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(54) Title: **TABLET FOR PULSED DELIVERY**

(57) **Abrégé/Abstract:**

A pharmaceutical tablet comprising an immediate release portion containing an active ingredient and a delayed release portion, wherein the delayed release portion comprises an enteric-coated layer and within the enteric-coated layer there is at least one member selected from the group consisting of enteric-coated microparticle dosage forms containing an active ingredient and enteric-coated mini-tablet dosage forms containing an active ingredient, is disclosed.



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(54) Title: TABLET FOR PULSED DELIVERY

(57) Abstract: A pharmaceutical tablet comprising an immediate release portion containing an active ingredient and a delayed release portion, wherein the delayed release portion comprises an enteric-coated layer and within the enteric-coated layer there is at least one member selected from the group consisting of enteric-coated microparticle dosage forms containing an active ingredient and enteric-coated mini-tablet dosage forms containing an active ingredient, is disclosed.

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TABLET FOR PULSED DELIVERY

This invention relates to a pharmaceutical composition in tablet form that provides for both immediate and enteric release of an active drug agent, and also relates to the use and formulation of such pharmaceutical composition. More particularly, the present invention relates to a drug delivery system, in tablet form, that is comprised of an immediate release portion and a delayed release portion.

In accordance with the invention an immediate release portion of the pharmaceutical composition contains an active ingredient, from which portion the initiation of release of said active agent is not substantially delayed after ingestion of the pharmaceutical composition.

In accordance with the invention a delayed release portion of the pharmaceutical composition contains an active ingredient, from which portion the initiation of release of said active agent is substantially delayed after ingestion of the pharmaceutical composition.

It is an aspect of the invention that the delayed release portion comprises an enteric coated layer, within which enteric coated layer there is a core tablet containing at least one member selected from the group consisting of enteric-coated microparticle dosage forms containing an active ingredient and enteric coated minitabket dosage forms containing an active ingredient.

In accordance with one aspect of the invention there is provided a delayed release portion that comprises a core tablet that includes an enteric coating, such that the core tablet does not disintegrate in the stomach; i.e., the core tablet disintegrates in the intestine. In accordance with a further aspect of the invention there is provided an immediate release portion whereby the

enteric coated core tablet has a non-enteric coating over all or a portion of the enteric coating and this non-enteric coating provides for an immediate release of active that is contained therein; i.e., the immediate release portion releases active ingredient in the stomach.

The core tablet includes therein particles and / or mini-tablets ("mini-tabs") that include therein an active agent and that have an enteric coating to thereby delay release of active agent from the particles and / or mini-tablets until a time that is subsequent to the disintegration of the core tablet in the intestine. Additionally, the core tablet may or may not include a dosage of uncoated active ingredient the release of which is initiated at the time that the core tablet disintegrates in the intestine.

In a preferred embodiment of the invention the core tablet, whether comprised of enteric-coated microparticles, enteric-coated mini-tabs, uncoated active ingredient, or combinations of the foregoing, is itself enteric-coated thereby to ensure its disintegration in the post-stomach GI tract.

In an alternative embodiment of the invention the matrix of the core tablet includes enteric materials that maintain the structure of the core tablet to thereby ensure its disintegration in the post-stomach GI tract, whereby coating the core tablet with an enteric coating is not necessary, though is still preferred.

It is to be understood that when it is disclosed herein that a dosage form initiates release after another dosage form, such terminology means that the dosage form is designed to produce, and is intended to produce, such later initiated release. It is known in the art, however, notwithstanding such design and intent, that some "leakage" of active ingredient may occur owing to known imperfections incident to current pharmaceutical manufacturing processes. Such "leakage" whether by flaking, chipping, or other means is not "release" as used herein.

The core tablet may be either, a multiparticulate core: containing one or more pellet types, designed to release drug in the post-stomach portions of the GI tract, wherein the pellet types provide about 1 to 95% of total core tablet weight; or a mini-tab core: containing one or

more mini-tabs also designed to release drug in the post-stomach GI tract, wherein the mini-tabs provide about 1 to 95% of total core tablet weight. The enteric polymer layer can be produced by spraying a number of different types of enteric polymers on top of the above-described core tablet. Thus, the enteric polymer coating delays the disintegration of the core tablet until the core tablet reaches the intestine. Additionally, the multiparticulates or mini-tabs comprising the core tablet may be formulated with further delayed and / or modified release materials, to thereby further delay and / or modify release of the active drug agents released therefrom.

In one embodiment the immediate release portion may be an immediate release drug layer that can be sprayed on top of the enteric-coated core tablet to thereby serve as an immediate releasing portion of the drug delivery system.

In one embodiment of the invention the immediate release drug layer completely engulfs the enteric polymer coated core tablet.

In one embodiment of the invention the immediate release drug layer does not completely engulf the enteric polymer coating of the core tablet; in this embodiment a portion of the enteric polymer coating is exposed.

In another embodiment of the invention the immediate release portion may comprise one layer of a bi-layer tablet in conjunction with the enteric-coated core tablet, or the immediate release portion may comprise a plurality of layers in a multi-layer tablet in conjunction with the enteric-coated core tablet.

The instant invention is also directed to a process for treating a patient in need of treatment with an active medicinal agent, which comprises administering to the patient the hereinabove and hereinbelow described pharmaceutical compositions containing such an active medicinal agent.

The instant invention is also directed to a method of making the hereinabove and hereinbelow described pharmaceutical compositions.

Although most enteric coatings are generally known in the art to be pH-sensitive coatings, as used herein the term "enteric coating" includes both coatings that are pH-sensitive and coatings that are pH-independent. More particularly the term "enteric coating" as used herein indicates that the coating is one that is selected for its ability to deliver active ingredients to the post-stomach GI tract.

As used herein the term "enteric coated tablet" means a tablet that is capable of delivering one or more pulses of active drug agent into the small intestinal region of the GI tract. Such enteric coated tablet is not limited to tablets engulfed by, or overlaid with, an enteric coating, but includes tablets having matrices comprising enteric materials that maintain the unit integrity of the core tablet at least until such tablet is delivered to the intestine. The core tablet of the instant invention is an enteric coated tablet in that it permits the delivery of a multi-particulate comprised (mini-tab, bead, microparticle, etc.) tablet into the GI tract as an intact unit. It is a beneficial aspect of the invention that the core tablet is passed from the stomach to the intestine substantially intact and that the core tablet does not disintegrate in the stomach.

Generally, in those embodiments wherein the core tablet contains mini-tabs of the desired drug agent, those mini-tabs are formulated so that they are small enough to fit into a standard sized tablet core. The mini-tabs can be coated with an enteric coating that is either a delayed release and / or modified release coating. In a preferred embodiment the mini-tabs are coated with a delayed release coating. In another preferred embodiment there is a plurality of different mini-tabs in that each is coated with a delayed release coating that results in each different mini-tab initiating release of active ingredient therefrom at different times, each of which different times is subsequent to the time at which the core tablet enters the small intestine. Depending on the size of the mini-tabs, a core tablet may comprise one or more mini-tabs each consisting of the same drug agent or different drug agents, along with known pharmaceutical fillers. The core tablet is thereafter coated with an enteric coating that is either a delayed release or a modified release coating. The immediate release portion containing an active drug agent may thereafter be layered over at least a portion of the enteric-coated core tablet to provide an immediate release of a desired active drug agent.

In one embodiment additional enteric materials are used to formulate the matrix of the above-described tablet core to thereby further modify release of active ingredient therefrom. In this embodiment an enteric polymer is sprayed on top of the core tablet, wherein enteric materials are used in formulating the matrix of the tablet core.

In one embodiment additional enteric materials are used to formulate the beads or mini-tabs of the above-described tablet core to thereby further modify release of active ingredient therefrom. In this embodiment an enteric polymer is sprayed on top of the core tablet, wherein enteric materials are used in formulating the beads or mini-tabs of the tablet core.

In one embodiment the core tablet comprises at least one mini-tab and an uncoated dosage of active ingredient, whereby after the core tablet's disintegration in the small intestine the uncoated dosage of active ingredient is immediately released at a first time and thereafter the at least one mini-tab initiates release of the active ingredient contained therein at a second time that is subsequent to said first time. This embodiment delivers at least three separate pulses of active ingredient in that the immediate release portion delivers a first pulse in the stomach, and the uncoated dosage of active ingredient and the at least one mini-tab deliver later-initiated pulses in the intestine, whereby the initiation of release of active ingredient from the at least one mini-tab is subsequent to the initiation of release of active ingredient from the uncoated dosage of active ingredient.

In one preferred embodiment the core tablet comprises at least two different mini-tabs, whereby after the core tablet's disintegration in the small intestine the first of the at least two different mini-tabs initiates release of the active ingredient contained therein at a first time, and the second of the at least two different mini-tabs initiates release of the active ingredient contained therein at a second time that is subsequent to said first time. This embodiment delivers at least three separate pulses of active ingredient in that the immediate release portion delivers a first pulse in the stomach, and the at least two different mini-tabs deliver later-initiated pulses in the intestine, whereby the initiation of release of active ingredient from the second mini-tab is subsequent to the initiation of release of active ingredient from the first mini-tab.

In one embodiment the core tablet comprises at least two mini-tabs and an uncoated dosage of active ingredient, whereby after the core tablet's disintegration in the small intestine the uncoated dosage of active ingredient is immediately released at a first time and thereafter the at least two mini-tabs initiate release of the active ingredients contained therein at second and third times that are each subsequent to said first time. This embodiment delivers at least four separate pulses of active ingredient in that the immediate release portion delivers a first pulse in the stomach, and the uncoated dosage of active ingredient and the at least two mini-tabs deliver later-initiated pulses in the intestine, whereby, the initiation of release of active ingredient from the at least two mini-tabs is subsequent to the initiation of release of active ingredient from the uncoated dosage of active ingredient, and the initiation of release of active ingredient from the second mini-tab is subsequent to the initiation of release of active ingredient from the first mini-tab.

In another preferred embodiment the core tablet comprises at least three different mini-tabs, whereby after the core tablet's disintegration in the small intestine the first of the at least three different mini-tabs initiates release of the active ingredient contained therein at a first time, the second of the at least three different mini-tabs initiates release of the active ingredient contained therein at a second time that is subsequent to said first time, and the third of the at least three different mini-tabs initiates release of the active ingredient contained therein at a third time that is subsequent to said second time. This embodiment delivers at least four separate pulses of active ingredient in that the immediate release portion delivers a first pulse in the stomach, and the at least three different mini-tabs deliver later-initiated pulses in the intestine, whereby the initiation of release of active ingredient from the second mini-tab is subsequent to the initiation of release of active ingredient from the first mini-tab, and the initiation of release of active ingredient from the third mini-tab is subsequent to the initiation of release of active ingredient from the second mini-tab.

In one embodiment the core tablet comprises at least three mini-tabs and an uncoated dosage of active ingredient, whereby after the core tablet's disintegration in the small intestine the uncoated dosage of active ingredient is immediately released at a first time and thereafter the

at least three mini-tabs initiate release of the active ingredients contained therein at second, third, and fourth times that are each subsequent to said first time. This embodiment delivers at least five separate pulses of active ingredient in that the immediate release portion delivers a first pulse in the stomach, and the uncoated dosage of active ingredient and the at least three mini-tabs deliver later-initiated pulses in the intestine whereby, the initiation of release of active ingredient from first of the at least three mini-tab is subsequent to the initiation of release of active ingredient from the uncoated dosage of active ingredient, the initiation of release of active ingredient from the second mini-tab is subsequent to the initiation of release of active ingredient from the first mini-tab, and the initiation of release of active ingredient from the third mini-tab is subsequent to the initiation of release of active ingredient from the second mini-tab.

The present invention may be used to decrease the variability of the absorption of any active drug agent, and it is particularly useful for decreasing the absorption variability of antibiotics. The invention is more particularly useful for decreasing the absorption variability of beta-lactam antibiotics, cephalosporin antibiotics, and macrolide antibiotics. Even more particularly, it is useful for decreasing the absorption variabilities of amoxicillin and clarithromycin, both in separate formulations, and in formulations that combine amoxicillin and clarithromycin.

Current multi-particulate and mini-tab tablet delivery systems, as applied to anti-infective agents, cannot prevent the pre-intestinal separation of microparticles or mini-tabs released in the stomach. These components generally exit the stomach through the pyloric valve or by the gastric emptying mechanisms of the stomach. In addition, the current tablet delivery systems are not staged, in other words they typically either dump the entire contents of the core tablet from the stomach into the small intestine as soon as the enteric coating is released, or they comprise a dosage form designed to give steady blood levels, as opposed to pulsatile blood levels, as soon as the enteric coating is released. This dumping of pellets into the stomach, inherent in the current state multi-particulate tablet dosage forms, can lead to pellet spread and a decrease in the strength of the pulses, resulting in significant variations in *in vivo* pharmacokinetics. Those variations can be expressed in any or all of C_{max}, T_{max}, Lag Time, and AUC. The dumping can also lead to local site concentration dilution. The present invention avoids these problems

through a pulsatile dosing profile, whereby the drug is released in the GI tract in a staged manner, creating an increase and decrease in plasma levels over time. By including multi-particulate and mini-tab components in the core tablet system, these components can be engineered to release drug in a staged, or sequential burst, fashion to achieve pulsatile plasma levels such as are described in U.S. Patents 6,544,555 and 6,723,341, the disclosures of which are hereby incorporated in their entireties.

The enteric-coated core tablet of the present invention is large enough that it does not pass through the pyloric sphincter until after the pyloric sphincter opens to discharge stomach contents into the small intestine. The size of the microparticulates or mini-tabs incorporated into the core tablet does not effect the performance of the product since they are enveloped in the core tablet/enteric coating system, that is emptied as a unit into the small intestine. Accordingly, the size of microparticles and mini-tabs that comprise the core tablet can be relatively small in comparison to the core tablet. By grouping all the down stream pulses together in a core tablet and applying an enteric coating over the core tablet so that they remain bundled together while in the stomach the present invention overcomes the earlier-discussed dumping problems. This allows the pellets or mini-tabs to enter the small intestine as a single bulk unit, thereby avoiding the gradual gastric emptying effects that plague the current art. By creating an outer drug layer an immediate release pulse is also provided.

The benefits of the present invention are not limited to a reduction of *in vivo* pharmacokinetic variabilities. The instant dual phase delivery paradigm is capable of facilitating high dose loading of a desired drug, and may deliver multiple pulses thereof. Additionally, the instant invention can deliver multiple drugs within the same dosing unit. This multi-dosing aspect allows the instant invention to deliver incompatible drug substances from the same tablet core. It also ensures that the delivery of one drug substance, or pulse of a drug substance, is not delivered until the desired previous substance, or pulse of a drug substance is delivered. The tablet of the present invention can also be used to deliver drugs that may be incompatible in the same dosage form, but which, when presented to the small intestine in combination via the core tablet, will work in tandem with respect to improving absorption or combatting specific infectious problems. The instant invention also allows different regions of the GI tract to be

specifically targeted for delivery. Also, the invention allows for once-a-day dosing to better ensure patient compliance; this avoids the possibility of overdosing the patient as only a portion of the drug is delivered at any time during the day. Furthermore, the instant invention permits for a smaller tablet size than can be achieved by way of more traditional multi-particulate tablets. In the more traditional multiparticulate tablets the pellets present greater surface area owing to the different functional coatings and different amounts of functional coatings that are applied to the pellets to create the pulsatile release in the GI tract. The traditional microparticulate tablet size is increased further still by the additions of the various fillers that hold the coated pellets together. In the traditional multiparticulate tablet models, much of the volume is occupied by the high polymer content of the individual pellets. In the instant invention, the first pulse is a coated layer on the surface of the enteric-coated core tablet, and the second pulse may be provided by the granulation inside the enteric coated core tablet that may also function as a cushioning agent or binder to hold the third pulse pellets together. Thus, the present invention provides a tablet in which the earlier pulses are concentrated and more dense, thereby presenting less surface area, and hence occupying less volume, in the tablet. Moreover, the instant drug delivery system allows the formulator to engineer pulses that release at any desired time.

The core tablet of the present invention contains an active drug agent in the form of a prepared compactable matrix and / or compacted pellet, bead, or mini-tab. The pharmaceutical active agent is contained within the enteric-coated core tablet for modified delivery, and a drug layer on top of the enteric-coated tablet provides immediate release delivery. By delivering two or more releases of an active drug agent along the GI tract in a pulsatile fashion the instant improvement may be formulated to comport with the PulsysTM technology. The PulsysTM technology (which provides for distinct pulsatile releases of active ingredient separated in time) is described at length in U.S. Patent 6,544,555 B2, issued to Rudnic *et al.*; the disclosures of which are hereby incorporated, by this reference, in their entireties. Like the PulsysTM technology, the dual phase delivery system of the instant invention provides distinctly discernible pharmacokinetic curves at specific points in time for each of the delivered pulses of active ingredient.

The core tablet may comprise of either or both of a multiparticulate active (pellet or bead) and/or a compressible active granule and / or matrix and / or mini-tab. A matrix could be made up of an active ingredient with enhancers to improve bioavailability or solubility of the active ingredient depending on limitations inherent to the particular active ingredient absorption characteristics. Active ingredient absorption limitations might be influenced by any or all of moisture content, pH, or active transport mechanisms. A typical pellet or multiparticulate active must be "robust" in that it must be capable of withstanding downstream processing activities. These processing operations may include, but are not limited to: wet granulation, extrusion, spheronization, fluid bed drying, fluid bed coating, roller compaction, tablet compression forces, and pan coating.

While the examples and preferred embodiments of the present invention will describe its exceptional utility with regard to antibiotics, the disclosures herein conceive of their application to myriad other active drug agents. Non-limiting examples of such myriad other active drug agents include other anti-infective agents such as the antifungals and the antivirals, and antineoplastic agents.

A wide variety of antibiotics have been used, and will be used, in order to combat bacterial infection. In general, such antibiotics can be administered by a repeated dosing of immediate release dosage forms, which results in poor compliance, or as controlled release formulations (slow release) at higher administered doses. In one embodiment the present invention is directed to providing for an improved antibiotic product.

In accordance with one aspect of the dual phase delivery system of the present invention, there is provided an antibiotic pharmaceutical product, as described hereinabove and hereinbelow, which contains at least two, preferably at least three, antibiotic dosage forms. Such dosage forms are formulated so that each of the dosage forms has a different release profile.

In a particularly preferred embodiment, there are at least two, preferably at least three dosage forms, each of which has a different release profile and the release profile of each of the

dosage forms is such that the dosage forms each start release of the antibiotic contained therein at different times after administration of the antibiotic product.

Thus, in accordance with an aspect of the present invention, there is provided a single or unitary antibiotic product that has contained therein at least two, preferably at least three antibiotic dosage forms, each of which has a different release profile, whereby the antibiotic contained in each of such dosage forms is released at different times.

In accordance with a further aspect of the invention, the antibiotic product may be comprised of at least four different dosage forms, each of which starts to release the antibiotic contained therein at different times after administration of the antibiotic product.

The antibiotic product generally does not include more than five dosage forms with different release times.

In accordance with a preferred embodiment, the antibiotic product has an overall release profile such that when administered the maximum serum concentration of the total antibiotic released from the product is reached in less than twelve hours, preferably in less than eleven hours. In an embodiment, the maximum serum concentration of the total antibiotic released from the antibiotic product is achieved no earlier than four hours after administration.

In accordance with one preferred embodiment of the invention, there are at least two dosage forms. One of the at least two dosage forms is an immediate release dosage form whereby initiation of release of the antibiotic therefrom is not substantially delayed after administration of the antibiotic product. The second of the at least two dosage forms is an enteric dosage form, whereby the antibiotic released therefrom is delayed until after initiation of release of the antibiotic from the immediate release dosage form, and is further delayed until after the second dosage form (contained in the core tablet) has passed through the pyloric sphincter of the stomach and into the intestinal portion of the GI tract. More particularly, the antibiotic released from the second of the at least two dosage forms achieves a $C_{\max}$ (maximum

serum concentration in the serum) at a time after the antibiotic released from the first of the at least two dosage forms achieves a $C_{\max}$ in the serum.

In accordance with another preferred embodiment of the invention, there are at least three dosage forms. One of the at least three dosage forms is an immediate release dosage form whereby initiation of release of the antibiotic therefrom is not substantially delayed after administration of the antibiotic product. The second and third of the at least three dosage forms are enteric dosage forms, whereby the antibiotic released therefrom is delayed until after initiation of release of the antibiotic from the immediate release dosage form and is further delayed until after the second and third dosage forms (contained in the core tablet) have passed through the pyloric sphincter of the stomach and into the intestinal portion of the GI tract. More particularly, the antibiotic released from the second of the at least three dosage forms achieves a $C_{\max}$ (maximum serum concentration in the serum) at a time after the antibiotic released from the first of the at least three dosage forms achieves a $C_{\max}$ in the serum, and the antibiotic released from the third dosage form achieves a $C_{\max}$ in the serum after the $C_{\max}$ of antibiotic released from the second dosage form.

In accordance with another preferred embodiment of the invention, the antibiotic is a beta-lactam antibiotic, a cephalosporin antibiotic, or a macrolide antibiotic.

In accordance with another preferred embodiment of the invention, the antibiotic is amoxicillin.

In accordance with another preferred embodiment of the invention, the antibiotic is clarithromycin.

In accordance with another preferred embodiment of the invention, the tablet contains both amoxicillin and clarithromycin.

In a more preferred embodiment of the invention, the antibiotic is amoxicillin and the complement of amoxicillin released from each subsequently releasing dosage form expresses a

maximum concentration in the serum that is equal to or exceeds the maximum concentration in the serum that is expressed by the complement of amoxicillin released by the dosage form immediately preceding that subsequently-releasing dosage form.

In one embodiment, the second of the at least three dosage forms initiates release of the antibiotic contained therein at least one hour after the first dosage form, with the initiation of the release therefrom generally occurring no more than six hours after initiation of release of antibiotic from the first dosage form of the at least three dosage forms.

In general, when three dosage forms are used, the immediate release dosage form produces a $C_{\max}$ for the antibiotic released therefrom within from about 0.5 to about 2 hours, with the second dosage form of the at least three dosage forms producing a $C_{\max}$ for the antibiotic released therefrom within about 6 hours. In general, the $C_{\max}$ for such second dosage form is achieved no earlier than two hours after administration of the antibiotic product; however, it is possible within the scope of the invention to achieve $C_{\max}$ in a shorter period of time.

As hereinabove indicated, the antibiotic product may contain at least three or at least four or more different dosage forms. For example, if the antibiotic product includes a third dosage form, the antibiotic released therefrom reaches a $C_{\max}$ at a time later than the $C_{\max}$ is achieved for the antibiotic released from each of the first and second dosage forms. In a preferred embodiment, release of antibiotic from the third dosage form is started after initiation of release of antibiotic from both the first dosage form and the second dosage form. In one embodiment, $C_{\max}$ for antibiotic release from the third dosage form is achieved within eight hours.

In another embodiment, the antibiotic product contains at least four dosage forms, with each of the at least four dosage forms having different release profiles, whereby the antibiotic released from each of the at least four different dosage forms achieves a $C_{\max}$ at a different time.

As hereinabove indicated, in a preferred embodiment, irrespective of whether the antibiotic contains at least two or at least three or at least four different dosage forms each with a

different release profile, $C_{\max}$ for all the antibiotic released from the antibiotic product is achieved in less than twelve hours, and more generally is achieved in less than eleven hours.

In a preferred embodiment, the antibiotic product is a once a day product, whereby after administration of the antibiotic product, no further product is administered during the day; i.e., the preferred regimen is that the product is administered only once over a twenty-four hour period. Thus, in accordance with the present invention, there is a single administration of an antibiotic product with the antibiotic being released in a manner such that overall antibiotic release is effected with different release profiles in a manner such that the overall $C_{\max}$ for the antibiotic product is reached in less than twelve hours. The term single administration means that the total antibiotic administered over a twenty-four hour period is administered at the same time, which can be a single tablet or two or more thereof, provided that they are administered at essentially the same time.

Applicant has found that a single dosage antibiotic product comprised of at least three antibiotic dosage forms each having a different release profile is an improvement over a single dosage antibiotic product comprised of an antibiotic dosage form having a single release profile. Each of the dosage forms of antibiotic in a pharmaceutically acceptable carrier may have one or more antibiotics and each of the dosage forms may have the same antibiotic or different antibiotics.

Notwithstanding that the preferred embodiment is a once-a-day product the dual phase delivery system herein described is not restricted thereto, and may also be used for twice-a-day administration of drugs that have more limited windows of absorption.

If at least four dosage forms are used, the fourth of the at least four dosage form may be a sustained release dosage form or a delayed release dosage form. If the fourth dosage form is a sustained release dosage form, even though $C_{\max}$ of the fourth dosage form of the at least four dosage forms is reached after the $C_{\max}$ of each of the other dosage forms is reached, antibiotic release from such fourth dosage form may be initiated prior to or after release from the second or third dosage form.

The antibiotic product of the present invention is formulated in a manner such that it is suitable for oral administration.

Alternatively, in formulating an oral delivery capsule system, several tablets may be put into a capsule to produce a unitary antibiotic product.

In formulating an antibiotic product in accordance with the invention, in one embodiment, the immediate release drug layer of the product sprayed onto the enteric coated core tablet generally provides from about 5% to about 85% of the total dosage of antibiotic to be delivered by the product, with such immediate release drug layer generally providing at least 30-40% of the total dosage of the antibiotic to be delivered by the product. In many cases, the immediate release drug layer provides from about 30% to about 40% of the total dosage of antibiotic to be delivered by the product; however, in some cases it may be desirable to have the immediate release drug layer provide for about 5% to about 20% or 75% to about 85% of the total dosage of antibiotic to be delivered by the product.

The remaining dosage forms deliver the remainder of the antibiotic. If more than one delayed release dosage form is used, in one embodiment, each of the delayed release dosage forms may provide about equal amounts of antibiotic; however, they may also be formulated so as to provide different amounts.

In accordance with one embodiment of the present invention, each of the dosage forms may contain the same antibiotic. In accordance with one embodiment of the present invention, each of the dosage forms may contain different antibiotics. In accordance with one embodiment of the present invention each of the dosage forms may contain more than one antibiotic.

In one embodiment, where the composition contains one immediate release component and two delayed release components, the immediate release component provides from 5% to 85% (preferably 30% to 40%), by weight, of the total antibiotic; where there are three delayed release components, the immediate release component provides from 5% to 75%, by weight, of

the total antibiotic; and where there are four delayed release components, the immediate release component provides from 5% to 70%, by weight, of the total antibiotic.

With respect to the delayed release components, where there are two delayed release components, the first delayed release component (the one released earlier in time) provides from 5% to 75%, by weight, of the total antibiotic provided by the two delayed release components with the second delayed release component providing the remainder of the antibiotic.

Where there are three delayed release components, the earliest released component provides 5% to 75% by weight of the total antibiotic provided by the three delayed release components, the next in time delayed release component provides from 5% to 75%, by weight, of the antibiotic provided by the three delayed release components and the last in time providing the remainder of the antibiotic provided by the three delayed release components.

When there are four delayed release components, the earliest delayed release component provides from 5% to 75%, by weight, the next in time delayed release component provides from 5% to 75%, by weight, the next in time delayed release component provides from 5% to 75%, by weight, and the last in time delayed release component provides from 5% to 75%, by weight, in each case of the total antibiotic provided by the four delayed release components.

The Immediate Release Component

The materials to be added to the active ingredients for the immediate release component can be, but are not limited to, microcrystalline cellulose, corn starch, pregelatinized starch, potato starch, rice starch, sodium carboxymethyl starch, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, ethylcellulose, chitosan, hydroxychitosan, hydroxymethylatedchitosan, cross-linked chitosan, cross-linked hydroxymethyl chitosan, maltodextrin, mannitol, sorbitol, dextrose, maltose, fructose, glucose, levulose, sucrose, polyvinylpyrrolidone (PVP), acrylic acid derivatives (Carbopol, Eudragit, etc.), polyethylene glycols, such a low molecular weight PEGs (PEG2000-10000) and high molecular weight PEGs (Polyox) with molecular weights above 20,000 daltons.

In addition, it may be useful to have other ingredients in this system to aid in the dissolution of the drug, or the breakdown of the component after ingestion or administration. These ingredients can be surfactants, such as sodium lauryl sulfate, sodium monoglycerate, sorbitan monooleate, sorbitan monooleate, polyoxyethylene sorbitan monooleate, glyceryl monostearate, glyceryl monooleate, glyceryl monobutyrate, one of the non-ionic surfactants such as the Pluronic line of surfactants, or any other material with surface active properties, or any combination of the above.

The non-pH Sensitive Delayed Release Component

The components in this composition are the same immediate release unit, but with additional polymers integrated into the composition, or as coatings over the pellet or granule.

Materials that can be used to obtain a delay in release suitable for this component of the invention can be, but are not limited to, polyethylene glycol (PEG) with molecular weight above 4,000 daltons (Carbowax, Polyox), waxes such as white wax or bees wax, paraffin, acrylic acid derivatives (Eudragit), propylene glycol, and ethylcellulose.

The pH Sensitive (Enteric) Release Component

The components in this composition are the same as the immediate release component, but with additional polymers integrated into the composition, or as coatings over the pellet or granule.

The kind of materials useful for this purpose can be, but are not limited to, cellulose acetate phthalate, Eudragit L, and other phthalate salts of cellulose derivatives.

Sustained Release Component

The components in this composition are the same as the immediate release component, but with additional polymers integrated into the composition, or as coatings over the pellet or granule.

The kind of materials useful for this purpose can be, but are not limited to, ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose,

carboxymethylcellulose, methylcellulose, nitrocellulose, Eudragit R, and Eudragit RL, Carbopol, or polyethylene glycols with molecular weights in excess of 8,000 daltons.

The following are non-limiting, representative examples of some antibiotics that may be used in the product of the invention: Cefadroxil, cefazolin, cephalixin, cephalothin, cephapirin, cephalor, cephprozil, cephradine, cefamandole, cefonicid, ceforanide, cefuroxime, cefixime, cefoperazone, cefotaxime, cefpodoxime, ceftaxidime, ceftibuten, ceftizoxime, ceftriaxone, cefepime, cefmetazole, cefotetan, cefoxitin, loracarbef, imipenem, erythromycin (and erythromycin salts such as estolate, ethylsuccinate, gluceptate, lactobionate, stearate), azithromycin, clarithromycin, dirithromycin, troleanomycin, penicillin V, penicillin salts, and complexes, methicillin, nafcillin, oxacillin, cloxacillin, dicloxacillin, amoxicillin, amoxicillin and clavulanate potassium, ampicillin, bacampicillin, carbenicillin indanyl sodium (and other salts of carbenicillin) mezlocillin, piperacillin, piperacillin and tazobactam, ticarcillin, ticarcillin and clavulanate potassium, clindamycin, vancomycin, novobiocin, aminosalicic acid, capreomycin, cycloserine, ethambutol HCl and other salts, ethionamide, and isoniazid, ciprofloxacin, levofloxacin, lomefloxacin, nalidixic acid, norfloxacin, ofloxacin, sparfloxacin, sulfacycline, suflamerazine, sulfamethazine, sulfamethoxazole, sulfasalazine, sulfisoxazole, sulfapyridine, sulfadiazine, sulfamethoxazole, sulfapyridine, metronidazole, methenamine, fosfomycin, nitrofurantoin, trimethoprim, clofazimine, co-trimoxazole, pentamidine, and trimetrexate.

The following are non-limiting, representative examples of some antivirals that may be used in the product of the invention: Acyclovir, Amantadine, Amprenavir, Cidofovir, Delavirdine, Didanosine, Famciclovir, Foscarnet, Ganciclovir, Indinavir, Interferon, Lamivudine, Nelfinavir, Nevirapine, Palivizumab, Penciclovir, Ribavirin, Rimantadine, Ritonavir, Saquinavir, Stavudine, Trifluridine, Valacyclovir, Vidarabine, Zalcitabine, Zidovudine.

The following are representative examples of some antifungals that may be used in the product of the invention: amphotericin B, flucytosine, fluconazole, griseofulvin, miconazole nitrate, terbinafine hydrochloride, ketoconazole, itraconazole, undecylenic acid and chloroxylenol, ciclopirox, clotrimazole, butenafine hydrochloride, nystatin, naftifine hydrochloride, oxiconazole nitrate, selenium sulfide, econazole nitrate, terconazole,

butoconazole nitrate, carbol-fuchsin, clioquinol, methylrosaniline chloride, sodium thiosulfate, sulconazole nitrate, terbinafine hydrochloride, tioconazole, tolnaftate, undecylenic acid and undecylenate salts (calcium undecylenate, copper undecylenate, zinc undecylenate).

EXAMPLES

General Procedure for Preparing Immediate Release Pellets

Dissolve binder and liquid ingredients in water. Place solid ingredients into a high shear blender (e.g. Glatt) and mix at low impeller speed (300 rpm) for 1 minute. At an impeller speed of 300 rpm and a chopper speed of 2500 rpm, slowly add the prepared binder solution to the dry mix (3-5 minutes). Add additional water as necessary. Continue to mix for 30 sec. Discharge material and transfer to an extruder. Extrude the granulation with a dome extruder at 50-100 rpm through a 0.6-1mm, or other appropriate, screen. Transfer the extrudate into a spheronizer. Spheronize at 610 rpm for 20-30 sec. Discharge pellets and transfer to a fluidbed dryer (FluidAir). Dry at 60°C inlet temp and 200 air flow until the loss on drying (LOD) does not change any further (approx. 60 min). Cool down the pellets at 25°C air temperature for approximately 15 minutes prior to discharge.

General Procedure for Coating Immediate Release Pellets to Make Enteric Release Pulse 3 and Pulse 4

Preparation of the coating solution. Dissolve sodium lauryl sulfate (SLS) and triethyl citrate (TEC) in water using an overhead mixer. Add polymer and mix for 30-45 min. Add Talc and mix for 30-45 min. Sieve dispersion across a 60 mesh screen prior to use. Continue mixing during the entire coating process in the fluidbed. Transfer the pellets to a pre-heated fluidbed dryer (FluidAir). Apply the coating solution to the pellets spraying at 60-65°C inlet temp, 170-180 scfm air flow and 30 psi atomization air pressure up to 40% weight gain. Dry pellets at 50°C and 10 psi for 10 minutes, and cool at 30°C prior to discharge. Sieve the final product across 20-40 mesh. Yield is typically > 95%.

General Procedure for Preparing Granulation (Pulse 2)

Dissolve binder in water. Place the active pharmaceutical ingredient into a high shear blender (e.g. Glatt). At impeller speed 300 rpm and chopper speed 2500 rpm, slowly add the binder solution (3-5 minutes). Add additional water if necessary. Continue to mix for 30 sec. Discharge material and transfer to a fluidbed dryer. Dry the granulation at 50°C for 60 minutes.

Mill through a Comil U10 at speed 50 using screen 7A040603122329B(1016)90. Dry in fluidbed for 30 minutes at 50°C. Sieve across a 20 mesh screen.

General Tableting Procedure

Weigh the appropriate amount of pulse 3 and/or 4 pellets, pulse 2 granulation, and remaining tableting excipients. Combine all components except Magnesium Stearate (lubricant) in a PK blender and mix for 5 minutes. Add the lubricant and mix for an additional 2 minutes. Compress the blend on a tablet press to an appropriate hardness.

General Procedure for Coating Tablets

To prepare enteric coating solution mix L30D and TEC for 30 minutes at low speed using an overhead mixer. In a separate container, mix water and talc, stirring vigorously. Add Talc slurry to the polymer dispersion. Sieve through 60 mesh screen prior to coating process. Keep stirring the dispersion at slow speed throughout the coating process. Coat tablets in a pan coater (LCDS) at 55°C inlet temperature, 25 cfm air flow, pump setting of 7-10, pan speed 19 rpm, and atomization pressure of 25-26 psi. Up to 8% weight gain is required for this coating procedure. Yields are typically > 95%.

General Procedure for Applying Immediate Release Active Coating

Dissolve HPMC in cold water. Add Amoxicillin, stirring with overhead stirrer at medium speed. Use LCDS 20/30 to apply the coating at inlet temp of 55°C, airflow 24 cfm, pump setting 10-12, pan speed 19 rpm, and 25-28 psi atomization air pressure until the desired weight gain is reached.

General Procedure for Optional

Immediate Release Cosmetic/Taste Masking Coating

A solution of 7% opadry solution in water is prepared by stirring. The coating is applied at inlet temp of 65°C, airflow 25 cfm, pump setting 8-9, pan speed 19 rpm, and 25 psi atomization air pressure to reach a total weight gain of 3-3.5%.

Example of an Immediate Release Robust Pellet Formulation:

Ingredient	%
Active Pharmaceutical Ingredient	85-95%
Microcrystalline Cellulose	4-8%
Povidone	1-5%
PEG-35 Castor Oil	0.5-2%
Water	As needed

Example of an Immediate Release Robust Pellet Formulation:

Ingredient	%
Active Pharmaceutical Ingredient	1-15%
Microcrystalline Cellulose	69-91%
Povidone	3-6%
PEG-35 Castor Oil	5-10%
Water	As needed

These immediate release pellets can also be coated with an enteric or modified release coating to deliver active ingredient to the required locations in the GI tract.

Examples of Core Tablet Formulations:

Ingredient	%
Active Granule	5-15%
Enteric Coated Pellets	55-75%
Microcrystalline Cellulose	5-10%
Povidone K30	1-5%
Croscarmellose Sodium	1-5%
Magnesium Stearate	1-3%

Ingredient	%
Active Granule	20-25%
Enteric Coated Pellets	40-50%
Microcrystalline Cellulose	20-30%
Povidone K30	1-8%
Croscarmellose Sodium	1-5%
Magnesium Stearate	1-2%

Ingredient	%
Active Granule	30-40%
Enteric Coated Pellets	1-15%
Microcrystalline Cellulose	40-60%
Povidone K30	1-5%
Croscarmellose Sodium	1-5%
Magnesium Stearate	1-3%

Ingredient	%W/W
Drug Granules	7.50%
Pulsatile Pellet 3	15.00%
Pulsatile Pellet 4	15.00%
SMCC	27.50%
Lactose Monohydrate	27.50%
PVP K30	3.00%
Croscarmellose Na	3.00%
Magnesium Stearate	1.00%

Ingredient	%W/W
Drug Granules	7.50%
Pulsatile Pellet 3	20.00%
Pulsatile Pellet 4	20.00%
SMCC	21.25%
Lactose Monohydrate	21.25%
PVP K30	5.00%
Croscarmellose Na	4.00%
Magnesium Stearate	1.00%

Ingredient	%W/W
Drug Granules	7.50%
Pulsatile Pellet 3	30.00%
Pulsatile Pellet 4	30.00%
SMCC	11.75%
Lactose Monohydrate	11.75%
PVP K30	5.00%
Croscarmellose Na	4.00%
Magnesium Stearate	1.00%

Enteric Tablet Coating

Any of the enteric or modified release coatings available can be used to layer the core tablet to provide intra-stomach protection thereof and prevent pre-intestinal emptying of the tablet contents. Enteric polymers include, but are not limited to polyethyl acrylate, methyl methacrylate, ethyl acrylate, and trimethylammonioethyl methacrylate chloride copolymers, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, cellulose acetate phthalate, ethylvinylacetate phthalate, polyvinylacetate phthalate, and carboxymethylethylcellulose. Tablet contents (i.e. active matrix / pellets) are encapsulated and protected from releasing before the targeted release point. The coating must withstand

downstream processing from further tablet compression forces and / or tablet coating operations. In-vivo, the enteric coating should protect the active contents as they pass through the upper GI tract and stomach until reaching the desired trigger point within the small or large intestine. This will ensure that all of the tablet contents will be emptied as a single packet at the target and prevent separation and dilution of the drug during transit.

Examples of Enteric Coating Formulations:

Ingredient	%
Methacrylic Copolymer	20-60%
Talc	1-30%
Triethyl Citrate	1-20%
Sodium Lauryl Sulfate	0.25-1.0%
Water	As needed

Ingredient	%W/W
Eudragit L30D-55	50.00%
Triethyl Citrate	2.00%
Glycerol Mono-Stearate	2.00%
Water	46.00%

Drug Layer

The active pharmaceutical layer or drug layer is applied on top of the protected enteric coated core tablet. The active layer delivers the first pulse or immediate release.

Ingredient	%
Active	1-40%
Hydroxypropylmethylcellulose	1-10%
Water	As needed

Ingredient	% W/W
Metronidazole	20.00%
HPMC (low viscosity)	5.00%
Water	75.00%

4 Pulse Amoxicillin Enteric Coated Tablet

Amoxicillin Pellet Formulation and Preparation Procedure

* Pellet Formulations for subsequent coating

The composition of the Amoxicillin trihydrate matrix pellets provided in Table 1.

Table 1 Composition of Amoxicillin Matrix Pellets

Component	Percentage (%)
Amoxicillin Trihydrate powder	92
Avicel PH 101	7.0
Hydroxypropyl methylcellulose, NF*	1.0
Total	100

*Hydroxypropyl methylcellulose was added as a 2.9% w/w aqueous solution during wet massing.

* Preparation Procedure for Amoxicillin Matrix Pellets

Blend Amoxicillin and Avicel® PH 101 using a low shear blender.

Add the hydroxypropyl methylcellulose binder solution slowly into the powder blend under continuous mixing.

Extrude the wet mass using an LCI Bench Top Granulator. The diameter of the screen of the Bench Top Granulator is 0.8 mm.

Spheronize the extrudate using a QJ-230 Spheronizer using a small cross section plate.

Dry the spheronized pellets at 60°C using a fluid bed dryer until the exhaust temperature reaches 40°C.

Pellets between 20 and 40 Mesh were collected for further processing.

* Preparation of an Eudragit® L 30 D-55 Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous Eudragit L30D-55 dispersion applied to the amoxicillin matrix pellets is provided below in Table 2.

Table 2 Eudragit® L 30 D-55 Aqueous Coating Dispersion

Component	Percentage (%)
Eudragit® L 30 D-55	41.6
Triethyl Citrate	2.5
Talc	5.0
Purified Water	50.9
Solids Content	20.0
Polymer Content	12.5

* Preparation Procedure for an Eudragit® L 30 D-55 Aqueous Dispersion

Suspend triethyl citrate and talc in deionized water.

The TEC/talc suspension is mixed using laboratory mixer.

Add the TEC/talc suspension from slowly to the Eudragit® L 30 D-55 latex dispersion while stirring.

Allow the coating dispersion to stir for one hour prior to application onto the amoxicillin matrix pellets.

* Preparation of an Eudragit® S 100 Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous Eudragit® S 100 dispersion applied to the Amoxicillin matrix pellets is provided below in Table 3.

Table 3 Eudragit® S 100 Aqueous Coating Dispersion

Component	Percentage (%)
Part A	
Eudragit® S 100	10.0
1 N Ammonium Hydroxide	5.1
Triethyl Citrate	5.0
Water	64.9
Part B	
Talc	5.0
Water	10.0
Solid Content	25.0
Polymer Content	10.0

* Preparation Procedure for an Eudragit® S 100 Aqueous Dispersion

Part A:

Dispense Eudragit® S 100 powder in deionized water with stirring.

Add ammonium hydroxide solution drop-wise into the dispersion with stirring.

Allow the partially neutralized dispersion to stir for 60 minutes.

Add triethyl citrate drop-wise into the dispersion with stirring and let stir overnight prior to the addition of Part B.

Part B:

Disperse talc in the required amount of water

Stir the dispersion using an overhead laboratory mixer.

Part B is then added slowly to the polymer dispersion in Part A with a mild stirring.

* Coating Conditions for the Application of Aqueous Coating Dispersions

The following coating parameters were used for both the Eudragit® L 30 D-55 and Eudragit® S 100 aqueous film coating processes.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	40 to 45 °C
Outlet Air Temperature	30 to 33 °C
Atomization Air Pressure	1.8 Bar
Pump Rate	2-6 gram per minute

Coat matrix pellets with L30 D-55 dispersion such that you apply 20% coat weight gain to the pellets.

Coat matrix pellets with S100 dispersion such that you apply 37% coat weight gain to the pellets.

* Preparation of Amoxicillin Granulation (Immediate Release Component) for tableting

Table 4 Composition of Amoxicillin Granulation

Component	Percentage (%)
Amoxicillin Trihydrate powder	92
Avicel PH 101	7.0
Hydroxypropyl methylcellulose, NF*	1.0
Total	100

*Hydroxypropyl methylcellulose was added as a 2.9% w/w aqueous solution during wet massing.

Blend Amoxicillin and Avicel® PH 101 using a low shear blender.

Add the hydroxypropyl methylcellulose binder solution slowly into the powder blend under continuous mixing.

Dry the granulation at 60°C using a fluid bed dryer until the exhaust temperature reaches 40°C.

Granules between 20 and 40 Mesh are collected for further processing.

* Tableting of the Amoxicillin Pellets

Table 5 Composition of Amoxicillin Tablets

Component	Percentage (%)
Amoxicillin granules	32.5
Avicel PH 200	5.0
Amoxicillin L30D-55 coated pellets	30
Amoxicillin S100 coated pellets	30
Colloidal silicon dioxide	1.5
Magnesium stearate	1.0
Total	100

Blend the Amoxicillin granules, Avicel PH-200, Amoxicillin pellets and colloidal silicon dioxide for 15 minutes in a tumble blender.

Add the magnesium stearate to the blender, and blend for 5 minutes.

Compress the blend on a rotary tablet press.

The fill weight should be adjusted to achieve a 500 mg dose tablet.

*** General Procedure for Enteric Coating of Tablets**

To prepare enteric coating solution mix L30D and TEC for 30 minutes at low speed using an overhead mixer, according to Table 2. In a separate container, mix water and talc, stirring vigorously. Add Talc slurry to the polymer dispersion. Sieve through 60 mesh screen prior to coating process. Keep stirring the dispersion at slow speed throughout the coating process.

Coat tablets in a pan coater (LCDS) at 55°C inlet temperature, 25 cfm air flow, pump setting of 7-10, pan speed 19 rpm, and atomization pressure of 25-26 psi. Up to 8% weight gain is desired for this coating procedure.

Coating Equipment	LCDS laboratory Pan Coater
pan speed	19 rpm
atomization pressure of	25-26 psi
Inlet Air Temperature	50-60 °C
Outlet Air Temperature	30 to 33 °C
Pump Rate	7-10 gram per minute

* **General Procedure for Applying Immediate Release Active Coating**

Dissolve HPMC in cold water. Add Amoxicillin, stirring with overhead stirrer at medium speed. Use LCDS 20/30 to apply the coating at inlet temp of 55°C, airflow 24 cfm, pump setting 10-12, pan speed 19 rpm, and 25-28 psi atomization air pressure until the desired weight gain is reached.

* **General Procedure for Optional**
Immediate Release Cosmetic/Taste Masking Coating

A solution of 7% opadry solution in water is prepared by stirring. The coating is applied at inlet temp of 65°C, airflow 25 cfm, pump setting 8-9, pan speed 19 rpm, and 25 psi atomization air pressure to reach a total weight gain of 3-3.5%.

This example makes a complete amoxicillin enteric coated tablet with 4 pulses containing 500-800 mg amoxicillin.

Four Pulse Clarithromycin Enteric Coated Tablet**Clarithromycin Pellet Formulation and Preparation Procedure***** Pellet Formulation**

The composition of the clarithromycin matrix pellets provided in Table 6.

Table 6 Composition of Clarithromycin Pellets

Component	Percentage (%)
Clarithromycin	50.6
Lactose monohydrate, spray dried	32.1
Silicified microcrystalline cellulose	14.6
Polyoxyl 35 Castor Oil*	1.7
Hydroxypropyl methylcellulose*	1.0
Total	100

*Hydroxypropyl methylcellulose and Polyoxyl 35 were added as an 8.7% w/w aqueous solution during wet massing.

*** Preparation Procedure for Clarithromycin Matrix Pellets**

Blend clarithromycin, silicified microcrystalline cellulose and lactose monohydrate using a Robot Coupe high shear granulator.

Prepare the binder solution by adding the Polyoxyl to the purified water while stirring. After that is mixed, slowly add the hydroxypropyl methylcellulose and continue to stir until a solution is achieved.

Add binder solution slowly into the powder blend under continuous mixing.

Granulate the powders in the high shear granulator with the binder solution.

Extrude the wet mass using an LCI Bench Top Granulator. The diameter of the screen of the Bench Top Granulator was 1.2 mm.

Spheronize the extrudate using a Model SPH20 Caleva Spheronizer.

Dry the spheronized pellets at 50°C overnight.

Pellets between 18 and 30 Mesh were collected for further processing

* Preparation of an Eudragit® L 30 D-55 Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous Eudragit L30D-55 dispersion applied to the clarithromycin matrix pellets is provided below in Table 7.

Table 7 Eudragit® L 30 D-55 Aqueous Coating Dispersion

Component	Percentage (%)
Eudragit® L 30 D-55	40.4
Triethyl Citrate	1.8
Talc	6.1
Water	51.7
Solids Content	20.0
Polymer Content	12.1

* Preparation Procedure for an Eudragit® L 30 D-55 Aqueous Dispersion

Suspend triethyl citrate and talc in deionized water.

The TEC/talc suspension is then homogenized using a PowerGen 700 high shear mixer.

Add the suspension from 4.2.2 slowly to the Eudragit® L 30 D-55 latex dispersion while stirring.

Allow the coating dispersion to stir for one hour prior to application onto the clarithromycin matrix pellets.

* Preparation of an Eudragit® S 100 Aqueous Coating Dispersion

Dispersion Formulation

The composition of the aqueous Eudragit® S 100 dispersion applied to the clarithromycin matrix pellets is provided below in Table 8.

Table 8 Eudragit® S 100 Aqueous Coating Dispersion

Component	Percentage (%)
Part A	
Eudragit® S 100	10.0
1 N Ammonium Hydroxide	5.1
Triethyl Citrate	5.0
Water	64.9
Part B	
Talc	5.0
Water	10.0
Solid Content	25.0
Polymer Content	10.0

* Preparation Procedure for an Eudragit® S 100 Aqueous Dispersion

Part A:

Dispense Eudragit® S 100 powder in deionized water with stirring.

Add ammonium hydroxide solution drop-wise into the dispersion with stirring.

Allow the partially neutralized dispersion to stir for 60 minutes

Add the triethyl citrate drop-wise to the dispersion and stir for 60 minutes prior to the addition of Part B.

Part B:

Disperse talc in the required amount of water

Homogenize the dispersion using a PowerGen 700D high shear mixer.

Part B is then added slowly to the polymer dispersion in Part A with a mild stirring.

*** Coating Conditions for the Application of Aqueous Coating Dispersions**

The following coating parameters were used for coating the matrix pellets with each of the Eudragit® L 30 D-55 and Eudragit® S 100 aqueous film coating.

Coating Equipment	STREA 1™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	40 to 45 °C
Outlet Air Temperature	30 to 33 °C
Atomization Air Pressure	1.6 Bar
Pump Rate	2 gram per minute

Coat matrix pellets with L30 D-55 dispersion such that you apply 20% coat weight gain to the pellets.

Coat matrix pellets with S100 dispersion such that you apply 37% coat weight gain to the pellets.

*** Preparation of clarithromycin Granulation (Immediate Release Component) for tableting**

Table 9 Composition of clarithromycin Granulation

Component	Percentage (%)
clarithromycin powder	92
Avicel PH 101	7.0
Hydroxypropyl methylcellulose, NF*	1.0
Total	100

*Hydroxypropyl methylcellulose was added as a 2.9% w/w aqueous solution during wet massing.

Blend clarithromycin and Avicel® PH 101 using a low shear blender.

Add the hydroxypropyl methylcellulose binder solution slowly into the powder blend under continuous mixing.

Dry the granulation at 60°C using a fluid bed dryer until the exhaust temperature reaches 40°C.

Granules between 20 and 40 Mesh are collected for further processing.

* Tableting of the Clarithromycin Pellets

Table 10 Composition of Clarithromycin Tablets

Component	Percentage (%)
clarithromycin granules	32.5
Avicel PH 200	5.0
clarithromycin L30D-55 coated pellets	30
clarithromycin S100 coated pellets	30
Colloidal silicon dioxide	1.5
Magnesium stearate	1.0
Total	100

Blend the clarithromycin granules, Avicel PH-200, clarithromycin pellets and colloidal silicon dioxide for 15 minutes in a tumble blender.

Add the magnesium stearate to the blender, and blend for 5 minutes.

Compress the blend on a rotary tablet press.

The fill weight should be adjusted to achieve a 500 mg dose tablet.

*** General Procedure for Enteric Coating of Tablets**

To prepare enteric coating solution mix L30D and TEC for 30 minutes at low speed using an overhead mixer, according to Table 2. In a separate container, mix water and talc, stirring vigorously. Add Talc slurry to the polymer dispersion. Sieve through 60 mesh screen prior to coating process. Keep stirring the dispersion at slow speed throughout the coating process.

Coat tablets in a pan coater (LCDS) at 55°C inlet temperature, 25 cfm air flow, pump setting of 7-10, pan speed 19 rpm, and atomization pressure of 25-26 psi. Up to 8% weight gain is desired for this coating procedure.

Coating Equipment	LCDS laboratory Pan Coater
pan speed	19 rpm
atomization pressure of	25-26 psi
Inlet Air Temperature	50-60 °C
Outlet Air Temperature	30 to 33 °C
Pump Rate	7-10 gram per minute

* **General Procedure for Applying Immediate Release Active Coating**

Dissolve HPMC in cold water. Add clarithromycin, stirring with overhead stirrer at medium speed. Use LCDS 20/30 to apply the coating at inlet temp of 55°C, airflow 24 cfm, pump setting 10-12, pan speed 19 rpm, and 25-28 psi atomization air pressure until the desired weight gain is reached.

* **General Procedure for Optional**

Immediate Release Cosmetic/Taste Masking Coating

A solution of 7% opadry solution in water is prepared by stirring. The coating is applied at inlet temp of 65°C, airflow 25 cfm, pump setting 8-9, pan speed 19 rpm, and 25 psi atomization air pressure to reach a total weight gain of 3-3.5%.

This makes a complete clarithromycin enteric coated tablet with 4 pulses.

We Claim:

1. A pharmaceutical tablet, said tablet comprising an immediate release portion containing an active ingredient and a delayed release portion, wherein said delayed release portion comprises an enteric-coated layer and within said enteric-coated layer there is at least one member selected from the group consisting of enteric-coated microparticle dosage forms containing an active ingredient and enteric-coated minitabket dosage forms containing an active ingredient.
2. The pharmaceutical tablet of claim 1, wherein said active ingredients consist of the same active ingredient.
3. The pharmaceutical tablet of claim 1, wherein said active ingredients comprise at least two different active ingredients.
4. The pharmaceutical tablet of claim 1, wherein said active ingredient is selected from the group consisting of antibiotics, antivirals, antifungals, and antineoplastics.
5. The pharmaceutical tablet of claim 4, wherein said antibiotic is selected from the group consisting of beta-lactams, cephalosporins, and macrolides.
6. The pharmaceutical tablet of claim 3, wherein said at least two different active ingredients comprise amoxicillin and clarithromycin.
7. The pharmaceutical tablet of claim 5, wherein said beta-lactam antibiotic is amoxicillin.
8. The pharmaceutical tablet of claim 7, wherein the compliment of amoxicillin released from each subsequently releasing dosage form expresses a maximum concentration in the serum that is equal to or exceeds the maximum concentration in the serum that is expressed by the compliment of amoxicillin released by the dosage form immediately preceeding that subsequently-releasing dosage form.

9. A method for preparing a pharmaceutical tablet having an immediate release portion and a delayed release portion for immediate and delayed release delivery of at least one active ingredient, said method comprising the steps of:
- (a) formulating a delayed release portion that comprises a core tablet and an enteric coating, such that said core tablet comprises at least one member selected from the group consisting of enteric-coated microparticle dosage forms containing an active ingredient and enteric-coated mini-tablet dosage forms containing an active ingredient; and such that said enteric coating covers said core tablet; and
 - (b) applying an immediate release portion containing an active ingredient as an immediate release layer over said delayed release portion such that said immediate release layer at least partially covers said delayed release portion.
10. A process for treating a bacterial infection in a host comprising: administering to a host the pharmaceutical tablet of Claim 1, once or twice, daily.
11. A process for treating a bacterial infection in a host comprising: administering to a host the pharmaceutical tablet of Claim 2, once or twice, daily.
12. A process for treating a bacterial infection in a host comprising: administering to a host the pharmaceutical tablet of Claim 3, once or twice, daily.
13. A process for treating a bacterial infection in a host comprising: administering to a host the pharmaceutical tablet of Claim 4, once or twice, daily.
14. A process for treating a bacterial infection in a host comprising: administering to a host the pharmaceutical tablet of Claim 5, once or twice, daily.
15. A process for treating a bacterial infection in a host comprising: administering to a host the pharmaceutical tablet of Claim 6, once or twice, daily.

16. A process for treating a bacterial infection in a host comprising: administering to a host the pharmaceutical tablet of Claim 7, once or twice, daily.
17. A process for treating a bacterial infection in a host comprising: administering to a host the pharmaceutical tablet of Claim 8, once or twice, daily.
18. A process for treating a bacterial infection in a host comprising: administering to a host the pharmaceutical tablet produced by the method of Claim 9, once or twice, daily.
19. The pharmaceutical tablet of claim 1, wherein said at least one member selected from the group consisting of enteric-coated microparticle dosage forms containing an active ingredient and enteric-coated minitabiet dosage forms containing an active ingredient, is a pH-sensitive dosage form.
20. The pharmaceutical tablet of claim 1, wherein said at least one member selected from the group consisting of enteric-coated microparticle dosage forms containing an active ingredient and enteric-coated minitabiet dosage forms containing an active ingredient, is a pH-independent dosage form.
21. A process for treating a bacterial infection in a host comprising: administering to a host the pharmaceutical tablet of Claim 19, once or twice, daily.
22. A process for treating a bacterial infection in a host comprising: administering to a host the pharmaceutical tablet of Claim 20, once or twice, daily.