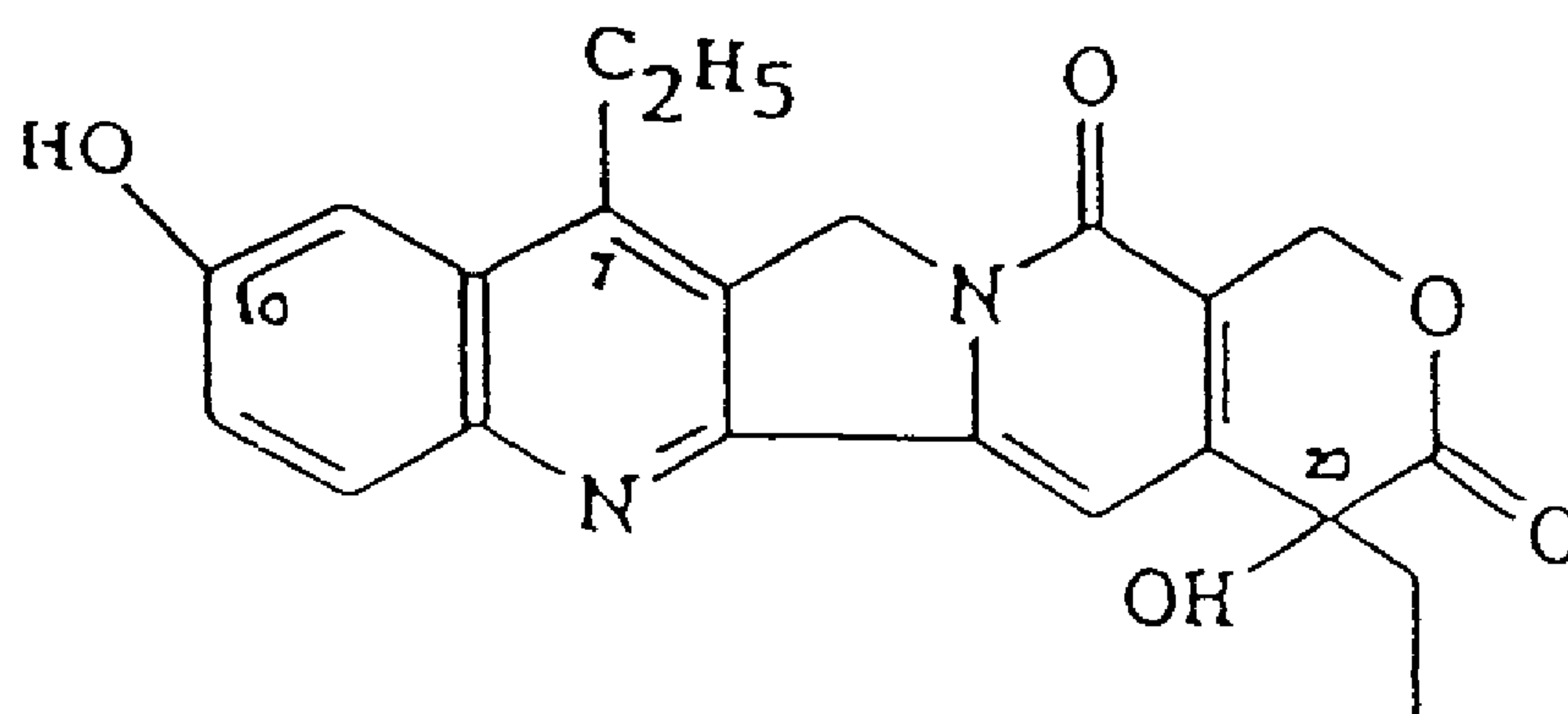




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(54) Titre : FORMULATION STABLE A LA LACTONE DE LA 10-HYDROXY 7-ETHYLE CAMPTOTHECINE  
 (54) Title: LACTONE STABLE FORMULATION OF 10-HYDROXY 7-ETHYL CAMPTOTHECIN



(1a)

(57) Abrégé/Abstract:

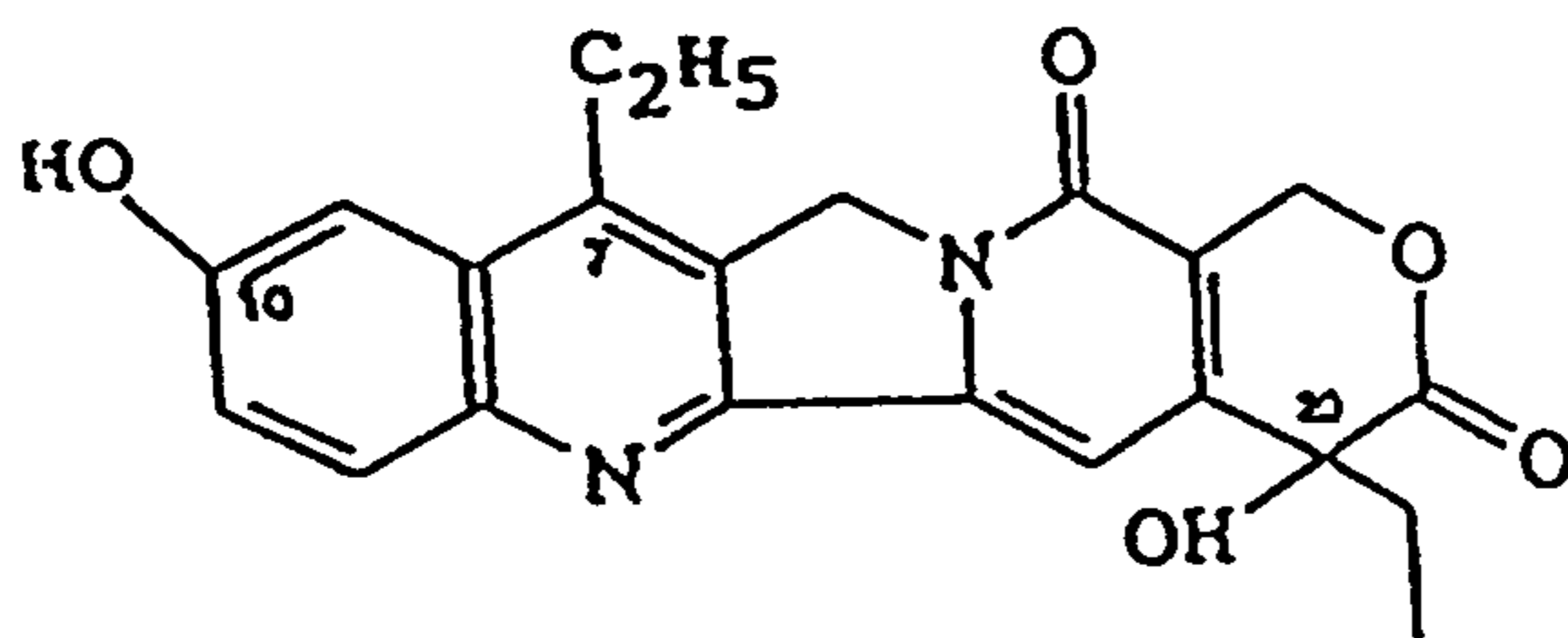
10-Hydroxy 7-ethyl camptothecin (HECPT), an active metabolite of the camptothecin analog CPT-11, is poorly soluble in water. Because of its poor solubility, HECPT has not been directly administered by parenteral or oral routes in human patients for the purpose of inhibiting the growth of tumors. The invention provides a pharmaceutically acceptable formulation in the form of an acidic solution or suspension comprising (1) HECPT, preponderantly in the desired lactone form (1a) and (2) dimethylisorbide or dimethylacetamide.



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(54) Title: LACTONE STABLE FORMULATION OF 10-HYDROXY 7-ETHYL CAMPTOTHECIN



(1a)

## (57) Abstract

10-Hydroxy 7-ethyl camptothecin (HECPT), an active metabolite of the camptothecin analog CPT-11, is poorly soluble in water. Because of its poor solubility, HECPT has not been directly administered by parenteral or oral routes in human patients for the purpose of inhibiting the growth of tumors. The invention provides a pharmaceutically acceptable formulation in the form of an acidic solution or suspension comprising (1) HECPT, preponderantly in the desired lactone form (1a) and (2) dimethylisorbide or dimethylacetamide.

LACTONE STABLE FORMULATION OF  
10-HYDROXY 7-ETHYL CAMPTOTHECIN

BACKGROUND OF THE INVENTION

5 1. FIELD OF THE INVENTION

10 10-hydroxy 7-ethyl camptothecin ("HECPT") is an active metabolite of the camptothecin analog CPT-11, which is undergoing trials as an anti-cancer drug. HECPT is also poorly soluble in water. Because of its poor water solubility, HECPT has not been directly administered by parenteral or oral routes in human subjects for the purpose of inhibiting the growth of cancer cells. This invention overcomes these limitations and claims novel pharmaceutically acceptable formulations of HECPT, and antitumor compositions comprising them, both per se and for use in human anti-cancer therapy.

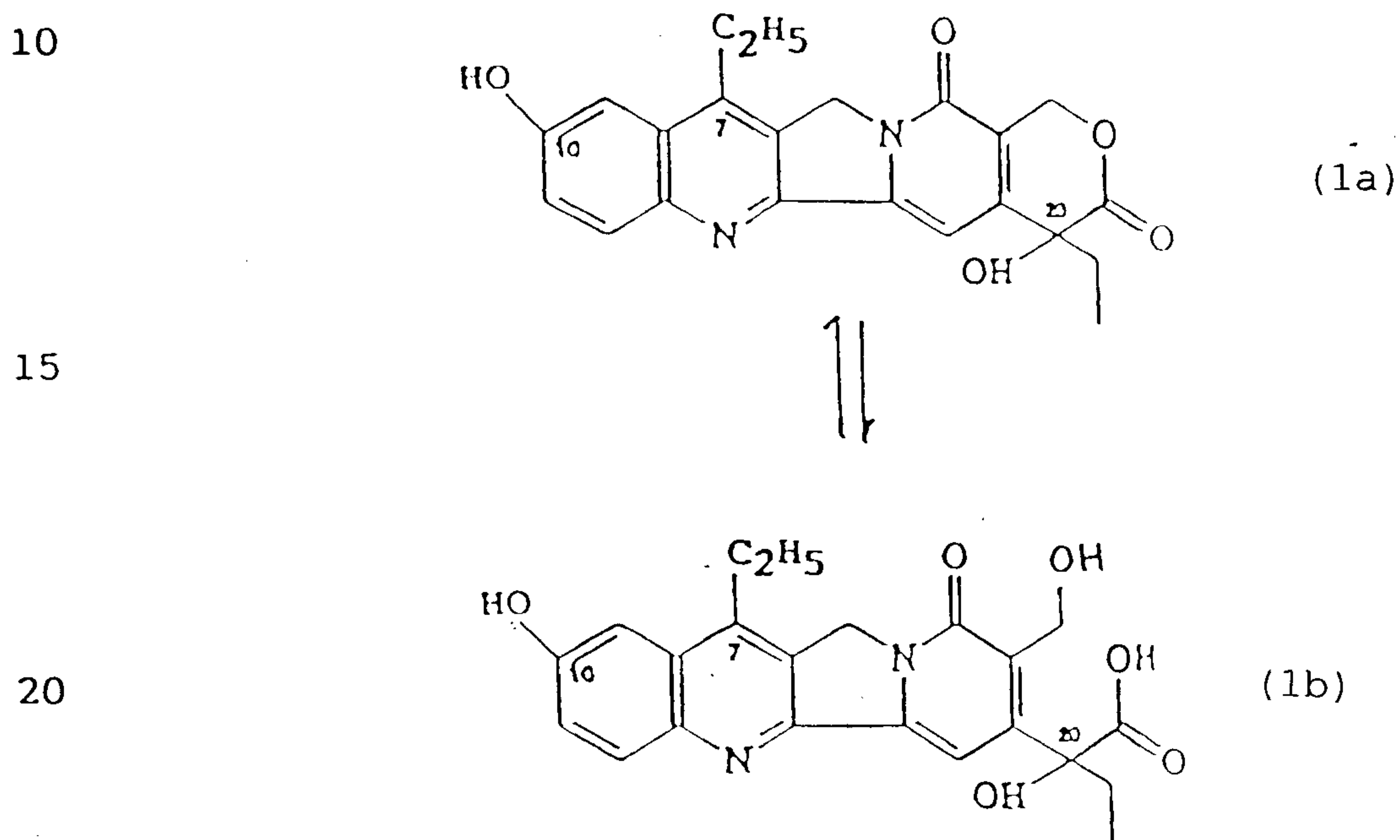
15 2. DESCRIPTION OF THE RELATED ART

20 Metabolic conversion of CPT-11 (a water soluble derivative of camptothecin) to its active metabolite 10-hydroxy 7-ethyl camptothecin (HECPT) varies from patient to patient and limits the utility of CPT-11 in achieving the highest plasma concentrations of HECPT which can be tolerated by the patient. HECPT's poor solubility in water has previously made the direct administration of HECPT impractical for the treatment of cancer. The conversion of CPT-11 to HECPT involves a putative carboxyl esterase enzyme, which is believed to be mainly responsible for the metabolic production of HECPT from CPT-11. Human lung cancer cell lines have been observed to convert less CPT-11 to HECPT than normal cells. The cancer cells' decreased metabolic conversion represents a form of resistance to CPT-11 and limits the utility of CPT-11 in terms of reliably and safely achieving adequate plasma concentrations of HECPT to inhibit the growth of cancer cells in humans.

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HECPT exists in two forms which are in equilibrium in vivo, namely a lactone ring form (1a) and an open, carboxylate form (1b). These isomeric forms are interconvertible: a reversible pH-dependent hydrolysis converts the lactone ring form, produced in acid conditions, to the open, carboxylate form produced in alkaline conditions. The equilibrium is shown below:



25 HECPT is considered to derive its activity by inhibiting the enzyme topoisomerase I, which is involved in DNA replication: it relieves the torsional strain introduced ahead of the moving replication fork. Only the lactone ring form inhibits topoisomerase I. See

30 M.L. Rothenberg et al., Journal of Chemical Oncology, 11, 2194 -2204 (November 1993).

It has been a problem that HECPT has been considered unsuitable for direct clinical use because it is poorly soluble in water.

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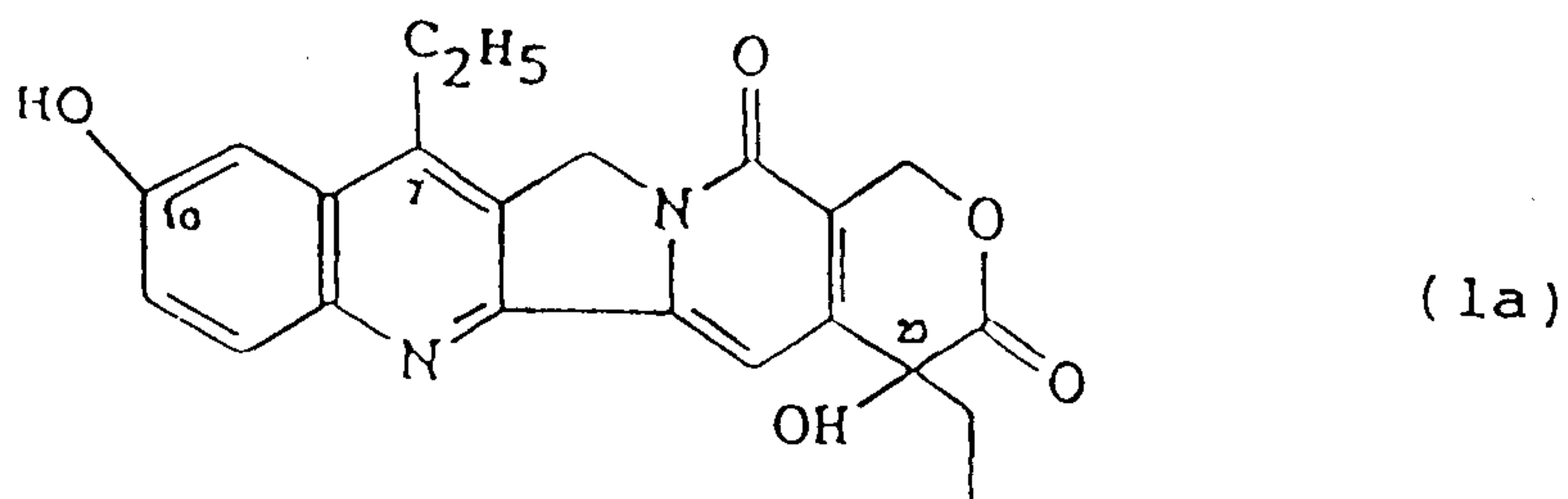
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SUMMARY OF THE INVENTION

This invention solves this problem by providing a stabilized formulation of lactone form HECPT, hereinafter called "lactone stable HECPT" for brevity.

The formulation of the invention is a solution of suspension comprising (1) HECPT, (2) dimethylisosorbide (DMI) or dimethylacetamide (DMA) and (3) a pharmaceutically acceptable acid.

In accordance with one embodiment of the present invention there is provided a pharmaceutically acceptable formulation, in the form of an acidic solution or suspension, comprising: (1) 10-hydroxy 7-ethyl camptothecin, the solution of suspension being sufficiently acidic to cause more than 50 mole % thereof to be in the lactone form (1a):



characterized in that it further comprises: (2) dimethyl-isosorbide or dimethylacetamide.

Several schedules and various dosages produce sufficient levels of lactone stable HECPT to yield beneficial antitumor effects in humans. The effective levels of HECPT are reasonably safe in terms of the incidence and severity of specific side effects that may occur with administration and are acceptable within standard medical practice for patients undergoing treatment for cancer.

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Direct administration of HECPT is likely to offer several important clinical advantages over administration of CPT-11. For example:

- 5 1. direct administration of HECPT allows the clinician to tailor the administration of the active cytotoxic species (lactone stable HECPT) to suit the patient's tolerance:
2. direct administration of HECPT overcomes interpatient variability which may be due to polymorphism of key  
10 enzyme(s) in the metabolism of CPT-11 to HECPT; and
3. clinicians can more consistently optimize the drug dosage and schedule to achieve the maximum tolerated dose of HECPT (the active species) which is likely to lead to the most beneficial clinical anti-cancer effect.

15       Regarding the clinical utility of HECPT for the treatment of human cancer, this invention provides the following:

1. lactone stable HECPT for administration to patients with cancer;

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2. solutions of lactone stable HECPT;
3. antitumor compositions comprising lactone stable HECPT;
4. lactone stable HECPT for parenteral administration;
- 5 5. lactone stable HECPT for administration according to pharmacologic schedules for achieving the maximum tolerated dose with acceptable clinical toxicity observed in standard clinical practice of cancer treatment;
- 10 6. lactone stable HECPT for oral administration;
7. lactone stable HECPT for the treatment of localized complications of cancer by direct administration via instillation into various body cavities.

#### DESCRIPTION OF THE PREFERRED EMBODIMENTS

15 Dimethylisosorbide (DMI) has been used as solvent for muscle relaxants (U.S. Pat. No. 3,699,230), tetracyclines (U.S. Pat. No. 3,219,529), aspirin (U.S. Pat. No. 4, 228,162), and steroids (U.S. Pat. No. 4,082,881). Dimethylacetamide (DMA) has been proposed as a solvent  
20 for 5-azacytosine arabinoside (ara-c) and 5-azacytidine at pH 7.0 to 8.3: see U.S. Patent 4,684,630 (Repta). DMI and DMA have very good toxicity profiles and are miscible with ethanol, propylene glycol, isopropyl myristate, water, diethyl ether, corn oil, acetone,  
25 cottonseed oil, and the like.

The formulations of the invention are solutions or suspensions. Suspensions will normally be apparent solutions, as appears to the naked eye. They will be liquids, for the purpose of convenient pharmaceutical  
30 administration and handling appropriate to the routes of administration mentioned below.

A concentrated solution or suspension is particularly useful for oral administration, especially as a filling solution for capsules. For parenteral use, e.g.  
35 for injection or infusion, a solution is the preferred

formulation.

The amount of HECPT contained in the formulations of this invention is not specifically restricted but may be any amount convenient for pharmaceutical purposes, and may be selected according to the dosage to be prepared. A preferred capsule filling solution contains from about 0.1 mg to about 3.0 mg of HECPT activity per ml of solution.

The formulations of the invention are sufficiently acidic to cause more than 50 mole % HECPT to be in the lactone form, preferably 100 mole %. Their pH will therefore be well below 7, normally from 2 to 5 and preferably from 3 to 4.

Any pharmaceutically acceptable acid may be used: for example, mineral acids such as hydrochloric acid; and organic carboxylic acids, such as tartaric, citric, succinic, fumaric, or maleic acids. An organic carboxylic acid is preferred, and citric acid is most preferred. The amount of acid used may be from about 0.005 to about 0.5 parts by weight of acid per part by weight of HECPT and preferably from about 0.01 to 0.3 part by weight of acid per part by weight of HECPT. Citric acid is preferably used in a proportion of from about 0.01 to about 0.5, especially from about 0.05 to about 0.1, or from about 0.1 part to about 0.5 by weight when taurocholic acid or a pharmaceutically acceptable salt thereof is included in the formulations, all per part by weight of HECPT.

In the formulations provided by the instant invention, HECPT is both soluble and maintained in its active lactone form. The non-enzymatic conversion of the pH labile E ring from the closed lactone (active) to the open carboxylate form (inactive) is reduced by formulating HECPT under acidic conditions (pH 2 to 5). The acid is preferably included to assure that an acidic pH

value is maintained upon dilution in the stomach. It is believed that this results in the formation of a micellar solution of HECPT in the stomach which is readily absorbed by the gastrointestinal tract. Applicants do not wish to be bound, however, by any theoretical explanation of the mechanism by which the superior oral bioavailability of the present HECPT formulation is achieved. Examples of preferred solid water-soluble organic carboxylic acids effective in this invention include citric, gluconic, maleic, tartaric, or ascorbic acids. Other acids may be employed, but citric acid is most preferred.

Yet another embodiment of the claimed invention is that the formulation of HECPT contains from about 0.1 mg to about 3.0 mg activity of 10-hydroxy 7-ethyl camptothecin per ml of solution. This concentration would be effective for both oral and parenteral administration of the HECPT.

When oral dosages are to be administered in a capsule form, it is clearly superior to have a concentrated solution of HECPT suitable for encapsulation within a soft or hard gelatin capsule. Concentrated solutions allow the preparation of capsules of smaller size which allows easier ingestion by the patient, and may also reduce the number of capsules to be swallowed. These factors are important in view of the generally poor condition of cancer patients.

Taurocholic acid, a bile acid, may enhance the intestinal absorption of the drug in certain patients. The present invention takes advantage of the discovery that taurocholic acid, or a pharmaceutically acceptable salt thereof, when included with HECPT in a solution dosage composition, results in improved absorption of the drug following ingestion of the composition. It is believed that this is due to the formation of a micellar

solution of HECPT on dilution thereof with the gastric contents.

The phenomenon of micellar solubilization of poorly water-soluble drugs mediated by bile acids, including taurocholic acid, has been previously reported with respect to glutethimide, hexestrol, griseofulvin (Bates et al.), reserpine (Malone et al.) and fatty acids and cholesterol (Westergaard et al.). The use of taurocholic acid or a pharmaceutically acceptable salt thereof in the present invention involves a pharmaceutical solution of HECPT which has the unique property of providing a stable solution or suspension of the drug upon dilution thereof with from 1 to 100 volumes of water. The solution or suspension is stable and free of precipitate for a period of at least two hours sufficient time to permit administration and absorption by the patient.

#### Antitumor Compositions Comprising HECPT

A preferred embodiment of the claimed invention is an antitumor composition comprising a solution or suspension of (1) 10-hydroxy 7-ethyl camptothecin, (2) dimethylisosorbide or dimethylacetamide, and (3) from about 0.01 to about 0.9 part by weight of a pharmaceutically acceptable organic carboxylic acid per part by weight of 10-hydroxy 7-ethyl camptothecin. Such a formulation could have a HECPT activity of 0.1 to 50 mg/ml, but 0.1 to 5 mg/ml is usual and 0.1 to 3 mg/ml is particularly aimed at. It is preferred to use 0.01 to 0.2 part by weight of a pharmaceutically acceptable organic carboxylic acid per part by weight of 10-hydroxy 7-ethyl camptothecin.

An additional embodiment of the claimed subject matter is wherein said pharmaceutically organic carboxylic acid is present in from about 0.05 to about 0.1 part by weight per part by weight of 10-hydroxy 7-ethyl

camptothecin and the acid is citric acid.

In another embodiment, the antitumor composition further comprises taurocholic acid or a pharmaceutically acceptable salt thereof, polyethylene glycol, and water.

5 Yet another embodiment of this invention is wherein the antitumor composition contains for each part by weight of 10-hydroxy 7-ethyl camptothecin, 1-10 parts by weight of dimethylisosorbide or dimethylacetamide, 0.005-0.5 parts by weight of a pharmaceutically accept-  
10 able acid, 1-10 parts by weight of taurocholic acid or a pharmaceutically acceptable salt thereof, 1-10 parts by weight of polyethylene glycol, and 0.1-2.0 parts by weight water. An additional embodiment is wherein said acid is an organic carboxylic acid, preferably citric  
15 acid.

Another embodiment of the claimed invention is the antitumor composition further comprising ethanol or benzyl alcohol (as a preservative) or both. Another  
20 embodiment of the claimed invention is the antitumor composition further comprising glycerin as a co-solvent.

Yet another embodiment of this invention is wherein the antitumor composition further comprises taurocholic acid or a pharmaceutically acceptable salt thereof, polyethylene glycol, water, ethanol, glycerin, and a  
25 buffer, such as sodium acetate, to maintain an acid pH.

An additional embodiment of this invention is wherein said composition contains for each part by weight of 10-hydroxy 7-ethyl camptothecin, 1-10 parts by weight of dimethylisosorbide or dimethylacetamide,  
30 0.005-0.5 parts by weight of a pharmaceutically acceptable acid, 1-10 parts by weight of taurocholic acid or a pharmaceutically acceptable salt thereof, 1-10 parts by weight of polyethylene glycol, 0.1-2 parts by weight of glycerin, 0.1-2 parts by weight of ethanol, 0.005-0.5  
35 parts of a buffer, and 0.1-2.0 parts by weight water.

Another embodiment of this invention is wherein said polyethylene glycol has a molecular weight of about 300. In another embodiment the antitumor composition further comprises a non-ionic surfactant. There are  
5 many different surfactants but the inventors prefer a poloxamer. The preferred poloxamer is poloxamer 407.

In yet another embodiment of this invention, the antitumor composition further comprises ethyl or benzyl alcohol, polyethylene glycol, and surfactant. Preferably,  
10 ly, the pharmaceutically acceptable organic acid is citric acid, the polyethylene glycol has a molecular weight of about 300, the alcohol is ethanol and the surfactant is polysorbate - 80.

Another embodiment of this invention is an antitumor composition comprising a solution or suspension of  
15 (1) about 0.1 mg to about 2.0 mg of 10-hydroxy 7-ethyl camptothecin, (2) 1 to 10 parts of dimethylisosorbide or dimethylacetamide and (3) about 0.1 to 0.5 parts of a pharmaceutically acceptable organic carboxylic acid, to  
20 adjust to a final pH of between 3 and 4. This antitumor composition further comprises about 5 to 9 parts by weight of polyethylene glycol, about 0.1 to 2.0 parts of a pharmaceutically acceptable alcohol, and about 1 to 10 parts of a non-ionic surfactant. Here and elsewhere  
25 herein where quantities of HECPT are given in mg., "parts" means per part by weight of HECPT. More preferred for this antitumor composition is when the acid is citric acid, the polyethylene glycol has a molecular weight of about 300, the alcohol is ethanol and the  
30 surfactant is polysorbate - 80.

Another embodiment of this invention is an antitumor composition comprising a solution or suspension of  
(1) about 0.1 mg to about 2.0 mg of 10-hydroxy 7-ethyl camptothecin, (2) 1 to 10 parts of dimethylisosorbide or  
35 dimethylacetamide and (3) 0.1 to 0.5 parts of a pharma-

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ceutically acceptable organic carboxylic acid. This solution further comprises about 0.1 to 2.0 parts of a pharmaceutically acceptable alcohol, and about 1 to about 10 parts of a non-ionic surfactant. Preferably, 5 for this antitumor composition, the acid is citric acid, the alcohol is ethanol, and the non-ionic surfactant comprises polyoxyethylated castor oil.

Another embodiment of this invention is an antitumor composition comprising a solution or suspension of 10 (1) 0.1 mg to about 2.0 mg of 10-hydroxy 7-ethyl camptothecin, (2) 1 to 10 parts of dimethylisosorbide or dimethylacetamide, and (3) about 0.1 to 0.9 parts citric acid, wherein this solution or suspension further comprises about 1 to 10 parts polyoxyethylated castor oil and about 0.1 to 2 parts by weight dehydrated ethyl 15 alcohol.

In a more preferred embodiment, HECPT is solubilized in a manner suitable for clinical use by forming a sterile, nonaqueous solution of 1 part of HECPT per 1 to 20 2 ml in a vehicle comprising dehydrated ethyl alcohol 0.1-2.0 parts by weight, benzyl alcohol 0.1-2.0 parts by weight, citric acid 0.1-0.9 parts by weight, polyethylene glycol (molecular weight 200-300) 4 to 10 parts by weight, polysorbate - 80 (\*Tween 80) 1 to 10 parts, and 25 dimethylisosorbide 1 to 10 parts in acidified medium with a pH of 3 to 4.

This preferred embodiment of an HECPT formulation using dimethylisosorbide is summarised in the table as follows:

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Ingredients	Parts by Weight
10-hydroxy 7-ethyl Camptothecin	1
EtOH	0.1-2.0
Benzyl Alcohol	0.1-2.0
Citric Acid	0.1-0.5
PEG 300	5-9
Dimethylisosorbide	1-10
Polysorbate 80 (*Tween-80)	1-10

Another more preferred parenteral formulation comprises HECPT formulated for dilution prior to parenteral administration made of 1 part HECPT in 2 ml of nonaqueous solvents including 1 to 10 parts Cremaphor EL (polyoxyethylated castor oil), 0.1 to 2 parts dehydrated ethyl alcohol, dimethylisosorbide 1 to 10 parts, and citric acid 0.1-0.9 parts to adjust the final pH to between 3 to 4.

This preferred embodiment of an HECPT formulation using dimethylisosorbide is as follows:

Ingredients	Parts by Weight
10-hydroxy 7-ethyl Camptothecin	1
Cremaphor EL	1-10
EtOH	0.1-2.0
Citric Acid	0.01-0.5
Dimethylisosorbide	1-10

Another embodiment of this invention is a lactone stable HECPT (a formulation of the invention) for use in administration to a patient with cancer.

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For the purpose of this invention, a previously untreated patient is one who has not been previously treated for said cancer with any chemotherapeutic drugs.

Preferred Dosages and Schedules for Parenteral Administration of HECPT Compositions

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- administration of HECPT to a patient with cancer comprising infusing from about 2.0 mg/m<sup>2</sup> to about 33.0 mg/m<sup>2</sup> of lactone stable HECPT over a duration of approximately 120 minutes every 21 to 28 days.

10

- administration of HECPT to a patient with cancer comprising infusing from about 1.0 mg/m<sup>2</sup> to about 16.0 mg/m<sup>2</sup> of lactone stable HECPT over a duration of approximately 120 minutes for three consecutive days every 21 to 28 days.

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- administration of HECPT to a patient with cancer comprising infusing from about 1.0 mg/m<sup>2</sup> to about 20.0 mg/m<sup>2</sup> of lactone stable HECPT over a duration of approximately 120 minutes given once per week for three consecutive weeks with 2 weeks rest after each 3 week cycle.

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- administration of HECPT to a previously untreated patient with cancer comprising infusing from about 2.0 mg/m<sup>2</sup> to about 24.0 mg/m<sup>2</sup> of lactone stable HECPT over a duration of approximately 120 minutes given once per week for three consecutive weeks with two weeks rest after each 3 week cycle.

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- administration of HECPT to a patient with cancer comprising continuously infusing from about 0.1 mg/m<sup>2</sup>/d to about 6.0 mg/m<sup>2</sup>/d of lactone stable HECPT over a duration of approximately 24 to 120 hours every 21 to 28 days.

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Preferred Dosages and Schedules for Oral Administration of HECPT Compositions

- oral administration of HECPT to a patient with cancer comprising an amount of HECPT given, as a single

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dose or divided into smaller doses, over a specified amount of time and repeated after a fixed amount of time.

5 - oral administration of HECPT to a patient with cancer comprising administering from about 2.5 mg/m<sup>2</sup> to about 100 mg/m<sup>2</sup> of lactone stable HECPT in single or divided dosages within a 24 hour period every 21 to 28 days.

10 - oral administration of HECPT to a patient with cancer comprising administering from about 1.0 mg/m<sup>2</sup> to about 50 mg/m<sup>2</sup> of lactone stable HECPT daily in single or divided doses for three consecutive days every 21 to 28 days.

15 - oral administration of HECPT to a patient with cancer comprising administering from about 1.0 mg/m<sup>2</sup> to about 60 mg/m<sup>2</sup> of lactone stable HECPT in single or divided dosages within a 24 hour period given once per week for three consecutive weeks with 2 weeks rest after each 3 week cycle.

20 - oral administration of HECPT to a previously untreated patient with cancer comprising administering from about 2.0 mg/m<sup>2</sup> to about 75 mg/m<sup>2</sup> of lactone stable HECPT in single or divided doses within a 24 hour period once per week for three consecutive weeks with 2 weeks rest after each 3 week cycle.

25 - oral administration of HECPT to a patient with cancer comprising administering from about 0.5 mg/m<sup>2</sup>/d to about 18.0 mg/m<sup>2</sup>/d of lactone stable HECPT in single or divided daily doses administered within each 24 hour period for two to five consecutive days and repeated every 21 to 28 days.

30 A further embodiment of this invention is encapsulating the oral formulations within a hard or soft gelatin capsule.

35 A more specific embodiment of the invention is an

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oral formulation of HECPT in soft gelatin capsules (comprised of gelatin/glycerin/sorbitol/purifiers/purified water) containing 1.0 part of HECPT in a vehicle comprising citric acid 0.1 to 0.9 parts by weight, purified water 1 part by weight, glycerin 1 to 10 parts by weight, polyethylene glycol (molecular weight 200 to 300) 5 to 9 parts by weight, dehydrated ethyl alcohol 10 to 20% by weight of total solution weight, sodium acetate 0.05 to 0.5 parts by weight, a surfactant, and 1 to 10 parts dimethylisosorbide. A more preferred oral formulation will include as a surfactant \*Pluronic F-127 poloxamer using 0.05 to 1.0 parts by weight.

Another preferred oral formulation includes the addition of taurocholic acid 2 to 10 parts by weight. The soft gelatin capsules may also be composed of any of a number of compounds used for this purpose including, for example, a mixture of gelatin, glycerin, sorbitol, purified water, and parabens.

The table below indicates parts by weight of different components to be included in the preferred oral formulation to be administered in capsules. Four components are marked with an "\*\*\*" which denotes that the components are "optional", even in this preferred formulation. For the purpose of this invention, inclusion of these components depends on a variety of different factors, i.e. type of cancer the patient has, whether pre-treated previously, etc.

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Ingredients	Parts by Weight
10-hydroxy 7-ethyl Camptothecin	1
Citric Acid	0.1-0.5
Purified Water	0.5-1.5
Glycerin **	0.4-2
PEG 300	5-9
EtOH **	10-20% by weight of total solution weight
Dimethylisosorbide	1-10
Poloxamer surfactant (Pluronic F-127) **	0.05-1.0
Sodium Acetate	0.05-0.5
Taurocholic Acid **	2-10

Clinicians will administer HECPT to human patients with cancer according to schedules that maximize its potential antitumor effects and diminish its potential toxic side effects. Except at extremely high doses which produce high plasma concentrations of the drugs, the antitumor activity of CPT-11 and HECPT can be increased by increasing the duration of exposure (time dependent) rather than increasing the dose (dose dependent) of the drug. The greater antitumor effects associated with increasing the duration of exposure are most likely related to the predominant S-phase mode of antitumor activity of CPT-11 and HECPT. HECPT is an S-phase-active agent; therefore, the greater antitumor effect in humans will likely be observed with prolonged infusion or closely spaced repetitive administration schedules. Such schedules of administration would expose more cycling tumor cells to the drug and increase the frequency of exposure to the tumor cells in S-phase

to sufficiently toxic levels of the drug.

The claimed formulations and compositions of the invention may be used in treatment of a number of tumors including, without limitation, human cancers of the lung, breast, colon, prostate, melanoma, pancreas, stomach (gastric), liver, brain, kidney, uterus, cervix, ovaries, and urinary tract.

The site and type of tumor to be treated will, in many cases, influence the preferred route of administration and therapeutic regimen to be applied. Consequently, although the formulations of the invention may be most usually administered by intravenous injection or infusion, they also can be delivered directly into the tumor site or by other methods designed to target the drug directly to the tumor site. For example, in patients with malignant pleural effusion, the intrapleural route may be preferred; in patients with poor venous access, the subcutaneous route of administration may be preferred; in patients with primary or metastatic cancer involving the brain or nervous system, the intracisternal or intrathecal route of administration may be most advantageous; in patients with malignant ascites secondary to cancer, one may select intraperitoneal administration; and in patients with bladder cancer direct intravesicular instillation may be most advantageous. Similarly, in tumors of the skin, the formulation may be topically applied. An oral formulation is also provided for use where suitable.

The formulations of the invention, sterilized where desirable, can be prepared for oral, intrapleural, intrathecal, subcutaneous, intracisternal, intravesicular, intraperitoneal, topical or parenteral administration to a patient with cancer.

The formulation of the invention may also be used in conjunction with other drugs in methods of convergent

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therapy whereupon an additional drug or drugs are co-administered along with the lactone stable HECPT composition, e.g. with CPT-11, topotecan, camptothecin, or 10,11-methylenedioxy camptothecin, using a pharmaceutically acceptable carrier, and the co-administration is based on an optimal dosage and schedule. For example, in a preferred embodiment, CPT-11 may be co-administered with the lactone stable HECPT. Also, the lactone stable HECPT may be co-administered with a combination of CPT-11, topotecan, camptothecin, and 10,11-methylenedioxy camptothecin, using a pharmaceutically acceptable carrier, and the co-administration is based on an optimal dosage and schedule. For example, CPT-11 and topotecan may be co-administered with the lactone stable HECPT.

A further embodiment is the lactone stable HECPT, for use in treatment of cancer in humans by convergent therapy or combination therapy, e.g. with one or more additional drugs selected from the group consisting of, but not limited to, carmustine, azathioprine, cisplatin, carboplatin, iproplatin, cyclophosphamide, ifosfamide, etoposide, ara-C, doxorubicin, daunorubicin, nitrogen mustard, 5-fluorouracil, bleomycin, mitomycin-C, fluoxymesterone, mechlorethamine, teniposide, hexamethylmelamine, leucovorin, melphelan, methotrexate, mercaptopurine, mitoxantrone, BCNU, CCNU, procarbazine, vincristine, vinblastine, vindesine, thioTEPA, amsacrine, G-CSF, GM-CSF, erythropoietin,  $\gamma$ -methylene-10-deazaaminopterin or  $\gamma$ -methylene-10-ethyl-10-deazaaminopterin, \*taxol, and 5-azacytidine. For the purpose of this invention, the terms convergent, co-administered, and combination are used interchangeably.

The lactone stable HECPT formulations of this invention for use when administered parenterally, are preferred diluted with an appropriate volume of a parenteral vehicle to a concentration of about 0.1 mg/ml or

\*Trade-mark

lower of HECPT activity. A further embodiment of the invention is a sterile solution or suspension of any of the claimed HECPT formulations for sterile administration to a patient with cancer upon dilution with a sterile parenteral vehicle. For the purposes of this invention, parenteral vehicles include dextrose 5 to 10% in water, 0.9% NaCl in water with or without 5% or 10% Dextrose, 0.45% NaCl in water with or without 5% or 10% Dextrose, and 3% NaCl in water with or without 5% to 10% Dextrose, or sterile lipid formulations, such as intralipid, used for parenteral nutritional support for cancer patients.

In its preferred embodiments, this invention involves preparation and administration of novel lactone stable HECPT (formulations of the invention) as described below.

The formulations of the invention can be prepared by mixing the components all at once, by first adding the HECPT to DMA or DMI and then adding the acid or by adding the acid to DMA or DMI and then adding the HECPT to the DMA/DMI-acid mixture. Various excipients, diluents, preservatives and other optional ingredients as described above may be added subsequently or with any of the essential components.

#### 25 EXAMPLES

The following examples illustrate selected modes for carrying out the claimed invention and are not to be construed as limiting the specification and claims in any way.

#### 30 EXAMPLE 1

For injection or infusion into aqueous body fluids, a formulation comprises from about 0.1 to about 2.0 mg of HECPT mixed with 1 to 10 parts of dimethylisosorbide in an acidified vehicle comprising between about 10 to about 40 percent of an acceptable alcohol, about 4 to

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about 10 parts by weight of polyether glycol, and about 1 to about 10 parts of a non-ionic surfactant. Suitable alcohols include dehydrated ethyl alcohol and benzyl alcohol. Suitable polyether glycols include polyethylene glycol 200, polyethylene glycol 300 and propylene glycol. Suitable non-ionic surfactants include polysorbate - 80. In a preferred embodiment, the formulation of HECPT is supplied for intravenous injection in a 1 mg vial comprising a sterile, nonaqueous solution of drug in a vehicle comprising dehydrated ethyl alcohol, benzyl alcohol, citric acid, polyethylene glycol 300, and polysorbate (\*Tween 80) in acidified medium with a pH of 3 to 4 at a final concentration of 1 mg per 1 to 2 ml.

#### EXAMPLE 2

A second formulation comprises from about 0.1 mg to about 2.0 mg of HECPT in an acidified vehicle comprising between about 0.1 to 2 parts of an alcohol and about 1 to 10 parts of a non-ionic surfactant. Suitable alcohols include dehydrated ethyl alcohol and benzyl alcohol. Suitable non-ionic surfactants include the polyoxyethylated oils, such as polyoxyethylated vegetable oils, such as castor oil, peanut oil, and olive oil. In a preferred embodiment 0.1 mg to 2 mg HECPT is formulated in 1 to 10 parts of dimethylisosorbide, 1 to 10 parts of Cremaphor EL (polyoxyethylated castor oil), 0.1 to 2 parts by weight dehydrated ethyl alcohol, and 0.1 to 0.9 parts citric acid to adjust the final pH between 3 to 4.

#### EXAMPLE 3

An oral formulation of HECPT in soft gelatin capsules (comprised of gelatin/glycerin/sorbitol/purifiers/purified water) containing 1.0 part of HECPT in 1 to 10 parts of dimethylisosorbide, citric acid 0.1 to 0.5 parts by weight, purified water 1 part by weight, glycerin 1 to 10 parts by weight, and polyethylene glycol

\*Trade-mark

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200 to 300 5 to 9 parts by weight, dehydrated ethyl  
alcohol 0.2 to 2 parts by weight of total solution  
weight, sodium acetate 0.05 to 0.5 parts by weight,  
\*Pluronic F-127 poloxamer using 0.05 to 1.0 parts by  
5 weight, and taurocholic acid 2 to 10 parts by weight.  
The soft gelatin capsules may also be composed of any of  
a number of compounds used for this purpose including,  
for example, a mixture of gelatin, glycerin, sorbitol,  
purified water, and parabens.

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\* \* \*

Maintaining an acidic pH as set forth above (espe-  
cially 3 to 4) in the formulation is particularly impor-  
15 tant to reduce the slow conversion of HECPT lactone to  
the E-ring-hydrolyzed carboxylate, which occurs at  
physiological pH.

To further prolong the stability and solubility of  
HECPT for clinical infusions, the lactone stable HECPT  
20 drug may be diluted in 5% Dextrose in water (D5W) to a  
final concentration of 0.001 mg/ml to about 0.1 mg/ml of  
HECPT prior to injection or infusion.

Initially, patients may be treated in a dose esca-  
lation protocol to determine the maximal tolerated dose  
25 of the HECPT formulation. In determining a safe start-  
ing dose for HECPT, the data from Ohe et al. and Rothen-  
berg et al. are helpful.

The administration of the lactone stable HECPT may  
be carried out using various schedules and dosages. For  
30 example:

1. For intravenous administration, a suitable dose is  
0.45 mg to 5.4 mg/m<sup>2</sup> per day using a 3 to 5 day  
continuous infusion schedule every 21 to 30 days or  
2.7 to 32.4 mg/m<sup>2</sup> given as a 30 to 90 minute infu-  
35 sion every 21 to 30 days.

\*Trade-mark

2. Another schedule involves the administration of 1.2 to 15.5 mg/m<sup>2</sup> daily for three consecutive days over 90 minutes intravenously every 21 to 28 days.

5 3. A suitable oral dose of the drug is 0.5 to 50 mg/m<sup>2</sup> per day using the lower dose for a period of 3 to 5 days and using divided dosages of administration of two to four times per day.

10 In addition, patients may be given the lactone stable HECPT as an inpatient or outpatient using the following exemplary schedules:

1. 2.7 to 32.4 mg/m<sup>2</sup> given over 90 minutes I.V. every 21 to 28 days;
2. 1.2 to 15.5 mg/m<sup>2</sup> given daily for three consecutive days over 90 minutes I.V. every 21 to 28 days;
- 15 3. 1.0 to 20.0 mg/m<sup>2</sup> given once per week X 3 consecutive weeks over 90 minutes I.V. with 2 weeks rest after each 3 week cycle for pretreated patients;
4. 2.25 to 24.3 mg/m<sup>2</sup> given once per week X 3 consecutive weeks over 90 minutes I.V. for previously  
20 untreated patients with 2 weeks rest after each 3 week cycle; and
5. 0.45 to 5.4 mg/m<sup>2</sup>/d X 3 to 5 consecutive days as a continuous I.V. infusion every 21 to 28 days.

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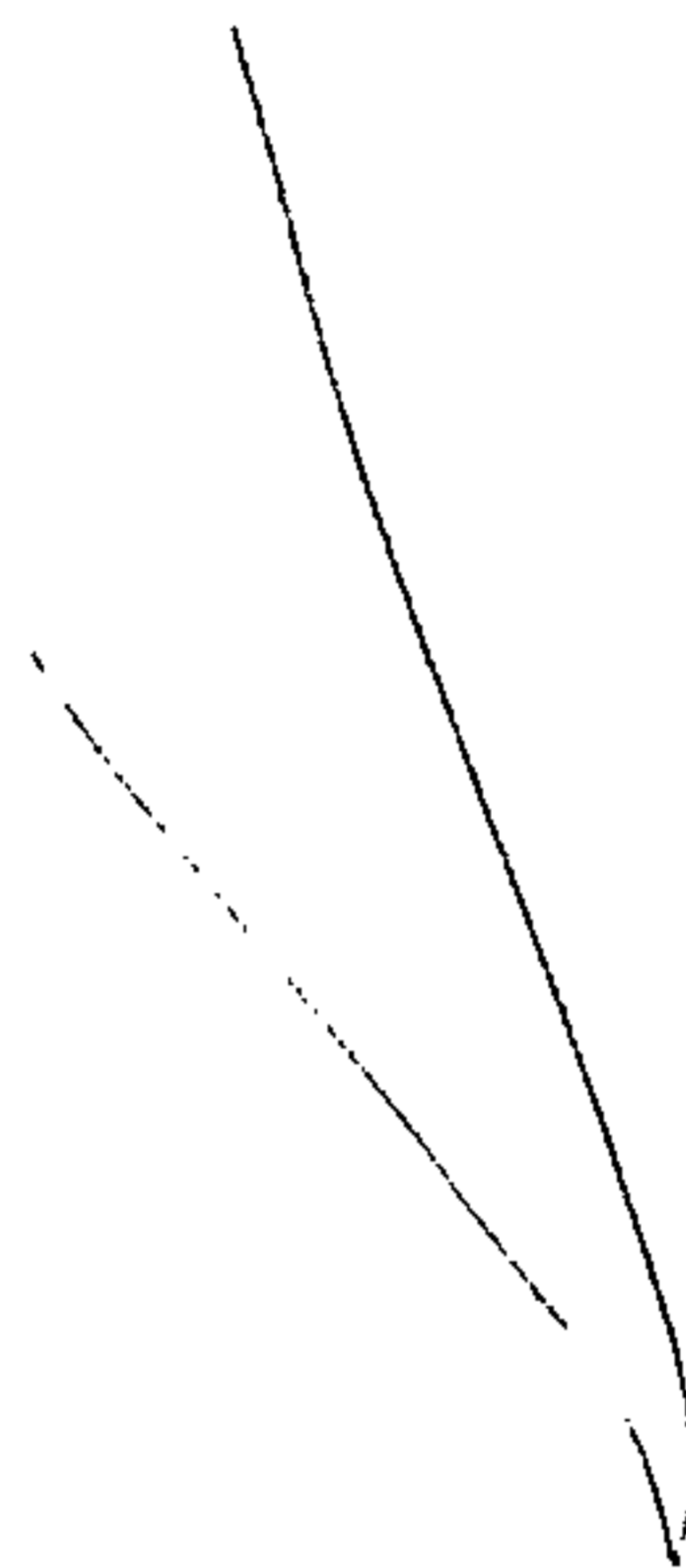
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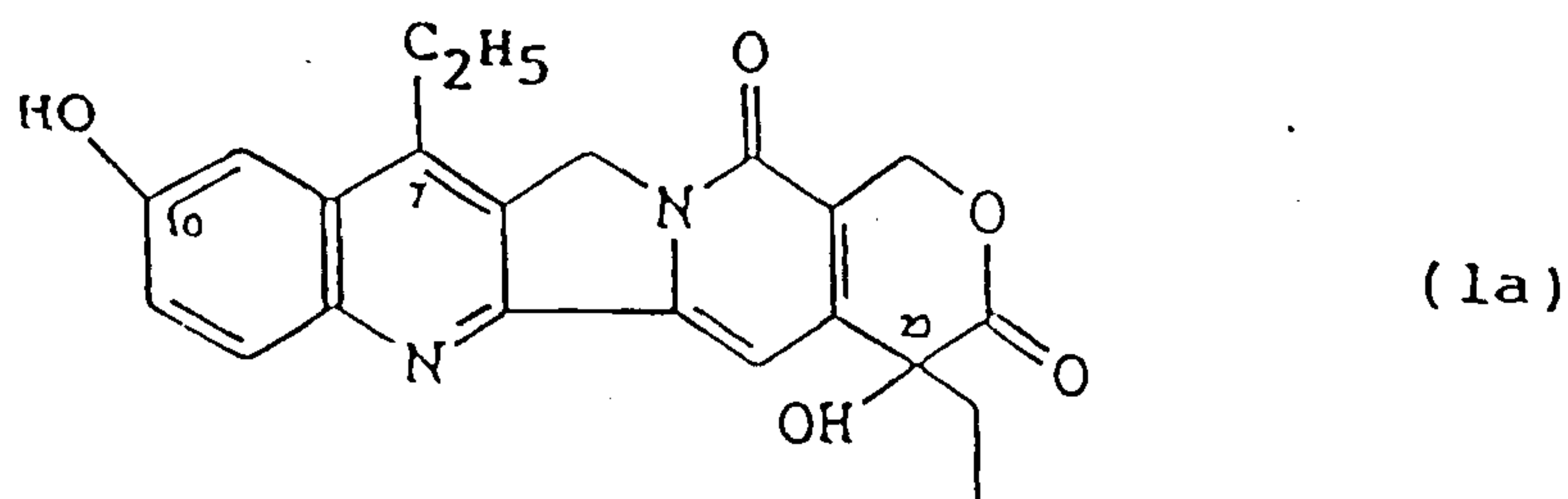


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THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A pharmaceutically acceptable formulation, in the form of an acidic solution or suspension, comprising:

(1) 10-hydroxy 7-ethyl camptothecin, the solution or suspension being sufficiently acidic to cause more than 50 mole % thereof to be in the lactone form (1a):



characterized in that it further comprises:

(2) dimethylisosorbide or dimethylacetamide.

2. The formulation according to claim 1, characterized by a pH of from 2 to 5.

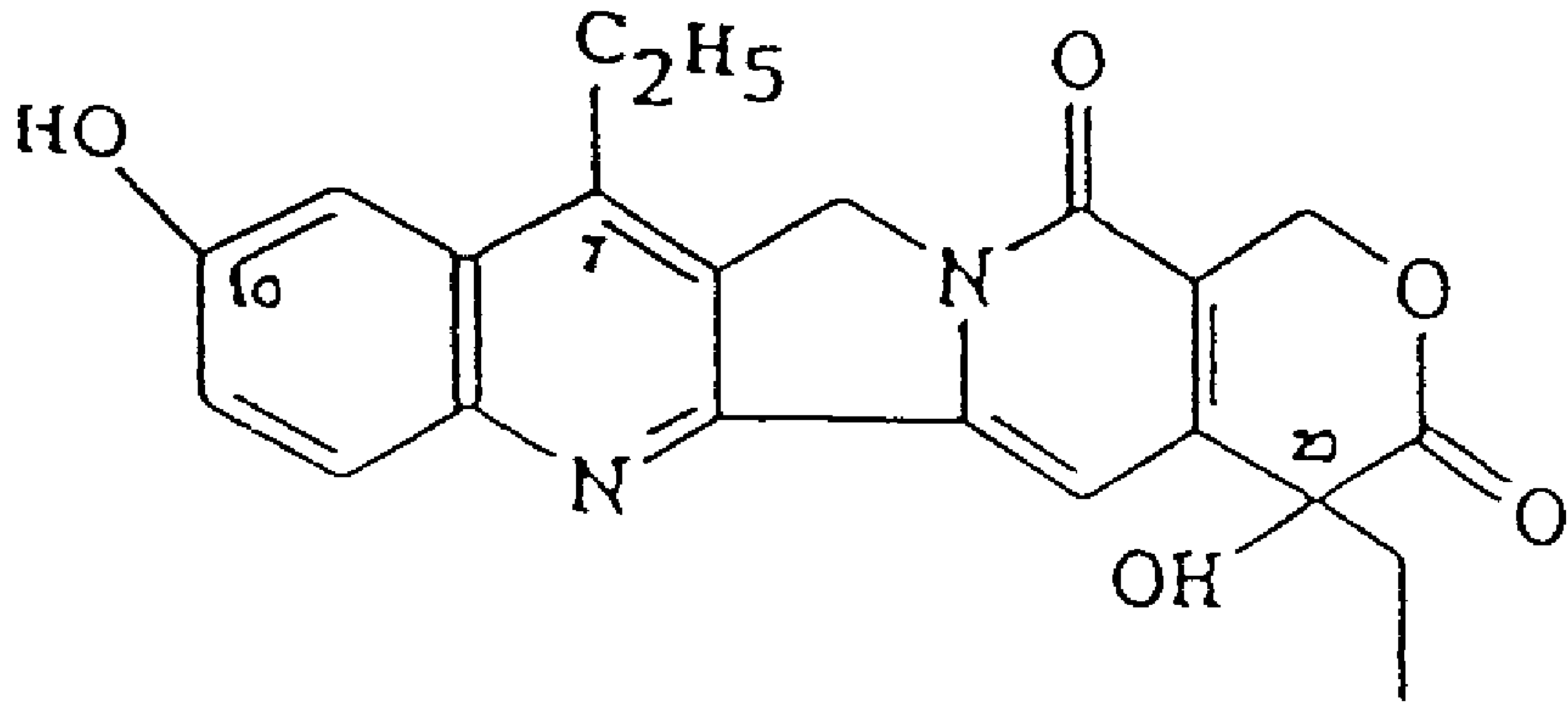
3. The formulation according to claim 2 characterized by a pH of from 3 to 4.

4. The formulation according to claim 1, 2 or 3, characterized in that it further comprises taurocholic acid or a pharmaceutically acceptable salt thereof, polyethylene glycol and water.

5. The formulation according to claim 4, characterized by containing for each part by weight of 10-hydroxy 7-ethyl camptothecin, 1-10 parts by weight of dimethylisosorbide or dimethylacetamide, 0.005-0.5 parts by weight of a pharmaceutically acceptable acid, 1-10 parts by weight of taurocholic acid or a pharmaceutically acceptable salt thereof, 1-10 parts by weight of polyethylene glycol, and 0.1-2.0 parts by weight of water.

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6. The formulation according to claim 4, characterized in that it further comprises benzyl alcohol or glycerin.
7. The formulation according to any one of claims 1 to 3, characterized in that it further comprises ethanol or benzyl alcohol, polyethylene glycol, and a surfactant.
8. The formulation according to claim 7, characterized by containing about 0.1 mg to about 2.0 mg of 10-hydroxy 7-ethyl camptothecin (HECPT), 1 to 10 parts of dimethyl-isosorbide or dimethylacetamide, 0.1 to 0.5 parts of a pharmaceutically acceptable organic carboxylic acid, 5 to 9 parts by weight of polyethylene glycol, 0.1 to 2.0 parts of ethyl or benzyl alcohol, and 1 to 10 parts of a non-ionic surfactant, all parts being per part by weight of HECPT.
9. The formulation according to any one of claims 1 to 8, characterized in that it contains citric acid.
10. The formulation according to any one of claims 1 to 9 in a form suitable for injection or infusion.
11. Capsules containing a formulation as claimed in any one of claims 1 to 9.
12. The formulation according to any one of claims 1 to 10 or capsules claimed in claim 11, for treatment of tumors.



(1a)