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(54) Title: THERAPEUTIC PRODUCT, USE AND FORMULATION THEREOF

(57) Abstract: A therapeutic product comprising: a first therapeutic dosage form, a second therapeutic dosage form, and a third therapeutic dosage form, each of said first, second and third therapeutic dosage forms comprising at least one therapeutic agent and a pharmaceutically acceptable carrier, said three dosage forms having different release profiles, said therapeutic product reaching a C_{max} in less than about twelve hours wherein said therapeutic is an antibiotic, an anti-fungal, an anti-viral or an anti-neoplastic agent.

THERAPEUTIC PRODUCT, USE AND FORMULATION THEREOF

This invention relates to an therapeutic product, as well as the use and formulation thereof.

A wide variety of antibiotics, anti-fungal, anti-viral and anti-neoplastic agents have been used, and will be used, in order to treat a patient. In general, such therapeutics can be administered by a repeated dosing of immediate release dosage forms, which results in poor compliance or as a controlled release formulation (slow release) at higher administered doses. The present invention is directed to providing for an improved therapeutic product.

In accordance with one aspect of the present invention, there is provided a pharmaceutical product which is comprised of at least two, preferably at least three, dosage forms, each comprised of at least one therapeutic agent and a pharmaceutically acceptable carrier. Such dosage forms are formulated so that each of the dosage forms has a different release profile. As used in this application the term "therapeutic" or "therapeutic agent" means an antibiotic, or an anti-fungal or an anti-viral or an anti-neoplastic agent.

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 therapeutic contained therein at different times after administration of the therapeutic product.

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

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

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

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

In accordance with one 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 therapeutic therefrom is not substantially delayed after administration of the therapeutic product. The second and third of the at least three dosage forms is a delayed dosage form (which may be a pH sensitive or a non-pH sensitive delayed dosage form, depending on the type of therapeutic product), whereby the therapeutic released therefrom is delayed until after initiation of release of the therapeutic from the immediate release dosage form. More particularly, the therapeutic release 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 therapeutic released from the first of the at least three dosage forms achieves a C_{max} in the serum, and the therapeutic released from the third dosage form achieves a C_{max} in the serum after the C_{max} of therapeutic released from the second dosage form.

In one embodiment, the second of the at least two dosage forms initiates release of the therapeutic 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 therapeutic from the first dosage form of the at least three dosage forms.

In general, the immediate release dosage form produces a C_{max} for the therapeutic 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 therapeutic released therefrom in no more than about four hours. In general, the C_{max} for such second dosage form is achieved no earlier than two hours after administration of the therapeutic 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 therapeutic product may contain at least three or at least four or more different dosage forms. For example, if the therapeutic product includes a third dosage form, the therapeutic released therefrom reaches a C_{max} at a time later than the C_{max} is achieved for the therapeutic released from each of the first and second dosage forms. In a preferred embodiment, release of therapeutic from the third dosage form is started after initiation of release of therapeutic from both the first dosage form and the second dosage form. In one embodiment, C_{max} for therapeutic released from the third dosage form is achieved within eight hours.

In another embodiment, the therapeutic product contains at least four dosage forms, with each of the at least four dosage forms having different release profiles, whereby the therapeutic 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 therapeutic 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 therapeutic released from the therapeutic product is achieved in less than twelve hours, and more generally is achieved in less than eleven hours.

In a preferred embodiment, the therapeutic product is a once a day product, whereby after administration of the therapeutic 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 a therapeutic product with the therapeutic being released in a manner such that overall therapeutic release is effected with different release profiles in a manner such that the overall C_{max} for the therapeutic product is reached in less than twelve hours. The term single administration means that the total therapeutic administered over a twenty-four hour period is administered at the same time, which can be a single tablet or capsule or two or more thereof, provided that they are administered at essentially the same time.

Applicant has found that a single dosage therapeutic product comprised of at least three therapeutic dosage forms each having a different release profile is an improvement over a single dosage therapeutic product comprised of an therapeutic dosage form having a single release profile. Each of the dosage forms of therapeutic in a pharmaceutically acceptable carrier may have one or more therapeutics of the same type (for example, one or more antibiotics; one or more anti-viral agents, etc.) and each of the dosage forms may have the same therapeutic or different therapeutics, each of the same type (the same or different antibiotics; the same or different anti-virals, etc.).

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 and is intended to produce such later initiated release. It is known in the art, however, notwithstanding such design and intent, some "leakage" of therapeutic may occur. Such "leakage" is not "release" as used herein.

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, therapeutic release from such fourth dosage form may be initiated prior to or after release from the second or third dosage form.

The therapeutic product of the present invention, as hereinabove described, may be formulated for administration by a variety of routes of administration. For example, the therapeutic product may be formulated in a way that is suitable for topical administration; administration in the eye or the ear; rectal or vaginal administration; as nose drops; by inhalation; as an injectable; or for oral administration. In a preferred embodiment, the therapeutic product is formulated in a manner such that it is suitable for oral administration.

For example, in formulating the therapeutic product for topical administration, such as by application to the skin, the at least two different dosage forms, each of which contains an therapeutic, may be formulated for topical administration by including such dosage forms in an oil-in-water emulsion, or a water-in-oil emulsion. In such a formulation, the immediate release dosage form is in the continuous phase, and the delayed release dosage form is in a discontinuous phase. The formulation may also be produced in a manner for delivery of three dosage forms as hereinabove described. For example, there may be provided an oil-in-water-in-oil emulsion, with oil being a continuous phase that contains the immediate release component, water dispersed in the oil containing a first delayed release dosage form, and oil dispersed in the water containing a third delayed release dosage form.

It is also within the scope of the invention to provide an therapeutic product in the form of a patch, which includes therapeutic dosage forms having different release profiles, as hereinabove described.

In addition, the therapeutic product may be formulated for use in the eye or ear or nose, for example, as a liquid emulsion. For example, the dosage form may be coated with a hydrophobic polymer whereby a dosage form is in the oil phase of the

emulsion, and a dosage form may be coated with hydrophilic polymer, whereby a dosage form is in the water phase of the emulsion.

Furthermore, the therapeutic product with at least three different dosage forms with different release profiles may be formulated for rectal or vaginal administration, as known in the art. This may take the form of a cream or emulsion, or other dissolvable dosage form similar to those used for topical administration.

As a further embodiment, the therapeutic product may be formulated for use in inhalation therapy by coating the particles and micronizing the particles for inhalation.

In a preferred embodiment, the therapeutic product is formulated in a manner suitable for oral administration. Thus, for example, for oral administration, each of the dosage forms may be used as a pellet or a particle, with a pellet or particle then being formed into a unitary pharmaceutical product, for example, in a capsule, or embedded in a tablet, or suspended in a liquid for oral administration.

Alternatively, in formulating an oral delivery system, each of the dosage forms of the product may be formulated as a tablet, with each of the tablets being put into a capsule to produce a unitary therapeutic product. Thus, for example, therapeutic products may include a first dosage form in the form of a tablet that is an immediate release tablet, and may also include two or more additional tablets, each of which provides for a delayed release of the therapeutic, as hereinabove described, whereby the C_{max} of the therapeutic released from each of the tablets is reached at different times, with the C_{max} of the total therapeutic released from the therapeutic product being achieved in less than twelve hours.

The formulation of an therapeutic product including at least three dosage forms with different release profiles for different routes of administration is deemed to be within the skill of the art from the teachings herein. As known in the art, with respect to delayed release, the time of release can be controlled by the concentration of therapeutics in the coating and/or the thickness of the coating.

In formulating a therapeutic product in accordance with the invention, in one embodiment, the immediate release dosage form of the product generally provides from about 20% to about 50% of the total dosage of therapeutic to be delivered by the product, with such immediate release dosage forms generally providing at least 25% of the total dosage of the therapeutic to be delivered by the product. In many cases, the immediate release dosage form provides from about 20% to about 30% of the total dosage of therapeutic to be delivered by the product; however, in some cases it may be desirable to have the immediate release dosage form provide for about 45% to about 50% of the total dosage of therapeutic to be delivered by the product.

The remaining dosage forms deliver the remainder of the therapeutic. 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 therapeutic; however, they may also be formulated so as to provide different amounts.

In accordance with the present invention, each of the dosage forms contains the same therapeutic; however, each of the dosage forms may contain more than one therapeutic.

In one embodiment, where the composition contains one immediate release component and two delayed release components, the immediate release component provides from 20% to 35% (preferably 20% to 30%), by weight, of the total therapeutic; where there is three delayed release components, the immediate release component provides from 15% to 30%, by weight, of the total therapeutic; and where there are four delayed release components, the immediate release component provides from 10% to 25%, by weight, of the total therapeutic.

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 30% to 60%, by weight, of the total therapeutic provided by the two delayed release components with the second delayed release component providing the remainder of the therapeutic.

Where there are three delayed release components, the earliest released component provides 20% to 35% by weight of the total therapeutic provided by the three delayed release components, the next in time delayed release component provides from 20% to 40%, by weight, of the therapeutic provided by the three delayed release components and the last in time providing the remainder of the therapeutic provided by the three delayed release components.

When there are four delayed release components, the earliest delayed release component provides from 15% to 30%, by weight, the next in time delayed release component provides from 15% to 30%, the next in time delayed release component provides from 20% to 35%, by weight, and the last in time delayed release component provides from 20% to 35%, by weight, in each case of the total therapeutic provided by the four delayed release components.

The Immediate Release Component

The immediate release portion of this system can be a mixture of ingredients that breaks down quickly after administration to release the therapeutic. This can take the form of either a discrete pellet or granule that is mixed in with, or compressed with, the other three components.

The materials to be added to the therapeutics 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.

It may be useful to have these materials present in the range of 1.0 to 60% (W/W).

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.

These materials may be present in the rate of 0.05-15% (W/W).

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.

Typically these materials can be present in the range of 0.5-25% (W/W) of this component.

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 pthalate, Eudragit L, and other pthalate salts of cellulose derivatives.

These materials can be present in concentrations from 4-20% (W/W).

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.

These materials can be present in concentrations from 4-20% (W/W).

As hereinabove indicated, the units comprising the therapeutic composition of the present invention can be in the form of discrete pellets or particles contained in the capsule, or particles embedded in a tablet or suspended in a liquid suspension.

The therapeutic composition of the present invention may be administered, for example, by any of the following routes of administration: sublingual, transmucosal, transdermal, parenteral, etc., and preferably is administered orally. The composition includes a therapeutically effective amount of the therapeutic, which amount will vary with the therapeutic to be used, the disease or infection to be treated, and the number of times that the composition is to be delivered in a day. The composition is administered to a host in an amount effective for treating the disease or infection. Thus, the therapeutic composition or product may be used for treating an infection in a host that is caused by bacteria or virus or fungus and may be used to treat cancer.

This system will be especially useful in extending the practial therapeutic activity for antibiotics with elimination half lives of less than 20 hours and more particularly with elimination half-lives of less than 12 hours, and will be particularly useful for those drugs with half-lives of 2-10 hours. The following are examples of some antibiotics with half-lives of about 1 to 12 hours: Cefadroxil, cefazolin, cephalexin, cephalothin, cephapirin, cephacelor, cephprozil, cephadrine, 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, clarithromycoin, dirithromycin, troleanomycin, penicillin V, peniciliin 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 taxobactam, ticarcillin, ticarcillin and clavulanate potassium, clindamycin, vancomycin, novobiocin, aminosalicylic acid, capreomycin, cycloserine, ethambutol HC1 and other salts, ethionamide, and isoniazid, ciprofloxacin, levofloxacin, lomefloxacin, nalidixic acid, norfloxacin, ofloxacin, sparfloxacin, sulfacytine, suflamerazine, sulfamethazine, sulfamethixole, sulfasalazine, sulfisoxazole, sulfapyrizine, sulfadiazine, sulfmethoxazole, sulfapyridine, metronidazole, methenamine, fosfomycin, nitrofurantoin, trimethoprim, clofazimine, co-triamoxazole, pentamidine, and trimetrexate.

The following are representative examples of some antifungals that can be employed in the composition 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)

The following are representative examples of some antivirals that may be used in 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 agents for the treatment of cancer that may be used in accordance with the invention: carboplatin, busulfan, cisplatin, thiotepa, melphalan hydrochloride, cyclophosphamide, ifosfamide, chlorambucil, mechlorethamine hydrochloride, carmustine, lomustine, streptozocin, polifeprosan 20, dexrazoxane, dronabinol, granisetron hydrochloride, fluconazole, erythropoietin, octreotide acetate, pilocarpine hydrochloride, etidronate disodium, pamidronate disodium, allopurinol sodium, amifostine, filgrastim, mesna, ondansetron hydrochloride, dolasetron mesylate, leucovorin calcium, sargramostim, levamisole hydrochloride, doxorubicin hydrochloride, idarubicin hydrochloride, mitomycin, daunorubicin citrate, plicamycin, daunorubicin hydrochloride, bleomycin sulfate, mitoxantrone hydrochloride, valrubicin, dactinomycin, fludarabine phosphate, cytarabine, mercaptopurine, thioguanine, methotrexate sodium, cladribine, floxuridine, capecitabine, anastrozole, bicalutamide, tamoxifen citrate, testolactone, nilutamide, methyltestosterone, flutamide, toremifene citrate, goserelin acetate, estramustine phosphate sodium, ethinyl estradiol, esterified estrogen, leuprolide acetate, conjugated estrogens, megestrol acetate, aldesleukin, medroxyprogesterone acetate, dacarbazine, hydroxyurea, etoposide phosphate, megestrol acetate, paclitaxel, etoposide, teniposide, trastuzumab, rituximab, vinorelbine tartrate, denileukin diftitox, gemcitabine hydrochloride, vincristine sulfate, vinblastine sulfate, asparaginase, edrophonium chloride, bacillus calmette and guerin, irinotecan hydrochloride, pegaspargase, docetaxel, interferon alfa-2a, recombinant, tretinoin, porfimer sodium, interferon alfa-2b, recombinant, procarbazine hydrochloride, topotecan hydrochloride, altretamine, fluorouracil, prednisolone sodium phosphate, cortisone acetate, dexamethasone, dexamethasone sodium sulfate, dexamethasone acetate, hydrocortisone sodium phosphate, hydrocortisone, prednisolone, methylprednisolone sodium succinate, betamethasone sodium phosphate, betamethasone acetate, letrozole, mithramycin, mitotane, pentostatin, perfosfamide, raloxifene

In accordance with another aspect of the present invention there is provided a procedure or regimen for treating a patient with a therapeutic agent that is an antibiotic, anti-viral, anti-fungal or anti-neoplastic agent by injection thereof that provides results similar to those achieved by the use of a product as hereinabove described that includes at least two and preferably at least three dosage forms.

In accordance with this aspect of the invention, there is provided a regimen for treating a patient with a therapeutic agent wherein the therapeutic agent is administered by injection, with the daily dosage being delivered over a period that is less than eleven hours (which period is measured from the first injection), and wherein there are at least two delivery pulses, and no more than thirty-two delivery pulses during a period of less than eleven hours, and preferably a period of less than eight hours. As used herein, "delivery pulses" means and may be accomplished by at least two spaced injections with periods between such spaced injections wherein essentially no therapeutic agent is injected into the host or alternatively, between the spaced injections, therapeutic agent is continuously injected in an amount different than that which is injected in the spaced injections. In addition, at least two delivery pulses can be achieved by continuous injection of the agent at one dosage, followed by continuous injection at a different dosage. In such a case there is a first continuous delivery pulse over a period of time, followed by a second continuous delivery pulse over a period of time. Thus, for example, in the latter case, there can be an initial injection wherein the therapeutic agent is continuously administered over a period of time followed by an increase in the dosage of the therapeutic agent that is administered by injection over a period of time whereby in effect there are two delivery pulses even though there may be continuous administration of the therapeutic agent.

In one embodiment, in less than an eleven hour period, there is at least two spaced injections of the therapeutic agent and generally no more than thirty-two spaced injections of the therapeutic agent. There may or may not be a continuous injection of the agent between the spaced injections and if there is such a continuous injection, the dosage of the agent is less than or more than the spaced injections. In a preferred embodiment, there is no injection of agent between the spaced injections.

In one preferred embodiment wherein there are spaced injections of the therapeutic agent, up to about sixty percent, and preferably up to about fifty percent of the dosage that is to be injected in a period of less than eleven hours is injected during the first four hours of such period.

In one embodiment, there is provided two injections in less than a six hour period. In another there is provided no more than six injections preferably in less than six hours. In a further embodiment there is provided at least four injections preferably over less than 6 hours.

In a preferred embodiment, the delivery pulses are accomplished by spaced injections of the therapeutic agent in a pharmaceutically acceptable carrier. There are at least two and no more than 32 spaced injections, all of which are delivered within 11 hours and preferably within 8 hours of the first injection. The daily dosage is delivered within such eleven or eight hour period and the spaced injections provide for at least 75%, preferably at least 90% and more preferably at least 100% of the agent that is to be delivered.

The therapeutic agent may be injected by any procedures known in the art. In a preferred embodiment, the therapeutic agent may be injected by use of a controlled pump of a type known in the art for injecting pharmaceutical products.

Alternatively, the regimen of the invention may be employed in a hospital wherein controlled injections are administered by use of a catheter. Injections can be made into any body structure, organ or blood vessel, such as intravenous, intramuscular, subcutaneous, intradermal, intrathecal, intraperitoneal, intraarticular, intraocular, or other routes of injectable delivery.

In accordance with the invention by employing delivery pulses for injecting the therapeutic agent in a period that is less than eleven hours and preferably less than eight hours, there is provided distinct maximum serum concentration pulses of the therapeutic agent in the blood of the patient in a period of less than 11 hours. In a preferred embodiment, such distinct Cmax pulses occur in a period of less than eight hours and preferably within a period of six hours.

In accordance with a preferred embodiment, all of the Cmax pulses are achieved in a period of less than 11 hours, preferably less than eight hours, and such pulses provide the daily dosage of the therapeutic agent; i.e., the therapeutic agent is injected in at least two delivery pulses within eleven hours and there is no further administration over the remainder of a twenty-four hour period.

All or a portion of the delivery pulses of the therapeutic agent delivered by spaced injections may be the same or different dosages of the therapeutic agent.

In general at a minimum each spaced injection provides at least 5% of the total daily dosage of the therapeutic agent.

It is to be understood that each delivery pulse may include one or more different therapeutic agents (for example two or more different antibiotics), and each delivery pulse may contain the same or different therapeutic agents (for example, one delivery pulse may contain two or more antibiotics and one may contain only one of the two or more antibiotics).

As hereinabove indicated the therapeutic agent is preferably an antibiotic or an anti-viral agent or an anti-fungal agent or an anti-neoplastic agent.

The invention will be further described with respect to the following examples; however, the scope of the invention is not limited thereby. All percentages in this specification, unless otherwise specified, are by weight.

Examples

Immediate Release Component (Antibiotic)

Formulate the composition by mixing the ingredients in a suitable pharmaceutical mixer or granulator such as a planetary mixer, high-shear granulator, fluid bed granulator, or extruder, in the presence of water or other solvent, or in a dry blend. If water or other solvent was used, dry the blend in a suitable pharmaceutical drier, such as a vacuum over or forced-air oven. The product may be sieved or granulated, and compressed using a suitable tablet press, such as a rotary tablet press.

	Ingredient	Conc. (% W/W)
Example 1:		
	Amoxicillin	65% (W/W)
	Microcrystalline cellulose	20
	Povidone	10
	Croscarmellose sodium	5
Example 2:		
	Amoxicillin	55% (W/W)
	Microcrystalline cellulose	25
	Povidone	10
	Croscarmellose sodium	10
Example 3:		
	Amoxicillin	65% (W/W)
	Microcrystalline cellulose	20
	Hydroxypropylcellulose	10
	Croscarmellose sodium	5
Example 4:		
	Amoxicillin	75% (W/W)
	Polyethylene glycol 4000	10
	Polyethylene glycol 2000	10
	Hydroxypropylcellulose	5
Example 5:		
	Amoxicillin	75% (W/W)
	Polyethylene glycol 8000	20
	Polyvinylpyrrolidone	5
Example 6:		
	Clarithromycin	65% (W/W)
	Microcrystalline cellulose	20
	Hydroxypropylcellulose	10

Croscarmellose sodium	5

Example 7:

Clarithromycin	75% (W/W)
Microcrystalline cellulose	15
Hydroxypropylcellulose	5
Croscarmellose sodium	5

Example 8:

Clarithromycin	75% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	10
Hydroxypropylcellulose	5

Example 9:

Clarithromycin	75% (W/W)
Polyethylene glycol 8000	20
Polyvinylpyrrolidone	5

Example 10:

Ciprofloxacin	65% (W/W)
Microcrystalline cellulose	20
Hydroxypropylcellulose	10
Croscarmellose sodium	5

Example 11:

Ciprofloxacin	75% (W/W)
Microcrystalline cellulose	15
Hydroxypropylcellulose	5
Croscarmellose sodium	5

Example 12:

Ciprofloxacin	75% (W/W)
Polyethylene glycol 4000	10
Polytheylene glycol 2000	10
Hydroxypropylcellulose	5

Example 13:

Cirpofloxacin	75% (W/W)
Polyethylene glycol 8000	20
Polyvinylpyrrolidone	5

Example 14:

Ceftibuten	75% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	10
Hydroxypropylcellulose	5

Example 15:

Ceftibuten	75% (W/W)

Polyethylene Glycol 4000	20
Polyvinylpyrrolidone	5

non-pH Sensitive Delayed Release Component (Antibiotic)

Formulate the composition by mixing the ingredients in a suitable pharmaceutical mixer or granulator such as a planetary mixer, high-shear granulator, fluid bed granulator, or extruder, in the presence of water or other solvent, or in a hot melt process. If water or other solvent was used, dry the blend in a suitable pharmaceutical drier, such as a vacuum over or forced-air oven. Allow the product to cool, the product may be sieved or granulated, and compressed using a suitable tablet press, such as a rotary tablet press.

	Ingredient	Conc. (% W/W)
Example 16:		
	Amoxicillin	65% (W/W)
	Microcrystalline cellulose	20
	Polyox	10
	Croscarmellose sodium	5
Example 17:		
	Amoxicillin	55% (W/W)
	Microcrystalline cellulose	25
	Polyox	10
	Glyceryl monooleate	10
Example 18:		
	Amoxicillin	65% (W/W)
	Polyox	20
	Hydroxypropylcellulose	10
	Croscarmellose sodium	5
Example 19:		
	Amoxicillin	75% (W/W)
	Polyethylene glycol 4000	10
	Polyethylene glycol 2000	10
	Eudragit RL 30D	5
Example 20:		
	Amoxicillin	75% (W/W)
	Polyethylene glycol 8000	20
	Ethylcellulose	5
Example 21:		
	Clarithromycin	70% (W/W)

Polyox	20
Hydroxypropylcellulose	5
Croscarmellose sodium	5

Example 22:

Clarithromycin	75% (W/W)
Polyox	15
Hydroxypropylcellulose	5
Ethylcellulose	5

Example 23:

Clarithromycin	75% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	10
Eudragit RL 30D	5

Example 24:

Clarithromycin	80% (W/W)
Polyethylene glycol 8000	10
Polyvinylpyrrolidone	5
Eudgragit R 30D	5

Example 25:

Ciprofloxacin	65% (W/W)
Polyethylene glycol 4000	20
Hydroxypropylcellulose	10
Eudragit RL 30D	5

Example 26:

Ciprofloxacin	75% (W/W)
Microcrystalline cellulose	15
Hydroxypropylcellulose	5
Ethylcellulose	5

Example 27:

Ciprofloxacin	80% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	5
Eudgragit RL 30D	5

Example 28:

Ciprofloxacin	75% (W/W)
Polyethylene glycol 8000	20
Ethylcellulose	5

Example 29:

Ceftibuten	75% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	10
Eudragit RL 30D	5

Example 30:

Ceftibuten	75% (W/W)
Polyethylene glycol 8000	20
Ethylcellulose	5

Enteric Release Component (Antibiotic)

Formulate the ingredients by mixing the ingredients in a suitable pharmaceutical mixer or granulator such as a planetary mixer, high-shear granulator, fluid bed granulator, or extruder, in the presence of water or other solvent, or in a hot melt process. If water or other solvent was used, dry the blend in a suitable pharmaceutical drier, such as a vacuum over or forced-air oven. Allow the product to cool, the product may be sieved or granulated, and compressed using a suitable tablet press, such as a rotary tablet press.

	Ingredient	Conc. (% W/W)
Example 31:		
	Amoxicillin	65% (W/W)
	Microcrystalline cellulose	20
	Cellulose Acetate Pthalate	15
Example 32:		
	Amoxicillin	55% (W/W)
	Microcrystalline cellulose	25
	Cellulose Acetate Pthalate	10
	Hydroxypropylmethylcellulose	10
Example 33:		
	Amoxicillin	65% (W/W)
	Polyox	20
	Hydroxypropylcellulose pthalate	10
	Eudragit L30D	5
Example 34:		
	Amoxicillin	75% (W/W)
	Polyethylene glycol 2000	10
	Eudragit L30D	10
	Eudragit RL 30D	5
Example 35:		
	Amoxicillin	40% (W/W)
	Microcrystalline Cellulose	40
	Cellulose Acetate Pthalate	10

Example 36:

Clarithromycin	70% (W/W)
Hydroxypropylcellulose pthalate	15
Croscarmellose sodium	10

Example 37:

Clarithromycin	70% (W/W)
Eudragit E30D	15
Hydroxypropylcellulose	10
Ethylcellulose	5

Example 38:

Clarithromycin	75% (W/W)
Polyethylene glycol 2000	10
Eudragit E 30D	15

Example 39:

Clarithromycin	40% (W/W)
Lactose	50
Eudgragit L 30D	10

Example 40:

Ciprofloxacin	65% (W/W)
Microcrystalline Cellulose	20
Eudragit L 30D	10

Example 41:

Ciprofloxacin	75% (W/W)
Microcrystalline Cellulose	15
Hydroxypropylcellulose pthalate	10

Example 42:

Ciprofloxacin	80% (W/W)
Lactose	10
Eudgragit L 30D	10

Example 43:

Ciprofloxacin	70% (W/W)
Polyethylene glycol 4000	20
Cellulose acetate pthalate	10

Example 44:

Ceftibuten	60% (W/W)
Polyethylene glycol 2000	10
Lactose	20
Eudragit L 30D	10

Example 45:

Ceftibuten	70% (W/W)
Microcrystalline cellulose	20
Cellulose acetate pthalate	10

Sustained Release Component (Antibiotic)

Formulate the composition by mixing the ingredients in a suitable pharmaceutical mixer or granulator such as a planetary mixer, high-shear granulator, fluid bed granulator, or extruder, in the presence of water or other solvent, or in a hot melt process. If water or other solvent was used, dry the blend in a suitable pharmaceutical drier, such as a vacuum over or forced-air oven. Allow the product to cool, the product may be sieved or granulated, and compressed using a suitable tablet press, such as a rotary tablet press.

	Ingredient	Conc. (% W/W)
Example 46:		
	Amoxicillin	65% (W/W)
	Ethylcellulose	20
	Polyox	10
	Hydroxypropylmethylcellulose	5
Example 47:		
	Amoxicillin	55% (W/W)
	Lactose	25
	Polyox	10
	Glyceryl monooleate	10
Example 48:		
	Amoxicillin	70% (W/W)
	Polyox	20
	Hydroxypropylcellulose	10
Example 49:		
	Clarithromycin	75% (W/W)
	Lactose	15
	Hydroxypropylcellulose	5
	Ethylcellulose	5
Example 50:		
	Clarithromycin	75% (W/W)
	Polyethylene glycol 4000	10
	Lactose	10
	Eudragit RL 30D	5

Example 51:

Clarithromycin	80% (W/W)
Polyethylene glycol 8000	10
Hydroxypropylmethylcellulose	5
Eudgragit RS 30D	5

Example 52:

Ciprofloxacin	75% (W/W)
Hydroxyethylcellulose	10
Polyethylene glycol 4000	10
Hydroxypropylcellulose	5

Example 53:

Ciprofloxacin	75% (W/W)
Lactose	10
Povidone (PVP)	10
Polyethylene glycol 2000	5

Example 54:

Ceftibuten	75% (W/W)
Polyethylene glycol 4000	10
Povidone (PVP)	10
Hydroxypropylcellulose	5

Example 55:

Ceftibuten	75% (W/W)
Lactose	15
Polyethylene glycol 4000	5
Polyvinylpyrrolidone	5

Immediate Release Component (Anti-fungal)

Formulate the composition by mixing the ingredients in a suitable pharmaceutical mixer or granulator such as a planetary mixer, high-shear granulator, fluid bed granulator, or extruder, in the presence of water or other solvent, or in a dry blend. If water or other solvent was used, dry the blend in a suitable pharmaceutical drier, such as a vacuum oven or forced-air oven. The product may be sieved or granulated, and compressed using a suitable tablet press, such as a rotary tablet press.

Example 56:

Fluconazole	65% (W/W)
Microcrystalline cellulose	20
Povidone	10
Croscarmellose sodium	5

Example 57:

Fluconazole	55% (W/W)
Microcrystalline cellulose	25
Povidone	10
Croscarmellose sodium	10

Example 58:

Fluconazole	65% (W/W)
Microcrystalline cellulose	20
Hydroxypropylcellulose	10
Croscarmellose sodium	5

Example 59:

Fluconazole	75% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	10
Hydroxypropylcellulose	5

Example 60:

Fluconazole	75% (W/W)
Polyethylene glycol 8000	20
Polyvinylpyrrolidone	5

Example 61:

Ketoconazole	65% (W/W)
Microcrystalline cellulose	20
Hydroxypropylcellulose	10
Croscarmellose sodium	5

Example 62:

Ketoconazole	75% (W/W)
Microcrystalline cellulose	15
Hydroxypropylcellulose	5
Croscarmellose sodium	5

Example 63:

Ketoconazole	75% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	10
Hydroxypropylcellulose	5

Example 64:

Ketoconazole	75% (W/W)
Polyethylene glycol 8000	20
Polyvinylpyrrolidone	5

Example 65:

Griseofulvin	65% (W/W)
Microcrystalline cellulose	20

	Hydroxypropylcellulose	10
	Croscarmellose sodium	5
Example 66:		
	Griseofulvin	75% (W/W)
	Microcrystalline cellulose	15
	Hydroxypropylcellulose	5
	Croscarmellose sodium	5
Example 67:		
	Griseofulvin	75% (W/W)
	Polyethylene glycol 4000	10
	Polytheylene glycol 2000	10
	Hydroxypropylcellulose	5
Example 68:		
	Cirpofloxacin	75% (W/W)
	Polyethylene glycol 8000	20
	Polyvinylpyrrolidone	5
Example 69:		
	Terbinafine HCl	75% (W/W)
	Polyethylene glycol 4000	10
	Polyethylene glycol 2000	10
	Hydroxypropylcellulose	5
Example 70:		
	Terbinafine HCl	75% (W/W)
	Polyethylene Glycol 4000	20
	Polyvinylpyrrolidone	5

Non pH Sensitive Delayed Release Component (Anti-fungal)

Formulate the composition by mixing the ingredients in a suitable pharmaceutical mixer or granulator such as a planetary mixer, high-shear granulator, fluid bed granulator, or extruder, in the presence of water or other solvent, or in a hot melt process. If water or other solvent was used, dry the blend in a suitable pharmaceutical drier, such as a vacuum oven or forced-air oven. Allow the product to cool, the product may be sieved or granulated, and compressed using a suitable tablet press, such as a rotary tablet press.

	Ingredient	Conc. (% W/W)
Example 71:		
	Fluconazole	65% (W/W)
	Microcrystalline cellulose	20

Polyox	10
Croscarmellose sodium	5

Example 72:

Fluconazole	55% (W/W)
Microcrystalline cellulose	25
Polyox	10
Glyceryl monooleate	10

Example 73:

Fluconazole	65% (W/W)
Polyox	20
Hydroxypropylcellulose	10
Croscarmellose sodium	5

Example 74:

Fluconazole	75% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	10
Eudragit RL 30D	5

Example 75:

Fluconazole	75% (W/W)
Polyethylene glycol 8000	20
Ethylcellulose	5

Example 76:

Ketoconazole	70% (W/W)
Polyox	20
Hydroxypropylcellulose	5
Croscarmellose sodium	5

Example 77:

Ketoconazole	75% (W/W)
Polyox	15
Hydroxypropylcellulose	5
Ethylcellulose	5

Example 78:

Ketoconazole	75% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	10
Eudragit RL 30D	5

Example 79:

Ketoconazole	80% (W/W)
Polyethylene glycol 8000	10
Polyvinylpyrrolidone	5
Eudgragit R 30D	5

Example 80:

Griseofulvin	65% (W/W)
Polyethylene glycol 4000	20
Hydroxypropylcellulose	10
Eudragit RL 30D	5

Example 81:

Griseofulvin	75% (W/W)
Microcrystalline cellulose	15
Hydroxypropylcellulose	5
Ethylcellulose	5

Example 82:

Griseofulvin	80% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	5
Eudgragit RL 30D	5

Example 83:

Griseofulvin	75% (W/W)
Polyethylene glycol 8000	20
Ethylcellulose	5

Example 84:

Terbinafine HCl	75% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	10
Eudragit RL 30D	5

Example 85:

Terbinafine HCl	75% (W/W)
Polyethylene glycol 8000	20
Ethylcellulose	5

Enteric Release Component (Anti-fungal)

Formulate the ingredients by mixing the ingredients in a suitable pharmaceutical mixer or granulator such as a planetary mixer, high-shear granulator, fluid bed granulator, or extruder, in the presence of water or other solvent, or in a hot melt process. If water or other solvent was used, dry the blend in a suitable pharmaceutical drier, such as a vacuum oven or forced-air oven. Allow the product to cool, the product may be sieved or granulated, and compressed using a suitable tablet press, such as a rotary tablet press.

Ingredient	Conc. (% W/W)

Example 86:

Fluconazole	65% (W/W)
Microcrystalline cellulose	20
Cellulose Acetate Pthalate	15

Example 87:

Fluconazole	55% (W/W)
Microcrystalline cellulose	25
Cellulose Acetate Pthalate	10
Hydroxypropylmethylcellulose	10

Example 88:

Fluconazole	65% (W/W)
Polyox	20
Hydroxypropylcellulose pthalate	10
Eudragit L30D	5

Example 89:

Fluconazole	75% (W/W)
Polyethylene glycol 2000	10
Eudragit L 30D	10
Eudragit RL 30D	5

Example 90:

Fluconazole	40% (W/W)
Microcrystalline Cellulose	40
Cellulose Acetate Pthalate	10

Example 91:

Ketoconazole	70% (W/W)
Hydroxypropylcellulose pthalate	15
Croscarmellose sodium	10

Example 92:

Ketoconazole	70% (W/W)
Eudragit L 30D	15
Hydroxypropylcellulose	10
Ethylcellulose	5

Example 93:

Ketoconazole	75% (W/W)
Polyethylene glycol 2000	10
Eudragit L 30D	15

Example 94:

Ketoconazole	40% (W/W)
Lactose	50
Eudgragit L 30D	10

Example 95:

Griseofulvin	65% (W/W)
Microcrystalline Cellulose	20
Eudragit L 30D	10

Example 96:

Griseofulvin	75% (W/W)
Microcrystalline Cellulose	15
Hydroxypropylcellulose pthalate	10

Example 97:

Griseofulvin	80% (W/W)
Lactose	10
Eudragit L 30D	10

Example 98:

Griseofulvin	70% (W/W)
Polyethylene glycol 4000	20
Cellulose acetate pthalate	10

Example 99:

Terbinafine HCl	60% (W/W)
Polyethylene glycol 2000	10
Lactose	20
Eudragit L 30D	10

Example 100:

Terbinafine HCl	70% (W/W)
Microcrystalline cellulose	20
Cellulose acetate pthalate	10

Sustained Release Component (Anti-fungal)

Formulate the composition by mixing the ingredients in a suitable pharmaceutical mixer or granulator such as a planetary mixer, high-shear granulator, fluid bed granulator, or extruder, in the presence of water or other solvent, or in a hot melt process. If water or other solvent was used, dry the blend in a suitable pharmaceutical drier, such as a vacuum oven or forced-air oven. Allow the product to cool, the product may be sieved or granulated, and compressed using a suitable tablet press, such as a rotary tablet press.

Ingredient	Conc. (% W/W)

Example 101:

Fluconazole	65% (W/W)
Ethylcellulose	20
Polyox	10
Hydroxypropylmethylcellulose	5

Example 102:

Fluconazole	55% (W/W)
Lactose	25
Polyox	10
Glyceryl monooleate	10

Example 103:

Fluconazole	70% (W/W)
Polyox	20
Hydroxypropylcellulose	10

Example 104:

Ketoconazole	75% (W/W)
Lactose	15
Hydroxypropylcellulose	5
Ethylcellulose	5

Example 105:

Ketoconazole	75% (W/W)
Polyethylene glycol 4000	10
Lactose	10
Eudragit RL 30D	5

Example 106:

Ketoconazole	80% (W/W)
Polyethylene glycol 8000	10
Hydroxypropylmethylcellulose	5
Eudgragit RS 30D	5

Example 107:

Griseofulvin	75% (W/W)
Hydroxyethylcellulose	10
Polyethylene glycol 4000	10
Hydroxypropylcellulose	5

Example 108:

Griseofulvin	75% (W/W)
Lactose	10
Povidone (PVP)	10
Polyethylene glycol 2000	5

Example 109:

Terbinafine HCl	75% (W/W)
Polyethylene glycol 4000	10
Povidone (PVP)	10

	Hydroxypropylcellulose	5
Example 110:		
	Terbinafine HCl	75% (W/W)
	Lactose	15
	Polyethylene glycol 4000	5
	Polyvinylpyrrolidone	5
Example 111:		
	Ketoconazole	40% (W/W)
	Eudragit S100	50
	Triethyl Citrate	10
Example 112:		
	Ketoconazole	50% (W/W)
	Sureteric	50
Example 113:		
	Ketoconazole	50% (W/W)
	Eudragit S100	45
	Triethyl Citrate	5

Immediate Release Component (Anti-viral)

Formulate the composition by mixing the ingredients in a suitable pharmaceutical mixer or granulator such as a planetary mixer, high-shear granulator, fluid bed granulator, or extruder, in the presence of water or other solvent, or in a dry blend. If water or other solvent was used, dry the blend in a suitable pharmaceutical drier, such as a vacuum over or forced-air oven. The product may be sieved or granulated, and compressed using a suitable tablet press, such as a rotary table press.

	Ingredient	Conc. (% W/W)
Example 114:		
	Acyclovir	65% (W/W)
	Microcrystalline cellulose	20
	Povidone	10
	Croscarmellose sodium	5
Example 115:		
	Acyclovir	55% (W/W)
	Microcrystalline cellulose	25
	Povidone	10
	Croscarmellose sodium	10

Example 116:

Acyclovir	65% (W/W)
Microcrystalline cellulose	20
Hydroxypropylcellulose	10
Croscarmellose sodium	5

Example 117:

Acyclovir	75% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	10
Hydroxypropylcellulose	5

Example 118:

Acyclovir	75% (W/W)
Polyethylene glycol 8000	20
Polyvinylpyrrolidone	5

Example 119:

Zidovudine	65% (W/W)
Microcrystalline cellulose	20
Hydroxypropylcellulose	10
Croscarmellose sodium	5

Example 120:

Zidovudine	75% (W/W)
Microcrystalline cellulose	15
Hydroxypropylcellulose	5
Croscarmellose sodium	5

Example 121:

Zidovudine	75% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	10
Hydroxypropylcellulose	5

Example 122:

Zidovudine	75% (W/W)
Polyethylene glycol 8000	20
Polyvinylpyrrolidone	5

Example 123:

Valacyclovir	65% (W/W)
Microcrystalline cellulose	20
Hydroxypropylcellulose	10
Croscarmellose sodium	5

Example 124:

Valacyclovir	75% (W/W)
Microcrystalline cellulose	15
Hydroxypropylcellulose	5
Croscarmellose sodium	5

Example 125:

Valacyclovir	75% (W/W)
Polyethylene glycol 4000	10
Polytheylene glycol 2000	10
Hydroxypropylcellulose	5

Example 126:

Cirpofloxacin	75% (W/W)
Polyethylene glycol 8000	20
Polyvinylpyrrolidone	5

Example 127:

Ribavirin	75% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	10
Hydroxypropylcellulose	5

Example 128:

Ribavirin	75% (W/W)
Polyethylene Glycol 4000	20
Polyvinylpyrrolidone	5

Non pH Sensitive Delayed Release Component (Anti-viral)

Formulate the composition by mixing the ingredients in a suitable pharmaceutical mixer or granulator such as a planetary mixer, high-shear granulator, fluid bed granulator, or extruder, in the presence of water or other solvent, or in a hot melt process. If water or other solvent was used, dry the blend in a suitable pharmaceutical drier, such as a vacuum over or forced-air oven. Allow the product to cool, the product may be sieved or granulated, and compressed using a suitable tablet press, such as a rotary tablet press.

Ingredient	Conc. (% W/W)

Example 129:

Acyclovir	65% (W/W)
Microcrystalline cellulose	20
Polyox	10
Croscarmellose sodium	5

Example 130:

Acyclovir	55% (W/W)
Microcrystalline cellulose	25
Polyox	10
Glyceryl monooleate	10

Example 131:

Acyclovir	65% (W/W)
Polyox	20
Hydroxypropylcellulose	10
Croscarmellose sodium	5

Example 132:

Acyclovir	75% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	10
Eudragit RL 30D	5

Example 133:

Acyclovir	75% (W/W)
Polyethylene glycol 8000	20
Ethylcellulose	5

Example 134:

Zidovudine	70% (W/W)
Polyox	20
Hydroxypropylcellulose	5
Croscarmellose sodium	5

Example 135:

Zidovudine	75% (W/W)
Polyox	15
Hydroxypropylcellulose	5
Ethylcellulose	5

Example 136:

Zidovudine	75% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	10
Eudragit RL 30D	5

Example 137:

Zidovudine	80% (W/W)
Polyethylene glycol 8000	10
Polyvinylpyrrolidone	5
Eudgragit R 30D	5

Example 138:

Valacyclovir	65% (W/W)
Polyethylene glycol 4000	20
Hydroxypropylcellulose	10
Eudragit RL 30D	5

Example 139:

Valacyclovir	75% (W/W)
Microcrystalline cellulose	15
Hydroxypropylcellulose	5
Ethylcellulose	5

Example 140:

Valacyclovir	80% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	5
Eudgragit RL 30D	5

Example 141:

Valacyclovir	75% (W/W)
Polyethylene glycol 8000	20
Ethylcellulose	5

Example 142:

Ribavirin	75% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	10
Eudragit RL 30D	5

Example 143:

Ribavirin	75% (W/W)
Polyethylene glycol 8000	20
Ethylcellulose	5

Enteric Release Component (Anti-viral)

Formulate the ingredients by mixing the ingredients in a suitable pharmaceutical mixer or granulator such as a planetary mixer, high-shear granulator, fluid bed granulator, or extruder, in the presence of water or other solvent, or in a hot melt process. If water or other solvent was used, dry the blend in a suitable pharmaceutical drier, such as a vacuum over or forced-air oven. Allow the product to cool, the product may be sieved or granulated, and compressed using a suitable tablet press, such as a rotary tablet press.

Ingredient	Conc. (% W/W)

Example 144:

Acyclovir	65% (W/W)
Microcrystalline cellulose	20
Cellulose Acetate Pthalate	15

Example 145:

Acyclovir	55% (W/W)
Microcrystalline cellulose	25
Cellulose Acetate Pthalate	10
Hydroxypropylmethylcellulose	10

Example 146:

Acyclovir	65% (W/W)
Polyox	20
Hydroxypropylcellulose pthalate	10
Eudragit L30D	5

Example 147:

Acyclovir	75% (W/W)
Polyethylene glycol 2000	10
Eudragit L 30D	10
Eudragit RL 30D	5

Example 148:

Acyclovir	40% (W/W)
Microcrystalline Cellulose	40
Cellulose Acetate Pthalate	10

Example 149:

Zidovudine	70% (W/W)
Hydroxypropylcellulose pthalate	15
Croscarmellose sodium	10

Example 150:

Zidovudine	70% (W/W)
Eudragit L 30D	15
Hydroxypropylcellulose	10
Ethylcellulose	5

Example 151:

Zidovudine	75% (W/W)
Polyethylene glycol 2000	10
Eudragit L 30D	15

Example 152:

Zidovudine	40% (W/W)
Lactose	50
Eudgragit L 30D	10

Example 153:

Valacyclovir	65% (W/W)
Microcrystalline Cellulose	20
Eudragit L 30D	10

Example 154:

Valacyclovir	75% (W/W)
Microcrystalline Cellulose	15
Hydroxypropylcellulose pthalate	10

Example 155:

Valacyclovir	80% (W/W)
Lactose	10
Eudragit L 30D	10

Example 156:

Valacyclovir	70% (W/W)
Polyethylene glycol 4000	20
Cellulose acetate pthalate	10

Example 157:

Ribavirin	60% (W/W)
Polyethylene glycol 2000	10
Lactose	20
Eudragit L 30D	10

Example 158:

Ribavirin	70% (W/W)
Microcrystalline cellulose	20
Cellulose acetate pthalate	10

Sustained Release Component (Anti-viral)

Formulate the composition by mixing the ingredients in a suitable pharmaceutical mixer or granulator such as a planetary mixer, high-shear granulator, fluid bed granulator, or extruder, in the presence of water or other solvent, or in a hot melt process. If water or other solvent was used, dry the blend in a suitable pharmaceutical drier, such as a vacuum over or forced-air oven. Allow the product to cool, the product may be sieved or granulated, and compressed using a suitable tablet press, such as a rotary tablet press.

Ingredient	Conc. (% W/W)

Example 159:

Acyclovir	65% (W/W)
Ethylcellulose	20
Polyox	10
Hydroxypropylmethylcellulose	5

Example 160:

Acyclovir	55% (W/W)
Lactose	25
Polyox	10
Glyceryl monooleate	10

Example 161:

Acyclovir	70% (W/W)
Polyox	20
Hydroxypropylcellulose	10

Example 162:

Zidovudine	75% (W/W)
Lactose	15
Hydroxypropylcellulose	5
Ethylcellulose	5

Example 163:

Zidovudine	75% (W/W)
Polyethylene glycol 4000	10
Lactose	10
Eudragit RL 30D	5

Example 164:

Zidovudine	80% (W/W)
Polyethylene glycol 8000	10
Hydroxypropylmethylcellulose	5
Eudgragit RS 30D	5

Example 165:

Valacyclovir	75% (W/W)
Hydroxyethylcellulose	10
Polyethylene glycol 4000	10
Hydroxypropylcellulose	5

Example 166:

Valacyclovir	75% (W/W)
Lactose	10
Povidone (PVP)	10
Polyethylene glycol 2000	5

Example 167:

Ribavirin	75% (W/W)
Polyethylene glycol 4000	10
Povidone (PVP)	10
Hydroxypropylcellulose	5

Example 168:

Ribavirin	75% (W/W)
Lactose	15
Polyethylene glycol 4000	5
Polyvinylpyrrolidone	5

Example 169:

Zidovudine	40% (W/W)
Eudragit S100	50
Triethyl Citrate	10

Example 170:

Zidovudine	50% (W/W)
Sureteric	50

Example 171:

Zidovudine	50% (W/W)
Eudragit S100	45
Triethyl Citrate	5

Immediate Release Component (Cancer)

Formulate the composition by mixing the ingredients in a suitable pharmaceutical mixer or granulator such as a planetary mixer, high-shear granulator, fluid bed granulator, or extruder, in the presence of water or other solvent, or in a dry blend. If water or other solvent was used, dry the blend in a suitable pharmaceutical drier, such as a vacuum oven or forced-air oven. The product may be sieved or granulated, and compressed using a suitable tablet press, such as a rotary tablet press.

Example 172:

Fluorouracil	65% (W/W)
Microcrystalline cellulose	20
Povidone	10
Croscarmellose sodium	5

Example 173:

Fluorouracil	55% (W/W)
Microcrystalline cellulose	25
Povidone	10

	Croscarmellose sodium	10

Example 174:

Fluorouracil	65% (W/W)
Microcrystalline cellulose	20
Hydroxypropylcellulose	10
Croscarmellose sodium	5

Example 175:

Fluorouracil	75% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	10
Hydroxypropylcellulose	5

Example 176:

Fluorouracil	75% (W/W)
Polyethylene glycol 8000	20
Polyvinylpyrrolidone	5

Example 177:

Dexamethasone	65% (W/W)
Microcrystalline cellulose	20
Hydroxypropylcellulose	10
Croscarmellose sodium	5

Example 178:

Dexamethasone	75% (W/W)
Microcrystalline cellulose	15
Hydroxypropylcellulose	5
Croscarmellose sodium	5

Example 179:

Dexamethasone	75% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	10
Hydroxypropylcellulose	5

Example 180:

Dexamethasone	75% (W/W)
Polyethylene glycol 8000	20
Polyvinylpyrrolidone	5

Example 181:

Valrubicin	65% (W/W)
Microcrystalline cellulose	20
Hydroxypropylcellulose	10
Croscarmellose sodium	5

Example 182:

Valrubicin	75% (W/W)

Microcrystalline cellulose	15
Hydroxypropylcellulose	5
Croscarmellose sodium	5

Example 183:

Valrubicin	75% (W/W)
Polyethylene glycol 4000	10
Polytheylene glycol 2000	10
Hydroxypropylcellulose	5

Example 184:

Cirpofloxacin	75% (W/W)
Polyethylene glycol 8000	20
Polyvinylpyrrolidone	5

Example 185:

Tretinoin	75% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	10
Hydroxypropylcellulose	5

Example 186:

Tretinoin	75% (W/W)
Polyethylene Glycol 4000	20
Polyvinylpyrrolidone	5

Non pH Sensitive Delayed Release Component (Cancer)

Formulate the composition by mixing the ingredients in a suitable pharmaceutical mixer or granulator such as a planetary mixer, high-shear granulator, fluid bed granulator, or extruder, in the presence of water or other solvent, or in a hot melt process. If water or other solvent was used, dry the blend in a suitable pharmaceutical drier, such as a vacuum oven or forced-air oven. Allow the product to cool, the product may be sieved or granulated, and compressed using a suitable tablet press, such as a rotary tablet press.

	Ingredient	Conc. (% W/W)
Example 187:		
	Fluorouracil	65% (W/W)
	Microcrystalline cellulose	20
	Polyox	10
	Croscarmellose sodium	5

Example 188:

Fluorouracil	55% (W/W)
Microcrystalline cellulose	25
Polyox	10
Glyceryl monooleate	10

Example 189:

Fluorouracil	65% (W/W)
Polyox	20
Hydroxypropylcellulose	10
Croscarmellose sodium	5

Example 190:

Fluorouracil	75% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	10
Eudragit RL 30D	5

Example 191:

Fluorouracil	75% (W/W)
Polyethylene glycol 8000	20
Ethylcellulose	5

Example 192:

Dexamethasone	70% (W/W)
Polyox	20
Hydroxypropylcellulose	5
Croscarmellose sodium	5

Example 193:

Dexamethasone	75% (W/W)
Polyox	15
Hydroxypropylcellulose	5
Ethylcellulose	5

Example 194:

Dexamethasone	75% (W/W)
Polyethylene glycol 4000	10
Polyethylene glycol 2000	10
Eudragit RL 30D	5

Example 195:

Dexamethasone	80% (W/W)
Polyethylene glycol 8000	10
Polyvinylpyrrolidone	5
Eudgragit R 30D	5

Example 196:

Valrubicin	65% (W/W)
Polyethylene glycol 4000	20

	Hydroxypropylcellulose	10
	Eudragit RL 30D	5
Example 197:		
	Valrubicin	75% (W/W)
	Microcrystalline cellulose	15
	Hydroxypropylcellulose	5
	Ethylcellulose	5
Example 198:		
	Valrubicin	80% (W/W)
	Polyethylene glycol 4000	10
	Polyethylene glycol 2000	5
	Eudgragit RL 30D	5
Example 199:		
	Valrubicin	75% (W/W)
	Polyethylene glycol 8000	20
	Ethylcellulose	5
Example 200:		
	Tretinoin	75% (W/W)
	Polyethylene glycol 4000	10
	Polyethylene glycol 2000	10
	Eudragit RL 30D	5
Example 201:		
	Tretinoin	75% (W/W)
	Polyethylene glycol 8000	20
	Ethylcellulose	5

Enteric Release Component (Cancer)

Formulate the ingredients by mixing the ingredients in a suitable pharmaceutical mixer or granulator such as a planetary mixer, high-shear granulator, fluid bed granulator, or extruder, in the presence of water or other solvent, or in a hot melt process. If water or other solvent was used, dry the blend in a suitable pharmaceutical drier, such as a vacuum oven or forced-air oven. Allow the product to cool, the product may be sieved or granulated, and compressed using a suitable tablet press, such as a rotary tablet press.

	Ingredient	Conc. (% W/W)
Example 202:		

Fluorouracil	65% (W/W)
Microcrystalline cellulose	20
Cellulose Acetate Pthalate	15

Example 203:

Fluorouracil	55% (W/W)
Microcrystalline cellulose	25
Cellulose Acetate Pthalate	10
Hydroxypropylmethylcellulose	10

Example 204:

Fluorouracil	65% (W/W)
Polyox	20
Hydroxypropylcellulose pthalate	10
Eudragit L30D	5

Example 205:

Fluorouracil	75% (W/W)
Polyethylene glycol 2000	10
Eudragit L 30D	10
Eudragit RL 30D	5

Example 206:

Fluorouracil	40% (W/W)
Microcrystalline Cellulose	40
Cellulose Acetate Pthalate	10

Example 207:

Dexamethasone	70% (W/W)
Hydroxypropylcellulose pthalate	15
Croscarmellose sodium	10

Example 208:

Dexamethasone	70% (W/W)
Eudragit L 30D	15
Hydroxypropylcellulose	10
Ethylcellulose	5

Example 209:

Dexamethasone	75% (W/W)
Polyethylene glycol 2000	10
Eudragit L 30D	15

Example 210:

Dexamethasone	40% (W/W)
Lactose	50
Eudgragit L 30D	10

Example 211:

Valrubicin	65% (W/W)

	Microcrystalline Cellulose	20
	Eudragit L 30D	10
Example 212:		
	Valrubicin	75% (W/W)
	Microcrystalline Cellulose	15
	Hydroxypropylcellulose pthalate	10
Example 213:		
	Valrubicin	80% (W/W)
	Lactose	10
	Eudragit L 30D	10
Example 214:		
	Valrubicin	70% (W/W)
	Polyethylene glycol 4000	20
	Cellulose acetate pthalate	10
Example 215:		
	Tretinoin	60% (W/W)
	Polyethylene glycol 2000	10
	Lactose	20
	Eudragit L 30D	10
Example 216:		
	Tretinoin	70% (W/W)
	Microcrystalline cellulose	20
	Cellulose acetate pthalate	10

Sustained Release Component (Cancer)

Formulate the composition by mixing the ingredients in a suitable pharmaceutical mixer or granulator such as a planetary mixer, high-shear granulator, fluid bed granulator, or extruder, in the presence of water or other solvent, or in a hot melt process. If water or other solvent was used, dry the blend in a suitable pharmaceutical drier, such as a vacuum oven or forced-air oven. Allow the product to cool, the product may be sieved or granulated, and compressed using a suitable tablet press, such as a rotary tablet press.

	Ingredient	Conc. (% W/W)
Example 217:		
	Fluorouracil	65% (W/W)
	Ethylcellulose	20

Polyox	10
Hydroxypropylmethylcellulose	5

Example 218:

Fluorouracil	55% (W/W)
Lactose	25
Polyox	10
Glyceryl monooleate	10

Example 219:

Fluorouracil	70% (W/W)
Polyox	20
Hydroxypropylcellulose	10

Example 220:

Dexamethasone	75% (W/W)
Lactose	15
Hydroxypropylcellulose	5
Ethylcellulose	5

Example 221:

Dexamethasone	75% (W/W)
Polyethylene glycol 4000	10
Lactose	10
Eudragit RL 30D	5

Example 222:

Dexamethasone	80% (W/W)
Polyethylene glycol 8000	10
Hydroxypropylmethylcellulose	5
Eudgragit RS 30D	5

Example 223:

Valrubicin	75% (W/W)
Hydroxyethylcellulose	10
Polyethylene glycol 4000	10
Hydroxypropylcellulose	5

Example 224:

Valrubicin	75% (W/W)
Lactose	10
Povidone (PVP)	10
Polyethylene glycol 2000	5

Example 225:

Tretinoin	75% (W/W)
Polyethylene glycol 4000	10
Povidone (PVP)	10
Hydroxypropylcellulose	5

Example 226:

Tretinoin	75% (W/W)
Lactose	15
Polyethylene glycol 4000	5
Polyvinylpyrrolidone	5

Example 227:

Dexamethasone	40% (W/W)
Eudragit S100	50
Triethyl Citrate	10

Example 228:

Dexamethasone	50% (W/W)
Sureteric	50

Example 229:

Dexamethasone	50% (W/W)
Eudragit S100	45
Triethyl Citrate	5

Three Pulses

Example 230.

1. Metronidazole Matrix Pellet Formulation and Preparation Procedure (Immediate Release)

A. Pellet Formulation

The composition of the metronidazole matrix pellets provided in Table 1.

Table 1 Composition of Metronidazole Pellets

Component	Percentage (%)
Metronidazole	50
Avicel PH 101	20
Lactose	20
PVP K29/32*	10

Purified Water	
Total	100

*PVP K29/32 was added as a 20% w/w aqueous solution during wet massing.

B. Preparation Procedure for Metronidazole Matrix Pellets

1.2.1 Blend metronidazole and Avicel® PH 101 using a Robot Coupe high shear granulator.

1.2.2 Add 20% Povidone K29/32 binder solution slowly into the powder blend under continuous mixing.

1.2.3 Extrude the wet mass using an LCI Bench Top Granulator. The diameter of the screen of the Bench Top Granulator was 1.0 mm.

1.2.4 Spheronize the extrudate using a Model SPH20 Caleva Spheronizer.

1.2.5 Dry the spheronized pellets at 50°C overnight.

1.2.6 Pellets between 16 and 30 Mesh were collected for further processing.

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

A. Dispersion Formulation

The composition of the aqueous Eudragit L30D-55 dispersion applied to the metronidazole 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	55.0
Triethyl Citrate	1.6
Talc	8.0
Purified Water	37.4
Solids Content	25.5
Polymer Content	15.9

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

1.2.7 Suspend triethyl citrate and talc in deionized water.

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

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

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

1.3 Preparation of an Eudragit® S 100 Aqueous Coating Dispersion

A. Dispersion Formulation

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

Table 3 Eudragit® S 100 Aqueous Coating Dispersion

Component	Percentage (%)
Part A	
Eudragit® S 100	12.0
1 N Ammonium Hydroxide	6.1
Triethyl Citrate	6.0
Purified Water	65.9
Part B	
Talc	2.0
Purified Water	8.0
Solid Content	20.0
Polymer Content	12.0

B. Preparation Procedure for an Eudragit® S 100 Aqueous Dispersion

Part I:

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

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

(iii) Allow the partially neutralized dispersion to stir for 60 minutes.

(iv) Add triethyl citrate drop-wise into the dispersion with stirring. Stir for about 2 hours prior to the addition of Part B.

Part II:

(i) Disperse talc in the required amount of water

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

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

1.4 Coating Conditions for the Application of Aqueous Coating Dispersions

The following coating parameters were used to coat 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	1.8 Bar
Pump Rate	2 gram per minute

(i) Coat matrix pellets with L30 D-55 dispersion such that you apply 12% coat weight gain to the pellets.

(ii) Coat matrix pellets with S100 dispersion such that you apply 20% coat weight gain to the pellets.

1.5 Encapsulation of the Metronidazole Pellets

Pellets are filled into size 00 hard gelatin capsules at a ratio of 30%: 30%: 40%: Immediate-release matrix pellets uncoated, L30 D-55 coated pellets and S100 coated pellets respectively.

The capsule is filled with the three different pellets to achieve a total dose of 375mg/capsule.

Three Pulses

Example 231

Amoxicillin Pellet Formulation and Preparation Procedure

231.1 Pellet Formulations for subsequent coating

The composition of the Amoxicillin trihydrate matrix pellets provided in Table 4.

Table 4 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.

231.2 Preparation Procedure for Amoxicillin Matrix Pellets

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

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

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

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

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

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

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

231.3.1 Dispersion Formulation

The composition of the aqueous Eudragit L30D-55 dispersion applied to the amoxicillin matrix pellets is provided below in Table 5.

Table 5 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

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

231.4.1 Suspend triethyl citrate and talc in deionized water.

231.4.2 The TEC/talc suspension is mixed using laboratory mixer.

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

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

231.5 Preparation of an Eudragit® S 100 Aqueous Coating Dispersion

231.5.1 Dispersion Formulation

The composition of the aqueous Eudragit® S 100 dispersion applied to the Amoxicillin matrix pellets is provided below in Table 6.

Table 6 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

231.6 Preparation Procedure for an Eudragit® S 100 Aqueous Dispersion

Part A:

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

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

231.6.3 Allow the partially neutralized dispersion to stir for 60 minutes.

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

Part B:

231.6.5 Disperse talc in the required amount of water

231.6.6 Stir the dispersion using an overhead laboratory mixer.

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

231.7 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

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

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

231.8 Preparation of Amoxicillin Granulation (Immediate Release Component) for tabletting

Table 7 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.

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

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

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

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

231.9 Tabletting of the Amoxicillin Pellets

Table 8 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

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

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

231.9.3 Compress the blend on a rotary tablet press.

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

Three Pulses

Example 232

Clarithromycin Pellet Formulation and Preparation Procedure

232.1 Pellet Formulation

The composition of the clarithromycin matrix pellets provided in Table 1.

Table 9 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.

232.2 Preparation Procedure for Clarithromycin Matrix Pellets

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

232.2.2 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.

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

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

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

232.2.6 Spheronize the extrudate using a Model SPH20 Caleva Spheronizer.

232.2.7 Dry the spheronized pellets at 50°C overnight.

232.2.8 Pellets between 18 and 30 Mesh were collected for further processing.

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

232.3.1 Dispersion Formulation

The composition of the aqueous Eudragit L30D-55 dispersion applied to the clarithromycin matrix pellets is provided below in Table 10.

Table 10 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

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

232.4.1 Suspend triethyl citrate and talc in deionized water.

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

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

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

232.5 Preparation of an Eudragit® S 100 Aqueous Coating Dispersion

232.5.1 Dispersion Formulation

The composition of the aqueous Eudragit® S 100 dispersion applied to the clarithromycin matrix pellets is provided below in Table 11.

Table 11 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

232.6 Preparation Procedure for an Eudragit® S 100 Aqueous Dispersion

Part A:

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

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

232.6.3 Allow the partially neutralized dispersion to stir for 60 minutes

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

Part B:

232.6.5 Disperse talc in the required amount of water

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

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

232.7 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

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

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

4. Capsules were filled with the uncoated pellets, the L30D-55 coated pellets and S100 coated pellets in weight percentages of 30%:30%:40%, respectively to provide 250 mg. capsules.

Four pulses

Example 233.

1 Metronidazole Matrix Pellet Formulation and Preparation Procedure

233..1 Pellet Formulation

The composition of the metronidazole matrix pellets provided in Table 12.

Table 12 Composition of Metronidazole Pellets

Component	Percentage (%)
Metronidazole	50
Avicel PH 101	20
Lactose	20
PVP K29/32*	10
Purified Water	
Total	100

*PVP K29/32 was added as a 20% w/w aqueous solution during wet massing.

233.2 Preparation Procedure for Metronidazole Matrix Pellets

233.2.1 Blend metronidazole and Avicel® PH 101 using a Robot Coupe high shear granulator.

233.2.2 Add 20% Povidone K29/32 binder solution slowly into the powder blend under continuous mixing.

233.2.3 Extrude the wet mass using an LCI Bench Top Granulator. The diameter of the screen of the Bench Top Granulator was 1.0 mm.

233.2.4 Spheronize the extrudate using a Model SPH20 Caleva Spheronizer.

233.2.5 Dry the spheronized pellets at 50°C overnight.

233.2.6 Pellets between 16 and 30 Mesh were collected for further processing.

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

233.3.1 Dispersion Formulation

The composition of the aqueous Eudragit L30D-55 dispersion applied to the metronidazole matrix pellets is provided below in Table 13.

Table 13 Eudragit® L 30 D-55 Aqueous Coating Dispersion

Component	Percentage (%)
Eudragit® L 30 D-55	55.0
Triethyl Citrate	1.6
Talc	8.0
Purified Water	37.4
Solids Content	25.5
Polymer Content	15.9

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

233.4.1 Suspend triethyl citrate and talc in deionized water.

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

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

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

233.5 Preparation of an Eudragit® S 100 Aqueous Coating Dispersion

233.5.1 Dispersion Formulation

The composition of the aqueous Eudragit® S 100 dispersion applied to the metronidazole matrix pellets is provided below in Table 14.

Table 14 Eudragit® S 100 Aqueous Coating Dispersion

Component	Percentage (%)
Part A	
Eudragit® S 100	12.0
1 N Ammonium Hydroxide	6.1
Triethyl Citrate	6.0
Purified Water	65.9
Part B	
Talc	2.0
Purified Water	8.0

Solid Content	20.0
Polymer Content	12.0

233.6 Preparation Procedure for an Eudragit® S 100 Aqueous Dispersion

Part A:

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

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

233.6.3 Allow the partially neutralized dispersion to stir for 60 minutes.

233.6.4 Add triethyl citrate drop-wise into the dispersion with stirring. Stir for about 2 hours prior to the addition of Part B.

Part B:

233.6.5 Disperse talc in the required amount of water

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

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

233.7 Coating Conditions for the Application of Aqueous Coating Dispersions

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

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 gram per minute

233.7.1 Coat matrix pellets with L30 D-55 dispersion such that you apply 12% coat weight gain to the pellets.

233.7.2 Coat matrix pellets with L30 D-55 dispersion such that you apply 30% coat weight gain to the pellets.

233.7.3 Coat matrix pellets with S100 dispersion such that you apply 20% coat weight gain to the pellets.

233.8 Encapsulation of the Metronidazole Pellets

Pellets are filled into size 00 hard gelatin capsules at a ratio of 20%: 30%: 20%: 30% Immediate-release matrix pellets (uncoated), L30 D-55 coated pellets 12% weight gain, L30D-55 coated pellets 30% weight gain and S100 coated pellets respectively. The capsule is filled with the four different pellets to achieve a total dose of 375mg/capsule.

Four Pulses

Example 234

Amoxicillin Pellet Formulation and Preparation Procedure

234.1 Pellet Formulations

The composition of the Amoxicillin trihydrate matrix pellets provided in Table 15.

Table 15 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.

234.2 Preparation Procedure for Amoxicillin Matrix Pellets

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

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

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

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

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

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

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

234.3.1 Dispersion Formulation

The composition of the aqueous Eudragit L30D-55 dispersion applied to the amoxicillin matrix pellets is provided below in Table 16.

Table 16 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

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

234.4.1 Suspend triethyl citrate and talc in deionized water.

234.4.2 The TEC/talc suspension is mixed using laboratory mixer.

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

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

234.5 Preparation of an Eudragit® S 100 Aqueous Coating Dispersion

234.6 Dispersion Formulation

The composition of the aqueous Eudragit® S 100 dispersion applied to the Amoxicillin matrix pellets is provided below in Table 17.

Table 17 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	2.0
Water	10.0
Solid Content	25.0
Polymer Content	10.0

234.7 Preparation Procedure for an Eudragit® S 100 Aqueous Dispersion

Part A:

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

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

234.7.3 Allow the partially neutralized dispersion to stir for 60 minutes.

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

Part B:

234.7.5 Disperse talc in the required amount of water

234.7.6 Stir the dispersion using an overhead laboratory mixer.

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

234.8 Preparation of Aquacoat Coating Dispersion

234.8.1 Dispersion Formulation

The composition of the aqueous Aquacoat dispersion applied to Amoxicillin L30 D-55 coated pellets is provided below in Table 18.

Table 18

Component	Percentage (%)
Aquacoat ECD	79.3
Hydroxypropyl methylcellulose	15.9
Dibutyl Sebacate	4.8
Purified Water (300g)	

234.8.1.1 Prepare Hydroxypropyl methylcellulose (Methocel E15) solution by dispersing in water with continuous stirring.

234.8.1.2 Add Aquacoat and dibutyl sebacate to the dispersion with stirring and continue to stir overnight.

234.9 Coating Conditions for the Application of Aqueous Coating Dispersions

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

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

234.9.1 Coat Amoxicillin matrix pellets with L30 D-55 dispersim to achieve a 20% coat weight gain.

234.9.2 Coat another batch of Amoxicillin matrix pellets with L30 D-55 dispersion to achieve a 20% weight gain. Coat the L30 D-55 pellets with the Aquacoat Dispersion to achieve a 10% coat weight gain.

234.9.3 Coat Amoxicillin matrix pellets with S100 dispersion to achieve a 37% coat weight gain.

234.10 Preparation of Amoxicillin Granulation for tabletting

Table 19 Composition of Amoxicillin Granulation (Immediate Release)

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.

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

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

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

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

234.11 Tabletting of the Amoxicillin Pellets

Table 20 Composition of Amoxicillin Tablets

Component	Percentage (%)
Amoxicillin granules	32.5
Avicel PH 200	5.0
Amoxicillin L30D-55 coated pellets	20
Amoxicillin Aquacoated pellets	20
Amoxicillin S100 coated pellets	20
Colloidal silicon dioxide	1.5
Magnesium stearate	1.0
Total	100

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

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

234.11.3 Compress the blend on a rotary tablet press.

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

Four Pulses

Example 235

Clarithromycin Pellet Formulation and Preparation Procedure

235.1 Pellet Formulation

The composition of the clarithromycin matrix pellets provided in Table 21.

Table 21 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.

235.2 Preparation Procedure for Clarithromycin Matrix Pellets

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

235.2.2 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.

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

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

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

235.2.6 Spheronize the extrudate using a Model SPH20 Caleva Spheronizer.

235.2.7 Dry the spheronized pellets at 50°C overnight.

235.2.8 Pellets between 18 and 30 Mesh were collected for further processing.

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

235.3.1 Dispersion Formulation

The composition of the aqueous Eudragit L30D-55 dispersion applied to the clarithromycin matrix pellets is provided below in Table 22.

Table 22 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

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

235.4.1 Suspend triethyl citrate and talc in deionized water.

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

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

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

235.5 Preparation of an Eudragit® S 100 Aqueous Coating Dispersion

235.5.1 Dispersion Formulation

The composition of the aqueous Eudragit® S 100 dispersion applied to the clarithromycin matrix pellets is provided below in Table 23.

Table 23 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

235.6 Preparation Procedure for an Eudragit® S 100 Aqueous Dispersion

Part A:

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

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

235.6.3 Allow the partially neutralized dispersion to stir for 60 minutes

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

Part B:

235.6.5 Disperse talc in the required amount of water

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

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

235.7 Coating Conditions for the Application of Aqueous Coating Dispersions

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

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

235.7.1 Coat matrix pellets with L30 D-55 dispersion such that you apply 12% coat weight gain to the pellets.

235.7.2 Coat matrix pellets with L30 D-55 dispersion such that you apply 30% coat weight gain to the pellets.

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

235.8 Encapsulation of the Clarithromycin Pellets

Pellets are filled into size 00 hard gelatin capsules at a ratio of 20%: 30%: 20%: 30% Immediate-release matrix pellets (uncoated), L30 D-55 coated pellets 12% weight gain, L30D-55 coated pellets 30% weight gain and S100 coated pellets respectively. The capsule is filled with the four different pellets to achieve a total dose of 250mg/capsule.

The antifungal, antiviral and antineoplastic dosage forms can be formulated into a single product (for example, a product containing three or four dosage forms of an antifungal) by a procedure similar to Examples 230-235, substituting the desired antifungal or antiviral or antineoplastic agent for the antibiotic.

The present invention is particularly advantageous in that there is provided an therapeutic product which provides an improvement over twice a day administration of the therapeutic and an improvement over a once a day administration of the therapeutic.

Numerous modification and variations of the present invention are possible in light of the above teachings and therefore, within the scope of the appended claims the invention may be practiced otherwise than as particularly described.

WHAT IS CLAIMED IS:

1. A therapeutic product comprising: a first therapeutic dosage form, a second therapeutic dosage form, and a third therapeutic dosage form, each of said first, second and third therapeutic dosage forms comprising at least one therapeutic agent and a pharmaceutically acceptable carrier, said three dosage forms having different release profiles, said therapeutic product reaching a C_{max} in less than about twelve hours wherein said therapeutic is an antibiotic, an anti-fungal, an anti-viral or an anti-neoplastic agent.

2. The product of Claim 1 wherein the first dosage form is an immediate release dosage form.

3. The product of Claim 2 wherein the C_{max} for the product is reached no earlier than four hours after administration.

4. The product of Claim 2 wherein the immediate release dosage form contains at least 20% and no more than 50% of the total dosage of therapeutic.

5. The product of Claim 4 wherein the product is an oral dosage form.

6. The product of Claim 5 wherein the therapeutic released from the second dosage form reaches a C_{max} in the serum after C_{max} is reached in the serum for therapeutic released from the first dosage form.

7. The product of Claim 6 wherein the therapeutic released from the third dosage form reaches a C_{max} in the serum after the therapeutic released from the second dosage form reaches a C_{max} in the serum.

8. The therapeutic product of Claim 1 wherein said therapeutic product includes a total dosage of therapeutic that is effective for a twenty four hour period.

9. The product of Claim 1 and further comprising a fourth therapeutic dosage form comprising a therapeutic and a pharmaceutically acceptable carrier, wherein therapeutic released from the fourth dosage form reaches a C_{max} in the serum after C_{max} is achieved in the serum for therapeutic released from each of the first, second and third dosage forms.

10. The product of Claim 1 wherein the therapeutic agent is an antibiotic.

11. The product of Claim 1 wherein the therapeutic agent is an anti-fungal.

12. The product of Claim 1 wherein the therapeutic agent is an anti-viral.

13. A process for treating a disease or infection in a patient, comprising administering to a patient in need thereof an effective amount of the product of Claim 1.

14. Use of a therapeutic agent for preparing a product for treating a disease or infection wherein the therapeutic product is as defined in Claim 1.

15. A process for treating a patient with a therapeutic agent, comprising:

treating a patient by injecting into the patient a therapeutic agent in at least two and not more than thirty-two delivery pulses in a period of no more than 11 hours, said therapeutic agent being selected from the group consisting of antiobiotics, anti-viral agents, anti-fungal agents and anti-neoplastic agents.

16. The process of Claim 15 wherein said delivery pulses are provided by spaced injections.

17. The process of Claim 16 wherein between at least a portion of the spaced injections there is essentially no administration of the therapeutic agent.

18. The process of Claim 16 wherein between at least a portion of the spaced injections there is continuous injection of the therapeutic agent in a dosage that is different from the dosage of the spaced injections.

19. The process of Claim 16 wherein at least a portion of the spaced injections deliver the therapeutic agent in different dosages.

20. The process of Claim 15 wherein there is at least four delivery pulses.

21. The process of Claim 20 wherein there is no more than six delivery pulses.

22. The process of Claim 21 wherein the total dosage of the therapeutic agent is injected in no more than 6 hours.

23. Use of a therapeutic agent for preparing a product for use in treating a patient by injecting into the patient a therapeutic agent in at least two and not more than thirty-two delivery pulses in a period of no more than 11 hours, said therapeutic agent being selected from the group consisting of antibiotics, anti-viral agents, anti-fungal agents and anti-neoplastic agents.

INTERNATIONAL SEARCH REPORT

Internal application No.
PCT/US01/05758

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 9/14, 9/16, 9/20, 9/22, 9/24, 9/127
US CL : 424/450, 464, 468, 472, 489, 490

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/450, 464, 468, 472, 489, 490

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST & STN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,827,531 A (MORRISON et al.) 27 October 1998 (27.10.1998), column 4, lines 60-67, column 18, lines 18-51, column 19, lines 41-59.	1, 10-14 ---------- 2-9
X --- Y	US 5,213,808 A (BAR-SHALOM et al.) 25 May 1993 (25.05.1993), column 6, lines 37-67, column 7, lines 28 through column 8, lines 1-38, column 9, line 68 through column 10, lines 1-59, column 17, lines 24-26.	1-3, 8-14 ---------- 4-7
X	US 4,831,025 A (GODTFREDSEN et al.) 16 May 1989 (16.05.1989), column 16, lines 1-27.	1, 10-14
A	US 5,213,808 A (BAR-SHALOM et al.) 25 May 1993 (25.05.1993), column 24, lines 30-40, column 25, lines 15-50, column 27, lines 40 through column 28, lines 1-54.	15-23

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 April 2001 (19.04.2001)	17 MAY 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No.	Authorized officer SUSAN TRAN Telephone No. (703) 308-1235

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