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(54) **Title**: DOCETAXEL LYOPHILIZED PARENTARAL FORMULATION FOR SAFE DRUG DELIVERY SYSTEM AND PROCESS OF MAKING THEREOF

(57) **Abstract**: A novel formulations of Docetaxel and process of making thereof, without using Polysorbate or Chremophor to avoid their known toxicological problems. Comprising the particularly Modified natural cyclodextrins, along with nonionic tensoactive plus additives,and a diluents, combined with the lyophilized Docetaxel in order to obtain a reconstituted solution that upon dilution in normal saline solution or 5 % dextrose solution.

Docetaxel lyophilized parentaral formulation for safe drug delivery and process of making thereof,

Field of the invention:-

The present invention relates to novel docetaxel formulation for parentaral administration for safe drug delivery system and process of making the same, containing docetaxel is an anti-neoplasic drug that has shown a proven efficacy in the treatment of the following carcinomas, such as breast, ovary, non small cells lung cancer, prostate, gastric, the formulation is able to be used as single dose or multi-dose formulations, and to their uses in medicaments.

Back Ground of the invention:-

WO 01/72299 which teaches about the composition for oral administration containing docetraxel, carrier such as saturated polyglycolysed glyceroids, modified castor oil, stearate esters, sorbitan esters, fatty acids, glycerides etc,

WO 2006/133510, which teaches about docetaxel formulation containing polysorbate, along with other carriers,

Where as in the present invention described the formulation without using the polysorbate to avoid toxicity, further embodiment of the present formulation contains the modified cyclodextrine.

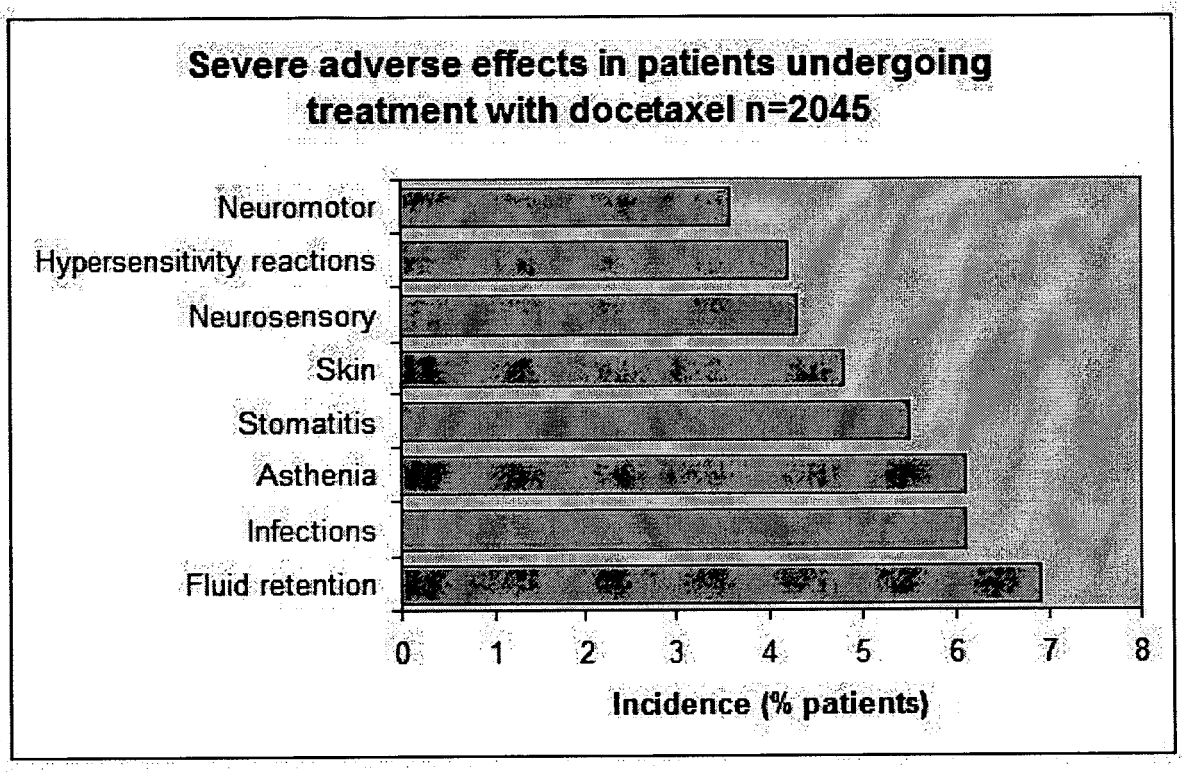
According with the different clinical trials and included in the PDR the present formulation of this medicine produces two serious adverse reactions that caused by Polysorbate 80:

Severe fluid retention appearing in 6.5% of patients (PDR reference)

Hypersensitivity reactions appear in 2.2% of patients (PDR reference)

Others severe or serious adverse events were reporting in different clinical trial,

Trials according to the following Table.



These reactions could become serious in some cases life threatening of the Patient's life, were informed in other opportunities less severe cases, could Produce the interruption of treatment.

Due to the adverse effects described before, this formulation requires theAdministration of a preventive medication previously to the product's Administration. The pre-medication scheme consists of the administration of 8 mg dose of dexametasone during three days.

As it is known, dexamethasone produces adverse reactions on the gastric or gastrointestinal tract. According to good medical practice, this pre-medication regimen requires a gastro-protective regimen including (cimetidine, ranitidine, omeprazole or lanzoprazole) in order to avoid said gastric injuries produced by the dexametasone administration.

Severe fluid retention occurred in 6.5% (6/92) of patients despite use of a 3-day dexamethasone premedication regimen.

Patients with a medical history of gastric pathologies (gastric ulcerative process) will be excluding to receive a Docetaxel treatment.

Based on these important considerations, we can be arrived to the following conclusions:

Objects:-

An important object of the present invention which produce a visible increase in the in the Health System expenses due to high cost and complexity involved by the administration of chemotherapy regimen, to which the pre-medication regimen increase the final total treatment cost.

• Further important object of the present invention is that the, Suspension of treatment in some cases in which the previously described reactions appear, also impacts indirectly on the system costs, specially, taking into account the possible complexity of the medical procedures needed in case of appearance of serious adverse reactions (in some cases the hospitalization in the intensive care unit could be necessary).

• Further most important object of the present invention is that the Negative impact on the psychical and physical integrity of patients treated with this medicine.

• Further object of the present invention that, this formulation could reduce in a very noticeable way the occurrence of adverse reactions

• Avoid or reduce the use and cost of pre-medication regimen in a direct relationship with the occurrence of the adverse events.

• Optimize the safety and efficacy profiles of the drug.

• Optimize the risk benefit relationship.

• Optimize the use of the chemotherapy hospitalization beds and the paramedic persons involved in the drug administration, as logical consequence decrease the total cost by patient administration.

• The therapeutically benefit of Docetaxel could increase, as this new Formulation would allow the use of the drug in patients that are presently excluded from receiving treatments with this drug due to the above mentioned adverse reactions.

• Several neoplastic pathologies would be including to Docetaxel list ofindications, presently limited due to the adverse reactions to polisorbate 80.

• Avoidance of drop-outs or delays, temporary or definitive, of the chemotherapy cycles in view of the presence of adverse reactions (increase patients compliance to the treatment).

Description of the invention:-

The present invention relates to novel formulations of Docetaxel and process of making thereof, without using Polysorbate or Chremophor to avoid their known toxicological problems. More particularly Modified natural cyclodextrins has been used for our novel formulation, such as glucosyl-alpha-Cyclodextrin & maltosyl-alpha-Cyclodextrin

Typically the modified cyclodextrins were selected owing to their basket-like structures which have a stronger capacity to encapsulate bulky molecules like docetaxel. Since very less concentrations of the cyclodextrins are required is being achieved, an advantage of minimizing the concentration of the solubilizer so as to make available the API in a considerably large amount with respect to the modified cyclodextrin. This has resulted in the absence of any

adverse reactions in the patients who were administered with these novel preparations.

The formulation storage will be at room temperature (possibility of include climatic zone 4) and avoiding the special cares requires by cold storage (temperature store between 2°C - 8°C). the process of making the formulation comrpsing the following stages,

The first formulation is obtained by the lyophilization of Docetaxel in an organic solvent to obtain a cake of pure Docetaxel. This cake can be easily dissolved with an aqueous solution of tensoactives with much less toxicity than Polysorbate.

The second formulation is obtained by a two lyophilization steps process in which the first one is the lyophilization of pure Docetaxel to obtain a lyophilized bulk. It is easily soluble in aqueous solutions of tensoactives to provide, under a second lyophilization step, a cake in a vial containing practically no residual solvent, and capable of being dissolved even in only water.

Formulations obtained applying these technologies are based on the facility to dissolve Docetaxel API, anhydrous or hydrates, in some solvents that are able of being processed by a lyophilization process to obtain a cake of Docetaxel lyophilized in the first case, or Docetaxel lyophilized together with nonionic tensoactive plus additives in the second case. When Docetaxel is obtained as pure active ingredient lyophilized in vials containing only some residual solvent, the formulation is accompanied by a diluent that should be combined with the lyophilized Docetaxel in order to obtain a reconstituted solution that upon dilution in normal saline solution or 5% dextrose solution, provide a solution ready for perfusion. When Docetaxel is subject of a double lyophilization process, a lyophilizate of Docetaxel accompanied by a tensoactive, a pH regulator (citric acid) and an additive to provide structural rigidity to the cake, is obtained. The

formulation is completed with a solution to reconstitute the cake that could be only Water, normal saline solution, 5% dextrose, or any of them accompanied by some tensoactive.

The time required for total lyophilization of docetaxel during final blending was less and more efficient,

The major advantages of the chemically modified cyclodextrins over Polysorbate 80 are:

Better solubilization of the docetaxel in water as compared to Polysorbate 80

Highly reduced concentrations are required in case of cyclodextrins due to their structure and efficiency in solubilization as compared to Polysorbate 80

The solutions containing cyclodextrins are more stable over long periods of time even at room temperature compared to solutions prepared with Polysorbate 80

No adverse reactions in patients were observed in case of cyclodextrin formulations which were administered as compared to Polysorbate 80 containing formulations

Thus modified cyclodextrin-based formulations vis-à-vis polysorbate based formulations have proved to be more efficacious than the polysorbate counterpart with better stability.

Examples:-

Modified natural cyclodextrins is taken in vesel, along with nonionic tensoactive added additives, and a diluents, combined with the lyophilized Docetaxel in order to obtain a reconstituted solution that upon diluted in normal saline solution or 5% dextrose solution,the formulation wherein the modified natural cylcodextrine used is selected from the group of glucosyl-alpha-Cyclodextrin & maltosyl-alpha-Cyclodextrin,

We claim,

1. **Docetaxel lyophilized parentaral formulation for safe drug delivery system and process of making thereof,** Comprising a Modified natural cyclodextrins , along with nonionic tensoactive plus additives,and a diluents, combined with the lyophilized Docetaxel in order to obtain a reconstituted solution that upon dilution in normal saline solution or 5% dextrose solution,
2. A novel formulation as claimed in claim 1, wherein the modified natural cylcodextrine used is selected from the group consisisiting of glucosyl-alpha-Cyclodextrin & maltosyl-alpha-Cyclodextrin,
3. A novel formulation as claimed in claim 1, wherein the modified cyclodextrins were selected owing to their basket-like structures which have a stronger capacity to encapsulate bulky molecules like docetaxel, Since very less concentrations of the cyclodextrins are required is being achieved,
4. A novellas claimed in the above claims, wherein the storage will be at room temperature (possibility of include climatic zone 4) and avoiding the special cares requires by cold storage (temperature store between 2°C - 8°C).
5. The process of making the formulation comrpsing the following stages,

    a) **Making the first formulation** by the lyophilization of Docetaxel in an organic solvent to obtain a cake of pure Docetaxel, this cake easily be dissolved with an aqueous solution of tensoactives with much less toxicity than Polysorbate,
    b) **making the second formulation** by a two lyophilization steps process in which the first one is the lyophilization of pure Docetaxel to obtain a lyophilized bulk, which is easily soluble in aqueous solutions of tensoactives to provide, under a second lyophilization step, a cake in a vial containing practically no residual solvent, and

capable of being dissolved even in only water,

c) **Formulations** final blending **obtained applying these technologies** to dissolve Docetaxel API, anhydrous or hydrates, in solvents that are able to process by a lyophilization process to obtain a cake of Docetaxel lyophilized in the first case, or Docetaxel lyophilized together with nonionic tensoactive plus additives in the second case. When Docetaxel is obtained as pure active ingredient lyophilized in vials containing only some residual solvent, the formulation is accompanied by a diluents combined with the lyophilized Docetaxel in order to obtain a reconstituted solution that upon dilution in normal saline solution or 5% dextrose solution, provide a solution ready for perfusion, when Docetaxel is subject of a double lyophilization process, a lyophilizate of Docetaxel accompanied by a tensoactive, a pH regulator (citric acid) and an additive to provide structural rigidity to the cake, is obtained. The formulation is completed with a solution to reconstitute the cake that could be only Water, normal saline solution, 5% dextrose, or any of them accompanied by some tensoactive,

6. A novel formulations of Docetaxel and process of making thereof, such as here in described with reference to an example,