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(54) **FORMULATIONS PHARMACEUTIQUES DE TAXANES**
(54) **PHARMACEUTICAL FORMULATIONS OF TAXANES**

(57) L'invention concerne une formulation pharmaceutique comprenant un agent antinéoplasique à base de taxanes, notamment le paclitaxel ou le docétaxel ou un de leurs sels pharmaceutiquement acceptables, ainsi que N-méthyl-pyrrolidin-2-one (NMP) et/ou diméthylacétamide (DMA) et/ou diméthylisosorbide (DMI). Cette formulation peut contenir d'autres excipients et/ou diluants, et convient à l'administration à des patients atteints du cancer.

(57) A pharmaceutical formulation of a taxane antineoplastic agent, particularly paclitaxel or docetaxel or a pharmaceutically acceptable salt thereof, and N-methylpyrrolidin-2-one (NMP), and/or Dimethylacetamide (DMA), and/or Dimethylisosorbide (DMI). The formulation may include other excipients and/or diluents, and is suitable for administration to patients with cancer.

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(54) Title: PHARMACEUTICAL FORMULATIONS OF TAXANES

(57) Abstract

A pharmaceutical formulation of a taxane antineoplastic agent, particularly paclitaxel or docetaxel or a pharmaceutically acceptable salt thereof, and N–methylpyrrolidin–2–one (NMP), and/or Dimethylacetamide (DMA), and/or Dimethylisosorbide (DMI). The formulation may include other excipients and/or diluents, and is suitable for administration to patients with cancer.

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PHARMACEUTICAL FORMULATIONS OF TAXANES

FIELD OF THE INVENTION

This invention relates to pharmaceutical formulations of taxanes, particularly the antitumor drugs Paclitaxel (Taxol®) and Docetaxel (Taxotere®), or derivatives thereof, and combinations of N-methylpyrrolidin-2-one (NMP), dimethylacetamide (DMA), and/or dimethylisosorbide (DMI).

BACKGROUND OF THE INVENTION

1. Background of Paclitaxel and Docetaxel

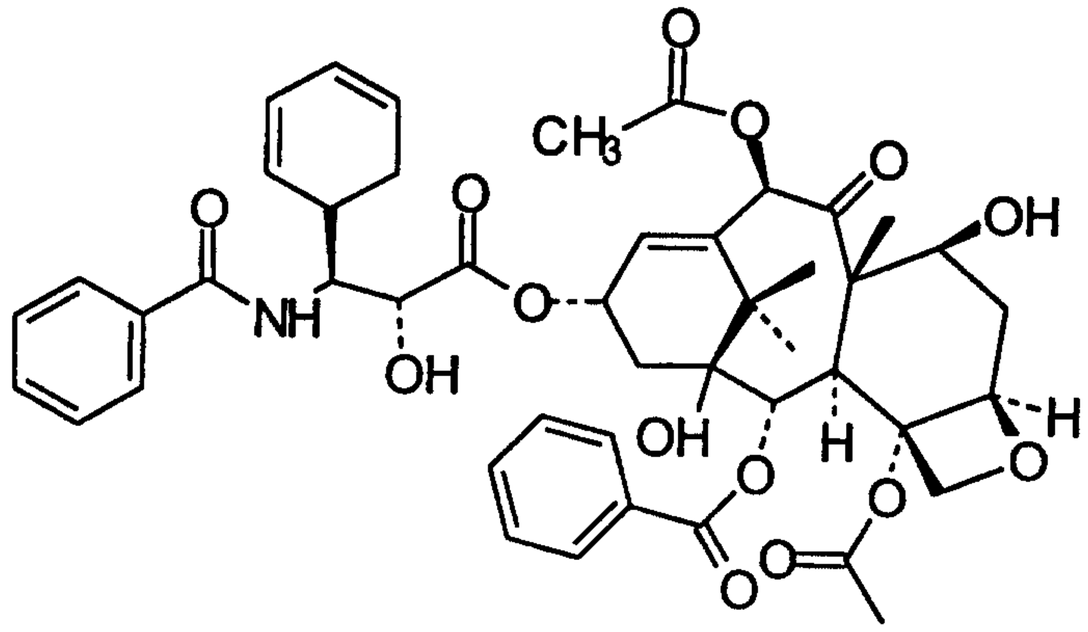
Taxanes, in particular, the two currently available drugs, Paclitaxel and Docetaxel, are potent antineoplastic agents. Taxanes are derived naturally or semi-synthetically from the bark or needles of certain yews. Paclitaxel was discovered in the late 1970s, and was found to be an effective antineoplastic agent with a mechanism of action different from existing chemotherapeutic agents.

In particular, Paclitaxel, Docetaxel and other taxanes are reported to exert cytotoxic effects by enhancing the polymerization of tubulin, which is an essential protein in the formation of spindle microtubules. The result is the formation of very stable, nonfunctional tubules, which is believed to inhibit cell replication and leads to neoplasm cell death. Taxanes are recognized as effective agents in the treatment of

many solid tumors which are refractory to other antineoplastic agents.

Paclitaxel has a complex structure and is shown below as Formula I:

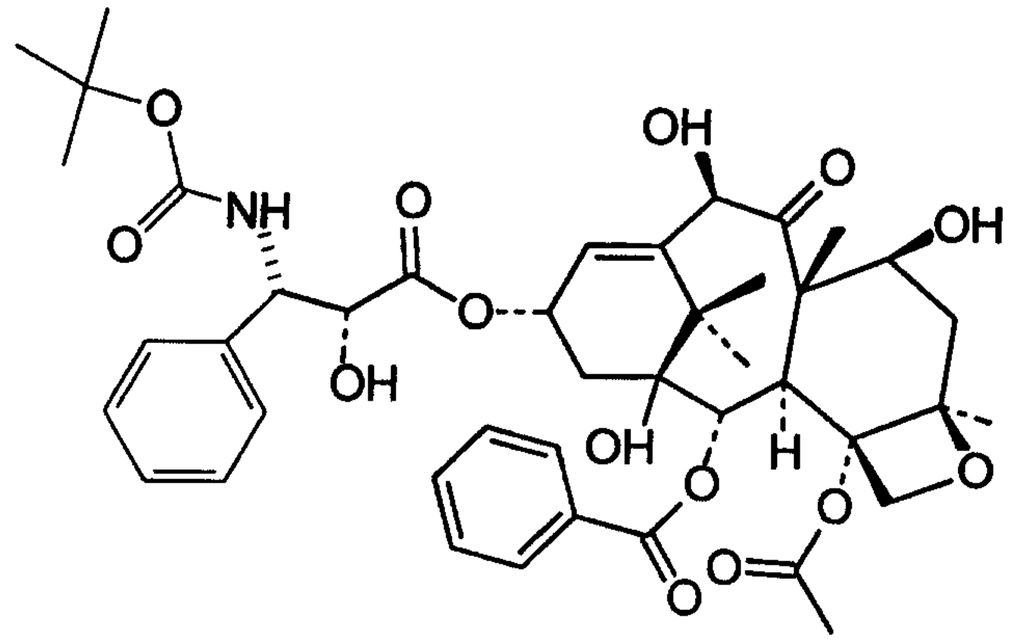
(I)



Paclitaxel is very poorly water soluble (less than 10 µg/mL), and as a result, cannot be practically formulated with water for IV administration. Currently, Paclitaxel is formulated for IV administration to patients with cancer in a solution with polyoxyethylated castor oil (Polyoxyl 35 or Cremaphor®) as the primary solvent. High concentrations of ethanol are employed as co-solvents. One of the major difficulties in the administration of Paclitaxel is the occurrence of hypersensitivity reactions. These reactions, which include severe skin rashes, hives, flushing, dyspnea, tachycardia, and others, may be attributed at least in part to the high concentrations of polyoxyl 35 used as solvents in the formulation. Also, the high concentrations of ethanol in the current Paclitaxel formulation tends to cause acute alcohol intoxication in many patients.

Docetaxel is an analogue of Paclitaxel, and was recently approved for administration to patients with cancer by the United States Food & Drug Administration. Docetaxel has the following structure:

(II)



Like Paclitaxel, Docetaxel is very poorly soluble in water. The current most preferred solvent used to dissolve Docetaxel is polysorbate 80 (Tween 80). Like Polyoxyl 35, polysorbate often causes hypersensitivity reactions in patients. Further, polysorbate cannot be used with PVC delivery apparatus, because of its tendency to leech diethylhexyl phthalate, which is highly toxic.

Due to the relatively high viscosity of Cremaphor, co-solvents must be employed to allow for intravenous infusion of the formulation to the patient. Some commonly employed co-solvents include various lower alcohols, vegetable and other oils, and combinations of other organic and inorganic solvents. Other pharmaceutical excipients are also employed in making formulations of these drugs. Currently, only intravenous formulations of paclitaxel or docetaxel are available for administration to patients.

2. N-Methylpyrrolidone

N-methylpyrrolidin-2-one, also referred to as N-methylpyrrolidone, 1-methyl-2-pyrrolidone, NMP, and other like names, is a common industrial solvent. NMP has also been used in pharmaceutical formulations as an excipient to enhance the skin penetration of topically applied agents. NMP is a slow evaporating, highly polar, aprotic general purpose solvent which is fully miscible with water and most organic solvents.

NMP has also been used in the preparation of pharmaceutical compounds as a solvent for various pharmaceuticals, namely Etoposide, Tetracycline, Doxycycline, Teniposide, Chlortetracycline, Camptothecins and other poorly water soluble pharmaceutical compounds. Prior patents regarding the pharmaceutical use of NMP include United States Patents 5,900,419; 5,880,133; 5,859,023; 5,859,022; 5,726,181; and others.

3. Dimethylacetamide and Dimethylisosorbide

Dimethylacetamide (DMA) and Dimethylisosorbide (DMI) are organic solvents which have previously been taught as possible solvents for highly lipophilic Camptothecin analogues. United States Patents 5,447,936; 5,468,754; 5,597,829; 5,604,233; 5,633,260; 5,674,873; and others.

teach the use of DMA and DMA as useful solvents for formulating various poorly water soluble analogues of Camptothecin. DMI has

also been employed as a solvent for other pharmaceutical agents, such as muscle relaxants, aspirin, and various steroids.

Both DMA and DMI have good safety profiles and are miscible with many organic solvents, such as ethanol, propylene glycol, isopropyl myristate, diethyl ether, vegetable oils, and also with water.

United States Patent 5,877,205 discloses a formulation of paclitaxel, using DMA/PEG as co-solvents, with the stock formulation diluted for administration to the patient in an aqueous lipid emulsion.

The '205 patent discloses the need for the final dilution of the paclitaxel/DMA/PEG stock solution in an aqueous lipid emulsion, namely soybean oil.

SUMMARY OF THE INVENTION

The pharmaceutical formulations of this invention include as principal ingredients an effective amount of a taxane (the active ingredient), an amount of NMP, and a co-solvent comprising an amount of DMA and/or DMI sufficient to dissolve the entire active ingredient. The formulation may also include other pharmaceutical excipients commonly found in formulations suitable for intravenous administration.

Accordingly, it is an object of this invention to provide for a novel pharmaceutical formulation which includes as one of the active ingredients, an effective amount of a taxane.

Another object of this invention is to provide for a pharmaceutical formulation of a taxane which is easy and safe to

administer to patients, and which is less toxic than currently administered formulations.

Other objects of this invention will become apparent upon reading the following specification.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The preferred embodiments herein described are not intended to be exhaustive or to limit the invention to the precise form disclosed. They are chosen and described to explain the principles of the invention and its application and practical use to enable others skilled in the art to follow its teachings.

The pharmaceutical formulations of this invention each include two basic ingredients: 1) a taxane (the active ingredient); and 2) a primary solvent in sufficient volume to dissolve the entire active ingredient. The solvent is preferably NMP, or DMA or DMI. The formulation is packaged for intravenous administration to a patient in need of treatment for cancer, the approved use of the active ingredient.

The formulation may also include quantities of various other excipients as desired. Excipients are used for a number of purposes in formulating pharmaceuticals, namely as surfactants, thickeners/thinners, pH controllers, stabilizers, etc. Examples of some typical excipients, and their general usage and function are described below.

Table 1

Polyethylene Glycol (PEG 200, PEG 300, PEG 400, etc.)	Thickening Agent/Solvent
Organic and Inorganic Acids	pH Lowering Agents
Organic and Inorganic Bases	pH Raising Agents
Epoxylated Castor Oil (Cremaphor)	Surfactant
Alcohols (Ethanol or Benzyl Alcohol preferred)	Co-solvents/antibacterials
Poloxamers and/or Polysorbates (407, PF-127, Tween 80, etc.)	Surfactant
Glycerin	Co-solvent
NMP, and DMA and/or DMI	Co-solvent
Water	Diluent
Saline	Diluent

All diluents, carriers and excipients used in the formulation are pharmaceutically acceptable compounds.

The formulation is preferably prepared in the following manner. First, the active ingredient is completely dissolved in the primary solvent. Second, the other additives and excipients are added, either individually or in combination to complete the formulation. The formulation is then typically packaged and shipped to the hospital or clinic.

Finally, the completed formulation is diluted with water, or a common parenteral delivery vehicle, such as a saline solution (0.1%-0.9% NaCl), Lactated Ringer's Solution, 5% Dextrose USP, or the like. The final dilution is usually performed at the hospital or treatment center just prior to administration to the patient.

Preferred pharmaceutical formulations of taxanes include a pharmaceutically effective amount of the taxane dissolved in an amount of primary solvent sufficient to dissolve all of the taxane, forming a solution.

The current recommended dosage range for Paclitaxel is between 100-250 mg/m^2 and the current recommended dosage for Docetaxel ranges from 50-150 mg/m^2. Since a typical adult patient's body surface area is between 1.5-2.0 m^2, a preferred total dose will range from 150-500 mg of Paclitaxel, and from 75-300 mg of Docetaxel. When the patient's body surface area is outside these ranges, dosage is adjusted to account for this variability.

The maximum solubility of Paclitaxel and Docetaxel in NMP has been determined to be approximately 40 mg/mL. Since an amount of NMP sufficient to dissolve all of the taxane is preferred, preferred formulations will include at least from 4-13 mL of NMP for Paclitaxel, and from 2-8 mL of NMP for Docetaxel. These volumes will often be higher, to ensure complete dissolution of the taxane in the primary solvent.

For DMA, the maximum solubility of Paclitaxel and Docetaxel has been observed more than 100 mg/mL. Since an amount of DMA sufficient to dissolve all of the taxane is preferred, preferred formulations will include about 1-5 mL of DMA for Paclitaxel and Docetaxel. These volumes will often be higher, to ensure complete dissolution of the taxane in the primary solvent.

For DMI, the maximum solubility of Paclitaxel and Docetaxel is about 40 mg/mL. Since an amount of DMI sufficient to dissolve all of the taxane is preferred, preferred formulations

will include at least from 4-15 mL of DMA for Paclitaxel, and from 2-10 mL of DMA for Docetaxel. These volumes will often be higher, to ensure complete dissolution of the taxane in the primary solvent.

The preferred formulations are prepared by adding the effective amount of the taxane to a volume of NMP predetermined to be sufficient to dissolve all of the taxane. To this NEAT formulation are added the desired excipients. The concentrated formulation is then packaged and distributed. The concentrated formulation is diluted in a conventional parenteral delivery carrier, *supra*, just prior to administration to the patient.

A preferred taxane/NMP formulation is shown below in Table 2.

Table 2

Ingredient	Specific Compound	Amount
Active Ingredient	Paclitaxel	200 mg
Solvent	NMP	10 mL
Co-solvent	DMA	0-10 mL
Diluent	Ethanol	10-100 mL
Surfactant	Cremaphor	0-500 mL
pH Adjuster	Citric Acid	1-5 mL
Excipient	PEG 200	10-500 mL
Surfactant	Tween 80	0-500 mL

A preferred taxane/DMA formulation is shown below in Table 3.

Table 3

Ingredient	Specific Compound	Amount
Active Ingredient	Paclitaxel	200 mg
Solvent	DMA	5-10 mL
Diluent	Ethanol	10-100 mL
Surfactant	Cremaphor	0-500 mL
pH Adjuster	Citric Acid	1-5 mL
Excipient	PEG 200	0-500 mL
Surfactant	Tween 80	0-500 mL

A preferred taxane/DMI formulation is shown below in Table 4.

Table 4

Ingredient	Specific Compound	Amount
Active Ingredient	Paclitaxel	200 mg
Solvent	NMP	0-10 mL
Solvent	DMI	5-10 mL
Diluent	Ethanol	10-100 mL
Surfactant	Cremaphor	10-500 mL
pH Adjuster	Citric Acid	1-5 mL
Excipient	PEG 200	0-500 mL
Surfactant	Tween 80	0-500 mL

After the formulation has been packaged, it is administered to a patient in accordance with the patient's treatment regimen,

taking into account the recommended dosage and rate schedules prescribed by the attending physician.

It is understood that the above description is presented for illustrative purposes only, and should in no way be construed as limiting the invention to the precise details above given.

What Is Claimed Is:

1. A pharmaceutical formulation comprising a taxane and NMP.

2. The pharmaceutical formulation of Claim 1 wherein said taxane is Paclitaxel.

3. The pharmaceutical formulation of Claim 1 wherein said taxane is Docetaxel.

4. The pharmaceutical formulation of Claim 1 wherein said formulation also includes a lower alcohol.

5. The pharmaceutical formulation of Claim 1 wherein said formulation further includes a non-ionic surfactant.

6. A pharmaceutical formulation comprising Paclitaxel or Docetaxel, or a pharmaceutically acceptable salt thereof, NMP and dimethylacetamide.

7. The pharmaceutical formulation of Claim 6 wherein said formulation further includes a lower alcohol.

8. The pharmaceutical formulation of Claim 6 wherein said formulation further includes a non-ionic surfactant.

9. A pharmaceutical formulation comprising a taxane and dimethylisosorbide.

10. The pharmaceutical formulation of Claim 9 wherein said taxane is Paclitaxel.

11. The pharmaceutical formulation of Claim 9 wherein said taxane is Docetaxel.

12. The pharmaceutical formulation of Claim 9 wherein said formulation also includes NMP as a co-solvent.

13. The pharmaceutical formulation of Claim 9 wherein said formulation further includes a non-ionic surfactant.

14. The pharmaceutical formulation of Claim 11 wherein said formulation further includes a non-ionic surfactant.