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(54) Title: PHARMACEUTICAL FORMULATION FOR CAMPTOTHECIN ANALOGUES IN GELATIN CAPSULE

(57) Abstract

The invention relates to a stable topotecan pharmaceutical composition in the form of a gelatin capsule. The invention specifically provides a hydrophobic matrix for formulation with topotecan HCl that is dispersed so as to minimize any chemical reaction between the active drug, the excipients and ambient moisture.

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PHARMACEUTICAL FORMULATION FOR CAMPTOTHECIN ANALOGUES IN GELATIN CAPSULE

FIELD OF THE INVENTION

The present invention provides an oral formulation for camptothecin analogues, such as topotecan, in the form of a gelatin capsule. In particular, the invention provides a non-aqueous fill matrix which enables camptothecin analogues such as topotecan HCl to be administered in a stable formulation of gelatin capsules. The formulation of the topotecan gelatin capsules further provides a fill matrix that minimizes diffusion of the topotecan into the capsule shell as well as migration of water from the shell into the matrix.

BACKGROUND OF THE INVENTION

Camptothecin analogues, such as (S)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihyroxy-1H-pyrano [3', 4': 6,7] indolizino [1, 2-b] quinolone-3, 14 (4H, 12H) dione monohydrochloride, commonly known as topotecan hydrochloride, have demonstrated usefulness as both antineoplastic and antiviral therapeutic agents. Topotecan is a semi-synthetic water-soluble analog of camptothecin which is an inhibitor of topoisomerase I. Therapeutic use is now focused on analogues such as topotecan since early clinical trials of (S)-camptothecin (CPT) in the sixties and seventies were discontinued due to the high toxicity and low potency of CPT.

Topotecan, like other camptothecin analogs, stabilizes the covalent complex between topoisomerase I and DNA, resulting in enzyme-linked DNA cleavage and single-strand breaks.

Early clinical studies of topotecan in which it was administered as a continuous infusion parenteral for up to 21 days, were shown to be safe and well tolerated. Subsequent studies performed in dogs demonstrated it to be very active in animal models of cancer when given orally. Subsequent clinical studies have demonstrated that other parenteral dosing regimens are effective in humans. Topotecan HCl for Injection (Hycamtin®, SmithKline Beecham) has been approved as safe and effective by the United States Food and Drug Administration for second

line therapy of refractory ovarian cancer. One drawback of parenteral administration is patient discomfort. Another drawback is that parenteral administration requires the patient to travel to the physician's office resulting in patient inconvenience. Thus, the need has arisen to develop an oral formulation of topotecan that would allow longer dosing regimens, as with continuous infusion, but without the inconvenience or discomfort to the patient.

It has long been known in the pharmaceutical industry that capsules are a convenient form for the oral administration of a variety of active agents. The outer shell of capsules typically have gelatin as the main ingredient and are presented as either hard or soft gelatin capsules. Gelatin capsules are particularly useful as a means of formulating drug substances, providing the advantage of allowing incorporation of the active ingredient in the form of a semi-solid, liquid or paste.

The basic ingredients of the outer shell of gelatin capsules are water and gelatin. The presence of water in the capsule shell, however, has presented a disadvantage in the formulation of a drug such as topotecan, which is soluble in water to an appreciable extent.

Topotecan HCl is hygroscopic and requires moisture protection during manufacture and storage. In addition, topotecan is classified as a Class I cytotoxic agent. As such, any form of leakage from a capsule would present a safety concern. Therefore, formulation as a tablet or powder-filled capsule is not commercially feasible since most manufacturing facilities are not appropriately equipped to handle cytotoxic drugs. Thus, in light of the issues and costs associated with the safe handling of topotecan, it is desirable to formulate it as a dispersion of topotecan HCl filled into hard gelatin capsules. In particular, a thermoplastic (hot-melt) type capsule formulation would result in enhanced stability and minimization of leakage concerns.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were individually and specifically indicated to be incorporated by reference herein as though fully set forth.

SUMMARY OF THE INVENTION

The present invention relates to the discovery of a hydrophobic or lipophilic matrix for formulation of camptothecin analogues such as topotecan HCl wherein the active drug is simply dispersed and not solubilized so as to minimize any chemical reaction between the active drug and the excipients. Although the fill matrix is hydrophobic in character, it melts or disperses at body temperature to allow dissolution of the capsule contents into the gastrointestinal tract. This allows for the desired absorption into the body. Accordingly, the present invention provides gelatin capsules constituting a stable formulation of topotecan that, due to the relatively hydrophobic, non-aqueous nature of the fill matrix, minimizes diffusion of the topotecan into the capsule shell while simultaneously curtailing migration of water from the shell into the matrix. A suitable fill matrix for the present formulation generally comprises two excipients: (1) a diluting matrix; and (2) thickening or dispersing agents, both of which are hydrophobic in nature. The diluting matrix comprises glycerides of fatty acids and polyethylene glycol esters of fatty acids.

DETAILED DESCRIPTION OF THE INVENTION

The stable topotecan formulation of the present invention is comprised of: (1) a diluting matrix; and (2) one or more thickening agents. The formulation may additionally contain dispersing agents or surfactants. Both the diluting matrix and thickeners are hydrophobic in nature.

The diluting matrix component is comprised of one or more glycerides of fatty acids and polyethylene glycol esters of fatty acids. Suitable fatty acid glycerides for use herein include one or more medium chain (C_8 to C_{12}) fatty acid glycerides. Preferred ones include a mixture of triglycerides of hydrogenated coconut oil or palm kernel oil, commonly known as M grade Wecobee™ (obtained from Stephan, Inc., NJ) or glycerides (e.g. triglycerides) of medium chain (e.g. C_8-C_{10}) fatty acids (e.g. fractionated C_8-C_{10} coconut fatty acids) commonly known as Miglyol 812™ (obtained from Dynamit Nobel Co.). Additional preferred oily excipients useful as thickeners include mineral oils such as liquid paraffin, solid

paraffins such as petrolatum, fatty alcohols such as cetyl and cetostearyl alcohols, and glycerol esters of fatty acids commonly known as Witepsol™ (obtained from Huls America).

A particularly preferred diluting matrix comprises a mixture of glycerides (e.g. mono, di-and/or tri- glycerides) of long chain (e.g. C_{12}-C_{18}) fatty acids. For example, such a mixture may be selected from the range of products commonly known under the trademark Gelucire® available from Gattefosse Corporation. In general such mixtures have in addition surfactant properties. The Gelucires®, in particular, are available with varying physical characteristics and are identified by their melting point/HLB value, where HLB (hydrophile-lipophile balance) value is a measure of the hydrophobic or hydrophilic nature of the substance. The lower the number, the more hydrophobic the material. In a particularly preferred embodiment, Gelucire® 33/01 is used according to the present invention.

The stable topotecan formulation also preferably contains at least one or more thickening agents. In a preferred embodiment of the invention, the matrix comprises two excipients. The first of which, the thickener or dispersing agent, may constitute from about 2 to 20% (w/w), more preferably from about 5 to 10 % of the filling. The second excipient, the diluting matrix, may then constitute from about 80 to about 95 % (w/w), more preferably from about 90 to 95 % (w/w) of the filling. Thus, a preferred embodiment may comprise glyceryl monostearate and hydrogenated vegetable oil. In a further embodiment the topotecan formulation contains at least one fatty acid glyceride such as Softisan 378 (obtained from Huls America) or glyceryl monostearate. A more preferred embodiment comprises topotecan hydrochloride, glyceryl monostearate and Wecobee™.

The compositions according to the invention may be prepared according to conventional techniques known in the pharmaceutical industry for the manufacture of gelatin capsules. For example, the fill matrix may be prepared by adding the topotecan HCl to a molten homogeneous mixture of the fatty acid glyceride(s) and/or mineral oil(s) or paraffin(s), and dispersing agent(s). This is then followed by thorough mixing and milling. Subsequent encapsulation is then achieved using standard techniques.

The process for preparation of the capsule fill involves the production of topotecan in a homogenous liquid dispersion having a viscosity in the range of 200-500 cps and a drug dispersal uniformity with a relative standard deviation of less then 3% as measured by a content uniformity assay.

In a further embodiment of the invention, a controlled absorption formulation of topotecan may be incorporated into the gelatin capsule and can be prepared by conventional techniques known to those skilled in the art. For example, suitable techniques are disclosed in U.S. Patent Nos. 4,871,548; 5,009,895; 4,389,393; 5,364,620; and 5,002,776; which are incorporated herein by reference. Once the controlled absorption composition is formulated, the composition can be filled into the gelatin capsules.

The pharmaceutical compositions of the invention may be administered to any animal which may experience the beneficial effects of the topotecan formulation of the invention. Foremost among such animals are humans, although the invention is not intended to be so limited. For mammals, including humans, the effective amounts can be administered on the basis of body surface area. The interrelationship of dosages for animals of various sizes, species and humans (based on mg/M^2 of body surface) is described by E.J. Freireich et al., *Cancer Chemother. Rep.*, 50(4):219 (1966). Body surface area may be approximately determined from the height and weight of an individual (see, e.g., *Scientific Tables*, Geigy Pharmaceuticals, Ardsley, N.Y. pp. 537-538 (1970).

The amount of topotecan HCl, in the preferred composition, is preferably in the range of about 0.2 to 5.0 mg, more preferably from about 0.25 to about 3.0 mg per dosage unit, expressed as the weight of free base. If the topotecan is administered with GCSF (granulocyte colony stimulating factor), more topotecan may be administered. For example, with parenteral administration, the m.t.d. (maximum tolerated dose) for topotecan is 2.0 mg/kg; however, when administered with GCSF, the m.t.d. is raised to 2.5 mg/kg. Although the following examples show the use of topotecan HCl, other camptothecin analogues may be used as well. Production of such analogues as well as topotecan may be found in U.S. Application

No. 95/004,758 and WO Patent Application No. 92/05785 (published April 16, 1992), incorporated herein by reference.

Generally, in a thermoplastic or hot-melt formulation the active component is dispersed or solubilized into a melted thermoplastic excipient, filled into capsules as liquid using fluid-filling pumps and allowed to solidify at ambient temperature. Such a formulation is solid at ambient conditions, providing better chemical stability and minimizing leakage problems. As is well known, thermoplastic excipients are selected based on physico-chemical and thermal characteristics, chemical compatibility, and rheological properties. In general, thermoplastic excipients should have a narrow melting temperature range in the region of about 30°C to 70°C and should solidify within about 10-15 minutes at ambient conditions to avoid leakage from capsules after filling and/or during the sealing operation. An added advantage of this dispersion type formulation is that dosage strengths can be changed easily without changing the vehicle composition or capsule size.

The optimal physical stability of the present formulation was determined by heating different concentrations of glyceryl monostearate and Wecobee™ mixtures together to 80°C to obtain a homogenous molten mixture, followed by cooling of the mixture to about 38°C. Wecobee™ (hydrogenated vegetable oil) was selected since it melts at 35°C; this temperature is a desirable target for preparation of a dispersion formulation as well as for physiological reasons. This resulted in a semisolid to solid dispersion, depending upon the level of glyceryl monostearate.

The preferred embodiment of the present invention comprises a matrix of 5% glyceryl monostearate in Wecobee™ which is solid at ambient storage conditions but in molten state at 38-40°C. This lipophilic mixture can be filled as liquid at 40°C and allowed to solidify at room temperature. In addition, the contents of the capsule melt when ingested to release the drug into gastric fluids.

The following Examples illustrate specific formulations and methods for their preparation. These examples are not intended to be a limitation on the scope of the invention in any respect and should not be so construed. In addition, the following examples are encompassed by the claims and their equivalents.

Example 1

A topotecan dispersion containing 5% glyceryl monostearate in Wecobee™ was prepared, filled into hard gelatin capsules and stored at various conditions. The results indicate that this formulation is stable for six months at 5°C and 30°C. however, it does show some potency loss and increased degradation (by percent peak area) at 40°C after six months. As the formulation exists in two different physical states at 30°C and 40°C, the results from 40°C may not be extrapolated to 30°C or lower temperatures.

Since the formulation is oil based, complete dissolution of drug in water or 0.001 N HCl could not be achieved, thus a surfactant was incorporated in the dissolution media. Preliminary experiments suggested that 1% sodium lauryl sulfate (SLS) was required to obtain adequate dissolution. Results showed no change in the dissolution profile at 5°C upon storage.

Based on the preformulation studies, thermal characteristics, chemical stability and safety considerations, a semi-solid matrix formulation containing 5% of glyceryl monostearate in Wecobee™ (hydrogenated vegetable oil) filled into hard gelatin capsules was selected. Wecobee™ is a mixture of triglycerides of hydrogenated coconut or palm kernel oil and has GRAS (generally regarded as safe substance) status as listed in 21 CFR 170.30 (FDA reference). It is also compatible with gelatin capsule shells.

Imwitor 191 (Glyceryl monostearate/palmitate, approx. 90% 1-monoglycerides) is used as emulsifier, dispersing agent, stabilizer and plasticizer in a variety of pharmaceutical, food and cosmetic products. Glyceryl monostearate (Imwitor 191) is compatible with gelatin capsule shells, and is available in NF grade.

Three clinical grade batches (U94223, U94224 and U94225) of topotecan hard gelatin capsules were manufactured. The capsule formulations for 0.25, 0.5 and 1.0 mg of topotecan per capsule are presented in Table 1. The stability of these batches was monitored and the stability data is summarized in Tables 2 to 4. The data indicates that there is no significant potency loss at 5°C and 30°C for up to 12 months. There was also no change in the level of degradation products at 5°C,

however, there was increase in degradation products at 30°C. At present, the recommended storage condition for the liquid-filled hard gelatin capsule is 2-8°C (refrigeration condition) based on the available stability data.

The process for formulation was to prepare the capsule fill by dispersing topotecan in a molten mixture of Imwitor 191/Wecobee™ using a high speed dispenser and media mill. This resulted in a homogenous liquid dispersion having the desired viscosity and drug dispersal uniformity.

A number of different mixers/dispersers were also evaluated. Satisfactory results were obtained using a high speed rotor/stator mixer for preliminary drug dispersion. For production, the combination of a high-shear mixer and a low speed mixing blade produces a uniform, homogenous dispersion. As the scale of production increases, the size of the equipment may typically be scaled up accordingly, with identical mechanical mixing properties.

The ball mill was used for size reduction of fine solid particles and disruption of agglomerates. A modified version of the ball mill, a horizontal media mill from Premier Inc., was evaluated for preparation of topotecan capsule fill dispersion. A horizontal grinding chamber with grinding beads ensures a uniform distribution of the grinding media throughout the chamber. A variable speed pump moves milling material (e.g., premixed suspension) through the chamber. The milling material is subject to both intense impact and high shear created by the grinding media, which quickly and efficiently reduces particle size. The grinding chamber is equipped with a water jacketed cooling/heating system, allowing the operator to accurately control the temperature of the milling process. For pharmaceutical processes, a ceramic grinding chamber and ceramic beads are recommended to avoid suspension contamination by metal particles.

Jacketed blending vessels with an effective temperature control system, both for heating and cooling, and adequate stirring capacity are required for preparing topotecan capsule fill suspension. Mixers should contain a high-speed rotor/static head, and a low speed stirring blade, as indicated above. Construction should be such that they may be covered so as to protect the product from light during

production. All product contact surfaces should preferably be constructed of 316L, electropolished stainless steel, or an equivalent that is not susceptible to corrosion.

Several capsule filling and sealing machines are available and should be chosen so as to be able to deliver liquids with a fill weight RSD (relative standard deviation) of 5% or less. The filling hopper should be temperature controlled in order to maintain a fluid material throughout the filling process. Preferably, the capsule filler may be outfitted with a cooling station, to facilitate solidification of semi-solid product. Sealing equipment should deliver a double-band (for safety), and have a running capacity similar to that of the selected capsule filler.

The type and size of the production equipment such as compounding vessels, receiving vessels and horizontal bead mills is dependent on batch size and should be selected based on manufacturing needs and economical analysis.

Preparation of Topotecan Bulk Suspension

1. Add the exact quantity of Imwitor 191 required for the batch into a temperature controlled compounding vessel.

2. Heat the product to 70-80°C and stir gently until a clear, smooth fluid is obtained.

3. Weigh out the exact quantity of Wecobee™ required for the batch.

4. With gentle mixing, add the preweighed amount of Wecobee™ into a temperature controlled compounding vessel and continue mixing until homogeneous mixture is obtained. It is important to have both the Inwitor 191 and Wecobee™ completely melted at this point prior to continuing. Reduce the temperature to about 37-40°C.

5. Weigh out the exact amount of the active drug substance required for the batch.

6. Add the active drug substance to the mixture while blending at a ¼ speed using rotor/stator head. Blend the ingredients for 20 minutes at ½ speed using both heads. Maintain the temperature at about 37-40°C. Heat or cool as needed.

7. Set up the horizontal supermill. Charge grinding chamber with 1.0-1.25 mm ceramic beads. The beads or powders may be obtained from SEPR Co. Preheat the mill chamber to about 37-40°C.

8. Pass the premixed suspension through the horizontal supermill twice. Collect each pass into a temperature controlled processing vessel. Maintain the product temperature at about 37-40°C. Heat or cool as needed.

9. Degas the suspension if necessary. Maintain the product temperature at about 37-40°C. Heat or cool as needed.

10. Using a suitable sampling device, take samples of the suspension from different sites in the vessel for in-process content uniformity test.

Capsule Filling

1. Fill the capsules with the prepared suspension to meet target and specification limits. Maintain constant gentle stirring during the filling process. Avoid air entrapment. Set each filling hopper temperature control to maintain a product temperature of not more than 40°C. Set each filling pump temperature control to suit product fill.

2. Check and record individual capsule weights at appropriate time intervals.

3. Collect filled capsules onto labeled trays and allow to cool. Remove any damaged capsules.

Capsule Sealing

1. Prepare capsule sealing gelatin mass.

2. Load filled capsules into capsule sealing carriers of capsule sealing machine.

3. Seal filled capsules by applying gelatin band with capsule sealing machine.

4. Collect banded capsules onto labeled trays and store overnight at room temperature to dry gelatin band.

5. Sort capsule visually, transferring good capsules for packing and rejecting damaged capsules.

Table 1. Topotecan Liquid Filled Hard Gelatin Formulation [per capsule]

1. Capsule Strength 0.25 mg (Lot U94223)

Topotecan	0.255 mg
Imwitor 191	13.750 mg
Wecobee™	260.995 mg
Total:	275.000 mg

2. Capsule Strength 0.5 mg (Lot U94224)

Topotecan	0.51 mg
Imwitor 191	13.75 mg
Wecobee™	260.74 mg
Total:	275.00 mg

3. Capsule Strength 1.0 mg (Lot U94225)

Topotecan	1.02 mg
Imwitor 191	13.75 mg
Wecobee™	260.23 mg
Total:	275.00 mg

Table 2. Stability Data for 0.25 mg Topotecan Liquid Filled Hard Gelatin Capsules, Lot U94223

Product Stability Data		
Product Name	Topotecan	
Dosage Form	Liquid filled hard gelatin capsule	
Strength	0.25 mg per capsule (as free base)	
Pkg. Components Count	40 cc amber glass bottle; 33 mm white plastic cap, CR; cotton coil 25 capsules/bottle	

Storage Condition	Age months	Assay (mg/capsule) (as free base)	Dissolution (% Dissolved @ 45 min)	General Appearance
Initial	00	0.248	103	Yellowish white capsule
5°C	01	0.250	103	same as initial
	06	0.254	106	same as initial
	09	0.249	102	same as initial
	12	0.243	100	same as initial
	18	0.250	101	same as initial
	24	0.246	99	same as initial
	36			
30°C	03	0.246	101	same as initial
	06	0.251	ND	same as initial
	09	0.244	ND	same as initial
	12	0.239	99	same as initial
	24	0.234	ND	same as initial
	36			
Limits:		0.225 to 0.275 mg/capsule	Q=75% @ 45 min	A white to pale yellow capsule

ND = not determined

Table 3. Stability Data for 0.5 mg Topotecan Liquid Filled Hard Gelatin Capsules, Lot U94224

Product Stability Data		
Product Name	Topotecan	
Dosage Form	Liquid filled hard gelatin capsule	
Strength	0.5 mg per capsule (as free base)	
Pkg. Components Count	40 cc amber glass bottle; 33 mm white plastic cap, CR; cotton coil 25 capsules/bottle	

Storage Condition	Age months	Assay (mg/capsule) (as free base)	Dissolution (% Dissolved @ 45 min)	General Appearance
Initial	00	0.51	105	Moderate Pink capsule
5°C	01	0.51	103	same as initial
	06	0.52	107	same as initial
	09	0.48	105	same as initial
	12	0.49	104	same as initial
	24	0.51	105	same as initial
	36			
30°C	03	0.50	102	same as initial
	06	0.52	ND	same as initial
	09	0.50	ND	same as initial
	12	0.49	100	same as initial
	24	0.48	ND	same as initial
	36			
Limits:		0.45 to 0.55 mg/capsule	Q=75% @ 45 min	A pink capsule

ND = not determined

Table 4. Stability Data for 1.0 mg Topotecan Liquid Filled Hard Gelatin Capsules, Lot U94225

Product Stability Data		
Product Name	Topotecan	
Dosage Form	Liquid filled hard gelatin capsule	
Strength	1.0 mg per capsule (as free base)	
Pkg. Components Count	40 cc amber glass bottle; 33 mm white plastic cap, CR; cotton coil 25 capsules/bottle	

Storage Condition	Age months	Assay (mg/capsule) (as free base)	Dissolution (% Dissolved @ 45 min)	General Appearance
Initial	00	0.99	103	Moderate yellow capsule
5°C	01	1.01	102	same as initial
	06	1.01	103	same as initial
	09	0.99	102	same as initial
	12	0.98	100	same as initial
	18	0.99	100	light yellow capsule
	24	0.99	102	same as initial
	36			
30°C	03	0.98	101	same as initial
	06	1.00	ND	same as initial
	09	0.98	ND	same as initial
	12	0.96	98	same as initial
	24	0.96	ND	same as initial
	36			
Limits:		0.90 to 1.10 mg/capsule	Q=75% @ 45 min	A yellow capsule

ND = not determined

Example 2

Formula A	mg per capsule For 0.25 mg capsule	mg per capsule For 1 mg capsule
Topotecan hydrochloride	0.25 mg*	1 mg*
Glyceryl monostearate	13.75 mg	13.75 mg
Hydrogenated vegetable oil	261 mg	260.25 mg
Fill weight per capsule	275 mg	275 mg

* as anhydrous free base

Formula B	mg per capsule For 0.25 mg capsule	mg per capsule For 1 mg capsule
Topotecan hydrochloride	0.25 mg*	1 mg*
Glyceryl monostearate	13.75 mg	13.75 mg
Gelucire® 33/01	261 mg	260.25 mg
Fill weight per capsule	275 mg	275 mg

* as anhydrous free base

The required quantities of glyceryl monostearate and hydrogenated vegetable oil (Formula A) or Gelucire® (Formula B) were added to a heated vessel, and the contents stirred until both excipients had melted and the mixture was clear. To a small portion of this molten mixture, topotecan hydrochloride was added, mixed and poured back to a heated vessel. A mixer was lowered into the vessel and the contents mixed for about 30 minutes. The resulting mixture was milled using a suitable milling apparatus to ensure that the powder was adequately wetted and that no aggregates remained. The filling was subsequently encapsulated to give hard gelatin capsules containing 0.25 mg or 1 mg topotecan HCl (as free base) per

capsule as required. The capsules were sealed with clear gelatin using standard equipment.

Example 3

Formula C	mg per capsule For 0.25 mg capsule	mg per capsule For 1 mg capsule
Topotecan hydrochloride	0.25 mg*	1 mg*
Softisan 378	120 mg	120 mg
Miglyol 812	79.75 mg	79 mg
Fill weight per capsule	200 mg	200 mg

* as anhydrous free base

The Miglyol 812 and Softisan 378 were mixed to give a homogeneous mixture. While this was being stirred, the topotecan hydrochloride was added slowly. The resulting homogeneous mixture was milled using a suitable apparatus, and subsequently encapsulated to give hard gelatin capsules containing 0.25 mg or 1 mg topotecan per capsule.

Based on example formula C, the fill matrix may also be prepared such that one excipient (Softisan 378 obtained from Huls of America, Inc.) may constitute for example 50% to 70% (w/w), more preferably 60% (w/w), of the filling. The second excipient (e.g., Miglyol™ 812, obtained from Dynamit Nobel Co.), may constitute for example 30% to 50% (w/w), more preferably 40% (w/w) of the filling.

What is Claimed:

1. A pharmaceutical composition suitable for use as a filling for gelatin capsules comprising an effective amount of a camptothecin analogue, or a physiologically acceptable salt thereof, and matrix consisting essentially of a diluting matrix and one or more thickening agents.

2. A pharmaceutical composition suitable for use as a filling for gelatin capsules comprising an effective amount of topotecan, or a physiologically acceptable salt thereof, and a matrix consisting essentially of a diluting matrix and one or more thickening agents.

3. A pharmaceutical composition according to claim 1, in which said diluting matrix comprises at least one dispersing agent or surfactant.

4. A pharmaceutical composition according to claim 3, wherein said diluting matrix further comprises one or more fatty acids.

5. A pharmaceutical composition of claim 4, wherein said fatty acid is a glyceride or polyethylene glycol ester.

6. A pharmaceutical composition of claim 4, wherein said fatty acid is a glyceride.

7. The pharmaceutical composition of claim 6, wherein said fatty acid glyceride comprises one or more medium chain fatty acid glycerides.

8. The pharmaceutical composition of claim 1, wherein said thickening agent is selected from the following: mineral oil, solid paraffin, fatty alcohol and glycerol esters of fatty acids.

9. The pharmaceutical composition of claim 6, wherein said fatty acid glycerides comprise one or more long chain fatty acids.

10. The pharmaceutical composition of claim 4, wherein said diluting matrix contains a fatty acid as a surfactant.

11. The pharmaceutical composition of claim 1, wherein said gelatin capsule is a soft gelatin capsule.

12. The pharmaceutical composition of claim 1, further comprising a controlled release component.

13. The pharmaceutical composition of claim 11, wherein said controlled release component comprises a rapid release component and a delayed release component.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/15908

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 9/64
US CL :424/456

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/456

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,028,432 A (CHOPRA et al.) 02 July 1991 (02.07.91) see entire document.	1-13
Y	US 5,633,260 (HAUSHEER et al.) 27 May 1997 (27.05.97) see entire document.	1-13
A,P	US 5,677,286 A (SHULL et al.) 14 October 1997 (14.10.97) see entire document.	1-13
A	US 5,225,404 A (GIOVANNELLA et al.) 06 July 1993 (06.07.93) see entire document.	1-13

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

*	Special categories of cited documents:	"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
"A"	document defining the general state of the art which is not considered to be of particular relevance	"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
"E"	earlier document published on or after the international filing date	"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
"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)	"&"	document member of the same patent family
"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		

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