The invention relates to a package and kit for dispensing and/or administering pharmaceuticals, particularly for dispensing and/or administering combinations of different formulations.
Figure 6
VARIABLE-DOSE PACKAGING SYSTEM

TECHNICAL FIELD

[0001] This invention relates to a variable-dose packaging system.

BACKGROUND OF THE-INVENTION

[0002] Control of dosage delivery is essential for patients in order that they receive the required quantity of medication at specified time intervals as is best suited to the individual based upon parameters such as body surface area (BSA). This is particularly important in the case of high potency drugs or those with a narrow therapeutic index, the potential adverse outcomes resulting from improper dosage consumption of which could substantially harm the patient. A patient who receives an excess of a high potency drug or those with a narrow therapeutic index could suffer from serious side effects or even death. Conversely, a patient receiving an insufficient amount of such a drug will not experience the therapeutic benefits desired.

[0003] It is usual in the art to address the issue of delivery of the required dose by providing the same active pharmaceutical agent in several different dosage strengths. The patient is prescribed one of these available dosage strengths or a combination thereof such that the desired total dosage is customized for that patient. For example, Synthroid® (levothyroxine sodium) is a synthetic thyroid hormone prescribed to patients with hypothyroidism and pituitary TSH suppression, as well being used to treat benign thyroid nodules and in conjunction with surgery and radioactive iodine therapy in the management of certain types of thyroid cancer. Synthroid® (levothyroxine sodium) is presented in multiple dosage formulations including 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg and 300 mcg (microgram) tablets. In another example, Coumadin® (warfarin) is an anticoagulant used to treat acute pulmonary embolism, atrial fibrillation, and deep vein thrombosis, as well as to prevent clotting after heart valve replacement, and to prevent a recurrence of heart attack or stroke. Coumadin® (warfarin) is available in numerous dosage formulations including 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 7.5 mg, and 10 mg tablets. The costs and difficulties incurred in manufacturing such a number of different dosage forms of these drugs, together with the significant potential for confusion of physicians, pharmacists, caregivers or patients by the various different strengths, are examples of the limitations and potential disadvantages of such a solution.

[0004] Oncology drugs are generally considered high-potency therapeutic agents, for which a careful dosage is required, often customized to a particular patient depending on the patient’s size, weight, age, condition, sex or other factors. There are a handful of oral oncology drugs currently on the market. However, none of them are currently available in packaging that is convenient and safe for the patient. For example, Xeloda® (capecitabine) is prescribed in 500 mg and 150 mg tablets, and is packaged in two separate bottles by dosage. The patient is prescribed a specific dose by the physician, which requires the patient to ingest the requisite combination of 500 mg and 150 mg tablets in order to achieve the prescribed dose. As can be seen from Table 1 (taken from the prescribing information of Xeloda®), various numbers and combinations of the two tablet-strengths are provided for, and the importance of strictly complying with such combinations need to be reliably conveyed to the patient. This mode of administration is prone to error in that it is simple to ingest the incorrect combination of tablets by, for instance, confusing the two bottles. This may be of particular concern for certain patients depending on, for example, the age of, visual acuity possessed by, language knowledge of, or the reading level of the patient. Furthermore, cancer patients are often stressed, emotionally disturbed or confused—often as many cancer patients are elderly, but also simply from the emotional trauma of coping with the knowledge that they suffer from such a disease.

[0005] In addition, by providing pills unprotected (such as loose or “uncoated” pills) in bottles, both the pharmacist and the patient must physically handle them. Handling pills may cause breakage, fracture, rupture or other damage to the pills, which may cause dust or other fragments of the pills to be lost or enter the local environment. This can be a problem with high potency drugs or those with a narrow therapeutic index that may be toxic to the handler. For example, Propecia® (finasteride) is prescribed in tablet form to treat male pattern hair loss on the vertex (top of head) and anterior mid-scalp area in men. The tablets are coated to prevent contact with the active ingredient during normal handling, and are thereby considered safe for men. However, women who are or may potentially be pregnant should not consume or handle the tablets, particularly if they are crushed or broken, because of the risk that the active ingredient may cause abnormalities to the sex organs of a male fetus.

[0006] The concept of a packaging system for storing and dispensing individual doses of medication is well known in the art. However, most of these solutions are aimed at addressing the labeling issues involved with proper medication administration. For example, U.S. Pat. No. 6,082,544. Other packaging systems provide child-resistant solutions such U.S. Pat. No. 6,412,636, U.S. Pat. No. 6,047,829, U.S. Pat. No. 6,230,893 and the “Surepak” system of MeadWestvaco Healthcare Packaging.

[0007] What is needed is a package for the administration of therapeutic agents, enabling the delivery of a customized dose of a variable-dose therapeutic regimen to a patient in such a way that provides advantages over other delivery or packaging solutions. Such advantages include those that may be provided by a package that allows multiple combinations of dosage levels to be achieved using a smaller number of standard units, a package that is safer for the patent or prescribing pharmacist, or a package that is easier for the patient to appropriately follow the therapeutic regimen. As an example, such an invention may provide a prescription package to aid an elderly prostate cancer patient to take the correct dose of powerful anti-cancer pills, and hence increase their chance of successful treatment or an increase in their quality of life.

SUMMARY OF THE INVENTION

[0008] The invention relates to packages that facilitate tailoring the administration of a drug to a particular patient or treatment regimen. Thus, in certain embodiments, the invention relates to a package for providing a customized dose of a variable-dose therapeutic regimen, comprising

[0009] (a) at least one subunit A comprising a plurality of interconnected unit dosage forms of formulation A;

[0010] (b) at least one subunit B comprising a plurality of interconnected unit dosage forms of formulation B; and
(c) means to physically associate at least one subunit A to at least one subunit B;

formulation A and formulation B are different; and

[0012] a dose comprises one unit dosage form from each subunit, and the dose is customized for a patient by adding or removing subunits A or B to or from the package.

[0013] The invention further relates to a kit for assembling or preparing a customized dosage of a variable-dose therapeutic regimen, comprising:

(a) at least one subunit A comprising a plurality of unit dosage forms of formulation A;

(b) at least one subunit B comprising a plurality of unit dosage forms of formulation B; and

(c) means to interconnect or physically associate the unit dosage forms of formulation A in a subunit A or the unit dosage forms of formulation B in a subunit B; wherein, formulation A and formulation B are different, and said customized dose is provided in a package.

[0017] In certain embodiments, each unit dosage form is enclosed in a rupturable cell. In preferred embodiments, each unit dosage form is enclosed in a blister pack or a foil pack. Most preferably, each unit dosage form is enclosed in a blister pack. In a preferred such embodiment, a subunit is a strip of blister packs, wherein each blister pack contains a single unit dosage form.

[0018] In certain embodiments, each subunit contains a plurality of unit dosage forms, wherein the number of unit dosage forms in each subunit may be equal or unequal to the number of unit dosage forms in any other subunit in the package or kit in order to achieve either consistent or tapered dosing, respectively. In preferred embodiments, the number of unit dosage forms in each subunit is equal.

[0019] In certain embodiments, at least one subunit A is physically associated with at least one subunit B. In a preferred embodiment, the unit dosage forms of formulation A and unit dosage forms of formulation B are arranged in a grid pattern such that each row is a dose and each column is a subunit. In a preferred such embodiment, the total number of doses in a kit or package is between 3 and 35, more preferably between 5 and 14, even more preferably about 14, about 7, or about 5. In a most preferred embodiment, the total number of doses in a kit or package is about 5. Each dose may be designated with a day of the week or month, though not necessarily labeled with consecutive days.

[0020] In a preferred embodiment, the package or kit provides a customized dose of an orally available platinum complex, such as satraplatin.

[0021] A kit or package of the invention may include means to physically associate at least one subunit A with at least one subunit B or unit dosage forms of formulation A with formulation B. In certain embodiments, means to physically associate subunit A with subunit B or unit dosage forms of formulation A with formulation B comprises positioning means. In particular embodiments the positioning means is a template or frame and one or more compartments, locations, adhesive positions, or slots adapted to receive an appropriate number of subunits A or B or unit dosage forms of formulation A or B. In certain such embodiments, the positioning means may be partially filled with a predefined set of subunits A or B or unit dosage forms of formulation A or B.

[0022] In certain embodiments, means to physically associate at least one subunit A with at least one subunit B comprises appendages on subunit A that are adapted to be put through receptacles of subunit B. In another embodiment, means to physically associate at least one subunit A with at least one subunit B comprises an adhesive unit region on subunit A that is adapted to adhere to subunit B. In another embodiment, the means to physically associate subunit A with subunit B comprises positioning means, such as a template and one or more compartments, locations, clips, fastenings, sockets, adhesive positions or slots adapted to receive an appropriate number of subunits A or B.

[0023] In a preferred such embodiment, each dose is individually removable from the kit or package.

[0024] In certain embodiments of the invention, the kit or package further comprises instructions for a patient to consume a unit dosage form from each of subunit(s) A and B of the kit or package at predetermined intervals. The instructions may or may not require the simultaneous or sequential consumption of unit dosage forms of formulations A and B.

[0025] In another embodiment, the kit or package further comprises a plurality of unit dosage forms of formulation C, wherein formulation C is different from each of formulations A and B. In preferred embodiments, the unit dosage forms of A, the unit dosage forms of B, and the unit dosage forms of C together are arranged in a grid pattern where each row is a dose and each column is a subunit. In certain such embodiments, formulation A, formulation B, and formulation C each comprise an active ingredient X, and the amount of active ingredient X in the unit dosage forms of each formulation A, B, and C is different from the amount of active ingredient X in the unit dosage forms of either of the other two formulations. In certain such embodiments, the kit or package further comprises instructions for a patient to consume a unit dosage form from each subunits C.

[0026] The invention further relates to a method to assemble or prepare a package of the invention. In another aspect, the invention relates to a method of treating a patient suffering from a disease by administering or dispensing a package or kit of the invention.

[0027] Other features and advantages of the invention will be apparent from the following description, and from the claims.

**BRIEF DESCRIPTION OF THE FIGURES**

[0028] FIG. 1a shows a constant dose rectangular package according to an embodiment of the invention, wherein subunits (1 and 2; shaded) are columns, doses (3; dot pattern) are rows, and each subunit comprises unit dosage forms of formulation A 4 or B 5.

[0029] FIG. 1b shows a tapered dose rectangular package according to an embodiment of the invention, wherein subunits (1 and 2; shaded) are columns, doses (3; dot pattern) are rows, and each subunit comprises unit dosage forms of formulation A 4 or B 5.

[0030] FIG. 2 shows a circular package according to an embodiment of the invention, wherein subunits (1 and 2; shaded) are concentric rings, doses (3; dot pattern) are radii, and each subunit comprises unit dosage forms of formulation A 4 or B 5.

[0031] FIG. 3 shows a rectangular kit according to an embodiment of the invention, wherein serially connected subunits 1 are integral to the package and are serially associated with a series of compartments 6 that are adapted to each receive a subunit B 2.
FIG. 4 shows a rectangular kit according to an embodiment of the invention, comprising serially connected compartments which are adapted to each receive a subunit A or B. FIG. 5 shows a rectangular package according to an embodiment of the invention, wherein the packaging surrounding each unit dosage form is perforated or scored such that each subunit A or B and each dose 3 is individually removably from the package. FIG. 6 shows a rectangular kit according to an embodiment of the invention, wherein subunits A are serially connected and are equipped with holes in the terminal subunit A. Subunit B 2 is equipped with hooks that are adapted to fit through the holes. FIG. 7 shows a rectangular kit according to an embodiment of the invention, wherein subunits A are serially connected and are equipped with slits in the terminal subunit A. Subunit B 2 is equipped with tabs that are adapted to fit through the slits. FIG. 8 shows a rectangular kit according to an embodiment of the invention, wherein subunits A are serially connected and are equipped with wells in the terminal subunit A. Subunit B 2 is equipped with plugs that are adapted to couple with the wells. FIG. 9 shows a rectangular kit, wherein subunits A are serially connected and are equipped with an adhesive strip on the terminal subunit A. Subunit B 2 is equipped with a strip of material that is adapted to be adhered to the adhesive strip. FIG. 10 shows a rectangular kit, wherein subunits A and subunits B are each equipped with protrusions such that subunit(s) A 1 and subunit(s) B 2 can be associated in the same manner as a jigsaw puzzle. FIG. 11 shows subunits supplied as a roll of unit dosage forms. FIG. 12 shows subunits supplied as a sheet of unit dosage forms. FIG. 13 shows subunits supplied as concentric rings comprising unit dosage forms. FIG. 14 shows subunits supplied as strips.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to packages and kits that facilitate the administration of a drug to a particular patient or treatment regimen. Generally, the invention provides kits and packages for associating unit dosage forms of at least two different pharmaceutical formulations for convenient administration. The different formulations can be combinations of different active ingredients, formulations that comprise the same active ingredient in different amounts, or formulations that have different release characteristics. For example, at least one of the unit dosage forms used in the various embodiments disclosed herein are orally administrable forms such as tablets, gelcaps, and capsules, although any other unit dosage forms may be used without departing from the spirit of the invention disclosed herein. In certain embodiments, the different formulations are presented in dosage forms that are different from each other. For example, as illustrated in FIG. 1a, the package may be rectangular. The package shown comprises a plurality of subunits A and a plurality of subunits B, which appear in FIG. 1a as columns. Each subunit comprises a plurality of interconnected unit dosage forms of formulation A or formulation B, such that the unit dosage forms are arranged in a grid, and the unit dosage forms within each subunit are preformulated with formulations that are identical to the other subunit dosage forms in that subunit, although they may be different from the unit dosage forms in other subunits within the package. The subunits that form part of the package may have preformed interconnections of any one or all of the formulations, or may be formed by the means to physically associate the formulations. In certain embodiments, the unit dosage forms are enclosed in a rupturable cell. Such rupturable cells may contain one or more unit dosage forms. In certain embodiments, each unit dosage form may be enclosed in a rupturable cell in a blister pack, a foil pack, a capsule, a container, or sachet. The multiple subunits are serially connected, such that each row is a dosing subunit. The dosing subunit may be easily taken at a particular time to provide a predetermined amount of the medication in the package at the predetermined time. The subunits that form part of the package may be preformed interconnections of any one or all of the unit dosage forms, or may be formed by the means to physically associate the formulations. For example, individual unit dosage forms of formulation A and/or B may be placed into a preformed paperboard blanks such as described in U.S. Pat. No. 5,954,202; by so doing, forming the subunits, the doses and a package of the instant invention. Formulation A and formulation B each comprise an active ingredient, which may be the same or different. In certain embodiments, both formulation A and formulation B are of different pharmaceutical or pharmacokinetic properties, for example, formulation A may be a sustained release formulation when formulation B is a rapid release formulation, or the amount of active ingredient X in formulation A may be unequal to the amount of active ingredient X in formulation B. In certain embodiments, the amount of active ingredient X in formulation A is greater than the amount of active ingredient X in formulation B (or vice versa) by a factor of about 2, about 4, about 5, about 10, about 25, about 50, or greater. In certain embodiments, active ingredient X is selected from a cytotoxic compound, a chemotherapeutic compound, a high potency compound, a compound with a narrow therapeutic index, and an orally available platinum complex. In certain embodiments, active ingredient X is a satraplatin or a produg or metabolite thereof, wherein formulation A comprises 10-100 mg, preferably 25-75 mg, or most preferably about 50 mg of active ingredient X and formulation B comprises 1-20 mg, 5-15 mg, or most preferably about 10 mg of active ingredient X. In certain embodiments, for example when a patient population is a pediatric population being treated with satraplatin, or where generally a limited amount of satraplatin is to be administered, such as when co-administered with radiotherapy, the unit dosage form of formulation A may comprise less than about 50 mg of
sarataplatin, such as an amount selected from about 25 mg, about 15 mg, about 10 mg, and about 5 mg, and a unit dosage form of formulation B may comprise less than about 10 mg of sarataplatin, such as an amount selected from about 5 mg, about 2 mg, about 1 mg, and about 0.5 mg.

In certain embodiments, formulation A comprises an active ingredient X and formulation B comprises an active ingredient Y, wherein active ingredient Y may be different from active ingredient X. In certain embodiments, formulation A does not contain active ingredient Y and, preferably, formulation B does not contain active ingredient X.

In certain embodiments, formulation A and formulation B have different pharmacological or pharmacokinetic properties. In certain such embodiments, active ingredient X is selected from a cytotoxic compound, a chemotherapeutic compound, a high potency compound, a compound with a narrow therapeutic index, and an orally available platinum complex and active ingredient Y is selected from a cytotoxic compound, a chemotherapeutic compound, an orally available platinum complex, a radiosensitizer, an anti-emetic, an anti-diarrheal, a high potency compound, a compound with a narrow therapeutic index, and a hormonal anti-cancer agent. In certain embodiments, active ingredient X is sarataplatin or a prodrug or metabolite thereof, e.g., wherein formulation A may comprise 5-75 mg of sarataplatin.

In further embodiments, each dose is individually removable from the kit or package.

In certain embodiments, the kit or package further comprises subunits comprising a plurality of unit dosage forms of formulation C, wherein formulation C may be different from each of formulations A and B. In certain such embodiments, formulation A, formulation B, and formulation C each comprise an active ingredient X and the amount of active ingredient X in the unit dosage forms of each formulation A, B, and C, is different from the amount of active ingredient X in the unit dosage forms of either of the other two formulations. In alternative such embodiments, formulation A comprises active ingredient X, formulation B comprises active ingredient Y, and formulation C comprises active ingredient Z, wherein each of active ingredients X, Y, and Z is different from the other two active ingredients (e.g., each of the three formulations comprises an active ingredient that is not present in either of the other two formulations). It is to be understood that any embodiment described herein may further comprise subunits comprising unit dosage forms of formulation C in an analogous manner to subunits of unit dosage forms comprising formulations A and/or B. In other embodiments, the package may comprise one or more further formulations, such as formulation D.

In certain embodiments, at least one subunit A is physically associated with at least one subunit B. In certain embodiments, the unit dosage forms of formulation A and unit dosage forms of formulation B are arranged in a grid pattern such that each row is a dose and each column is a subunit. In a certain such embodiment, the total number of doses in a kit or package is between 3 and 35, between 5 and 14, about 14, about 7, or about 5. Each dose may be designated with a day of the week or month, though not necessarily designated with consecutive days. Alternatively, each dose may be designated with consecutive day numbers (Day 1, Day 2, etc.), dose numbers (Dose 1, Dose 2, etc.), time intervals indicating the number of hours that should elapse between administration of doses (6 h, 4 h, etc.), or more general temporal classifications such as “Morning”, “Evening”, “Breakfast”, “Lunch”, or “Dinner”, optionally comprising one or more further temporal designations such as “Monday morning” etc. In such embodiments, the doses may be designated in any appropriate manner, for example, coloring, labeling, printing, scoring, embossing, or other distinguishing features. Additionally, a package or kit of the invention may be labeled with information about the names of the active ingredient(s), the amount of active ingredient in each unit dosage form, or information or warnings about any of the active ingredients in the unit dosage forms of the package. These designations or labels may be an integral part of the package added during the manufacturing process, or they may be added by the pharmacist or patient to customize the designation or label to the patient since, for example, some patients may start a variable-dose regimen on a Monday, while some may start the regimen on a Thursday.

In certain embodiments, the package may be used to administer a tapered dose. This can be accomplished as shown in the embodiment of FIG. 1b, where formulations A and B are, for example, formulations of the same active ingredient in different dosages. In the embodiment depicted, assuming that one dose is to be taken each day, six unit dosage forms of both formulations A 4 and B 5 are included for the first day of administration, while by the fifth day, the number of unit dosages of formulation B 5 in each dose decreases such that there are no longer any unit dosage forms of formulation B, thereby lowering the overall dose of the active ingredient.

A similar strategy may be employed for attaining a dose that cycles between high and low doses over time, alternating between different doses, or otherwise cycles between doses of different compositions. In certain such embodiments, for example, dose 1 may comprise, two unit dosage dose forms of formulation A and one unit dosage dose form of formulation B, whereas dose 2 comprises one unit dosage form of formulation B but has no unit dosage forms of formulation A, while dose 3 comprises two unit dose forms of formulation A and one unit dose form of formulation B, etc. This could be accomplished by leaving spaces, akin to those illustrated in the tapered dose FIG. 1b, or by having placebos in the A subunits. For example, if the active ingredient of a formulation induces drowsiness, it may be desirable for a dose taken in the morning to be lower than a dose taken in the evening before the patient sleeps. Accordingly, a package according to the invention might include fewer unit dosage forms of a formulation that induces drowsiness for a morning dose than are included in a dose that will be taken in the evening. Alternatively, morning doses might include unit dosage forms of a formulation that comprises an active agent that counters drowsiness, while unit dosage forms of this formulation might be excluded from doses to be taken in the evening. In such embodiments, some subunits may have fewer unit dosage forms than other subunits in the package.

The kit or package may be of any shape, and the subunits comprising unit dosage forms arranged in any pattern, as long as the patient can readily determine which unit dosage forms are part of each dose. For example, the unit dosage forms may be arranged to form a circular, triangular, trapezoidal, hexagonal or other shape. In other embodiments, the shape may be three dimensional. Preferably, the kit or package is configured such that subunits can easily be added to or removed from the kit or package. For example, as illustrated in FIG. 2, the kit or package may be circular. In a certain such embodiments, each subunit 1 is a circular ring, wherein
multiple subunits are concentric rings, and each dose 2 is a radial segment of the package. Removing a subunit, such as the outermost ring of unit dosage forms, permits the doses to be varied as described herein. Other suitable shapes will be apparent to those of skill in the art following the disclosure herein.

[0055] FIG. 3 depicts yet another embodiment of the invention, wherein a kit is supplied as a partially filled template and comprises at least one subunit A 1 that is integral to the kit, multiple subunits A 1 being serially connected and integral to the kit, coupled to a plurality of serially connected compartments 6, wherein each compartment is capable of receiving a subunit B 1. In this embodiment, each column of the kit is a subunit 1 and each row is a dose 2, such that subunits B 1 added to the compartments increase the dose of the variable-dose therapeutic regimen, thereby allowing the dose to be customized for a patient.

[0056] In certain embodiments, each subunit contains an equal number of unit dosage forms. In certain such embodiments, such as is depicted in FIG. 3, the subunits A 1 and B 2 are arranged such that the unit dosage forms of formulation A 4 together with the unit dosage forms of formulation B 5 form a grid, wherein each column is a subunit 1 or 2 and each row is a dose 3 (or vice versa). In preferred such embodiments, each subunit B 2 is a strip of blister packs, wherein each blister pack contains a single unit dosage form. Compartments 6 may be any structure capable of receiving a subunit B 2, either reversibly or irreversibly, such as slots, openings, gaps, notches, cavities, or receptacles. In kits according to FIG. 3, subunit B 2 strips can be added to the kit by sliding the strip into the slot 6. In a kit according to FIG. 3, the subunit B strip, and subunit A-compartment components may be supplied either separately or together and a pharmacist could fill a prescription by adding the appropriate number of subunit B strips to the kit to afford a package that contains a customized dose for a patient. In certain embodiments, all of the compartments are empty, thereby providing a kit that contains only subunits A.

[0057] In another aspect, the invention relates to a kit or package for a variable-dose therapeutic regimen, as shown in FIG. 4, comprising a plurality of serially connected compartments 6 and 7 in a template, including at least one compartment A 6, capable of receiving a subunit A 1 and at least one compartment B 7, capable of receiving a subunit B 2, wherein a dose 3 comprises a unit dosage form from each subunit of the kit, such that subunits A 1 and subunits B 2 added to the compartments increase the dose of the variable-dose therapeutic regimen, and wherein compartment(s) A 6 and compartment(s) B 7 may be the same or different. Examples of alternative frames or templates that may be used to bring subunits into association with each other may be found in U.S. Pat. No. 5,954,202, the disclosure of which is incorporated in its entirety by reference, which is directed to paperboard blanks including a blister pack which are used to form self-contained, reclosable packages. Such structures of this type, generally, are comprised of one piece of paperboard that when folded acts as an outer package when sealed and a reclosable package after being opened. Another alternative frame or template that may be used to bring subunits into association with each other may be found in U.S. Pat. No. 6,082,544, the disclosure of which is incorporated in its entirety by reference, which is directed to a system for exchanging medication blister strips that includes a reusable dispensing frame that holds a plurality of reusable blister strip cartridges. A medicine filled blister strip having individually sealed spaced blisters is dropped down onto each blister strip cartridge base when a locking arm is in an open position and then is locked thereto when the locking arm is moved into a closed position, the locking arm including an open hold down frame for each individual blister, through which the blister is visually exposed, thereby locating the blister strip in operative assembly with the cartridge. The cartridge also includes a pillbox with an identification card having information indicia, the card being attachable to the top. The information indicia is readable through slots in the top, floor, and dispensing frame floor, and from beneath the dispensing frame floor when the cartridge is functionally engaged with the dispensing frame.

[0058] In certain embodiments, a package may contain only subunit(s) A or only subunit(s) B rather than a combination of subunit(s) A and subunit(s) B. This situation may arise when a given number of subunit(s) A provides the appropriate amount of an active ingredient X for a customized dose for a patient.

[0059] In preferred embodiments, the compartments are slots that are adapted to receive each subunit and subunit(s) A 1 and/or B 2 are strips of blister packs that are adapted to each fit in a slot, as shown in FIG. 4. In certain such embodiments, the package further comprises holes in the backing of the slots 8 such that a unit dosage form may be pushed out of the package without removing the subunit from the package. In a kit according to FIG. 4, the compartment component 6 and 7, subunits A 1, and subunits B 2 may be supplied either together or separately. A pharmacist filling a prescription for a variable-dose therapeutic regimen would add the appropriate number of subunit A 1 and subunit B 2 strips to the kit to afford a package that contains a customized dose for a patient. In certain embodiments, subunit(s) A and/or subunit(s) B could be added by sliding the subunit strips 1 and/or 2 into a slot 6 or 7. In certain embodiments of the invention, the subunits A 1 and B 2 and their corresponding compartments 6 and 7 may be differently dimensioned, for instance, such that subunits A 1 are too large to fit in compartments for subunits B 7, and, optionally, subunits B 2 are too small to be retained in compartments for subunits A 6. For example, in FIG. 4, a wide strip may be used for subunits A 1 and a narrow strip for subunits B 2. In such an embodiment, subunits A 1 will be too large to fit in the slots for subunits B 7, while the strips for subunits B 2 may easily fall out of the wider subunit A 6 slots. In certain other embodiments, the compartments 6 and 7 have the same dimensions such that a compartment 6 or 7 is adapted to receive any of the subunits of the kit.

[0060] Preferably, in the embodiments disclosed herein, each dose is individually removable from the package, e.g., so that empty packaging can be removed after a dose has been taken, or so that a dose can be removed from the package so as to be more conveniently administered away from the patient's home, obviating any need to carry a complete, bulky package on short trips, for example. Thus, as shown in FIG. 5, a package may comprise a plurality of serially connected subunits A 1 and B 2 comprising at least one subunit A 1, itself comprising a plurality of unit dosage forms of formulation A 4, and at least one subunit B 2, itself comprising a plurality of unit dosage forms of formulation B 5, wherein a dose 3 comprises a unit dosage form from each subunit of the package and each subunit is removable from the package, such that the dose of the variable-dose therapeutic regimen decreases when units are removed, with the proviso that there is always
at least one subunit A in the package, thereby allowing the dose to be customized for a patient.

[0061] Various ways are known in the art for facilitating such removal, such as scoring or perforating the structural material of the package. In certain embodiments, the package is adapted, such as by scoring or perforation, such that each subunit and/or each dose is individually removable from the package. FIG. 5 shows an example of such a package, wherein each subunit A 1 or B 2 as well as each dose 3 is removable from the package due to scoring or perforations 9 arrayed over the package.

[0062] As will be obvious to those of skill in the art, a wide variety of systems may be employed to bring subunits 1 and 2 into association with each other. While certain embodiments depicted above contemplate the use of a template to bring subunits A 1 and B 2 into association, the individual subunits may be adapted to be coupled to each other without external support. For example, in the embodiment shown in FIG. 6, multiple subunits 1 and 2 are serially connected by means of holes 11 that fixably receive hooks 12 in a reversible or irreversible fashion. Alternatively, as shown in FIG. 7, the terminal subunit A may be equipped with slits 13 and the subunit(s) B may be equipped with tabs 14 and slits 13. In another embodiment shown in FIG. 8, the terminal subunit A may be equipped with wells 15 and subunit(s) B may be equipped with plugs 16 and wells 15 that can be fixably inserted into the wells in a reversible or irreversible fashion. Subunit(s) A 1 and subunit(s) B 2 may be supplied either separately or together. A pharmacist could fill a prescription using a kit to assemble a package according to the invention using subunits as exemplified by any one of FIGS. 6 to 8 by inserting appendages 12, 14, or 16 into receptacles 11, 13, or 15. Reversible attachment carries with it the advantage that the pharmacist can readily correct errors in assembling a package; irreversible attachment may be helpful in preventing inadvertent detachment of subunits by the patient, which may result in an undesirable change in the dose being administered to the patient. Additionally, each subunit 1 or 2 may be optionally equipped with appendages 12, 14, or 16 and receptacles 11, 13, or 15, respectively, thus allowing an infinite number of subunits to be associated with one another. Other positioning means suitable to associate subunit(s) A with subunit(s) B may include clips, fastenings, sockets or locating appendages.

[0063] In certain embodiments, the package can be illustrated by FIG. 9, wherein the terminal subunit A 1 is equipped with an adhesive or fastening material 17 and the subunit(s) B 2 is equipped with material 18 adapted to be affixed to 17. In certain embodiments, the adhesive is applied during the manufacturing process and is protected with a removable cover that may be removed by the pharmacist to expose the adhesive. In another embodiment, the adhesive is supplied separately and is applied to the subunit(s) when the package is prepared. In certain embodiments, the adhesive or fastening material 17 is selected from glue, tape, mushrooms, and hooks and the material adapted to be affixed to 18 is selected from glue, tape, cardboard, plastic, foil, mushrooms, and loops. In a kit exemplified by FIG. 9, a pharmacist could provide a package by exposing the adhesive 17 on subunit(s) A and adhering subunit(s) A 1 to subunit(s) B 2. Again, the attachment could be made reversible or irreversible in certain of these embodiments.

[0064] In another embodiment, the kit can be illustrated by FIG. 9, wherein the terminal subunit A 1 is equipped with a groove 17 that is adapted to receive a tongue and the terminal subunit B 2 is equipped with a tongue 18 that is adapted to fit into groove 17.

[0065] In certain embodiments, the kit can be illustrated by FIG. 10, wherein each subunit 1 and 2 is equipped with protrusions 19, such that the subunits fit together in a manner similar to a jigsaw puzzle. A kit exemplified by FIG. 10 has the advantage that an unlimited number of subunits 1 and 2 can be associated with one another.

[0066] In certain embodiments of the kits or packages shown in any one of FIGS. 6 to 9, multiple subunits B may be brought into association by further adapting subunit B to have the means comprised on subunit A, e.g., that each such subunit has both “male” and “female” attachment parts. In this way, many or an unlimited number of subunits B can be associated with each other in a “daisy-chained” configuration. In other embodiments, the subunits A may be so associated in such a manner, and in yet other embodiments all subunits comprising the kit or package are so associated.

[0067] In certain embodiments of the kits or packages, it may be desirable to render the package or kit child-resistant. In such embodiments, the package or the kit may include, comprise or be included in a child-resistant enclosure, system or solution. Examples of suitable child-resistant packages are disclosed in U.S. Pat. No. 6,412,636, U.S. 6,047,829, and 6,230,893, which are incorporated herein by reference in their entirety. These containers are directed generally to a two-piece package for housing and dispensing a unit dose product. The product to be dispensed is contained on an internal slide card that is removable and lockably engaged within an outer sleeve. The package provides a child resistant and user-friendly dosing means that can be opened and closed numerous times while in use, then disposed of when all the unit doses are exhausted. One embodiment of a child-resistant container is the “Surepak” system from MeadWestvaco Healthcare Packaging which is a semi-rigid blister reclosable package that includes a fiberboard and plastic outer carton containing an affixed blister card. The front of the blister card covers each tablet with a clear semi-rigid plastic and the back of the card is made of foil. The package may be opened by pushing a finger through a hole located on the back of the outer carton, and pulling back on a trigger to release a latch while lifting one of the two tabs on the front of the outer carton, thereby exposing the blister card. Once the blister card is exposed, a tablet may be released by pushing it through the foil backing. The package further comprises a combination of written text and graphical illustrations that provide the patient with instructions on how to properly access the blister card inside the carton.

[0068] In another aspect, the invention relates to a method for assembling or preparing any one of the packages described above comprising determining the appropriate number of unit dosage forms of formulations A and B (or A, B, and C, etc.) to achieve a prescribed dose of a variable-dose therapeutic regimen, and adding or removing subunits from the package or kit so as to customize the dose of the variable-dose therapeutic regimen for a patient. The subunits may be supplied in bulk as on a roll as shown in FIG. 11, a sheet as shown in FIG. 12, concentric rings as shown in FIG. 13, strips as shown in FIG. 14, or in another pre-formed interconnection. In certain such embodiments, the subunits may be supplied as foil packs or blister packs on a roll, a sheet, concentric rings, strips, or other pre-formed interconnections. Such bulk subunits or interconnected unit dosage forms may be adapted,
such as with perforations, scores, or designations, to aid the partition of a subunit comprising an appropriate number of unit dosage forms. Additionally, the subunits may be supplied together with, or separate from, a package frame or template. Subunits A and subunits B may be supplied in the same form (e.g., strips) or they may be supplied as two different forms (e.g., subunits A are integral to the frame or template and subunits B are strips). In certain embodiments, subunits A and subunits B are available separately to accommodate separate manufacturing, supplying and ordering of each type of subunit. In preferred embodiments, the kit further comprises instructions for assembling the package. In certain embodiments, the assembly of a package may further comprise calculating the appropriate amount of active ingredient(s) required by a patient. Once the appropriate amount of active ingredient(s) has been calculated, the appropriate type and number of subunit(s) can be determined to achieve the appropriate dose of the variable-dose regimen for a patient.

In certain embodiments of the kits disclosed herein, different classes of subunits for a given formulation A and/or B are provided, each class with different number of unit dosage forms of the given formulation, optionally with blank or placebo units. Such different classes of subunits would be advantageous to form a package the shown in Fig. 1A. In other embodiments of the kits of the inventions, the unit dosage forms of the different formulations are provided loose in bulk, such as in a bottle, vessel, box or bag. In such embodiments, the kit of the instant invention may include a means to physically associate the unit dosage forms, for example a medicine cartridge of U.S. Pat. No. 6,082,544, or a paperboard blank as disclosed in U.S. Pat. No. 5,954,202, together with instructions to form the customized dose by inserting in such cartridge or paperboard blank, the appropriate number of individual unit dosage forms of formulation A and/or B so as to form the customized dose.

The invention further relates to a method for treating a patient suffering from a disease or condition, comprising, determining the appropriate dose of a variable-dose therapeutic regimen, prescribing a customized dose of the variable-dose therapeutic regimen, and instructing the patient to consume a unit dosage form from each subunit of the package at predetermined intervals. In certain embodiments, the disease or condition is selected from cancer, hypertension, hypothyroidism, heart-related ailments, and depression. In certain such embodiments, the disease or condition is a cancer selected from liver, stomach, colon, breast, pancreatic, skin, cervical, ovarian, testicular, lung, head and neck, prostate, hormone resistant prostate, small cell lung, and metastases thereof. In certain embodiments, the invention relates to combination therapy, wherein a variable-dose therapeutic regimen package is co-administered with another therapeutic agent, or with another therapeutic regimen such as radiotherapy.

In another embodiment of the invention, a kit or package may be associated with at least one other kit or package such that the kit or packages are dispensed to a pharmacist or patient as a combination kit or package.

Definitions

The term “chemotherapeutic” or “chemotherapy” is art-recognized and includes compounds that are selectively toxic to the causative agent of the disease, such as cancer cells. Examples of chemotherapeutic compounds include, but are not limited to, Iressa (gefitinib), Tarceva (erlotinib HCI), Xeloda (capecitabine), mitoxantrone, estramustine phosphate, etoposide, and doxorubicin.

The term “high potency” herein is defined as a compound that has a therapeutic effect at a very low dose, e.g., less than a few milligrams, and overdose of such a compound by a small fraction can lead to severe adverse or toxic reactions.

Examples of high potency compounds or those having a narrow therapeutic index include, but are not limited to, levothyroxine sodium, warfarin, paclitaxel, haloperidol, pimozide, difluorotolone, ropinrole hydrochloride, and betamethasone.

The term “co-administer” as used herein refers to at least two therapeutic agents that are administered as part of a single therapeutic regimen. Such combination treatment may be achieved by way of the simultaneous, sequential, or separate dosing of the individual components of the treatment.

The term “cytotoxic” as art-recognized and includes any compound that is directly toxic to cells, preventing their reproduction or growth. Examples of cytotoxic compounds include, but are not limited to, irinotecan, melphalan, chlorambucil, vincristine, vinblastine, azathioprine, cyclophosphamide, methotrexate, and mitomycin-C.

The term “hormonal anti-cancer agent” includes, but is not limited to, leuprolide, goserelin, flutamide, bicalutamide, nilutamide, and ketoconazole.

The term “narrow therapeutic index” as used herein is defined to describe a compound, whose optimal therapeutic effect of which is achieved by precise dosing of the compound to suit a particular patient. Factors that can influence the suitability of an optimal dose for such a compound can include the size, weight, age, condition, sex or other factors of the patient. For example, administration of too little of such a compound for a heavy patient may not cause a therapeutic effect, while administration of too much of such a compound may cause undesirable side effects.

The term “radiosensitizer” is art-recognized and includes any compound with the ability to increase tissue radiosensitivity. Examples of radiosensitizers include, but are not limited to, 5-fluorouracil, topotecan, and tirapazamine.

Examples of anti-emetics include, but are not limited to, ondansetron, granisetron, dolasetron, diphenhydramine, hydroxyzine, metoclopramide, lorzapam, (alprazolam), haloperidol, droperidol, dronabinol, dexmethasone, prochlorperazine, and tropisetrin.

Examples of anti-diarrheals include, but are not limited to, bismuth subsalicylate, absorbent clay, calcium polycarbophil, and loperamide.

The term “kit” is herein defined as a set of parts or a subset thereof that may be used to assemble a package. This may include, for example, subunits A, B, and/or C (or unit dosage forms of formulations A, B and/or C, etc.) supplied to a pharmacist in bulk quantities, instructions for the assembly of a package from a kit, and any label(s) or adhesives that are appropriate for a given package.

“Heart-related ailments” includes any chronic or acute pathological event involving the heart and/or associated tissue (e.g., the pericardium, aorta and other associated blood vessels), including ischemia-reperfusion injury; congestive heart failure; cardiomyopathy; myocardial infarction; cardiac toxicity caused by compounds such as drugs (e.g., doxorubicin, heparin, thioridazine and cisapride); cardiac damage due to parasitic infection (bacteria, fungi, rickettsiae, and viruses, e.g., syphilis, chronic Trypanosoma cruzi infection); fulminating cardiac amyloidosis; heart surgery; heart transplanta-
tion; traumatic cardiac injury (e.g., penetrating or blunt cardiac injury, and aortic valve rupture), surgical repair of a thoracic aortic aneurysm; a suprarenal aortic aneurysm; cardiogenic shock due to myocardial infarction or cardiac failure; neurogenic shock and anaphylaxis.

[0084] “Instruction(s)” as used herein means a product label and/or documents describing relevant materials or methodologies pertaining to assembly, preparation, or use of a kit or packaged pharmaceutical. These materials may include any combination of the following: background information, steps or procedures to follow, list of components, proposed dosages, warnings regarding possible side effects, instructions for administering the drug, technical support, and any other related documents.

[0085] The term “metabolite” as used herein is art-recognized and includes any substance derived from an active ingredient by any physical, chemical, biological, or biochemical process in the body or a cell after the active ingredient is administered. Metabolites may be formed outside of the target cell (such as in the GI tract) or may be formed by synthetic reactions from suitable starting material and administered directly to a cell or body. For example, JM118 may be synthesized according to the method disclosed in EP 0147926, GB 2060615, and U.S. Pat. No. 4,329,299, U.S. Pat. No. 6,350,737, U.S. 6,503,943, EP 1186610, the contents of which are hereby incorporated by reference in their entirety, or may be formed via biotransformation of JM216 in a separate fermentation step.

[0086] The term “orally available” as used herein is art-recognized and includes any agent that has biological, physiological, pharmacological, therapeutic, medical, or clinically significant activity when administered orally.

[0087] “Orally available platinum complexes” as used herein include, but are not limited to satraplatin (JM216), JM118, JM383, or a pharmaceutically acceptable salt, isomer, or prodrug thereof, as well as platinum complexes disclosed in EP 0147926, U.S. Pat. No. 5,072,011, U.S. Pat. No. 5,244,919, U.S. Pat. No. 6,503,943, U.S. Pat. No. 6,350,737, and U.S. Pat. No. 5,519,155, which are all hereby incorporated by reference in their entirety. Raynaud, et al. (1996 Cancer Chemother. Pharmacol. 38: 155-162) shows exemplar metabolites of satraplatin, and is hereby incorporated in its entirety by reference.

[0088] The term “prophylactic or therapeutic” treatment is art-recognized and includes administration to the host of one or more of the subject compositions. If the composition is administered prior to clinical manifestation of the unwanted condition (e.g., disease or other unwanted state of the host animal) then the treatment is prophylactic; (i.e., it protects the host against developing the unwanted condition), whereas if it is administered after manifestation of the unwanted condition, the treatment is therapeutic, (i.e., it is intended to diminish, ameliorate, or stabilize the existing unwanted condition or side effects thereof).

[0089] The term “preventing” is art-recognized, and when used in relation to a condition, such as a local recurrence (e.g., pain), a disease such as cancer, a syndrome complex such as heart failure or any other medical condition, is well understood in the art, and includes administration of a composition the intent of which is to reduce the frequency of, or delay the onset of, symptoms of a medical condition in a subject relative to a subject which does not receive the composition. Thus, prevention of cancer includes, for example, reducing the number of detectable cancerous growths in a population of patients receiving a prophylactic treatment relative to an untreated control population, delaying the appearance of detectable cancerous growths in a treated population versus an untreated control population, and/or delaying disease progression and/or improving the quality of patient life, e.g., by a statistically and/or clinically significant amount. Prevention of an infection includes, for example, reducing the number of diagnoses of the infection in a treated population versus an untreated control population, and/or delaying the onset of symptoms of the infection in a treated population versus an untreated control population. Prevention of pain includes, for example, reducing the magnitude of, or alternatively delaying, pain sensations experienced by subjects in a treated population versus an untreated control population.

[0090] The term “prodrug” encompasses compounds that, under physiological conditions, are converted into therapeutically active agents. A common method for making a prodrug is to include selected moieties that are hydrolyzed under physiological conditions to reveal the desired molecule. In other embodiments, the prodrug is converted by an enzymatic activity of the host animal. For example, JM518 may be considered a prodrug of JM118, as JM118 (a subject active ingredient) is formed by metabolism of JM518. Analogously, JM216 may be considered a prodrug of JM118.

[0091] The term “sachet” as used herein refers to a small bag or packet containing a dose of medicine.

[0092] The term “template” as used herein refers to any frame, scaffold, skeleton, basis, construction, arrangement, configuration, structure, or support that is adapted to accommodate unit dosage forms or subunits as described herein, especially in a predetermined configuration. Non-limiting examples of a template are given by a cardboard blank of U.S. Pat. No. 5,954,202, a medicine cartridge or U.S. Pat. No. 6,082,544 and a connected-compartment 6 of FIG. 4 herein.

[0093] A “therapeutically effective amount” of a compound, with respect to the subject method of treatment, refers to an amount of the compound(s) in a preparation which, when administered as part of a desired dosage regimen (to a mammal, preferably a human) alleviates a symptom, ameliorates a condition, or slows the onset of disease conditions according to clinically acceptable standards for the disorder or condition to be treated or the cosmetic purpose, e.g., at a reasonable benefit/risk ratio applicable to any medical treatment.

[0094] A “unit dosage form” is defined herein as a discrete unit that comprises a formulation of a therapeutic agent. Examples of suitable unit dosage forms include, but are not limited to tablets, capsules, or gelcaps.

[0095] “Variable-dose therapeutic regimen” as used herein refers to a regimen wherein the dose is adjusted based on the needs of the individual patient to which the medication is to be prescribed and/or administered. Some factors that may be used in the determination of the dose include, but are not limited to, age, body weight, body surface area, and the severity of the diseased or medical condition.

Administration

[0096] Unit dosage forms prepared as described herein can be administered in various forms, depending on the disorder to be treated and the age, condition, and body weight of the patient, as is well known in the art. For example, where the compounds are to be administered orally, they may be formulated as tablets, capsules, or gelcaps; or for parenteral administration, they may be formulated as suppositories. These
formulations can be prepared by conventional means, and, if desired, the active ingredient may be mixed with any conventional additive, such as an excipient, a binder, a disintegrating agent, a lubricant, a corrigent, a solubilizing agent, a suspension aid, an emulsifying agent, or a coating agent. Although the dosage will vary depending on the symptoms, age and body weight of the patient, the nature and severity of the disorder to be treated or prevented, the route of administration and the form of the drug, in general, a daily dosage of from 0.01 to 2000 mg of the compound is recommended for an adult human patient, and this may be administered in a single dose or divided into a plurality of doses, preferably forming a patient customized dose.

The precise time of administration and/or amount of the unit dosage form that will yield the most effective results in terms of efficacy of treatment in a given patient will depend upon the activity, pharmacokinetics, and bioavailability of a particular compound, physiological condition of the patient (including age, sex, disease type and stage, general physical condition, responsiveness to a given dosage, and type of medication), route of administration, etc. However, the above guidelines can be used as the basis for fine-tuning the treatment, e.g., determining the optimum time and/or amount of administration, which will require no more than routine experimentation consisting of monitoring the subject and adjusting the dosage and/or timing.

The phrase “pharmaceutically acceptable” is employed herein to refer to those ligands, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase “pharmaceutically acceptable carrier” as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject chemical from one organ or portion of the body, to another organ or portion of the body. Each carrier must be “acceptable” in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose, and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil, and soybean oil; (10) glycols, such as propylene glycol; (11) polyeols, such as glycerin, sorbitol, mannitol, and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laureate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer’s solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations. In certain embodiments, pharmaceutical compositions of the present invention are non-pyrogenic, i.e., do not induce significant temperature elevations when administered to a patient.

The term “pharmaceutically acceptable salts” refers to the relatively non-toxic, inorganic and organic acid addition salts of the unit dosage form(s). These salts can be prepared in situ during the final isolation and purification of the unit dosage form(s), or by separately reacting a purified unit dosage form(s) in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, lanurate, benzoate, lactate, phosphate, tosylate, citrate, malate, fumarate, succinate, tartrate, naphthalene, mesylate, glucosonate, lactobionate, and laurylsulfonate salts, and the like. (See, for example, Berge et al. (1977) “Pharmaceutical Salts”, J. Pharm. Sci. 66:1-19)

In other cases, the unit dosage forms useful in the methods of the present invention may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable bases. The term “pharmaceutically acceptable salts” in these instances refers to the relatively non-toxic inorganic and organic base addition salts of a unit dosage form(s). These salts can likewise be prepared in situ during the final isolation and purification of the unit dosage form(s), or by separately reacting the purified unit dosage form(s) in its free acid form with a suitable base, such as the hydroxide, carbonate, or bicarbonate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts, and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperezine, and the like (see, for example, Berge et al., supra). Wetting agents, emulsifiers, and lubricants, such as sodium laurel sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring, and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Examples of pharmaceutically acceptable antioxidants include: (1) water-soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfite, sodium metabisulfite, sodium sulfite, and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediaminetetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

Formulations useful in the methods of the present invention include those suitable for oral, rectal, vaginal, and/or parenteral administration. The formulations may conventionally be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated and the particular mode of administration. The amount of active ingredient which may be combined with a pharmaceutically acceptable carrier to produce a single dosage form will generally be that amount of the compound which produces the desired therapeutic effect. It should be understood that in certain embodiments the amount of active ingredient required to produce the desired therapeutic effect may be lower when used in combination with another active ingredient. In certain embodi-
ments, the amount that produces a desired therapeutic effect is determined in the context of a combination therapy contemplated or provided by a package of the instant invention. Generally, out of one hundred per cent, the amount of active ingredient will range from about 1 percent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent.

Methods of preparing these formulations or compositions include the step of bringing into association a therapeutic agent(s) with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a liquid with a carrier, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations suitable for oral administration may be in the form of capsules, sachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia), each containing a predetermined amount of a unit dosage form(s) as an active ingredient.

In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules, and the like), the active ingredient is mixed with one or more pharmacologically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, algamtes, gelatin, polyvinyl pyrrolidone, sucrose, and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, acetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as, a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets, and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using excipients such as lactose or milk sugars, as well as high molecular weight polyethylene glycols, and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered peptide or peptideominic moistened with an inert liquid diluent.

Tablets, and other solid dosage forms, such as dragees, capsules, pills, and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes, and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming, and preservative agents.

Formulations for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more unit dosage form(s) with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active agent.

Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be assured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

When the unit dosage form(s) of the present invention are administered as pharmaceuticals to humans and animals, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

The preparations of agents may be given orally, parenterally, or rectally. They are of course given by forms suitable for each administration route. For example, orally they are administered in tablet or capsule form, and rectally they are administered by suppository. Oral administration is preferred.

The phrases “systemic administration,” “administered systemically,” “peripheral administration” and “administered peripherally” as used herein mean the administration of a ligand, drug, or other material other than directly into the central nervous system, such that it enters the patient’s system
and thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

Regardless of the route of administration selected, the unit dosage form(s), which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art.

Actual dosage levels of the active ingredients in the pharmaceutical compositions and or numbers of formulations A and/or B included in the packages or kits of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims. Those skilled in the art will also recognize that all combinations of embodiments or features of the claims described herein are within the scope of the invention.

All of the above-cited references and publications are hereby incorporated by reference.

107. A package for providing a customized dose of a variable-dose therapeutic regimen, comprising
   (a) at least one subunit A comprising a plurality of interconnected unit dosage forms of formulation A;
   (b) at least one subunit B comprising a plurality of interconnected unit dosage forms of formulation B; and
   (c) means to physically associate at least one subunit A to at least one subunit B; wherein formulation A and formulation B each comprise an active ingredient X, and the amount of active ingredient X in a unit dosage form of formulation A is not equal to the amount of active ingredient X in a unit dosage form of formulation B, and a dose comprises one unit dosage form from each subunit, and the dose is customized for a patient by adding or removing subunits A or B from or to the package.

108. The package of claim 107, wherein at least one of the unit dosage forms is enclosed in a rupturable cell.

109. The package of claim 107, wherein at least one subunit comprises fewer unit dosage forms than another subunit.

110. The package of claim 107, wherein each subunit includes an equal number of unit dosage forms.

111. The package of claim 107, wherein the unit dosage forms of formulation A and unit dosage forms of formulation B together are associated in a grid pattern such that each row is a dose and each column is a subunit.

112. The package of claim 107, wherein the means to physically associate a subunit A with a subunit B comprises positioning means.

113. The package of claim 112, wherein the positioning means is partially filled with a predefined set of subunits A or B.

114. The package of claim 107, wherein the means to physically associate a subunit A with a subunit B comprises appendages on subunit A that are adapted to be put through receptacles of a subunit B.

115. The package of claim 107, wherein the means to physically associate a subunit A with a subunit B comprises an adhesive on a subunit A that is adapted to adhere to a subunit B.

116. The package of claim 107, wherein each dose is independently removable from the package.

117. The package of claim 107, wherein the subunits A and/or B are provided with pre-formed interconnections.

118. The package of claim 117, wherein the subunits A and/or B are provided on a roll, a sheet, concentric rings, strips, or another pre-formed interconnection.

119. The package of claim 107, wherein said subunits A and/or B comprise a number of unit dosage forms appropriate for the therapeutic regimen, or is adapted to partition such appropriate number of unit dosage forms from a larger number of interconnected unit dosage forms.

120. The package of claim 119, wherein said larger number of interconnected unit dosage forms is adapted to aid the partition of a subunit comprising an appropriate number of unit dosage forms.

121. The package of claim 107, wherein said means provides for a plurality of subunits A or B to be added to a template so as to create the customized dose or an appropriate number of customized doses.

122. The package of claim 107, wherein said means provides for a plurality of subunits A or B to be removed from a template, so as to create the customized dose or an appropriate number of customized doses.

123. The package of claim 121, wherein said template comprises a predefined set of unit dosage forms of formulation A or B.

124. The package of claim 107, wherein said package comprises instructions to interconnect an appropriate number of unit dosage forms of formulation A or B for a patient, so as to create a patient-customized dose of the therapeutic regimen.

125. The package of claim 107, wherein said package comprises instructions to physically associate an appropriate number of subunits A with subunits B so as to create the customized dose.

126. The package of claim 107, wherein at least one subunit A is physically associated with at least one subunit B.

127. The package of claim 107, further comprising instructions for a patient to consume a unit dosage form from each of subunits A and B of the package at predetermined intervals or times.

128. The package of claim 107, wherein formulation A and formulation B have different pharmacological or pharmacokinetic properties.

129. The package of claim 128, wherein formulation A is a sustained release formulation and formulation B is a rapid release formulation.

130. The package of claim 107, wherein a unit dosage form of formulation A comprises an amount of active ingredient X that is greater than the amount of active ingredient X in a unit dosage form of formulation B by a factor of about 2, about 4, about 5, about 10, about 25, or about 50.

131. The package of claim 107, wherein the active ingredient X is selected from a cytotoxic compound, a chemotherapeutic compound, a high potency compound, and an orally available platinum complex.

132. The package of claim 107, wherein at least one of the unit dosage forms of at least one of formulations A or B are adapted for oral administration.
133. The package of claim 132, wherein the unit dosage form suitable for oral administration is selected from tablets, pills, capsules, or gelcaps.

134. The package of claim 107, wherein the active ingredient X is satraplatin, or a metabolite or a prodrg thereof.

135. The package of claim 134, wherein said package provides a customized dose of satraplatin.

136. The package of claim 134, wherein a unit dosage form of formulation A comprises an amount of satraplatin selected from about 75 mg, about 50 mg, about 25 mg, about 10 mg, and about 5 mg.

137. The package of claim 134, wherein a unit dosage form of formulation A comprises about 50 mg of satraplatin and a unit dosage form of formulation B comprises about 10 mg of satraplatin.

138. The package of claim 107, wherein the number of doses is selected from between 3 and 35, about 14, about 10, about 7, and about 5.

139. The package of claim 107, wherein each dose is designated with a day of the week or month.

140. The package of claim 107, further comprising a plurality of unit dosage forms of formulation C, wherein formulation C is different from formulations A and B.

141. The package of claim 140, wherein said formulation C comprises an active ingredient selected from a cytotoxic compound, a chemotherapeutic compound, an orally available platinum complex, a radiosensitizer, an anti-emetic, an anti-diarrheal, a high potency compound, a compound with a narrow therapeutic index, and a hormonal anti-cancer agent.

142. A package for providing a customized dose of satraplatin, said package comprising:

(a) at least one subunit A comprising a plurality of interconnected unit dosage forms of formulation A, formulation A comprising an amount of satraplatin;

(b) at least one subunit B comprising a plurality of interconnected unit dosage forms of formulation B, formulation B comprising an amount of satraplatin that is not equal to the amount in a unit dosage form of formulation A;

such that a dose comprises one unit dosage form from each subunit, and the dose is customized for a patient by adding or removing subunits A or B.

143. The package of claim 136, wherein a unit dosage form of formulation A comprises an amount of satraplatin selected from about 75 mg, about 50 mg, about 25 mg, about 10 mg, and about 5 mg.

144. The package of claim 136, wherein a unit dosage form of formulation A comprises an amount of satraplatin that is greater than the amount in a unit dosage form of formulation B by a factor of about 2, about 4, about 5, about 10, about 25, and about 50.

145. The package of claim 142, further adapted for a consistent dose over an administration cycle selected from between 3 and 35 days, about 14 days, about 10 days, about 7 days, and about 5 days.

146. Use of the package of claim 107 in a variable-dose therapeutic regimen for the treatment of a patient suffering from a disease.

147. The use of claim 146, wherein the disease is selected from cancer, hypertension, hypothyroidism, heart-related ailments, and depression.

148. The use of claim 147, wherein the disease is a cancer selected from liver, stomach, colon, breast, pancreatic, skin, cervical, ovarian, testicular, lung, and head and neck, prostate, hormone resistant prostate, small cell lung, and metastasises thereof.

149. A kit for assembling or preparing a customized dosage of a variable-dose therapeutic regimen, comprising:

(a) at least one subunit A comprising a plurality of unit dosage forms of formulation A;

(b) at least one subunit B comprising a plurality of unit dosage forms of formulation B;

(c) means to interconnect or physically associate the unit dosage forms of formulation A in a subunit A or the unit dosage forms of formulation B in a subunit B; wherein said customized dose is provided in a package of claim 107 or 142.

150. A method for assembling or preparing a package of claim 107, comprising determining the appropriate number of unit dosage forms of formulations A and B to achieve a prescribed dose of a variable-dose therapeutic regimen, and

(a) adding to or removing subunits from the package, or

(b) using the kit of claim 149, thereby customizing the dose for a patient.

151. A method for treating a patient suffering from a disease comprising:

(a) determining for said patient the appropriate dose of a variable-dose therapeutic regimen;

(b) prescribing for said patient a customized dose of a variable-dose therapeutic regimen in a package of claim 107 or 142; and

(c) instructing said patient to consume a unit dosage form from each of subunits A and B of the package at predetermined intervals.

152. The method of claim 151, further comprising:

instructing said patient to consume a unit dosage form of formulation C at predetermined intervals, wherein formulation C is different from formulations A and B.

153. The method of claim 151, wherein the disease is selected from cancer, hypertension, hypothyroidism, heart-related ailments, and depression.

154. The method of claim 151, wherein the disease is a cancer selected from liver, stomach, colon, breast, pancreatic, skin, cervical, ovarian, testicular, lung, and head and neck, prostate, hormone resistant prostate, small cell lung, and metastasises thereof.

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