Title: DRUG COMBINATIONS TO TREAT LIVER CANCER

Abstract: Drug combinations and methods for treating virus-related liver cancer.
DRUG COMBINATIONS TO TREAT LIVER CANCER

TECHNICAL FIELD OF THE INVENTION

The present invention relates to drug combinations of an antiviral drug and a cancer drug for treating virus-related liver cancer.

BACKGROUND OF THE INVENTION

Heptocellular carcinoma (HCC), also known as malignant heptoma, is the most prevalent type of liver cancer and is the fifth most common type of cancer in the world.

Current management of HCC can include liver transplantation, surgical liver resectioning, radiation therapy, ablation, or administration of a multikinase inhibitor drug. One of the more promising new multikinase inhibitor drugs for the treatment of HCC is sorafenib. Sorafenib is a small molecule that inhibits tumor-cell proliferation and tumor angionesis and has been shown to increase the rate of apoptosis. Sorafenib, also known as 4-[4-[[4-chloro-3-(trifluoromethyl)phenyl]carbamoylamino]phenoxy]-N-methyl-pyridine-2-carboxamide, is an inhibitor of several Tyrosine protein kinases (VEGFR and PDGFR) and Raf kinases (more avidly C-Raf than B-Raf) and is unique in targeting the Raf/Mek/Erk pathway (MAP Kinase pathway).

Sorafenib was first approved by the U.S. FDA in December 2005 for use in the treatment of advanced renal cancer. In November 2007, sorafenib received FDA approval for the treatment of HCC. Currently, sorafenib is marketed under the trade name NEXAVAR® for the treatment of HCC and is available as a 200 mg oral tablet.

The most common risk factors for developing HCC are the presence of cirrhosis and co-infection with hepatitis B virus (HBV) and hepatitis C virus (HCV). Current management of
HBV and HCV is by administration of antiviral drugs such as adefovir, entecavir, telbivudine and lamivudine.

Despite recent advances in the management of HCC, HCC remains the third most common cause of cancer death. Therefore, a need exists for improved methods and drug combinations for the treatment of HCC.

Thus, it is an object of the present invention to provide drug combinations for the treatment of virus-related liver cancer.

It is also an object of the present invention to provide dosing regimens of drug combinations for the treatment of virus-related liver cancer.

It is additionally an object of the present invention to provide methods for the treatment of virus-related liver cancer.

**SUMMARY OF THE INVENTION**

The present invention accomplishes the above objects and others by providing a drug combination of a cancer drug and an antiviral drug for the treatment of virus-related liver cancer.

In another embodiment of the present invention there is provided a method for treating virus-related liver cancer by administering to a patient a drug combination comprising a cancer drug and an antiviral drug.

The daily dose of the drug combination of the present invention is about 100 to about 1600 mg of a cancer drug and about 0.1 mg to about 3000 mg of an antiviral drug. The drug combination of the present invention may be administered as a single fixed-dose combination or may be administered as separate doses of a cancer drug and an antiviral drug, respectively. In embodiments of the present invention where the drug combination is administered as a single fixed-dose combination, the drug may be administered one or more times daily. In embodiments
of the present invention where the drug combination is administered as separate dosages, each one of the cancer drug and antiviral drug may be administered one or more times daily. The fixed-dose dosage form and the separate cancer drug and antiviral drug dosage forms may be an immediate release or controlled release dosage form. The immediate or controlled release dosage form may optionally be coated with a delayed release coating to reduce adverse effects and increase patient compliance.

The fixed dose combination dosage form and the separate cancer drug and antiviral drug dosage forms may be a capsule, tablet, multilayer tablet, multicoated tablet, sublingual tablet or orally disintegrating tablet that is designed to dissolve in a patient's mouth, solution, suspension, syrup or powder that can be mixed with food or liquids for easier administration.

The cancer drug of the drug combination of the present invention may be an agent which is targeted to liver or kidney cancer. The antiviral drug of the drug combination of the present invention may be an agent used to treat hepatitis viruses.

**DETAILED DESCRIPTION OF THE INVENTION**

As used herein the term "cancer drug" refers to any substance capable of controlling the growth of cancerous cells. In an embodiment of the present invention, the cancer drug is a multikinase inhibitor such as vemurafenib, sorafenib, sunitinib, vandetanib, cabozantinib, ponatinib, axitinib, ruxolitinib, regorafenib, crizotinib, pharmaceutically acceptable salts thereof and combinations thereof. In an embodiment of the present invention the cancer drug is sorafenib or a pharmaceutically acceptable salt thereof. The cancer drug may be administered at about 100 to about 1600 mg per day, preferably about 200 mg to about 800 mg per day and more preferably about 400 mg per day. The dose may be administered once a day or in doses throughout the day, such as every 4, 6, 8 or 12 hours.
As used herein the term "antiviral drug" refers to any substance which inhibits the development of a pathogen. In an embodiment of the present invention, the antiviral drug is an interferon, protease inhibitor, purine nucleoside, nucleoside reverse transcriptase inhibitor, nonnucleoside reverse transcriptase inhibitor and the like. Suitable antiviral drugs for use in the present invention include entecavir, adefovir, lamivudine, tenofovir, telbivudine, boceprevir, ribavirin, telaprevir, zidovudine, pharmaceutically acceptable salts thereof and combinations thereof. In embodiments of the present invention, the drug is selected from the group consisting of entecavir, adefovir, lamivudine, tenofovir, telbivudine, boceprevir, ribavirin, telaprevir, pharmaceutically acceptable salts thereof and combinations thereof. The antiviral drug may be administered at about 0.1 mg to about 3000 mg per day and preferably about 1 mg to about 1000 mg per day. The dose may be administered once a day or in doses throughout the day, such as every 4, 6, 8 or 12 hours.

In embodiments of the present invention where the antiviral drug is entecavir or a pharmaceutically acceptable salt thereof, the entecavir may be administered at about 0.1 mg to about 5 mg per day, preferably about 0.5 mg to about 2.5 mg per day and more preferably about 0.5 mg or about 1 mg per day.

In embodiments of the present invention where the antiviral drug is adefovir or a pharmaceutically acceptable salt thereof, the adefovir may be administered at about 1 mg to about 100 mg per day, preferably about 5 mg to about 50 mg per day and more preferably about 10 mg per day.

In embodiments of the present invention where the antiviral drug is lamivudine or a pharmaceutically acceptable salt thereof, the lamivudine may be administered at about 10 mg to
about 1000 mg per day, preferably about 50 mg to about 500 mg per day and more preferably about 100 mg or about 300 mg per day.

In embodiments of the present invention where the antiviral drug is tenofovir or a pharmaceutically acceptable salt thereof, the tenofovir is administered at about 10 mg to about 2000 mg per day, preferably about 100 mg to about 1000 mg per day and more preferably about 150 mg, about 300 mg or about 600 mg per day.

In embodiments of the present invention where the antiviral drug is telbivudine or a pharmaceutically acceptable salt thereof, the telbivudine is administered at about 50 mg to about 3000 mg per day, preferably about 300 mg to about 1000 mg per day and more preferably about 600 mg per day.

In embodiments of the present invention where the antiviral drug is boceprevir or a pharmaceutically acceptable salt thereof, the boceprevir is administered at about 20 mg to about 500 mg per day, preferably about 100 mg to about 350 mg per day and more preferably about 200 mg per day.

In embodiments of the present invention where the antiviral drug is ribavirin or a pharmaceutically acceptable salt thereof, the ribavirin is administered at about 20 mg to about 3000 mg per day, preferably about 100 mg to about 1000 mg per day and more preferably about 200 mg, about 400 mg, about 500 mg or about 600 mg per day.

In embodiments of the present invention where the antiviral drug is telaprevir or a pharmaceutically acceptable salt thereof, the telaprevir is administered at about 50 mg to about 1000 mg per day, preferably about 200 mg to about 500 mg per day and more preferably about 375 mg per day.
In embodiments of the present invention, the cancer drug and the antiviral drug may be combined into a single dosage form such as a tablet, including a multilayer or multicoated tablet, capsule, solution, syrup, suspension or sachet. Alternatively, the cancer drug and the antiviral drug may be provided to a patient in separate dosage forms selected from tablets, including a multilayer or multicoated tablet, capsules, solutions, syrups, suspensions, sachets and combination thereof. In embodiments of the present invention where the cancer drug and antiviral drug are provided to a patient in separate dosage forms, the ratio of dosages of cancer drug to antiviral drug administered to a patient per week may range from about 7:1 to about 1:7, preferably about 3.5:1 to about 1:3.5, and more preferably 1:1.

The dosage forms of the present invention, whether as a fixed-dose combination or separate dosage forms of a cancer drug and an antiviral drug, may be formulated to be immediate release, controlled release or a combination thereof. The immediate release and controlled release dosage forms may also additionally comprise a delayed release coating designed to delay release of the immediate or controlled release portion of the drug until the drug passes a patient’s stomach.

In embodiments of the present invention where the dosage form is immediate release the cancer drug, antiviral drug or combination thereof, may be combined with pharmaceutically acceptable excipients such as fillers, diluents, binders, stabilizing agents, lubricants, disintegrants or mixtures thereof. These pharmaceutically acceptable excipients are well known in the art and are described in Remington, the Science and Practice of Pharmacy, 21st Ed. (2006), pp. 1058-1092, published by Lippincott Williams & Wilkins; United States Pharmacopeia 27 (2004), pp. 2809-2812; and Handbook of Pharmaceutical Excipients, 5th Ed. (2006), published by the Pharmaceutical Press, both incorporated by reference. The dosage forms are made by methods
commonly known in the art such as direct compression, wet or dry granulation, and extrusion spherionization.

Examples of acceptable fillers, sometimes referred to as diluents, include water; sugars such as lactose, dextrose, sucrose, maltose, or microcrystalline cellulose; clays; and mixtures thereof.

Binders that are useful in the present invention include pharmaceutically acceptable substances with cohesive properties. Some examples include cellulosics such as hydroxypropyl methycellulose, hydroxypropyl cellulose and carboxymethycellulose sodium; polyvinylpyrrolidone; sugars; starches; and mixtures thereof.

Examples of stabilizing agents that are useful in the present invention include organic acids and alkaline metal salts of organic acids, such as succinic acid, fumaric acid, citric acid, sodium citrate, and mixtures thereof.

Examples of lubricants, glidants and/or antiadherents that may be used in the present invention include talc, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oils, polyethylene glycols, silicon dioxide, and mixtures thereof.

Examples of disintegrating agents that can be used in the present invention include corn starch, croscarmelose sodium, crospovidone (polyplasdone XL-10), sodium starch glycolate (EXPLOTAB® or PRIMOJEL®) or any combination of the foregoing.

An embodiment of an immediate release dosage form that may be used in the present invention, especially for those that have trouble swallowing tablets or capsules, is a rapidly or orally disintegrating tablet. The rapidly or orally disintegrating tablets are designed to dissolve within 5 minutes or less when placed into an aqueous media such as a patient's mouth. Rapidly or orally disintegrating dosage forms are generally described in U.S. Patent Nos. 4,371,516;
5,178,878; 5,298,261; 5,464,632; 5,587,180; 5,720,974; 5,807,576; 5,866,163; 5,869,098;
6,024,981; 6,048,541; 6,149,938 and 6,316,029, which are incorporated by reference.

Another form of an immediate dosage form that may be used in the present invention, especially for those that have trouble swallowing tablets or capsules, are liquid dosage forms such as syrups, solutions or suspensions. The syrups, solutions or suspensions of the present invention typically contain pharmaceutically acceptable excipients such as a liquid carrier, i.e., water and/or alcohol, flavoring agents, stabilizing agents, coloring agents, thickening agents or mixtures thereof. The pharmaceutically acceptable excipients employed in the syrups, solutions or suspensions of the present invention are described in Remington, the Science and Practice of Pharmacy, 21st Ed. (2006), pp. 745-775, published by Lippincott Williams & Wilkins; United States Pharmacopeia 27 (2004), pp. 2809-2812; and Handbook of Pharmaceutical Excipients, 5th Ed. (2006), published by the Pharmaceutical Press, incorporated by reference and further described below.

Flavoring agents that may be used in the present invention include peppermint, spearmint, wintergreen, cinnamon, coconut, coffee, chocolate, vanilla, menthol, licorice, anise, apricot, caramel, pineapple, strawberry, raspberry, grape, cherry, mixed berry, tropical fruits, mint and mixtures thereof.

Coloring agents that may be employed in the present invention include FD&C-type dyes and lakes, fruit and vegetable extracts, titanium dioxide and mixtures thereof.

Thickening agents that may be used include methylcellulose, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, carbomer, acacia, agar, alginate, carrageenan, gum tragacanth, collagen, carboxypolymethylene, glycercyl monostearate, monostearate, polyvinylpyrrolidone, polyacrylamide and mixtures thereof.
A further form of an immediate release dosage form that may be used in the present invention are packets or sachets containing a cancer drug, antiviral drug or combination thereof and the pharmaceutically acceptable excipients as previously described. The material in the individual packet or sachets are in a powder form that can be easily removed from the packet or sachet and added to food or a liquid, such as water, for administration to the patient.

The immediate release dosage form of the present invention can optionally be coated with a seal coating or an aesthetic coating. The seal coating or aesthetic coating typically is a coating or layer that is soluble or rapidly disintegrating in water and does not materially affect the release of the active ingredients from the tablet core. The most common seal coatings comprise low molecular weight hydroxypropyl methylcellulose or polyvinyl alcohol. Some typical seal coats are described in U.S. Pat. Nos. 4,786,505; 6,099,859 and 5,314,697, which are incorporated herein by reference.

The following table provides an exemplary immediate release composition that can be prepared in accordance with the present invention:

<table>
<thead>
<tr>
<th>Materials</th>
<th>Preferred (% w/w)</th>
<th>Most Preferred (% w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer and Antiviral Drug</td>
<td>40 - 95</td>
<td>50 - 90</td>
</tr>
<tr>
<td>Filler</td>
<td>0 – 60</td>
<td>2 – 50</td>
</tr>
<tr>
<td>Binder</td>
<td>0 – 25</td>
<td>1 – 20</td>
</tr>
<tr>
<td>Lubricant</td>
<td>0 - 5</td>
<td>0.1 – 3</td>
</tr>
</tbody>
</table>

In an embodiment of the present invention, the dosage form is a bilayer tablet containing a cancer drug layer and a separate antiviral drug layer. In another embodiment of the present invention, the dosage form is a trilayer tablet containing a cancer drug layer and two separate antiviral drug layers. The layers of the bilayer or trilayer tablet can be formulated to be immediate release, controlled release, delayed release and combinations thereof. Bilayer and trilayer tablet dosage forms are generally described in U.S. Patent Nos. 6,576,256; 6,706,283;
In an additional embodiment of the present invention, the dosage form is a tablet comprising a cancer drug core and an immediate release antiviral drug coating. In a further embodiment of the present invention, the dosage form is a tablet comprising an antiviral drug core and an immediate release cancer drug coating.

A controlled release dosage form in accordance with the present invention may also be prepared using techniques commonly known in the art. Some of the controlled release dosage forms that are useful in the present invention include, but are not limited, to matrix tablets, osmotic tablets, pellet filled capsules or combinations of the foregoing. The controlled release dosage form in accordance with the present invention should release therapeutically effective amounts of the cancer drug, antiviral drug or combination thereof over a period of 4-24 hours, preferably 8-24 hours, so the dosage form can be administered once or twice daily.

One embodiment of a controlled release dosage form in accordance with the present invention is a matrix tablet. The matrix forming agent can be a hydrophobic material such as a wax, a hydrophilic material such as a hydrogel polymer or a combination of the two. As used herein, a hydrogel polymer is a polymeric material that gels or swells when placed in an aqueous environment. The matrix forming agent will control the release of the cancer and antiviral drugs by diffusion of the drug from the matrix, erosion of the matrix or a combination of diffusion and erosion. The amount of diffusion and erosion will depend upon the materials selected for the formation of the matrix.

Examples of hydrogel forming polymers include hydroxypropyl methylcellulose, carboxymethylcellulose calcium, carboxymethylcellulose sodium, guar gum, hydroxyethyl
cellulose, hydroxypropyl cellulose, methyl cellulose, acrylic polymers and copolymers, sodium alginate, polyethylene oxides and mixtures thereof as described in U.S. Patent Nos. 5,082,668; 4,783,337; 4,612,008 and 4,327,725, which are incorporated by reference herein.

Examples of hydrophobic materials that can be used to form a non-gelling or non-swelling controlled release matrix include beeswax, white wax, emulsifying wax, hydrogenated vegetable oil, hydrogenated castor oil, microcrystalline wax, cetyl alcohol, stearyl alcohol, free wax acids such as stearic acid, esters of wax acids, propylene glycol monostearate, glycerol monostearate, carnauba wax, palm wax, candelilla wax, lignite wax, ozokerite, ceresin wax, lardaceine, China wax and mixtures thereof. Other possible rate controlling excipients useful in the present invention include saturated hydrocarbons having from 25 to 31 carbon atoms, saturated alcohols having from 25 to 31 carbon atoms, saturated monocarboxylic acids having from 25 to 31 carbon atoms, esters obtained from said alcohols and monocarboxylic acids which are described in U.S. Patent No. 6,923,984, incorporated herein by reference.

The controlled release matrix in accordance with the present invention may comprise release controlling excipients such as hydrophilic and hydrophobic matrix polymers and polymeric coatings. Release controlling excipients such as hydrophilic and hydrophobic matrix polymers and polymeric coatings are known in the art and described in Rowe et al., Handbook of Pharmaceutically Acceptable Excipients (4th ed. 2003), which is incorporated herein by reference. A combination of hydrophobic and hydrophilic materials may also be used in preparing a controlled release matrix of the present invention.

The controlled release matrix in accordance with the present invention may further comprise conventional excipients that improve the processing or modify the release
characteristics. Examples of these conventional excipients include fillers, glidants and lubricants described previously.

Additional examples of controlled release matrix dosage forms suitable for use in the present invention are described in U.S. Patent Nos. 4,259,314; 5,451,409; 4,369,172; 4,389,393; 4,983,396; 6,586,005; 6,509,037; 6,312,724; 6,372,252; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 4,710,384; 5,674,533; 5,059,595; 5,591,767; 5,073,543; 5,639,476; 5,354,556 and 5,733,566, which are incorporated herein by reference. In another embodiment, the controlled release dosage form may be a multilayer matrix as described in U.S. Patent Nos. 4,839,177 or 5,422,123, incorporated herein by reference.

The following table provides an exemplary controlled release composition that can be prepared in accordance with the present invention:

<table>
<thead>
<tr>
<th>Materials</th>
<th>Preferred (% w/w)</th>
<th>Most Preferred (% w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer and Antiviral Drug</td>
<td>40-90</td>
<td>50-80</td>
</tr>
<tr>
<td>Rate Controlling Matrix Excipient</td>
<td>1-30</td>
<td>3-20</td>
</tr>
<tr>
<td>Filler</td>
<td>0-25</td>
<td>1-20</td>
</tr>
<tr>
<td>Glidant/Lubricant</td>
<td>0-15</td>
<td>0.1-10</td>
</tr>
</tbody>
</table>

Once the matrix tablet has been formed, it may optionally be seal coated or coated with an aesthetic coating as described above with respect to the immediate release composition.

An immediate release coating comprising the cancer and antiviral drugs can be coated directly onto the controlled release matrix core or applied over the sealed coated controlled release matrix core. The immediate release coating comprises the cancer and antiviral drugs and a film forming material or binder and, optionally, other conventional additives such as lubricants, fillers and antiadherents.
The immediate release coating may be applied by any conventional technique such as pan coating or spray coating. In an embodiment of the present invention, the immediate release coating is applied by spraying an aqueous solution or suspension over a pan containing the matrix cores. The film forming material or binder employed in the immediate release coating is preferably a water soluble or rapidly dispersing material such as a low molecular weight hydroxypropyl methylcellulose or povidone.

Another embodiment of the controlled release dosage form in accordance with the present invention is an osmotic tablet. The osmotic tablet may comprise: a core containing a therapeutic amount of the cancer and antiviral drugs, a semi permeable membrane surrounding the core, and a passageway in the semi permeable membrane for release of the drugs.

The core of the osmotic tablet can be prepared with or without a gelling or swelling polymer. The core of the osmotic tablet can be a homogenous blend of the cancer and antiviral drugs and pharmaceutical excipients as described in U.S. Patent No. 5,654,005 or a multilayered structure comprising a drug composition and a push composition as described in U.S. Patent No. 4,612,008 and 4,873,337. The aforementioned patents are incorporated herein by reference.

The osmotic core can optionally be seal coated prior to the application of the semi permeable membrane. The semi permeable membrane should be permeable to the passage of an external fluid such as water or aqueous biological fluids and should be impermeable to the passage of the active ingredients in the osmotic core. Materials that are useful in forming the semi permeable membranes are ethylcellulose, cellulose esters, cellulose diesters, cellulose triesters, cellulose ethers, cellulose ester-ether, cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose acetate propionate and cellulose acetate butyrate. Other suitable polymers are described in U.S. Patent Nos.
3,845,770; 3,916,899; 4,008,719; 4,036,228 and 4,612,008, which are incorporated herein by reference. A preferred semi permeable membrane material is cellulose acetate comprising an acetyl content of 39.3% to 40.3%, and is commercially available from Eastman Fine Chemicals.

In an alternative embodiment, the semipermeable membrane can include one of the above-described polymers and a flux-enhancing agent. The flux-enhancing agent can increase the volume of fluid imbibed into the core to enable the composition to dispense substantially all of the active ingredients through the passageway and/or the pores created in the membrane by the dissolution of the flux-enhancing agent. The flux-enhancing agent can be a water-soluble material or an enteric material. Examples of the preferred materials that are useful as flux enhancers are sodium chloride, potassium chloride, sucrose, sorbitol, mannitol, polyethylene glycol (PEG), propylene glycol, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, polyvinyl alcohols, methacrylic acid copolymers, poloxamers (such as LUTROL F68, LUTROL F127, LUTROL F108, which are commercially available from BASF) and mixtures thereof. A preferred flux enhancer is PEG 400.

The flux-enhancing agent comprises approximately 0% to about 40% of the total weight of the membrane coating, most preferably about 2% to about 20% of the total weight of the membrane coating. The flux-enhancing agent dissolves or leaches from the semipermeable membrane to form paths in the semipermeable membrane which enables fluid to enter the osmotic core and dissolve the cancer and antiviral drugs.

The semipermeable membrane may also be formed using a commonly known excipient such as a plasticizer. Some commonly known plasticizers include adipate, azelate, enzoate, citrate, stearate, isoebucate, sebacate, triethyl citrate, tri-n-butyl citrate, acetyl tri-n-butyl citrate,
citric acid esters, and those described in the Encyclopedia of Polymer Science and Technology, Vol. 10 (1969), published by John Wiley & Sons. The preferred plasticizers are triacetin, acetylated monoglyceride, grape seed oil, olive oil, sesame oil, acetyltributylcitrate, acetyltriethylcitrate, glycerin sorbitol, diethyloxalate, diethylmalate, diethylfumarate, dibutylsuccinate, diethylmalonate, dioctylphthalate, dibutylsebacate, triethylcitrate, tributylcitrate, glyceroltributyrate and combinations thereof. Depending on the particular plasticizer, amounts from about 0% to about 25%, and preferably about 2% to about 15%, of the plasticizer can be used based upon the total weight of the membrane coating.

Generally, the membrane coating around the core will comprise from about 1% to about 5%, and preferably about 2% to about 3%, based upon the total weight of the core and coating.

In a preferred embodiment, the membrane coating surrounding the core further comprises a passageway that will allow for controlled release of the drug from the core. As used herein, the term "passageway" includes an aperture, orifice, bore, hole, weakened area or an erodible element such as a gelatin plug that erodes to form an osmotic passageway for the release of the active ingredients from the dosage form. Passageways used in accordance with the subject invention are well known and are described in U.S. Patent Nos. 3,845,770; 3,916,899; 4,034,758; 4,077,407; 4,783,337 and 5,071,607, which are incorporated herein by reference.

An immediate release coating(s) may be applied to the semipermeable membrane. The immediate release coatings are described above and may be applied by, but would not be limited to, the processes selected from the group consisting of drug layering, lamination or dry compression. In a preferred embodiment, a seal coat is applied to the semi-permeable membrane before the immediate release layer is applied.
Another embodiment of the controlled release dosage form in accordance with the present invention comprises beads, pellets or mini-tablets comprising the active ingredients. The beads, pellets or mini-tablets may be filled into hard or soft gelatin capsules or compressed into a tablet.

The bead, pellets or mini-tablets are prepared by methods commonly known in the art and typically range in size from about 0.1 mm to about 3 mm in diameter. Ideally, the beads or pellets are about 0.2 to about 1 mm in diameter and the mini-tablets are about 0.5 to about 2.5 mm in diameter.

Active or immediate release beads or pellets are prepared by layering a composition in accordance with the present invention onto an inert substrate such as a non-pariel seed or a microcrystalline cellulose seed commercially available under the tradename CELPHERE®. Active beads or pellets can also be prepared by preparing a composition in accordance with the present invention and subjecting the composition to extrusion spheronization techniques. The composition should comprise a mixture of a cancer and antiviral drug and at least one additional conventional pharmaceutical excipient such as a binder and/or filler. The mixture of active ingredients and conventional pharmaceutical excipients can also be compressed in mini-tablets. The active or immediate release beads or pellets can be also prepared by the methods described in U.S. Patent Nos. 5,529,791 and 4,984,240, which are incorporated herein by reference.

Once the active or immediate release beads, pellets or mini-tablets are prepared, they may be coated with a release controlling polymer coating. The controlled release coating should comprise a water insoluble, water permeable polymer and, optionally, a water or acid soluble channeling agent. The controlled release coating may also comprise a lubricating or dusting agent and, optionally, a surfactant.
Suitable water insoluble, water permeable polymers are ethylcellulose, cellulose acetate and polyacrylates or mixtures thereof. Additional water insoluble polymers are described in U.S. Patent No. 5,002,776, which is incorporated herein by reference.

One embodiment of the controlled release bead, pellet or mini-tablet dosage form of the present invention employs a water insoluble, water permeable polymer coating such as a polymethacrylate ester copolymer, preferably a poly(ethylacrylate methylmethacrylate) copolymer which is commercially available from Rohm Pharma under the tradename EUDRAGIT NE 30D.

The channeling agent employed in the bead, pellet or mini-tablet coating can be any type of water or acid soluble pharmaceutically acceptable substance commonly known in the art such as polyvinyl pyrrolidone, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, sucrose or any combination of the foregoing. The preferred channeling agent is a water or acid soluble polymer such as a low viscosity hydroxypropyl methylcellulose.

Suitable surfactants that may optionally be used in the controlled release coating for the beads, pellets or mini-tablets are sodium lauryl sulfate, sodium taurocholate or a polysorbate.

The controlled release coating can be applied to the active beads, pellets or mini-tablets by any means commonly known in the industry such as a rotary granulator, pan coater or a fluidized bed coater.

Once the bead, pellets or mini-tablets are coated they may be dusted with a suitable lubricant such as talc, magnesium stearate, silicon dioxide, kaolin or a mixture of the foregoing. The lubricant will prevent the beads, pellets or mini-tablets from sticking to one another during processing.
In one embodiment of the present invention, the active or immediate release beads, pellets or mini-tablets comprising the cancer and antiviral drug are prepared. A portion of the active or immediate release beads, pellets or mini-tablets are then subsequently coated with a controlled release coating. Various blends of the active and controlled release coated beads, pellets or mini-tablets are blended and filled into hard gelatin capsules. For example, a blend of 20-50% active beads and 80-50% controlled release beads are filled into a hard gelatin capsule to prepare a once-a-day capsule dosage form in accordance with the present invention.

A delayed release dosage form in accordance with the present invention may also be prepared by first preparing an immediate release tablet core, a controlled release matrix core or active bead, pellet or mini-tablet core as described above. The cores are then coated with an enteric or pH sensitive coating using techniques commonly known in the art.

The enteric or pH dependent coating material useful in preparing a delayed release coating include zein, shellac, methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, cellulose acetate trimellitate, polyvinyl acetate phthalate or mixtures thereof.

The delayed release coating should be applied so that the cancer and antiviral drugs present in the core are released only after the composition has passed through the stomach. To insure that the cancer and antiviral drugs present in the core are not released until the composition has left the stomach, the delayed release coating should be designed to dissolve at a pH greater than 4.5, preferably greater than 5.5 and most preferably greater than a pH of 6.

The delayed release coating may also comprise plasticizers and other conventional processing aids as described above.
The delayed release dosage form in accordance with the present invention may also comprise an immediate release component. For example, in the case of a delayed release tablet, the enteric or pH dependent coated tablet may be coated with an immediate release layer as described previously. In the case of enteric coated pellets, a blend of enteric coated pellets and immediate release pellets can be blended together and filled into a hard gelatin capsule or compressed into a tablet. The combination of enteric or pH coated compositions and immediate release component will allow the pulsatile delivery of the cancer and antiviral drugs from a single dosage form.

In an additional embodiment of the present invention is a method for treating virus-related liver cancer by administering to a patient suffering from virus-related liver cancer a fixed-dose combination comprising a cancer drug and an antiviral drug wherein the fixed-dose combination is administered by a dosage form as described above. In a further embodiment of the present invention is a method for treating virus-related liver cancer by administering to a patient suffering from virus-related liver cancer a dosage of a cancer drug and a separate dosage of an antiviral drug wherein each dosage is administered by one or more of the dosage forms as described above.

In embodiments of the method of the present invention where the cancer drug and antiviral drug are administered separately, the ratio of dosages of cancer drug to antiviral drug that is administered to a patient on a weekly basis ranges from about 7:1 to about 1:7, preferably 3.5:1 to 1:35 and more preferably 1:1.

In the methods of the present invention, the dosage form(s) may be administered at least once a day without food (at least 1 hour before or 2 hours after a meal). If administered once daily, the dosage form(s) should contain a full daily dosage of the cancer drug and/or antiviral
drug as set forth above. The dosage form(s) may contain less than a fully daily dosage of the
drug and be administered more frequently than once a day, e.g., contain half the full daily dosage
and be administered twice daily.

**EXAMPLES**

The following are provided by way of example only and are not intended to limit the
scope of the present invention.

**Example 1**

An immediate release tablet comprising 200-500 mg sorafenib as a cancer drug and an
antiviral drug selected from the group consisting of 0.1 to 5 mg entecavir, 1 to 100 mg of
adefovir, 50 to 500 mg of lamivudine, 75 to 750 mg of tenofovir, 200 to 800 mg of telbivudine,
100 to 500 mg of boceprevir, 100 to 800 mg of ribavirin and 100 to 600 mg of telaprevir can be
prepared by mixing the following materials and compressing the mixture into a tablet:

<table>
<thead>
<tr>
<th>Material</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>cancer and antiviral drug</td>
<td>50-90 wt%</td>
</tr>
<tr>
<td>filler</td>
<td>10-50 wt%</td>
</tr>
<tr>
<td>binder</td>
<td>1-10 wt%</td>
</tr>
<tr>
<td>lubricant</td>
<td>0.2-5 wt%</td>
</tr>
</tbody>
</table>

**Example 2**

A bilayer immediate release tablet comprising a layer of 200-500 mg sorafenib as a
cancer drug and a separate layer comprising an antiviral drug selected from the group consisting
of 0.1 to 5 mg entecavir, 1 to 100 mg of adefovir, 50 to 500 mg of lamivudine, 75 to 750 mg of
tenofovir, 200 to 800 mg of telbivudine, 100 to 500 mg of boceprevir, 100 to 800 mg of ribavirin
and 100 to 600 mg of telaprevir can be prepared by mixing the following materials separately
and compressing the final mixtures into a single tablet:

<table>
<thead>
<tr>
<th>Mixture 1</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Material</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>cancer and antiviral drug</td>
<td>50-90 wt%</td>
</tr>
<tr>
<td>filler</td>
<td>10-50 wt%</td>
</tr>
<tr>
<td>binder</td>
<td>1-10 wt%</td>
</tr>
<tr>
<td>lubricant</td>
<td>0.2-5 wt%</td>
</tr>
</tbody>
</table>
mixture 2

<table>
<thead>
<tr>
<th>component</th>
<th>weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>cancer drug</td>
<td>50-90</td>
</tr>
<tr>
<td>filler</td>
<td>10-50</td>
</tr>
<tr>
<td>binder</td>
<td>1-10</td>
</tr>
<tr>
<td>lubricant</td>
<td>0.2-5</td>
</tr>
</tbody>
</table>

Example 3

An immediate release coated tablet comprising a core of 200-500 mg sorafenib as a cancer drug and an outer coating layer comprising an antiviral drug selected from the group consisting of 0.1 to 5 mg entecavir, 1 to 100 mg of adefovir, 50 to 500 mg of lamivudine, 75 to 750 mg of tenofovir, 200 to 800 mg of telbivudine, 100 to 500 mg of boceprevir, 100 to 800 mg of ribavirin and 100 to 600 mg of telaprevir can be prepared by mixing the following materials and compressing into a drug core:

<table>
<thead>
<tr>
<th>component</th>
<th>weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>cancer drug</td>
<td>50-90</td>
</tr>
<tr>
<td>filler</td>
<td>10-50</td>
</tr>
<tr>
<td>binder</td>
<td>1-10</td>
</tr>
<tr>
<td>lubricant</td>
<td>0.2-5</td>
</tr>
</tbody>
</table>

followed by spraying the following coating onto the cancer drug core:

<table>
<thead>
<tr>
<th>component</th>
<th>weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>antiviral drug</td>
<td>50-90</td>
</tr>
<tr>
<td>coating agent</td>
<td>10-50</td>
</tr>
<tr>
<td>binder</td>
<td>1-10</td>
</tr>
<tr>
<td>lubricant</td>
<td>0.2-5</td>
</tr>
</tbody>
</table>

Example 4
A controlled release tablet comprising 200-500 mg sorafenib as a cancer drug and an outer coating layer comprising an antiviral drug selected from the group consisting of 0.1 to 5 mg entecavir, 1 to 100 mg of adefovir, 50 to 500 mg of lamivudine, 75 to 750 mg of tenofovir, 200 to 800 mg of telbivudine, 100 to 500 mg of boceprevir, 100 to 800 mg of ribavirin and 100 to 600 mg of telaprevir can be prepared by mixing the following materials and compressing the mixture into a tablet:

<table>
<thead>
<tr>
<th>Material</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>cancer and antiviral drug</td>
<td>25-75 wt%</td>
</tr>
<tr>
<td>rate controlling excipient</td>
<td>1-25 wt%</td>
</tr>
<tr>
<td>filler</td>
<td>0.5-25 wt%</td>
</tr>
<tr>
<td>lubricant/glidant</td>
<td>0-15 wt%</td>
</tr>
</tbody>
</table>

**Example 5**

A controlled release osmotic tablet comprising 200-500 mg sorafenib as a cancer drug and an antiviral drug selected from the group consisting of 0.1 to 5 mg entecavir, 1 to 100 mg of adefovir, 50 to 500 mg of lamivudine, 75 to 750 mg of tenofovir, 200 to 800 mg of telbivudine, 100 to 500 mg of boceprevir, 100 to 800 mg of ribavirin and 100 to 600 mg of telaprevir can be prepared by mixing the following materials and compressing the mixture into a core:

<table>
<thead>
<tr>
<th>Material</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>cancer and antiviral drug</td>
<td>50-90 wt%</td>
</tr>
<tr>
<td>filler</td>
<td>10-50 wt%</td>
</tr>
<tr>
<td>binder</td>
<td>1-10 wt%</td>
</tr>
<tr>
<td>lubricant</td>
<td>0.2-5 wt%</td>
</tr>
</tbody>
</table>

followed by spraying the following semi-permeable membrane coating onto the drug core until the weight of the coating is about 1% to about 5% of the total weight of the tablet:

<table>
<thead>
<tr>
<th>Material</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>coating agent</td>
<td>50-90 wt%</td>
</tr>
<tr>
<td>flux-enhancing agent</td>
<td>2-20 wt%</td>
</tr>
<tr>
<td>plasticizer</td>
<td>1-10 wt%</td>
</tr>
</tbody>
</table>
The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. Thus, for example, in each instance herein, any of the terms "comprising," "consisting essentially of" and "consisting of" may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims.
CLAIMS

1. A dosage form comprising a cancer drug and an antiviral drug.

2. The dosage form of claim 1 wherein the cancer drug is targeted to the liver.

3. The dosage form of claim 2 wherein the cancer drug is sorafenib or a pharmaceutically acceptable salt thereof.

4. The dosage form of claim 1 wherein the antiviral drug is effective against hepatitis viruses.

5. The dosage form of claim 4 wherein the antiviral drug is selected from the group consisting of entecavir, adefovir, lamivudine, tenofovir, telbivudine, boceprevir, ribavirin, telaprevir, pharmaceutically acceptable salts thereof and combinations thereof.

6. The dosage form of claim 1 wherein the cancer drug is present in an amount effective to treat liver cancer and the antiviral drug is present in an amount effective to treat a hepatitis virus.

7. A method of treating virus-related liver cancer comprising the step of administering to a patient a drug combination of a cancer drug and an antiviral drug.

8. The method of claim 7 wherein the cancer drug is targeted to the liver.

9. The method of claim 8 wherein the cancer drug is sorafenib or a pharmaceutically acceptable salt thereof.

10. The method of claim 7 wherein the antiviral drug is effective against hepatitis viruses.

11. The method of claim 10 wherein the antiviral drug is selected from the group consisting of entecavir, adefovir, lamivudine, tenofovir, telbivudine, boceprevir, ribavirin, telaprevir, pharmaceutically acceptable salts thereof and combinations thereof.

12. The method of claim 7 wherein the cancer drug and the antiviral drug are administered in a single dosage form.
13. The method of claim 7 wherein the cancer drug and the antiviral drug are administered in separate dosage forms.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

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)

A61K 9/00, 45/00, 45/06, 3 1/00, 3 1/33, 3 1/395, 3 1/44, 3 1/435, 3 1/40, 3 1/495, 3 1/505, 3 1/513, 3 1/52, 3 1/522, 3 1/519, 3 1/506, 3 1/41, 3 1/4965, 3 1/497, 3 1/4976, 3 1/4978, A61P 3 1/00, 3 1/12, 35/00

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>US 2007/0 173464 A1 (FLAMEL TECHNOLOGIES) 26.07.2007, abstract, p. 3, paragraphs [0041], [0044]</td>
<td>1, 2, 4-6</td>
</tr>
<tr>
<td>Y</td>
<td>A</td>
<td>LP-007799-03 101 1, 03.10.201 1. Instruktsiya po primeneniyu lekarstvennogo preparata «Viread» [online] [Retrieved 06.05.2013] Retrieved from the Internet:<a href="">URL:ht^://grls/rosminzdrav.ru/InstrImgMZ.aspx?idReg=37002&amp;page=1&amp;t=grlsView</a></td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

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

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"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

16 May 2013 (16.05.2013)

Date of mailing of the international search report

04 July 2013 (04.07.20 13)

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Classification of subject matter

International application No.
PCT/US 2013/026730

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A61K 31/522 (2006.01)
A61K 31/52 (2006.01)
A61K 31/506 (2006.01)
A61K 31/40 (2006.01)
A61K 31/4196 (2006.01)
A61K 31/497 (2006.01)
A61P 31/12 (2006.01)
A61P 35/00 (2006.01)