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Non Aqueous Formulations and Evaluation of Fosaprepitant Liquid Injectable Dosage Form

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ABSTRACT

Fosaprepitant Dimeglumine is the dimeglumine salt form of fosaprepitant, the water-soluble, N-phosphorylated prodrug of Aprepitant, with antiemetic activity. Antiemetics are typically used to treat motion sickness and the side effects of opioid analgesics, general anesthetics, and chemotherapy directed against cancer. They may be used for severe cases of gastroenteritis, especially if the patient is dehydrated. The lyophilized formulation of Fosaprepitant Dimeglumine is available in the market. It is observed that there is no commercially availability of Fosaprepitant in the solution form. The drug substance is found very unstable in the liquid dosage form due to severe hydrolytic degradation in the presence of water. Therefore, an attempt for developing a simple non-aqueous-based Fosaprepitant dimeglumine was made attempted and based on the available data, it is understood that the nonaqueous formulations data was found satisfactory when compared to aqueous formulations.

INTRODUCTION:

An antiemetic is a drug that is effective against vomiting and nausea. Some antiemetics previously thought to cause birth defects, appear safe for use by pregnant women in the treatment of morning sickness and the more serious hyperemesis gravidarum [1][2].

Antiemetic drugs are types of chemicals that help ease symptoms of nausea or vomiting. Antiemetic drugs may also be used to treat nausea and vomiting caused by other medications, frequent motion sickness, infections, or stomach flu. Antiemetic drugs help to block specific neurotransmitters in the body. These neurotransmitters trigger impulses such as nausea and vomiting, so blocking the impulses will help shut them down. Fosaprepitant dimeglumine is a new drug indicated to prevent nausea and vomiting associated with highly emetogenic cisplatin-based and moderately emetogenic cancer chemotherapy in adults. Due to its complexity in managing, since it requires reconstitution and dilution before intravenous administration. It is a phosphorylated prodrug that is rapidly converted to aprepitant, an oral selective neurokinin-I receptor antagonist approved[1-4].

Fosaprepitant (as Dimeglumine salt) is approved by the DCGI for the usage of the anti-emetic drug. In India, the drug product is approved as the Lyophilized powder Injection of 150 mg/ vial. Lyophilization is a time consuming, tedious, and involves cumbersome procedures. Further, it involves expensive technology to develop a lyophilized product. Hence, an attempt to develop a non-lyophilized drug product such as liquid formulation which would offer convenience for practitioners by avoiding the reconstitution step when preparing the drug for administration.

Fosaprepitant dimeglumine (FPD) is chemically known as 1-Deoxy-1-(Methylamino)-DGlucitol [3-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4 morpholinyl]methyl]-2,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl]phosphonate (2:1), molecular formula is C23H22F7N4O6P.2(C7H17NO5) and molecular weight is 1004.83. It has the below structure.

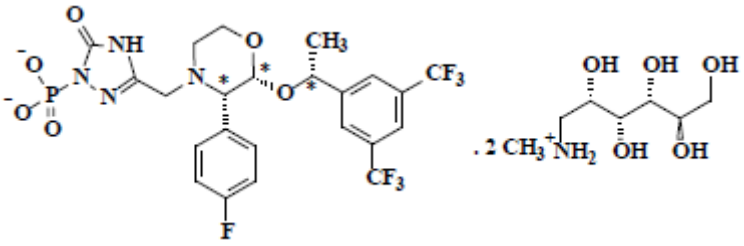

Figure No. 1: Chemical structure of Fosaprepitant dimeglumine

As per the literature available, Fosaprepitant active substance undergoes severe degradation in the aqueous environment. Hence, an attempt to develop a composition focusing on adequate stability of Fosaprepitant while enhancing the solubility necessary for the required therapeutic dose. Hence, an attempt is made to evaluate the simple aqueous-based formulations of Fosaprepitant dimeglumine.

MATERIALS AND METHODS:

Fosaprepitant was procured from pharmafflicates. DMSO and was sourced from Sigma-Aldrich, Polyox castor oil 35, Propylene Glycol, PEG 400, and Soyabean oil was purchased from the commercial sources. All required chemicals used were of standard grade.

Preparation of Fosaprepitant Formulations

A total of 3 formulations were prepared. The concentration chosen of Fosaprepitant is 25 mg/mL based on the solubility. Initially, the drug substance was dissolved in DMSO and later on, one by one excipient was added per below composition table. Finally, the volume is made to 100% using polyoxy castor oil 40. The pH of the formulations was adjusted using pH adjusting agents.

Table No. 1: Formulation of Fosaprepitant Injection

Sl. No.	Ingredients	NFF1	NFF2	NFF3
1	Fosaprepitant (as Dimeglumine)	25 mg/mL	25 mg/mL	25 mg/mL
2	Dimethyl Sulfoxide	20 mg/mL	20 mg/mL	20 mg/mL
3	Soyabean Oil	300 mg/mL	--	--
4	Propylene Glycol	400 mg/mL	--	400 mg/mL
5	PEG 400	--	300 mg/mL	300 mg/mL
6	Glycerin	--	400 mg/mL	--
7	Sodium Hydroxide	Qs to pH	Qs to pH	Qs to pH
8	Hydrochloric Acid	Qs to pH	Qs to pH	Qs to pH
9	Polyoxycastor Oil 40	QS to 1 mL	QS to 1 mL	QS to 1 mL

NFF stands for Non-aqueous Fosaprepitant Formulations

Note: 40.8 mg of Fosaprepitant Dimeglumine equivalent to 25 mg of Fosaprepitant Free Acid

Evaluation of Fosaprepitant Formulations

Physical evaluation

***Description*:** This is a physical observation made by an individual.

pH: pH was measured using a pH meter at about 25°C temperature by diluting the one part of the formulations with 10 mL of water.

Water Content: Water content of all the formulations was measured using Karl-Fischer USP 921 <1a>.

Light Transmission: All the formulations were tested for light transmission at 650 nm using a UV spectrophotometer. The formulations were diluted in 1:10 ratio with water and then measured.

Chemical Evaluation:

Assay: HPLC method was adopted to measure the active drug content from the 3 formulations. The active obtained is expressed as a percent of the labelled amount of Fosaprepitant content. The obtained value of drug content is expected to be within limits of 90.0% to 110.0% (General compendia like USP & BP requirement).

Related Substances: % Content of known and unknown impurities were determined by the HPLC method.

RESULTS AND DISCUSSION:

The results are compiled in table 2. A clear colorless to the light yellow color solution was observed in all three formulations. The pH of all 3 formulations was adjusted to 8.5± 0.1. Light transmission measured for the three formulations found close to 100% indicating the clear transmission of the liquid formulation when each of the formulations was transmitted through a UV spectrophotometer at 650 nm. Concerning the chemical analysis of all the three formulations, it was observed that all the three formulations have shown satisfactory assay levels indicating the correct input of % content of Fosaprepitant vs label claim. It also indicates that the analytical method employed for estimating the % content of Fosaprepitant is correct. From the analysis of the related substance, it was observed that all the 3 known formulations have satisfactory levels of known and unknown impurities.

Table No. 2: Physical and Chemical Evaluation of Aqueous Fosaprepitant Formulations

Sl. No.	Formulation Codes	Description	pH	LT (in%)	Assay (in %)	Water Content	Related Substances
1	NFF1	@	8.12	98.6	98.4%	0.45%	Aprepitant : 0.17% Impurity A: 0.13% Imp B: 0.12% Imp C: 0.09% Imp D: 0.13% Dimer Impurity: 0.14% Single Highest UNK Imp: 0.08% Total Imp: 0.94%
2	NFF2	@	8.23	98.5	99.2%	0.53%	Aprepitant : 0.25% Impurity A: 0.17% Imp B: 0.17% Imp C: 0.13% Imp D: 0.18% Dimer Impurity: 0.24% Single Highest UNK Imp: 0.13% Total Imp: 1.38%
3	NFF3	@	8.09	99.4	97.9%	0.51%	Aprepitant : 0.14% Impurity A: 0.18% Imp B: 0.18% Imp C: 0.13% Imp D: 0.18% Dimer Impurity: 0.18% Single Highest UNK Imp: 0.11% Total Imp: 1.18%

@: Description: A clear colorless solution. LT is Light Transmission.

Imp A: N-benzyl Impurity

Imp B: Desfluro Impurity

Imp C: Dibenzylester Impurity

Imp D: Fosaprepitant N-Oxide

CONCLUSION:

Studied formulations were subjected to physical observation and it is found that no physical description complications was observed. Also, the studied analytical test parameters of pH, light transmission, and water content results were found satisfactory. It is learnt that the pH of the formulations is on the alkaline side due to stable nature of the drug substance in the alkaline compared to an acidic environment. The drug substances has four functional groups which have pKa values of 3.05 ± 0.03, 4.92 ± 0.02, 9.67 ± 0.01, and 10.59 ± 0.03. The pka value of 3.05 corresponds to the morpholinium group, the pka of 4.92 corresponds to the monophosphate group, the pka of 9.67 corresponds to the meglumine counter ion, and the pka of 10.59 corresponds to the triazolinone NH group. The water content of the formulation is found around a 0.5% level. Chemical evaluation such as assay test parameter result was observed satisfactory wherein the level of the assay in all the three formulations is around 98%. However, concerning impurities formation, all the known impurities such as Aprpitant, Impurity A, B, C, and D impurity levels were found satisfactory levels in nonaqueous formulations indicating less degradation when compared to degradation in the aqueous environment. It is also to be noted that % content of unknown impurity is on the higher side in the second formulation; however, the level is found satisfactory in the first and third formulations. From the above experiment, it can be concluded that further fine-tuning to arrest the degradation impurities in the formulation can be worked out.

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