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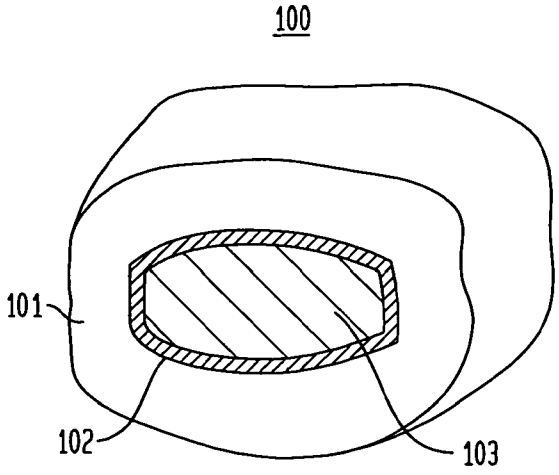
(54) **Title:** COMBINATION TABLET WITH CHEWABLE OUTER LAYER

FIG. 1



(57) **Abstract:** A pharmaceutical composition in the form of a combination tablet is described. The tablet has a rapidly absorbed component that enters the circulation by traversing the buccal mucosa, and a more slowly absorbed component that is swallowed. The therapeutic agent in the swallowed portion is absorbed across the gastric mucosa. The rapid and slow components may have identical or different therapeutic agents depending on the application to a specific medical condition One embodiment of the combination tablet includes a prostaglandin inhibitor in the rapidly absorbed component in order to mitigate the side effects of immediate release niacin that is in the slow absorbing component. Such combination compositions will increase patient compliance by reducing the number of tablets that a patient would need to take on a daily basis.

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COMBINATION TABLET WITH CHEWABLE OUTER LAYER

Background Of The Invention

The combination tablet of the present invention relates to the technical fields of medicine, pharmacology and drug delivery. More specifically, the invention disclosed herein relates to developing formulations for co-administering in a patient, two or more therapeutic agents.

In the medical arts it is known that the benefits obtained from administering a particular therapeutic agent must be assessed, *inter alia*, in relation to any side effects that the patient may experience. Side effects from administering a single therapeutic agent are most often mitigated by modifying dosing regimens, or by determining if alternative dosage forms are available that lessen or eradicate a side effect while still providing the therapeutic benefit. In cases where there are no alternative dosage forms that will achieve a therapeutic benefit while lessening side effect, one approach has simply been to administer a secondary therapeutic agent to counteract the side effects of the primary therapeutic agent. It should be clear that the suitability of a candidate drug for its role as a secondary therapeutic agent for lessening the side effects of the primary therapeutic agent is dependent on the secondary therapeutic agent not lessening the primary therapeutic agent's efficacy.

From a pharmacokinetic perspective, the goal of co-administering a secondary therapeutic agent with the primary therapeutic agent is to achieve an effective level of the secondary therapeutic agent at the relevant target site (i.e., cell type, tissue, organ, and the like) during the time period that the side effects caused by the primary therapeutic agent would have been demonstrable had the primary therapeutic been administered individually. The problem becomes more complex when the pharmacokinetic parameters of the primary and secondary therapeutic agents are incompatible.

For example, consider the situation where a secondary therapeutic agent is co-administered with a particular primary therapeutic agent, and the secondary therapeutic agent is cleared at a significantly faster rate than the primary therapeutic agent. It is likely that by the time the side effects caused by the primary therapeutic agent are underway, the levels of secondary therapeutic agent will be too low to provide its side-effect lessening effect. Conversely, if the secondary therapeutic agent reaches its effective levels significantly more slowly than the primary therapeutic agent, then the patient will experience significant side effects before secondary therapeutic agent reaches an effective level. Therefore, the timing of the release of

the two therapeutic agents must be properly coordinated.

Co-administering a COX inhibitor as a second therapeutic agent to mitigate the side effects of the primary therapeutic agent niacin is known to present challenges similar to those outlined above. Niacin, also known as nicotinic acid was introduced in the 1950s as the first effective lipid-modifying compound. Niacin was found to inhibit the mobilization of free fatty acids from peripheral tissues, reduce hepatic synthesis of triglycerides and secretion of very low-density lipoprotein (VLDL). Niacin has been shown to significantly lower levels of total cholesterol, LDL cholesterol, and triglyceride while increasing HDL cholesterol by blocking hepatic uptake of apolipoprotein A-1. Further, niacin is perhaps the only available therapeutic agent that significantly lowers lipoprotein (a) and provides the greatest HDL cholesterol-raising effects of all available therapeutic agents.

However, niacin administration also results in patients experiencing several side effects that have limited its widespread use. Most notably, the immediate release form of niacin (niacin IR) stimulates prostaglandin-mediated flushing of the face and trunk over a period of days after beginning treatment. In addition, the extended and sustained release forms also cause the flushing reaction, although not to as great an extent. Patients experiencing the flushing side effect experience a diminution of symptoms over time and eventually develop a tolerance to the flushing, but not against the lipid-lowering effects (Zoltan Benyo et al, December 2005). However, the level of discomfort is such that many patients stop therapy in the early period of treatment and never reach the tolerant stage. In addition, the dosing of niacin IR was three times per day, a factor that also contributed to low patient compliance.

Attempts were made to mitigate the side effects of niacin IR, which is completely absorbed in 1-2 hours, with a sustained release form of niacin, i.e., niacin SR. The niacin SR, which requires a period of at least 12 hours for complete absorption, has met with only modest success. It was observed that niacin SR, was significantly less effective in lowering than the IR form, (e.g., see Knopp et al, June 1985), and also was associated with an increased incidence of hepatotoxicity and gastrointestinal intolerance. More recently, an intermediate or extended release form of niacin, niacin ER has been developed that has an absorption rate in the 8-12 hour range. Niacin ER lowers the rate of flushing observed with niacin IR, and lowers the hepatotoxicity incidence seen with niacin SR.

It is known in the medical arts that administering a non-steroidal anti-inflammation drug (NSAID) from about 30 minutes to about 120 minutes prior to administering niacin IR has

been shown to significantly lower the flushing side effect. NSAIDS, e.g., aspirin, or other COX inhibitor is currently the most common adjuvant to niacin IR.

Cyclooxygenase (COX) is an enzyme (EC 1.14.99.1) that is responsible for formation of important biological mediators collectively referred to as the prostanoids (including prostaglandins, prostacyclin and thromboxane). Administering pharmacological inhibitors of COX, such as NSAIDs, provide relief from the symptoms of inflammation and pain. NSAIDs include well-known compounds such as aspirin and ibuprofen. The most relevant reaction catalyzed by COX is the conversion of the fatty acid arachidonic acid to prostaglandin, although other fatty acids are converted to additional prostanoids. It is noteworthy that prostaglandins are important cofactors in the niacin-mediated flushing effect.

There are two major forms of COX, COX-1 and COX-2. In addition, a newer splice variant of COX-1 has been identified and referred to COX-3 or COX-1b. Different tissues express varying levels of COX-1 and COX-2. Although both enzymes act basically in the same fashion, selective inhibition can make a difference in terms of side-effects. COX-1 is considered a constitutive enzyme, being found in most mammalian cells. It is an inducible enzyme, becoming abundant in activated macrophages and other cells at sites of inflammation.

The dosing regimen of niacin IR requires that it be taken three times per day, thereby requiring that a patient also take at least one NSAID tablet, tablet, caplet, capsule, and the like, with each niacin dose. It is clear that a patient would need a minimum of six tablets daily during the initial phase of niacin IR therapy; i.e., the period prior to tolerance development. The need to take at least six tablets is likely a major contributor to low compliance to niacin IR therapy.

Therefore, there is still a need to develop formulations of niacin IR that are effective in lowering blood lipid levels while reducing or even eradicating the flushing side effect and will help patients to comply with the dosing requirements of the therapy.

Summary of the Invention

The need for more readily compliant dosing regimens for niacin IR is believed to be met by the pharmaceutical composition of the present invention, as well and the methods described for treating patients in need thereof.

One aspect of the invention is to provide a solid pharmaceutical composition comprising an effective dose of one or more NSAID and an effective dose of a niacin IR compound or composition.

An additional aspect of the invention is to regulate the release of the effective amounts of the one or more NSAID in relation to the niacin IR in order to significantly inhibit COX prior to the increase in niacin IR levels. In this way, niacin IR-mediated prostaglandin mobilization will be impaired at the time that serum niacin levels start to increase. More specifically, it is preferable to have the one or more NSAID be released and absorbed more rapidly than the niacin IR. Thus, the inhibition of either COX-1 and/or COX-2 by the NSAID will maintain these enzymes in an inhibited state thereby diminishing the prostaglandin-mediated flush side effect. The regulation of release of these therapeutic agents, are achieved by the design of the pharmaceutical composition of the present invention.

The pharmaceutical composition of the present invention is a combination tablet contemplated as comprising two or more therapeutic compositions, each of which, independently, is formulated to enter the circulation by different routes of administration. The combination tablet of the present invention is further applicable to instances where differential release kinetics are preferred. Thus, the proximate release of a therapeutic agent across the buccal mucosa may be expected to provide more rapid release kinetics than another therapeutic agent that traverses the gastrointestinal mucosa, i.e., the enteral route. Specifically, the pharmaceutical composition is therefore formulated to provide (a) a rapidly absorbed therapeutic component that traverses the buccal mucosa lining the oral cavity and sublingual region; and (b) a slower release component that enters the circulation by traversing the mucosa of the gastrointestinal (GI) tract. In preferred embodiments, the more rapid release component (i.e., that which traverses the buccal mucosa) encompasses one or more COX inhibitors, while the more slowly absorbed component (i.e., traversing the GI tract mucosae) comprises niacin IR.

The pharmaceutical composition of the present invention may be prepared in different ways so that the rapid release and slower release forms are not commingled particulates, but each existing as at least one distinct layer within the solid pharmaceutical composition. For example, the COX inhibitor may be mixed with "rapid release" excipients and formed into a layer, while niacin is compounded into a distinct layer with "slower release" excipients. In this embodiment, the excipients selected for each layer will affect the rate of absorption of the

therapeutic agent therein.

Persons of ordinary skill in the art would readily appreciate that the combination tablet of the present invention may be applicable to any circumstance where a rapidly released therapeutic agent and a more slowly released therapeutic agent will be beneficial to a patient. By any circumstance is meant that any therapeutic agent that can traverse the buccal mucosa. Such a therapeutic agent can be formulated within the combination pill's rapid release component, and can be combined with a more slowly and enterically absorbed component comprising a therapeutic agent that is identical or distinct from that present in the rapidly released component.

The ensuing detailed description includes several non-limiting embodiments illustrating some of the ways the pharmaceutical composition of the present invention may be modified for a particular combination of NSAID and niacin. These modifications are for illustrative purposes only, and are not meant to limit the scope of the invention.

Brief Description Of Drawings

FIG. 1 is a perspective view of the combination tablet with chewable outer layer before being chewed or masticated.

FIG. 2 is a side view of the combination tablet with chewable outer layer, after mastication has commenced.

FIG. 3 is a top view of the combination tablet with a liquid or powder or chewable outer layer enclosed by a thin outer "skin" that provides an easily rupturable barrier. The skin is easily disrupted by minimal pressure generated during mastication. The outer pulverizable layer is just below the skin and in this embodiment, is in the form of a liquid, a gel, a powder or other form that rapidly dissolves and is easily absorbed through mucous membranes; (same as 102 and 106); (same as 103 and 105)

Detailed Description Of The Invention

This invention is a design of a combination tablet, which allows one (or more) medications within the tablet to be absorbed quickly, while an additional one (or more) medications in the tablet is absorbed slowly.

The present invention that is disclosed herein in detail provides for a pharmaceutical

composition comprising;

(a) a hard inner component comprising an effective amount of a first therapeutic agent, wherein the hard ingestible component releases the first therapeutic agent by dissolving in the gastrointestinal tract; and

(b) a pulverizable outer layer comprising an effective amount of a second therapeutic agent, wherein the pulverizable layer is dispersed in the oral cavity by masticating, thereby releasing the second therapeutic agent into the oral cavity where it enters the circulatory system by traversing the buccal mucosa;

wherein (a) and (b) further comprise one or more pharmaceutically acceptable excipients, carriers or diluents.

In one preferred embodiment the outer slow-release component (b) comprises one or more prostaglandin inhibitors as the second therapeutic agent. In the context of describing the present invention, the term "prostaglandin inhibitor" is any compound that impairs the functioning or action of one or more prostanoid compounds, including prostaglandins, prostacyclin and thromboxane. It is understood that this definition prostaglandin inhibitor is not limited to any single specific form of inhibition. The prostaglandin inhibitor may slow or completely inhibit the synthesis of a prostanoids compound. In addition, the prostaglandin inhibitor may accelerate the clearance or metabolic inactivation of one or more prostanoids. In an additional embodiment, the prostaglandin inhbitor may interfere with any prostanoid compound and its receptor or cellular targets, binding proteins, and the like. Therefore, compounds that are inhibitors of the enzymes cyclooxygenase-1 (COX-1) and cycloxygenase-2 (COX-2), which are collectively known as NSAID, are included as inhibitors. Similarly, the compound laropiprant ((2-[(3R)-4-[(4-chlorophenyl)methyl]-7-fluoro-5-methylsulfonyl-2,3-dihydro-1H-cyclopenta[b]indol-3-yl]acetic acid) is known to be a prostaglandin D2 receptor 1 antagonist, and accordingly, would be considered a prostaglandin inhibitor. As it is the COX-1 receptors that have been implicated in the deleterious side effects of aspirin (GI ulcers and bleeding), this may allow for longer use or higher-dose use of the flush-blocking adjuvant.

The present invention described and claimed herein is directed to pharmaceutical compositions providing distinct release rates that are, in part, determined on whether the particular agent is absorbed through the buccal mucosa or the GI tract. In one such nonlimiting embodiment, the rapidly absorbed therapeutic agent is a COX inhibitor that when

absorbed in the proper time frame offsets the side effects of niacin IR therapy; specifically the flushing of the skin on the face and trunk. *With this goal in mind, an embodiment of the* present invention suitable for preventing the flushing reaction comprises a pharmaceutical composition in the form of a combination tablet or other solid dosage form, wherein the combination of components comprises,

(a) a hard inner component comprising an effective amount of a niacin, wherein the hard ingestible component releases the niacin by dissolving in the gastrointestinal tract; and

(b) a pulverizable outer layer comprising an effective amount of a prostaglandin inhibitor, wherein the pulverizable layer is dispersed in the oral cavity by masticating, thereby releasing the prostaglandin inhibitor into the oral cavity where it enters the circulatory system by traversing the buccal mucosa,

wherein the rapid-release composition comprises a chewable layer that is absorbed through the buccal mucosa, and wherein (a) and (b) further comprise one or more pharmaceutically acceptable excipients, carriers or diluents.

It is noteworthy that the specific form of niacin is unimportant as the combination tablet of the present invention is contemplated to be effective with either the immediate-, extended-, or sustained-release forms of niacin.

The composition so described above are useful in treatment regimens directed to:

- reducing the serum levels in a subject in need thereof, of one or more of the following, triglycerides, total cholesterol, low density lipoprotein cholesterol, lipoprotein (a), by administering to said subject an effective amount of the combination tablet described herein;

- a method of preventing elevated serum levels in a subject in need thereof, of one or more of the following, triglycerides, total cholesterol, low density lipoprotein cholesterol, lipoprotein (a), by administering to said subject an effective amount of the composition of the combination tablet described herein;

- a method of increasing HDL cholesterol in a subject in need thereof, by administering to said subject an effective amount of the combination tablet

described herein; and

- additional cardiovascular and non-cardiovascular benefits.

The benefits of the pharmaceutical composition of the present invention can be expanded to other clinical applications, such as, e.g.,

- wherein (a) is a therapeutic agent that is known to be accompanied by nausea as a side effect, and (b) is an anti-emetic;
- wherein (a) and (b) comprise the identical therapeutic agents, therefore providing different efficacies for the same therapeutic agent;
- wherein (a) comprises an opioid, and (b) comprises, for example, acetaminophen (N-(4-hydroxyphenyl)acetamide), Percocet™ (mixture of acetaminophen and 4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one), or an NSAID, a prostaglandin D2 receptor 1 antagonist, or combinations thereof, in order to provide similar benefits by administering compounds with distinct mechanisms of action; and
- wherein (a) comprises a premedication for anesthesia such as a anticholinergic, for example atropine, and (b) comprises sedative, anesthetic or amnesiatic which is commonly given with such premedication.

In the context of the present invention, the use of the term *hard* in reference to the inner layer or core particle comprising a first therapeutic agent is used to connote that the inner layer and/or core particle is not pulverized by the force of masticating or chewing that effectively pulverizes the outer layer of the pharmaceutical composition of the present invention. Further, in referring to the inner layer or core particle as being *ingestible*, it is meant that the inner layer is capable of being taken up and absorbed by one or more portions of the gastrointestinal tract. The inner core portion of the combination tablet may be conventionally covered with one or more layers of coatings to permit a timed release of the active contained therein following ingestion by a subject. The present invention contemplates a release profile of the ingested core particle of from 30 minutes to 24 hours.

In the context of the present invention, the term *pulverizable* or *easily pulverizable* refers to a layer of a material that is ground or dispersed into small particles within the oral cavity by

gentle pressure generated by chewing or masticating the layer to be ground. There is no intent to imply any particular size or fineness of the resulting particles, as it is contemplated herein that it is only required that the pulverized material release a therapeutic agent within the oral cavity.

The term *masticating* or *chewing*, in the context of the present invention, is meant to signify that the pulverizing or grinding is being performed by a patient's or subject's teeth, or gums. A specific embodiment of the combination pill may cause the first bite(s) to rupture or dislodge the outer layer thereby releasing it from the central core and can then be chewed. There is no intent to signify any particular degree of force required or generated by the masticating teeth or gums. The requirement is that the force actually used to produce the pulverized granules, particles, powder and the like, is sufficient to disrupt the outer layer of the pharmaceutical composition of the present invention while leaving the inner layer or core particle *intact*. For the purpose of this description, the term *intact* does not require that the inner layer or core remain in one piece. Instead, it signifies that at least 50% of the inner layer or core particle is swallowed, but preferably that 75% of the inner core material is swallowed; even more preferably that approximately 75% to about 85% of the inner core material is swallowed, and most preferably, from about 85% to about 95% of the inner core material is swallowed, and most particularly, that greater than 95% of the inner core material is swallowed.

The *buccal mucosa* is meant to refer to the epithelium lining the oral cavity, including the sublingual region. The *buccal mucosa* further includes the sub-epithelial tissue; i.e., the tissue and macromolecular layers that accumulate underneath the epithelium. The sub-epithelial tissue includes, *inter alia*, connective tissue cells (fibroblasts, adipocytes, lymphocytes, and the like), extracellular matrix, basement membrane, smooth muscle, and vascular elements, etc. The buccal mucosa is a highly vascular tissue, and therefore a desirable route of entry into the general circulation

Fig. 1 provides a sectional view through the combination tablet of the present invention. The outer pulverizable layer (101) surrounds the inner core (103) that comprises the slowly absorbed therapeutic agent. Additional embodiments of the combination tablet may have an optional intermediate layer (102) between the outer pulverizable layer (101) and the inner core that serves to protect the inner core (103). The intermediate layer (102) may help protect the inner layer or core (103) from being unintentionally cracked or fragmented during

the mastication of the outer layer (101) of the combination tablet. In addition, depending upon its composition, the intermediate layer (102) may also slow absorption of inner core medication.

Fig. 2 illustrates an intermediate stage in the pulverizing and dissolution of the outer layer (104), which is depicted as somewhat intact but no longer adhering to the intermediate layer (106) and/or the inner core (105).

Fig. 3 provides a sectional view through an embodiment of the combination tablet. The illustrated embodiment provides a modification of the previously illustrated embodiments in that the outer layer (202), i.e., the rapidly absorbed layer (202), is commercially provided in either a liquid, a gel or a pulverized form (i.e., powder, granules, fragments, and the like). However, in order to keep the combination tablet intact, a very fragile outer coat (201) is applied and extends over the entire surface of the combination tablet. The coating or skin may result from several layers or coats of e.g. a conventional flavored or non-flavored coating. This type of skin may be prepared from several types of compositions such as fragile dried layers of sugar.

Example 1. <u>OUTER LAYER: CHEWABLE</u>

The first embodiment has a chewable outer layer, such that it can be absorbed quickly. This chewable layer may be adhered directly to the inner layer, or it may be such designed that when it is bitten lightly (e.g. with minimal force, such as the force needed to chew a banana), this outer chewable layer breaks off into many pieces within the mouth, and can be chewed and thus absorbed, leaving the hard inner layers in the mouth to be swallowed. By making the chewable layer "crumble" in such a way, the patient will avoid biting hard through the hard inner layer of the tablet, which could be uncomfortable if the inner tablet is very hard, or could damage the integrity of the inner tablet, allowing it to be absorbed earlier than desired.

This may be similar to eating a cherry, where one bites the outer layer off and eats it, but does not bite too hard to chip their tooth on the hard inner pit. However, in the inventive tablet the patient would then swallow the inner tablet, instead of spitting out the cherry pit.

The outer chewable layer can be formulated, e.g., with a water soluble sugar and/or a sugar substitutes. Suitable water-soluble sugars and/or sugar substitutes are glucose, maltose,

sucrose, dextrose, fructose, sorbitol, mannitol or other types of natural or artificial sweeteners. Mixtures of various sugars or sugar substitutes are also suitable.

The chewable layer can also be formulated with, e.g., a gel forming agent. Examples of such suitable gel formers are xanthan gum, methylcelluloses such as sodium carboxymethylcellulose or hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, alginates, tragacanth or soluble starch. These substances are all commercially available and usually meet the purity requirements and quality regulations for pharmaceutical products. All such gel formers and coatings contemplated are GRAS.

Wetting agents and lubricants such as sodium lauryl sulfate, as well as coloring agents, flavoring agents, sweetening agents (including other nonnutritive sweeteners), tableting agents, stabilizers, antioxidants, cooling agents, and preservatives, can also be present.

A binding agent can also be present such as cellulose, cellulosic derivatives, polyvinyl pyrrolidone, starch, modified starch, and mixtures thereof, and, in particular, microcrystalline cellulose.

One example of a manufacturing technique to formulate the chewable component over the solid dosage form is compression coating. The compression coating can be prepared by, e.g., a Manesty Dry-Cota press, which consists of two side by side interconnected tablet presses where the core is made on one press then mechanically transferred to the next press for compression coating. Each "press" has an independent powder feed mechanism so that core blend is loaded on one machine and coating blend on the other. Mechanical transfer arms rotate between the machines to remove cores from one press and transfer them to the coating press. Other and more modern types of presses which may be used (e.g. Elizabeth Hata HT-AP44-MSU-C, Killian RUD, Fette PT 4090) have a dual feed system for coating blend and pre-made cores. This configuration is more flexible, in that cores can be pan coated with a functional or cosmetic coating before compression coating. However, any conventional, art-recognized manufacturing technique that permits the formulation of a chewable component over a solid dosage form will be readily appreciated by the skilled artisan and is contemplated by the present invention.

Example 2. ***OUTER LAYER: CHEWABLE WITH THIS OUTER SHELL***

A similar embodiment would not only have an outer chewable layer, but also a thin shell outside of the chewable layer. This would be similar to the thin candy shell of an M&M

candy. With this thin outer shell helping to hold the tablet together, the chewable layer can be designed to more easily crumble and dissolve than if there was no outer shell, e.g., by reducing the amount of binder or by reducing the compression to that which will minimally hold the chewable component together until the outer shell is applied.

The outer shell can be a sugar coating or a polymer coating such as hydroxypropylmethylcelluose or polyvinylalcohol or combinations thereof, for example.

Example 3. **OUTER LAYER: LIQUID / POWDER**

Another embodiment contemplated by the present invention is an outer layer made from liquid, within a thin outer skin or shell. When the patient bites lightly on the tablet , this outer skin would fracture, allowing the liquid (or gel) of a fast-absorbing medication to release into the mouth and thus be absorbed quickly, starting at the mouth's mucous membranes.

There are several possible embodiments of this outer layer, including viscous liquids, gels, quick absorbable substances, powder within a breakable skin, substances that "melt" in the mouth (quickly absorb) and more.

When the outer layer is manufactured to absorb quickly, the drug can be formulated with a water soluble excipient such as a sugar, sugar alcohol, polyethylene glycol (PEG), or polyethylene oxide. The preferred water-soluble excipients are the sugar alcohols including, but not limited to sorbitol, mannitol, maltitol, reduced starch saccharide, xylitol, reduced paratinose, erythritol, and combinations thereof. The preferred sugar is glucose. Other suitable water-soluble excipients include gelatin, partially hydrolyzed gelatin, hydrolyzed dextran, dextrin, alginate and mixtures thereof. A disintigrating agent such as sodium starch "meltable" formulation can be readily determined by one of skill in the art.

When the outer layer contains a liquid within an outer skin, the outer skin can be gelatin and the drug can be mixed with water or miscible solvents such as propylene glycol; PEG's and ethanol, or an oleaginous medium, e.g., peanut oil, liquid paraffin or olive oil.

Example 4. **OUTER LAYER: QUICK DISSOLVE**

Another embodiment has an outer layer which rapidly dissolves when sucked on. When the inner layer is reached, the patient would swallow the tablet. This embodiment can be designed such that the outer surface of the inner, hard layer has a texture that is easily recognized by the tongue, so that it is clear to the patient when the outer layer is fully

dissolved, and thus when it is time to swallow the inner layer. This would be similar to a Tootsie Pop®, in that the Tootsie Roll® center is easily recognized by the tongue as feeling very different than the outer dissolvable candy.

In such an embodiments, the outer drug can be formulated in a dissolvable matrix material. The dissolvable matrix may include carbohydrates, fats, proteins, waxes (natural and synthetic), hydrocarbons, and other materials which safely and rapidly dissolve in the mouth.

Example 5. INNER LAYER: ENTERIC COATING

The inner "slow absorb" or "extended release" layer contemplated by the present invention has any number of art-recognized constituencies. In one embodiment, the inner layer is designed similar to a standard tablet. In another embodiment, the inner layer is enteric coated, further slowing the release of the medication. In still another embodiment the inner layer can be an extended release dosage form.

When the inner layer has an enteric coating, the coating can be, e.g., a material selected from the group consisting of one or more of the following: cellulose acetate phthalate, alginates, alkali-soluble acrylic resins, hydroxypropyl methylcellulose phthalate, methacrylate-methacrylic acid copolymers, polyvinyl acetate phthalate and styrol maleic acid copolymers. The coating can also be multilayered; i.e. one or more coatings are contemplated to provide extended release kinetics which permit the inner tablet to release over a period of from 15 minutes to 24 hours or more.

The extended release dosage form can be formulated with the drug dispersed in a matrix or with an extended release coating. Suitable materials form inclusion in an extended release matrix or coating can be, e.g., a cellulosic material, an acrylic polymer, or a combination thereof.

Example 6. INNER LAYER: PLIABLE (OUTER LAYER: CHEWABLE)

The contemplated inner layer can also be made of a substance which is softer and more pliable than a standard hard tablet, e.g. similar to a hard taffy. In this way, the patient could not chip their teeth when biting the tablet, as the inner layer will absorb some of the shock of the bite without breaking or dissolving. It can then by swallowed to be absorbed in the GI system, after the outer layer was absorbed in the mouth.

The "taffy" can be prepared, e.g., with an admixture of a sugar melt having at least 40%

sugar, such as fructose and a surface active agent. However, the skilled artisan can readily prepare alternative formulations of sugar-based substances to achieve an inner core that absorbs the shock of the chewing force exerted by an individual in the normal course of taking a chewable medication.

Example 7. ADDITIONAL EMBODIMENTS

In other embodiments, niacin can be prepared as an extended release powder and dispersed throughout a chewable tablet containing the COX inhibitor. In these embodiments the whole tablet could be chewed without destroying the integrity of the extended release powder, which can be subsequently swallowed.

In such an embodiment, the extended release powder can be microspheres comprised of micronized niacin coated with a polymer such as poly (lactic-co-glycolic) acid (PLGA).

Example 8. NIACIN / ASPIRIN

In the context of the contemplated niacin example, the outer layer can be the adjuvant COX inhibitor, which can include medications such as aspirin, other NSAIDs such as naproxen sodium (sodium (2S)-2-(6-methoxynaphthalen-2-yl)propanoate) and ibuprofen (2-[4-(2-methylpropyl)phenyl]propanoic acid) COX-2specific inhibitors such as colecoxib (Celebrex™) (4-[5-(4-methylphenyl)-3-(trifluoromethyl)pyrazol-1-yl]benzenesulfonamide) and rofecoxib (Vioxx™) (4-(4-methylsulfonylphenyl)-3-phenyl-5H-furan-2-one), Vitamins such as Vitamin C, and more, or any combination of the above. The inner "slow release" or "extended release" layer can be niacin, or slow release niacin or other combination drugs such as statins, other cholesterol medications, other diabetes or hypertension medications, and the like.

In a preferred embodiment, niacin released from the core can have an in vitro dissolution profile, when measured in a type I dissolution apparatus (basket) according to U.S. Pharmacopeia XXII, at about 37 degrees C in deionized water at about 100 rpm, as follows (a) less than about 15% of the niacin is released after about 1 hour in the apparatus, (b) between about 15% and about 30% of the niacin is released after about 3 hours in the apparatus, (c) between about 30% and about 45% of the niacin is released after about 6 hours in the apparatus, (d) between about 40% and about 60% of the niacin is released after about 9 hours in the apparatus, (e) between about 50% and about 75% of the niacin is released after about 12 hours in the apparatus, and (f) at least about 75% of the niacin is released after about

20 hours in the apparatus.

Even antipsychotic medications may make sense to put in combination, as schizophrenics have been shown to have lower baseline flush response to niacin due to their low levels of arachidonic acid, making them particularly a good match for niacin medications, especially due to their high rates of obesity, bad cholesterol, and poor compliance (this combination tablet should greatly increase compliance due to requirements for less tablets per day).

Example 9 METHOD OF STARTING NIACIN/ASPIRIN REGIMEN, AND DIFFERENT DOSES

This invention also contemplates several methods for the initial and ongoing adaptation of niacin, or the above described niacin combination tablet. Niacin is best started at a low dose and ramped up over time as tolerance to the flush is achieved. The contemplated dosages are readily understood by the skilled physician based on the age, weight, sex and physiological characteristics of the patient. The COX inhibitor (e.g. aspirin) should be started first, and at a higher dose, and ramped down to a lower level as the tolerance is achieved. COX inhibitors have the side effect of ulcers and GI bleeds, which must be weighed against the beneficial effect of decreasing flush.

Patients buildup a tolerance to the niacin flush from a matter of days to months of use, and can therefore be weaned off of the COX inhibitor, or more likely given a low permanent dose (low dose aspirin has been shown to be relatively safe, and has many other very beneficial side effects, and therefore is taken by many patients with cardiovascular disease).

1. PRELOAD WITH ASPIRIN

The first aspect is to pre-load the patient with COX inhibitor. Therefore, for several days before their first dose of niacin, the patient would first take COX inhibitor for several days.

2. TAKE ON FULL STOMACH

The combination tablets should be taken on a full stomach, after food, as the fast-absorb layer will be mostly absorbed through mucous membranes, and the slow-absorb will be delayed due to recent food in the GI tract, helping to reach the desired gap in absorption of the two medications.

3. RAMP UP DOSE OF NIACIN

For example, during the first week the patient may take a combination tablet that has 100mg

niacin and 325mg aspiring, while the week-two combination tablet will have 250mg niacin and still 325mg aspirin, and so forth.

4. TAPER DOSE OF ASPIRIN

In addition, over time the amount of COX inhibitor may be tapered. After the patient has been on their maximum niacin dose for some time and has developed a tolerance, the aspirin dose may be tapered. For example, the patient may be taking a combination tablet with 1000mg niacin and 325mg aspirin, three times per day, then a tablet with 1000mg niacin and 162mg aspirin, and then 1000mg niacin and 81 mg aspirin, which may be the maintenance dose.

5. DIFFERENT COLORS AND SHAPES

Each of these combination tablets could look different, with different colors, shapes, or writing. In addition the combination tablets contemplated by the present invention can be conventionally flavored with palatable flavorants known in the art.

6. CARDS, POSTERS, & TABLET BOXES TO MAKE CLEAR TO PATIENTS

To help the patient know when to take which tablets, the regimen should be made very simple, through posters or cards describing which tablets to take during which weeks. Patients could be encouraged to switch earlier to the next tablet if they feel the flush has decreased, or to delay switch if they still need time to develop tolerance. Also, tablet boxes can be employed to help with this compliance.

Through such a method patients are able to start a regimen of niacin and develop a tolerance to flush in a tolerable way. Below is one example of a regimen of the combination tablets of the present invention. The first number of each tablet is the amount of niacin, and second is the amount of aspirin.

Week 1:	Aspirin only, 325mg, 3x/day	
Week 2:	100mg/325mg	3x/day
Week 3:	250mg/325mg	3x/day
Week 4:	500mg/325mg	3x/day
Week 5:	750mg/325mg	3x/day
Week 6:	1000mg/325mg	3x/day
Week 7:	1000mg/162mg	3x/day

Week 8: and beyond	1000mg/81mg	3x/day

Persons of ordinary skill in the art will readily appreciate that this regimen is just one non-limiting illustration. For example the regimen may be much simpler, i.e., may be a much simpler chart, for example starting with 325mg + 500mg, then going to 81mg + 500mg).

Obviously, the above regimen is only an example, and a better standard regimen could be developed with more research into the timing of tolerance, as well as additional regimens designed for specific patient populations (such as schizophrenics, those with cardiovascular disease and in need of low-dose aspiring as a blood thinner, and more), or specific patients.

Another aspect of the present invention is to use one or more prostaglandin inhibitors as the second therapeutic agent in the rapid release layer of the combination tablet. In the context of describing the present invention, the term "prostaglandin inhibitor" is any compound that impairs the function of one or more prostanoid compounds, including prostaglandins, prostacyclin and thromboxane. COX-2 specific inhibitor, ideally an irreversible one. As it is the COX-1 receptors that have been implicated in the deleterious side effects of aspirin (GI ulcers and bleeding), this may allow for longer use or higher-dose use of the flush-blocking adjuvant.

Another aspect of the present invention is to use a COX-2 specific inhibitor, ideally an irreversible one. As it is the COX-1 receptors that have been implicated in the deleterious side effects of aspirin (GI ulcers and bleeding), this may allow for longer use or higher-dose use of the flush-blocking adjuvant.

While the foregoing written description of the invention enables one of ordinary skill to make and use what is considered presently to be the best mode thereof, those of ordinary skill will understand and appreciate the existence of variations, combinations, and equivalents of the specific embodiment, method, and examples herein. The invention should therefore not be limited by the above described embodiment, method, and examples, but by all embodiments and methods within the scope and spirit of the invention as claimed.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising;

(a) a hard inner component comprising an effective amount of a first therapeutic agent, wherein the hard ingestible component releases the first therapeutic agent by dissolving in the gastrointestinal tract; and

(b) a pulverizable outer layer comprising an effective amount of a second therapeutic agent, wherein the pulverizable layer is dispersed in the oral cavity by masticating, thereby releasing the second therapeutic agent into the oral cavity where it enters the circulatory system by traversing the buccal mucosa;

wherein (a) and (b) further comprise one or more pharmaceutically acceptable excipients, carriers or diluents.

2. The pharmaceutical composition of claim 1, wherein the hard inner component is a delayed or extended release dosage form that is at least partially enclosed by the pulverizable outer layer.

3. The pharmaceutical composition of claim 1, wherein the hard inner component further comprises an effective amount of the second therapeutic agent.

4. The pharmaceutical composition of claim 1, wherein the first therapeutic agent is a medication known to be accompanied by nausea as a side effect, and the second therapeutic agent is an anti-emetic.

5. The pharmaceutical composition of claim 1, wherein the first therapeutic agent is an opioid, and the second therapeutic agent is Percocet, Tylenol or an NSAID.

6. The pharmaceutical composition of claim 1, wherein the first therapeutic agent comprises a premedication for anesthesia and the second therapeutic agent comprises a sedative, anesthetic or amnesiatic, which is commonly given with such premedication.

7. The pharmaceutical composition of claim 6, wherein the first therapeutic agent comprises an anti-cholinergic compound.

8. The pharmaceutical composition of claim 6, wherein the first therapeutic agent comprises atropine.

9. The pharmaceutical composition of claim 1, wherein the first therapeutic agent is niacin.

10. The pharmaceutical composition of claim 9, wherein the niacin is an immediate-release or an extended release niacin.

11. The pharmaceutical composition of claim 1, wherein the second therapeutic agent is an NSAID (non-steroidal anti-inflammatory drug).

12. The pharmaceutical composition of claim 1, wherein the second therapeutic agent is an inhibitor of either cylcooxygenase I and/or cyclooxygenase II.

13. The pharmaceutical composition of claim 1, wherein the second therapeutic agent is laropiprant.

14. The pharmaceutical composition of claim 1, wherein the hard inner component comprises an effective amount of niacin and optionally, an effective amount of either an NSAID or a COX inhibitor, and wherein the pulverizable outer layer comprises either an NSAID or a COX inhibitor.

15. The pharmaceutical composition of claim 1, wherein (b) is a chewable layer comprises at least one pharmaceutically acceptable excipient, carrier or diluent, selected from the group consisting of glucose, maltose, sucrose, dextrose, fructose, sorbitol, mannitol, natural and artificial sweeteners, xanthan gum, methylcelluloses such as sodium carboxymethylcellulose or hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, alginates, tragacanth or soluble starch.

16. The pharmaceutical composition of claim 1, wherein (b) is a hydrophilic layer and comprises at least one pharmaceutically acceptable excipient, carrier or diluent, selected from the group consisting of sugar, sugar alcohol, polyethylene glycol (PEG), or polyethylene oxide, sorbitol, mannitol, maltitol, reduced starch saccharide, xylitol, reduced paratinose, erythritol, glucose, gelatin, partially hydrolyzed gelatin, hydrolyzed dextran, dextrin, alginate and mixtures thereof.

17. The pharmaceutical composition of claim 1, wherein (b) comprises at least one pharmaceutically acceptable excipient, carrier or diluent, selected from the group consisting of, sugars polyalcohols, microcrystalline cellulose, magnesium stearate,carboxymethyl cellulose or low-substituted hydroxypropyl cellulose (L-HPC), polyvinylpyrrolidone XL and

carboxymethylamide.

18. The pharmaceutical composition of claim 1, wherein (a) comprises an enteric coating selected from the group consisting of copolymecellulose acetate phthalate, alginates, alkali-soluble acrylic resins, hydroxypropyl methylcellulose phthalate, methacrylate-methacrylic acid copolymers, polyvinyl acetate phthalate and styrol maleic acid copolymers.

19. The pharmaceutical composition of claim 1, wherein (a) is a therapeutic agent that is known to be accompanied by nausea as a side effect, and (b) is an anti-emetic.

20. The pharmaceutical composition of claim 1, wherein (a) and (b) comprise the identical therapeutic agents.

21. The pharmaceutical composition of claim 1, wherein (a) comprises an opioid, and (b) comprises percocet, Tylenol or an NSAID, or combinations thereof.

22. A pharmaceutical composition suitable for treating or preventing high serum lipid levels or poor cholesterol profile, the composition comprising,

(a) a hard inner component comprising an effective amount of a niacin, wherein the hard ingestible component releases the niacin by dissolving in the gastrointestinal tract; and

(b) a pulverizable outer layer comprising an effective amount of a prostaglandin inhibitor, wherein the pulverizable layer is dispersed in the oral cavity by masticating, thereby releasing the prostaglandin inhibitor into the oral cavity where it enters the circulatory system by traversing the buccal mucosa,

wherein the rapid-release composition comprises a chewable layer that is absorbed through the buccal mucosa, and wherein (a) and (b) further comprise one or more pharmaceutically acceptable excipients, carriers or diluents.

23. The pharmaceutical composition of claim 22, wherein the COX inhibitor is rofecoxib, colecoxib, ibuprofen, naproxen sodium, or a combination thereof.

24. The pharmaceutical composition of claim 22, wherein the prostaglandin inhibitor is laropiprant.

25. A method of reducing the serum levels in a subject in need thereof, of one or more of

the following, triglycerides, total cholesterol, low density lipoprotein cholesterol, and lipoprotein (a), by administering to said subject an effective amount of the composition of claim 17.

26. A method of preventing elevated serum levels in a subject in need thereof, of one or more of the following, triglycerides, total cholesterol, low density lipoprotein cholesterol, lipoprotein (a), by administering to said subject an effective amount of the composition of claim 17.

27. A method of increasing HDL cholesterol in a subject in need thereof, by administering to said subject an effective amount of the composition of claim 17.

FIG. 1

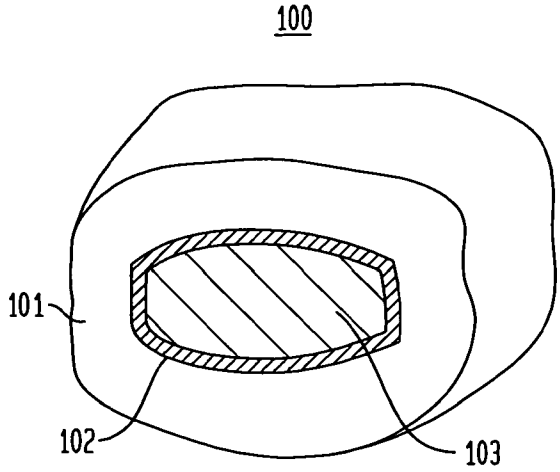


FIG. 2

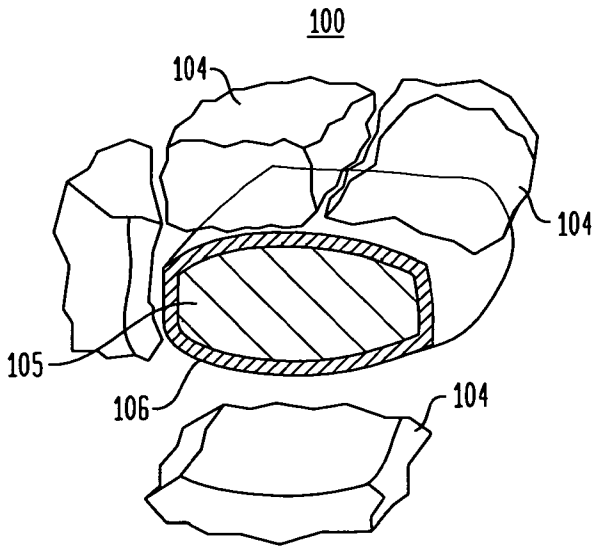
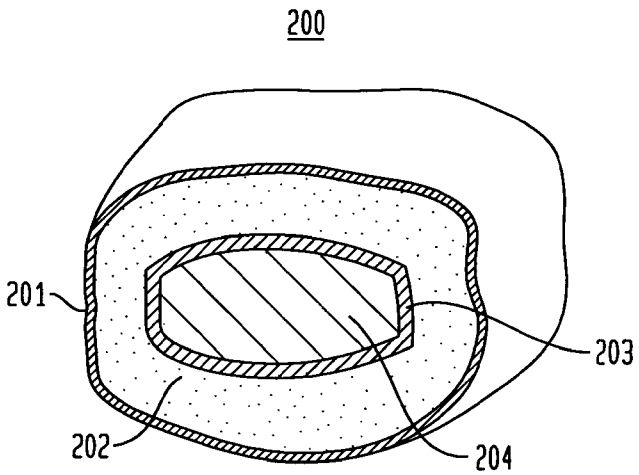


FIG. 3



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/08191

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 37/36 (2008.04)
USPC - 514/165
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)
USPC - 514/165; 514/356,420,569,570; 424/464

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST (all five databases) - terms: drug, pharmaceutic$, therapeutic$, medication, medicament, chew, masticate, hard, rigid, core
Dialog files 348,349,344,345,351,65,155 - terms: drug, pharmaceutic?, therapeutic?, medication, medicament, medicine, chew, masticat?, hard, rigid, core, second

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,552,152 A (SHEN), 03 September 1996 (03.09.1996), claim 1	1-27
Y	EP 1260216 A1 (HIRSH et al.), 27 November 2002 (27.11.2002), abstract	1-27
Y	US 2005/0045197 A1 (GELDER), 03 March 2005 (03.03.2005), paragraph [0033]	4, 19
Y	WO 2006/061624 A1 (HEAL et al.), 15 June 2006 (15.06.2006), page 1, lines 5-14	6
Y	US 6,114,370 A (WALL), 05 September 2000 (05.09.2000), abstract	7
Y	US 6,004,945 A (FUKUNAGA), 21 December 1999 (21.12.1999), table 7 in column 17	8
Y	US 2006/0276416 A1 (SINCLAIR et al.), 07 December 2006 (07.12.2006), paragraphs [1121], [0105], [1049], and [1050]	9-10, 14, 22-27
Y	E Lai et al (2007). "Suppression of Niacin-induced Vasodilation with an Antagonist to Prostaglandin D2 Receptor Subtype 1". Clinical Pharmacology & Therapeutics 81: 849-857. (advance online publication, March 28, 2007), abstract	13, 24

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 September 2008 (11.09.2008)	26 SEP 2008
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)