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(54) Title: GEMCABENE COMBINATIONS FOR THE TREATMENT OF CARDIOVASCULAR DISEASE

(57) Abstract: The present invention provides pharmaceutical compositions formulated to include a statin and gemcabene, wherein the composition is useful for treating, preventing, or reducing symptoms of cardiovascular and metabolic indications that involve elevate levels of LDL cholesterol, triglycerides, or both.

GEMCABENE COMBINATIONS FOR THE TREATMENT OF CARDIOVASCULAR DISEASE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Application Serial Nos.: 62/252,195, filed on November 6, 2015, and 62/252,147, filed on November 6, 2015, the disclosures of both of which are hereby incorporated by reference in their entireties.

FIELD OF THE INVENTION

[0002] This invention relates to formulations of fixed dose combinations of a statin and gemcabene, and for a fixed dose combination of a statin, gemcabene and a third agent which is selected from lipid lowering agents, anti-inflammatory agents, anti-hypertensive agents, anti-diabetic agents, anti-obesity agents, anti-fibrotic or an anti-coagulation agents. These combinations are useful for treating mixed dyslipidemia and diseases that result as a consequence of disorders of lipoprotein metabolism, disorders of glucose metabolism, cardiovascular disorders, diseases of the liver, diseases of the kidney, diseases of the lung, disease of the muscle and inflammation.

BACKGROUND

[0003] The combination of gemcabene with a statin has been shown to significantly reduce plasma levels of LDL cholesterol (LDL-C) below that of a statin alone. In addition, gemcabene has been shown to further reduce LDL-C levels in patients on a stable dose of statin that are not able to reach the target LDL-C goal. In addition, in patients having type IIb hyperlipidemia certain dose combinations of gemcabene with statins show surprising ability to lower triglycerides when compared with either gemcabene alone or statin alone. The combination of gemcabene and a statin may have other benefits as well. For example, the addition of gemcabene on top of a statin has been shown to reduce c-reactive protein to an extent greater than the statin treatment alone. In addition, certain combinations of a gemcabene and a statin lower fibrinogen in hypercholesterolemic human subjects with elevated fibrinogen levels.

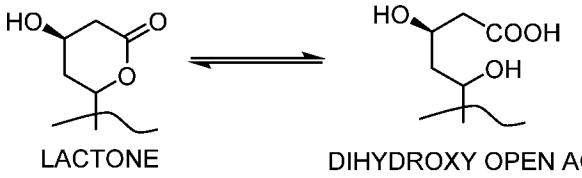
[0004] Compliance by patients that may be taking multiple medications is important to properly treat the disease or condition for which they are taking the medication. Reducing the number of pills, tablets, or the like may help in patient compliance.

[0005] Although gemcabene has been shown not to significantly affect the pharmacokinetics of simvastatin and atorvastatin *in vivo,* prior attempts at the formulation of combination tablets by means of common tableting techniques reduced stability of such formulations due to solid state drug-ingredient or drug-drug interactions. For instance, common tableting of atorvastatin

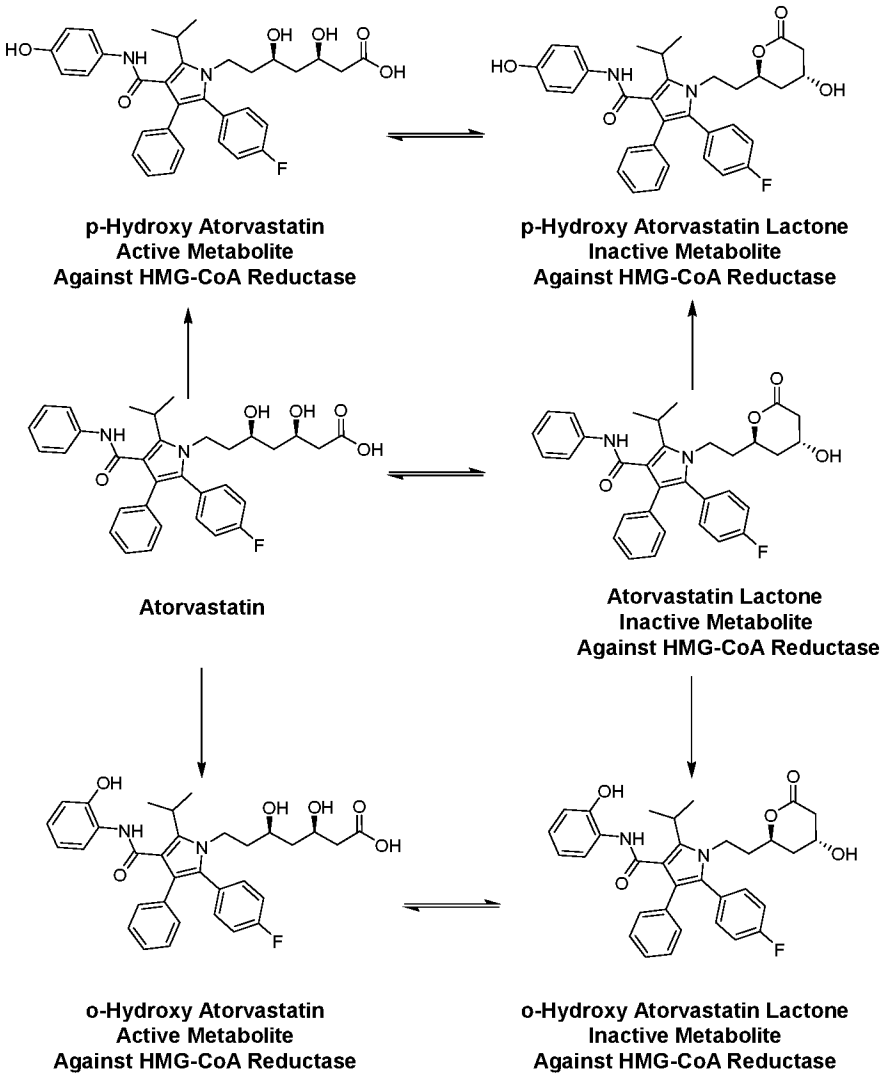
calcium with PVP and gemcabene calcium generates a drug product that possesses a reduced shelf life due to the rapid formation of product-related degradation products. Similarly, in other tablets that are formulated with atorvastatin calcium and acidic excipients or acidic drugs, atorvastatin has shown poor shelf life. Therefore, creation of long term stable formulations that combine gemcabene with a statin is challenging. Furthermore, desirable pharmacokinetic, pharmacodynamics and safety properties of such combination formulations need to maintain reasonable similarity or superiority to the agents when dosed individually.

Atorvastatin has been observed to undergo an acid-mediated conversion to an undesirable lactone in the stomach. Moreover, the atorvastatin metabolites, 2-hydroxy-atrovastatin and 4-hydroxy-atorvastatin, are active towards HMG-CoA reductase undergo lactonization in the gastrointestinal tract along with atorvastatin (Figure 1). A comprehensive overview of the clinical pharmacokinetics of atorvastatin is presented in *Hans Lennernas, Clin Pharmacokinet* 2003*; 42* (13): 1141-1160.

Scheme 1: General Scheme for Lactone- Dihydroxy Acid Interconversion



Scheme 2: Atorvastatin Metabolites – Interconversion of Dihydroxy-Acid to Lactone



[0006] The gastrointestinal tract is comprised of a series of interrelated anatomical organs that have both functional and regional differences that collectively aid in the absorption of nutrients and pharmaceuticals. The series of connected organs of the gastrointestinal tract, also collectively known as the digestive tract, the GI tract, the gut or the alimentary canal, is comprised of the mouth, esophagus, stomach and intestines. The intestines are comprised of the small intestine connected to the stomach and the large intestine connected to the small intestine. The small intestine is comprised of three sections: the duodenun, the shortest section (~20-25 cm

long), which is also most proximal and connected to the stomach; and from which the alimentary bolus exits into the jejunum or mid-intestine where most absorption occurs. The jejunum, which is about 2.5 m long and exists into the final distal most section of the small intestine dejects the bolus into the ileum, which is about 3 m long and empties into the large intestine. The large intestine is subdivided and sequentially comprised of the cecum (the proximal most region), followed by the colon, the rectum and the anal canal.

[0007] The duodenum receives acidic, partially digested food called "chyme" from the stomach, bile from the gall bladder and liver, and pancreatic fluid enriched with digestive enzymes from the pancreas. Bile and pancreatic fluids both arrive in the duodenum via the common bile duct. Combined, the pancreatic fluid/bile mixture facilitates the emulsification of fat and breakdown of food proteins and carbohydrates. The duodenum also contains Brunner's glands, which releases a mucus-rich, bicarbonate containing, alkaline secretion. In addition, the pancreas also secretes a bicarbonate solution into the duodenum which collectively neutralizes the stomach chyme.

[0008] The surface area of the jejunum is highly increased by the presence of villi, and is where most of the intestinal absorption of food nutrients, such as sugars, amino acids, fatty acids and cholesterol, occurs. The structure of the ileum is similar to the jejunum, and its surface is also enriched by villi; here vitamin B12, bile acids, and remaining nutrients are absorbed. The main function of the large intestine is the absorption of water.

[0009] The absorption, distribution, metabolism, and excretion (ADME) of orally administered drugs is dependent on many factors including the intestinal environment, intestinal transit time and the formulation of the pharmaceutical agent. Some agents, such as gemcabene, exhibit almost complete absorption in the intestines. With gemcabene, the completeness of absorption by the intestines is essentially unchanged in either absence or presence of food. Some statins such as lovastatin and simvastatin are HMG-CoA reductase drugs marketed as lactones of their active di-hydroxyl open acid forms. Their lactonized forms are prodrugs that release the di-hydroxyl active forms in the acidic media of the digestive tract (mainly in the stomach). Other agents such as atorvastatin are incompletely absorbed, dependent on the presence of food, and subject to lactone formation of the parent compounds or metabolites based on the pH of the intestinal tract.

[0010] The role of the pH in the interconversion of the hydroxyacid and lactone forms of atorvastatin has been described by Kearney at al., *Pharmaceutical Research* 1993: *10* (10), 1461-1465, showing that the interconversion of the lactone and dihydroxy acid forms of atorvastatin is pH dependent, as well as is the solubility of the dihyroxy acid forms. At pH <6, there is an equilibrium between the dihydroxy acid and the lactone (which slightly favors the dihydroxy

acid); whereas, at pH >6, the equilibrium is no longer apparent and greatly favors the dihydroxy form.

[0011] Modulating the metabolism of atorvastatin by controlling its release and its metabolites is important. Certain metabolites of atorvastatin have been proven clinically to be responsible for adverse events, such as musculoskeletal events, among them rhabdomyolysis, conditions which are collectively named statin-induced myopathy (SIM). The formation and absorption of atorvastatin lactones is undesirable, as these lactones are associated with musculoskeletal adverse effects, such as myalgia, myositis, and rhabdomyolysis. Lactone metabolites of atorvastatin have been revealed to be responsible for statin myotoxicity (Skottheim et al. *Mol Diagn Ther* 2011: *15* (4), 221-226, and Hermann et al. *Clin Pharmacol Ther* 2006: 79, 532-539) Stormo et al. *Mol. Diagn Ther* 2013:17, 233-237). Another approach to reduce muscle toxicity is development of hepatic selective statins minimizing the distribution of these agents and their metabolites to muscle (Park et al. *Bioorg Med Chem Lett* 2008: 18, 1151-1156, and Pfefferkorn et al. *Bioorg Med Chem Lett* 2011: 21, 2725-2731) . Combination of hepatoselective statins with gemcabene are also useful for having improved medical benefit of the combination and reduced muscle toxicity.

[0012] Accordingly, it is desirable to reduce the amount of atorvastatin lactone formation *in vivo*.

BRIEF DESCRIPTION OF THE FIGURES

[0013] **Figure 1** is a dissolution profile of atorvastatin from immediate release atorvastatin capsules, 20 mg.

[0014] **Figure 2** is a dissolution profile of gemcabene from immediate release gemcabene capsules, 150 mg.

[0015] **Figure 3** is a table providing the composition of atorvastatin modified release formulations with triggered pH release from 5.5 to 7.5.

[0016] **Figure 4** is a dissolution profile of atorvastatin from enteric coated atorvastatin calcium tablets, 20 mg (prototype 1).

[0017] **Figure 5** is a dissolution profile of atorvastatin from enteric coated atorvastatin calcium tablets, 20 mg (prototype 2).

[0018] **Figure 6A** is a graph showing the pharmacokinetic profiles of total atorvastatin (non-lactone plus lactone), atorvastatin non-lactone, atorvastatin lactone metabolites for phase 1 – immediate release atorvastatin (Example canine A).

[0019] **Figure 6B** is a graph showing the pharmacokinetic profiles of total atorvastatin (non-lactone plus lactone), atorvastatin non-lactone, atorvastatin lactone metabolites for phase 3 – modified release atorvastatin prototype 1 and gemcabene (Example canine A).

[0020] Figure 6C is a graph showing the pharmacokinetic profiles of total atorvastatin (non-lactone plus lactone), atorvastatin non-lactone, atorvastatin lactone metabolites for phase 4 – modified release atorvastatin prototype 2 and gemcabene (Example canine A).

[0021] Figure 7A is a graph showing the pharmacokinetic profiles of total atorvastatin (non-lactone plus lactone), atorvastatin non-lactone, atorvastatin lactone metabolites for phase 1 – immediate release atorvastatin (Example canine C).

[0022] Figure 7B is a graph showing the pharmacokinetic profiles of total atorvastatin (non-lactone plus lactone), atorvastatin non-lactone, atorvastatin lactone metabolites for phase 3 – modified release atorvastatin prototype 1 and gemcabene (Example canine C).

[0023] Figure 7C is a graph showing the pharmacokinetic profiles of total atorvastatin (non-lactone plus lactone), atorvastatin non-lactone, atorvastatin lactone metabolites for phase 4 – modified release atorvastatin prototype 2 and gemcabene (Example canine C).

[0024] Figure 8 is a graph showing the pharmacokinetic profile of gemcabene (composite data from all animals), as follows: a) phase 2 – immediate release gemcabene, b) phase 3 – modified release atorvastatin prototype 1 and gemcabene and c) phase 4 – modified release atorvastatin prototype 2 and gemcabene.

SUMMARY

[0025] The present disclosure provides pharmaceutical formulations that: (i) reduce or eliminate drug-drug and excipient-drug interactions during storage of formulations of statins and gemcabene as a combined fixed dose form, and (ii) allow modulated and differed release profiles of the statin compared to gemcabene in order to improve the combination pharmacokinetics. One aspect of the present invention provides specific pharmaceutical compositions comprising a statin or a pharmaceutically acceptable salt thereof and gemcabene or a pharmaceutically acceptable salt thereof and excipients selected to reduce or eliminate possible stability issues during storage of gemcabene and a statin in combined dose form. In some embodiments the pharmaceutical compositions are formulated to provide fixed dose combinations with modified pharmacokinetics for reducing the adverse effects which would require the discontinuation of the drug.

[0026] The present invention includes a pharmaceutical product designed as a single administration unit (capsule, tablet, tablet-in-capsule, etc.) comprised of gemcabene and atorvastatin, each drug being contained in microparticles (microcapsules, beads, microtablets, etc.) having different pharmacokinetics, as follows:

a. Gemcabene is released immediately and sustained over an extended period; and
b. Atorvastatin is released on an extended and sustained period (triggered to be about 8 hours) not immediately after administration, but with a lag time in atorvastatin

delivery from formulation of about 2 to about 4 hours. The lag is identified as the transit time from the administration of the drug to a targeted site of release in the digestive system.

[0027] The approach to generate the lag for atorvastatin delivery is based on the design of a drug delivery system able to protect atorvastatin from fast release in the stomach, duodenum and jejunum, with release in the distal part of the small intestine, *i.e.*, delaying release to a region of the small intestine where the pH levels are elevated and do not favor formation of atorvastatin lactones. This is possible experimentally by means of methodologies well-known in the drug industry applied to delayed formulations. One of them is the pH-controlled release. The human intestinal system is characterized by the variation of the pH between its different segments. Fallingborg J, et. al. *Aliment Pharmacol Ther.* **1989,** 3, 605-13, describes a reference clinical study of the variations in pH and the residence times in various parts of the gastrointestinal tract by means of recording parameters for a pH-sensitive, radiotransmitting capsule. An exemplary overview providing an estimate of the pH in different sections and residence time of the digestive tract is provided in Table 1 below based on data from the cited clinical trial.

Table 1: pH Variation in the Gastrointestinal Tract and Residence Time of a Capsule

	Stomach	**Duodenum**	**Jejunum**	**Ileum**	**Colon**
Fasting pH	1.4 – 2.1	4.6	4.4 – 6.6	6.8 – 8.6	5 – 8
Time, hr	1.2-2.1	2.4 - 6.8	6-7	~6	~17 hr
Fed pH	3 – 5	4.5 – 5.5	5.2 – 6.2	6.8 – 8.0	5 – 8
Time, hr	0.1	1	2	No data (>6)	~17 hr

[0028] Various film coating agents are drug delivery systems that insure site specific delivery in the intestine. Most enteric coatings work by presenting a surface that is stable at the highly acidic pH found in the stomach, but breaks down rapidly at a relatively more basic pH. For example, they will not dissolve in the acidic juices of the stomach (pH ~3), but they will in the alkaline (pH 7-9) environment present in the distal small intestine. Various methacrylic acid copolymers have targeted drug release areas due to their specific dissolution pH.

[0029] The modeling of the pH for the drug release at a specific transition time can be achieved by the combination of two film coating agents: Methacrylic Acid Copolymer type C (Eudragit® L100-55) with the upper bowel as the targeted drug release area and with a dissolution pH of 6, and Methacrylic Acid Copolymer type B (Eudragit® S100), which targeted delivery area is the colon and with a dissolution pH of 7.

[0030] In another aspect, in order to reduce or eliminate possible stability issues during storage of the pharmaceutical compositions, the present invention provides for dosage forms that separate the active pharmaceutical ingredients (APIs) comprised by the dosage form.

[0031] In another aspect, the invention reveals environmental conditions, including temperature, humidity and enclosure specifications that largely maintain the long term stability of each API component of the formulation when prepared as a fixed dose.

[0032] In yet another embodiment, the present invention also provides for dosage forms that afford modified release of one or both APIs.

[0033] In some embodiments, the statin is any HMG-CoA reductase inhibitor selected from, but not limited to, atorvastatin, simvastatin, pravastatin, rosuvastatin, fluvastatin, lovastatin, pitavastatin, or any hepatoselective statin and pharmaceutically acceptable salts thereof.

[0034] In some embodiments, the gemcabene is a calcium salt of gemcabene.

[0035] In other embodiments, the statin is a calcium salt of atorvastatin.

[0036] In yet other embodiments, the statin - gemcabene combination is administered once per day.

[0037] In another aspect, the present invention provides a pharmaceutical composition comprising a combination of at least two APIs. One embodiment of the pharmaceutical composition of the present specification is a pharmaceutical composition comprising: a) a combination of two APIs selected from the group consisting of a statin and gemcabene; and b) optionally one or more additional APIs wherein the combination of the two APIs comprises

from about 0.1 wt% to about 61.5 wt% of a statin or a pharmaceutically acceptable salt thereof by weight of the combination; and

from about 38.5 wt% to about 99.9 wt% of gemcabene or a pharmaceutically acceptable salt thereof by weight of the combination.

[0038] Another embodiment of the present disclosure is a pharmaceutical composition comprising: a) a combination of two APIs selected from the group consisting of a statin and gemcabene; and b) optionally one or more additional APIs wherein the combination of the two APIs comprises

from about 2 wt% to about 35 wt% of a statin or a pharmaceutically acceptable salt thereof by weight of the combination; and

from about 65 wt% to about 98 wt% of gemcabene or a pharmaceutically acceptable salt thereof by weight of the combination.

[0039] A pharmaceutical composition comprising: a) a combination of two APIs selected from the group consisting of a statin and gemcabene; and b) optionally one or more additional APIs wherein the combination of the two APIs comprises

from about 2 wt% to about 21 wt% of a statin or a pharmaceutically acceptable salt thereof by weight of the combination; and

from about 79 wt% to about 98 wt% of gemcabene or a pharmaceutically acceptable salt thereof by weight of the combination.

[0040] In some embodiments, the pharmaceutical composition is in the form of a tablet. In some instances, the tablet comprises one or more excipients selected from a diluent, a disintegrant, a wetting agent, a binder, a glidant, a lubricant, a (film) coating vehicle, a diluent, an anti-foaming agent, a stabilizing agent or any combination thereof. For example, the tablet comprises a binder selected from microcrystalline cellulose, dibasic calcium phosphate, sucrose, corn starch, polyvinylpyrridone, hydroxyporopyl cellulose, hydroxymethyl cellulose, or any combination thereof. In another example, the tablet comprises a disintegrant. The tablet may comprise a disintegrant such as sodium croscarmellose or sodium starch glycolate, or combinations of disintegrants. In other examples, the tablet comprises a lubricant such as but not limited to stearic acid as free acid or as a salt, such as magnesium stearate, sodium stearyl fumarate, hydrogenated oils, colloidal silicon dioxide as unique components or any combination thereof.

[0041] In some embodiments, the tablet comprises from about 1 mg to about 80 mg of the statin and from about 50 mg to about 900 mg of gemcabene. In some of these examples, the statin is the calcium salt of atorvastatin. In other examples, the gemcabene is the calcium salt of gemcabene. And, in some examples, the tablet further comprises calcium carbonate, potassium carbonate, or a combination thereof.

[0042] In some aspects, the present invention provides a pharmaceutical composition comprising a tablet, wherein the tablet comprises from about 10 mg to about 40 mg of a statin or a pharmaceutically acceptable salt thereof; from about 150 mg to about 600 mg of gemcabene or a pharmaceutically acceptable salt thereof; and one or more excipients selected from a diluent, a disintegrant, a wetting agent, a binder, a glidant, a lubricant, a (film) coating vehicle, a diluent, an anti-foaming agent, a stabilizing agent or any combination thereof.

[0043] In some embodiments, the pharmaceutical composition further comprises from about 10 mg to about 40 mg of the statin.

[0044] In some embodiments, the statin is atorvastatin, simvastatin, pravastatin, rosuvastatin, fluvastatin, lovastatin, pitavastatin or any pharmaceutically acceptable salts thereof. For example, the statin is atorvastatin, simvastatin, or pharmaceutically acceptable salts thereof. In other examples, the statin is a calcium salt of atorvastatin.

[0045] In some embodiments, the tablet comprises a binder such as any of the binders described herein.

[0046] In some embodiments, the tablet comprises a disintegrant such as any of the disintegrants described herein.

[0047] In some embodiments, the tablet comprises a lubricant such as any of the lubricants described herein.

[0048] In some embodiments, the gemcabene is the calcium salt of gemcabene.

[0049] In some embodiments, the pharmaceutical composition further comprises calcium carbonate, potassium carbonate, or a combination thereof.

[0050] Another aspect of the present invention provides a pharmaceutical composition in the form of a capsule, wherein the capsule comprises from about 10 mg to about 80 mg of a statin or a pharmaceutically acceptable salt thereof; and from about 50 mg to about 900 mg of gemcabene or a pharmaceutically acceptable salt thereof; wherein the statin is in the form of a plurality of first particles and the gemcabene is in the form of a plurality of second particles.

[0051] In some embodiments, the first particles, the second particles, or both further comprise a binder. In some embodiments, the first particles, the second particles, or both further comprise an extended release coating.

[0052] Another aspect of the present invention provides a kit comprising a capsule which comprises a first single dose formulation comprising from about 1 mg to about 80 mg of a statin and a second single dose formulation comprising from about 50 mg to about 900 mg of gemcabene and instructions for the use thereof. In some embodiments, the kit comprises a capsule which comprises a first single dose formulation comprising from about 10 mg to about 60 mg of a statin and a second single dose formulation comprising from about 150 mg to about 600 mg of gemcabene kit provides instructions for the use thereof. In other embodiments, the kit comprises a capsule which comprises a first single dose formulation comprising from about 10 mg to about 40 mg of a statin and a second single dose formulation comprising from about 150 mg to about 450 mg of gemcabene kit provides instructions for the use thereof. In still other embodiments, the kit comprises a capsule which comprises a first single dose formulation comprising from about 10 mg to about 60 mg of a statin and a second single dose formulation comprising from about 50 mg to about 300 mg of gemcabene kit provides instructions for the use thereof. The single dose combinations comprised in the kit include, but are not limited to, microtablets, microbeads and capsules.

[0053] In some embodiments, the first single dose formulation and the second single dose formulation are formulated in separate containers, such as, but not limited to, beads or microparticles formulated separately and stored in capsules.

[0054] In some embodiments, the first single dose formulation and the second single dose formulation are stored in the same container, such as a capsule.

[0055] In some embodiments, the statin is formulated as a controlled release core of the combination formulation, while gemcabene is disposed for an immediate release in the outer layer of the formulation, which signifies that the first single dose formulation and the second single dose formulation are formulated in separate containers of the combination therapy.

[0056] In some embodiments, the above described first single dose formulation and second single dose formulation are stored in different compartments of the container, with different release profiles.

[0057] In some embodiments, the container is a capsule, a tablet, a bottle, vial, blister pack, or any combination thereof.

[0058] Another aspect of the present invention provides a kit comprising a single dose formulation comprising from about 1 mg to about 80 mg of a statin and from about 150 mg to about 900 mg of gemcabene; and instructions for the use thereof.

[0059] In some embodiments, the statin is any HMG-CoA reductase inhibitor such as, but not limited to, atorvastatin, simvastatin, pravastatin, rosuvastatin, fluvastatin, lovastatin, pitavastatin a hepatoselective statin or any pharmaceutically acceptable salt thereof.

[0060] In some embodiments, the statin is atorvastatin or a pharmaceutically acceptable salt thereof.

[0061] In some embodiments, the single dose formulation is in the form of a tablet or a capsule.

[0062] In some embodiments, the tablet comprises one or more excipients selected from a diluent, a disintegrant, a wetting agent, a binder, a glidant, a lubricant, or any combination thereof.

[0063] In yet another embodiment, a third API is added to the kit. In some embodiments the third API is a lipid-reducing agent. In other embodiments the third API the lipid-reducing agent is as niacin, a bile-acid resin, a fibric acid derivative, or a cholesterol absorption inhibitor. In any of the above embodiments of a single dose formulation including a third API, the fixed dose combination is provided in a single container, such as a capsule, or tablet.

[0064] In yet another embodiment, the third API is a lipid-reducing agent and the lipid reducing agent is ezetimibe. In yet another embodiment, the third API is a lipid-reducing agent and the lipid reducing agent is nicotinic acid. In yet another embodiment, the third API is a lipid-reducing agent and the lipid-reducing agent is a PCSK9 inhibitor. In still another embodiment, the third API is ezetimibe. In another embodiment the third API is gemfibrozil. In another embodiment the third API is nicotinic acid.

[0065] In yet another embodiment, the third API is a lipid-reducing agent and the lipid reducing agent is ezetimibe. In yet another embodiment, the third API is a lipid-reducing agent and the lipid reducing agent is nicotinic acid. In yet another embodiment, the third API is a lipid-

reducing agent and the lipid-reducing agent is a PCSK9 inhibitor. In another embodiment, the third API is a lipid-reducing agent and the lipid-reducing agent is bempedoic acid. In a further embodiment, the pharmaceutical composition described herein comprises from about 10 mg to about 300 mg bempedoic acid (for example from about 20 mg to about 280 mg, from about 30 mg to about 260 mg, from about 40 mg to about 240 mg, from about 60 mg to about 220 mg, from about 80 mg to about 200 mg, from about 100 mg to about 200 mg, from about 120 mg to about 180 mg, from about 50 mg to about 100 mg, from about 50 mg to about 150 mg, from about 100 mg to about 150 mg, or from about 150 mg to about 300 mg). In another further embodiment, the pharmaceutical composition described herein comprises about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 120 mg, about 140 mg, about 150 mg, about 160 mg, about 180 mg, about 200 mg, about 220 mg, about 240 mg, about 250 mg, about 260 mg, about 280 mg, or about 300 mg bempedoic acid.

[0066] In yet another embodiment, the third API is an anti-inflammatory agent, an anti-hypertensive agent, an anti-diabetic agent, an anti-obesity, an anti-fibrotic or an anti-coagulation agent.

[0067] In one aspect, the invention includes a pharmaceutical composition in the form of a tablet-in-capsule, wherein the pharmaceutical composition comprises

from about 1 mg to about 80 mg of a statin or a pharmaceutically acceptable salt thereof;

from about 50 mg to about 900 mg of gemcabene or a pharmaceutically acceptable salt thereof; and optionally

from about 5 mg to about 100 mg of the third API or a pharmaceutically acceptable salt thereof; and

one or more excipients selected from a diluent, a disintegrant, a wetting agent, a stabilizing agent, a plasticizer, a coating agent, a film coating agent, a binder, a glidant, a lubricant, or any combination thereof.

[0068] In one embodiment of this aspect, the composition comprises:

a. a tablet comprising from about 1 mg to about 80 mg of a statin or a pharmaceutically acceptable salt thereof; and
b. a capsule comprising from about 50 mg to about 900 mg of gemcabene or a pharmaceutically acceptable salt thereof,

wherein the tablet comprising a statin, and the gemcabene are both encompassed inside the capsule.

[0069] In another embodiment of this aspect, the statin is a HMG-CoA reductase inhibitor.

[0070] In a further embodiment, the statin is selected from the group consisting of atorvastatin, simvastatin, pravastatin, rosuvastatin, fluvastatin, lovastatin, pitavastatin.

[0071] In still a further embodiment, the statin is atorvastatin. In yet a further embodiment, atorvastatin calcium.

[0072] In another embodiment, the gemcabene is gemcabene calcium.

[0073] In one embodiment, the gemcabene is formulated as an immediate release formulation.

[0074] In another embodiment, atorvastatin is formulated as a delayed release formulation.

[0075] In a further embodiment, the atorvastatin formulation does not allow release of atorvastatin until after the medicament passes the stomach.

[0076] In one embodiment of this aspect, the capsule is filled with gemcabene microparticles nesting an atorvastatin calcium tablet, said tablet being comprised of

(i) a core comprised of about 10 to about 80% atorvastatin calcium, about 15 to about 12% lactose monohydrate, about 10 to about 25% microcrystalline cellulose, 0 to about 10% polyvinylpyrrolidone, 0 to about 10% croscaramellose sodium, 0 to about 10% magnesium stearate;

(ii) a subcoat barrier of about 1 to about 5% weight gain relative to the core eight comprising a suitable excipient such as Opadry or mixtures of suitable excipients; and

(iii) an enteric coating composition applied at about 2 to about 15% weight relative to the core weight, comprised of methacrylic acid, methyl acrylate, methyl methacrylate copolymer of about 0% to about 10%, methacrylic acid copolymer type C of about 10% to about 0%, and triethyl citrate of about 0% to about 2%.

[0077] In a further embodiment, the gemcabene microparticals comprise:

a. About 48 to about 50 wt% gemcabene;
b. About 24 to about 26 wt% Lactose Monohydrate;
c. About 1.5 to about 2.5 wt% Hydroxypropylcellulose;
d. About 19 to about 21 wt% Microcrystalline Cellulose ;
e. About 2 to about 4 wt% Croscarmellose Sodium; and
f. About 0.4 to about 0.6 wt% Magnesium stearate.

[0078] In another further embodiment, the atorvastatin calcium tablet core comprises:

a. about 13 to about 14 wt% atorvastatin calcium;
b. about 39 to about 41 wt% lactose monohydrate;
c. about 22 to about 23 wt% calcium carbonate
d. about 18 to about 20 wt% microcrystalline cellulose;
e. about 1.5 to about 2.5 wt% polyvinylpyrrolidone;

f. about 0.2 to about 0.3 wt% polysorbate 80;

g. about 2 to about 3 wt% croscaramellose sodium; and

h. about 0.3 to about 0.5 wt% magnesium stearate.

[0079] In one aspect, the invention includes a method for reducing musculoskeletal discomfort in a patient being administered a statin-gemcabene combination formulation, comprising administering to the patient a pharmaceutical composition of any one of claims 1-61 instead of a formulation comprising a more immediate release composition of the statin.

[0080] In one embodiment of this aspect, the musculoskeletal discomfort in a patient being administered a statin is due to myalgia.

[0081] In another embodiment of this aspect, the musculoskeletal discomfort in a patient being administered a statin is due to myositis.

[0082] In one embodiment, the musculoskeletal discomfort in a patient being administered a statin is an adverse event arising from the conversion of the acid form of the statin into the lactone form of the statin.

[0083] In a further embodiment, the pharmaceutical composition of any one of claims 1-63 reduces the amount of lactone form of a statin compared to a formulation comprising a more immediate release composition of the statin.

[0084] In one aspect, the invention includes a modified release atorvastatin and gemcabene fixed dose formulation in the form of any of their salts with a lag phase before atorvastatin delivery suitable for oral once a day administration for treating lipid disorders without causing drug-induced hepatotoxicity and musculoskeletal disorders.

[0085] In another aspect, the invention includes a modified release atorvastatin and gemcabene fixed dose combination formulation or any of its salts with a lag phase before atorvastatin delivery suitable for oral once a day administration for treating lipid disorders where the atorvastatin component exhibits a release pattern characterized by two phases, a lag phase and an extended release phase;

wherein the lag phase is characterized in that less than 10% of the absorbable atorvastatin dose administered is absorbed between about 0.5 and about 1.5 hours following ingestion;

wherein the extended release phase being characterized in that more than about 20% but less than 78% of the absorbable atorvastatin administered being absorbed between about 1.5 and 4 hours following ingestion; and

wherein less than 90% of the absorbable atorvastatin administered being absorbed by 9 hours following ingestion.

[0086] In still another aspect, the invention includes a gemcabene microparticle having a coating ratio of about 2.5% to about 15%, wherein the amount of gemcabene is about 80% to about 98%,

the amount of ethylcellulose is about 1% to about 10%, the amount of castor oil is about 0.01% to about 1.5%, the amount of povidone is about 0.05% to about 1%, the amount of tartaric acid is about 0% to about 1%, and the amount of magnesium stearate is about 0% to about 2%.

[0087] In one aspect, the invention includes an atorvastatin microparticle having a coating ratio of about 10% to about 30%, wherein the amount of atorvastatin is about 60% to about 95%, the amount of methacrylic acid copolymer type C (L100-55) is about 0% to about 15%, the amount of methacrylic acid copolymer type B (S100) is about 0% to about 15%, and the amount of cottonseed oil is about 0% to about 15%.

[0088] In another aspect, the invention includes a pharmaceutical formulation comprised of a capsule filled with gemcabene microparticles and an atorvastatin calcium microtablet, said microtablet being comprised of

(i) a core comprised of about 10 to about 80% atorvastatin calcium, about 15 to about 12% lactose monohydrate, about 10 to about 25% microcrystalline cellulose, about 0 to about 10% polyvinylpyrrolidone, about 0 to about 10% croscaramellose sodium, about 0 to about 10% magnesium stearate; (ii) a subcoat barrier of about 1 to about 5% weight gain relative to the core eight comprising a suitable excipient such as Opadry or mixtures of suitable excipients; (iii) an enteric coating composition applied at about 2 to about 15% weight relative to the core weight, comprised of methacrylic acid, methyl acrylate, methyl methacrylate copolymer of about 0% to about 10%, methacrylic acid copolymer type C of about 10% to about 0%, and triethyl citrate of about 0% to about 2%.

[0089] In one aspect, the invention includes a pharmaceutical composition, comprising gemcabene calcium from about 50 mg to about 900 mg, and atorvastatin calcium from about 5 mg to about 80 mg, and a pharmaceutically acceptable carrier, wherein said gemcabene is released about 50% at about 4 to about 6 hours with a Tmax at about 1 to about 2 hours, and wherein said atorvastatin is released from the composition with a lag time of about 1.5 to about 4 hours.

[0090] In another aspect, the invention includes a pharmaceutical composition comprising atorvastatin microparticles having a pH-dependent release profile, and gemcabene microparticles having a pH-independent release profile, wherein the atorvastatin microparticles have a reduced capacity to provoke musculoskeletal reactions in a subject, wherein the gemcabene is present in an amount effective to reduce triglycerides and LDL-cholesterol with at least 10% in addition to the effect of atorvastatin alone, and wherein there is a lag time between release of atorvastatin or gemcabene following administration of the composition.

[0091] In still another aspect, the invention includes a use of a pharmaceutical composition described herein in the manufacture of a medicament for treating or preventing a disease or disorder selected from the group consisting of:

a) disorders of lipoprotein metabolism, wherein the disorder is dyslipidemia, dyslipoproteinemia, lipoprotein overproduction or deficiency, elevation of total cholesterol, elevation of low density lipoprotein concentration, elevation of triglyceride concentration, lipid elimination in bile, metabolic disorder, phospholipid elimination in bile, oxysterol elimination in bile, abnormal bile production, or peroxisome proliferator activated receptor-associated disorder;

(b) disorders of glucose metabolism, wherein the disorder is insulin resistance, impaired glucose tolerance, impaired fasting glucose levels in blood, diabetes mellitus, lipodystrophy, central obesity, peripheral lipoatrophy, diabetic nephropathy, diabetic retinopathy, renal disease, or septicemia;

(c) cardiovascular disorders and related vascular disorders, wherein the disorder is atherosclerosis, hypertension, coronary artery disease, myocardial infarction, arrhythmia, atrial fibrillation, heart valve disease, heart failure, cardiomyopathy, myopathy, pericarditis, impotence, or thrombotic disorder;

d) diseases of the liver including NAFLD, NASH, alcoholic steatohepatitis , cirrhosis, inflammation fibrosis, primary biliary cirrhosis;

(e) modulating inflammation markers and/or C-reactive protein and related disorders, wherein the disorder is inflammation, ischemic necrosis, or thrombotic disorder; and

(f) aging, Alzheimer's Disease, Parkinson's disease, pancreatitis, pulmonary disorders, and pancreatitis.

[0092] In one aspect, the invention includes a pharmaceutical composition comprising:

a) a combination of two APIs selected from the group consisting of a statin and gemcabene; and

b) optionally one or more additional APIs

wherein the combination of the two APIs comprises from about 0.1 wt% to about 61.5 wt% of a statin or a pharmaceutically acceptable salt thereof by weight of the combination; and

from about 38.5 wt% to about 99.9 wt% of gemcabene or a pharmaceutically acceptable salt thereof by weight of the combination.

[0093] In another aspect, the invention includes a pharmaceutical composition comprising:

a) a combination of two APIs selected from the group consisting of a statin and gemcabene; and

b) optionally one or more additional APIs

wherein the combination of the two APIs comprises from about 2 wt% to about 35 wt% of a statin or a pharmaceutically acceptable salt thereof by weight of the combination; and

from about 65 wt% to about 98 wt% of gemcabene or a pharmaceutically acceptable salt thereof by weight of the combination.

[0094] In another aspect, the invention includes a pharmaceutical composition comprising:

a) a combination of two APIs selected from the group consisting of a statin and gemcabene; and

b) optionally one or more additional APIs

wherein the combination of the two APIs comprises from about 2 wt% to about 21 wt% of a statin or a pharmaceutically acceptable salt thereof by weight of the combination; and

from about 79 wt% to about 98 wt% of gemcabene or a pharmaceutically acceptable salt thereof by weight of the combination.

[0095] In one embodiment of this aspect, the statin is atorvastatin, simvastatin, pravastatin, rosuvastatin, fluvastatin, lovastatin, pitavastatin or any pharmaceutically acceptable salts thereof.

[0096] In a further embodiment, the statin is atorvastatin calcium. In another embodiment, the gemcabene is gemcabene calcium.

[0097] In one embodiment, the statin and the gemcabene are independently formulated and the independently formulated pharmaceutical compositions of the statin and gemcabene are comprised in a container.

[0098] In another embodiment, the statin and the gemcabene are independently formulated, and the independently formulated pharmaceutical compositions of the statin and gemcabene are comprised in a capsule.

[0099] In one embodiment, the pharmaceutical composition comprises a third API and the statin, gemcabene and the third API are comprised in a container or kit. In a further embodiment, container is a capsule.

[00100] In one embodiment, the pharmaceutical composition is in the form of a tablet.

[00101] In another embodiment, the pharmaceutical composition comprises a third API. In a further embodiment, the pharmaceutical composition the third API is ezetimibe immediate release. In another further embodiment, the pharmaceutical composition the third API is ezetimibe modified release. In another further embodiment, the pharmaceutical composition the third API is ezetimibe slow and extended release.

[00102] In one embodiment, the formulation comprises one or more excipients selected from a diluent, a disintegrant, a film coating agent, a plasticizer, a wetting agent, a binder, a glidant, a lubricant, a stabilizing agent, or any combination thereof.

[00103] In one embodiment, the tablet comprises a binder wherein the binder comprises microcrystalline cellulose, dibasic calcium phosphate, sucrose, corn starch, polyvinylpyrridone, hydroxyporopyl cellulose, hydroxymethyl cellulose, or any combination thereof.

[00104] In another embodiment, the tablet comprises a disintegrant and the disintegrant comprises sodium croscarmellose, sodium starch glycolate, or any combination thereof.

[00105] In another embodiment, the tablet comprises a lubricant and the lubricant comprises magnesium stearate stearic acid, hydrogenated oil, sodium stearyl fumarate, or any combination thereof.

[00106] In one embodiment, the pharmaceutical composition comprises from about 1 mg to about 80 mg of the statin and from about 50 mg to about 900 mg of gemcabene.

[00107] In one embodiment, the pharmaceutical composition comprises from about 10 mg to about 80 mg of the statin and from about 50 mg to about 600 mg of gemcabene.

[00108] In one embodiment, the pharmaceutical composition comprises from about 10 mg to about 40 mg of the statin and from about 150 mg to about 450 mg of gemcabene.

[00109] In another embodiment, the pharmaceutical composition comprises from about 10 mg to about 40 mg of the statin and from about 150 mg to about 300 mg of gemcabene.

[00110] In another embodiment, the statin is atorvastatin calcium. In another further embodiment, the gemcabene is gemcabene calcium.

[00111] In one embodiment, each component of the combination is delivered in the same compartment of the digestive tract. In another embodiment, each component of the combination is delivered in different compartments of the digestive tract.

[00112] In one aspect, the invention includes a pharmaceutical composition comprising

from about 1 mg to about 80 mg of a statin or a pharmaceutically acceptable salt thereof;

from about 50 mg to about 900 mg of gemcabene or a pharmaceutically acceptable salt thereof; and optionally

from about 0.25 mg to about 500 mg of a third API or a pharmaceutically acceptable salt thereof; and

one or more excipients selected from a diluent, a disintegrant, a wetting agent, a binder, a glidant, a lubricant, a film coating agent, a coating agent, a plasticizer, or any combination thereof.

[00113] In another aspect, the invention includes a pharmaceutical composition in the form of a capsule, wherein the pharmaceutical composition comprises

from about 1 mg to about 80 mg of a statin or a pharmaceutically acceptable salt thereof;

from about 50 mg to about 900 mg of gemcabene or a pharmaceutically acceptable salt thereof; and optionally

from about 0.25 mg to about 500 mg of the third API or a pharmaceutically acceptable salt thereof; and

one or more excipients selected from a diluent, a disintegrant, a wetting agent, a stabilizing agent, a plasticizer, a coating agent, a film coating agent, a binder, a glidant, a lubricant, or any combination thereof.

[00114] In one embodiment of this aspect, the statin is in the form of a plurality of first particles in a formulation comprising one or more excipients selected from a diluent, a disintegrant, a wetting agent, a stabilizing agent, a plasticizer, a coating agent, a film coating agent, a binder, a glidant, a lubricant, or any combination thereof, and the gemcabene is in the form of a plurality of second particles in a formulation comprising one or more excipients selected from a diluent, a disintegrant, a wetting agent, a stabilizing agent, a plasticizer, a coating agent, a film coating agent, a binder, a glidant, a lubricant, or any combination thereof, and the optional API is in the form of a plurality of third particles in a formulation comprising one or more excipients selected from a diluent, a disintegrant, a wetting agent, a stabilizing agent, a plasticizer, a coating agent, a film coating agent, a binder, a glidant, a lubricant, or any combination thereof.

[00115] In one aspect, the invention includes a pharmaceutical composition in the form of a tablet, wherein the pharmaceutical composition comprises

from about 1 mg to about 80 mg of a statin or a pharmaceutically acceptable salt thereof;

from about 50 mg to about 900 mg of gemcabene or a pharmaceutically acceptable salt thereof; and

from about 0.25 mg to about 500 mg of the third API or a pharmaceutically acceptable salt thereof; and

one or more excipients selected from a diluent, a disintegrant, a wetting agent, a binder, a glidant, a lubricant, a stabilizing agent, a plasticizer, a coating agent, a film coating agent, or any combination thereof.

[00116] In one embodiment, the statin, gemcabene, and third API are released in different compartments of the digestive tract.

[00117] In one embodiment, the third API is ezetimibe.

[00118] In another embodiment, the pharmaceutical composition comprises from about 10 mg to about 80 mg of the statin and from about 50 mg to about 900 mg of the gemcabene.

[00119] In one embodiment, the pharmaceutical composition comprises from about 10 mg to about 40 mg of the statin and from about 50 to about 600 mg of the gemcabene. In a further embodiment, the pharmaceutical composition comprises from about 10 mg to about 40 mg of the statin and from about 50 to about 450 mg of the gemcabene. In yet a further embodiment, the pharmaceutical composition comprises from about 10 mg to about 40 mg of the statin and from about 50 to about 300 mg of the gemcabene.

[00120] In one embodiment, the statin is atorvastatin, simvastatin, pravastatin, rosuvastatin, fluvastatin, lovastatin, pitavastatin or any pharmaceutically acceptable salt thereof.

[00121] In one embodiment, the disintegrant comprises sodium croscarmellose, sodium starch glycolate, or any combination thereof.

[00122] In one embodiment, the lubricant comprises magnesium stearate stearic acid, hydrogenated oil, sodium stearyl fumarate, or any combination thereof.

[00123] In a further embodiment, the statin is the calcium salt of atorvastatin.

[00124] In a further embodiment, the gemcabene is the calcium salt of gemcabene.

[00125] In a further embodiment, the pharmaceutical composition further comprises calcium carbonate, potassium carbonate, or a combination thereof.

[00126] In one embodiment, the independently formulated pharmaceutical composition of the statin comprises single tablet, and the independently formulated pharmaceutical composition of the gemcabene comprises a powder formulation. In a further embodiment, the powder formulation of gemcabene is an immediate release formulation.

[00127] In one embodiment, the tablet formulation of the statin is a delayed release formulation. In a further embodiment, the tablet formulation of the statin further comprises an enteric coating on the tablet.

[00128] In another embodiment, the pharmaceutical composition is contained within a capsule.

[00129] In one embodiment, pharmaceutical composition comprises from about 1 mg to about 80 mg of the statin and from about 50 mg to about 900 mg of gemcabene. In a further embodiment, the pharmaceutical composition comprises from about 10 mg to about 60 mg of the statin and from about 150 mg to about 600 mg of gemcabene. In yet a further embodiment, the pharmaceutical composition comprises from about 10 mg to about 40 mg of the statin and from about 150 mg to about 450 mg of gemcabene. In still a further embodiment, the pharmaceutical composition comprises from about 10 mg to about 40 mg of the statin and from about 150 mg to about 300 mg of gemcabene.

[00130] In one embodiment, the statin is atorvastatin calcium. In another embodiment, the gemcabene is gemcabene calcium.

[00131] In one embodiment, the claims 58-68, where each component of the combination is delivered in the same compartment of the digestive tract.

[00132] In another embodiment, the claims 58-69 where each component of the combination is delivered in different compartments of the digestive tract.

[00133] In one aspect, the invention includes a kit comprising

a single dose formulation comprising from about 10 mg to about 40 mg of a statin and from about 50 mg to about 600 mg of gemcabene; and

instructions for the use thereof.

[00134] In one embodiment of this aspect, the statin is atorvastatin, simvastatin, pravastatin, rosuvastatin, fluvastatin, lovastatin, pitavastatin or any pharmaceutically acceptable salts thereof.

[00135] In one embodiment, the statin is atorvastatin or a pharmaceutically acceptable salt thereof.

[00136] In one embodiment, the single dose formulation is in the form of a tablet or a capsule.

[00137] In another embodiment, the tablet comprises one or more excipients selected from a diluent, a disintegrant, a wetting agent, a binder, a glidant, a lubricant, or any combination thereof.

[00138] In another embodiment, the binder comprises microcrystalline cellulose, dibasic calcium phosphate, sucrose, corn starch, polyvinylpyrridone, hydroxypropyl cellulose, hydroxymethyl cellulose, or any combination thereof.

[00139] In another embodiment, the disintegrant comprises sodium croscarmellose, sodium starch glycolate, or any combination thereof.

[00140] In another embodiment, the lubricant comprises magnesium stearate stearic acid, hydrogenated oil, sodium stearyl fumarate, or any combination thereof.

[00141] In another embodiment, the statin is the calcium salt of atorvastatin.

[00142] In another embodiment, the gemcabene is a calcium salt of gemcabene.

[00143] In a further embodiment, the tablet further comprises calcium carbonate, potassium carbonate, or a combination thereof.

DETAILED DESCRIPTION

[00144] The present invention provides methods of reducing circulating triglycerides in patients possessing elevated concentrations of triglycerides (e.g., greater than 150 mg/dL) in their blood stream before the onset of treatment, by administering a statin or a pharmaceutically

acceptable salt thereof and gemcabene or a pharmaceutically acceptable salt thereof. This invention also provides pharmaceutical compositions comprising a statin or a pharmaceutically acceptable salt thereof and gemcabene or a pharmaceutically acceptable salt thereof.

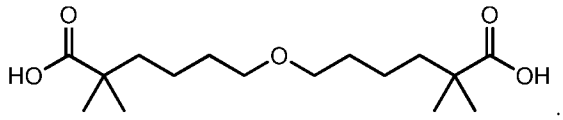
[00145] DEFINITIONS

[00146] As used herein, the terms "API", "active pharmaceutical ingredient", and "active pharmaceutical agent" are used interchangeably to refer to a biologically active compound. Examples of APIs include, without limitation, gemcabene, statins, or any combination thereof.

[00147] As used herein, the terms polyvinylpyrrolidone (PVP), polypovidone, and povidone are used interchangeably and have the same meaning.

[00148] As used herein, the term "statin" refers to a class of APIs or drugs that inhibit the enzyme HMG-CoA reductase and are generally known to lower LDL cholesterol in patients. Examples of statins include atorvastatin, simvastatin, pravastatin, rosuvastatin, fluvastatin, lovastatin, and pitavastatin.

[00149] As used herein, the term "gemcabene" refers to the compound 6,6'-oxybis(2,2-dimethylhexanoic acid) having the structure



[00150] As used herein, the term "tablet" can be any reasonably sized tablet suitable for oral ingestion. The term "tablet" is also used interchangeably with the term "minitablet" and "microtablet".

[00151] As used herein, the term "excipient" refers to an inactive ingredient in a pharmaceutical composition. Examples of excipients include fillers or diluents, wetting agents (e.g., surfactants), binders, glidants, lubricants, disintegrants, or the like.

[00152] As used herein, a "disintegrant" is an excipient that hydrates a pharmaceutical composition and aids in tablet dispersion. Examples of disintegrants include sodium croscarmellose and/or sodium starch glycolate.

[00153] As used herein, a "diluent" or "filler" is an excipient that adds bulkiness to a pharmaceutical composition. Examples of fillers include lactose, sorbitol, celluloses, calcium phosphates, starches, sugars (e.g., mannitol, sucrose, or the like) or any combination thereof.

[00154] As used herein, a "wetting agent" or a "surfactant" is an excipient that imparts pharmaceutical compositions with enhanced solubility and/or wetability. Examples of wetting agents include sodium lauryl sulfate (SLS), sodium stearyl fumarate (SSF), polyoxyethylene 20 sorbitan mono-oleate (e.g., Tween™), or any combination thereof.

[00155] As used herein, a "binder" is an excipient that imparts a pharmaceutical composition with enhanced cohesion or tensile strength (e.g., hardness). Examples of binders include dibasic calcium phosphate, sucrose, corn (maize) starch, microcrystalline cellulose, modified cellulose (e.g., hydroxymethyl cellulose (HMC) or hydroxypropyl cellulose (HPC)), and polyvinylpyrrolidone (PVP).

[00156] As used herein, a "glidant" is an excipient that imparts a pharmaceutical compositions with enhanced flow properties. Examples of glidants include colloidal silica and/or talc.

[00157] As used herein, a "colorant" is an excipient that imparts a pharmaceutical composition with a desired color. Examples of colorants include commercially available pigments such as FD&C Blue # 1 Aluminum Lake, FD&C Blue #2, other FD&C Blue colors, titanium dioxide, iron oxide, and/or combinations thereof. Other colorants include commercially available pigments such as FD&C Green #3.

[00158] As used herein, a "lubricant" is an excipient that is added to pharmaceutical compositions that are pressed into tablets. The lubricant aids in compaction of granules into tablets and ejection of a tablet of a pharmaceutical composition from a die press. Examples of lubricants include magnesium stearate, stearic acid (stearin), hydrogenated oil, sodium stearyl fumarate, or any combination thereof.

[00159] As used herein, the term "single dose formulation" or "fixed dose combination" refers to a pharmaceutical composition in the form in which it is marketed for use, formulated with mixture of two or more APIs and one or more excipients, along with other optional non-reusable material that may not be considered either ingredient or packaging (e.g., a capsule shell). As used herein, the terms "single dose formulation" and “fixed dose combination” are used interchangeably. Common single dose formulations include pills, tablets, or capsules.

[00160] As used herein, the term "modified release" refers to a dosage form in which the rate or place of release of the active ingredient(s) is different from that of an immediate dosage form when administered by the same route. Modified release dosage forms include delayed-, extended-, prolonged-, extended-, pulsatile- or pulsed-, controlled-, accelerated- and fast-, targeted-, programmed-release, and/or gastric retention dosage forms. The pharmaceutical compositions in modified release dosage forms can be prepared using a variety of modified release devices and methods known to those skilled in the art, including, but not limited to, matrix controlled release devices, osmotic controlled release devices, multiparticulate controlled release devices, ion-exchange resins, enteric coatings, multilayered coatings, microspheres, liposomes, and combinations thereof. The release rate of the active ingredient(s) can also be modified by varying the particle sizes and polymorphorism of the active ingredient(s).

PHARMACEUTICAL COMPOSITIONS

[00161] The present invention provides a pharmaceutical composition comprising a combination of two APIs selected from the group consisting of a statin or any pharmaceutically acceptable salt thereof and gemcabene or a pharmaceutically acceptable salt thereof. In some embodiments the pharmaceutical composition comprising a combination of two APIs selected from the group consisting of atorvastatin or any pharmaceutically acceptable salt thereof and gemcabene or a pharmaceutically acceptable salt thereof.

[00162] In another aspect, the present invention provides a pharmaceutical composition comprising a combination of at least two APIs. One embodiment of the pharmaceutical composition of the present specification is a pharmaceutical composition comprising: a) a combination of two APIs selected from the group consisting of a statin and gemcabene; and b) optionally one or more additional APIs wherein the combination of the two APIs comprises

from about 0.1 wt% to about 61.5 wt% of a statin or a pharmaceutically acceptable salt thereof by weight of the combination; and

from about 38.5 wt% to about 99.9 wt% of gemcabene or a pharmaceutically acceptable salt thereof by weight of the combination.

[00163] Another embodiment of the present disclosure is a pharmaceutical composition comprising: a) a combination of two APIs selected from the group consisting of a statin and gemcabene; and b) optionally one or more additional APIs wherein the combination of the two APIs comprises

from about 2 wt% to about 35 wt% of a statin or a pharmaceutically acceptable salt thereof by weight of the combination; and

from about 65 wt% to about 98 wt% of gemcabene or a pharmaceutically acceptable salt thereof by weight of the combination.

[00164] A pharmaceutical composition comprising: a) a combination of two APIs selected from the group consisting of a statin and gemcabene; and b) optionally one or more additional APIs wherein the combination of the two APIs comprises

from about 2 wt% to about 21 wt% of a statin or a pharmaceutically acceptable salt thereof by weight of the combination; and

from about 79 wt% to about 98 wt% of gemcabene or a pharmaceutically acceptable salt thereof by weight of the combination.

[00165] In some embodiments, the statin is selected from atorvastatin, simvastatin, pravastatin, , mevastatin, fluvastatin, dalvastatin, dihydrocompactin, cerivastatin, or lovastatin; or any pharmaceutically acceptable salts thereof. For instance, the statin is atorvastatin,

simvastatin, or pharmaceutically acceptable salts thereof. In other instances, the statin is the calcium salt of atorvastatin.

[00166] In yet another embodiment, the third API is a lipid-reducing agent and the lipid reducing agent is ezetimibe. In yet another embodiment, the third API is a lipid-reducing agent and the lipid reducing agent is nicotinic acid. In yet another embodiment, the third API is a lipid-reducing agent and the lipid-reducing agent is gemfibrozil. In yet another embodiment, the third API is bempedoic acid.

[00167] In yet another embodiment, the third API is an anti-inflammatory agent, an anti-hypertensive agent, an anti-diabetic agent, an anti-obesity, an anti-fibrotic or an anti-coagulation agent.

A. Modified Release Formulations

[00168] In some embodiments, the pharmaceutical composition is formulated as a modified release dosage form comprising from about 1 mg to about 80 mg of the statin and from about 150 mg to about 900 mg of gemcabene. In some examples, the pharmaceutical composition comprises from about 10 mg to about 40 mg of the statin and from about 300 mg to about 600 mg of gemcabene, and the gemcabene, the statin, or both APIs comprise a controlled release form. In those embodiments where both the gemcabene and the statin comprise controlled release forms, the controlled release form of gemcabene may be the same as or different from the controlled release form of the statin.

[00169] In some embodiments, the pharmaceutical composition is formulated as a modified release dosage form comprising from about 1 mg to about 80 mg of the statin, from about 150 mg to about 900 mg of gemcabene, and from about 10 mg to 100 mg of a third API wherein the third API is a lipid-lowering agent. In some examples, the pharmaceutical composition comprises from about 10 mg to about 40 mg of the statin and from about 300 mg to about 600 mg of gemcabene, and from about 5 mg to 50 mg of a third API wherein the third API is a lipid modifying agent, anti-fibrolytic agent, or an anti-inflammatory agent; the gemcabene, the statin, the third agent or all APIs are in a controlled release form.

[00170] Examples of modified release dosage forms suited for pharmaceutical compositions of the instant invention are described, without limitation, in U.S. Pat. Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 5,639,480; 5,733,566; 5,739,108; 5,891,474; 5,922,356; 5,972,891; 5,980,945; 5,993,855; 6,045,830; 6,087,324; 6,113,943; 6,197,350; 6,248,363; 6,264,970; 6,267,981; 6,376,461; 6,419,961; 6,589,548; 6,613,358; and 6,699,500.

1. Matrix-Controlled Release

[00171] In some embodiments, the pharmaceutical composition is formulated as a matrix-controlled release dosage form. For example, the pharmaceutical composition comprises from about 10 mg to about 40 mg of the statin and from about 300 mg to about 600 mg of gemcabene, wherein the statin, the gemcabene, or both are provided as matrix-controlled release forms. And, in those embodiments comprising matrix-controlled release forms of the statin and the gemcabene, the matrix-controlled release form of the statin may be the same as or different from the matrix-controlled release form of the gemcabene. Suitable matrix-controlled release dosage forms for statins and gemcabene are described, for example, in Takada et al in "Encyclopedia of Controlled Drug Delivery," Vol. 2, Mathiowitz ed., Wiley, 1999.

[00172] In some embodiments, the pharmaceutical composition comprises from about 10 mg to about 40 mg of the statin and from about 300 mg to about 600 mg of gemcabene, wherein the gemcabene comprises a matrix-controlled modified release dosage form. In other embodiments, the pharmaceutical composition comprises from about 10 mg to about 40 mg of the statin and from about 300 mg to about 600 mg of gemcabene, wherein the statin comprises a matrix-controlled modified release dosage form.

[00173] In some embodiments, the matrix-controlled release form of the statin, the gemcabene, or both, is formulated as a matrix-controlled release dosage form that comprises an erodible matrix comprising water-swellable, erodible, or soluble polymers, including synthetic polymers, and naturally occurring polymers and derivatives, such as polysaccharides and proteins.

[00174] In some embodiments, the erodible matrix of the matrix-controlled release form comprises chitin, chitosan, dextran, or pullulan; gum agar, gum arabic, gum karaya, locust bean gum, gum tragacanth, carrageenans, gum ghatti, guar gum, xanthan gum, or scleroglucan; starches, such as dextrin or maltodextrin; hydrophilic colloids, such as pectin; phosphatides, such as lecithin; alginates; propylene glycol alginate; gelatin; collagen; cellulosics, such as ethyl cellulose (EC), methylethyl cellulose (MEC), carboxymethyl cellulose (CMC), CMEC, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), cellulose acetate (CA), cellulose propionate (CP), cellulose butyrate (CB), cellulose acetate butyrate (CAB), CAP, CAT, hydroxypropyl methyl cellulose (HPMC), HPMCP, HPMCAS, hydroxypropyl methyl cellulose acetate trimellitate (HPMCAT), or ethylhydroxy ethylcellulose (EHEC); polyvinyl pyrrolidone; polyvinyl alcohol; polyvinyl acetate; glycerol fatty acid esters; polyacrylamide; polyacrylic acid; copolymers of ethacrylic acid or methacrylic acid (EUDRAGIT®, Rohm America, Inc., Piscataway, NJ); poly(2-hydroxyethyl-methacrylate); polylactides; copolymers of L-glutamic acid and ethyl-L-glutamate; degradable lactic acid-glycolic acid copolymers; poly-D-(-)-3-

hydroxybutyric acid; or other acrylic acid derivatives, such as homopolymers and copolymers of butylmethacrylate, methylmethacrylate, ethylmethacrylate, ethylacrylate, (2-dimethylaminoethyl)methacrylate, or (trimethylaminoethyl)methacrylate chloride; or any combination thereof.

[00175] In another embodiment, the pharmaceutical composition comprises a matrix-controlled modified release form comprising a non-erodible matrix. In some of these embodiments, the statin, the gemcabene, or both, is dissolved or dispersed in an inert matrix and is released primarily by diffusion through the inert matrix once administered. In some embodiments, the non-erodible matrix of the matrix-controlled release form comprises one or more insoluble plastics, such as polyethylene, polypropylene, polyisoprene, polyisobutylene, polybutadiene, polymethylmethacrylate, polybutylmethacrylate, chlorinated polyethylene, polyvinylchloride, methyl acrylate-methyl methacrylate copolymers, ethylene-vinylacetate copolymers, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene or propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, polyvinyl chloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, or hydrophilic polymers, such as ethyl cellulose, cellulose acetate, crospovidone, or cross-linked partially hydrolyzed polyvinyl acetate; fatty compounds, such as carnauba wax, microcrystalline wax, or triglycerides; or any combination thereof.

[00176] In a matrix-controlled release system, the desired release kinetics can be controlled, for example, via the polymer type employed, the polymer viscosity, the particle sizes of the polymer and/or the API(s), the ratio of the API(s) versus the polymer, and other excipients in the composition.

[00177] The pharmaceutical composition of the instant invention comprising a modified release dosage form may be prepared by methods known to those skilled in the art, including direct compression, dry or wet granulation followed by compression, melt-granulation followed by compression.

2. Tablets-In-Capsule System

[00178] In some embodiments, the pharmaceutical composition comprises a tablets-in-capsule system, which is a multifunctional and multiple unit system comprising versatile mini-tablets in a hard gelatin capsule. The mini-tablets may be rapid-release, extended-release, pulsatile, delayed-onset extended-release minitablets, or any combination thereof. In yet another

embodiment, combinations of mini-tablets or combinations of mini-tablets and minibeads comprising multiple APIs may each have specific lag times, of release multiplied pulsatile drug delivery system (DDS), site-specific DDS, slow-quick DDS, quick/slow DDS and zero-order DDS.

3. Osmotic-Controlled Release Devices

[00179] In some embodiments, the pharmaceutical composition comprises from about 1 mg to about 80 mg of the statin and from about 50 mg to about 900 mg of gemcabene, wherein the gemcabene, the statin, or both comprises an osmotic-controlled release dosage form.

[00180] In some examples, the osmotic-controlled release device comprises a one-chamber system, a two-chamber system, asymmetric membrane technology (AMT), an extruding core system (ECS), or any combination thereof. Generally, such devices have at least two components: (a) the core which contains the API(s); and (b) a semipermeable membrane with at least one delivery port, which encapsulates the core. The semipermeable membrane controls the influx of water to the core from an aqueous environment of use so as to cause drug release by extrusion through the delivery port(s).

[00181] In some embodiments, the core of the osmotic device optionally comprises an osmotic agent, which creates a driving force for transport of water from the environment of use into the core of the device. One class of osmotic agents useful in the present invention comprises water-swellable hydrophilic polymers, which are also referred to as "osmopolymers" or "hydrogels," including, but not limited to, hydrophilic vinyl and acrylic polymers, polysaccharides such as calcium alginate, polyethylene oxide (PEO), polyethylene glycol (PEG), polypropylene glycol (PPG), poly(2-hydroxyethyl methacrylate), poly(acrylic) acid, poly(methacrylic) acid, polyvinylpyrrolidone (PVP), cross-linked PVP, polyvinyl alcohol (PVA), PVA/PVP copolymers, PVA/PVP copolymers with hydrophobic monomers such as methyl methacrylate and vinyl acetate, hydrophilic polyurethanes containing large PEO blocks, sodium croscarmellose, carrageenan, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose (CMC) and carboxyethyl, cellulose (CEC), sodium alginate, polycarbophil, gelatin, xanthan gum, and sodium starch glycolate.

[00182] Another class of osmotic agents comprises osmogens, which are capable of imbibing water to affect an osmotic pressure gradient across the barrier of the surrounding coating. Suitable osmogens include, but are not limited to, inorganic salts, such as magnesium sulfate, magnesium chloride, calcium chloride, sodium chloride, lithium chloride, potassium sulfate, potassium phosphates, sodium carbonate, sodium sulfite, lithium sulfate, potassium

chloride, and sodium sulfate; sugars, such as dextrose, fructose, glucose, inositol, lactose, maltose, mannitol, raffinose, sorbitol, sucrose, trehalose, and xylitol; organic acids, such as ascorbic acid, benzoic acid, fumaric acid, citric acid, maleic acid, sebacic acid, sorbic acid, adipic acid, edetic acid, glutamic acid, p-tolunesulfonic acid, succinic acid, and tartaric acid; urea; and mixtures thereof.

[00183] Osmotic agents of different dissolution rates may be employed to influence how rapidly the API(s) is initially delivered from the dosage form. For example, amorphous sugars, such as Mannogeme EZ (SPI Pharma, Lewes, DE) can be used to provide faster delivery during the first couple of hours (e.g., about 1 to about 5 hrs) to promptly produce the desired therapeutic effect, and gradually and continually release of the remaining amount to maintain the desired level of therapeutic or prophylactic effect over an extended period of time. In this case, the API(s) is released at such a rate to replace the amount of the active ingredient metabolized and excreted by the patient.

[00184] The core may also include a wide variety of other excipients and carriers as described herein to enhance the performance of the dosage form or to promote stability or processing.

[00185] Materials useful in forming the semipermeable membrane include various grades of acrylics, vinyls, ethers, polyamides, polyesters, and cellulosic derivatives that are water-permeable and water-insoluble at physiologically relevant pHs, or are susceptible to being rendered water-insoluble by chemical alteration, such as crosslinking. Examples of suitable polymers useful in forming the coating, include plasticized, unplasticized, and reinforced cellulose acetate (CA), cellulose diacetate, cellulose triacetate, CA propionate, cellulose nitrate, cellulose acetate butyrate (CAB), CA ethyl carbamate, CAP, CA methyl carbamate, CA succinate, cellulose acetate trimellitate (CAT), CA dimethylaminoacetate, CA ethyl carbonate, CA chloroacetate, CA ethyl oxalate, CA methyl sulfonate, CA butyl sulfonate, CA p-toluene sulfonate, agar acetate, amylose triacetate, beta glucan acetate, beta glucan triacetate, acetaldehyde dimethyl acetate, triacetate of locust bean gum, hydroxlated ethylene-vinylacetate, EC, PEG, PPG, PEG/PPG copolymers, PVP, HEC, HPC, CMC, CMEC, HPMC, HPMCP, HPMCAS, HPMCAT, poly(acrylic) acids and esters and poly-(methacrylic) acids and esters and copolymers thereof, starch, dextran, dextrin, chitosan, collagen, gelatin, polyalkenes, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinyl esters and ethers, natural waxes, and synthetic waxes.

[00186] The semipermeable membranes may also be a hydrophobic microporous membrane, wherein the pores are substantially filled with a gas and are not wetted by the aqueous medium but are permeable to water vapor, as disclosed in U.S. Pat. No. 5,798,119.

Such hydrophobic but water-vapor permeable membrane are typically composed of hydrophobic polymers such as polyalkenes, polyethylene, polypropylene, polytetrafluoroethylene, polyacrylic acid derivatives, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinylidene fluoride, polyvinyl esters and ethers, natural waxes, and synthetic waxes.

[00187] The delivery port(s) on the semipermeable membrane may be formed post-coating by mechanical or laser drilling. Delivery port(s) may also be formed *in situ* by erosion of a plug of water-soluble material or by rupture of a thinner portion of the membrane over an indentation in the core. In addition, delivery ports may be formed during coating process, as in the case of asymmetric membrane coatings of the type disclosed in U.S. Pat. Nos. 5,612,059 and 5,698,220.

[00188] The total amount of the API(s) released and the release rate can substantially be modulated via the thickness and porosity of the semipermeable membrane, the composition of the core, and the number, size, and position of the delivery ports.

[00189] In some embodiments, the pharmaceutical composition in an osmotic controlled-release dosage form may further comprise additional conventional excipients as described herein to promote performance or processing of the formulation.

[00190] The osmotic controlled-release dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (*see, Remington: The Science and Practice of Pharmacy*, supra; Santus and Baker, *J. Controlled Release* **1995**, *35*, 1-21; Verma et al., *Drug Development and Industrial Pharmacy* **2000**, *26*, 695-708; Verma et al., *J. Controlled Release* **2002**, *79*, 7-27).

[00191] In some embodiments, the pharmaceutical composition provided herein is formulated as AMT controlled-release dosage form that comprises an asymmetric osmotic membrane that coats a core comprising the active ingredient(s) and other pharmaceutically acceptable excipients. *See*, U.S. Pat. No. 5,612,059 and WO 2002/17918. The AMT controlled-release dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art, including direct compression, dry granulation, wet granulation, and a dip-coating method.

[00192] In some embodiments, the pharmaceutical composition provided herein is formulated as ESC controlled-release dosage form that comprises an osmotic membrane that coats a core comprising the API(s), hydroxylethyl cellulose, and other pharmaceutically acceptable excipients.

4. Multiparticulate-Controlled Release Devices

[00193] In some embodiments, the pharmaceutical composition comprises a modified release dosage form that is fabricated as a multiparticulate-controlled release dosage form that

comprises a plurality of particles, granules, or pellets, microparticulates, beads, microcapsules and microtablets, ranging from about 10 μm to about 3 mm, about 50 μm to about 2.5 mm, or from about 100 μm to 1 mm in diameter.

[00194] The multiparticulate-controlled release dosage forms can provide a prolonged release dosage form with an improved bioavailability. Suitable carriers to sustain the release rate of API(s) include, without limitation, ethyl cellulose, HPMC, HPMC-phtalate, colloidal silicondioxide and Eudragit-RSPM.

[00195] Pellets suitable to be used in the provided compositions and methods contain 50-80% (w/w) of a drug and 20-50% (w/w) of microcrystalline cellulose or other polymers. Suitable polymers include, but are not limited to, microcrystalline wax, pregelatinized starch and maltose dextrin.

[00196] Beads can be prepared in capsule and tablet dosage forms. Beads in tablet dosage form may demonstrate a slower dissolution profile than microparticles in capsule form. Microparticle fillers suitable for compositions and methods of the instant invention include, without limitation, sorbitan monooleate (Span 80), HPMC, or any combination thereof. Suitable dispersions for controlled release latex include, for example, ethyl-acrylate and methyl-acrylate.

[00197] In some embodiments, the pharmaceutical composition comprises microcapsules and/or microtablets. In one embodiment, microcapsules comprise extended release polymer microcapsules containing statin and gemcabene with various solubility characteristics. Extended release polymer microcapsules can be prepared with colloidal polymer dispersion in an aqueous environment. In another embodiment, microcapsules suitable for the compositions and methods provided herein can be prepared using conventional microencapsulating techniques (Bodmeier & Wang, 1993).

[00198] Such multiparticulates may be made by the processes known to those skilled in the art, including wet-and dry-granulation, extrusion/spheronization, roller-compaction, melt-congealing, and by spray-coating seed cores. *See,* for example, *Multiparticulate Oral Drug Delivery*; Marcel Dekker: 1994; and *Pharmaceutical Pelletization Technology*; Marcel Dekker: 1989. Such materials used to form microparticulates are commercially available, for example, gemcabene is commercially available as Lonza gemcabene granular.

[00199] Other excipients as described herein may be blended with the pharmaceutical compositions to aid in processing and forming the multiparticulates. The resulting particles may themselves constitute the multiparticulate dosage form or may be coated by various film-forming materials, such as enteric polymers, water-swellable, or water-soluble polymers. The multiparticulates can be further processed as a capsule or a tablet.

[00200] In other embodiments, the pharmaceutical composition comprises a dosage form that has an instant releasing component and at least one delayed releasing component, and is capable of giving a discontinuous release of the compound in the form of at least two consecutive pulses separated in time from 0.1 hrs to 24 hrs.

B. Oral Administration

[00201] The pharmaceutical compositions provided herein may comprise solid, semisolid, gelmatrix or liquid dosage forms for oral administration. As used herein, oral administration also include buccal, lingual, and sublingual administration. Suitable oral dosage forms include, without limitation, tablets, capsules, pills, troches, lozenges, pastilles, cachets, pellets, medicated chewing gum, granules, bulk powders, effervescent or non-effervescent powders or granules, solutions, emulsions, suspensions, solutions, wafers, sprinkles, elixirs, syrups or any combination thereof. In addition to the APIs, the pharmaceutical composition may contain one or more pharmaceutically acceptable carriers or excipients, including, but not limited to, binders, fillers, diluents, disintegrants, wetting agents, lubricants, glidants, coloring agents, dye-migration inhibitors, sweetening agents, and flavoring agents.

[00202] Binders or granulators impart cohesiveness to a tablet to ensure the tablet remaining intact after compression. Suitable binders or granulators include, but are not limited to, starches, such as corn starch, potato starch, and pre-gelatinized starch (e.g., STARCH 1500); gelatin; sugars, such as sucrose, glucose, dextrose, molasses, and lactose; natural and synthetic gums, such as acacia, alginic acid, alginates, extract of Irish moss, Panwar gum, ghatti gum, mucilage of isabgol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone (PVP), Veegum, larch arabogalactan, powdered tragacanth, and guar gum; celluloses, such as ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose, methyl cellulose, hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropyl methyl cellulose (HPMC); microcrystalline celluloses, such as AVICEL-PH-101, AVICEL-PH-103, AVICEL RC-581, AVICEL-PH-105 (FMC Corp., Marcus Hook, PA); and mixtures thereof.

[00203] Suitable fillers include, but are not limited to, talc, calcium carbonate, microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler may be present from about 5 to about 49% by weight in the pharmaceutical compositions provided herein.

[00204] Suitable diluents include, but are not limited to, dicalcium phosphate, calcium sulfate, lactose, sorbitol, sucrose, inositol, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and

inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such compressed tablets can be used as chewable tablets.

[00205] Suitable disintegrants include, but are not limited to, agar; bentonite; celluloses, such as methylcellulose and carboxymethylcellulose; wood products; natural sponge; cation-exchange resins; alginic acid; gums, such as guar gum and Veegum HV; citrus pulp; cross-linked celluloses, such as croscarmellose; cross-linked polymers, such as crospovidone; cross-linked starches; calcium carbonate; microcrystalline cellulose, such as sodium starch glycolate; polacrilin potassium; starches, such as corn starch, potato starch, tapioca starch, and pre-gelatinized starch; clays; aligns; and mixtures thereof. The amount of disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The pharmaceutical compositions provided herein may contain from about 0.5 to about 15% or from about 1 to about 5% by weight of a disintegrant.

[00206] Suitable lubricants include, but are not limited to, calcium stearate; magnesium stearate; mineral oil; light mineral oil; glycerin; sorbitol; mannitol; glycols, such as glycerol behenate and polyethylene glycol (PEG); stearic acid; sodium lauryl sulfate; talc; hydrogenated vegetable oil, including peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil; zinc stearate; ethyl oleate; ethyl laureate; agar; starch; lycopodium; silica or silica gels, such as AEROSIL® 200 (W.R. Grace Co., Baltimore, MD) and CAB-O-SIL® (Cabot Co. of Boston, MA); and mixtures thereof. The pharmaceutical compositions provided herein may contain about 0.1 to about 5% by weight of a lubricant.

[00207] Suitable glidants include colloidal silicon dioxide, CAB-O-SIL® (Cabot Co. of Boston, MA), and asbestos-free talc.

[00208] Coloring agents include any of the approved, certified, water soluble FD&C dyes, and water insoluble FD&C dyes suspended on alumina hydrate, and color lakes and mixtures thereof. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal, resulting in an insoluble form of the dye.

[00209] Flavoring agents include natural flavors extracted from plants, such as fruits, and synthetic blends of compounds which produce a pleasant taste sensation, such as peppermint and methyl salicylate.

[00210] Sweetening agents include sucrose, lactose, mannitol, syrups, glycerin, sucralose, and artificial sweeteners, such as saccharin and aspartame.

[00211] Suitable emulsifying agents include gelatin, acacia, tragacanth, bentonite, and surfactants, such as polyoxyethylene sorbitan monooleate (TWEEN® 20), polyoxyethylene

sorbitan monooleate 80 (TWEEN® 80), and triethanolamine oleate. Suspending and dispersing agents include sodium carboxymethylcellulose, pectin, tragacanth, Veegum, acacia, sodium carbomethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrolidone. Preservatives include glycerin, methyl and propylparaben, benzoic add, sodium benzoate and alcohol. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate, and polyoxyethylene lauryl ether.

[00212] Solvents include glycerin, sorbitol, ethyl alcohol, and syrup.

[00213] Examples of non-aqueous liquids utilized in emulsions include mineral oil and cottonseed oil. Organic acids include citric and tartaric acid. Sources of carbon dioxide include sodium bicarbonate and sodium carbonate.

[00214] It should be understood that many carriers and excipients may serve several functions, even within the same formulation.

[00215] The pharmaceutical compositions provided herein may be provided as compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed tablets, or enteric-coating tablets, sugar-coated, or film-coated tablets. Enteric-coated tablets are compressed tablets coated with substances that resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredients from the acidic environment of the stomach. Enteric-coatings include, but are not limited to, fatty acids, fats, phenylsalicylate, waxes, shellac, ammoniated shellac, and cellulose acetate phthalates. Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which may be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. Film coating imparts the same general characteristics as sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets.

[00216] The pharmaceutical compositions provided herein may be soft or hard capsules, which can be made from gelatin, methylcellulose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule (SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth of microorganisms. Suitable preservatives are those as described herein, including methyl- and propyl-parabens, and sorbic acid. The liquid, semisolid, and solid dosage forms

provided herein may be encapsulated in a capsule. Suitable liquid and semisolid dosage forms include solutions and suspensions in propylene carbonate, vegetable oils, or triglycerides. Capsules containing such solutions can be prepared as described in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. The capsules may also be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient.

[00217] The pharmaceutical compositions provided herein may be provided in liquid and semisolid dosage forms, including emulsions, solutions, suspensions, elixirs, and syrups. An emulsion is a two-phase system, in which one liquid is dispersed in the form of small globules throughout another liquid, which can be oil-in-water or water-in-oil. Emulsions may include a pharmaceutically acceptable non-aqueous liquids or solvent, emulsifying agent, and preservative. Suspensions may include a pharmaceutically acceptable suspending agent and preservative. Aqueous alcoholic solutions may include a pharmaceutically acceptable acetal, such as a di(lower alkyl)acetal of a lower alkyl aldehyde (the term "lower" means an alkyl having between 1 and 6 carbon atoms), e.g., acetaldehyde diethyl acetal; and a water-miscible solvent having one or more hydroxyl groups, such as propylene glycol and ethanol. Elixirs are clear, sweetened, and hydroalcoholic solutions. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may also contain a preservative. For a liquid dosage form, for example, a solution in a polyethylene glycol may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, *e.g.*, water, to be measured conveniently for administration.

[00218] The pharmaceutical compositions provided herein for oral administration may be also provided in the forms of liposomes, micelles, microspheres, or nanosystems. Miccellar dosage forms can be prepared as described in U.S. Pat. No. 6,350,458.

[00219] The pharmaceutical compositions provided herein may be provided as non-effervescent or effervescent, granules and powders, to be reconstituted into a liquid dosage form. Pharmaceutically acceptable carriers and excipients used in the non-effervescent granules or powders may include diluents, sweeteners, and wetting agents. Pharmaceutically acceptable carriers and excipients used in the effervescent granules or powders may include organic acids and a source of carbon dioxide.

[00220] Coloring and flavoring agents can be used in all of the above dosage forms. And, flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

[00221] The pharmaceutical compositions provided herein may be formulated as immediate or modified release dosage forms, including delayed-, extended, pulsed-, controlled, targeted-, and programmed-release forms.

[00222] The pharmaceutical compositions provided herein may be co-formulated with other active ingredients which do not impair the desired therapeutic action, or with substances that supplement the desired action.

[00223] The tablet dosage forms may be prepared from the active ingredient in powdered, crystalline, or granular forms, alone or in combination with one or more carriers or excipients described herein, including binders, disintegrants, controlled-release polymers, lubricants, diluents, and/or colorants.

[00224] In some aspects, the present invention provides a pharmaceutical composition in the form of a tablet, wherein the tablet comprises from about 1 mg to about 80 mg of a statin or a pharmaceutically acceptable salt thereof; from about 50 mg to about 900 mg of gemcabene or a pharmaceutically acceptable salt thereof; and one or more excipients.

[00225] In some embodiments, the pharmaceutical composition is in the form of a tablet and the tablet comprises from about 1 mg to about 80 mg of a statin or a pharmaceutically acceptable salt thereof; from about 50 mg to about 900 mg of gemcabene or a pharmaceutically acceptable salt thereof; and one or more excipients selected from a diluent, a disintegrant, a wetting agent, a binder, a glidant, a lubricant, or any combination thereof. For example, the tablet comprises a binder. And, in some instances, the binder comprises microcrystalline cellulose, dibasic calcium phosphate, sucrose, corn starch, polyvinylpyrridone, hydroxypropyl cellulose, hydroxymethyl cellulose, or any combination thereof. In another example, the tablet comprises a disintegrant. In some instances, the disintegrant comprises sodium croscarmellose, sodium starch glycolate, or any combination thereof. In other examples, the tablet comprises a lubricant. And, in some instances, the lubricant comprises magnesium stearate stearic acid, hydrogenated oil, sodium stearyl fumarate, or any combination thereof.

[00226] In one embodiment, the tablet comprises from about 10 mg to about 40 mg of the statin and from about 150 mg to about 600 mg of gemcabene. In another embodiment the tablet comprises from about 10 mg to about 40 mg of the statin and from about 150 mg to about 300 mg of gemcabene In some of these examples, the statin is the calcium salt of atorvastatin. In other examples, the gemcabene is the calcium salt of gemcabene. And, in some examples, the tablet further comprises calcium carbonate, potassium carbonate, or a combination thereof.

[00227] In some embodiments, the tablet comprises from about 10 to about 60 mg of a statin.

[00228] In some embodiments, the statin is selected from atorvastatin, simvastatin, pravastatin, rivastatin, mevastatin, fluindostatin, velostatin, fluvastatin, dalvastatin, dihydrocompactin, compactin, cerivastatin, or lovastatin, or any pharmaceutically acceptable

salts thereof. For example, the statin is atorvastatin, simvastatin, or pharmaceutically acceptable salts thereof. In other examples, the statin is a calcium salt of atorvastatin.

[00229] In some embodiments, the tablet comprises a binder such as any of the binders described herein.

[00230] In some embodiments, the tablet comprises a disintegrant such as any of the disintegrants described herein.

[00231] In some embodiments, the tablet comprises a lubricant such as any of the lubricants described herein.

[00232] In some embodiments, the gemcabene is the calcium salt of gemcabene.

[00233] In some embodiments, the pharmaceutical composition further comprises calcium carbonate, potassium carbonate, or a combination thereof.

C. Kits

[00234] Another aspect of the present invention provides a kit comprising a first single dose formulation comprising from about 50 mg to about 60 mg of a statin and a second single dose formulation comprising from about 50 mg to about 900 mg of gemcabene; and instructions for the use thereof.

[00235] In some embodiments, the first single dose formulation and the second single dose formulation are stored in separate containers.

[00236] In some embodiments, the first single dose formulation and the second single dose formulation are stored in the same container.

[00237] In some embodiments, the container is a bottle, vial, blister pack, or any combination thereof.

[00238] Another aspect of the present invention provides a kit comprising a single dose formulation comprising from about 10 mg to about 40 mg of a statin and from about 300 mg to about 600 mg of gemcabene; and instructions for the use thereof.

[00239] In some embodiments, the statin is atorvastatin, simvastatin, pravastatin, rosuvastatin, fluvastatin, lovastatin, pitavastatin or any pharmaceutically acceptable salt thereof. In some embodiments, the statin is atorvastatin or a pharmaceutically acceptable salt thereof.

[00240] In some embodiments, the single dose formulation further comprises a tablet.

[00241] In some embodiments, the tablet comprises one or more excipients selected from a diluent, a disintegrant, a wetting agent, a binder, a glidant, a lubricant, or any combination thereof.

EXAMPLES

Example 1: Atorvastatin-Gemcabene Tablet Formulation

[00242] Table 2and Table 3 show the compositions of formulations containing polyvinylpyrrolidone (PVP) and hydroxypropyl cellulose (HPC), respectively.

Table 2: Composition of Formulations Containing PVP as a Binder

Ingredients	**Example 1A**	**Example 1B**	**Example 1C**
Base Granulation		wt%	
Gemcabene Calcium Salt	58.1	58.1	19.3
Atorvastatin Calcium	0.588	2.4	4.7
$CaCO_3$	0-1.77	0-7.1	0-14.1
Microcrystalline Cellulose (PH 101)	15-13.8	13.7-6.7	50.1-36.0
PVP K-30[a]	6.7	6.7	6.7
Croscarmellose Sodium	3.0	3.0	3.0
Final Blend		wt%	
Microcrystalline Cellulose (PH 102)	12.3	12.3	12.3
Croscarmellose Sodium	3.0	3.0	3.0
Magnesium stearate (non-bovine)	0.8	0.8	0.8
Gemcabene/Atorvastatin (mg/mg)	225/2.5	225/10	75/20

[a] Binder added partially as powder (3%) and partially as solution (3.7%)

Table 3: Composition of Formulations Containing Hydroxypropyl Cellulose as a Binder

Ingredients	**Example 1D**	**Example 1E**	**Example 1F**
Base Granulation		wt%	
Gemcabene Calcium Salt	58.1	58.1	19.3
Atorvastatin Calcium	0.588	2.4	4.7
$CaCO_3$	0-1.76	0-7.1	0-14.1

Microcrystalline Cellulose (PH 101)	4.2-2.5	2.5-0	38.9-24.8
Starch, Pregelatinized, 1500 Corn	10.0	10.0	10.0
Hydroxypropyl Cellulose-EXF[a]	8.0	8.0	8.0
Croscarmellose Sodium	3.0	3.0	3.0
Final Blend		wt%	
Microcrystalline Cellulose (PH 102)	12.2	12.2-7.7	12.2
Croscarmellose Sodium	3.0	3.0	3.0
Magnesium stearate (non-bovine)	0.8	0.8	0.8
Gemcabene/Atorvastatin (mg/mg)	225/2.5	225/10	75/20

[a] Binder added partially as powder (4%) and partially as solution (4%)

[00243] The following major equipment were used in the manufacture of the tablets for this study:

Tekmar RW20 DZM mixer;

Masterflex pump, model 7523-10;

Bohle Mini-Granulator equipped with 4 L bowl;

Hotpack Benchtop Oven (Model 213023-25);

Computrac Max 2000 moisture analyzer;

Quadro Comil 193AS (equipped with 0.045 inch screen, impeller 1601, and spacer 175);

Patterson-Kelly Blendmaster twin-shell blender (4 qt); and

Korsch EKO (SN K0000060) equipped with 14/32 inch round concave (plain-faced) tooling.

[00244] Binder solution (15% w/w) was prepared by slow addition of either HPC or PVP to the required weight of water while mixing using a Tekmar mixer. The mixing was continued for at least 2 hours until all the binder was in solution. The solution was then allowed to stand for few hours (typically overnight) before use to ensure that there were no air-bubbles.

[00245] Base granulations were prepared at 300 g scale using the Bohle High-Shear minigranulator equipped with a 4 L bowl. All the ingredients of the base granulation including a portion of binder that is added as powder (Table 2 and Table 3) were taken in a plastic bag and

mixed. The mixture was charged into the 4 L bowl and mixed further using the impeller at 300 rpm, typically for 1 to 2 minutes. Binder solution was then added at a constant flow rate (9.3 g/min for PVP and 20 g/min for HPC) while mixing using an impeller speed of 300 rpm and a chopper speed of 1500 rpm. After complete addition of the binder solution, water was added without changing the pump setting or the impeller and chopper speeds. The quantity of total water added for granulation varied for each formulation, with a higher percentage of water required to aid formation of granules as the microcrystalline cellulose (PH 101) content was increased. The granulation was mixed further at the same impeller/chopper speed until the granulation end-point was reached (based on visual appearance). Typical total granulation times were about 9 to 11 or 16 to 19 minutes for formulations containing HPC and PVP, respectively. The granulations were tray-dried in a Hotpack benchtop oven at 50°C until about 2% LOD (loss on drying) was reached.

[00246] The base granulations were milled using a Quadro Comil Model 193AS equipped with a 0.045 inch screen, impeller 1601, and spacer 175, at 2220 rpm (Setting 6) or 2920 rpm (Setting 8). The milled base granulation was blended with microcrystalline cellulose (PH 102) and croscarmellose sodium for 5 minutes using a 4 qt twin-shell blender. Magnesium stearate was added to a small portion of this blend, and the mixture was passed through 30-mesh screen. After addition of this screened material to the rest of the batch in the blender, blending was continued for another 3 minutes to obtain the final blend.

[00247] The final blend was compressed into compacts using a single station stationary press, Korsch EKO, equipped with 14/32 inch round concave (plain-faced) tooling. The target weight and hardness for the tablets were 465 mg and 15-25 kP, respectively.

[00248] The tablets of Examples 1A-1F were subjected to accelerated stability testing, wherein 15 tablets of each example tablet were stored in 60 cc high-density polyethylene bottles. Test bottles of the tablets included unsealed bottles ("Open") and bottles sealed by foil induction ("Closed"). A first test group of Open bottles was subjected to 40 °C and 75% relative humidity; a second test group of Closed bottles was subjected to the same conditions; and a third test group of Closed bottles was subjected to 60 °C and ambient humidity. Tablets were analyzed for oxidized atorvastatin and lactone formation using HPLC and UV spectroscopy analytical methods. Tablets from the second test group were tested for initial stability. Selected tablets from each of the bottles of the test groups were analyzed at 1 month intervals. The tablets of Examples 1A-1C that were formulated with PVP demonstrated unacceptable levels of oxidation at the 1-month time point, so testing of these tablets ceased. The remaining tablets of examples 1D-1F continued to be tested for a period of more than 7 months.

[00249] Shelf life for each of the tablets of examples 1D-1F was determined using the stability data of this test to estimate pseudo zeroth order rate constants at both 40 °C and 60 °C. The shelf lives for the tablets of examples 1E and 1F at 25 °C were estimated to be about 4 years while the shelf life for the tablet of example 1D was estimated to be less than 2 years.

[00250] Moreover, it was observed that the addition of $CaCO_3$ in the tablet formulations suppressed lactone formation. For a given time, storage condition, and mass of gemcabene per mass atorvastatin, the lactone formation was higher in the 0 x $CaCO_3$ versus the 3 x $CaCO_3$. And surprisingly, atorvastatin lactone formation rates were found to be greatest in the tablets of example 1D and least in the tablets of example 1F, which indicates that little or no correlation exists between the rate of lactone formation and the loading of gemcabene in the tablet formulation.

Example 2: Formulation Suitability Study for Combination Atorvastatin and Gemcabene Tablets

[00251] This study was an open label, single dose, randomized, 6-sequence, 6-period, 6-treatment crossover study conducted in healthy volunteers. Eighteen subjects entered the study and were to receive each of the following treatments:

Reference: Atorvastatin 40 mg tablet alone (Lipitor®)

Tests: Gemcabene + Atorvastatin tablet Formulations containing 450 mg gemcabene and 40 mg atorvastatin in Experiments 2A – 2D, and containing 300 mg gemcabene and 10 mg atorvastatin in Experiment 2E as described in Tables 4 and 5.

Table 4: Gemcabene/Atorvastatin (G/A) Formulations 2A-2C (% w/w = % of the total tablet weight)

Internal Ingredients	**Example 2A (450/40 mg G/A)**		**Example 2B (450/40 mg G/A)**		**Example 2C (450/40 mg G/A)**	
	% w/w	mg/Tablet	% w/w	mg/Tablet	% w/w	mg/Tablet
Gemcabene Calcium salt	56.91	540.61	50.18	540.61	54.06	540.61
Atorvastatin Ca	4.61	43.78	4.06	43.78	4.38	43.78
Calcium Carbonate	0.00	0.00	12.19	131.32	0.00	0.00
Microcrystalline Cellulose, NF (PH 101)	4.00	38.00	3.50	37.71	3.80	38.01
Starch 1500	0.00	0.00	0.00	0.00	0.00	0.00

Croscarmellose Sodium	3.00	28.50	3.00	32.32	2.85	28.50
Hydroxypropyl Cellulose EXF	5.00	47.50	5.30	57.10	4.75	47.50
External Ingredients	**Example 2A (450/40 mg G/A)**		**Example 2B (450/40 mg G/A)**		**Example 2C (450/40 mg G/A)**	
	% w/w	mg/Tablet	% w/w	mg/Tablet	% w/w	mg/Tablet
Microcrystalline Cellulose, NF (PH 102)	22.49	213.62	17.77	191.49	20.01	200.11
Mannitol	0.00	0.00	0.00	0.00	6.00	60.00
Croscarmellose Sodium	3.00	28.50	3.00	32.32	3.15	31.50
Magnesium Stearate (Nonbovine)	1.00	9.50	1.00	10.77	1.00	10.00
To make core Tablets	100.00	950.00	100.00	1077.42	100.00	1000.01
	Without $CaCO_3$		With $CaCO_3$		Fast, Without $CaCO_3$	
% Atorvastatin Dissolution at 10 Min	22		22		43	
% Atorvastatin Dissolution at 20 Min	49		59		66	
Hardness (kP)	30 kP		30 kP		31 kP	
Disintegration Time (Min)	17.2		13.8		10.4	

Table 5: Gemcabene/Atorvastatin (G/A) Formulations 4D and 4E (% w/w = % of the total tablet weight)

Internal Ingredients	**Example 2D (450/40 mg G/A)**		**Example 2E (300/10 mg G/A)**	
	% w/w	mg/Tablet	% w/w	mg/Tablet

Gemcabene Calcium salt	50.18	540.61	56.91	360.40
Atorvastatin Ca	4.06	43.78	1.73	10.94
Calcium Carbonate	12.19	131.32	0.00	0.00
Microcrystalline Cellulose, NF (PH 101)	3.50	37.71	4.00	25.33
Starch 1500	6.50	70.03	0.00	0.00
Croscarmellose Sodium	3.00	32.32	3.00	19.00
Hydroxypropyl Cellulose EXF	5.30	57.10	5.00	31.67
External Ingredients	**Example 2D (450/40 mg G/A)**		**Example 2E (300/10 mg G/A)**	
	% w/w	mg/Tablet	% w/w	mg/Tablet
Microcrystalline Cellulose, NF (PH 102)	11.27	121.46	25.37	160.65
Mannitol	0.00	0.00	0.00	0.00
Croscarmellose Sodium	3.00	32.32	3.00	19.00
Magnesium Stearate (Nonbovine)	1.00	10.77	1.00	6.33
To make core Tablets	100.00	950.00	100.00	1077.42
	Slow, With $CaCO_3$		(300/10) No $CaCO_3$	
% Atorvastatin Dissolution at 10 Min	18		Disintegration Faster Than 450/40	
% Atorvastatin Dissolution at 20 Min	41			

Hardness (kP)	29 kP	17 kP
Disintegration Time (Min)	29.8	12.3

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Diagnosis and Main Criteria for Inclusion:

Healthy subjects of any race and either gender; age 18 to 65 (inclusive), with a body weight of 45 kg or greater and a body mass index (BMI) ≤ 35 kg/m^2 (weight [kg]/height [meters]^2); females required to be of non-reproductive potential (postmenopausal ≥ 1 year, hysterectomy, or tubal ligation).

Exclusion Criteria:

Use of any medication not considered acceptable by the clinical investigators during the 14-day period before the start of the study (Day 1). Hormone replacement therapy is acceptable;

Donation of a unit of blood or participation in a study of investigational or marketed drugs during the 30-day period before the start of the study (Day 1);

If female, of childbearing potential or lactating;

Use of St. John's wort during the 7-day period before the start of the study (Day 1);

Consumption of grapefruit juice or food products containing grapefruit during the 7-day period before the start of study (Day 1);

History of significant adverse reaction to any lipid-lowering agent; or

Significant urine concentration of any drug that could interfere with the study.

Duration of Treatment:

Single dose Gemcabene + atorvastatin tablet formulations 1-5 with a minimum 2-week washout period between treatments.

[00252] On Days 1, 15, 29, 50, 64, and 78 subjects were randomized to receive an oral, single dose of one of the five gemcabene + atorvastatin formulations or atorvastatin tablets. Each single dose is administered with 40 mL (8 oz.) of water.

Results:

[00253] Eighteen subjects (12 male, 6 female) entered the study, and were withdrawn from the study on Day 64 due to the early termination of the study. Subjects had a mean (range) age of 52.6 (28-64) years, a mean (range) weight of 88.7 (55.4-111) kg, and a mean (range) BMI of 29.0 (21.6-34.1) kg/m^2.

[00254] Formulation 2A: 8 of 12 subjects reported adverse events. There were no severe adverse events. The most frequently occurring adverse event was infection (3 subjects). All other adverse events were single occurrences. Three subjects reported adverse events that were considered treatment associated: Anorexia, dizziness, and dry mouth (1 subject each). Ten adverse events were considered mild in intensity, and 1 adverse event was considered moderate in intensity.

[00255] Formulation 2B: 7 of 12 subjects reported adverse events. The most frequently occurring adverse events were headache and somnolence (2 subjects). All other adverse events were single occurrences. 5 subjects reported adverse events that were considered treatment associated: Somnolence (2 subjects) and diarrhea, asthenia, and dyspepsia (1 subject each). Eight adverse events were considered mild in intensity, 1 adverse event was considered moderate in intensity, and 1 adverse event (headache) was considered severe in intensity. The severe adverse event was not considered treatment associated.

[00256] Formulation 2C: 9 of 12 subjects reported adverse events. There were no severe adverse events. The most frequently occurring adverse events were infection (3 subjects) and headache and somnolence (2 subjects). All other adverse events were single occurrences. Four subjects reported adverse events that were considered treatment associated: Headache, asthenia, somnolence, and tachycardia, (1 subject each). Eight adverse events were considered mild in intensity and 4 adverse events were considered moderate in intensity.

[00257] Formulation 2D: 8 of 12 subjects reported adverse events. There were no severe adverse events. The most frequently occurring adverse events were headache (3 subjects) and somnolence (2 subjects). All other adverse events were single occurrences. 4 subjects reported adverse events that were considered treatment associated: Somnolence (2 subjects) and headache and dyspepsia (1 subject each). Seven adverse events were considered mild in intensity, and 5 adverse events were considered moderate in intensity.

[00258] Formulation 2E: 6 of 12 subjects reported adverse events. There were no severe adverse events. The most frequently occurring adverse event was headache (2 subjects). All other adverse events were single occurrences. Three subjects reported adverse events that were considered treatment associated: Headache (2 subjects) and diarrhea (1 subject). 8 adverse events were considered mild in intensity, and 3 adverse events were considered moderate in intensity.

[00259] Atorvastatin 40 mg: 8 of 11 subjects reported adverse events. There were no severe adverse events. The most frequently occurring adverse events were headache (3 subjects) and dizziness and pain (2 subjects). All other adverse events were single occurrences. 2 subjects reported adverse events that were considered treatment associated: Headache and diarrhea (1

subject each). Nine adverse events were considered mild in intensity and 3 adverse events were considered moderate in intensity.

Conclusions:

[00260] Single doses of combination gemcabene/atorvastatin Formulations 4A-4E are safe and well-tolerated by healthy volunteers.

Example 3: Immediate Release Atorvastatin Capsules

[00261] Immediate release Atorvastatin Capsules, 20 mg were prepared as neat drug substance in capsules as batch 121-16001. Atorvastatin Calcium Trihydrate drug substance was manually filled into size 0 white opaque gelatin capsules shells, by weight, to give a dosage strength of 20 mg Atorvastatin (see Table 6 below).

Table 6: Formulation Composition and Batch Size of the Atorvastatin Capsules

Item No.	Ingredient	Concentration % w/w	Amount/ Capsule (mg)	Amount/ Batch (g)
1	Atorvastatin Calcium Salt, Trihydrate	18.85	21.79[1]	1.3074[3]
2	Size 0 White Opaque Gelatin Capsules	81.15	93.8[2]	5.628[3]
	Total	100.0	115.29	6.9354

Dissolution Profile:

[00262] Dissolution testing is performed using USP Apparatus 2 (paddles) at 75 RPM in 900mL deionized water with samples collected at 10, 20, 30, 45, and 60 minutes (Figure 1).

Example 4: Immediate Release Gemcabene Capsules

[00263] Immediate release Gemcabene Capsules, 150 mg were prepared as batch 121-16002. The capsule fill was prepared as a high-shear wet granulation using a lab-scale high-shear granulator (Vector/Freund GMX-LabMini). The ingredients, items 1-5, were added to the granulator bowl and granulated by the addition of 20% w/w (relative to the granulator charge) purified water. Resulting granulation was sieved through a #10 mesh sieve and subsequently dried in a lab-scale fluid-bed dryer (Vector/Freund MFL-01) to a final loss on drying (LOD) value of <3% as determined by a moisture balance. The dried granulation was passed through a #20 mesh sieve and blended in a diffusional blender (PK V-Blender) with magnesium stearate (Ingredient Item 6). The final blended material was encapsulated in size 00 white opaque capsule shells, using a Profil (Torpac) hand encapsulation tray, at 360 mg per capsule to give a

final Gemcabene (free di acid) potency of 150 mg. The quantitative composition of gemcabene immediate release capsules, 150 mg and Batch Size are provided in Table 7 below.

Table 7: Formulation Composition and Batch Size of the Gemcabene Capsules

Item No.	Ingredient	Concentration % w/w	Mg/Tablet	Amount/ Batch (g)
1	Gemcabene*	49.02	176.47	114.706
2	Lactose Monohydrate, NF (Granulac 70)	25.48	91.73	59.624
3	Hydroxypropylcellulose, NF (Klucel EXF)	2.0	7.2	4.68
4	Microcrystalline Cellulose, NF (Avicel PH102)	20.0	72.0	46.8
5	Croscarmellose Sodium, NF	3.0	10.8	7.02
6	Water, Purified[2]	-	-	47.3[2]
7	Magnesium stearate	0.5	1.8	1.17
	Total	100.0	360.0	234.0

* Gemcabene (calcium salt) is adjusted for potency to give a final Di acid strength of 150mg per capsule

Dissolution profile:

[00264] Dissolution testing is performed using USP Apparatus 2 (paddles) at 75 RPM in 900mL deionized water with samples collected at 10, 20, 30, 45, and 60 minutes (Figure 2).

Example 5: Modified Release Atorvastatin Prototype 1

[00265] Compositions of various prototypes for modified release atorvastatin having various triggered pH values are presented in Figure 3.

[00266] Enteric coated Atorvastatin tablets targeting release of the drug substance at a pH of 7.0 were prepared as batch 121-16005.

[00267] These tablets were designed such that they could be inserted into a standard size 0 capsule shell for combination administration with gemcabene and optionally additional components, in which gemcabene and optionally additional components are individually and subsequently filled in the capsule. The tablet cores were prepared as a high-shear wet granulation using a lab-scale high-shear granulator (Vector/Freund GMX-LabMini). The granulation was passed through a #10 mesh sieve and subsequently dried in a lab-scale fluid-bed dryer (Vector/Freund MFL-01) to a final loss on drying (LOD) value of <2% as determined by a moisture balance. Dried granules were sieved through a #16 mesh sieve and blended with croscarmellose sodium and magnesium stearate in a diffusional blender (PK V-Blender). The final blend was compressed into tablets using ¼" (6.35mm) tablet tooling on a lab-scale rotary tablet press (Dynamic Exim 10 station tablet press). Tablets were then charged into a lab-scale

fully perforated coating pan (Vector/Freund LDCS pan coater) and a Hypromellose sub-coating (Opadry Clear, Colorcon) was applied at a 3% weight gain, relative to the tablet core weight, to provide a barrier between the slightly alkaline tablet core and the pH sensitive enteric coating. Table 8 below described the batch composition.

Table 8: Formulation Composition and Batch Size of the Atorvastatin Tablet Cores

Item No.	Ingredient	Concentration % w/w	Mg/ Tablet	Amount/ Batch (g)
Intra-Granular Ingrdeients				
1	Atorvastatin Calcium (Trihydrate)[1]	13.67	21.87	272.375
2	Calcium Carbonate	22.5	36.0	450.0
3	Lactose Monohydrate (Tabletose 70)	40.08	64.13	801.625
4	Microcrystalline Cellulose (PH102)	18.75	30.0	375.0
5	Polyvinylpyrrolidone (Plasdone K29/32)	1.88	3.0	37.5
6	Polysorbate 80	0.25	0.4	5.0
7	Water, Purified*	-	-	357.5
Extra-Granular Ingredients				
8	Croscarmellose Sodium	2.5	4.0	50.0
9	Magnesium stearate	0.38	0.6	7.5
	Total	100.0	160.0	2000.0

[00268] An enteric coating comprised of a combination of Methacrylic acid, Methyl Acrylate, Methacrylate polymer and Methacrylic Acid Copolymer Type C was then applied to the sub-coated tablet cores at a target 10% weight gain, relative to the uncoated tablet core, using a lab-scale fully perforated coating pan (Vector/Freund LDCS pan coater). The enteric coating composition is described in Table 9 below.

Table 9: Enteric Coating of the Atorvastatin Minitablets Prototype 1

Item No.	Ingredient	% (W/W)[1]	Mg/Tablet	Amount/ Batch (g)
1	Atorvastatin Tablets, 20mg	88.5	160.0	1000.0
Sub-Coat Formula[4]				
2	Purified Water, USP[3]	n/a	n/a	405.0
3	Opadry (Clear)	2.65	4.8	45.0
Enteric-Coat Formula[4]				
4	Eudragit FS30D	3.77	6.8[2]	333.3
5	Eudragit L30D55	1.89	3.4[2]	166.7
6	Triethyl Citrate, NF	0.39	0.7	10.0

7	Talc USP/EP (Luzenac Pharma M)	2.82	5.1	75.0
8	Purified Water, USP[3]	n/a	n/a	590.0
	Total	100.0	180.8	

Dissolution Profile:

[00269] The dissolution testing is performed per USP <711> Delayed Release Dosage Forms Method A using Apparatus 2 (paddles) at 100RPM (Figure 4). Stage 1 dissolution medium was 0.1N HCl, and after 2 hours 250 mL of sodium phosphate buffer solution was added to adjust medium's pH to 7.2. Samples collected for analysis after 2 hours in the acid stage and then at 30, 45, 60, 75, 90, 105, and 120 minutes post media change.

Example 6: Modified Release Atorvastatin Combination Prototype 2

[00270] The composition of Prototype 2 is described in Formula 3 of Figure 3.

[00271] Prototype 2 was prepared as described above for prototype 1, using the same granulated blend as for Prototype 1.

[00272] An enteric coating comprised of a combination of Methacrylic acid, Methyl Acrylate, Methacrylate polymer and Methacrylic Acid Copolymer Type C was then applied to the sub-coated tablet cores at a target 10% weight gain, relative to the uncoated tablet core, using a lab-scale fully perforated coating pan (Vector/Freund LDCS pan coater). The enteric coating composition is described in Table 10 below.

Table 10: Enteric Coating of the Atorvastatin Minitablets Prototype 2

Item No.	Ingredient	% (W/W)[1]	Mg/Tablet	Amount/ Batch (g)
1	Atorvastatin Tablets, 20mg	88.5	160.0	1000.0
Sub-Coat Formula[4]				
2	Purified Water, USP[3]	n/a	n/a	405.0
3	Opadry (Clear)	2.65	4.8	45.0
Enteric-Coat Formula[4]				
4	Eudragit FS30D	2.45	6.8[2]	333.3
5	Eudragit L30D55	3.20	3.4[2]	166.7
6	Triethyl Citrate, NF	0.39	0.7	10.0
7	Talc USP/EP (Luzenac Pharma M)	2.82	5.1	75.0
8	Purified Water, USP[3]	n/a	n/a	590.0
	Total	100.0	180.8	

[00273] *Dissolution Profile:* The dissolution testing is performed per USP <711> Delayed Release Dosage Forms Method A using Apparatus 2 (paddles) at 100RPM. Stage 1 dissolution medium was 0.1N HCl, and after 2 hours 250 mL of sodium phosphate buffer solution was added to adjust medium's pH to 6.8. Samples collected for analysis after 2 hours in the acid stage and then at 30, 45, 60, 75, 90, 105, and 120 minutes post media change (Figure 5).

Example 7: Determination of the Pharmacokinetics of Prototype Combinations of Atorvastatin and Gemcabene After a Single Oral Dose to Male Dogs

[00274] Plasma samples were collected in order to determine the pharmacokinetics (PK) of Atorvastatin and Gemcabene administered in combination prototype formulations after a single oral dose to male dogs. This study was conducted in accordance with the applicable Covance Laboratories Inc., Greenfield, Indiana (USA) standard operating procedures (SOPs), in a non-glp (Good Laboratory Practice Regulations) fashion. All procedures in the protocol are in compliance with the Animal Welfare Act Regulations (9 CFR 3).

[00275] The study was performed in 6 months to 3 years, male, purebred beagle dogs, drug naïve from the Covance stock colony of 7 to 15 kg weight. Animals were identified via individual cage cards, ear tag, tattoo, and implantable microchip identification devices (IMID), as applicable. Animals were housed in stainless steel cages, and would not be commingled for at least 24 hours after test article administration, to allow monitoring of any test article-related effects. Also, animals were acclimated in the study room one day prior to treatment administration. Animals were not randomized, and were fed approximately 500 g per day of 2021, 21% Protein Dog Diet (Envigo RMS, Inc.) and/or Purina Labdiet 5006, unless otherwise specified for dose administration. Greenfield city water was provided ad libitum. Animals were treated in accordance with the Animal Welfare Act, the Guide for the Care and Use of Laboratory Animals, and the Office of Laboratory Animal Welfare.

[00276] The test articles are presented in Table 10 below. All animals were fasted overnight through approximately 6 hours postdose. The capsule doses were administered orally by placing the capsule(s) in the back of the throat and administering approximately 10 mL water to encourage the dog to swallow.

[00277] Specifically, the doses were administered as follows: (i) for Phase 1, individual doses were 20 mg Atorvastatin IR capsule/animal; (ii) for Phase 2, individual doses were 150 mg Gemcabene IR capsule/animal; (iii) for Phase 3, individual doses were a prototype combination 20 mg Atorvastatin MR and 150 mg Gemcabene IR capsule /animal; (iv) for Phase 4, individual doses were a second prototype combination 20 mg Atorvastatin MR and 150 mg Gemcabene IR

capsule/animal. The test articles are provided in Table 11 and the experimental design is provided in Table 12.

Table 11: Test Articles

Test Article	Storage	Formulation
Atorvastatin IR	15-30°C	Capsule 20 mg active
Gemcabene IR	15-30°C	Capsule 150 mg active
Prototype 1 (Atorvastatin MR + Gemcabene IR)	15-30°C	Capsule 20 mg Atorva and 150 mg Gemcabene
Prototype 2 (Atorvastatin MR + Gemcabene IR)	15-30°C	Capsule 20 mg Atorva and 150 mg Gemcabene

Table 12: Experimental Design; Phase and Group Designations and Dose Levels

Phase/ Group	Number of Male Animals	Test Article	Dose Route	Target Dose Level (mg/dog)	Target Dose (mg/ Capsule)	Target Dose (capsules/ animal)
1/1	4	Atorvastatin IR	PO	20	20	1
2/1	4	Gemcabene IR	PO	150	150	1
3/1	4	Prototype 1 (Atorvastatin MR + Gemcabene IR)	PO	20 + 150	20 + 150	1 + 1
4/1	4	Prototype 2 (Atorvastatin MR + Gemcabene IR)	PO	20 + 150	20 + 150	1 + 1

PO Oral.
IR Immediate release
Notes: Extra animals may be dosed for use as replacements in the event of a misdose or other unforeseen event, as applicable. There will be an approximately 7-day washout period after Phase 1, and an approximate 12-day washout period between Phases 2, 3, and 4.

Animals were observed for mortality and signs of pain and distress at least once daily, and cageside observations for general health and appearance were done once daily. Body Weights were recorded at the time of animal selection, on the day of dose administration. Detailed observations were performed on all available animals predose and 0.5, 2, 24 and 48 hours

postdose for each phase. Upon completion of the in-life portion of the study, animals will be returned to the Covance stock colony.

Sample collection.

[00278] For each phase, blood (approximately 3 mL) was collected via a jugular vein into tubes containing K_2EDTA from each animal predose and at approximately 0.5, 1, 2, 4, 6, 12, 24, 36, 48, 60, 72, 96, 120, 144 and 168 hours postdose. Blood was maintained on wet ice or at approximately 5°C prior to centrifugation to obtain plasma. Centrifugation began within 1 hour of collection. Resulting samples were harvested within 40 minutes of the start of centrifugation. Plasma samples were identified with the Covance study number, test article lot number, group, animal identification, phase, matrix, and collection time point or interval, and were placed into individually labeled 96-well tubes with barcodes, and maintained on dry ice prior to storage at ≤-60°C. Samples were analyzed for concentrations of Atorvastatin and Gemcabene at Medpace Bioanalytical Laboratories, Ohio (USA). Results were provided to Covance Laboratories Inc. for pharmacokinetic analysis.

Pharmacokinetic Analysis.

[00279] Pharmacokinetic parameters were estimated using Phoenix® WinNonlin® version 6.4 or higher (Certara USA, Inc., Princeton, NJ). A non-compartmental approach consistent with the oral route of administration will be used for parameter estimation. The individual plasma concentration-time data were used for pharmacokinetic calculations. In addition to parameter estimates for individual animals, descriptive statistics (e.g. mean, standard deviation, coefficient of variation) were reported, as appropriate. All parameters were generated from individual test article and metabolite concentrations in plasma. Samples that are below the lower limit of quantitation were treated as zero for determination of descriptive statistics and pharmacokinetic analysis. Embedded values below the lower limit of quantitation were excluded from pharmacokinetic analysis. Parameters were estimated using nominal dose levels. Parameters were estimated using nominal sampling times; if bioanalytical sample collection deviations are documented, actual sampling times will be used at the affected time points. Pharmacokinetic parameters were calculated and presented in the units provided by the analytical laboratory. Bioanalytical data were used as received from the pharmacokinetic analysis and were presented in tables and figures in the units provided. Descriptive statistics and pharmacokinetic parameters were reported to three significant figures. Pharmacokinetic parameters estimated are presented in Table 13.

Table 13: Pharmacokinetic Parameters Measured

Parameter	Description
C_{max}	Maximum observed concentration
T_{max}	Time of maximum observed concentration
AUC_{0-t}	Area under the curve from time 0 to the time of the last measurable concentration, calculated using the linear trapezoidal rule.
AUC_{0-inf}	Area under the curve from time 0 to infinity, calculated as $AUC_{0-inf} = AUC_{0-t} + C_t / \lambda_z$, where C_t is the last observed quantifiable concentration and λ_z is the elimination rate constant.
$AUC_{0-□}$ % extrap	Percentage of the area under the concentration-time curve from hour 0 to infinity determined by extrapolation:
$t_{1/2}$	Elimination half-life, calculated as ln(2) / λ_z.
F_{rel}	Relative bioavailability, calculated as: [AUC_{0-inf} or AUC_{0-t} Prototype 1 or 2] / [AUC_{0-inf} or AUC_{0-t} Reference] [Dose Reference] / [Dose Prototype 1 or 2]
M:P	Metabolite to parent ratio, calculated as: [AUC_{0-t} metabolite] / [AUC_{0-t} parent]

[00280] Based on these parameters, the mass weight of atorvastatin and the sum of the two hydroxyl-atorvastatin active metabolites was compared with the mass weight of the three lactone inactive metabolites. Tables 14 and 15 present the % mass (which is identical to %mol/mol, given that molecular weights are essentially similar) of atorvastatin lactones at 24 hrs.

Table 14: Percent Atorvastatin Lactone Formation for Dosing Phases 1, 3, and 4 in Four Test Canines

Phase	Atorvastatin	Non-Lactones	Lactones	Time of release into blood after dosing (Hr)
Example Canine A				
1	100.0%	80.3%	19.7%	0.5
3	100.0%	100.0%	0.0%	6
4	100.0%	100.0%	0.0%	4
Example Canine B				
1	100.0%	75.3%	24.7%	1
3	100.0%	76.0%	24.0%	4
4	100.0%	72.1%	27.9%	4
Example Canine C				

1	100.0%	85.2%	23.0%	0.5
3	100.0%	84.8%	15.2%	2
4	100.0%	100.0%	0.0%	4
Example Canine D				
1	100.0%	86.8%	13.2%	0.5
3	100.0%	91.4%	8.6%	2
4	100.0%	78.1%	21.9%	4

Table 15: AUC Readings for Atorvastatin Lactone and Atorvastatin Non-Lactone Blood Levels in the Four\ Test Canines (sum of the mass (ng) of atorvastatin all metabolites, atorvastatin non-lactones, and atorvastatin lactones for all time points)

	Canine A	Canine B	Canine C	Canine D
Phase 1				
Atorvastatin	40.158	20.844	22.566	22.531
Non-Lactones	32.239	15.694	17.763	19.547
Lactones	7.919	5.15	4.803	2.984
Phase 3				
Atorvastatin	0.91	4.31	3.242	2.874
Non-Lactones	0.91	3.274	2.749	2.627
Lactones	0	1.036	0.493	0.247
Phase 4				
Atorvastatin	0.503	2.713	0.183	1.268
Non-Lactones	0.503	1.957	0.183	0.99
Lactones	0	0.756	0	0.278

[00281] Profiles for canine examples A and C provided in Figures 6A – 6C and Figures 7A – 7C, respectively.

[00282] Table 11 describes the storage temperature and information on test articles administered to each dog during each test phases, in the first phase, dogs received immediate release 20 mg atorvastatin alone, in the second phase, dogs received immediate release 150 mg gemcabene alone, in the third phase, dogs received prototype 1 , in which the invention is a formulation comprised of immediate release 150 mg gemcabene and modified release 20 mg atorvastatin, designed for atorvastatin release at pH 7.2, and in the fourth phase dogs received prototype 2 , in which the invention is a formulation comprised of immediate release 150 mg gemcabene and modified release 20 mg atorvastatin, designed for atorvastatin release at pH 6.5.

[00283] Table 12 describes each phase of the study, indicates one group of four male dogs were used for the entire study, with each dog dosed with each test agent (Table 11) once during each phase as indicated for each phase of the study, that the oral route (PO) was used to

administer each test agent, with the composition of each test agent, and the amount administered to each dog during each test phase.

[00284] Table 13 shows pharmacokinetic parameters calculated from the time course measurements of atorvastatin and each atorvastatin metabolite (atorvastatin lactone, 2-hydroxy atorvastatin, 2-hydroxy atorvastatin lactone, 4-hydroxy atorvastatin, and 4-hydroxy atorvastatin lactone) in the plasma of each dog, following the administration of test article containing atorvastatin during each test phase.

[00285] Table 14 summarizes the percent distribution between the atorvastatin non-lactones (atorvastatin parent, 2-hydroxy atorvastatin, 4-hydroxy atorvastatin) and atorvastatin lactones (atorvastatin lactone, 2-hydroxy atorvastatin lactone, 4-hydroxy atorvastatin lactone) and the time of appearance in the blood of any atorvastatin analyte for each dog for each study phase dogs received a formulation containing atorvastatin.

[00286] Table 15 is the sum of all atorvastatin analytes (atorvastatin non-lactones plus atorvastatin lactones), atorvastatin non-lactones (atorvastatin parent, 2-hydroxy atorvastatin, 4-hydroxy atorvastatin) and atorvastatin lactones (atorvastatin lactone, 2-hydroxy atorvastatin lactone, 4-hydroxy atorvastatin lactone) for all time points collected for each phase of the study and for each dog. Each time point was reported as ng/mL and each value in the table represents the sum for all the time points colleted for each phase of the study for each dog. The data in table 14 is derived from the data in Table 15).

[00287] The gemcabene profile is essentially the same in combination with atorvastatin prototype as administered alone (Figure 9), in support of the lack of drug-drug interaction during absorption.

Example 8: Microbeads of atorvastatin and gemcabene in unique encapsulation

Gemcabene microbeads

[00288] The gemcabene crystals are coated using a spray-coating technique in a bottom-spray fluidized bed equipment. The coating suspension is prepared by mixing the coating excipients in an acetone/isopropyl alcohol mixture in a stainless steel vessel equipped with a stirring device. The suspension is sprayed at room temperature onto the gemcabene crystals, in a fluidized bed apparatus working under nitrogen. During the process, the solvents are evaporated by the fluidization stream, allowing the composition to deposit around the crystals as a continuous coating membrane, thus forming the gemcabene microparticles.

[00289] The gemcabene microparticles are mixed with the capsule filling excipients in order to obtain a free flowing blend. This blend is achieved in a drum-type blender of appropriate capacity. The resulting blend is used as a component in the fixed dose combination.

[00290] Examples of compositions of gemcabene microbeads are indicated in Tables 16a – 16c. These compositions do not comprise delay release excipients, but only extended release.

Table 16a – Examples Composition of Gemcabene Dose

Ingredient	**Function**	**Composition A1**	
		Composition (mg/capsule)	Centesimal Composition (%)
Gemcabene	Active ingredient	151.00	94.70
Ethylcellulose	Film coating agent	4.36	2.73
Castor oil	Plasticiser	0.36	0.23
PVP	Film coating agent	0.24	0.15
Tartaric acid	Stabilising agent	0.60	0.38
Magnesium stearate*	Lubricant	0.32	0.20
Anhydrous colloidal silica	Glidant	0.86	0.53
Talc	Lubricant	1.70	1.08
Total		**159.44**	100.00

Table 16b – Examples Composition of Gemcabene Dose

Ingredient	**Function**	**Composition A2**	
		Composition (mg/capsule)	Centesimal Composition (%)
Gemcabene	Active ingredient	151.00	93.70
Ethylcellulose	Film coating agent	5.78	3.60

Castor oil	Plasticiser	0.24	0.15
PVP	Film coating agent	0.32	0.20
Tartaric acid	Stabilising agent	0.80	0.50
Magnesium stearate*	Lubricant	0.42	0.25
Anhydrous colloidal silica	Glidant	0.86	0.53
Talc	Lubricant	1.72	1.07
Total		**161.14**	100.00

Table 16c – Examples Composition of Gemcabene Dose

Ingredient	**Function**	**Composition A3**	
		Composition (mg/capsule)	Centesimal Composition (%)
Gemcabene	Active ingredient	151.00	92.20
Ethylcellulose	Film coating agent	7.52	4.59
Castor oil	Plasticiser	0.64	0.39
PVP	Film coating agent	0.42	0.26
Tartaric acid	Stabilising agent	1.04	0.63
Magnesium stearate*	Lubricant	0.54	0.33
Anhydrous colloidal silica	Glidant	0.88	0.54
Talc	Lubricant	1.74	1.06
Total		**163.78**	100.00

Atorvastatin microbeads

[00239] Atorvastatin crystals are coated using a spray-coating technique in a bottom-spray fluidized bed equipment. The coating solution is prepared by dissolving the coating excipients in hot isopropyl alcohol using a jacketed appropriate vessel equipped with a stirring device. The solution is sprayed at about 75°C onto the atorvastatin granules, in the fluidized bed apparatus. During the process, the solvent is evaporated by the fluidization air stream, allowing the composition to deposit around the granules as a continuous coating membrane, thus forming microparticles.

The atorvastatin microparticles are mixed with the capsule filling excipients in a drum-type blender of appropriate capacity.

[00240] Modified-release atorvastatin batches with different lag times between swallowing and release starting point allowed selection of the targeted release sites. The products are obtained by coating atorvastatin particles with a composition suitable for safe passage through the stomach after swallowing, then allowing release in different gastrointestinal tract segments. The product behavior (resistance in the stomach combined with release in a further specific location of GIT) is based on an association of three components in the coating composition: two hydrophilic methacrylic polymers, with different pH dependent solubilities, and one hydrophobic material. It is inferred that the difference in lag times *in vivo* between the three formulae is determined by the different polymer ratios in the coating composition. Examples of compositions for atorvastatin microbead prototypes are indicated in Tables 17a – 17c. Different ratios of combinations of film coating agents insure the pH modulation from 6.5 to 7.5. Examples of w/w ratios between the two coating agents are described in Table 18.

Table 17a – Examples of Composition of Atorvastatin Microbead Prototypes

Ingredient	**Function**	**Composition B1 (triggered pH 6)**		**Composition B2 (triggered pH 6.5)**	
		mg/ capsule	**%**	**mg/ capsule**	**%**
Atorvastatin	Active substance	20.50	82.07	20.50	82.80
Methacrylic Acid Copolymer type C (Eudragit® L100-55)	Film coating agent	2.12	8.49	2.00	8.08

Methacrylic Acid Copolymer type B (Eudragit® S100)	Film coating agent	0.42	1.68	1.00	4.04
Hydrogenated Cottonseed Oil (Lubritab®)	Coating agent	1.70	6.80	1.00	4.04
Magnesium stearate*	Lubricant	0.12	0.48	0.13	0.52
Colloidal Silicon Dioxide	Glidant	0.12	0.48	0.13	0.52
Total		**24.98**	**100.00**	**24.76**	**100.00**

Table 17b – Examples of Composition of Atorvastatin Microbead Prototypes

Ingredient	**Function**	**Composition B3 (triggered pH 7)**		**Composition B4 (triggered pH 7)**	
		mg/ capsule	**%**	**mg/ capsule**	**%**
Atorvastatin	Active substance	20.50	79.58	20.50	78.97
Methacrylic Acid Copolymer type C (Eudragit® L100-55)	Film coating agent	1.00	3.88	0.80	3.08
Methacrylic Acid Copolymer type B (Eudragit® S100)	Film coating agent	2.00	7.77	2.40	9.24
Hydrogenated Cottonseed Oil (Lubritab®)	Coating agent	2.00	7.77	2.00	7.71
Magnesium stearate*	Lubricant	0.13	0.50	0.13	0.50
Colloidal Silicon Dioxide	Glidant	0.13	0.50	0.13	0.50
Total		**25.76**	**100.00**	**25.96**	**100.00**

Table 17c – Examples of Composition of Atorvastatin Microbead Prototypes

Ingredient	Function	Composition B5 (triggered pH 7)	
		mg/ capsule	%
Atorvastatin	Active substance	20.50	79.58
Methacrylic Acid Copolymer type C (Eudragit® L100-55)	Film coating agent	0.25	0.97
Methacrylic Acid Copolymer type B (Eudragit® S100)	Film coating agent	2.75	10.68
Hydrogenated Cottonseed Oil (Lubritab®)	Coating agent	2.00	7.77
Magnesium stearate*	Lubricant	0.13	0.50
Colloidal Silicon Dioxide	Glidant	0.13	0.50
Total		**25.76**	**100.00**

Table 18 – Examples of Mass Ratios of Enteric Coating Components for Atorvastatin Microbead Prototypes

Enteric coating	Dissolution pH	B1	B2	B3	B4	B5
Methacrylic Acid Copolymer type C (Eudragit® L100-55)	6	5	2	1	1	1

Methacrylic Acid Copolymer type B (Eudragit® S100)	7	1	1	2	4	10

Encapsulation:

Gemcabene and atorvastatin blends prepared as described above are combined in a fixed dose combination, and the mixture is filled into hard gelatin capsules.

OTHER EMBODIMENTS

[00241] All publications and patents referred to in this disclosure are incorporated herein by reference to the same extent as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Should the meaning of the terms in any of the patents or publications incorporated by reference conflict with the meaning of the terms bused in this disclosure, the meaning of the terms in this disclosure are intended to be controlling. Furthermore, the foregoing discussion discloses and describes merely exemplary embodiments of the present invention. One skilled in the art will readily recognize from such discussion and from the accompanying drawings and claims, that various changes, modifications and variations can be made therein without departing from the spirit and scope of the invention as defined in the following claims.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition in the form of a tablet-in-capsule, wherein the pharmaceutical composition comprises

from about 1 mg to about 80 mg of a statin or a pharmaceutically acceptable salt thereof;

from about 50 mg to about 900 mg of gemcabene or a pharmaceutically acceptable salt thereof; and optionally

from about 5 mg to about 100 mg of the third API or a pharmaceutically acceptable salt thereof; and

one or more excipients selected from a diluent, a disintegrant, a wetting agent, a stabilizing agent, a plasticizer, a coating agent, a film coating agent, a binder, a glidant, a lubricant, or any combination thereof.

2. The pharmaceutical composition of claim 1, wherein the composition comprises:

a. a tablet comprising from about 1 mg to about 80 mg of a statin or a pharmaceutically acceptable salt thereof; and
b. a capsule comprising from about 50 mg to about 900 mg of gemcabene or a pharmaceutically acceptable salt thereof,

wherein the tablet comprising a statin, and the gemcabene are both encompassed inside the capsule.

3. The pharmaceutical composition of any of claims 1-2, wherein the statin is a HMG-CoA reductase inhibitor.

4. The pharmaceutical composition of any of claims 1-3, wherein the statin is selected from the group consisting of atorvastatin, simvastatin, pravastatin, rosuvastatin, fluvastatin, lovastatin, pitavastatin.

5. The pharmaceutical composition of any of claims 1-4, wherein the statin is atorvastatin.

6. The pharmaceutical composition of any of claims 1-5, wherein the statin is atorvastatin calcium.

7. The pharmaceutical composition of any of claims 1-6, wherein the gemcabene is gemcabene calcium.

8. The pharmaceutical composition of any of claims 1-7, wherein the gemcabene is formulated as an immediate release formulation.

9. The pharmaceutical composition of any of claims 1-8, wherein the atorvastatin is formulated as a delayed release formulation.

10. The pharmaceutical composition of any of claims 1-9, wherein the atorvastatin formulation does not allow release of atorvastatin until after the medicament passes the stomach.

11. The pharmaceutical composition of any of claims 1-10, wherein the capsule is filled with gemcabene microparticles nesting an atorvastatin calcium tablet, said tablet being comprised of

(i) a core comprised of about 10 to about 80% atorvastatin calcium, about 15 to about 12% lactose monohydrate, about 10 to about 25% microcrystalline cellulose, 0 to about 10% polyvinylpyrrolidone, 0 to about 10% croscaramellose sodium, 0 to about 10% magnesium stearate;

(ii) a subcoat barrier of about 1 to about 5% weight gain relative to the core eight comprising a suitable excipient such as Opadry or mixtures of suitable excipients; and

(iii) an enteric coating composition applied at about 2 to about 15% weight relative to the core weight, comprised of methacrylic acid, methyl acrylate, methyl methacrylate copolymer of about 0% to about 10%, methacrylic acid copolymer type C of about 10% to about 0%, and triethyl citrate of about 0% to about 2%.

12. The pharmaceutical composition of claim 11, wherein the gemcabene microparticals comprise:

a. About 48 to about 50 wt% gemcabene;
b. About 24 to about 26 wt% Lactose Monohydrate;
c. About 1.5 to about 2.5 wt% Hydroxypropylcellulose;
d. About 19 to about 21 wt% Microcrystalline Cellulose ;
e. About 2 to about 4 wt% Croscarmellose Sodium; and
f. About 0.4 to about 0.6 wt% Magnesium stearate.

13. The pharmaceutical composition of claim 11, wherein the atorvastatin calcium tablet core comprises:

a. about 13 to about 14 wt% atorvastatin calcium;
b. about 39 to about 41 wt% lactose monohydrate;
c. about 22 to about 23 wt% calcium carbonate
d. about 18 to about 20 wt% microcrystalline cellulose;
e. about 1.5 to about 2.5 wt% polyvinylpyrrolidone;
f. about 0.2 to about 0.3 wt% polysorbate 80;
g. about 2 to about 3 wt% croscaramellose sodium; and
h. about 0.3 to about 0.5 wt% magnesium stearate.

14. A pharmaceutical composition comprising:

a) a combination of two APIs selected from the group consisting of a statin and gemcabene; and

b) optionally one or more additional APIs

wherein the combination of the two APIs comprises from about 0.1 wt% to about 61.5 wt% of a statin or a pharmaceutically acceptable salt thereof by weight of the combination; and

from about 38.5 wt% to about 99.9 wt% of gemcabene or a pharmaceutically acceptable salt thereof by weight of the combination.

15. A pharmaceutical composition comprising:

a) a combination of two APIs selected from the group consisting of a statin and gemcabene; and

b) optionally one or more additional APIs

wherein the combination of the two APIs comprises from about 2 wt% to about 35 wt% of a statin or a pharmaceutically acceptable salt thereof by weight of the combination; and

from about 65 wt% to about 98 wt% of gemcabene or a pharmaceutically acceptable salt thereof by weight of the combination.

16. A pharmaceutical composition comprising:

a) a combination of two APIs selected from the group consisting of a statin and gemcabene; and

b) optionally one or more additional APIs

wherein the combination of the two APIs comprises from about 2 wt% to about 21 wt% of a statin or a pharmaceutically acceptable salt thereof by weight of the combination; and

from about 79 wt% to about 98 wt% of gemcabene or a pharmaceutically acceptable salt thereof by weight of the combination.

17. The pharmaceutical composition of any one of claims 14-16, wherein the statin is atorvastatin, simvastatin, pravastatin, rosuvastatin, fluvastatin, lovastatin, pitavastatin or any pharmaceutically acceptable salts thereof.

18. The pharmaceutical composition of any one of claims 14-17, wherein the statin is atorvastatin calcium.

19. The pharmaceutical composition of any one of claims 14-18, wherein the gemcabene is gemcabene calcium.

20. The pharmaceutical composition of claim 19, wherein the statin and the gemcabene are independently formulated and the independently formulated pharmaceutical compositions of the statin and gemcabene are comprised in a container.

21. The pharmaceutical composition of claim 20, wherein the statin and the gemcabene are independently formulated, and the independently formulated pharmaceutical compositions of the statin and gemcabene are comprised in a capsule.

22. The pharmaceutical composition of any one of claims 19-21, wherein the pharmaceutical composition comprises a third API and the statin, gemcabene and the third API are comprised in a container or kit.

23. The pharmaceutical composition of claim 22, wherein container is a capsule.

24. The pharmaceutical composition of claim 22, wherein the pharmaceutical composition is in the form of a tablet.

25. The pharmaceutical composition of claim 22, where in the pharmaceutical composition comprises a third API.

26. The pharmaceutical composition of claim 25, where in the pharmaceutical composition the third API is ezetimibe immediate release.

27. The pharmaceutical composition of claim 26, where in the pharmaceutical composition the third API is ezetimibe modified release.

28. The pharmaceutical composition of claim 27, where in the pharmaceutical composition the third API is ezetimibe slow and extended release.

29. The pharmaceutical composition of claim 24 or claim 25, wherein the formulation comprises one or more excipients selected from a diluent, a disintegrant, a film coating agent, a plasticizer, a wetting agent, a binder, a glidant, a lubricant, a stabilizing agent, or any combination thereof.

30. The tablet of claim 29, wherein the pharmaceutical composition comprises a binder wherein the binder comprises microcrystalline cellulose, dibasic calcium phosphate, sucrose, corn starch, polyvinylpyrridone, hydroxyporopyl cellulose, hydroxymethyl cellulose, or any combination thereof.

31. The pharmaceutical composition of claim 29 or 30, wherein the tablet comprises a disintegrant and the disintegrant comprises sodium croscarmellose, sodium starch glycolate, or any combination thereof.

32. The pharmaceutical composition of any one of claims 29-31, wherein the tablet comprises a lubricant and the lubricant comprises magnesium stearate stearic acid, hydrogenated oil, sodium stearyl fumarate, or any combination thereof.

33. The pharmaceutical composition of any one of claims 14-32 wherein the pharmaceutical composition comprises from about 1 mg to about 80 mg of the statin and from about 50 mg to about 900 mg of gemcabene.

34. The pharmaceutical composition of claim 33, wherein the pharmaceutical composition comprises from about 10 mg to about 80 mg of the statin and from about 50 mg to about 600 mg of gemcabene.

35. The pharmaceutical composition of claim 34 wherein the pharmaceutical composition comprises from about 10 mg to about 40 mg of the statin and from about 150 mg to about 450 mg of gemcabene.

36. The pharmaceutical composition of claim 35, wherein the pharmaceutical composition comprises from about 10 mg to about 40 mg of the statin and from about 150 mg to about 300 mg of gemcabene.

37. The pharmaceutical composition of any one of claims 19-36, wherein the statin is atorvastatin calcium.

38. The pharmaceutical composition of any one of claims 19-37, wherein the gemcabene is gemcabene calcium.

39. The pharmaceutical composition of any one of the claims 19-38 where each component of the combination is delivered in the same compartment of the digestive tract.

40. The pharmaceutical composition of any one of the claims 14-39 where each component of the combination is delivered in different compartments of the digestive tract.

41. A pharmaceutical composition comprising

from about 1 mg to about 80 mg of a statin or a pharmaceutically acceptable salt thereof;

from about 50 mg to about 900 mg of gemcabene or a pharmaceutically acceptable salt thereof; and optionally

from about 0.25 mg to about 500 mg of a third API or a pharmaceutically acceptable salt thereof; and

one or more excipients selected from a diluent, a disintegrant, a wetting agent, a binder, a glidant, a lubricant, a film coating agent, a coating agent, a plasticizer, or any combination thereof.

42. A pharmaceutical composition in the form of a capsule, wherein the pharmaceutical composition comprises

from about 1 mg to about 80 mg of a statin or a pharmaceutically acceptable salt thereof;

from about 50 mg to about 900 mg of gemcabene or a pharmaceutically acceptable salt thereof; and optionally

from about 0.25 mg to about 500 mg of the third API or a pharmaceutically acceptable salt thereof; and

one or more excipients selected from a diluent, a disintegrant, a wetting agent, a stabilizing agent, a plasticizer, a coating agent, a film coating agent, a binder, a glidant, a lubricant, or any combination thereof.

43. The pharmaceutical composition of claim 42 wherein the statin is in the form of a plurality of first particles in a formulation comprising one or more excipients selected from a diluent, a disintegrant, a wetting agent, a stabilizing agent, a plasticizer, a coating agent, a film coating agent, a binder, a glidant, a lubricant, or any combination thereof, and the gemcabene is in the form of a plurality of second particles in a formulation comprising one or more excipients selected from a diluent, a disintegrant, a wetting agent, a stabilizing agent, a plasticizer, a coating agent, a film coating agent, a binder, a glidant, a lubricant, or any combination thereof, and the optional API is in the form of a plurality of third particles in a formulation comprising one or more excipients selected from a diluent, a disintegrant, a wetting agent, a stabilizing agent, a plasticizer, a coating agent, a film coating agent, a binder, a glidant, a lubricant, or any combination thereof.

44. A pharmaceutical composition in the form of a tablet, wherein the pharmaceutical composition comprises

from about 1 mg to about 80 mg of a statin or a pharmaceutically acceptable salt thereof;

from about 50 mg to about 900 mg of gemcabene or a pharmaceutically acceptable salt thereof; and

from about 0.25 mg to about 500 mg of the third API or a pharmaceutically acceptable salt thereof; and

one or more excipients selected from a diluent, a disintegrant, a wetting agent, a binder, a glidant, a lubricant, a stabilizing agent, a plasticizer, a coating agent, a film coating agent, or any combination thereof.

45. The pharmaceutical composition of any one of claims 41-44, where the statin, gemcabene, and third API are released in different compartments of the digestive tract.

46. The pharmaceutical composition of any one of claims 41-44, wherein third API is ezetimibe.

47. The pharmaceutical composition of any one of claims 41-46, wherein the pharmaceutical composition comprises from about 10 mg to about 80 mg of the statin and from about 50 mg to about 900 mg of the gemcabene.

48. The pharmaceutical composition of claim 47, wherein the pharmaceutical composition comprises from about 10 mg to about 40 mg of the statin and from about 50 to about 600 mg of the gemcabene.

49. The pharmaceutical composition of claim 47, wherein the pharmaceutical composition comprises from about 10 mg to about 40 mg of the statin and from about 50 to about 450 mg of the gemcabene.

50. The pharmaceutical composition of claim 47, wherein the pharmaceutical composition comprises from about 10 mg to about 40 mg of the statin and from about 50 to about 300 mg of the gemcabene

51. The pharmaceutical composition of any one of claims 41-50, wherein the statin is atorvastatin, simvastatin, pravastatin, rosuvastatin, fluvastatin, lovastatin, pitavastatin or any pharmaceutically acceptable salt thereof.

52. The pharmaceutical composition of any one of claims 41-51, wherein the disintegrant comprises sodium croscarmellose, sodium starch glycolate, or any combination thereof.

53. The pharmaceutical composition of any one of claims 41-52, wherein the lubricant comprises magnesium stearate stearic acid, hydrogenated oil, sodium stearyl fumarate, or any combination thereof.

54. The pharmaceutical composition of claim 53, wherein the statin is the calcium salt of atorvastatin.

55. The pharmaceutical composition of claim 53 or claim 54, wherein the gemcabene is the calcium salt of gemcabene.

56. The pharmaceutical composition of claim 55, further comprising calcium carbonate, potassium carbonate, or a combination thereof.

57. The pharmaceutical composition of any one of claims 19-21, wherein the independently formulated pharmaceutical composition of the statin comprises single tablet, and the independently formulated pharmaceutical composition of the gemcabene comprises a powder formulation.

58. The pharmaceutical composition of claim 57, wherein the powder formulation of gemcabene is an immediate release formulation.

59. The pharmaceutical composition of claim 57 or claim 58, wherein the tablet formulation of the statin is a delayed release formulation.

60. The pharmaceutical composition of any one of claims 57-59, wherein the tablet formulation of the statin further comprises an enteric coating on the tablet.

61. The pharmaceutical composition of any one of claims 57-60, wherein the pharmaceutical composition is contained within a capsule.

62. The pharmaceutical composition of any one of claims 57-61, wherein the pharmaceutical composition comprises from about 1 mg to about 80 mg of the statin and from about 50 mg to about 900 mg of gemcabene.

63. The pharmaceutical composition of claims 57-62, wherein the pharmaceutical composition comprises from about 10 mg to about 60 mg of the statin and from about 150 mg to about 600 mg of gemcabene.

64. The pharmaceutical composition of claims 57-63, wherein the pharmaceutical composition comprises from about 10 mg to about 40 mg of the statin and from about 150 mg to about 450 mg of gemcabene.

65. The pharmaceutical composition of claims 57-64, wherein the pharmaceutical composition comprises from about 10 mg to about 40 mg of the statin and from about 150 mg to about 300 mg of gemcabene.

66. The pharmaceutical composition of any one of claims 57-65, the statin is atorvastatin calcium.

67. The pharmaceutical composition of any one of claims 57-66, wherein the gemcabene is gemcabene calcium.

68. The pharmaceutical composition of any one of claims 57-67, where each component of the combination is delivered in the same compartment of the digestive tract.

69. The pharmaceutical composition of any one of the claims 57-68 where each component of the combination is delivered in different compartments of the digestive tract.

70. A kit comprising

a single dose formulation comprising from about 10 mg to about 40 mg of a statin and from about 50 mg to about 600 mg of gemcabene; and

instructions for the use thereof.

71. The kit of claim 70, wherein the statin is atorvastatin, simvastatin, pravastatin, rosuvastatin, fluvastatin, lovastatin, pitavastatin or any pharmaceutically acceptable salts thereof.

72. The kit of claim 71, wherein the statin is atorvastatin or a pharmaceutically acceptable salt thereof.

73. The kit of any one of claims 70-72, wherein the single dose formulation is in the form of a tablet or a capsule.

74. The kit of claim 73, wherein the tablet comprises one or more excipients selected from a diluent, a disintegrant, a wetting agent, a binder, a glidant, a lubricant, or any combination thereof.

75. The kit of claim 74, wherein the binder comprises microcrystalline cellulose, dibasic calcium phosphate, sucrose, corn starch, polyvinylpyrridone, hydroxypropyl cellulose, hydroxymethyl cellulose, or any combination thereof.

76. The kit of either of claims 74 or 75, wherein the disintegrant comprises sodium croscarmellose, sodium starch glycolate, or any combination thereof.

77. The kit of any one of claims 74-76, wherein the lubricant comprises magnesium stearate stearic acid, hydrogenated oil, sodium stearyl fumarate, or any combination thereof.

78. The kit of any one of claims 74-77, wherein the statin is the calcium salt of atorvastatin.

79. The kit of any one of claims 74-78, wherein the gemcabene is a calcium salt of gemcabene.

80. The kit of claim 79, wherein the tablet further comprises calcium carbonate, potassium carbonate, or a combination thereof.

81. A method for reducing musculoskeletal discomfort in a patient being administered a statin-gemcabene combination formulation, comprising administering to the patient a pharmaceutical composition of any one of claims 1-69 instead of a formulation comprising a more immediate release composition of the statin.

82. The method of claim 81, wherein the musculoskeletal discomfort in a patient being administered a statin is due to myalgia.

83. The method of claim 81, wherein the musculoskeletal discomfort in a patient being administered a statin is due to myositis.

84. The method of any one of claims 81-83, wherein the musculoskeletal discomfort in a patient being administered a statin is an adverse event arising from the conversion of the acid form of the statin into the lactone form of the statin.

85. The method of any one of claims 81-84, wherein the pharmaceutical composition of any one of claims 1-63 reduces the amount of lactone form of a statin compared to a formulation comprising a more immediate release composition of the statin.

86. A modified release atorvastatin and gemcabene fixed dose formulation in the form of any of their salts with a lag phase before atorvastatin delivery suitable for oral once a day administration for treating lipid disorders without causing drug-induced hepatotoxicity and musculoskeletal disorders.

87. A modified release atorvastatin and gemcabene fixed dose combination formulation or any of its salts with a lag phase before atorvastatin delivery suitable for oral once a day administration for treating lipid disorders where the atorvastatin component exhibits a release pattern characterized by two phases, a lag phase and an extended release phase;

wherein the lag phase is characterized in that less than 10% of the absorbable atorvastatin dose administered is absorbed between about 0.5 and about 1.5 hours following ingestion;

wherein the extended release phase being characterized in that more than about 20% but less than 78% of the absorbable atorvastatin administered being absorbed between about 1.5 and 4 hours following ingestion; and

wherein less than 90% of the absorbable atorvastatin administered being absorbed by 9 hours following ingestion.

88. A gemcabene microparticle having a coating ratio of about 2.5% to about 15%, wherein the amount of gemcabene is about 80% to about 98%, the amount of ethylcellulose is about 1% to about 10%, the amount of castor oil is about 0.01% to about 1.5%, the amount of povidone is about 0.05% to about 1%, the amount of tartaric acid is about 0% to about 1%, and the amount of magnesium stearate is about 0% to about 2%.

89. An atorvastatin microparticle having a coating ratio of about 10% to about 30%, wherein the amount of atorvastatin is about 60% to about 95%, the amount of methacrylic acid copolymer type C (L100-55) is about 0% to about 15%, the amount of methacrylic acid copolymer type B (S100) is about 0% to about 15%, and the amount of cottonseed oil is about 0% to about 15%.

90. A pharmaceutical formulation comprised of a capsule filled with gemcabene microparticles and an atorvastatin calcium microtablet, said microtablet being comprised of (i) a core comprised of about 10 to about 80% atorvastatin calcium, about 15 to about 12% lactose monohydrate, about 10 to about 25% microcrystalline cellulose, about 0 to about 10% polyvinylpyrrolidone, about 0 to about 10% croscaramellose sodium, about 0 to about 10% magnesium stearate; (ii) a subcoat barrier of about 1 to about 5% weight gain relative to the core eight comprising a suitable excipient such as Opadry or mixtures of suitable excipients; (iii) an enteric coating composition applied at about 2 to about 15% weight relative to the core weight, comprised of methacrylic acid, methyl acrylate, methyl methacrylate copolymer of about 0% to about 10%, methacrylic acid copolymer type C of about 10% to about 0%, and triethyl citrate of about 0% to about 2%.

91. A pharmaceutical composition, comprising gemcabene calcium from about 50 mg to about 900 mg, and atorvastatin calcium from about 5 mg to about 80 mg, and a pharmaceutically acceptable carrier, wherein said gemcabene is released about 50% at about 4 to about 6 hours with a Tmax at about 1 to about 2 hours, and wherein said atorvastatin is released from the composition with a lag time of about 1.5 to about 4 hours.

92. A pharmaceutical composition comprising atorvastatin microparticles having a pH-dependent release profile, and gemcabene microparticles having a pH-independent release profile, wherein the atorvastatin microparticles have a reduced capacity to provoke musculoskeletal reactions in a subject, wherein the gemcabene is present in an amount effective to reduce triglycerides and LDL-cholesterol with at least 10% in addition to the effect of atorvastatin alone, and wherein there is a lag time between release of atorvastatin or gemcabene following administration of the composition.

93. Use of the pharmaceutical composition of any one of claims 1-85, for manufacturing of a medicament for treating or preventing a disease or disorder selected from the group consisting of:

a) disorders of lipoprotein metabolism, wherein the disorder is dyslipidemia, dyslipoproteinemia, lipoprotein overproduction or deficiency, elevation of total cholesterol, elevation of low density lipoprotein concentration, elevation of triglyceride concentration, lipid elimination in bile, metabolic disorder, phospholipid elimination in bile, oxysterol elimination in bile, abnormal bile production, or peroxisome proliferator activated receptor-associated disorder;

(b) disorders of glucose metabolism, wherein the disorder is insulin resistance, impaired glucose tolerance, impaired fasting glucose levels in blood, diabetes mellitus, lipodystrophy, central obesity, peripheral lipoatrophy, diabetic nephropathy, diabetic retinopathy, renal disease, or septicemia;

(c) cardiovascular disorders and related vascular disorders, wherein the disorder is atherosclerosis, hypertension, coronary artery disease, myocardial infarction, arrhythmia, atrial fibrillation, heart valve disease, heart failure, cardiomyopathy, myopathy, pericarditis, impotence, or thrombotic disorder;

d) diseases of the liver including NAFLD, NASH, alcoholic steatohepatitis , cirrhosis, inflammation fibrosis, primary biliary cirrhosis;

(e) modulating inflammation markers and/or C-reactive protein and related disorders, wherein the disorder is inflammation, ischemic necrosis, or thrombotic disorder; and

(f) aging, Alzheimer's Disease, Parkinson's disease, pancreatitis, pulmonary disorders, and pancreatitis.

FIG. 1

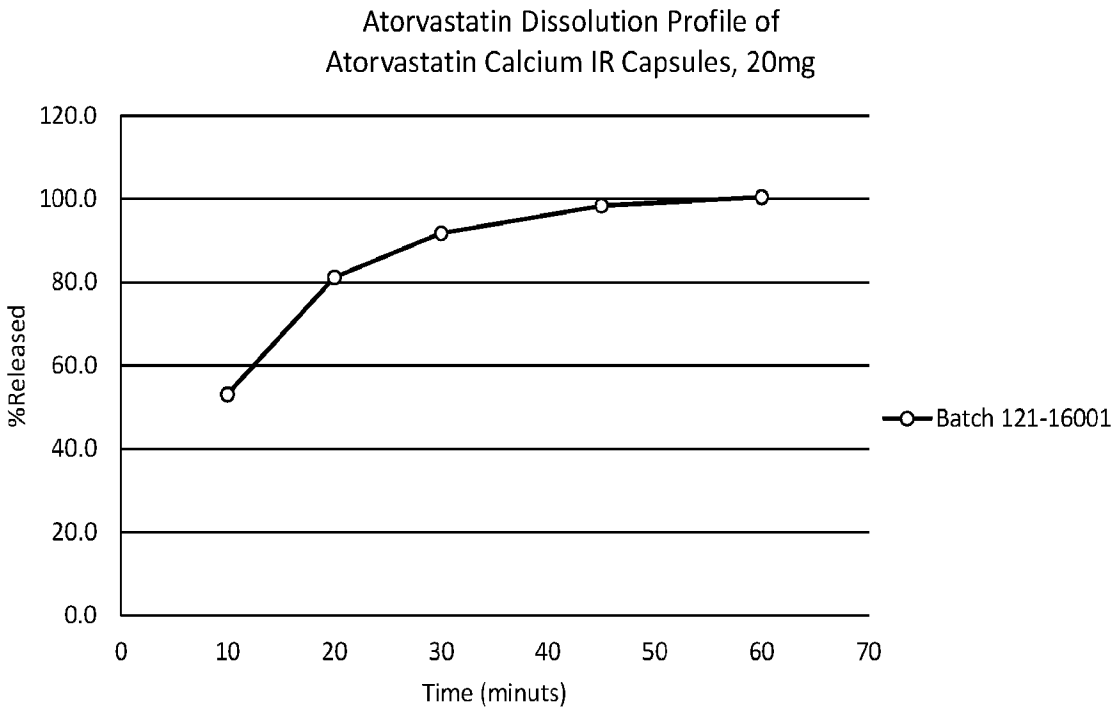

Atorvastatin Dissolution Profile of
Atorvastatin Calcium IR Capsules, 20mg
120.0
100.0
80.0
60.0
40.0
20.0
0.0
%Released
0
10
20
30
40
50
60
70
Time (minuts)
Batch 121-16001

FIG. 2

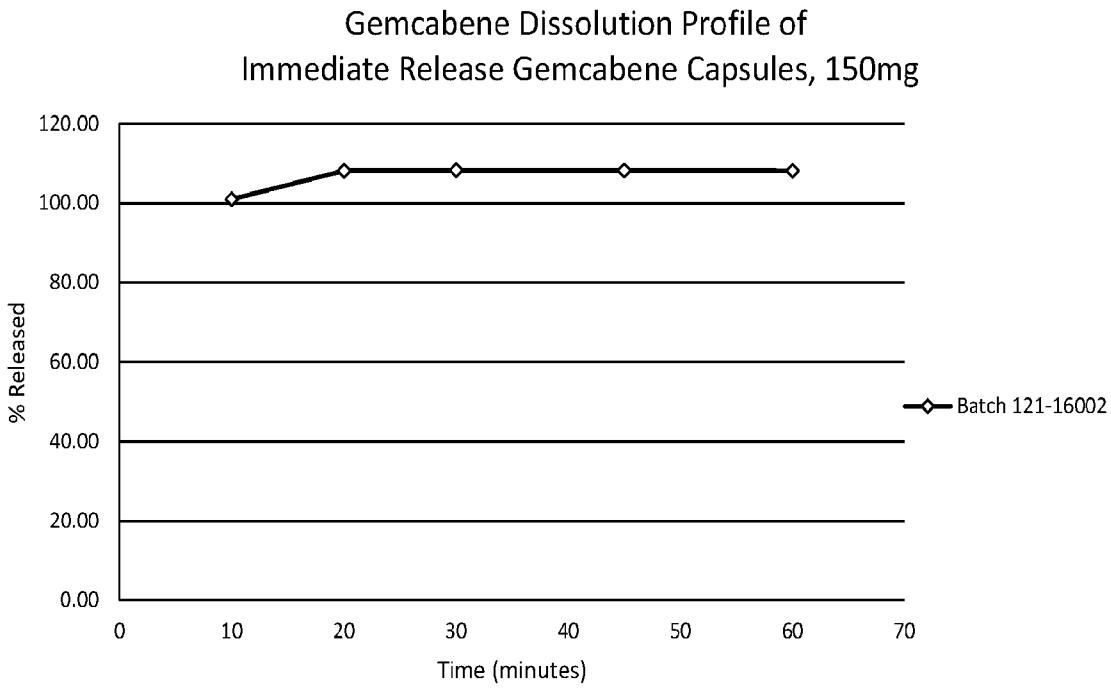

Gemcabene Dissolution Profile of
Immediate Release Gemcabene Capsules, 150mg
120.00
100.00
80.00
60.00
40.00
20.00
0.00
% Released
0
10
20
30
40
50
60
70
Time (minutes)
Batch 121-16002

FIG. 3

Ingredient	Composition Formula 1 (Triggered @pH 5.5)		Composition Formula 2 (Triggered @pH 6.0)		Composition Formula 3[a] (Triggered @pH 6.5)		Composition Formula 4[b] (Triggered @pH 7.0)		Composition Formula 5 (Triggered @pH 7.2)	
	% w/w	mg/Unit Dose	% w/w	mg/Unit Dose	% w/w	mg/Unit Dose	% w/w	mg/Unit Dose	% w/w	mg/Unit Dose
Tablet Core Composition										
Atorvastatin Calcium Trihydrate)	12.10	21.87	12.10	21.87	12.10	21.87	12.10	21.87	12.10	21.87
Calcium Carbonate	19.91	36.0	19.91	36.0	19.91	36.0	19.91	36.0	19.91	36.0
Lactose Monohydrate (Tablettose 70)	35.47	64.13	35.47	64.13	35.47	64.13	35.47	64.13	35.47	64.13
Microcrystalline Cellulose (PH102)	16.59	30.0	16.59	30.0	16.59	30.0	16.59	30.0	16.59	30.0
Polyvinylpyrrolidone (Plasdone K29/32)	1.66	3.0	1.66	3.0	1.66	3.0	1.66	3.0	1.66	3.0
Polysorbate 80	0.22	0.4	0.22	0.4	0.22	0.4	0.22	0.4	0.22	0.4
Croscarmellose Sodium	2.21	4.0	2.21	4.0	2.21	4.0	2.21	4.0	2.21	4.0
Magnesium Stearate, NF	0.33	0.6	0.33	0.6	0.33	0.6	0.33	0.6	0.33	0.6
Sub-Coat (Barrier) Composition (Applied at 3% Weight Gain Relative to Core Weight)										
Opadry Clear (03K19229)	2.65	4.8	2.65	4.8	2.65	4.8	2.65	4.8	2.65	4.8
Enteric Coating Composition (Applied at 10% Weight Gain Relative to Core Weight)										
Methacrylic Acid, Methyl Acrylate, Methyl Methacrylate Polymer (Eudragit FS30D)	—	—	1.88	3.4	2.45	4.422	3.77	6.82	3.71	10.33
Methacrylic Acid Copolymer, Type C (Eudragit L30D55)	3.33	10.0	3.76	6.8	3.39	5.782	3.89	3.42	—	—
Triethyl Citrate, NF	0.55	1.0	0.39	0.7	0.39	0.7	0.39	0.7	0.29	0.52
Talc USP/EP (Luzenac Pharma M)	2.77	5.0	2.82	5.1	2.82	5.1	2.82	5.1	2.85	5.15
Totals	100.0	180.8	100.0	180.8	100.0	180.8	100.0	180.8	100.0	180.8

[a]Atorvastatin Calcium Trihydrate dosed as Atorvastatin based on 99.6% assay (anhydrous basis) and 4.9% water content: 21.87mg Atorvastatin Calcium Trihydrate = 20mg Atorvastatin

[b]Formula 4 was prepared as Batch 121-16005 (Prototype 1) for Example 5

[c]Formula 3 was prepared as Batch 121-16007 (Prototype 2) for Example 6

FIG. 4

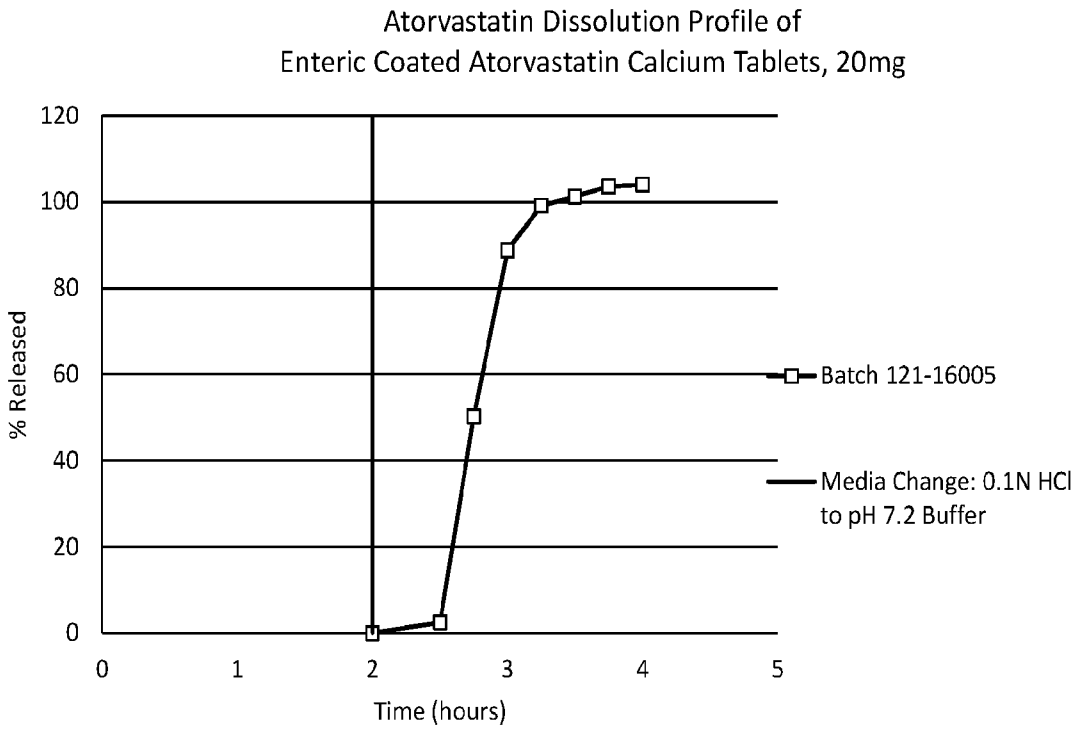

Atorvastatin Dissolution Profile of
Enteric Coated Atorvastatin Calcium Tablets, 20mg
% Released
120
100
80
60
40
20
0
0
1
2
3
4
5
Time (hours)
Batch 121-16005
Media Change: 0.1N HCl
to pH 7.2 Buffer

FIG. 5

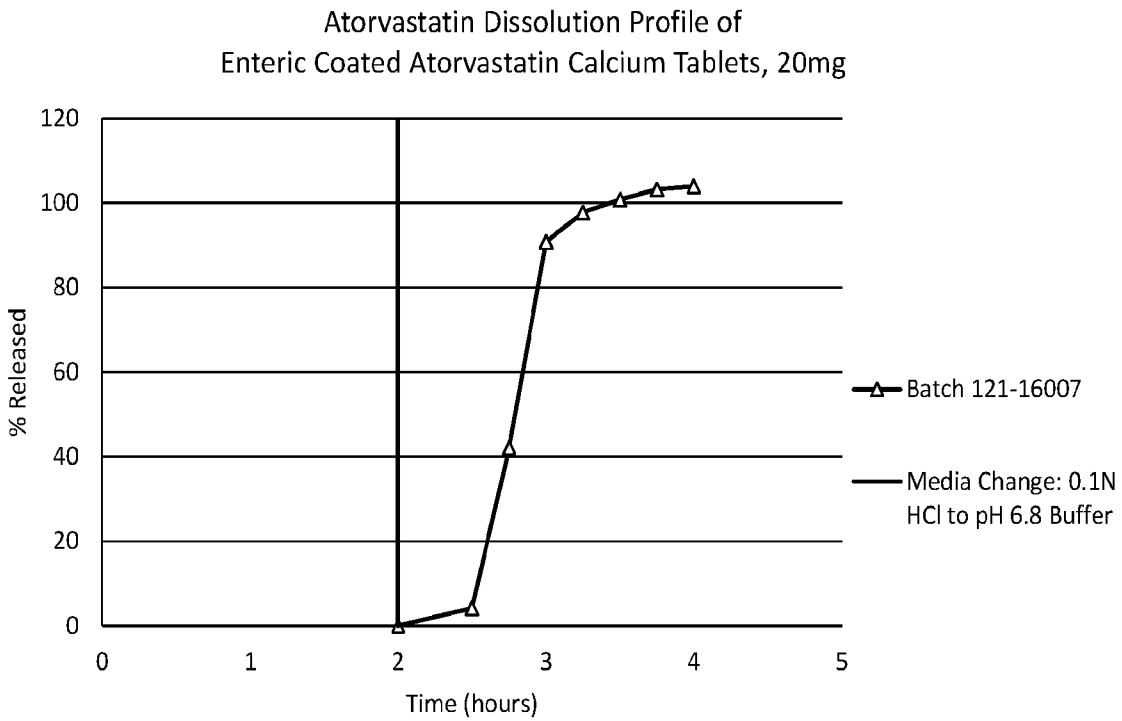

Atorvastatin Dissolution Profile of
Enteric Coated Atorvastatin Calcium Tablets, 20mg
% Released
120
100
80
60
40
20
0
0
1
2
3
4
5
Time (hours)
Batch 121-16007
Media Change: 0.1N HCl to pH 6.8 Buffer

FIG. 6A

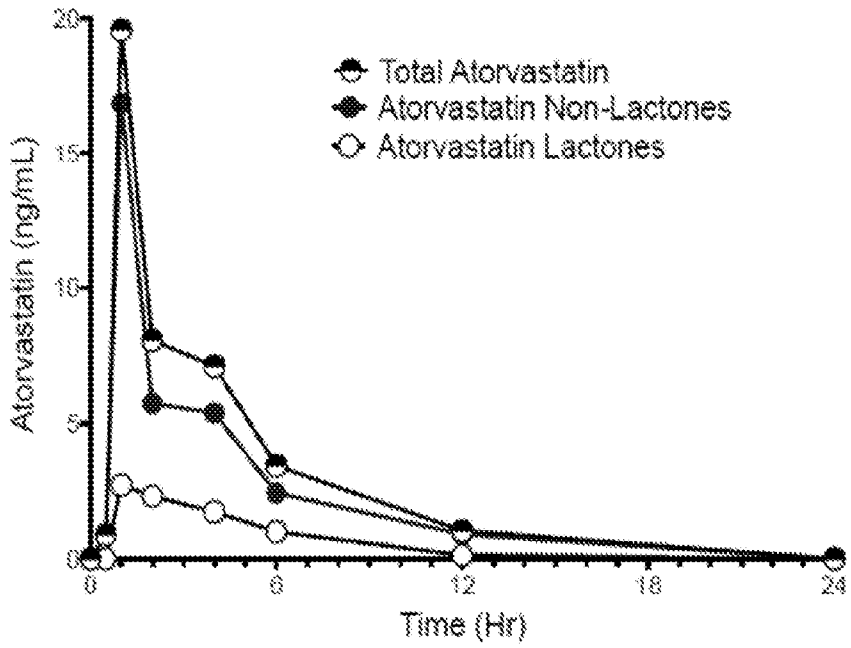

Total Atorvastatin
Atorvastatin Non-Lactones
Atorvastatin Lactones
Atorvastatin (ng/mL)
20
15
10
5
0
0
6
12
18
24
Time (Hr)

FIG. 6B

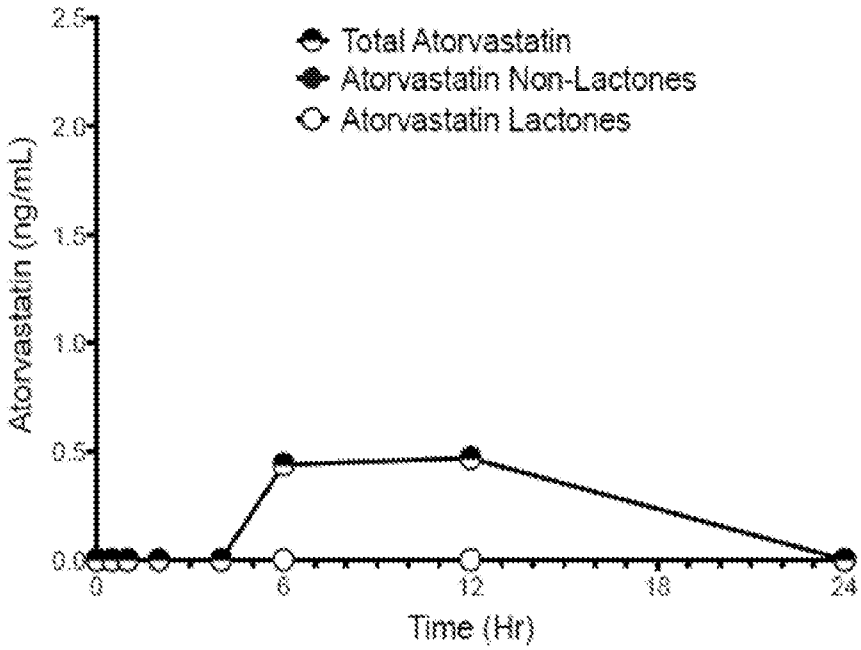

Total Atorvastatin
Atorvastatin Non-Lactones
Atorvastatin Lactones
Atorvastatin (ng/mL)
2.5
2.0
1.5
1.0
0.5
0.0
0
6
12
18
24
Time (Hr)

FIG. 6C

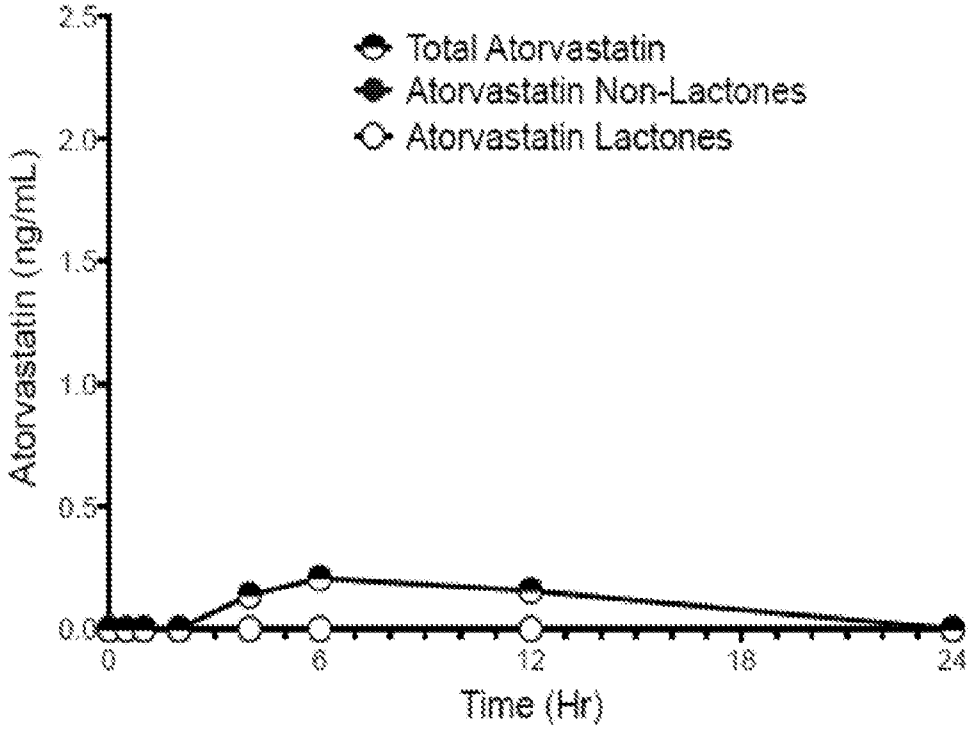

Total Atorvastatin
Atorvastatin Non-Lactones
Atorvastatin Lactones
Atorvastatin (ng/mL)
2.5
2.0
1.5
1.0
0.5
0.0
0
6
12
18
24
Time (Hr)

FIG. 7A

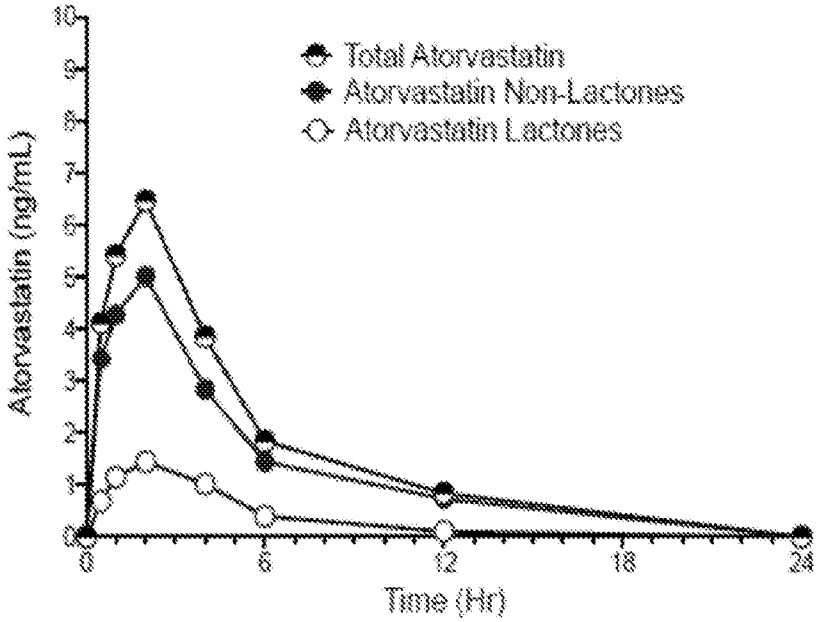

Total Atorvastatin
Atorvastatin Non-Lactones
Atorvastatin Lactones
Atorvastatin (ng/mL)
Time (Hr)
0
6
12
18
24

FIG. 7B

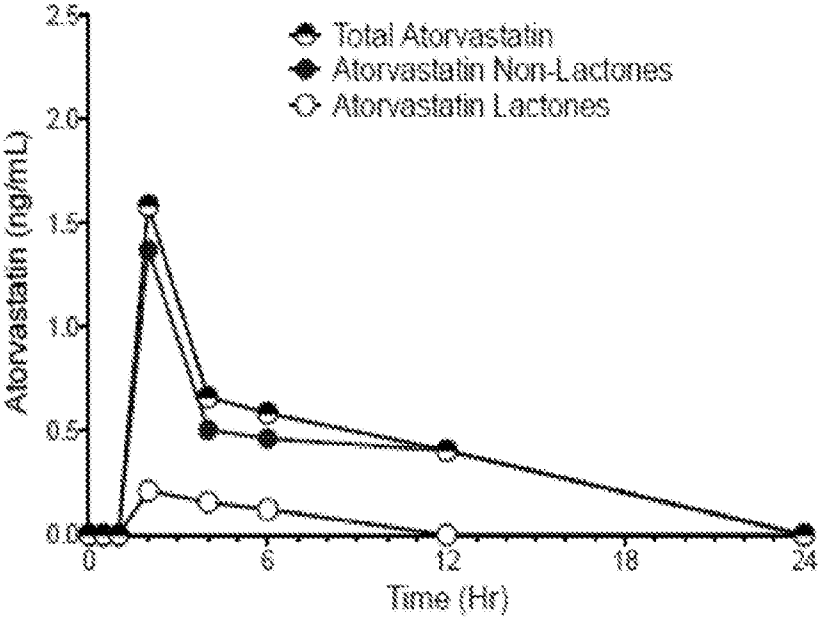

Total Atorvastatin
Atorvastatin Non-Lactones
Atorvastatin Lactones
Atorvastatin (ng/mL)
Time (Hr)
0
6
12
18
24

FIG. 7C

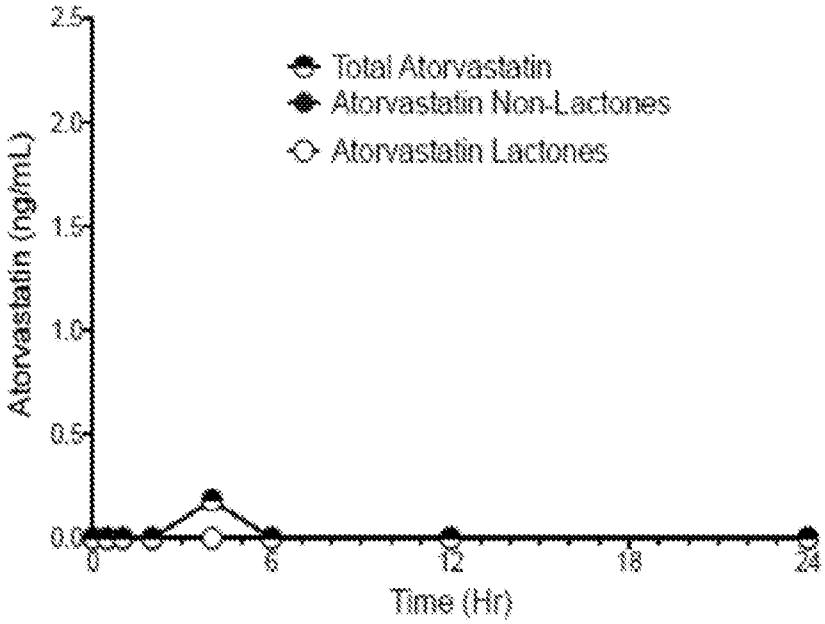
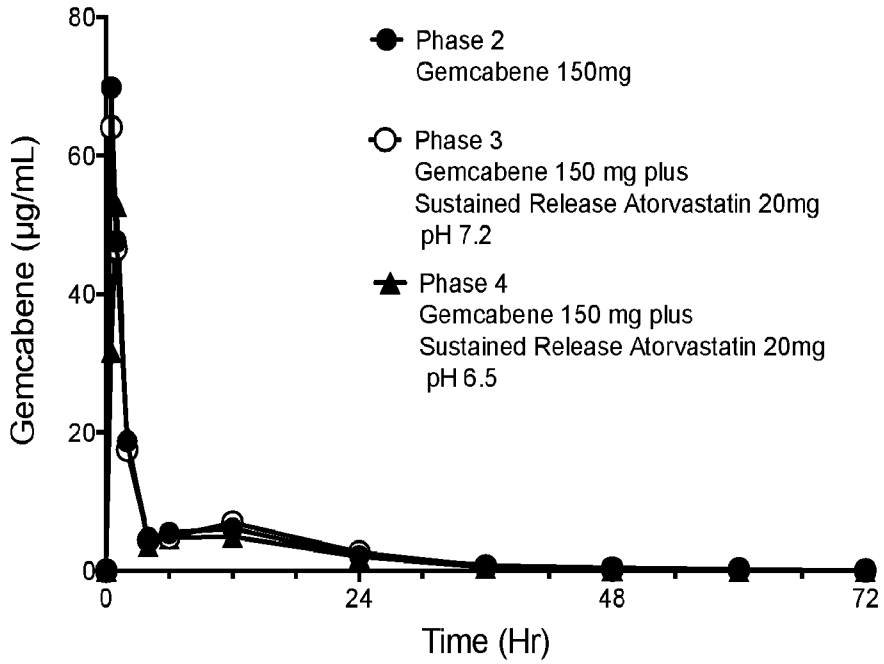

Total Atorvastatin
Atorvastatin Non-Lactones
Atorvastatin Lactones
Atorvastatin (ng/mL)
2.5
2.0
1.5
1.0
0.5
0.0
0
6
12
18
24
Time (Hr)

FIG. 8


Gemcabene (µg/mL)
80
60
40
20
0
0
24
48
72
Time (Hr)
Phase 2
Gemcabene 150mg
Phase 3
Gemcabene 150 mg plus
Sustained Release Atorvastatin 20mg
pH 7.2
Phase 4
Gemcabene 150 mg plus
Sustained Release Atorvastatin 20mg
pH 6.5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/60849

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 9/00 (2017.01)
CPC - A61K9/2077; Y10S514/96; Y10S514/964; A61K9/5084; A61K45/06
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(8): A61K 9/00 (2017.01)
CPC: A61K9/2077; Y10S514/96; Y10S514/964; A61K9/5084; A61K45/06; A61K31/00; A61K47/00; A61K45/00; Y10S514/00; A61K9/00

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)
Pat Base (AU BE BR CA CH CN DE DK EP ES FI FR GB IN JP KR SE TH TW US WO), Google Patent, Google Scholar; Search terms: statin gemcabene atorvastatin microparticle excipient dosage tablet-in capsule HMG-CoA reductase inhibitor release ezetimibe kit instructions calcium carrier lag phase Tmax coat musculoskeletal triglyceride LDL-C enteric

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- A	US 2013/0123354 A1 (CURRIE et al.) 16 May 2013 (16.05.2013) para [0004], [0040], [0042], [0046], [0067], [0074]-[0075], [0077], [0145], [0148], [0167]-[0171], [0177], [0180]; abstract	1-3, 41-43 and 70-75 ---------- 91
X	US 2012/0165411 A1 (BISGAIER) 28 June 2012 (28.06.2012) para [0012], [0063], [0073], [0075]-[0076]	14-17
X ---- Y ---- A	US 2015/0005386 A1 (BISGAIER) 1 January 2015 (01.01.2015) para [0013], [0015], [0051], [0071], [0109]-[0111], [0118], [0120], [0123]-[0133]; example 1; tables 3-4	44 and 46 ---------- 45, 86-87 and 90 ---------- 92
X	US 2010/0015220 A1 (WETTERAU et al.) 21 January 2010 (21.01.2010) para [0057], [0059], [0073], [0148]-[0149], [0159], [0163], [0270], [0310], [0318]; claims 78, 100-103 and 118	89
Y ---- A	US 2009/0220611 A1 (DARGELAS et al.) 3 September 2009 (03.09.2009) para [0004]-[0005], [0018]-[0019], [0025]-[0026], [0035], [0041]-[0047], [0067], [0070], [0074], [0153], [0186], [0206], [0240]-[0241]	45, 86-87 ---------- 91-92
Y	WO 2009/135949 A2 (ATACAMA LABS OY) 12 November 2009 (12.11.2009) pg 2, ln 16-20; pg 3, ln 3-5; pg 6, ln 29-30; pg 7, ln 1-3 and ln 21-28; pg 11, ln 1-8; pg 24, ln 26-34; pg 25; pg 26; pg 27, ln 1-13; pg 43, ln 24-25	88

☒ 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
09 February 2017	13 MAR 2017
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. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/60849

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,133,974 A (PARADISSIS et al.) 28 July 1992 (28.07.1992) col 6, ln 1-8; col 8, ln 4-24 and ln 64-67	88
Y ---- A	US 2012/0164221 A1 (BOVA et al.) 28 June 2012 (28.06.2012) para [0025], [0043], [0046]-[0047], [0066]-[0067]; claim 5	86 ------- 92
Y	US 2009/0220613 A1 (ODIDI et al.) 3 September 2009 (03.09.2009) para [0050], [0100], [0139], [0157], [0161]-[0162], [0167]-[0170]; examples 1-2	90
Y	US 2009/0208539 A1 (PENHASI et al.) 20 August 2009 (20.08.2009) para [0004], [0028], [0075], [0081], [0094], [0098]	90
A	US 2015/0094303 A1 (BACHOVCHIN et al.) 2 April 2015 (02.04.2015) para [0018]-[0020], [0247], [0362]	91

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/60849

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

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

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

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

3. ☒ Claims Nos.: 4-13, 18-40, 47-69, 76-85, 93
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

This International Searching Authority found multiple inventions in this international application, as follows:
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-3, 14-17, 41-46, 70-75 and 91, directed to a pharmaceutical composition comprising gemcabene and a statin; wherein the statin must be between 10 mg to about 40 mg, or 2 wt% to about 21 wt%; and wherein the gemcabene must be between 50 mg to about 600 mg or 79 wt% to about 98 wt%.
Group II: Claims 86-87, directed to a modified release atorvastatin and gemcabene fixed dose formulation.
Group III: Claims 88-90, directed to gemcabene microparticles, atorvastatin microparticles, and their pharmaceutical formulations.
Group IV: Claim 92, directed to a pharmaceutical composition comprising atorvastatin microparticles having a pH-dependent release profile.
The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:
Please see the continuation at the end of this form

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

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

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

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

Remark on Protest

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

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

☒ No protest accompanied the payment of additional search fees.

Continuation of Box III (Lack of Unity)
Special Technical Features:

Group I requires that the pharmaceutical composition has statin between 10 mg to 40 mg, or 2 wt% to 21 wt%; and gemcabene between 50 mg to 600 mg or 79 wt% to 98 wt%, not required by group II-IV.

Group II requires a modified release atorvastatin and gemcabene fixed dose formulation in the form of any of their salts with a lag phase before atorvastatin delivery suitable for oral once a day administration for treating lipid disorders, not required by group I and III-IV.

Group III requires the use of coatings on the particles; methacrylic acid copolymer type C; magnesium stearate; and cellulose, not required by group I-II and IV.

Group IV requires atorvastatin microparticles having a pH-dependent release profile, and gemcabene microparticles having a pH-independent release profile, wherein the atorvastatin microparticles have a reduced capacity to provoke musculoskeletal reactions in a subject, wherein the gemcabene is present in an amount effective to reduce triglycerides and LDL-cholesterol with at least 10% in addition to the effect of atorvastatin alone, and wherein there is a lag time between release of atorvastatin or gemcabene following administration of the composition, not required by group I-III.

Common Technical Features:

Groups I, II, III and IV share the technical feature of a pharmaceutical composition/formulation including a statin and gemcabene. However, these shared technical features do not represent a contribution over prior art, because the shared technical feature is being anticipated by US 2012/0165411 A1 (Bisgaier). Bisgaier teaches a pharmaceutical composition/formulation including a statin and gemcabene (para [0062], [0063]; claims 1, 6 and 9-10; A compound to decrease a subject's risk for developing pancreatitis, where the compound can be gemcabene, and can be administered with an agent, such as statin).

Groups I, II and IV share the technical feature of a pharmaceutical composition/formulation including a statin and gemcabene; lag time/phase and release. However, these shared technical features do not represent a contribution over prior art, because the shared technical feature is being anticipated by US 2015/0283202 A1 (Shailubhai). Shailubhai teaches a pharmaceutical composition/formulation including a statin and gemcabene (para [0145]-[0150]; a chemotherapeutic composition including GCRA peptide, which can be used in combination with gemcabene and atorvastatin); lag time/phase and release (para [0118]; It can be useful to formulate opioid antagonists of this type is a delayed and sustained release formulation such that initial release of the antagonist is in the mid to distal small intestine and/or ascending colon).

Groups I and II share the technical feature of a pharmaceutical composition/formulation including a statin and gemcabene; lag time/phase and release; and hours. However, these shared technical features do not represent a contribution over prior art, because the shared technical feature is being anticipated by Shailubhai. Shailubhai teaches a pharmaceutical composition/formulation including a statin and gemcabene (para [0145]-[0150]; a chemotherapeutic composition including GCRA peptide, which can be used in combination with gemcabene and atorvastatin); lag time/phase and release (para [0118]; It can be useful to formulate opioid antagonists of this type is a delayed and sustained release formulation such that initial release of the antagonist is in the mid to distal small intestine and/or ascending colon); and hours (para [0092]; hours).

Groups I and III share the technical feature of a pharmaceutical composition/formulation including a statin and gemcabene; and excipient. However, these shared technical features do not represent a contribution over prior art, because the shared technical feature is being anticipated by Bisgaier. Bisgaier teaches a pharmaceutical composition/formulation including a statin and gemcabene (para [0062], [0063]; claims 1, 6 and 9-10; A compound to decrease a subject's risk for developing pancreatitis, where the compound can be gemcabene, and can be administered with an agent, such as statin); and excipient (para [0120]; Gemcabene can additionally be formulated with saline and other common excipients for administration by the intravenous route).

Groups III and IV share the technical feature of a pharmaceutical composition/formulation including a statin and gemcabene; and gemcabene microparticles. However, these shared technical features do not represent a contribution over prior art, because the shared technical feature is being anticipated by Shailubhai. Shailubhai teaches a pharmaceutical composition/formulation including a statin and gemcabene (para [0145]-[0150]; a chemotherapeutic composition including GCRA peptide, which can be used in combination with gemcabene and atorvastatin); gemcabene microparticles (para [0036]; the formulation may be in the form of microspheres).

As the shared technical features were known in the art at the time of the invention, they cannot be considered common technical features that would otherwise unify the groups. Therefore, Groups I-IV lack unity under PCT Rule 13.