mercaptop-D-valine); flurbiprofen ([1,1-biphenyl]-4-acetic acid, 2-fluoro-aphamethyl, (+)); etodolac (1-8-diethyl-13,4,9,tetra hydropyrano-[3-4-13]indole-1-acetic acid; mefenamic acid (N-(2,3-xylyl)anthranilic acid; and diphenhydramine hydrochloride (2-diphenyl methoxy-N,N-di-methylethamine hydrochloride).

The method of claim 27, wherein said NSAID is ibuprofen (2-(isobutylphenyl)-propionic acid).

The method of claim 28, wherein said ibuprofen is in an amount of between 1% to 20% w/w.

The method of claim 26, wherein said a condition that would benefit from administration of an NSAID is at least one condition selected from the group consisting of: inflammation, mild to moderate pain, fever and arterial thrombosis.
31. A pharmaceutical composition according to any one of claims 1 to 20 for rapid delivery of a pharmaceutical ingredient across the oral mucosa.

32. A pharmaceutical composition according to any one of claims 1 to 13 for use in treating erectile dysfunction in a subject in need thereof, wherein said pharmaceutical ingredient is an erectile dysfunction medication.

33. The pharmaceutical composition of claim 32, wherein said erectile dysfunction medication is selected from the group consisting of: sildenafil citrate, a prostaglandin, a testosterone, yohimbine, pentoxifylline, trazodone, apomorphine, tadafil, minoxidil, misoprostol, papaverine, nitroglycerin, phentolamine, moxisylyte, linsidomine, and a pyridylguanidine compound flibanserin.

34. The pharmaceutical composition of claim 33, wherein said erectile dysfunction medication is selected from the group consisting of: sildenafil citrate.

35. The pharmaceutical composition of claim 34, wherein said sildenafil citrate is in an amount of between 1% to 3% w/w.

36. A pharmaceutical composition according to any one of claims 1 to 13 for use in treating a condition that would benefit from administration of an NSAID in a subject in need thereof, wherein said pharmaceutical ingredient is an NSAID.

37. The pharmaceutical composition of claim 36, wherein said NSAID is selected from the group consisting of: ibuprofen (2-(isobutylphenyl)-propionic acid); methotrexate (N-[4-(2, 4 diamino 6-pteridinyl-methyl][methylamino]benzoyl]-L-glutamic acid); aspirin (acetylsalicylic acid); salicylic acid; diphenhydramine (2-(diphenylmethoxy)-NN-dimethylethylamine hydrochloride); naproxen (2-naphthaleacetic acid, 6-methoxy-9-methyl-, sodium salt, (−)); phenylbutazone (4-buty1-l,2-diphenyl-3,5-pyrazolidinedione); sulindac-(2)-5-fuoro-2-methyl-l -[[p-(methylsulfinyl)phenyl]methylene]- 1-H-indene-3-acetic acid; diflunisal (2',4', -difluoro-4-hydroxy-3-biphenylcarboxylic acid; piroxicam (4-hydroxy-2-methyl-N-2-pyridinyl-2H-l ,2-benzothiazine-2-carboxamide 1,1-dioxide, meloxicam (4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-l ,2-benzothiazine-3-carboxamide 1,1-dioxide); an oxicam; indomethacin (l-(4-chlorobenzoyl)-5-methoxy-2-methyl-H-indole-3-acetic acid); meclofenamate sodium (N-(2,6-dichloro-m-toly) anthranilic acid, sodium salt, monohydrate);
nabumetone (4-(6-methoxy-2-naphthalenyl)-2-butanon); ketoprofen (2-(3-benzoylphenyl)-propionic acid; tolmetin sodium (sodium l-methyl-5-(4-methylbenzoyl-lH-pyrrole-2-acetate dihydrate); diclofenac sodium (2-[(2,6-dichlorophenyl)amino]benzeneic acid, monosodium salt); hydroxychloroquine sulphate (2-[[4-[(7-chloro-4-quinolyl)] amino]pentyl]ethylamino)ethanol sulfate (1:1); penicillamine (3-mercapto-D-valine); flurbiprofen ([l,l-biphenyl]-4-acetic acid, 2-fluoro-aphamethyl-, (+-)); etodolac (l-8-diethyl-13,4,9,tetra hydropyano-[3-4-13]indole-l-acetic acid; mefenamic acid (N-(2,3-xylyl)anthranilic acid; and diphenhydramine hydrochloride (2-diphenyl methoxy-N,N-di-methylethamine hydrochloride).

38. The pharmaceutical composition of claim 37, wherein said NSAID is ibuprofen (2-(isobutylphenyl)-propionic acid).

39. The pharmaceutical composition of claim 38, wherein said ibuprofen is in an amount of between 1% to 20% w/w.

40. The pharmaceutical composition of claim 36, wherein said a condition that would benefit from administration of an NSAID is at least one condition selected from the group consisting of: inflammation, mild to moderate pain, fever and arterial thrombosis.
Figure 1
Figure 2

The graph shows the AUC (ng min/ml) for different time ranges (0-10, 0-20, 0-30, 0-60 minutes) with two conditions:

- Oral (10 mg/kg)
- TMOD (5 mg/kg)
Ibuprofen concentration in swine plasma

Figure 3
# INTERNATIONAL SEARCH REPORT

## A. CLASSIFICATION OF SUBJECT MATTER

**IPC (2013.01)** A61K 47/20, A61K 9/107

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)

**IPC (2013.01)** A61K 47/20, A61K 9/107

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

Electronic database consulted during the international search (name of data base and where practicable, search terms used)

Databases consulted: SCIRUS, PATENTSCOPE, THOMSON INNOVATION, Esp@cenet, CAPLUS, WPI Data, EPODOC, Google Scholar

Search terms used: Methylsulfonylmethane, MSM, dimethyl sulfone, organic sulfur, rapid delivery, enhance* deliver*, Oral mucosa, mucous membrane, oral cavity, NSAIID, erectile dysfunction, Ibuprofen, sildenafil

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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**Further documents are listed in the continuation of Box C.**

**See patent family annex.**

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**Document written by:**

- Special categories of cited documents:
  - "A" document defining the general state of the art which is not considered to be of particular relevance
  - "K" 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 relevant to establish the publication date of the prior art document(s) (as cited by applicant(s))
  - "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

- **Date of the actual completion of the International search:** 26 Nov 2013

- **Date of mailing of the international search report:** 27 Nov 2013

- **Name and mailing address of the ISA:**
  - Israel Patent Office
  - Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel
  - Facsimile No. 972-2-5651616

- **Authorized officer:** AMITAY Noam

- **Telephone No:** 972-2-5651725

Form PCT/ISA/210 (second sheet) (July 2009)
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