IMMEDIATE RELEASE COMPOSITIONS AND METHODS FOR DELIVERING DRUG FORMULATIONS USING WEAK ACID ION EXCHANGE RESINS IN ABNORMALLY HIGH PH ENVIRONMENTS

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ABSTRACT

Multi-layer solid oral dosage immediate release and extended release compositions and methods for delivering drugs in abnormally high pH environments wherein the extended release layer is formed from a drug resinate of a strong acid ion-exchange resin and a release rate retarding polymer compressed together.

IR Layer (Drug/IRP88 Resinate +FeCl₃)

ER Layer
(Drug/IRP69 resinate + Release Rate Retarding Polymer Compressed Together)

An unbound drug layer
Figure 1

- **IR Layer (Drug/IRP88 Resinate + FeCl₃)**
- **ER Layer (Drug/IRP69 Resinate + Release Rate Retarding Polymer Compressed Together)**
- An unbound drug layer
Figure 3

Dissolution Profile of Pseudoephedrine HCL

Cumulative % released vs Time (h)
Figure 4

Dissolution of Hydrocodone from Neat HCBT/IRP69 Resinate

% Cumulative % Drug Released

0 10 20 30 40 50 60 70 80 90 100

Time (min)

900 ml 0.1 N HCl 50 RPM Paddle
Figure 5

Dissolution of Codeine & Pseudoephedrine HCl in 0.1N HCl

Tri-layer tablet

- Codeine in 0.1N HCl
- Pseudoephedrine HCl in 0.1N HCl

% Dissolution vs. Time (hr)
Figure 6

Dissolution of Codeine from Neat Codeine/lRP69 Resinate

900 ml 0.1 N HCl 50 RPM Paddle

Cumulative % Drug Released

Time (min)
IMMEDIATE RELEASE COMPOSITIONS AND METHODS FOR DELIVERING DRUG FORMULATIONS USING WEAK ACID ION EXCHANGE RESINS IN ABNORMALLY HIGH PH ENVIRONMENTS

CROSS REFERENCE TO RELATED APPLICATIONS


BACKGROUND OF THE INVENTION

[0002] The present invention relates to novel pharmaceutical compositions that provide both immediate drug release (IR) and extended drug release even at higher than normal stomach pH levels. The formulations are based on drug resins of weak acid ion exchange resins.

[0003] Formulations containing weak acid ion exchange resins are frequently used for immediate release of pharmaceutical agents in a patient’s stomach. However, release from weak acid resins is slowed and/or reduced at higher than normal stomach pH levels. High pH levels could occur if the patient is taking medications such as proton pump inhibitors (PPIs) or has a disease state that induces hyperchlohydria or achlorhydria. In either case, a weak acid formulation may not release the medicament at a rate or to an extent adequate to achieve the desired therapeutic effect.

[0004] Approximately 60 million prescriptions were written for PPIs in 2006. Additionally, in the U.S., another 10 million people were reported to have self medicated with PPIs in 2008. Furthermore, about one in three adults used antacids on a regular basis. Collectively, these statistics suggest that close to 100 million people in the U.S. could be taking a drug that could significantly interfere with the release profile of a weak acid ion exchange resin formulation. The history of prior art dosage forms indicates that a serious need has existed for novel and useful solid oral dosage forms that provide the immediate release properties of weak acid IER formulations when administered to a patient with stomach pH environments at about 1.5 to 2.0 and above. This need was met in part by commonly owned U.S. Pat. No. 8,187,617. It was shown that weak acid resins can be formulated to have immediate release characteristics at pH levels above about 1.5 to 2.0 by adding a release enhancing agent to the formulation to increase the rate and extent of drug release from the formulation.

[0005] It is also desirable in many instances that a drug be released in a sustained manner over a period of about 8 hours. Both immediate release (IR) and extended release (ER) of one or more drugs may be needed.

[0006] An extended release preparation is usually achieved using a release rate retarding coating over the drug-resin complex using polymers like, hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC) Eudragit® polymers (manufactured by Degussa Rohm Pharma Polymers of Germany), polyvinyl alcohol either alone or in combination over the drug-resin particles/beads.

[0007] However, achieving extended release by coating drug-resin particles/beads is beset with multiple issues like, (i) non-uniform coating over individual particles/beads, (ii) agglomeration of the particles/beads during coating and rupturing of the coat during subsequent sieving/sifting operation, (iii) issues in reproducibility of in vitro drug release kinetics due to (i) & (ii) above, and (iv) cracking of the coating during a tablet compression process. For the reasons mentioned above extended release polymer coated particles/beads can cause dose dumping on oral administration. For reasons (iv) extended release beads are usually filled into capsules rather than being tableted.

[0008] Surprisingly and unexpectedly, an extended release profile can be created without the use of coated particles.

SUMMARY OF THE INVENTION

[0009] As described in commonly owned U.S. Pat. No. 8,187,617 B2, it has been found that by adding a release enhancing agent with a strong affinity for the ionic resin to a weak acid resin drug formulation, much more rapid and complete release of a resinated drug can be attained in abnormal gastric fluid than otherwise would occur without the presence of the release enhancing agent, in abnormal human gastric fluid wherein the pH is much higher than normal due to the use of drugs such as PPI or the presence of disease states such as H. pylori or atrophic gastritis that can lead to hypochlohydria and achlorhydria.

[0010] Thus, one can attain the rapid release properties of weak acid resins while retaining the low sensitivity to pH change associated strong acid resins by adding a release enhancing agent to the weak acid drug formulation.

[0011] It is also desirable in many instances that a drug be released in a sustained manner over a period of about 8 hours. Both immediate release (IR) and extended release (ER) of one or more drugs may be needed.

[0012] Immediate release is defined as at least 80% release of a pharmacologically active agent within 45 minutes in a standard dissolution apparatus according to the USP 34 NF 26 section 711.

[0013] An extended release drug preparation is usually achieved using a release rate retarding coating over the drug-resin complex. However, as noted above, achieving extended release by coating drug-resin particles/beads is beset with multiple issues.

[0014] Surprisingly and unexpectedly, an extended release profile can be created without the use of coated particles. Instead of coating the particles, the present invention uses wet and dry granulation techniques to generate a dry blend of granules of particles/beads of a drug resinate mixed with a release rate retarding polymer. By compressing this blend of particles/beads of drug resinate with these release rate retarding polymers, an extended release profile is obtained while significant reduction in processing complexity is realized. More specifically the need for spray coating of the ion exchange resinate is avoided while at the same time extended release behavior is assured by having the ion exchange resinate enveloped in the blend of polymeric material. It is well known to those versed in the technology that particle coating is a time intensive as well as a problematic process. This is avoided by using the polymeric material and ion exchange resinate blend during compression of the desired dosage form.
In a first embodiment, the invention is a multi-layer solid oral pharmaceutical composition comprising:

(i) a first distinct layer comprising:

(a) a first pharmaceutically active agent bound to a weak acid ion exchange resin to form a weak acid ion-exchange resinate; and

(b) a release-enhancing agent consisting of FeCl₃;

(ii) at least a second distinct layer comprising:

(a) a drug selected from the group consisting of said first pharmaceutically active agent and a second pharmaceutically active agent, said drug being bound to a strong acid ion exchange resin to form a strong acid ion-exchange resinate; and

(b) a release rate retarding polymer susceptible to gastrointestinal dissolution to slow and extend release of the drug contained in said at least second layer;

wherein said strong acid ion-exchange resinate and said polymer have been compressed together; and wherein said pharmaceutical composition is capable of immediate release of said first pharmaceutically active agent from said weak acid resinate at a pH of at least 1.5, immediate release being defined as at least 80% release of said pharmaceutically active agent within 45 minutes in a standard dissolution apparatus according to USP 34 NF 26 section 711; and, wherein said release of the drug from said strong acid resinate continues over a period of at least 8 hours after ingestion.

In a second embodiment, the invention is the method of treating a patient with a stomach pH of at least about 1.5 comprising administration of a multilayer solid oral dosage form, said dosage form comprising:

(i) a first distinct layer comprising:

(a) a first pharmaceutically active agent bound to a weak acid ion exchange resin to form a weak acid ion-exchange resinate; and

(b) a release-enhancing agent selected from the group consisting of an inorganic salt and an organic base;

(ii) at least a second distinct layer comprising:

(a) a drug selected from the group consisting of said first pharmaceutically active agent and a second pharmaceutically active agent, said drug being bound to a strong acid ion exchange resin to form a strong acid ion-exchange resinate; and,

(b) a release rate retarding polymer susceptible to gastrointestinal dissolution to slow and extend release of the drug contained in said at least second layer;

wherein said strong acid ion-exchange resinate and said polymer have been compressed together; and wherein said pharmaceutical composition is capable of immediate release of said first pharmaceutically active agent from said weak acid resinate at a pH of at least 1.5, immediate release being defined as at least 80% release of said pharmaceutically active agent within 45 minutes in a standard dissolution apparatus according to USP 34 NF 26 section 711; and, wherein said release of the drug from said strong acid resinate continues over a period of at least 8 hours after ingestion; and wherein said first condition is selected from the group consisting of Helicobacter pylori infection, atrophic gastritis, hypochlorhydria and achlorhydria in the stomach; and wherein said second condition is a condition other than said first condition.

In a fourth embodiment, the invention is a method of treating a patient wherein the patient has within the past 24 hours been administered a compound selected from the group consisting of a proton pump inhibitor, an H₂ receptor antagonist, and an antacid, said method comprising the step of administering a solid oral dosage pharmaceutical composition, said solid oral dosage pharmaceutical composition comprising:

(i) a first distinct layer comprising:

(a) a first pharmaceutically active agent bound to a weak acid ion exchange resin to form a weak acid ion-exchange resinate; and,

(b) a release-enhancing agent selected from the group consisting of an inorganic salt and an organic base;

(ii) at least a second distinct layer comprising:

(a) a pharmaceutically active agent selected from the group consisting of said first pharmaceutically active agent and a second pharmaceutically active agent, said pharmaceutically active agent bound to a strong acid ion exchange resin to form a strong acid ion-exchange resinate; and,

(b) a release rate retarding polymer susceptible to gastrointestinal dissolution to slow and extend release of the drug contained in said at least second layer;

wherein said strong acid ion-exchange resinate and said polymer have been compressed together; and
wherein said pharmaceutical composition is capable of immediate release of said first pharmaceutically active agent from said weak acid resinate at a pH of at least 1.5, immediate release being defined as at least 80% release of said pharmaceutically active agent within 45 minutes in a standard dissolution apparatus according to USP 34 NF 26 section 711; and, wherein release of the drug from said strong acid resinate continues over a period of at least 8 hours after ingestion.

In a fifth embodiment, the invention is method of delivering a pharmaceutically active agent to a patient, said method comprising orally administering a solid oral dosage composition comprising:

(i) a first distinct layer comprising:
(a) a first pharmaceutically active agent bound to a weak acid ion exchange resin to form a weak acid ion-exchange resinate; and
(b) a release-enhancing agent selected from the group consisting of an inorganic salt and an organic base;

(ii) at least a second distinct layer comprising:
(a) a pharmaceutically active agent selected from the group consisting of said first pharmaceutically active agent and a second pharmaceutically active agent, said pharmaceutically active agent bound to a strong acid ion exchange resin to form a strong acid ion-exchange resinate; and,

b) a release rate retarding polymer susceptible to gastrointestinal dissolution to slow and extend release of the drug contained in said at least second layer;

wherein said strong acid ion-exchange resinate and said polymer have been compressed together; and wherein said pharmaceutical composition is capable of immediate release of said first pharmaceutically active agent from said weak acid resinate at a pH of at least 1.5, immediate release being defined as at least 80% release of said pharmaceutically active agent within 45 minutes in a standard dissolution apparatus according to USP 34 NF 26 section 711; and, wherein release of the drug from said strong acid resinate continues over a period of at least 8 hours after ingestion.

In a second embodiment, the invention is method of treating a patient with a stomach pH of at least about 1.5 comprising administration of a multilayer solid oral dosage form, said dosage form comprising:

(ij) a first distinct layer comprising:
(a) a first pharmaceutically active agent bound to a weak acid ion exchange resin to form a weak acid ion-exchange resinate; and
(b) a release-enhancing agent selected from the group consisting of an inorganic salt and an organic base;

(ii) at least a second distinct layer comprising:
(a) a drug selected from the group consisting of said first pharmaceutically active agent and a second pharmaceutically active agent, said drug being bound to a strong acid ion exchange resin to form a strong acid ion-exchange resinate; and,

(b) a release rate retarding polymer susceptible to gastrointestinal dissolution to slow and extend release of the drug contained in said at least second layer;

wherein said strong acid ion-exchange resinate and said polymer have been compressed together; and wherein said pharmaceutical composition is capable of immediate release of said first pharmaceutically active agent from said weak acid resinate at a pH of at least 1.5, immediate release being defined as at least 80% release of said pharmaceutically active agent within 45 minutes in a standard dissolution apparatus according to USP 34 NF 26 section 711; and, wherein release of the drug from said strong acid resinate continues over a period of at least 8 hours after ingestion.

The pharmaceutical compositions of the invention are characterized by faster, and/or more complete, drug release compared to a weak acid resin formulation without the release enhancing agent in pH environments at or above
about 1.5 to 2.0. When administered to a patient, the release-enhancing agent results in immediate release of the pharmaceutically active agent(s) from the weak acid ion exchange resin in pH environments at or above about 1.5 to 2.0.

[0078] The multilayer pharmaceutical compositions of the invention are formed as compressed tablets. However, the tablets of the invention can be of miniature dimension such that many miniature tablets can be inserted into a capsule of a size suitable for oral ingestion. The invention includes such capsules.

[0079] The drug release kinetics of weak acid resins can be affected by higher pH levels in the gastric fluid such that the rate and/or extent of drug release can be greatly reduced. Adding a release-enhancing agent to a weak acid formulation is useful for assuring that the resinated drug is released from an IER formulation when stomach acid is reduced or eliminated (hypochlorhydria and achlorhydria) by disease states such as Helicobacter (H.) pylori infection or atrophic gastritis.

[0080] By adding a release-enhancing agent with a strong affinity for the ion exchange resins used in the invention, for example, the potassium salt of carboxylated polymethacrylates such as Amberlite™ IRP88 (CAS Registry Number 39394-76-5) manufactured by Dow Chemical, and DowEX MAC-3, manufactured by Dow Chemical but other weak acid ion exchange resins may be used.

[0081] Weak acid ion exchange resins useful in the invention include, for example, the potassium salt of carboxylated polymethacrylates such as Amberlite™ IRP88 (CAS Registry Number 39394-76-5) manufactured by Dow Chemical, and DowEX MAC-3, manufactured by Dow Chemical but other weak acid ion exchange resins may be used.

[0082] The release-enhancing agent can be, for example, a highly soluble inorganic salt (e.g., FeCl₃, Fe₂(C₂O₄)₃, CaCl₂, Na₂CO₃, MgCl₂) or an organic base (e.g., thymine, guanine, or cytosine).

[0083] The pharmaceutical composition includes at least a second distinct layer. This second layer comprises: (a) a pharmaceutical active agent bound to strong acid ion exchange resin forming a reservoir; and, (b) a release rate retarding polymer susceptible to gastrointestinal dissolution to slow and extend release of the drug contained in said at least second layer wherein said strong acid ion-exchange reservoir and said polymer are compressed together.

[0084] The strong acid ion exchange resin in the second layer can be bound to the same or different pharmaceutically active agent as the weak acid ion exchange resin.

[0085] Strong acid ion exchange agents useful in the invention include sulfonated polysyrenic resins such as Amberlite IRP69, and Dowex 88, but other strong acid ion exchange resins may be used.

[0086] The release rate retarding polymer can be any of a number of non-toxic materials susceptible to gastrointestinal dissolution. It may be a polymer conventionally used in coatings for extending drug release such as, but not limited to, hydroxypropyl methylcellulose (hpmcellose), ethyl cellulose (EC), polyethylene oxide, Eudragit™ polymers (manufactured by Degussa Rohm Pharma Polymers of Germany), the Carboxop™ polymers (manufactured by Lubrizol Corp.), polyvinyl alcohol, hydrogenated vegetable oil, methacrylate copolymers, polyacrylic acid, and their combinations with one another or with other suitable polymers.

[0087] The tablets of the invention may comprise three or more layers. A pharmaceutical active agent in the third, or yet additional layers, may be bound to ion-exchange resin, or it may be unbound, i.e., not bound to an ion-exchange resin.

[0088] The weight ratio of drug to ion-exchange resin in either a weak acid or strong acid resinate can be varied to adjust a release profile. Preferably, the drug to resin weight ratio in a resinate is from about 1:0.5 to about 1:10. More preferably, the drug to resin weight ratio in a resinate is from about 1:0.75 to about 1:5. Most preferably, the drug to resin weight ratio in a resinate is from about 1:1 to about 1:3.

[0089] The drug/ion-exchange resinate employed in the inventive compositions and methods are produced by known methods, as for example as described in Example 1 of U.S. Pat. No. 8,187,617 B2. After formation of a resinate, the resinate is preferably granulated and sieved into particles that pass a screen size of about 1000 microns (#18 screen). Preferably, resinate particles pass a 841 micron (#20 screen), and most preferably pass a screen size of about 420 microns (#40 screen).

[0090] The weight ratio of release enhancing agent to drug resinate in the IER layer is preferably from about 1:50 to about 1:1. More preferably, the release enhancing agent to drug resinate weight ratio is from about 1:20 to about 1:2.

[0091] The weight ratio of drug in first distinct layer (IER layer) to the drug in the second distinct layer (ER layer) can also be varied to adjust a release profile. The weight ratio of IER drug to ER drug is preferably from about 10:90 to about 90:10. More preferably, the weight ratio of IER drug to ER drug is from about 20:80 to about 80:20; yet more preferably from about 30:70 to about 70:30; and most preferably from about 40:60 to about 60:40.

[0092] The weight of release rate retarding polymer in an ER layer is preferably from about 5 to about 90 percent by weight of the layer, and more preferably from about 10 to about 80 percent by weight of the layer.

[0093] Compression of an ER layer preferably occurs during the tabletting operation. Tabletting is at a compression force of from about 100 Newtons to about 300 Newtons. The person of ordinary skill in the art will adjust the tabletting pressure to obtain the desired tablet thickness and strength.

[0094] By “release-enhancing agent” it meant an agent that, when added to a drug resin formulation, increases the rate and/or the extent of drug release than would otherwise occur without the release-enhancing agent in the same formulation.

[0095] By “pharmaceutically active agent” meant agents other than food articles that are intended to diagnose, cure, mitigate, treat or prevent disease in man or other animals or that are intended to affect the structure or any function of the body of man or other animals that are physiologically acceptable. The agent could be a combination of drug therapies as well as a single agent.

[0096] By “physiologically acceptable” meant those substances that are adequately tolerated without causing unacceptable negative side effects.

[0097] By “ion exchange resin” is meant an insoluble solid matrix that carries exchangeable ions with either a positive or negative charge. The trapping of ions takes place only with simultaneous releasing of other ions. Ions are exchanged in stoichiometrically equivalent amounts of other ions with the same electrical charge when the ion exchange material is in contact with an electrolyte solution.
By "resinate" is meant the complex formed when a drug exchanges an ion with a resin particle in the stoichiometric process described above and a drug/resin compound is formed.

By "weak acid ion exchange resin" is meant in a weak acid resin the ionizable group introduced to the polymer is a carboxylic acid (COOH) as opposed to the sulfonic acid group (SO₃H) used in strong acid resins. These resins behave similarly to weak organic acids so are weakly dissociated i.e. have fewer ions available for exchange.

"Immediate release" (IR) is meant that the pharmaceutically active agent is released from the IR portion of the formulation such that 80%, 85%, 90%, or even 95% of the pharmaceutically active agent in the IR portion is released within 45 minutes when dissolution is measured according to the USP 34 NF 26 section 711.

"Extended release" is meant that the pharmaceutically active agent is released from the formulation at a controlled rate such that the formulation allows for a reduction in dosing frequency as compared to that presented by a conventional dosage form, e.g. an immediate release dosage form.

"Strong acid ion exchange resin" is meant a cation exchange resin in which the ion exchange groups are completely dissociated at all pHs. As an example, in a strong acid resin the ionizable group introduced to the polymer is a sulfonic acid group (SO₃H) as opposed to the carboxylic acid (COOH) used in weak acid resins.

Release-Enhancing Agents

The drug-containing weak acid ion exchange resins of the invention are formulated with release-enhancing agents. These release-enhancing agents result in immediate release of the drug from the weak acid ion exchange resins in pH environments at or above 2.0. Examples of suitable release-enhancing agents are:

Inorganic Agents:
- FeCl₃
- Fe₂(SO₄)₃
- CaCl₂
- MgCl₂
- FeCl₂

Organic Agents:
- Thymine
- Guanine
- Cytosine

The release rate retarding polymer can be any of a number of non-toxic materials susceptible to gastrointestinal dissolution. It may be a polymer conventionally used in coatings for extending drug release such as, but not limited to, hydroxypropyl methylcellulose (hpmc), ethyl cellulose (ec), polyethylene oxide, Eudragit™, polymers (manufactured by Degussa Rohm Pharma Polymers of Germany), the Carbopol™ polymers (manufactured by Lubrizol Corp), polyvinyl alcohol, hydrogenated vegetable oil, and their combinations with one another or with other suitable polymers.

Pharmaceutically Active Agents

The invention features methods and compositions for immediate release of pharmaceutically active agents using a weak acid ion exchange resin.

Examples of such pharmaceutically active agents suitable for the compounds and methods of the inventions are:

- Anti-tussives, e.g., benzotanate, caramphene ecdysate, chlorphedianol, codeine, dextromethorphan hydrobromide, hydrocortone, levopropoxyphene, morphine codeine, ethylmorphine, dicycloverine, benzylmorphine, laudanum, dicycloxycodeine, nicocodeine, nicocholine, hydromorphone, acetyldihydrocodeine, thebacon, diamorphine (heroin), acetylmorphine, noscapine, and pholcodine.

- Narcotic analgesics, e.g., codeine, oxycodone, hydrocodone, diamorphine, pethidine, morphine, oxymorphone, nalorphine, naloxone, nalbixone, opioid, hydromorphone, nicomorphine, dihydrocodeine, and papaveretum.

- Decongestants, e.g., pseudoephedrine hydrochloride, phemylephrine bitartrate, phemylephrine hydrochloride and pseudoephedrine sulfate.

- Non-steroidal anti-inflammatory drugs, e.g., aspirin, magnesium salicylate, diclofenac, etodolac, indometacin, naproxetone, sultindac, tolmetin, ibuprofen, ketoprofen, nafenamic acid, meclofenamic acid, phenylbutazone, piroxicam, meloxicam, celecoxib, parecoxib, rofecoxib, valdecoxib, and naproxen sodium.

- Anti-emetics, e.g., dolasetron, granisetron, ondansetron, tropisetron, palonosetron, mirtazapine, metoclopramide, cyclizine, diphenhydramine, dimenhydrinate, meclizine, promethazine, and hydroxyzine.

- Anti-histamines, e.g., diphenhydramine, loratadine, desloratadine, meclozine, fexofenadine, pheniramine, cetirizine, promethazine, brompheniramine, clemastine fumarate and chlorpheniramine.

- Proton pump inhibitors (PPI), e.g., omeprazole, esomeprazole, pantoprazole, lansoprazole, and rabeprazol.

- H2 Antagonists, e.g., cimetidine, ranitidine, and famotidine.

- Anti-depressants, e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, desvenlafaxine, duloxetine, milnacipran, venlafaxine, atomoxetine, mazindol, reboxetine, vloxazine, amitriptyline, clomipramine, doxepin, imipramine, trimipramine, desipramine, norltryptiline, prontryptiline, moclobemide, phenalexine, and selegiline.

- Tranquilizers, e.g., amobarbital, pentobarbital, secobarbital, phenobarbital, clozaepam, dizepam, estazolam, flurazepam, lorazepam, midazolam, nitrazepam, ozaepam, triazolam, temazepam, chlorzaidepoxide, and alprazolam.

- Anti-convulsants, e.g., felbamate, carbamazepine, oxicarbazepine, vigabatrin, progabide, tiagabine, topiramate, gabapentin, pregabalin, ethtoin, and phenytoin.

- Hypnotics, e.g., zolpidem, zaleplon, zopiclone, and eszopiclone.

- Muscle relaxants, e.g., methocarbamol, carisoprodol, chlorzoxazine, cyclobenzaprine, gabapentin, metaxalone, and orphenadrine.

- Anti-psychotics, e.g., haloperidol, droperidol, chlorpromazine, fluphenazine, perphenazine, prochlorperazine, thioridazine, trifluoperazine, mesoridazine, promazine, trifluropromazine, levoemepromazine, mehtothrimpeprazine, pimozide, chlorprothixene, flupenthixol, thiouixene, zuclopenthixol, clozapine, olanzapine, risperidone, quetiapine, ziprasidone, amisulpride, asenapine, and paliperidone.

- Anti-microbial, e.g., EDTA, zinc compounds, trickson, domiphen, cetyl pyridium chloride, domiphen bromide, fluorides, alexidine, and ochintidine.

- Anti-diarrheals, e.g., bismuth subsalicylate and loperamide.

- CNS stimulants, e.g., caffeine, cocaine, and amphetamines.
0135] S: Attention Deficit and Hyperactivity Disorder drugs, e.g., methylphenidate, dextroamphetamine sulfate, amphetamine, and atomoxetine hydrochloride.

0136] The invention also includes methods and compositions for delivering combinations of pharmaceutically active compounds. Examples of such combinations are:

0137] A: an anti-tussive and an antihistamine

0138] B: an anti-tussive and a decongestant

0139] C: an anti-tussive and an analgesic

0140] D: an anti-tussive and an NSAID

0141] E: an anti-tussive and an antihistamine and a decongestant

0142] F: an anti-tussive and an antihistamine and an analgesic

0143] G: an anti-tussive and an antihistamine and an NSAID

0144] H: an anti-tussive and an antihistamine and a decongestant and an analgesic

0145] I: a muscle relaxant and an analgesic

0146] J: a muscle relaxant and an NSAID

0147] K: a muscle relaxant and an analgesic and an NSAID

0148] L: a PPI and an NSAID

0149] M: an H2 antagonist and an NSAID

0150] N: a PPI and an analgesic

0151] O: an H2 antagonist and an analgesic

0152] Dosage Forms

0153] Suitable dosage forms include a multiple layer compressed tablet and a capsule containing multiple miniature compressed tablets.

0154] In a third embodiment, the invention is a method of treating a patient having a first condition and a second condition with a pharmaceutically active agent effective for treating said second condition, said method comprising the step of administering a solid oral dosage pharmaceutical composition, said solid oral dosage pharmaceutical composition comprising:

0155] (i) a first distinct layer comprising:

0156] (a) a first pharmaceutically active agent bound to a weak acid ion exchange resin to form a weak acid ion-exchange resinate; and,

0157] (b) a release-enhancing agent selected from the group consisting of an inorganic salt and an organic base;

0158] (ii) at least a second distinct layer comprising:

0159] (a) pharmaceutically active agent selected from the group consisting of said first pharmaceutically active agent and a second pharmaceutically active agent, said pharmaceutically active agent bound to a strong acid ion exchange resin to form a strong acid ion-exchange resinate; and,

0160] (b) a release rate retarding polymer susceptible to gastrointestinal dissolution to slow and extend release of the drug contained in said at least second layer;

0161] wherein said strong acid ion-exchange resinate and said polymer have been compressed together; and wherein said pharmaceutical composition is capable of immediate release of said first pharmaceutically active agent from said weak acid resinate at a pH of at least 1.5, immediate release being defined as at least 80% release of said pharmaceutically active agent within 45 minutes in a standard dissolution apparatus according to USP 34 NF 26 section 711; wherein release of the drug from said strong acid resinate continues over a period of at least 8 hours after ingestion; and wherein said first condition is selected from the group consisting of Helicobacter pylori infection, atrophic gastritis, hypochlorhydria and achlorhydria in the stomach; and wherein said second condition is a condition other than said first condition.

0162] In a fourth embodiment, the invention is a method of treating a patient wherein the patient has within the past 24 hours been administered a compound selected from the group consisting of a proton pump inhibitor, an H2 receptor antagonist, and an antacid, said method comprising the step of administering a solid oral dosage pharmaceutical composition, said solid oral dosage pharmaceutical composition comprising:

0163] (i) a first distinct layer comprising:

0164] (a) a first pharmaceutically active agent bound to a weak acid ion exchange resin to form a weak acid ion-exchange resinate; and,

0165] (b) a release-enhancing agent selected from the group consisting of an inorganic salt and an organic base;

0166] (ii) at least a second distinct layer comprising:

0167] (a) pharmaceutically active agent selected from the group consisting of said first pharmaceutically active agent and a second pharmaceutically active agent, said pharmaceutically active agent bound to a strong acid ion exchange resin to form a strong acid ion-exchange resinate; and

0168] (b) a release rate retarding polymer susceptible to gastrointestinal dissolution to slow and extend release of the drug contained in said at least second layer;

0169] wherein said strong acid ion-exchange resinate and said polymer have been compressed together; and wherein said pharmaceutical composition is capable of immediate release of said first pharmaceutically active agent from said weak acid resinate at a pH of at least 1.5, immediate release being defined as at least 80% release of said pharmaceutically active agent within 45 minutes in a standard dissolution apparatus according to USP 34 NF 26 section 711; and, wherein release of the drug from said strong acid resinate continues over a period of at least 8 hours after ingestion.

0170] In a fifth embodiment, the invention is a method of delivering a pharmaceutically active agent to a patient, said method comprising orally administering a solid oral dosage pharmaceutical composition comprising:

0171] (i) a first distinct layer comprising:

0172] (a) a first pharmaceutically active agent bound to a weak acid ion exchange resin to form a weak acid ion-exchange resinate; and

0173] (b) a release-enhancing agent selected from the group consisting of an inorganic salt and an organic base;

0174] (ii) at least a second distinct layer comprising:

0175] (a) pharmaceutically active agent selected from the group consisting of said first pharmaceutically active agent and a second pharmaceutically active agent, said pharmaceutically active agent bound to a strong acid ion exchange resin to form a strong acid ion-exchange resinate; and,
a release rate retarding polymer susceptible to gastrointestinal dissolution to slow and extend release of the drug contained in said at least second layer;

wherein said strong acid ion-exchange resin and said polymer have been compressed together; and

wherein said pharmaceutical composition is capable of immediate release of said first pharmaceutically active agent from said weak acid resinate at a pH of at least 1.5, immediate release being defined as at least 80% release of said pharmaceutically active agent within 45 minutes in a standard dissolution apparatus according to USP 34 NF 26 section 711; and, wherein release of the drug from said strong acid resinate continues over a period of at least 8 hours after ingestion.

EXAMPLES

Example 1

The following example of the invention is a tablet consisting of three distinct layers containing in total 10 mg equivalent of hydrocodone bitartrate and 120 mg of pseudoephedrine.

A resinate of hydrocodone bitartrate (HCBT) and the weak acid ion-exchange resin AMBERLITE™ IRP88 was prepared as described in Example 1 of U.S. Pat. No. 8,187,617 B2. The drug loading in the resinate was tested and showed 33% drug load or approximately 33 mg of HCBT per 100 mg of resinate. The resinate was granulated and sieved through a #40 screen.

A second resinate of hydrocodone bitartrate was prepared, but this time with the strong acid ion-exchange resin AMBERLITE™ IRP69. The procedure for preparing the resinate was substantially the same as in Example 1 of U.S. Pat. No. 8,187,617 B2, but using the strong acid resin in place of the weak acid resin. The drug loading in the resinate was tested and showed 33% drug load or approximately 33 mg of HCBT per 100 mg of resinate.

The HCBT resinate was granulated and sieved through a #40 screen and divided into two parts. The first part of this HCBT/IR69 resinate was used in forming a three layer tablet as described below. The second part of this HCBT/IR69 resinate was used in Comparative Example 1 as will be described below.

Table Composition

A three layer tablet was formed having the composition shown in Table 1 consisting of a hydrocodone immediate release layer (identified as layer“A”), a hydrocodone extended release layer (layer “B”) and a pseudoephedrine layer (layer “C”). The pseudoephedrine was unbound, i.e. not bound to an ion-exchange resin.

Table 1

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Qty (mg/tab)</th>
<th>% (w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone Resinate (Amberlite IRP-88)</td>
<td>6.00</td>
<td>0.7</td>
</tr>
<tr>
<td>to 2.0 mg Hydrocodone Bitartrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferric chloride</td>
<td>2.00</td>
<td>0.2</td>
</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td>119.00</td>
<td>13.2</td>
</tr>
<tr>
<td>Lactose Monohydrate</td>
<td>100.00</td>
<td>11.1</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>3.00</td>
<td>0.4</td>
</tr>
<tr>
<td>Sodium Starch Glycolate</td>
<td>15.00</td>
<td>1.7</td>
</tr>
<tr>
<td>Colloidal Silicon dioxide</td>
<td>2.50</td>
<td>0.3</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>2.50</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Total (A) | 250.00 |

Hydrocodone Resinate (Amberlite IRP-69) | 24.00 | 2.7 |
| to 8.0 mg Hydrocodone Bitartrate | | |
| Lactose Monohydrate | 55.00 | 6.1 |
| Microcrystalline Cellulose | 7.00 | 0.8 |
| Hypropelone | 120.00 | 13.3 |
| Povidone K30 | 10.00 | 1.1 |
| Calcium Chloride | 1.50 | 1.7 |
| Colloidal Silicon dioxide | 3.0 | 0.3 |
| Magnesium Stearate | 3.0 | 0.3 |

Total (B) | 300.00 |

Pseudoephedrine HCl layer | 120.00 | 13.3 |
| qty to 120 mg | | |
| Lactose Monohydrate | 67.00 | 7.4 |
| Colloidal Silicon dioxide | 5.00 | 0.6 |
| Magnesium Stearate | 3.00 | 0.3 |

Total (C) | 350.00 |

Total (A) + (B) + (C) | 900.00 | 100.0 |

A. Hydrocodone Immediate Release (IR) Layer

B. Hydrocodone Extended Release (ER) Layer

A. Hydrocodone Immediate Release (IR) Layer

1. The microcrystalline cellulose and lactose monohydrate were sieved through a #40 (420 micron) screen and thoroughly mixed together.

2. The hydrocodone resinate of the weak acid ion-exchange resin, ferric chloride, stearic acid, sodium starch glycolate and colloidal silicon dioxide were thoroughly mixed together and sieved through a #40 screen.

3. The blend of step 2 was gradually added to the blend of step 1 with continued mixing.

4. Magnesium stearate lubricant was sieved through a #40 screen and thoroughly mixed into the blend of step 3.

B. Hydrocodone Extended Release (ER) Layer

5. The lactose monohydrate and about half of the hypropelone were mixed together and granulated with purified water.

6. The wet granules of step 5 were dried and sieved through a #20 screen.

7. The first part of the HCBT/IRP69 resinate prepared above, the microcrystalline cellulose, the remaining
portion of the hypromellose, the calcium chloride, the colloidal silicon dioxide and the lactose monohydrate were individually sieved through a #40 screen, thoroughly mixed together and the mixture re-sieved through a #40 screen.

[0194] 8. The granules of step 6 were thoroughly mixed with the dry mix of step 7.

[0195] 9. Magnesium stearate lubricant was sieved through a #40 screen and thoroughly mixed into the blend of step 8.

C. Pseudoephedrine HCl Layer

[0196] 10. The pseudoephedrine HCl and mannitol were thoroughly mixed together and sieved through a #80 (177 micron) screen.

[0197] 11. The hydrogenated vegetable oil was melted at 70-80°C.

[0198] 12. The pseudoephedrine HCl and mannitol were slowly added to the melted hydrogenated vegetable oil with continuous stirring and mixed thoroughly. The mixture was then cooled to room temperature under stirring.

[0199] 13. The cooled mixture of step 12 was milled through a co-mill fitted with a #40 screen.

[0200] 14. The lactose monohydrate and colloidal silicon dioxide were individually sieved through a #40 screen and thoroughly mixed together.

[0201] 15. The mixture of step 14 was added to the granules of step 13 and thoroughly mixed together.

[0202] 16. Magnesium stearate lubricant was sieved through a #60 screen and thoroughly mixed into the blend of step 15.

Tri-Layer Compression

[0203] The lubricated blends of steps 4, 9 and 16 were fed to a rotary tablet compression machine and compressed into tri-layer tablets using 13.30 mm round shape punches. The tablets were of 6.50±0.30 mm thickness, were of 900±5% mg weight, and had a tablet breaking force of 225 N (200-250 N).

Example 2

[0204] A tri-layer tablet prepared as described in Example 1 was subjected to simulated gastrointestinal dissolution testing in a standard dissolution apparatus according to USP 34 NF 26 section 711. The measured dissolution profiles of hydrocodone and pseudoephedrine are shown below in Table II and are plotted in FIGS. 2 and 3 respectively.

[0205] It will be seen that 29% of the total hydrocodone content of the tri-layer tablet (2.9/10 mg) was released in 45 minutes. While the release from the IR component alone cannot be determined from these data, it is clear that the immediate release exceeded the total hydrocodone loading of the IR layer.

[0206] It will also be seen that extended release of the hydrocodone continued for at least 8 hours. It is to be noted that this extended release was accomplished without having coated the drug resinate.

<table>
<thead>
<tr>
<th>Time (Hr)</th>
<th>Hydrocodone Bitartrate</th>
<th>Pseudoephedrine HCl</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.25</td>
<td>22</td>
<td>15</td>
</tr>
<tr>
<td>0.5</td>
<td>26</td>
<td>22</td>
</tr>
<tr>
<td>0.75</td>
<td>29</td>
<td>27</td>
</tr>
<tr>
<td>1</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>43</td>
</tr>
<tr>
<td>4</td>
<td>62</td>
<td>64</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
<td>86</td>
</tr>
<tr>
<td>8</td>
<td>90</td>
<td>98</td>
</tr>
<tr>
<td>10</td>
<td>94</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>95</td>
<td>104</td>
</tr>
</tbody>
</table>

Comparative Example 1

[0207] Tableting of the second part of the HCBT/IRP69 resinate prepared in Example 1 was attempted. However, the maximum pressure exerted by a tablet press was insufficient to form a stable tablet of this resinate. Consequently, 24 mg from the second part of the HCBT/IRP69 resinate prepared in Example 1 was loaded into a gelatin capsule. This capsule containing only the neat resinate was subjected to simulated gastrointestinal dissolution testing in a standard dissolution apparatus according to USP 34 NF 26 section 711.

[0208] The measured dissolution profile of hydrocodone is plotted in FIG. 4. It is seen that the cumulative HCBT release from the neat resinate at the end of 45 minutes was 70 percent of 24 mg or 16.8 mg. This may be compared with 29% release of 30 mg or only 8.7 mg from the tri-layer tablet even including the immediate release component.

[0209] Moreover, the HCBT release from the neat resinate had essentially ended after about 2 hours whereas the HCBT release from the tri-layer tablet continued for at least 8 hours.

[0210] Both of these comparisons show the effectiveness of compressing a mixture of a release rate retarding polymer with a drug/ion-exchange resin to form an extended release tablet or tablet layer.

Example 3

[0211] The following example of the invention is a tablet consisting of three distinct layers containing in total 45 mg equivalent of codeine and 120 mg of pseudoephedrine.

[0212] A resinate of codeine and the weak acid ion-exchange resin AMBERLITE™ IRP88 was prepared in the manner described in Example 1 of U.S. Pat. No. 8,187,617 B2 except that codeine was used in place of hydrocodone. The drug loading in the resinate was tested and showed approximately 46.3% % drug load or approximately 46.3 mg of codeine per 100 mg of resinate. The resinate was granulated and sieved through a #40 screen.

[0213] A second resinate of codeine was prepared, but this time with the strong acid ion-exchange resin AMBERLITE™ IRP99. The method of preparing the resinate was substantially the same as in Example 1 of U.S. Pat. No. 8,187,617 B2, but using codeine in place of hydrocodone and using the strong acid resin in place of the weak acid resin. The drug
loading in the resinate was tested and showed 46.8% drug load or approximately 46.8 mg of codeine per 100 mg of resinate.

[0214] The codeine resinate was granulated and sieved through a #40 screen and divided into two parts. The first part this codeine/IR69 resinate was used in forming a three layer tablet as described below. The second part of this codeine/IR69 resinate used in Comparative Example 2 as will be described below.

[0215] Tablet Composition

[0216] A three layer tablet was formed having the composition shown in Table III below consisting of a codeine immediate release layer (identified as layer “A”), a codeine extended release layer (layer “B”) and a pseudoephedrine layer (layer “C”).

[0217] Tablet Preparation

[0218] The codeine tri-layer tablet was prepared using the same steps described in detail for the hydrocodone tri-layer tablet in Example 1 above.

Tri-Layer Compression

[0219] The lubricated blends of steps 4, 9 and 16 described above were fed to a rotary tablet compression machine and compressed into tri-layer tablets using 13.30 mm round shape punches. The tablets were of 6.50±0.30 mm thickness, were of 935±5% mg weight, and had a tablet breaking force of 190 N (170-210 N).

[0220] It will be noted that the preparation procedure did not involve coating of the drug resinate.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Qty (mg/tab)</th>
<th>% (w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose Monohydrate</td>
<td>67.00</td>
<td>7.4</td>
</tr>
<tr>
<td>Colloidal Silicon dioxide</td>
<td>5.00</td>
<td>0.6</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>3.00</td>
<td>0.3</td>
</tr>
<tr>
<td>Total (C)</td>
<td>350.00</td>
<td>37.4</td>
</tr>
<tr>
<td>Total (A) + (B) + (C) Tri-layer</td>
<td>935.00</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Example 4

[0221] A tri-layer tablet prepared as described in Example 3 was subjected to simulated gastrointestinal dissolution testing in a standard dissolution apparatus according to USP 34 NF 26 section 711. The measured dissolution profiles of codeine and pseudoephedrine are shown below in Table IV and are plotted in FIG. 4.

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Codeine</th>
<th>Pseudoephedrine HCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.25</td>
<td>23</td>
<td>15</td>
</tr>
<tr>
<td>0.5</td>
<td>28</td>
<td>21</td>
</tr>
<tr>
<td>0.75</td>
<td>32</td>
<td>26</td>
</tr>
<tr>
<td>1</td>
<td>36</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
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<tr>
<td>6</td>
<td>78</td>
<td>82</td>
</tr>
<tr>
<td>8</td>
<td>88</td>
<td>93</td>
</tr>
<tr>
<td>10</td>
<td>94</td>
<td>97</td>
</tr>
<tr>
<td>12</td>
<td>96</td>
<td>98</td>
</tr>
</tbody>
</table>

[0222] It is seen that 32% of the total codeine content of the tri-layer tablet (14.4/45 mg) was released in 45 minutes. While the release from the IR component alone cannot be determined from these data, it is clear that the immediate release exceeded the total codeine loading of the IR layer.

[0223] It will also be seen that extended release of the codeine continued for at least 8 hours. It is to be noted that this extended release was accomplished without having coated the drug resinate.

Comparative Example 2

[0224] Tabtletting of the second part of the codeine/IRP69 resinate prepared in Example 3 was attempted. However, the maximum pressure exerted by a tablet press was insufficient to form a stable tablet of this resinate. Consequently, 77 mg from the second part of the codeine/IRP69 resinate prepared in Example 3 was loaded into a gelatin capsule. This capsule containing only the neat resinate was subjected to simulated gastrointestinal dissolution testing in a standard dissolution apparatus according to USP 34 NF 26 section 711.

[0225] The measured dissolution profile of codeine is plotted in FIG. 6. It is seen that the cumulative codeine release from the neat resinate at the end of 45 minutes was about 82 percent of 77 mg or about 63 mg. This may be compared with 52% release of 96.44 mg or only 30.8 mg from the tri-layer tablet even including the immediate release component.

TABLE III-continued

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Qty (mg/tab)</th>
<th>% (w.f.w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose Monohydrate</td>
<td>67.00</td>
<td>7.4</td>
</tr>
<tr>
<td>Colloidal Silicon dioxide</td>
<td>5.00</td>
<td>0.6</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>3.00</td>
<td>0.3</td>
</tr>
<tr>
<td>Total (C)</td>
<td>350.00</td>
<td>37.4</td>
</tr>
<tr>
<td>Total (A) + (B) + (C) Tri-layer</td>
<td>935.00</td>
<td>100.0</td>
</tr>
</tbody>
</table>

TABLE IV

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Codeine</th>
<th>Pseudoephedrine HCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.25</td>
<td>23</td>
<td>15</td>
</tr>
<tr>
<td>0.5</td>
<td>28</td>
<td>21</td>
</tr>
<tr>
<td>0.75</td>
<td>32</td>
<td>26</td>
</tr>
<tr>
<td>1</td>
<td>36</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td>62</td>
<td>62</td>
</tr>
<tr>
<td>6</td>
<td>78</td>
<td>82</td>
</tr>
<tr>
<td>8</td>
<td>88</td>
<td>93</td>
</tr>
<tr>
<td>10</td>
<td>94</td>
<td>97</td>
</tr>
<tr>
<td>12</td>
<td>96</td>
<td>98</td>
</tr>
</tbody>
</table>

TABLE III-continued
Moreover, the codeine release from the neat resinate had essentially ended after about 45 minutes whereas the HCBT release from the tri-layer tablet continued for at least 8 hours.

Both of these comparisons show the effectiveness of compressing a mixture of a release rate retarding polymer with a drug/ion-exchange resin to form an extended release tablet or tablet layer.

OTHER EMBODIMENTS

All publications, patent applications, and patents mentioned in this specification are herein incorporated by reference to the extent not incompatible herewith.

Various modifications and variations of the described method and system of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific desired embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention that are obvious to those skilled in the fields of medicine, immunology, pharmacology, endocrinology, or related fields are intended to be within the scope of the invention.

What is claimed is:

1. A multi-layer solid oral pharmaceutical composition comprising:
   (i) a first distinct layer comprising:
      (a) a first pharmaceutically active agent bound to a weak acid ion exchange resin to form a weak acid ion-exchange resinate; and
      (b) a release-enhancing agent consisting of FeCl₃;
   (ii) at least a second distinct layer comprising:
      (a) a drug selected from the group consisting of said first pharmaceutically active agent and a second pharmaceutically active agent, said drug being bound to a strong acid ion exchange resin to form a strong acid ion-exchange resinate; and
      (b) a release rate retarding polymer susceptible to gastrointestinal dissolution to slow and extend release of the drug contained in said at least second layer;
   wherein said strong acid ion-exchange resinate and said polymer have been compressed together and
   wherein said pharmaceutical composition is capable of immediate release of said first pharmaceutically active agent from said weak acid resinate at a pH of at least 1.5, immediate release being defined as at least 80% release of said pharmaceutically active agent within 45 minutes in a standard dissolution apparatus according to USP 34 NF 26 section 711; and,
   wherein release of the drug from said strong acid resinate continues over a period of at least 8 hours after ingestion.

2. The multi-layer solid oral pharmaceutical composition of claim 1 having at least three distinct layers, each said layer comprising pharmaceutically active agents in a form selected from the group consisting of ion-exchange resinates and unbound pharmaceutically active agents.

3. The multi-layer solid oral pharmaceutical composition of claim 1 wherein said first layer comprises a member of the group consisting of hydrocodone bitartrate polacrilrex weak acid resinate, codeine polacrilrex weak acid resinate and dextromethorphan polacrilrex weak acid resinate; and said second layer comprises a member of the group consisting of hydrocodone polistirex strong acid resinate, codeine polistirex strong acid resinate and dextromethorphan polistirex strong acid resinate.

4. The multi-layer solid oral pharmaceutical composition of claim 2, wherein, at least one of said layers comprises an unbound pharmaceutically active agent.

5. The multi-layer solid oral pharmaceutical composition of claim 4 wherein said first layer comprises a member of the group consisting of hydrocodone bitartrate polacrilrex weak acid resinate, codeine polacrilrex weak acid resinate and dextromethorphan polacrilrex weak acid resinate; and said second layer comprises a member of the group consisting of hydrocodone polistirex strong acid resinate, codeine polistirex strong acid resinate and dextromethorphan polistirex strong acid resinate; and
   wherein a third layer consists of an unbound pharmaceutically active agent.

6. A method of treating a patient with a stomach pH of at least about 1.5 comprising administration of a multilayer solid oral dosage form, said dosage form comprising:
   (i) a first distinct layer comprising:
      (a) a first pharmaceutically active agent bound to a weak acid ion exchange resin to form a weak acid ion-exchange resinate; and
      (b) a release-enhancing agent selected from the group consisting of an inorganic salt and an organic base;
   (ii) at least a second distinct layer comprising:
      (a) a drug selected from the group consisting of said first pharmaceutically active agent and a second pharmaceutically active agent, said drug being bound to a strong acid ion exchange resin to form a strong acid ion-exchange resinate; and
      (b) a release rate retarding polymer susceptible to gastrointestinal dissolution to slow and extend release of the drug contained in said at least second layer;
   wherein said strong acid ion-exchange resinate and said polymer have been compressed together and
   wherein said pharmaceutical composition is capable of immediate release of said first pharmaceutically active agent from said weak acid resinate at a pH of at least 1.5, immediate release being defined as at least 80% release of said pharmaceutically active agent within 45 minutes in a standard dissolution apparatus according to USP 34 NF 26 section 711; and,
   wherein release of the drug from said strong acid resinate continues over a period of at least 8 hours after ingestion.

7. The method of treating a patient with a stomach pH of at least about 1.5 as in claim 6, wherein said patient has a first condition and a second condition, said first condition being selected from the group consisting of Helicobacter pylori infection, atrophic gastritis, hypochlorhydria and achlorhydria in the stomach; and wherein said second condition is a condition other than said first condition.

8. The method of treating a patient with a stomach pH of at least about 1.5 as in claim 6, wherein the patient has within the past 24 hours been administered a compound selected from the group consisting of a proton pump inhibitor, an H₂ receptor antagonist.

9. A method of delivering a pharmaceutically active agent to a patient, said method comprising orally administering a solid oral dosage composition comprising:
   (i) a first distinct layer comprising:
      (a) a first pharmaceutically active agent bound to a weak acid ion exchange resin to form a weak acid ion-exchange resinate; and
(b) a release-enhancing agent selected from the group consisting of an inorganic salt and an organic base;

(ii.) at least a second distinct layer comprising:

(a) pharmaceutically active agent selected from the group consisting of said first pharmaceutically active agent and a second pharmaceutically active agent, said pharmaceutically active agent bound to a strong acid ion exchange resin to form a strong acid ion exchange resinate; and,

b) a release rate retarding polymer susceptible to gastrointestinal dissolution to slow and extend release of the drug contained in said at least second layer;

wherein said strong acid ion-exchange resinate and said polymer have been compressed together; and

wherein said pharmaceutical composition is capable of immediate release of said first pharmaceutically active agent from said weak acid resinate at a pH of at least 1.5, immediate release being defined as at least 80% release of said pharmaceutically active agent within 45 minutes in a standard dissolution apparatus according to USP 34 NF 26 section 711; and,

wherein release of the drug from said strong acid resinate continues over a period of at least 8 hours after ingestion.

10. The multi-layer solid oral pharmaceutical composition of claim 1, wherein the release rate retarding polymer is selected from the group consisting of hydroxypropyl methylcellulose, ethyl cellulose, polyethylene oxide, polyvinyl alcohol, hydrogenated vegetable oil, methacrylate copolymer, polyacrylic acid, and their combinations.

11. The method of delivering a pharmaceutically active agent to a patient of claim 9, wherein the release rate retarding polymer is selected from the group consisting of hydroxypropyl methylcellulose, ethyl cellulose, polyethylene oxide, polyvinyl alcohol, hydrogenated vegetable oil, methacrylate copolymers, polyacrylic acid, and their combinations.

12. The method of treating a patient with a stomach pH of at least about 1.5 of claim 6, wherein the release rate retarding polymer is selected from the group consisting of hydroxypropyl methylcellulose, ethyl cellulose, polyethylene oxide, polyvinyl alcohol, hydrogenated vegetable oil, methacrylate copolymers, polyacrylic acid, and their combination.

* * * * *