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(54) **GASTRIC RETENTIVE EXTENDED-RELEASE DOSAGE FORMS COMPRISING COMBINATIONS OF ACETAMINOPHEN AND PHENYLEPHRINE**

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A61P 11/02	(2006.01)

(52) **U.S. Cl.** **424/465**; 424/484; 514/629

(57) **ABSTRACT**

Compositions and methods for the treatment of a mammal suffering from pain and from nasal congestion or ophthalmic disorders are described. More specifically, a dosage form designed for release of acetaminophen and phenylephrine is described, wherein the dosage form provides delivery of the drugs to the upper gastrointestinal tract ("GI") of a mammal for an extended period of time.

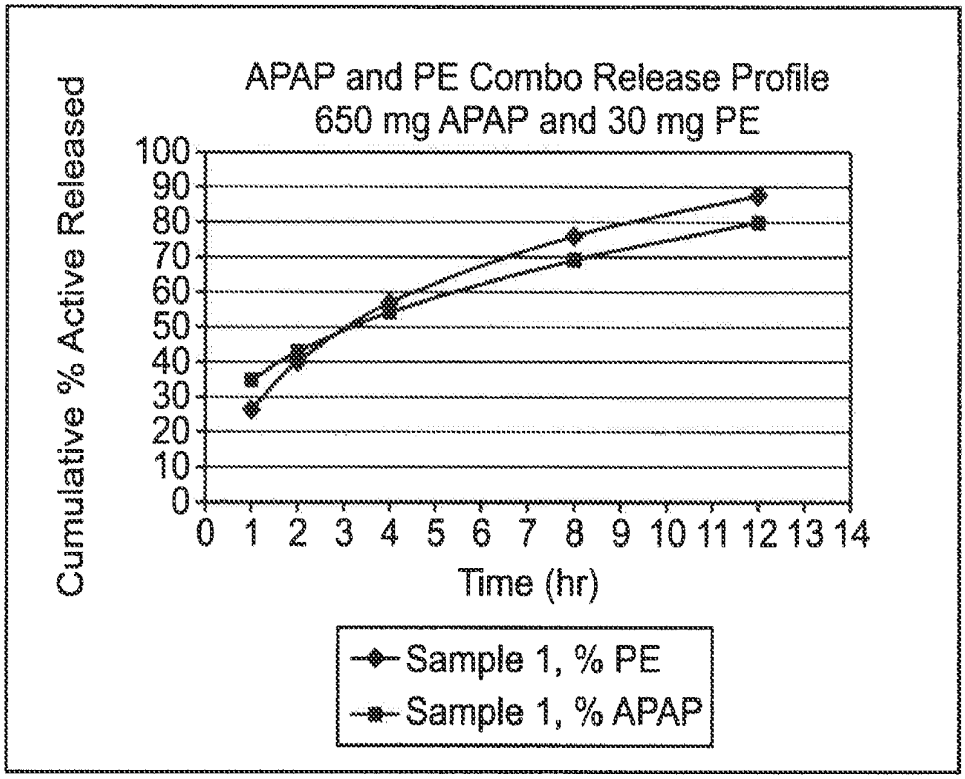
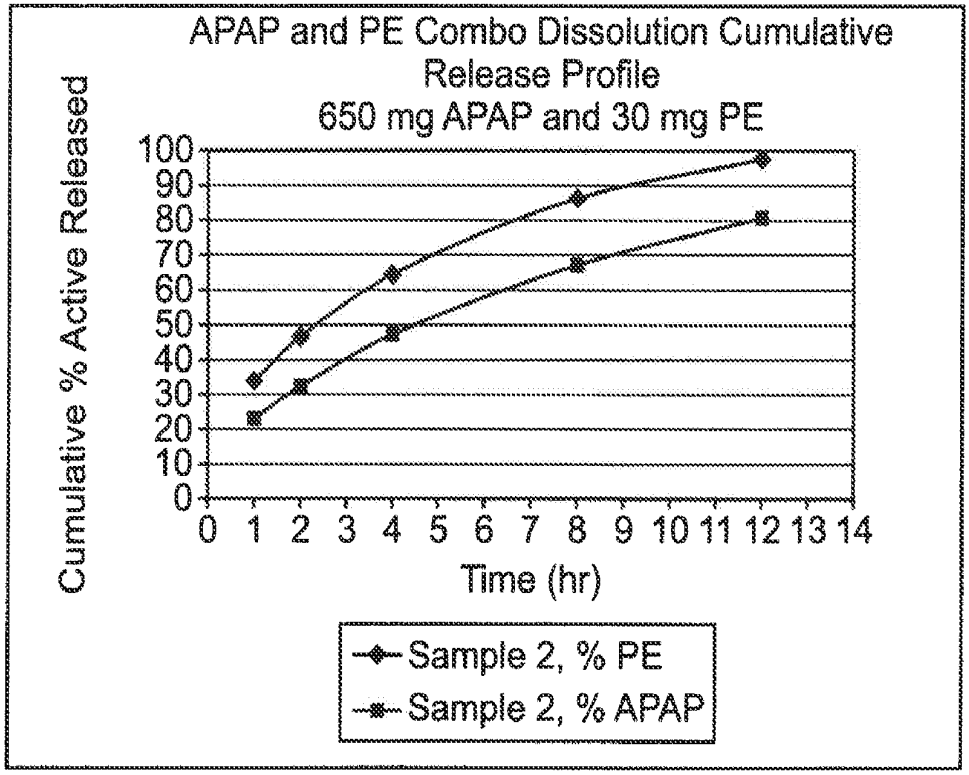

APAP and PE Combo Release Profile
650 mg APAP and 30 mg PE
Cumulative % Active Released
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Time (hr)
Sample 1, % PE
Sample 1, % APAP

FIG. 1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650 mg APAP and 30 mg PE
Cumulative % Active Released
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Time (hr)
Sample 2, % PE
Sample 2, % APAP

FIG. 2

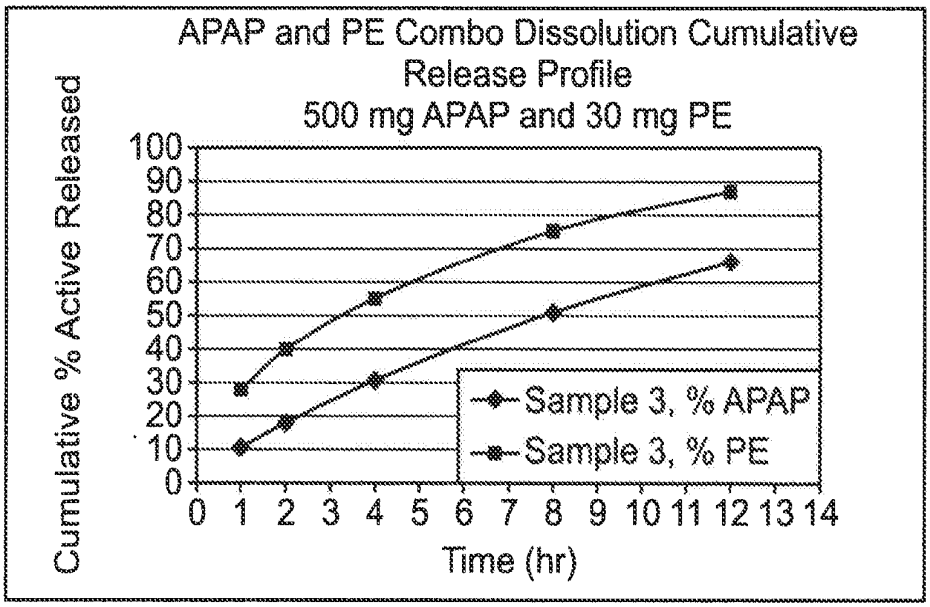
APAP and PE Combo Dissolution Cumulative Release Profile
500 mg APAP and 30 mg PE
Cumulative % Active Released
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Time (hr)
Sample 3, % APAP
Sample 3, % PE

FIG. 3

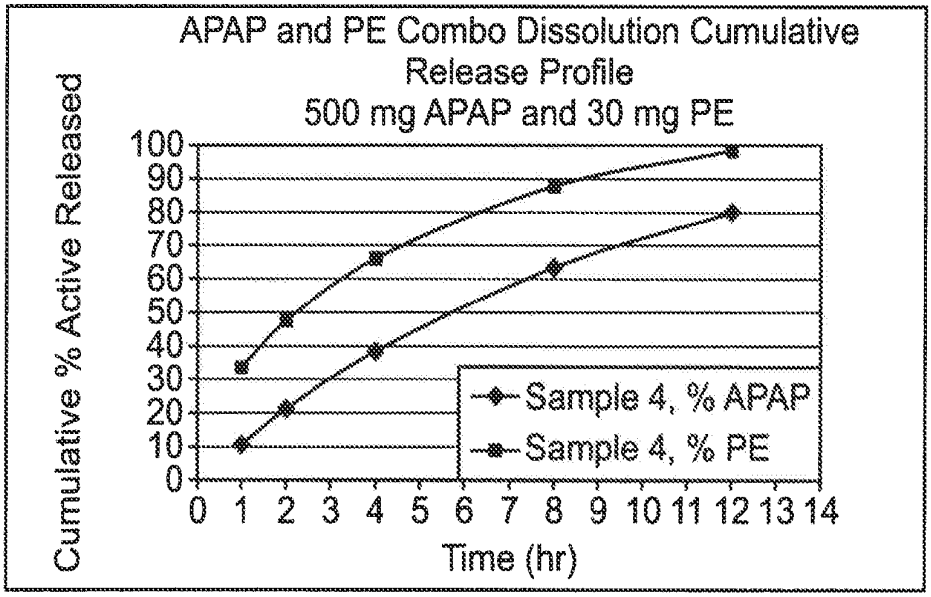
APAP and PE Combo Dissolution Cumulative Release Profile
500 mg APAP and 30 mg PE
Cumulative % Active Released
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Time (hr)
Sample 4, % APAP
Sample 4, % PE

FIG. 4

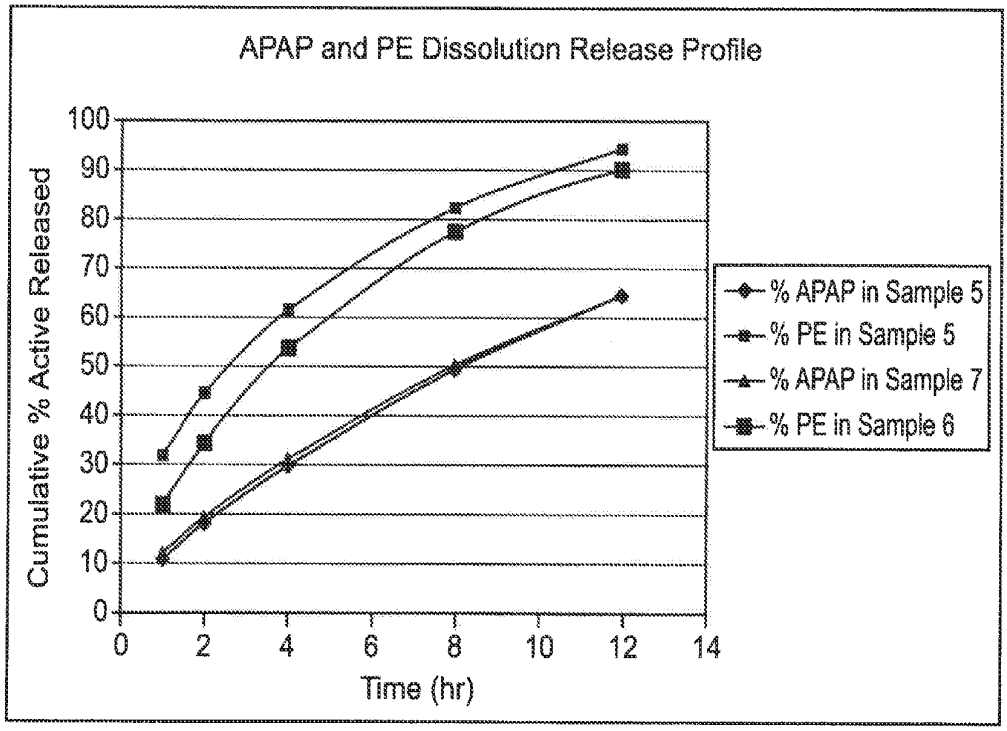
APAP and PE Dissolution Release Profile
Cumulative % Active Released
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
Time (hr)
% APAP in Sample 5
% PE in Sample 5
% APAP in Sample 7
% PE in Sample 6

FIG. 5

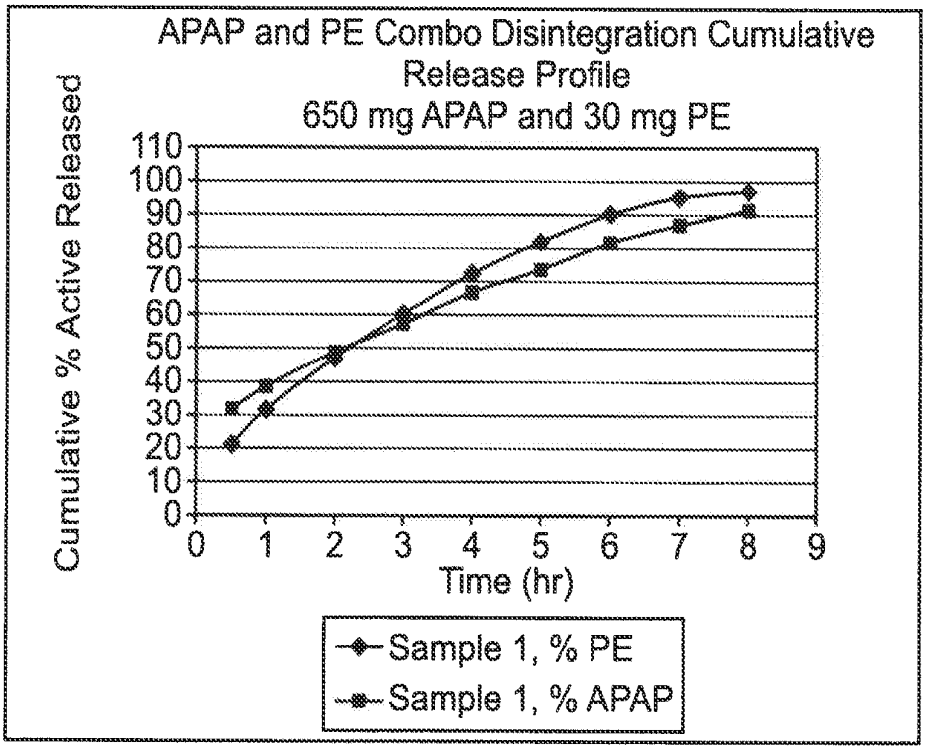
APAP and PE Combo Disintegration Cumulative Release Profile
650 mg APAP and 30 mg PE
Cumulative % Active Released
110
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9
Time (hr)
Sample 1, % PE
Sample 1, % APAP

FIG. 6

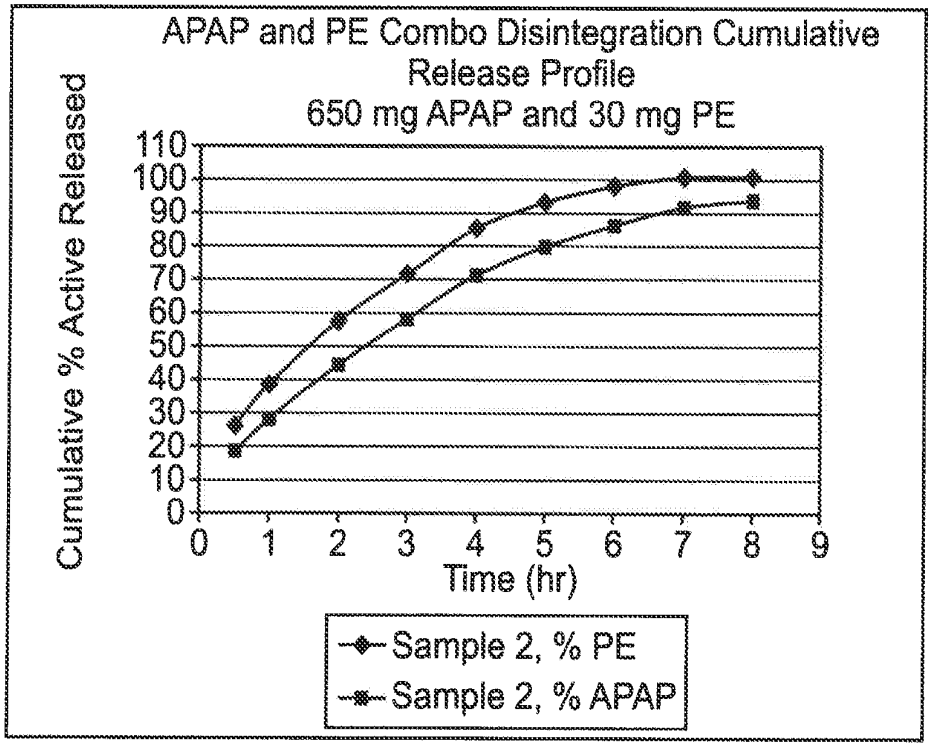
APAP and PE Combo Disintegration Cumulative Release Profile
650 mg APAP and 30 mg PE
Cumulative % Active Released
110
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9
Time (hr)
Sample 2, % PE
Sample 2, % APAP

FIG. 7

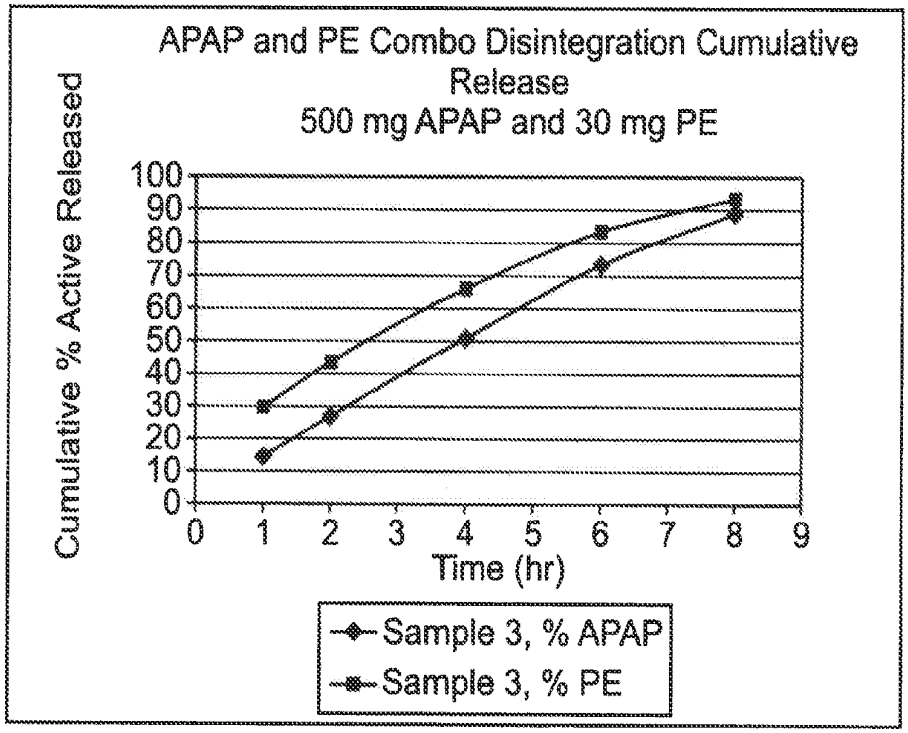
APAP and PE Combo Disintegration Cumulative Release
500 mg APAP and 30 mg PE
Cumulative % Active Released
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9
Time (hr)
Sample 3, % APAP
Sample 3, % PE

FIG. 8

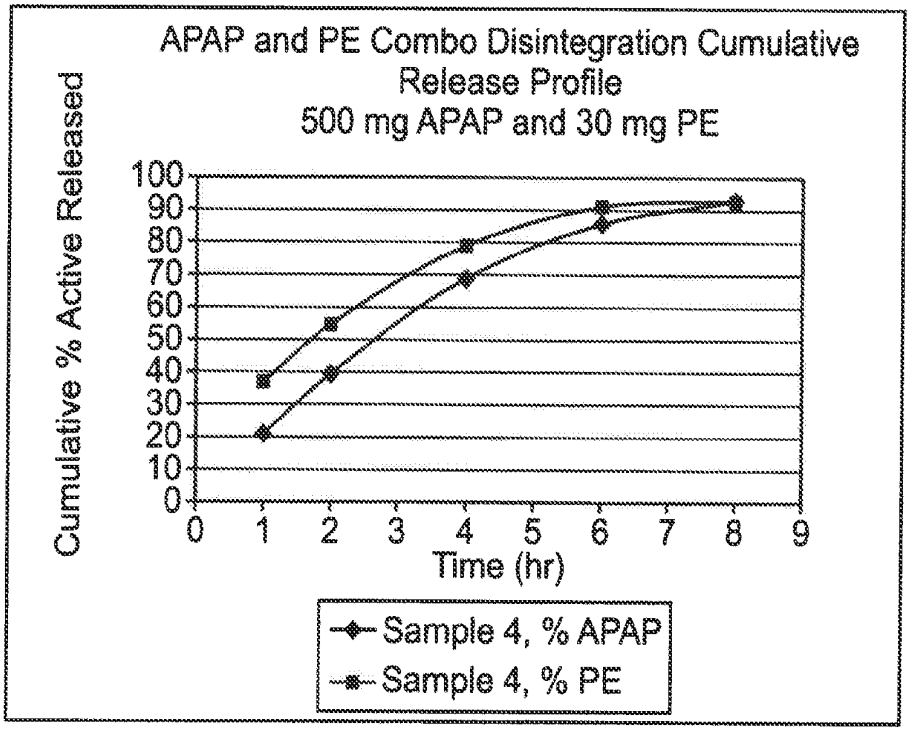
APAP and PE Combo Disintegration Cumulative Release Profile
500 mg APAP and 30 mg PE
Cumulative % Active Released
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9
Time (hr)
Sample 4, % APAP
Sample 4, % PE

FIG. 9

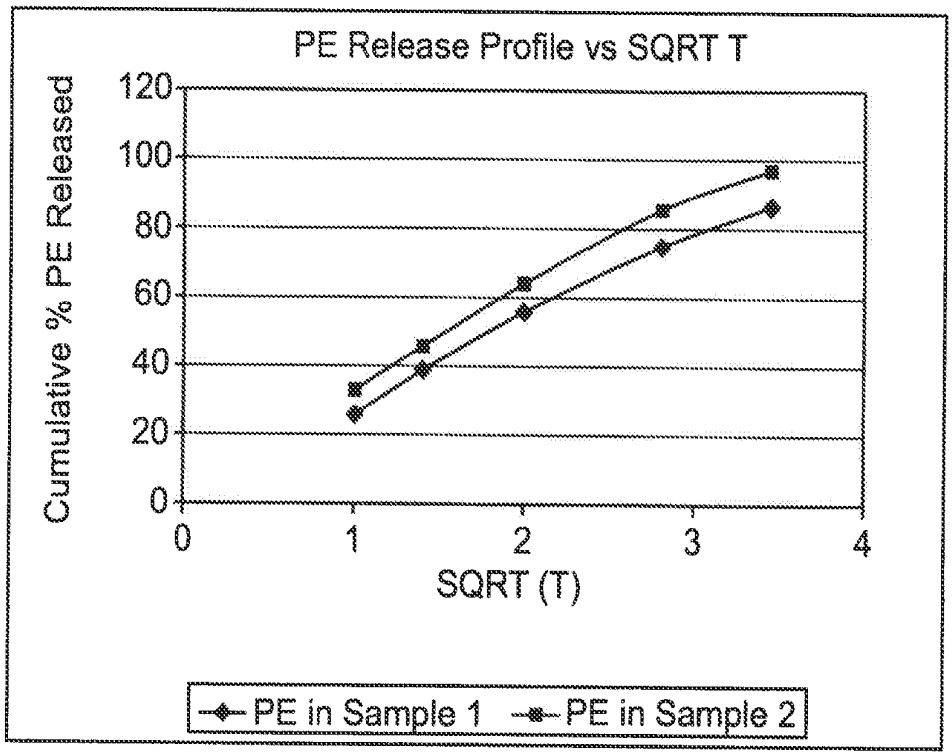
PE Release Profile vs SQRT T
Cumulative % PE Released
120
100
80
60
40
20
0
0
1
2
3
4
SQRT (T)
PE in Sample 1
PE in Sample 2

FIG. 10

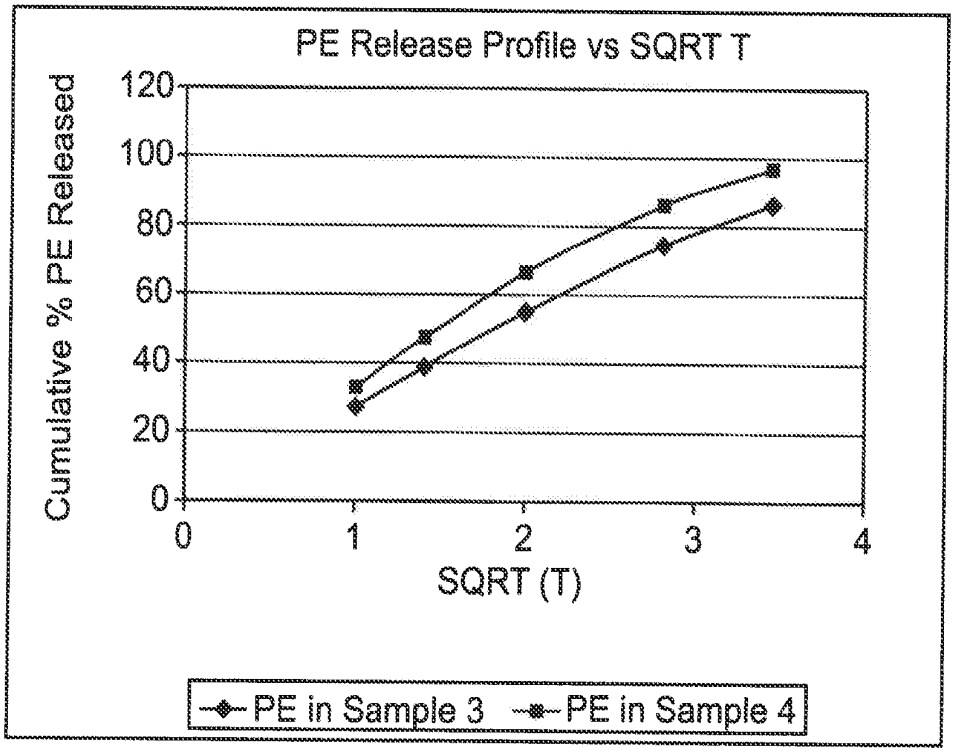
PE Release Profile vs SQRT T
Cumulative % PE Released
120
100
80
60
40
20
0
0
1
2
3
4
SQRT (T)
PE in Sample 3
PE in Sample 4

FIG. 11

GASTRIC RETENTIVE EXTENDED-RELEASE DOSAGE FORMS COMPRISING COMBINATIONS OF ACETAMINOPHEN AND PHENYLEPHRINE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 61/258,488, filed Nov. 5, 2009, which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

[0002] Compositions and methods are described for relief or treatment of existing or anticipated pain associated with nasal congestion and ophthalmic disorders. In some embodiments, gastric retentive ("GR") dosage forms comprise acetaminophen (APAP) in combination with phenylephrine (PE). The dosage forms when administered to a mammal, typically provide about 6 hours to about 12 hours of delivery of one or both of the drugs to the upper gastrointestinal ("GI") of the mammal. The present disclosure also relates to a method for treating pain associated with nasal congestion and ophthalmic disorders by providing the gastric retentive dosage forms, and to methods of making the gastric retentive dosage forms.

BACKGROUND

[0003] Upper respiratory mucosal congestion caused by infections such as the common cold and influenza, or allergic rhinitis, can lead to a number of nasal and ocular symptoms. These include rhinitis and sinusitis, nasal and sinus congestion or excessive secretions, sneezing and itching and excessive lacrimation. It is common for a person suffering from such ailments, to simultaneously experience pain such as a headache. For this reason, it is desirable to administer to the person a single therapeutic composition which is able to treat all symptoms. One such therapeutic composition is phenylephrine (PE) combined with an analgesic agent, for example, acetaminophen (APAP). This combination can provide relief for example, from the symptoms of a common cold, including nasal congestion and headache.

[0004] Such combination formulations provide the advantage of combining analgesic effects with therapeutic efficacy provided by phenylephrine, resulting in the ability to treat a subject suffering from pain associated with, for example, nasal congestion, or ophthalmic disorders. When treating a mammalian subject suffering from pain associated with, for example, nasal congestion, it is highly desirable to maintain and achieve both analgesia and decongestive activity continuously. Immediate release formulations of the appropriate therapeutic agents require frequent and/or continuous dosing throughout the day (or night) for continuous relief. This is often inconvenient and difficult to maintain regularly dosing, causing unnecessary pain and suffering.

[0005] Hence, it would be desirable and beneficial to provide extended release delivery of a drug product that comprises both phenylephrine and acetaminophen. Such a dosage form would reduce the frequency of administration to a subject while sustaining plasma drug levels and analgesic/decongestive effects throughout the day (or night). Such an extended release dosage form would eliminate the need to dose frequently to maintain therapeutic efficacy.

[0006] Phenylephrine, is a relatively selective α1-adrenergic receptor agonist used primarily as a decongestant, as an agent to dilate the pupil, and to increase blood pressure. Phenylephrine has recently been marketed as a substitute for pseudoephedrine (e.g., Pfizer's Sudafed (Original Formulation)). Acetaminophen is a well-known analgesic commonly used to treat both acute and chronic pain.

[0007] Gastric retentive dosage forms have demonstrated success in providing extended delivery of active ingredients. Drugs that are delivered from a gastric retained dosage form continuously bathe the stomach, duodenum and upper part of the small intestine for many hours. Release of the drug from the dosage form upstream of absorption sites provides extended and controlled exposure of the absorption sites to the released drug, thus increasing bioavailability. Acetaminophen demonstrates reduced bioavailability when administered rectally (about 35-50%) as compared to oral administration (about 60-70%). The increasingly dry environment of the colon is unfavorable for absorption. Accordingly, a gastric retentive extended release dosage form would provide several significant advantages as it would obviate the bioavailability reduction seen in the colon with non-gastric retentive extended release dosage forms.

[0008] Although gastric retentive dosage forms containing a drug dispersed in a swellable polymer matrix have been previously described, new challenges arise when formulating dosage forms that can provide the therapeutically effective delivery of a combination of drugs, which include, for example, acetaminophen and phenylephrine. Firstly, these two active agents have very different solubilities. Acetaminophen is a sparingly soluble drug in water, having a solubility of about 1-5 milligrams/milliliter (mg/ml) in water at 22° C. In contrast, phenylephrine, which are formulated as acid salts in drug products, is highly soluble in water. Such disparities in solubility must be taken into account when formulating a dosage form that releases the two active agents at rates proportional to each other. Secondly, acetaminophen is known to be difficult for the production of solid oral dosage forms. It can be particularly difficult to produce a tablet having acetaminophen because acetaminophen powder does not compress easily to form a stable tablet. Moreover, preparation of tablets having necessary dosage levels requires a relatively high weight percent of the drug. As a result, production of a useful tablet size allows only low amounts of excipients. This contributes to the difficulties involved in producing a tablet that relies on the use of a swellable polymer for extended release.

[0009] The present disclosure meets these challenges and needs, among others.

SUMMARY

[0010] The present disclosure provides, among other aspects, gastric retentive dosage forms for oral administration to a subject, such as a human patient, for relief from a pain state which accompanies ophthalmic disorders (hyperaemia of conjunctiva, posterior synechiae, acute atopic), nasal congestion, hemorrhoids, hypotension, shock, hypotension during spinal anesthesia, and paroxysmal supraventricular tachycardia. The dosage form in some embodiments is a gastric retentive dosage form that contains a first dose of at least one drug as an extended release ("ER") portion, and a second dose of at least one drug as an immediate release ("IR") component. The dosage forms typically contain a therapeutically

effective amount of acetaminophen (APAP) and a therapeutically effective amount of phenylephrine.

[0011] In one aspect, the ER portion of the dosage form comprises a first dose of acetaminophen and a first dose of phenylephrine. In another aspect, the ER portion of the dosage form comprises the first dose of acetaminophen and the first dose of phenylephrine dispersed in a polymer matrix comprising at least one hydrophilic polymer. Upon administration, the polymer matrix is able to swell upon imbibition of fluid to a size sufficient such that the ER portion of the dosage form is retained in a stomach of a subject in a fed mode and the first dose of acetaminophen and the first dose of phenylephrine are released over an extended period of time.

[0012] In another aspect, the dosage form releases the acetaminophen through erosion of the polymer matrix and the phenylephrine is released at a rate proportional to the release of the acetaminophen. In another embodiment, the dosage form releases the acetaminophen through both erosion and diffusion. In additional embodiments, the rate of release of the phenylephrine is about 2% to about 10%, or about 4% to about 8%, or about 5% or about 7% of the rate of release of the acetaminophen, over a period of release from between about 2 to about 10 hours, or about 4 to about 6 hours, or about 4 to about 8 hours.

[0013] In one embodiment, the ER portion of the dosage form comprises a first dose of acetaminophen of about 100 milligrams (mg) to about 800 mg and is delivered over an extended period of time. In another embodiment, the first dose of acetaminophen is about 200 mg to about 800 mg. In yet another embodiment, the first dose of acetaminophen is about 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 375 mg, 400 mg, 425 mg, 450 mg, 475 mg, 500 mg, 525 mg, 550 mg, 575 mg, 600 mg, 625 mg, 650 mg, 675 mg, 700 mg, 725 mg, 750 mg, 775 mg or 800 mg. In another aspect, the ER portion of the dosage form comprises a first dose of acetaminophen that is approximately 25 wt % (weight percent), 30 wt %, 35 wt %, 38 wt %, 39 wt %, 40 wt %, 41 wt %, 42 wt %, 43 wt %, 44 wt %, 45 wt %, 47 wt %, 50 wt %, 52 wt %, 55 wt %, 60 wt %, 65 wt % or 70 wt % of the total weight of the dosage form.

[0014] In one embodiment, the ER portion of the dosage form comprises a first dose of phenylephrine of about 5 mg to about 60 mg. In another embodiment, the first dose of phenylephrine is about 5 mg to about 50 mg. In an additional embodiment, the first dose of phenylephrine is about 7.5 mg to about 30 mg. In another embodiment, the first dose of phenylephrine is about 10 mg to about 20 mg. In yet another embodiment, the first dose of phenylephrine is about 5.0 mg, 7.5 mg, 10.0 mg, 12.5 mg, 15.0 mg, 15.5 mg, 16.0 mg, 16.5 mg, 17.0 mg, 17.5 mg, 18.0 mg, 18.5 mg, 19.0 mg, 19.5 mg, 20.0 mg, 25.0 mg, 30.0 mg, 35.0 mg, 40.0 mg, 45.0 mg, 50.0 mg, 55.0 mg, or 60.0 mg. In yet another embodiment, the ER portion of the polymer matrix comprises a first dose of phenylephrine that is approximately 1.0 wt %, 1.5 wt %, 2.0 wt %, 2.2 wt %, 2.5 wt %, 2.6 wt %, 2.7 wt %, 2.8 wt %, 3.0 wt %, 3.2 wt %, 3.5 wt %, 4.0 wt %, 4.5 wt %, 5.0 wt %, 5.5 wt %, 6.0 wt %, 6.5 wt %, 7.0 wt %, 7.5 wt %, 8.0 wt %, 8.5 wt %, 9.0 wt %, 9.5 wt % or 10 wt % of the total wt % of the ER portion of the dosage form.

[0015] In another embodiment, the weight percent of acetaminophen is typically between about 15 to 25 times, between about 20 to 50 times, about 75 to 90 times the weight percent of phenylephrine in the ER portion of the dosage form.

[0016] In one embodiment, the at least one polymer is a polyalkylene oxide. In another aspect, the polyalkylene oxide is poly(ethylene) oxide. In a further embodiment, the poly(ethylene) oxide has an approximate molecular weight between 500,000 Daltons (Da) and about 12,000,000 Da or between about 2,000,000 Da and about 5,000,000 Da. In yet a further embodiment, the poly(ethylene) oxide has a molecular weight of approximately 600,000 Da, 900,000 Da, 1,000,000 Da, 2,000,000 Da, 4,000,000 Da, 5,000,000 Da, 7,000,000 Da, 800,000 Da, 9,000,000 Da, 10,000,000 Da, 11,000,000 Da or 10,000,000 Da.

[0017] In another embodiment, the polymer is present in the ER portion of the dosage form from about 15 wt % to about 70 wt %, or about 20 wt % to about 60 wt %, or about 25 wt % to about 55 wt % of the total wt % of the dosage form of the ER portion. In another embodiment, the polymer is present in the ER portion of the dosage form in an amount ranging from about 30 wt % to about 50%, or about 35 wt % to about 45 wt %. In yet another embodiment, the polymer is present in the ER portion of the dosage form in an amount equal to approximately 30%, 35%, 40%, 45%, 50%, 55% or 60% of the ER portion.

[0018] In one embodiment, the ER portion of the dosage form further comprises a binder. In another embodiment, the binder is povidone, polyvinylpyrrolidone (PVP), lactose or hydroxypropylcellulose (HPC). In another embodiment, the ER portion of the dosage form comprises a binder that is present in an amount that is about 2.0 wt %, 2.5 wt %, 3.0 wt %, 3.5 wt %, 4.0 wt %, 4.5 wt %, 5.0 wt %, 5.5 wt %, 6.0 wt %, 6.5 wt %, 7.0 wt %, 7.5 wt % or 8.0 wt % of the ER portion.

[0019] In one embodiment, the ER portion of the dosage form further comprises a filler. In another embodiment, the filler is microcrystalline cellulose (MCC). In another embodiment, the ER portion of the dosage form comprises a filler that is present in an amount that is about 1.0 wt %, 1.5 wt %, 2.0 wt %, 2.5 wt %, 3.0 wt %, 3.5 wt %, 4.0 wt %, 4.5 wt %, 5.0 wt %, 5.5 wt %, 6.0 wt %, 6.5 wt %, 7.0 wt %, 7.5 wt %, 8.0 wt %, 8.5 wt %, 9.0 wt %, 9.5 wt % or 10 wt % of the ER portion of the dosage form.

[0020] In one embodiment, the ER portion of the dosage form further comprises a lubricant. In another embodiment, the lubricant is magnesium stearate. In another embodiment, the ER portion of the dosage form comprises a lubricant that is present in an amount that is about 0.1 wt %, 0.5 wt %, 0.75 wt %, 1.0 wt %, 1.5 wt %, 1.75 wt %, 1.80 wt %, 1.85 wt %, 1.90 wt % or 2.0 wt % of the ER portion.

[0021] In one embodiment, the ER portion of the dosage form comprises a color agent. In another embodiment, the color agent is present in an amount that is about 2.0-5.0 wt % of the ER portion of the dosage form. In yet another embodiment, the color agent is present in an amount that is about 1.0 wt %, 1.5 wt %, 2.0 wt %, 2.5 wt %, 3.0 wt %, 3.5 wt %, 4.0 wt %, 4.5 wt %, or 5.0 wt % of the ER portion.

[0022] In one embodiment, the ER layer comprises an antioxidant which is ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, a mixture of 2 and 3 tertiary-butyl-4-hydroxyanisole, butylated hydroxytoluene, sodium isoascorbate, dihydroguaretic acid, potassium sorbate, sodium bisulfate, sodium metabisulfate, sorbic acid, potassium ascorbate, vitamin E, 4-chloro-2,6-ditertiarybutylphenol, alphatocopherol, or propylgallate. In another embodiment, the antioxidant is present in the dosage for at a wt % (weight percent) of approximately 0.01 wt %, 0.05 wt %, 0.1 wt %, 0.5 wt %, 0.75 wt %, 1 wt %, 2 wt %, 3 wt % or 4 wt %.

[0023] In one embodiment, the ER layer comprises a chelating agent which is ethylenediamine tetracetic acid (EDTA) and its salts, ethylene glycol tetraacetic acid (EGTA) and its salts, dihydroxy ethyl glycine, citric acid or tartaric acid. In another embodiment, the chelating agent is present in the dosage at a wt % of approximately 0.01 wt %, 0.05 wt %, 0.1 wt %, 0.5 wt %, 0.75 wt %, 1 wt %, 2 wt %, 3 wt % or 4 wt %.

[0024] In another embodiment, the ER portion of the dosage form comprises particles of acetaminophen admixed with the phenylephrine and the polymer.

[0025] In one embodiment, the ER portion of the dosage form comprises particles wherein at least about 50% of the particles are greater than about 250 microns in size. In another embodiment, about 20-30% of the particles are greater than about 150 microns and less than about 250 microns.

[0026] In another embodiment, after oral administration to a subject, the phenylephrine is released from ER portion of the dosage form at a rate proportional to release of the acetaminophen for a period of at least about 4 hours. In another embodiment, the proportional rate of release occurs for a period of at least about 5, 6, 7, or 8 hours. In yet another embodiment, the first dose of phenylephrine is released from the ER portion of the dosage form at a rate proportional to release of the first dose of acetaminophen for a period of about 4 to about 8 hours. In another embodiment, the proportional rate of release occurs over a period of about 5 to about 6 hours. In another embodiment, the ER portion of the dosage form comprises particles of acetaminophen admixed with the phenylephrine and the polymer.

[0027] In some embodiments, the ER portion of the dosage form swells upon administration to a size that is about 110% to about 180%, or about 120% to about 150%, or about 125% to about 145%, or about 130% to about 145% of the size of the dosage form within 30 minutes of administration. In other embodiments, the ER portion of the dosage form swells to a size that is at least approximately 130% or at least approximately 160% of the size of the dosage form within 30 minutes of administration.

[0028] In another embodiment, upon administering of the dosage form to a subject, the dosage form provides at least about 4 to about 12 hours of drug delivery to the upper gastrointestinal tract, which includes the stomach and the small intestine. In another embodiment, the dosage form provides at least 6 hours of drug delivery to the upper gastrointestinal tract. In yet a further embodiment, the dosage form provides at least 8 hours of drug delivery to the upper gastrointestinal tract. In yet a further embodiment, the dosage form provides at least 9 hours, 10 hours, 11 hours or 12 hours of drug delivery to the upper gastrointestinal tract.

[0029] In some embodiments, the dosage form provides a dissolution profile wherein for each of the first dose of acetaminophen and the first dose of the phenylephrine, between about 40% to about 50% of the first dose remains in the dosage form between about 1 and 2 hours after administration. In one embodiment, not more than 50% of the first dose of acetaminophen and first dose of phenylephrine is released within about the first hour. In a further embodiment, not more than 45% or not more than 40% of the first dose of acetaminophen and first dose of phenylephrine is released within about the first hour. In another embodiment, not more than 85% of the first dose of acetaminophen and first dose of phenylephrine is released within about 4 hours. In another embodiment, not less than 50% is released after about 6 hours. In yet another embodiment, not less than 60% is released after about 6 hours.

[0030] In one embodiment, the dosage form further comprises an IR portion. The IR portion of the dosage form typically comprises a second dose of phenylephrine and a second dose of acetaminophen. In another embodiment, the phenylephrine and the acetaminophen are dispersed in the IR portion of the dosage form. In yet another embodiment, a dosage form comprising an IR portion in contact with an ER portion is provided.

[0031] In one embodiment, the IR portion of the dosage form comprises about 50 mg to about 900 mg, or about 75 to about 700 mg, or about 100 mg to about 600 mg of acetaminophen. In yet another embodiment, the IR portion of the dosage form comprises about 200 mg to about 400 mg of acetaminophen. In yet another embodiment, the IR portion of the dosage form comprises about 200 mg, 205 mg, 210 mg, 215 mg, 220 mg, 225 mg, 230 mg or 235 mg of acetaminophen.

[0032] In another embodiment, the IR portion of the dosage form comprises about 5 mg to about 60 mg, or about 10 mg to about 40 mg, or about 15 to about 20 mg of the phenylephrine. In yet another embodiment, the IR portion of the dosage form comprises about 5.0 mg, 7.5 mg, 10.0 mg, 12.5 mg, 14.0 mg, 15.0 mg, 20.0 mg or 25.0 mg of the phenylephrine.

[0033] In another embodiment, the amount of acetaminophen in the IR portion is typically between about 10 to about 20, more typically between about 12 to about 16 times the amount of phenylephrine in the IR portion.

[0034] In yet another embodiment, the IR portion of the dosage form further comprises a binder. In some embodiments, the binder chosen from among povidone, polyvinylpyrrolidone and hydroxypropylcellulose. In another embodiment, the binder is present in the IR portion of the dosage form in an amount that is about 4.5 wt %, 5.0 wt %, 5.5 wt %, 6.0 wt %, 6.5 wt %, 7.0 wt %, 7.5 wt %, 8.0 wt %, 8.5 wt %, 9.0 wt %, 9.5 wt % or 10.0 wt % of the IR portion.

[0035] In one embodiment, the IR portion of the dosage form comprises particles of acetaminophen admixed with the phenylephrine and the binder.

[0036] In one embodiment, the IR portion comprises an anti-oxidant which is ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, a mixture of 2 and 3 tertiary-butyl-4-hydroxyanisole, butylated hydroxytoluene, sodium isoascorbate, dihydroguaretic acid, potassium sorbate, sodium bisulfate, sodium metabisulfate, sorbic acid, potassium ascorbate, vitamin E, 4-chloro-2,6-ditertiarybutylphenol, alphatocopherol, or propylgallate. In another embodiment, the antioxidant is present in the dosage for at a wt % (weight percent) of approximately 0.01 wt %, 0.05 wt %, 0.1 wt %, 0.5 wt %, 0.75 wt %, 1 wt %, 2 wt %, 3 wt % or 4 wt %.

[0037] In one embodiment, the IR layer comprises a chelating agent which is ethylenediamine tetracetic acid (EDTA) and its salts, ethylene glycol tetraacetic acid (EGTA) and its salts, dihydroxy ethyl glycine, citric acid or tartaric acid. In another embodiment, the chelating agent is present in the dosage at a wt % of approximately 0.01 wt %, 0.05 wt %, 0.1 wt %, 0.5 wt %, 0.75 wt %, 1 wt %, 2 wt %, 3 wt % or 4 wt %.

[0038] In one embodiment, the IR portion of the dosage form comprises particles, wherein at least 30% of the particles have a size greater than 250 microns (μm).

[0039] In one embodiment, the dosage form is a pharmaceutical tablet, such as a gastric retentive tablet for the

extended release of the phenylephrine and the acetaminophen. In another embodiment, the tablet is a monolithic tablet comprising an ER portion. In another embodiment, the tablet is a monolithic tablet comprising an ER portion and an IR portion. In another embodiment, the tablet is a bilayer tablet, comprising an ER portion and an IR portion. The bilayer tablet is typically a monolithic tablet. In another embodiment, the dosage form is a capsule comprising an ER portion. In another embodiment, the dosage form is a capsule comprising ER portion and an IR portion.

[0040] In some embodiments, the bilayer tablet has a friability of no greater than about 0.1%, 0.2% 0.3%, 0.4%, 0.5%, 0.7% or 1.0%.

[0041] In some embodiments, the bilayer tablet has a hardness of at least about 10 kilopond (also known as kilopons) (kp). In some embodiments, the tablet has a hardness of about 9 kp to about 25 kp, or about 12 kp to about 20 kp. In further embodiments, the tablet has a hardness of about 11, 12, 13, 14, 15, or 16 kp.

[0042] In some embodiments, the tablets have a content uniformity of from about 85 to about 115 percent by weight or from about 90 to about 110 percent by weight, or from about 95 to about 105 percent by weight. In other embodiments, the content uniformity has a relative standard deviation (RSD) equal to or less than about 3.5%, 3.0%, 2.5%, 2.0%, 1.5%, 1.0% or 0.5%.

[0043] In one embodiment, acetaminophen can be present in the dosage form in an amount ranging from about 100 milligrams (mg) to about 1300 mg.

[0044] In another embodiment, acetaminophen is present in the dosage form at an amount of about 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 400 mg, 425 mg, 450 mg, 500 mg, 525 mg, 530 mg, 535 mg, 540 mg, 545 mg, 550 mg, 600 mg, 650 mg or about 700 mg.

[0045] In some embodiments, the phenylephrine is present in the dosage form at an amount of about 5 mg, 7.5 mg, 10 mg, 12 mg, 15 mg, 20 mg, 22.5 mg, 25 mg, 30 mg, 32 mg, 34 mg, 35 mg, 37 mg, 40 mg, 50 mg, or 60 mg or higher.

[0046] In another aspect, a pharmaceutical or gastric retentive oral dosage form comprising acetaminophen and phenylephrine, wherein the formulation is administered to a mammal once in a 24 hour period (q.d. or once-daily), two times in a 24 hour period (b.i.d. or twice-daily) or three times in a 24 hour period (t.i.d. or three times daily) is provided.

[0047] Also provided, is a method of making a pharmaceutical or gastric retentive dosage form comprising a first dose of phenylephrine, a first dose of acetaminophen dispersed in an ER polymer matrix comprised of a polymer that swells upon imbibition of fluid to a size sufficient for gastric retention in the upper gastrointestinal tract in a fed mode.

[0048] In some embodiments, the method comprises wet granulating a first mixture that comprises phenylephrine, acetaminophen and a binder to produce a first granulation mixture. In another embodiment, the wet granulating comprises spraying a solution of binder dissolved in water onto acetaminophen particles. In a further embodiment, the particles of the first granulation mixture are blended with a polymer and one or more excipients to form an ER portion of a dosage form.

[0049] In some embodiments, the one or more excipients blended with the first granulation mixture are chosen from among a filler, a lubricant and a color agent.

[0050] In another embodiment, the method comprises dry blending the acetaminophen, phenylephrine, polymer and other excipients prior to compressing the blended mixture into a tablet.

[0051] In further embodiments, the wet granulating is a fluid bed granulation method. In other embodiments, the wet granulating is a high shear granulation method.

[0052] In some embodiments, the wet granulation comprises making a solution containing phenylephrine and a binder and spraying the solution onto the acetaminophen particles in a fluid bed granulator.

[0053] In a further embodiment, the method comprises compressing the ER portion of the dosage form into a tablet.

[0054] In some embodiments, the wet granulation of the ER portion of the dosage form produces particles with a bulk density ranging from about 0.30 to 0.40 grams/milliliter (g/ml). In other aspects, the wet granulation produces particles with a tap density ranging from about 0.35 to about 0.45 g/ml. In other embodiments, the wet granulation produces particles, wherein at least about 50% of the particles have a size greater than 250μ. In still other embodiments, the wet granulation produces particles wherein about 20% to about 30% of the particles have a size greater than about 150μ and less than about 250μ.

[0055] In one embodiment, the method of making a pharmaceutical and/or gastric retentive oral dosage form comprising acetaminophen and phenylephrine further comprises wet granulating a second mixture comprising the acetaminophen, the phenylephrine, and the binder to form a second granulation mixture. In a further embodiment, the second granulation mixture is blended with one or more excipients to produce an IR portion of the dosage form. In yet a further embodiment, the IR portion is compressed with the ER portion of the dosage form to produce a bilayer tablet.

[0056] In further embodiments, wet granulating the second mixture is achieved by fluid bed granulation. In other embodiments, wet granulating the second mixture is achieved by a high shear granulation method.

[0057] Also provided is a method of treating a subject suffering from both pain and nasal congestion in need of such treatment comprising administering a therapeutic effective amount of any of the describe dosage forms or pharmaceutical formulations herein. In one embodiment, the subject is suffering from both pain and an ophthalmic disorder.

[0058] In one embodiment, a gastric retained dosage form comprising acetaminophen, phenylephrine and a swellable polymer is administered to a subject suffering from or diagnosed with a pain state. In other embodiments, the subject is suffering from pain and is suffering from ophthalmic disorders (hyperaemia of conjunctiva, posterior synechiae, acute atopic), nasal congestion, hemorrhoids, hypotension, shock, hypotension during spinal anesthesia, and paroxysmal supraventricular tachycardia. In yet another embodiment, the subject is suffering from chronic and/or acute pain.

[0059] In one embodiment, a gastric retained dosage form is administered to a subject in a fed mode. In another embodiment, the dosage form is administered with a meal to a subject once in a 24 hour period. In other embodiments, the dosage form is administered with a meal to the subject twice in a 24 hour period. In some embodiments, the dosage form is administered with a meal to the subject three times in a 24 hour period.

[0060] Additional embodiments of the present method, compositions, and the like will be apparent from the follow-

ing description, drawings, examples, and claims. As can be appreciated from the foregoing and following description, each and every feature described herein, and each and every combination of two or more of such features, is included within the scope of the present disclosure provided that the features included in such a combination are not mutually inconsistent. In addition, any feature or combination of features may be specifically excluded from any embodiment or aspect. Additional aspects and embodiments are set forth in the following description and claims, particularly when considered in conjunction with the accompanying examples and drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0061] FIG. **1** is a graphical representation of the dissolution profile of a 960 mg tablet containing 650 mg acetaminophen, 30 mg phenylephrine, and 24.28 wt % POLYOX® PEO N-60K.

[0062] FIG. **2** is a graphical representation of the dissolution profile of a 960 mg tablet containing 650 mg acetaminophen, 30 mg phenylephrine, and 24.28 wt % POLYOX® PEO 1105.

[0063] FIG. **3** is a graphical representation of the dissolution release profile of a 960 mg tablet containing 500 mg acetaminophen, 30 mg phenylephrine, 24.22 wt % POLYOX® PEO N-60K and 16.60 wt % MCC.

[0064] FIG. **4** is a graphical representation of the dissolution release profile of a 960 mg tablet containing 500 mg acetaminophen, 30 mg phenylephrine, 24.22 (wt %) POLYOX® PEO 1105 and 16.60 wt % MCC.

[0065] FIG. **5** is a graphical representation of the dissolution profile of a 1000 mg tablet containing 31 weight percent POLYOX® PEO N-60K and varying amounts of microcrystalline cellulose.

[0066] FIG. **6** is a graphical representation of the disintegration profile of a 960 mg tablet containing 650 mg acetaminophen, 30 mg phenylephrine, and 24.28 wt % POLYOX® PEO N-60K.

[0067] FIG. **7** is a graphical representation of the disintegration profile of a 960 mg tablet containing 650 mg acetaminophen, 30 mg phenylephrine, and 24.28 wt % POLYOX® PEO 1105.

[0068] FIG. **8** is a graphical representation of the disintegration release profile of a 960 mg tablet containing 500 mg acetaminophen, 30 mg phenylephrine, 24.22 wt % POLYOX® PEO N-60K and 16.60 wt % MCC.

[0069] FIG. **9** is a graphical representation of the disintegration release profile of a 960 mg tablet containing 500 mg acetaminophen, 30 mg phenylephrine, 24.22 wt % POLYOX® PEO 1105 and 16.60 wt % MCC.

[0070] FIG. **10** is a graphical representation of Phenylephrine (PE) release vs. the square root of time of a tablet having 24.28 wt % POLYOX® PEO N-60K (sample 1), and a tablet having 24.28 wt % POLYOX® PEO 1105 (sample 2).

[0071] FIG. **11** is a graphical representation of PE release vs. the square root of time generated by a tablet having 24.22 wt % POLYOX® PEO N-60K and 16.60 wt % MCC (sample 3) and a tablet having 24.22 wt % POLYOX® PEO 1105 and 16.60 wt % MCC (sample 4).

DETAILED DESCRIPTION

[0072] The various aspects and embodiments will now be fully described herein. These aspects and embodiments may, however, be embodied in many different forms and should not be construed as limiting; rather, these embodiments are provided so the disclosure will be thorough and complete, and will fully convey the scope of the present subject matter to those skilled in the art.

[0073] All publications, patents and patent applications cited herein, whether supra or infra, are hereby incorporated by reference in their entirety.

I. DEFINITIONS

[0074] It must be noted that, as used in this specification, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise.

[0075] Compounds useful in the compositions and methods include those described herein in any of their pharmaceutically acceptable forms, including isomers such as diastereomers and enantiomers, salts, solvates, and polymorphs, as well as racemic mixtures and pure isomers of the compounds described herein, where applicable.

[0076] "Pharmaceutically acceptable salt" includes, but is not limited to, amino acid salts, salts prepared with inorganic acids, such as chloride, sulfate, phosphate, diphosphate, bromide, and nitrate salts, or salts prepared from the corresponding inorganic acid form of any of the preceding, e.g., hydrochloride, etc., or salts prepared with an organic acid, such as malate, maleate, fumarate, tartrate, succinate, ethylsuccinate, citrate, acetate, lactate, methanesulfonate, benzoate, ascorbate, para-toluenesulfonate, palmoate, salicylate and stearate, as well as estolate, gluceptate and lactobionate salts. Similarly salts containing pharmaceutically acceptable cations include, but are not limited to, sodium, potassium, calcium, aluminum, lithium, and ammonium (including substituted ammonium).

[0077] "Optional" or "optionally" means that the subsequently described element, component or circumstance may or may not occur, so that the description includes instances where the element, component, or circumstance occurs and instances where it does not.

[0078] The terms "subject," "individual" or "patient" are used interchangeably herein and refer to a vertebrate, preferably a mammal. Mammals include, but are not limited to, humans.

[0079] The term "drug" or "active agent" is used herein to refer to any chemical that elicits a biochemical response when administered to a human or an animal. The drug may act as a substrate or product of a biochemical reaction, or the drug may interact with a cell receptor and elicit a physiological response, or the drug may bind with and block a receptor from eliciting a physiological response.

[0080] The term "sparingly soluble," as used herein, refers to a drug having a solubility (measured in water at 37° C.) in the range of about 0.001% to about 2% by weight, more preferably about 0.001% to about 0.5% by weight. The term "soluble," as used herein, refers to a drug having a solubility (measured in water at 37° C.) in the range of about 2% to about 10% by weight, more preferably about 2% to about 5% by weight.

[0081] The term "fed mode," as used herein, refers to a state which is typically induced in a patient by the presence of food in the stomach, the food giving rise to two signals, one that is said to stem from stomach distension and the other a chemical signal based on food in the stomach. It has been determined that once the fed mode has been induced, larger particles are retained in the stomach for a longer period of time than

smaller particles. Thus, the fed mode is typically induced in a patient by the presence of food in the stomach.

[0082] Administration of a dosage form "with a meal," as used herein, refers to administration before, during or after a meal, and more particularly refers to administration of a dosage form about 1, 2, 3, 4, 5, 10, 15 minutes before commencement of a meal, during the meal, or about 1, 2, 3, 4, 5, 10, 15 minutes after completion of a meal.

[0083] A drug "release rate," as used herein, refers to the quantity of drug released from a dosage form or pharmaceutical composition per unit time, e.g., milligrams of drug released per hour (mg/hr). Drug release rates for drug dosage forms are typically measured as an in vitro rate of dissolution, i.e., a quantity of drug released from the dosage form or pharmaceutical composition per unit time measured under appropriate conditions and in a suitable fluid. The specific results of dissolution tests claimed herein are performed on dosage forms or pharmaceutical compositions in a USP Type II apparatus and immersed in 900 ml of simulated intestinal fluid (SIF) at pH 6.8 and equilibrated in a constant temperature water bath at 37° C. Suitable aliquots of the release rate solutions are tested to determine the amount of drug released from the dosage form or pharmaceutical composition. For example, the drug can be assayed or injected into a chromatographic system to quantify the amounts of drug released during the testing intervals.

[0084] The term "swellable polymer," as used herein, refers to a polymer that will swell in the presence of a fluid. It is understood that a given polymer may or may not swell when present in a defined drug formulation. Accordingly, the term "swellable polymer" defines a structural feature of a polymer which is dependent upon the composition in which the polymer is formulated. Whether or not a polymer swells in the presence of fluid will depend upon a variety of factors, including the specific type of polymer and the percentage of that polymer in a particular formulation. For example, the term "polyethylene oxide" or "PEO" refers to a polyethylene oxide polymer that has a wide range of molecular weights. PEO is a linear polymer of unsubstituted ethylene oxide and has a wide range of viscosity-average molecular weights. Examples of commercially available PEOs and their approximate molecular weights are: POLYOX® NF, grade WSR coagulant, molecular weight 5 million, POLYOX® grade WSR 301, molecular weight 4 million, POLYOX® grade WSR 303, molecular weight 7 million, and POLYOX® grade WSR N-60K, molecular weight 2 million. It will be understood by a person with ordinary skill in the art that an oral dosage form which comprises a swellable polymer will swell upon imbibition of water or fluid from gastric fluid

[0085] The term "friability," as used herein, refers to the ease with which a tablet will break or fracture. The test for friability is a standard test known to one skilled in the art. Friability is measured under standardized conditions by weighing out a certain number of tablets (generally 20 tablets or less), placing them in a rotating Plexiglas drum in which they are lifted during replicate revolutions by a radial lever, and then dropped approximately 8 inches. After replicate revolutions (typically 100 revolutions at 25 rpm), the tablets are reweighed and the percentage of formulation abraded or chipped is calculated. The friability of the tablets, of the present invention, is preferably in the range of about 0% to 3%, and values about 1%, or less, are considered acceptable for most drug and food tablet contexts. Friability which approaches 0% is particularly preferred.

[0086] The term "tap density" or "tapped density," as used herein, refers to a measure of the density of a powder. The tapped density of a pharmaceutical powder is determined using a tapped density tester, which is set to tap the powder at a fixed impact force and frequency. Tapped density by the USP method is determined by a linear progression of the number of taps.

[0087] The term "bulk density," as used herein, refers to a property of powders and is defined as the mass of many particles of the material divided by the total volume they occupy. The total volume includes particle volume, interparticle void volume and internal pore volume.

[0088] The term "capping," as used herein, refers to the partial or complete separation of top or bottom crowns of the tablet main body. For multilayer tablets, capping refers to separation of a portion of an individual layer within the multilayer tablet. Unintended separation of layers within a multilayer tablet prior to administration is referred to herein as "splitting."

[0089] The term "content uniformity," as used herein refers to the testing of compressed tablets to provide an assessment of how uniformly the micronized or submicron active ingredient is dispersed in the powder mixture. Content uniformity is measured by use of USP Method (General Chapters, Uniformity of Dosage Forms), unless otherwise indicated. A plurality refers to five, ten or more tablet compositions.

II. ACETAMINOPHEN

[0090] Acetaminophen (N-(4-hydroxyphenyl)acetamine) is a white, crystalline powder, which is poorly soluble in water, and has a molecular weight of about 151. As acetaminophen powder does not possess properties conducive to direct compression to form a tablet, the acetaminophen may first be granulated with one or more excipients using a method such as fluid bed or dry granulation. Alternatively, tablets as described herein may be manufactured using a pregranulated composition such as COMPAP®, COMPAP® L, COMPAP® COARSE L, COMPAP® WSE, or COMPAP® PVP, all of which are manufactured by Mallinckrodt, Inc. The pregranulated compositions have been specially processed to yield an active agent that has flow properties, particle size distribution, and compression characteristics that enhance the ability to manufacture a stable tablet.

III. PHENYLEPHRINE

[0091] Phenylephrine, known chemically (R)-3-[-1-hydroxy-2-(methylamino)ethyl]phenol, is a synthetic, optically active sympathomimetic amine which has one hydroxyl group on the benzene ring. The hydroxyl group is placed in the position meta to the aliphatic side chain. The meta position affords optimal activity and phenylephrine (neo-synephrine) replaced an older preparation, synephrine, in which the hydroxyl was in the para position. Phenylephrine has an approximate molecular weight of 167 and is highly soluble in water. As used herein, phenylephrine The term phenylephrine includes, but is not limited to pharmaceutically acceptable salts, esters, isomers or derivatives thereof, such as (R)-3-[-1-hydroxy-2-(methylamino)ethyl]phenol hydrochloride.

IV. GASTRIC RETENTIVE EXTENDED RELEASE DOSAGE FORM

[0092] It has been surprisingly discovered that a pharmaceutically acceptable gastric retentive dosage form can be

formulated to provide release in the stomach of a combination of a sparingly soluble drug and a highly soluble drug at rates proportional to one another over an extended period of time. Described herein is a pharmaceutically acceptable dosage form for treating a subject suffering from both pain and from ophthalmic disorders (hyperaemia of conjunctiva, posterior synechiae, acute atopic), nasal congestion, hemorrhoids, hypotension, shock, hypotension during spinal anesthesia, or paroxysmal supraventricular tachycardia, comprising acetaminophen and phenylephrine dispersed in a polymer matrix that, upon oral administration, swells dimensionally unrestrained, with the imbibition of fluid to a size sufficient for gastric retention in a stomach of a subject in a fed mode. In the presently described dosage form, acetaminophen is released from the dosage form through erosion and the phenylephrine also present in the dosage form is released at a rate proportional to that of the acetaminophen. This proportional rate of release may occur over a period of 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours or more.

[0093] Gastric retentive dosage forms described herein typically contain at least one hydrophilic polymer in a water-swellable polymer matrix having at least one drug dispersed therein. The polymer matrix, where in the at least one drug is dispersed absorbs water, causing the matrix to swell, which in turn promotes retention of the dosage form in the upper gastrointestinal tract (GI) of a subject. In addition, the matrices become slippery, which provides resistance to peristalsis and further promotes gastric retention.

[0094] The imbibition of water and subsequent swelling also allows drugs to diffuse out of the matrix, to be released from the matrix as a result of physical erosion, i.e., degradation, or a combination of the two. Whether the drugs are released via diffusion or erosion depends, in part, on the solubility of the drug in the relevant environment

[0095] Thus, successful formulation of effective oral pharmaceutical dosage forms may be highly dependent upon the solubility of the incorporated drugs. For example, compositions in a tablet may differ when the tablet contains a high solubility drug as compared to when the tablet contains a low solubility drug.

[0096] With the dosage forms described herein, the rate at which the drugs are released by the gastric retentive dosage form into the gastrointestinal tract is largely dependent on the rate at and the degree to which the polymer matrix swells. The polymer used in the dosage forms of the present invention should not release the drug at too rapid a rate so as to result in a drug overdose or rapid passage into and through the gastrointestinal tract, nor should the polymer release drug too slowly to achieve the desired biological effect. Thus, polymers that permit a rate of drug release that achieves the requisite pharmacokinetics for both the acetaminophen and phenylephrine for a desired duration, as may be determined using a USP Disintegration Test or Dissolution Test, are determined for use in the dosage forms described herein.

[0097] Polymers suitable for use in the dosage forms described herein include those that both swell upon absorption of gastric fluid and gradually erode over a time period of hours. Upon swelling of the polymer matrix, soluble drugs dispersed in the matrix will slowly dissolve in the permeating fluid and diffuse out from the matrix. Drugs that are poorly, or sparingly, soluble are released primarily via erosion of the polymer matrix. Erosion initiates simultaneously with the swelling process, upon contact of the surface of the dosage form with gastric fluid. Erosion reflects the dissolution of the polymer beyond the polymer gel-solution interface where the polymer has become sufficiently dilute that it can be transported away from the dosage form by diffusion or convection. This may also depend on the hydrodynamic and mechanical forces present in the gastrointestinal tract during the digestive process. While swelling and erosion occur at the same time, it is preferred herein that drug release should be erosion-controlled, meaning that the selected polymer should be such that complete drug release occurs primarily as a result of erosion rather than swelling and dissolution. However, swelling should take place at a rate that is sufficiently fast to allow the tablet to be retained in the stomach. At minimum, for an erosional gastric retentive dosage form, there should be an extended period during which the dosage form maintains its size before it is diminished by erosion. Furthermore, the polymer which imbibes fluid to form a gastric retained, extended release polymer matrix is any polymer that is non-toxic, that swells in a dimensionally unrestricted manner upon imbibition of water, and that provides for sustained release of at least one incorporated drug.

[0098] Suitable polymers for use in the present dosage forms may be linear, branched, dendrimeric, or star polymers, and include synthetic hydrophilic polymers as well as semi-synthetic and naturally occurring hydrophilic polymers. The polymers may be homopolymers or copolymers, if copolymers, either random copolymers, block copolymers or graft copolymers. Synthetic hydrophilic polymers useful herein include, but are not limited to: polyalkylene oxides, particularly poly(ethylene oxide), polyethylene glycol and poly(ethylene oxide)-poly(propylene oxide) copolymers; cellulosic polymers; acrylic acid and methacrylic acid polymers, copolymers and esters thereof, preferably formed from acrylic acid, methacrylic acid, methyl acrylate, ethyl acrylate, methyl metbacrylate, ethyl methacrylate, and copolymers thereof, with each other or with additional acrylate species such as aminoethyl acrylate; maleic anhydride copolymers; polymaleic acid; poly(acrylamides) such as polyacrylamide per se, poly(methacrylamide), poly(dimethylacrylamide), and poly(N-isopropyl-acrylamide); poly(olefinic alcohol)s such as poly(vinyl alcohol); poly(N-vinyl lactams) such as poly(vinyl pyrrolidone), poly(N-vinyl caprolactam), and copolymers thereof; polyols such as glycerol, polyglycerol (particularly highly branched polyglycerol), propylene glycol and trimethylene glycol substituted with one or more polyalkylene oxides, e.g., mono-, di- and tri-polyoxyethylated glycerol, mono- and di-polyoxyethylated propylene glycol, and mono- and di-polyoxyethylated trimethylene glycol; polyoxyethylated sorbitol and polyoxyethylated glucose; polyoxazolines, including poly(methyloxazoline) and poly (ethyloxazoline); polyvinylamines; polyvinylacetates, including polyvinylacetate per se as well as ethylene-vinyl acetate copolymers, polyvinyl acetate phthalate, and the like, polyimines, such as polyethyleneimine; starch and starch-based polymers; polyurethane hydrogels; chitosan; polysaccharide gums; zein; and shellac, ammoniated shellac, shellac-acetyl alcohol, and shellac n-butyl stearate.

[0099] Examples of polymers suitable for use in this invention are cellulose polymers and their derivatives (such as for example, hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, and microcrystalline cellulose, polysaccharides and their derivatives, polyalkylene oxides, polyethylene glycols, chitosan, poly(vinyl alcohol), xanthan gum, maleic anhydride copolymers, poly(vinyl pyrrolidone),

starch and starch-based polymers, poly (2-ethyl-2-oxazoline), poly(ethyleneimine), polyurethane hydrogels, and crosslinked polyacrylic acids and their derivatives. Further examples are copolymers of the polymers listed in the preceding sentence, including block copolymers and grafted polymers.

[0100] The terms "cellulose" and "cellulosic" are used herein to denote a linear polymer of anhydroglucose. Preferred cellulosic polymers are alkyl-substituted cellulosic polymers that ultimately dissolve in the gastrointestinal (GI) tract in a predictably delayed manner. Preferred alkyl-substituted cellulose derivatives are those substituted with alkyl groups of 1 to 3 carbon atoms each. Examples are methylcellulose, hydroxymethyl-cellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and carboxymethylcellulose. In terms of their viscosities, one class of preferred alkyl-substituted celluloses includes those whose viscosity is within the range of about 100 to about 110,000 centipoise as a 2% aqueous solution at 20° C. Another class includes those whose viscosity is within the range of about 1,000 to about 4,000 centipoise as a 1% aqueous solution at 20° C.

[0101] The amount of polymer relative to the drug can vary, depending on the drug release rate desired and on the polymer, its molecular weight, and excipients that may be present in the formulation. The amount of polymer will be sufficient however to retain at least about 50% of the drugs within the matrix one hour after ingestion (or immersion in the gastric fluid). Preferably, the amount of polymer is such that at least 55%, 60%, 65%, 70%, 75%, or 80% of the drugs remains in the extended release matrix one hour after ingestion. The amount of polymer is such that at least 20%, 25%, 30%, 35%, 40% or 45% of the drugs remains in the extended release matrix four hours after ingestion. The amount of polymer is such that at least 75%, 80%, or 85% of the drugs is released within six hours after ingestion. In all cases, however, the drugs will be substantially all released from the matrix within about ten hours, and preferably within about eight hours, after ingestion, and the polymeric matrix will remain substantially intact until all of the drug is released. The term "substantially intact" is used herein to denote a polymeric matrix in which the polymer portion substantially retains its size and shape without deterioration due to becoming solubilized in the gastric fluid or due to breakage into fragments or small particles.

[0102] The water-swellable polymers can be used individually or in combination. Certain combinations will often provide a more controlled release of the drug than their components when used individually. Examples are cellulose-based polymers combined with gums, such as hydroxyethyl cellulose or hydroxypropyl cellulose combined with xanthan gum. Another example is poly(ethylene oxide) combined with xanthan gum.

[0103] As discussed above, the gastric retentive nature and release profiles of a dosage form will depend partially upon the molecular weight of the swellable polymer. The polymers are preferably of a moderate to high molecular weight (900,000 Da to 4,000,000 Da) to enhance swelling and provide control of the release of the phenylephrine and acetaminophen via erosion of the polymer matrix. An example of suitable polyethylene oxide polymers are those having molecular weights (viscosity average) on the order of 900,000 Da to 2,000,000 Da. Using a lower molecular weight ("MW") polyethylene oxide, such as POLYOX™ 1105 (900,000 MW) release for both drugs are higher. Using a higher molecular weight polyethylene oxide (such as POLYOX™ N-60K (2,000,000 MW) or POLYOX™ WSR-301 (4,000,000 MW) reduces the rate of release for both drugs. In one embodiment of the invention, a hydroxypropylmethylcellulose polymer of such molecular weight is utilized so that the viscosity of a 1% aqueous solution is about 4000 cps to greater than 100,000 cps.

[0104] A typical dosage form should swell to approximately 115%, 130%, or 150% of its original volume within 30 minutes after administration, and at a later time should swell to a volume that is at least 130% or more of the original volume.

[0105] The acetaminophen and phenylephrine are dispersed within the polymeric matrix described above. The acetaminophen as used herein is preferably a USP powder. Such powders of acetaminophen are known in the art as difficult to compress into tablet forms. In alternative gastric retentive extended release oral dosage forms comprising acetaminophen and phenylephrine, the acetaminophen used may be a milled form, for example, various COMPAP® compositions (Mallinckrodt, Inc.).

[0106] Dosage forms prepared for oral administration according to the present disclosure will generally contain other inactive additives (excipients) such as binders, lubricants, disintegrants, fillers, stabilizers, surfactants, coloring agents, and the like. Binders are used to impart cohesive qualities to a tablet, and thus ensure that the tablet remains intact after compression. Suitable binder materials include, but are not limited to, starch (including corn starch and pregelatinized starch), gelatin, sugars (including sucrose, glucose, dextrose and lactose), polyethylene glycol, waxes, and natural and synthetic gums, e.g., acacia sodium alginate, polyvinylpyrrolidone, cellulosic polymers (including hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, microcrystalline cellulose, ethyl cellulose, hydroxyethyl cellulose, and the like), and Veegum. Lubricants are used to facilitate tablet manufacture, promoting powder flow and preventing particle capping (i.e., particle breakage) when pressure is relieved. Useful lubricants are magnesium stearate (in a concentration of from 0.25 wt % to 3 wt %, preferably 0.2 wt % to 1.0 wt %, more preferably about 0.3 wt %), calcium stearate, stearic acid, and hydrogenated vegetable oil (preferably comprised of hydrogenated and refined triglycerides of stearic and palmitic acids at about 1 wt % to 5 wt %, most preferably less than about 2 wt %). Disintegrants are used to facilitate disintegration of the tablet, thereby increasing the erosion rate relative to the dissolution rate, and are generally starches, clays, celluloses, algins, gums, or crosslinked polymers (e.g., crosslinked polyvinyl pyrrolidone). Fillers include, for example, materials such as silicon dioxide, titanium dioxide, alumina, talc, kaolin, powdered cellulose, and microcrystalline cellulose, as well as soluble materials such as mannitol, urea, sucrose, lactose, lactose monohydrate, dextrose, sodium chloride, and sorbitol. Solubility-enhancers, including solubilizers per se, emulsifiers, and complexing agents (e.g., cyclodextrins), may also be advantageously included in the present formulations. Stabilizers, as well known in the art, are used to inhibit or retard drug decomposition reactions that include, by way of example, oxidative reactions.

[0107] The oral formulations described herein may also comprise chelating agents. Chelating agents tend to form complexes with trace amount of heavy metal ions inactivating their catalytic activity in the oxidation of medicaments. Eth-

ylenediamine tetracetic acid (EDTA) and its salts, dihydroxy ethyl glycine, citric Acid and tartaric acid are most commonly used chelators.

[0108] The formulations are typically in the form of tablets. Other formulations contain the matrix/active agent particles in capsules. The encapsulating material should be highly soluble so that the particles are freed and rapidly dispersed in the stomach after the capsule is ingested. Such dosage forms are prepared using conventional methods known to those in the field of pharmaceutical formulation and described in the pertinent texts, e.g., in Gennaro, A. R., editor. "Remington: The Science & Practice of Pharmacy", 21st ed., Williams & Williams, and in the "Physician's Desk Reference", 2006, Thomson Healthcare.

[0109] The tablets described herein may have individual layers containing one or both drugs for delivering the component drug(s) in the immediate release or the extended release mode. For example, a layer for immediate release of acetaminophen or both acetaminophen and phenylephrine can be added to the layer containing both drugs for extended release. As to acetaminophen in this embodiment, although at steady state, unlike single dose administration, bioavailability is quite constant between the doses of 325 mg and 2000 mg. This may be desirable for prompt relief or bioavailability enhancement due to first-pass metabolism of acetaminophen or the phenylephrine.

[0110] Alternative gastric retentive drug delivery systems include the swellable bilayer described by Franz, et al., U.S. Pat. No. 5,232,704; the multi-layer tablet with a band described by Wong, et al., U.S. Pat. No. 6,120,803; the membrane sac and gas generating agent described in Sinnreich, U.S. Pat. No. 4,996,058; the swellable, hydrophilic polymer system described in Shell, et al., U.S. Pat. No. 5,972,389, and Shell, et al., WO 9855107, and the pulsatile gastric retentive dosage form by Cowles et al., U.S. Pub. No. 2009/0028941, all of which are incorporated herein by reference.

[0111] If a substantially different release profile is required for the phenylephrine than that achievable from a matrix tablet within which both drugs are combined or if the two drugs are not chemically compatible, a bilayer tablet can be made with one layer containing only the phenylephrine and the other layer containing only the acetaminophen.

[0112] It is also envisioned that a third layer containing one or more drugs for immediate release can be added to the dosage form.

[0113] Thus, the dosage forms provide controlled delivery of acetaminophen, and phenylephrine to the upper GI tract by a polymer matrix that swells unrestrained dimensionally, and is retained in the stomach when taken with food, i.e., in the fed mode. In an environment of use, the dosage forms swell on contact with water from gastric fluid due to the component hydrophilic polymers, (for example, polyethylene oxide and/or hypromellose), and increase in size to be retained in the fed stomach. Acetaminophen and phenylephrine will be released from these gastric retained dosage forms over an extended period of time, about 3 to about 12 hours, preferably about 4 to about 10 hours, more preferably at least about 8 hours, or about 10 hours to the upper gastrointestinal (GI) tract where acetaminophen, and potentially the phenylephrine, is best absorbed,

[0114] The pharmaceutically acceptable dosage form described herein further comprises an immediate release component. The immediate release component comprises acetaminophen and phenylephrine at lower amounts as compared to the amounts of the phenylephrine and the acetaminophen the gastric retained extended release portion of the dosage form. In another aspect, the amount of acetaminophen in generally between about 10 to 20, more typically between 12 to 16 times the amount of phenylephrine in the immediate release component.

[0115] In a preferred aspect, the immediate release component is in contact with the extended release component.

[0116] The immediate release component may further comprise excipients such as binders, lubricants, disintegrants, fillers, stabilizers, surfactants, coloring agents, and the like, as described above for the extended release component.

[0117] The immediate release component may release at least 80-100% of the active agents within the first hour of oral administration.

[0118] It is understood by the skilled artisan that delivery time or duration of drug release by a particular dosage form is distinct from the duration of drug delivery by the dosage form. As an example, while an extended release dosage form may release one or more drugs over a period of 3, 4 or more hours, depending on the half-life of the drug and the time of transit of that drug through the gastrointestinal tract, the relevant sites of absorption will be exposed for a period of time beyond the time of drug release from the dosage form. Thus, for example, a dosage form that releases one or more drugs over a period of approximately 8 hours may be providing delivery of that drug for a period of approximately 12 hours.

[0119] The dosage form, as presently described, possesses the additional advantageous feature of being formulated as a standard oral dosage size, then after administration, imbibing water from the gastric fluid and swelling to a size large enough to be retained in the stomach in a fed mode.

VI. METHODS FOR MAKING SOLID DOSAGE FORMS

[0120] The presently described dosage forms provide for extended release of both acetaminophen and phenylephrine in the stomach at rates proportional to one another wherein the dosage forms are comprised of a polymer matrix that swells upon imbibition of fluid to a size sufficient for gastric retention. Thus, in formulating the dosage forms, it is critical to provide the properties which simultaneously allow: a) an extent of swelling to provide gastric retention over an extended period, and b) a rate of swelling and erosion that allows extended and proportional release of both a highly soluble and poorly soluble drug.

[0121] Furthermore, the formulation of these pharmaceutical oral dosage forms must result in final products that meet the requirements of the Food and Drug Administration. For example, final products must have a stable product that does not fracture during storage and transport. This is measured, in part, in terms of friability and hardness. Dosage forms must also meet the requirements for content uniformity, which essentially means that the dispersion of the active ingredient (s) is uniform throughout the mixture used to make the dosage form, such that the composition of tablets formed from a particular formulation does not vary significantly from one tablet to another. The FDA requires a content uniformity within a range of 95% to 105%.

[0122] It is significant to note that acetaminophen can be a particularly challenging pharmaceutical ingredient with which to formulate solid oral dosage forms. Acetaminophen powders are difficult to compress into a tablet form which will not break or fall apart.

[0123] The ability to formulate a pharmaceutical oral dosage form which both delivers the desired therapeutically effective ingredient and meets FDA requirements depends, in part, upon the process by which the product is made.

[0124] In the case of tablets, as disclosed herein, a first step may involve the granulation. How the granulation is carried out has great impact on the properties of the final product.

[0125] Granulation is a manufacturing process which increases the size and homogeneity of active pharmaceutical ingredients and excipients which comprise a solid dose formulation. The granulation process, which is often referred to as agglomeration, changes important physical characteristics of the dry formulation, with the aim of improving manufacturability, and therefore, product quality.

[0126] Granulation technology can be classified into one of two basic types: Wet granulation and dry granulation. Wet granulation is by far the more prevalent agglomeration process utilized within the pharmaceutical industry.

[0127] Most wet granulation procedures follow some basic steps; the drug(s) and excipients are mixed together, and a binder solution is prepared and added to the powder mixture to form a wet mass. The moist particles are then dried and sized by milling or by screening through a sieve. In some cases, the wet granulation is "wet milled" or sized through screens before the drying step. There are four basic types of wet granulation; high shear granulation, fluid bed granulation, extrusion and spheronization and spray drying.

A. Fluid Bed Granulation

[0128] The fluid bed granulation process involves the suspension of particulates within an air stream while a granulation solution is sprayed down onto the fluidized bed. During the process, the particles are gradually wetted as they pass through the spay zone, where they become tacky as a result of the moisture and the presence of binder within the spray solution. These wetted particles come into contact with, and adhere to, other wetted particles resulting in the formation of particles.

[0129] A fluid bed granulator consists of a product container into which the dry powders are charged, an expansion chamber which sits directly on top of the product container, a spray gun assembly, which protrudes through the expansion chamber and is directed down onto the product bed, and air handling equipment positioned upstream and downstream from the processing chamber.

[0130] The fluidized bed is maintained by a downstream blower which creates negative pressure within the product container/expansion chamber by pulling air through the system. Upstream, the air is "pre-conditioned" to target values for humidity, temperature and dew point, while special product retention screens and filters keep the powder within the fluid bed system.

[0131] As the air is drawn through the product retention screen it "lifts" the powder out of the product container and into the expansion chamber. Since the diameter of the expansion chamber is greater than that of the product container, the air velocity becomes lower within the expansion chamber. This design allows for a higher velocity of air to fluidize the powder bed causing the material to enter the spray zone where granulation occurs before loosing velocity and falling back down into the product container. This cycle continues throughout the granulation process.

[0132] The fluid bed granulation process can be characterized as having three distinct phases; pre-conditioning, granulation and drying. In the initial phase, the process air is pre-conditioned to achieve target values for temperature and humidity, while by-passing the product container altogether. Once the optimal conditions are met, the process air is re-directed to flow through the product container, and the process air volume is adjusted to a level which will maintain sufficient fluidization of the powder bed. This pre-conditioning phase completes when the product bed temperature is within the target range specified for the process.

[0133] In the next phase of the process, the spraying of the granulating solution begins. The spray rate is set to a fall within a pre-determined range, and the process continues until all of the solution has been sprayed into the batch. It is in this phase where the actual granulation, or agglomeration, takes place.

[0134] Once the binder solution is exhausted, the product continues to be fluidized with warm process air until the desired end-point for moisture content is reached. This end-point often correlates well with product bed temperature, therefore in a manufacturing environment, the process can usually be terminated once the target product bed temperature is reached. A typical fluid bed process may require only about thirty to forty-five minutes for the granulation step, plus ten to fifteen minutes on either side for pre-conditioning and drying.

[0135] As with any of the wet granulation processes, the most important variable is the amount of moisture required to achieve successful agglomeration. The fluid bed granulation process requires a "thermodynamic" balance between process air temperature, process air humidity, process air volume and granulation spray rate. While higher process air temperature and process air volume add more heat to the system and remove moisture, more granulating solution and a higher solution spray rate add moisture and remove heat via evaporative cooling. These are the critical process parameters which must be evaluated as a manufacturing process is developed, and the key is understanding the interdependency of each variable.

[0136] Additional factors affecting the outcome of the fluid bed granulation process are the amount and type of binder solution, and the method by which the binder is incorporated within the granulation. However, the most important process variables are the total amount of moisture added through the process, and the rate at which the moisture content is increased. These parameters can have a significant effect on the quality and the characteristics of the granulation. For instance, a wetter fluid bed granulation process tends to result in a stronger granule with a higher bulk density. However, an overly aggressive process, where moisture is added too rapidly, can loose control over achieving the final particle size and particle size distribution objectives.

B. High Shear Granulation

[0137] Most pharmaceutical products manufactured by wet granulation utilize a high shear process, where blending and wet massing are accomplished by the mechanical energy generated by an impeller and a chopper. Mixing, densification and agglomeration are achieved through the "shear" forces exerted by the impeller; hence the process is referred to as high shear granulation.

[0138] The process begins by adding the dry powders of the formulation to the high shear granulator, which is a sealed "mixing bowl" with an impellor which rotates through the powder bed, and a chopper blade which breaks up over-agglomerates which can form during the process. There are

typically three phases to the high shear process; dry mixing, solution addition, or wet massing and high shear granulation.

[0139] In the first phase, dry powders are mixed together by the impeller blade which rotates through the powder bed. The impeller blade is positioned just off the bottom of the product container. There is a similar tolerance between the tips of the impeller blade and the sides of the container. The impeller blades rotation trough the powder bed creates a "roping" vortex of powder movement. The dry mixing phase typically lasts for only a few minutes.

[0140] In the second phase of the process, a granulating liquid is added to the sealed product container, usually by use of a peristaltic pump. The solution most often contains a binder with sufficient viscosity to cause the wet massed particles to stick together or agglomerate. It is common for the solution addition phase to last over a period of from three to five minutes. While the impeller is rotating rather slowly during this step of the process, the chopper blade is turning at a fairly high rate of speed, and is positioned within the product container to chop up over-sized agglomerates, while not interfering with the impellers movement.

[0141] Once the binder solution has been added to the product container, the final stage of the granulation process begins. In this phase, high shear forces are generated as the impeller blades push through the wet massed powder bed, further distributing the binder and intimately mixing the ingredients contained therein. The impeller and chopper tool continue to rotate until the process is discontinued when the desired granule particle size and density end-points are reached. This end-point is often determined by the power consumption and/or torque on the impeller.

[0142] Once the high shear granulation process has been completed, the material is transferred to a fluid bed dryer, or alternatively, spread out onto trays which are then placed in a drying oven, where the product is dried until the desired moisture content is achieved, usually on the order of 1-2% as measured by Loss On Drying technique.

[0143] The most important variable which affects the high shear process is the amount of moisture required to achieve a successful granulation. A key to the process is having the right amount of moisture to allow for agglomeration to occur. Too little moisture will result in an under-granulated batch, with weak bonds between particles and smaller, to non-existent particles, with properties similar to those of the dry powder starting materials. On the other hand, excess moisture can result in a "crashed" batch with results varying from severe over-agglomeration to a batch which appears more like soup.

[0144] Other critical formulation parameters affecting the outcome of the high shear granulation process are the amount and type of binder solution, and the method by which the binder is incorporated within the granulation. For example, it is possible to include some of the binder in the dry powder mixture as well as in the granulating solution, or it may be incorporated only in the granulating solution or only in the dry powder, as is the case where water is used as the granulating solution.

[0145] The high shear granulation process parameters which are variable include impeller and chopper speeds, the solution addition rate, and the amount of time allocated to the various phases of the process. Of these, the most important variables are the solution addition rate and the amount of time the wet massed product is under high shear mixing

C. Extrusion and Spheronization

[0146] This specialized wet granulation technique involves multiple processing steps and was developed to produce very uniform, spherical particles ideally suited for multi-particulate drug delivery of delayed and sustained release dosage forms.

[0147] Similar to high shear granulation initially, the first step involves the mixing and wet massing of the formulation. Once this step is complete, the wet particles are transferred to an extruder which generates very high forces used to press the material out through small holes in the extruder head. The extrudate is of uniform diameter and is then transferred onto a rotating plate for spheronization. The forces generated by the rotating plate initially break up the extruded formulation strands into uniform lengths. Additional dwell time within the spheronizer creates particles which are quite round and very uniform in size. These pellets or spheres must then be dried to the target moisture content, usually within a fluid bed system.

[0148] Particles produced in this manner tend to be very dense, and have a capacity for high drug loading, approaching 90% or more in some cases. Importantly, the particle size is very uniform, and the size distribution is very narrow, as compared to other granulation approaches. This quality assures consistent surface area within and between batches, which is extremely important when functional coatings are subsequently applied to create sustained release formulations, delayed release formulations and formulations designed to target a specific area within the body.

[0149] Uniform surface area is important because the pharmaceutical coating process endpoint is determined not by coating thickness, but by the theoretical batch weight gain of the coating material. If the batch surface area is consistent, then the coating thickness will also be consistent for a given weight gain, and coating thickness is the primary variable in determining the functionality of the coating system, whether the goal is controlling the duration of sustained release formulations or imparting an acid resistant characteristic to "beads" necessary to protect certain compounds which would otherwise be severely degraded in the presence of the acidic environment of the stomach.

D. Spray Drying

[0150] Spray drying is a unique and specialized process which converts liquids into dry powders. The process involves the spraying of very finely atomized droplets of solution into a "bed" or stream of hot process air or other suitable gas. Not typically utilized for the conventional granulation of dosage form intermediates, spray drying has gained acceptance within the industry as a robust process which can improve drug solubility and bioavailability.

[0151] Spray drying can be used to create co-precipitates of a drug/carrier which can have improved dissolution and solubility characteristics. In addition, the process can also be useful as a processing aid. For example, it is much more difficult to maintain the uniformity of a drug in suspension, as compared to the same compound in solution. One may have a need to develop an aqueous coating or drug layering process utilizing a drug which is otherwise not soluble in water. By creating a co-precipitate of the drug and a suitable water soluble carrier, often a low molecular weight polymer, the co-precipitate will remain in solution throughout the manufacturing process, improving uniformity of the spray solution and the dosage form created by the coating process. Uniformity is particularly important where lower doses of potent compounds are intended to be coated onto beads or tablet cores.

[0152] This same process may be used to enhance the solubility and bioavailability of poorly soluble drugs. By complexing certain excipients and the active ingredient within a solvent system which is then spray dried, it is possible to enhance the drugs absorption within the body. Selection of the solvent system, the complexing agent(s) and the ratios utilized within the formulation are all important formulation variables which determine the effectiveness of solubility enhancement utilizing the spray drying technique. Important process parameters which also have a profound effect on drug solubility are the temperatures of the spray solution and process gas, the spray rate and droplet size and the rate of recrystallization. The spray dried granulations created by these techniques can then be incorporated into capsules or tablets by conventional manufacturing processes.

E. Dry Granulation

[0153] The dry granulation process involves three basic steps; the drug(s) and excipients(s) are mixed (along with a suitable binder if needed) and some form of lubrication, the powder mixture is compressed into dry "compacts," and then the compacts are sized by a milling step. The two methods by which dry granulation can be accomplished are slugging and roller compaction.

VII. METHODS OF MAKING THE EXTENDED RELEASE GASTRIC RETENTIVE DOSAGE FORMS DISCLOSED HEREIN

[0154] In one aspect, a method of making a gastric retentive extended-release dosage form as a single layer tablet comprising wet granulation of the phenylephrine and the acetaminophen with the binder is provided. The wet granulation can be a fluid-bed or high shear granulation method. The granulated particles are then blended with additional excipients as needed to form a mixture which is then compressed to form tablets.

[0155] Extended release polymer matrices comprising acetaminophen and phenylephrine are made using either POLYOX™ 1105 (approximate molecular weight of 900,000 Daltons), POLYOX™ N-60K (approximate molecular weight of 2,000,000 Daltons), or POLYOX™ WSR-301 (approximate molecular weight of 4,000,000 Daltons). Prior to compression, components are granulated using a top spray fluid bed granulator A solution of povidone (PVP) in water is sprayed onto the acetaminophen and fluid-bed granulated.

[0156] After fluid bed granulation and drying of the resultant particles, batches are characterized with respect to properties such as final Loss on Drying (LOD), bulk density, tap density, and particle size.

[0157] Loss on Drying (LOD) is determined after each granulation using the Moisture Analyzer. A 1 g samples are taken and loaded into the moisture analyzer. The sample is run for 5 minutes at a temperature of 105° C.

[0158] Bulk and tap densities can be determined as follows. A graduated cylinder is filled with a certain amount of material (82-88 g), and the volume recorded to determine the material bulk density. Tap density can be determined with a help of a Tap Density Tester by exposing the material to 100 taps per test and recording the new volume.

[0159] Particle size determination is performed immediately after granulation, after sieving through 20 mesh screen to remove agglomerates. Particle diameter is determined with a sieve-type particle diameter distribution gauge using sieves with openings of 44, 53, 75, 106, 150, and 250 mesh. Fractions are weighed on Mettler balance to estimate size distribution. This provides determination of the quantitative ratio by particle diameter of composition comprising extended release particles. Sieve analysis according to standard United States Pharmacopoeia methods (e.g., USP-23 NF 18), may be done such as by using a Meinzer II Sieve Shaker.

[0160] The granulated mixture can be blended with the polymer, filler and lubricant in a V-blender. The resultant mixture can be compressed into monolithic, single-layer tablets using a Manesty® BB4 press, with a modified oval 0.3937" width×0.6299" length×0.075" cup depth tool. Tablets may be prepared at a rate, for example, of approximately 800 tablets per minute.

[0161] Tablets are then characterized with respect to disintegration and dissolution release profiles as well as tablet hardness, friability and content uniformity.

[0162] The dissolution profiles for the tablets are determined in USP apparatus (40 mesh baskets), 100 rpm, in pH 5.8 phosphate buffer (0.1 N HCl), 37° C. Samples of 5 ml at each time-point, are taken without media replacement at 1, 2, 4, 6, 8 and 12 hours. The resulting cumulative dissolution profiles for the tablets are based upon a theoretical percent active added to the formulations.

[0163] A tablet must disintegrate before it dissolves. A disintegration tester measures the time it takes a tablet to break apart in solution. The tester suspends tablets in a solution bath for visual monitoring of the disintegration rate. Both the time to disintegration and the disintegration consistency of all tablets are measured. The disintegration profile is determined in a USP Disintegration Tester in pH 5.8 phosphate buffer. Samples, 1 ml at each time-point, may be taken, for example, without media replacement at 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 hours. The resulting cumulative disintegration profiles are based upon a theoretical percent active added to the formulation is determined.

[0164] Tablet hardness changes rapidly after compression as the tablet cools. A tablet that is too hard may not break up and dissolve into solution before it passes through the body. In the case of the presently disclosed gastric retentive dosage forms, a tablet that is too hard may not be able to imbibe fluid rapidly enough to prevent passage through the pylorus in a stomach in a fed mode. A tablet that is too soft may break apart, not handle well, and can create other defects in manufacturing. A soft tablet may not package well or may not stay together in transit.

[0165] After tablets are formed by compression, it is desired that the tablets have a strength of at least 9-25 Kiloponds (Kp)/cm^2, preferably at least about 12-20 (Kp)/cm^2. A hardness tester is used to determine the load required to diametrically break the tablets (crushing strength) into two equal halves. The fracture force may be measured using a Venkel Tablet Hardness Tester, using standard USP protocols.

[0166] Friability is a well-known measure of a tablet's resistance to surface abrasion that measures weight loss in percentage after subjecting the tablets to a standardized agitation procedure. Friability properties are especially important during any transport of the dosage form as any fracturing of the final dosage form will result in a subject receiving less than the prescribed medication. Friability can be determined using a Roche Friability Drum according to standard USP guidelines which specifies the number of samples, the total number of drum revolutions and the drum rpm to be used.

Friability values of from 0.8 to 1.0% are regarded as constituting the upper limit of acceptability.

[0167] The prepared tablets are tested for content uniformity to determine if they meet the pharmaceutical requirement of <6% relative standard deviation (RSD). Each tablet is placed in a solution of 1.0 N HCl and stirred at room temperature until all fragments have visibly dissolved. The solution containing the dissolved tablet is analyzed by HPLC.

[0168] In another aspect, a method of making a bilayer tablet comprising a gastric retentive extended-release layer and an immediate release layer is provided. In a further aspect, the gastric retentive extended-release layer is wet-granulated using the fluid bed or high shear granulation process. In yet a further aspect, the immediate release layer is wet-granulated using the fluid bed or high shear granulation process.

VIII. STABILITY OF PHENYLEPHRINE EXTENDED RELEASE FORMULATIONS

[0169] Stability testing is the primary tool used to assess expiration dating and storage conditions for pharmaceutical products. Many protocols have been used for stability testing, but most in the industry are now standardizing on the recommendations of the International Conference on Harmonization (ICH). These guidelines were developed as a cooperative effort between regulatory agencies and industry officials from Europe, Japan, and the United States.

[0170] Stability testing includes long-term studies, where the product is stored at room temperature and humidity conditions, as well as accelerated studies where the product is stored under conditions of high heat and humidity. Proper design, implementation, monitoring and evaluation of the studies are crucial for obtaining useful and accurate stability data. Stability studies are linked to the establishment and assurance of safety, quality and efficacy of the drug product from early phase development through the lifecycle of the drug product. Stability data for the drug substance are used to determine optimal storage and packaging conditions for bulk lots of the material. The stability studies for the drug product are designed to determine the expiration date (or shelf life). In order to assess stability, the appropriate physical, chemical, biological and microbiological testing must be performed. Usually this testing is a subset of the release testing.

[0171] Studies are designed to degrade the solid drug substance and appropriate solutions, allowing the determination of the degradation profile. The drug substance is usually challenged under a variety of accelerated environmental conditions to evaluate its intrinsic stability and degradation profile.

[0172] HPLC is the predominant tool used to analyze the drug substance and the impurities, particularly for small molecules. Frequently, the same HPLC method may be used for drug substance and drug product, although different sample preparation methods would normally be required. Often the assay and impurity testing can be performed using a single HPLC method. However, the assay and purity determinations may also be separate methods. At least in the U.S., full validation of the analytical method is not required until the end of Phase 2 clinical trials, but the establishment of specificity, linearity and limit of quantification (for impurities) is considered at the earliest stages, since verification of stability hinges on a suitable method for separating impurities from the active ingredient and at least quantifying the impurities relative to the drug substance.

[0173] Stress studies at elevated temperature (e.g., 50° C., 60° C. and 70° C.) for several weeks may be performed to assess thermal stability. Provided the degradation mechanism is the same at the different temperatures used, kinetic or statistical models can be used to determine the rate of degradation at other temperatures (e.g., 25° C.). The solid stability should also be performed in the presence and absence of water vapor to assess the dependence of stability on humidity.

[0174] Degradation studies should also be performed in solution. The solvent used for the solution testing will depend on the solubility of the drug substance and should include water, if the drug substance is water-soluble. Other solutions or solvent systems may be evaluated depending on the anticipated formulation or the synthetic process. A series of buffered solutions in the pH range 2-9 are useful in assessing the impact of solution pH on the degradation. Photostability should also be evaluated. A xenon light source can be used as a stress condition. Alternatively, one can use an accelerated version of either Options 1 or 2 as described in the ICH guideline for determination of photostability. Oxidation of the drug substance under accelerated conditions (e.g., hydrogen peroxide), may also be performed to establish oxidation products that could be formed and sensitivity to oxidative attack.

[0175] Early drug product stability studies are designed to help establish a suitable formulation for delivery of the drug substance. Compatibility studies of the drug substance with excipients should be performed to eliminate excipients that are not compatible with the drug substance.

IX. Methods of Treatment

[0176] In another aspect, a subject suffering from pain and also suffering from ophthalmic disorders (hyperaemia of conjunctiva, posterior synechiae, acute atopic), nasal congestion, hemorrhoids, hypotension, shock, hypotension during spinal anesthesia, or paroxysmal supraventricular tachycardia, by oral administration of a gastric retentive extended release dosage form as described above is provided. Treatment of both acute pain and chronic pain are contemplated.

[0177] Generally, the frequency of administration of a particular dosage form is determined to provide the most effective results in an efficient manner without overdosing and varies according to the following criteria: (1) the characteristics of the particular drug(s), including both its pharmacological characteristics and its physical characteristics, such as solubility; (2) the characteristics of the swellable matrix, such as its permeability; and (3) the relative amounts of the drug and polymer. In most cases, the dosage form is prepared such that effective results are achieved with administration once every eight hours, once every twelve hours, or once every twenty-four hours. As previously discussed, due to the physical constraints placed on a tablet or capsule that is to be swallowed by a patient, most dosage forms can only support a limited amount of drug within a single dosage unit.

[0178] In one embodiment, the dosage form allows a dosing frequency of two times a day (b.i.d.) or three times a day (t.i.d.) to result in sustained plasma concentration of both drugs as compared to current immediate release products which require more frequent administration for effective sustained pain relief.

[0179] Within the context of the present disclosure, the gastric retentive dosage forms have the advantage of improving patient compliance with administration protocols because the drugs may be administered in a once-daily or twice-daily

dosing regimen, rather than the multiple dosing administrations necessary for the immediate release dosage forms of acetaminophen and/or phenylephrine in order to maintain a desired level of therapeutic efficacy. One embodiment of the invention relates to a method of administering a therapeutically effective amount of a combination of acetaminophen and phenylephrine to a patient in need thereof, comprising administering the acetaminophen and phenylephrine or pharmaceutically acceptable salts thereof, in a gastric retentive dosage form once in the morning or evening in a once a day daily regime. Another embodiment comprises administering the gastric retentive dosage form twice a day, for example once in the morning and once in the evening in a twice a day daily dosage regime.

[0180] For all modes of administration, the gastric retentive dosage forms described herein are preferably administered in the fed mode, i.e., with or just after consumption of a small meal (see U.S. Publication No. 2003/0104062, herein incorporated by reference). When administered in the evening fed mode, the gastric retentive dosage form may provide the subject with continued relief from pain through the night and into the next day. The gastric retentive dosage form of the present invention is able to provide pain relief for an extended period of time because the dosage form allows for both extended release of the acetaminophen and phenylephrine and the superior absorption of the drugs in the GI tract.

[0181] In some aspects, the postprandial or fed mode can also be induced pharmacologically, by the administration of pharmacological agents that have an effect that is the same or similar to that of a meal. These fed-mode inducing agents may be administered separately or they may be included in the dosage form as an ingredient dispersed in the shell, in both the shell and the core, or in an outer immediate release coating. Examples of pharmacological fed-mode inducing agents are disclosed in U.S. Pat. No. 7,405,238, entitled "Pharmacological Inducement of the Fed Mode for Enhanced Drug Administration to the Stomach," inventors Markey, Shell, and Berner, the contents of which are incorporated herein by reference.

EXAMPLES

[0182] The following examples illustrate certain aspects and advantages of the subject matter, however, the present invention is in no way considered to be limited to the particular embodiments described below.

Example 1

Acetaminophen (APAP) and Phenylephrine (PE) Combination Formulations

[0183] Dosage forms were made using an phenylephrine HCl ("PE") model. Phenylephrine is highly soluble in water (500 mg/ml) with a molecular weight of 203.67 Daltons (Da).

[0184] Four formulations for the production of extended release 960 mg tablets comprising acetaminophen (APAP), phenylephrine (PE) and a swellable polymer were manufactured using a dry blend process, and hand made on a Carver Auto C Press (Fred Carver, Inc., Indiana). The formulations also included polyvinylpyrrolidone (PVP) and magnesium stearate. In formulations (samples) 3 and 4, microcrystalline cellulose (MCC) was also added. The dry blend process consisted of blending all the ingredients in a glass jar, and compressing into a 960 mg tablet using a 0.3937"×0.7086" Modified Oval die (Natoli Engineering, St. Charles, Mo.). The parameters for the operation of the carver Auto C Press were as follows: 3000 lbs force, 0 second dwell time (the setting on the Carver Press), and 100% pump speed. Samples 1 and 2 contain 650 mg acetaminophen and 30 mg phenylephrine. Samples 3 and 4 contain 500 mg acetaminophen and 30 mg phenylephrine. The formulations for the tablets are set forth below in Tables 1-4:

TABLE 1

	FORMULATION COMPOSITION (wt %)				
Sample No.	APAP	PE	PVP	PEO N-60K	Mg Stearate
1	67.71	3.13	3.88	24.28	1

TABLE 2

	FORMULATION COMPOSITION (wt %)				
Sample No.	APAP	PE	PVP	PEO 1105	Mg Stearate
2	67.71	3.13	3.88	24.28	1

TABLE 3

	FORMULATION COMPOSITION (wt %)					
Sample No.	APAP	PE	PVP	PEO N-60K	MCC	Mg Stearate
3	52.08	3.13	3.88	24.22	16.60	1

TABLE 4

	FORMULATION COMPOSITION (wt %)					
Sample No.	APAP	PE	PVP	PEO 1105	MCC	Mg Stearate
4	52.08	3.13	2.97	24.22	16.60	1

[0185] Gastric retentive acetaminophen (APAP) and phenylephrine (PE) combination 1000 mg tablets were manufactured using a dry blend process, and hand made on a Carver Auto C Press (Fred Carver, Inc., Indiana). The dry blend process consisted of blending all the ingredients in a glass jar, and compressing into a 1000 mg tablet (650 mg APAP and 30 mg PE dose) using a 0.3937"×0.7086" Modified Oval die (Natoli Engineering, St. Charles, Mo.). The parameters for the operation of the carver Auto C Press were as follows: 3000 lbs force, 0 second dwell time (the setting on the Carver Press), and 100% pump speed. The formulations for the tablets are set forth in Table 9:

TABLE 5

	FORMULATION COMPOSITION (wt %)				
Sample No.	APAP	PE	MCC	PEO N-60K	Mg Stearate
5	65	3	0	31	1
6	0	3	65	31	1
7	65	0	3	31	1

[0186] The dissolution profiles for the above samples 1-7 were determined in USP apparatus (40 mesh baskets), 100 rpm, in pH 5.8 phosphate buffer. Samples of 5 ml at each

time-point, were taken without media replacement at 1, 2, 4, 6, 8 and 12 hours. The resulting cumulative dissolution profiles for samples 1-4, based upon a theoretical percent active added to the formulations, are set forth in Tables 6 and 7 below.

TABLE 6

	THEORETICAL wt % OF ACTIVE RELEASED			
	SAMPLE 1		SAMPLE 2	
TIME (HOURS)	APAP	PE	APAP	PE
1	34.0	26.5	22.1	33.6
2	42.5	39.5	32.1	46.5
4	53.8	56.4	46.8	64.5
8	68.4	76.2	66.8	86.4
12	79.0	87.5	80.4	97.6

TABLE 7

	THEORETICAL wt % OF ACTIVE RELEASED			
	SAMPLE 3		SAMPLE 4	
TIME (HOURS)	APAP	PE	APAP	PE
1	10.9	28	11.4	33.7
2	18.3	39.5	21.4	47.7
4	31.1	55.3	38.5	66.3
8	66.5	87.1	79.3	97.7
12	51.5	75.3	62.6	87.3

[0187] The cumulative dissolution release profiles of formulation samples 1-4 are shown in FIG. **1**-FIG. **4**. In each case, an approximately proportional release of the acetaminophen and phenylephrine is observed over a time period of approximately 12 hours.

[0188] The cumulative dissolution profiles for 5, 6 and 7, based upon a theoretical percent active added to the formulations is set forth in Table 8:

TABLE 8

	THEORETICAL wt % OF ACTIVE RELEASED			
	SAMPLE 5		SAMPLE 6	SAMPLE 7
TIME (HOURS)	APAP	PE	PE	APAP
1	11	31.5	21.9	11.7
2	18	44.2	34.4	18.9
4	30	61.3	53.9	30.8
8	49	82.1	77.4	49.5
12	64.6	94	90.2	64.6

[0189] The cumulative dissolution release profiles of samples 5, 6 and 7 are shown in FIG. **5**.

[0190] The disintegration was determined in USP Disintegration Tester in pH 5.8 phosphate buffer. Samples, 1 ml at each time-point, were taken without media replacement at 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 hours. The resulting cumulative disintegration profile, based upon a theoretical percent active added to the formulation is set forth in Tables 7 and 8 below.

TABLE 9

	THEORETICAL wt % OF ACTIVE RELEASED			
	SAMPLE 1		SAMPLE 2	
TIME (HOURS)	APAP	PE	APAP	PE
0.5	31.0	21.2	18.5	26.7
1	38.1	31.7	28.5	38.8
2	48.3	47.1	44.6	57.4
3	57.2	59.9	58.4	72.0
4	66.3	72.4	70.9	85.3
5	73.5	81.5	79.3	93.2
6	81.5	90.3	86.0	98.2
7	87.3	95.5	91.4	100.5
8	91.5	97.6	93.3	100.6

TABLE 10

	THEORETICAL wt % OF ACTIVE RELEASED			
	SAMPLE 3		SAMPLE 4	
TIME (HOURS)	APAP	PE	APAP	PE
1	14.8	29.4	20.9	36.4
2	27.2	43.1	39.9	54.4
4	51.1	65.5	68.7	78.9
6	73.0	82.9	85.8	91.1
8	89.5	93.0	93.3	92.6

[0191] The disintegration release profiles of samples 1-4 are shown in FIG. **6**-FIG. **9**.

[0192] Phenylephrine (PE) release profiles vs. square root of time (SQRT (T)) in samples 1-4 are shown in FIG. **10** and FIG. **11**, respectively. The graphs show that PE release mechanism in the samples are the mixture of diffusion and erosion. The PE release profiles vs. the square root of time for samples 1 and 2 are shown in FIG. **10**. The PE release profiles vs. the square root of time for samples 3 and 4 are shown in FIG. **11**.

[0193] The use of the higher molecular weight polyethylene oxide N60K resulted in a slower rate of release as compared to the use of polyethylene oxide 1105 (for example, compare FIG. **1** and FIG. **2** and compare FIG. **3** and FIG. **4**). Adding microcrystalline cellulose to the formulation having 500 mg acetaminophen and polyethylene oxide N60K resulted in a slower release of acetaminophen as compared to the release of phenylephrine (for example, compare FIG. **1** and FIG. **3** and compare FIG. **6** and FIG. **8**).

Example 2

Manufacture of Gastric Retentive Dosage Forms Having Acetaminophen and Phenylephrine via a Fluid Bed Granulation Process

[0194] An extended release matrix comprising acetaminophen, phenylephrine hydrochloride and one of two poly (ethylene oxide) polymers (POLYOX®) is manufactured using a fluid bed granulation process followed by screening, blending and compression. Each formulation is prepared in a batch (lot) of 1000 g and contains acetaminophen, phenylephrine hydrochloride, and povidone USP (K-29/32). After the granulation, the API granules are screened through USP #20

mesh screen, and blended with various amount of two different grades of POLYOX®, microcrystalline cellulose (Avicel® PH 101 NF), and Magnesium Stearate, NF. The blend is then compressed into tablets and analyzed. Each batch varies in the amount and type of polymer present. Table 11 below shows a sample formulation of each batch with POLYOX® 1105 and POLYOX® N60K. Amounts of microcrystalline cellulose (Avicel® PH 101) are varied based on the amounts of the polymer.

TABLE 11

Polymer (wt/wt %)	Polymer (mg/tablet)	Microcrystalline Cellulose (wt/wt %)	Microcrystalline Cellulose (mg/tablet)
POLYOX ® 1105 (20%)	142.8 mg	(32.9%;)	235.3 mg
POLYOX ® 1105 (32%)	228.8 mg	(20.9%;)	149.4 mg
POLYOX ® 1105 (50%)	356.3 mg	(3.2%;)	23.1 mg
POLYOX ® N60K (10%)	72.0 mg	(42.9%;)	306.5 mg
POLYOX ® N60K (32%)	229.0 mg	(20.9%;)	149.4 mg
POLYOX ® N60K (45%)	322.0 mg	(7.9%;)	56.4 mg

[0195] Batches (lots) of 1 kg each are prepared for each formulation. For each formulation, the acetaminophen is sprayed with a solution of povidone and phenylephrine in water in a fluid bed granulator (GLATT® top spray GPCG1). Fluid bed process parameters including spray rate (10-30 g/ml), inlet air temperature (50-70° C.), and fluidized air volume are varied to maintain the granule product temperature at a range of 28-35° C. Atomization air pressure is maintained at 1.5 bar for the entire granulation process. Granules are dried and blended with the polymer, filler and lubricant using a V-blender (PK blender, Patterson-Kelly Harsco). The polymer and filler are first blended for 10-15 minutes, the lubricant is then added, and blending is continued for another 4 minutes.

[0196] Tablets are then prepared using a Manesty® Beta press, tooled with a modified oval cup depth die. A compression force of 7-13 kN (kilo Newton) is used.

[0197] Disintegration profiles for the tablets produced from the batches described above are determined in USP Disintegration Tester in pH 1.2, 0.1 N HCl at 37±2° C. Samples are taken without media replacement at 1, 2, 4, 6, 7 and 8 hours.

[0198] Content uniformity analysis of the tablets is done by analyzing five tablets from each batch. Each tablet is weighed then transferred to a 250 mL volumetric flask to which 200 mL 0.1 N HCl is added. The flask is then set on a magnetic stirrer, a magnetic stir bar is put into the flash and the solution is stirred at approximately 1000 rpm overnight at room temperature, until all fragments visibly dissolve. Additional 0.1 N HCl is then added to the flask to a final volume of 250 mL and stirred for an additional 30 minutes. One mL of each solution for each tablet is placed into a separate flask and diluted with mobile phase solution (97% water/3% IPA/0.1% TFA, apparent pH=3.0±0.1) for analysis on a Agilent 1100/1200 HPLC system.

[0199] Tablets are tested for hardness using a Venkel Tablet Tester according to standard USP protocol.

Example 3

[0200] Studies are done in vivo to determine erosion time of the gastric retentive dosage form comprising acetaminophen and phenylephrine dispersed in a polymer matrix that swells to a size sufficient for retention in the stomach in the fed mode.

[0201] A randomized 2-way crossover study in 5 healthy female beagle dogs weighing between 12-16 kg is done. Following an overnight fast of at least 14 hours, the dogs are fed 100 g of canned dog food (Pedigree® Traditional ground Dinner with Chunky Chicken).

[0202] Fifteen minutes after the animals consume the food, the dosage forms are administered. In addition to the initial feeding the animals are fed another 100 gm of food 4 hours after the first meal.

[0203] Erosion of the gastric retentive extended-release tablets is assessed using fluoroscopy. Each tablet contains two radio-opaque strings in the shape of an "X". Separation of the strings is considered to signify complete erosion of the tablets. Images are obtained every 30 min until the strings separate. Individual and mean tablet erosion times are determined.

[0204] While a number of exemplary aspects and embodiments have been discussed above, those of skill in the art will recognize certain modifications, permutations, additions and sub-combinations thereof. It is therefore intended that the following appended claims and claims hereafter introduced are interpreted to include all such modifications, permutations, additions and sub-combinations as are within their true spirit and scope.

It is claimed:

1. A dosage form for extended release of acetaminophen and phenylephrine, comprising:

an extended release portion comprising a first dose of acetaminophen and a first dose of phenylephrine, both dispersed in a polymer matrix comprised of at least one hydrophilic polymer that swells upon imbibition of fluid to a size sufficient for gastric retention in a gastrointestinal tract of a subject in a fed mode, said first dose of acetaminophen released from the dosage form through erosion of the polymer matrix, and said first dose of phenylephrine released from the dosage form at a rate proportional to release of the acetaminophen during a period of gastric retention of between about 4 to about 8 hours.

2. The dosage form of claim **1**, wherein the first dose of phenylephrine is released from the polymer matrix by diffusion.

3. The dosage form of claim **1**, wherein the polymer matrix erodes during a period of drug release, wherein the period of drug release is at least 8, 9, 10, 11 or 12 hours.

4. The dosage form of claim **1**, wherein the first dose of acetaminophen is approximately 400 mg to 800 mg and the first dose of phenylephrine is approximately 7.5-30 mg.

5. The dosage form of claim **1**, wherein the polymer is a poly(ethylene oxide) having a molecular weight of between about 500,000 Daltons to about 12,000,000 Daltons.

6. The dosage form of claim **1**, wherein the polymer is present in an amount ranging from about 35 weight percent to about 50 weight percent of the extended release portion.

7. The dosage form of claim **1**, further comprising an immediate release portion comprising a second dose of acetaminophen and a second dose of phenylephrine, both of the second doses dispersed in the immediate release portion, said immediate release portion in contact with said extended release portion.

8. A method of making a dosage form for the extended release of acetaminophen and phenylephrine comprising, dry-blending the acetaminophen and the phenylephrine with at least one excipient to make a dry-blend mixture.

9. The method of claim **8**, further comprising compressing the dry-blend mixture into a tablet and coating the tablet with an outer layer comprising a second drug, wherein the second drug is release immediately after ingestion or immersion in fluid.

10. The method of claim **9**, wherein the second drug is phenylephrine.

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