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Formulations and Evaluation of Fosaprepitant Liquid Injectable Dosage Form

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ABSTRACT

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. Fosaprepitant Dimeglumine is commercially available in the market as a lyophilized dosage form in various geographies. Commercially, there is no availability of the drug candidate in the solution form. Literature suggested that the drug candidate is very unstable in the liquid dosage form. It undergoes hydrolytic degradation in the presence of water. Hence an attempt for developing a simple aqueous-based Fosaprepitant dimeglumine was attempted and the data indicated that non-aqueous formulations evaluation needs to be worked out for better control of impurities.

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.

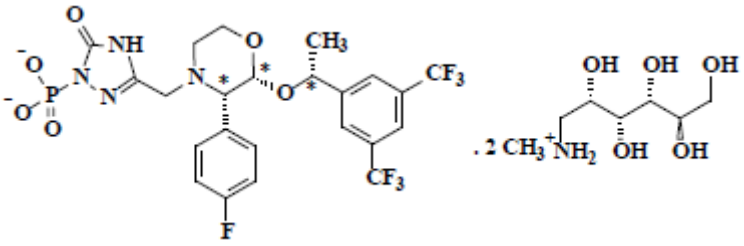

Figure No. 1: Chemical structure of Fosaprepitant dimeglumine

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 and was sourced from Sigma-Aldrich, L-Arginine, Mannitol, Dextrose & Edetate Disodium were received as a gift sample from Merck. Polysorbate 80 was purchased from 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 the water, later on, one by one excipient was added per below composition table. The pH of the formulation was then adjusted and finally, the volume is made to 100% using water.

Table No. 1: Formulation of Fosaprepitant Injection

Sr. No.	Ingredients	FF1	FF2	FF3
1	Fosaprepitant (as Dimeglumine)	25 mg/mL	25 mg/mL	25 mg/mL
2	Polysorbate 80	5 mg/mL	5 mg/mL	5 mg/mL
3	L-Arginine	50 mg/mL	--	--
4	Dextrose	--	50 mg/mL	--
5	Mannitol	--	--	50 mg/mL
6	Edetate Disodium	2 mg/mL	2 mg/ml	2 mg/mL
7	Hydrochloric Acid	Qs to pH	Qs to pH	Qs to pH
8	Sodium Hydroxide	Qs to pH	Qs to pH	Qs to pH
9	Purified Water	QS to 1 mL	QS to 1 mL	QS to 1 mL

FF stands for 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.

Light Transmission: All the formulations were tested for light transmission at 650 nm using a UV spectrophotometer.

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 a 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 a higher amount 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 %)	Related Substances
1	FF1	@	8.54	98.6	96.9%	Aprepitant : 0.87% Impurity A: 0.38% Imp B: 0.27% Imp C: 0.31% Imp D: 0.38% Dimer Impurity: 0.67% Single Highest UNK Imp: 0.19% Total Imp: 3.42%
2	FF2	@	8.42	98.5	96.4%	Aprepitant : 0.92% Impurity A: 0.41% Imp B: 0.23% Imp C: 0.32% Imp D: 0.34% Dimer Impurity: 0.71% Single Highest UNK Imp: 0.21% Total Imp: 3.48%
3	FF3	@	8.59	99.4	95.9%	Aprepitant : 0.88% Impurity A: 0.44% Imp B: 0.25% Imp C: 0.35% Imp D: 0.36% Dimer Impurity: 0.74% Single Highest UNK Imp: 0.23% Total Imp: 3.62%

@: 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:

The overall characterization of all the three formulations concluded that no physical description complications were observed. Analytical results of pH and light transmission test parameters were found satisfactory. The pH of the formulations is on the alkaline side as the drug is stable towards alkaline compared to an acidic environment. Fosaprepitant dimeglumine 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. Chemical evaluation such as assay test parameter result was observed satisfactory wherein the level of an assay in all three formulations is around 95%. However, concerning impurities formation, all the known impurities such as Aprpitant, Impurity A, B, C and D impurity levels were found on the higher side. It is also to be noted that % content of unknown impurity is on the higher side in all the three formulations. Significant levels of Aprepitant formation is observed in all three formulations. Fosaprepitant is a prodrug of aprepitant and accordingly, its antiemetic effects are attributable to aprepitant. From the above experiment, it can be concluded that Fosaprepitant needs fine-tuning concerning a lesser quantity of water to arrest the degradation impurities in the formulation. It is understood that the level of water in the formulation plays an important role. As an alternate, the scope of developing nonaqueous Fosaprepitant shall be attempted.

REFERENCES:

1. Roila F, Herrstedt J, Aapro M, Gralla RJ, Einhorn LH, et al. (2010) Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. Ann Oncol 21 Suppl 5: v232-243.
2. European Medicines Agency (2014) Ivemend® 150MG-EMEA/H/C/000743 -PSUV/0022. EPAR-Product information.
3. Feyer P, Jordan K (2011) Update and new trends in antiemetic therapy: the continuing need for novel therapies. Ann Oncol 22: 30-38.
4. Celio L, Ricchini F, De Braud F (2013) Safety, efficacy, and patient acceptability of single-dose fosaprepitant regimen for the prevention of chemotherapy-induced nausea and vomiting. Patient Prefer Adherence 7: 391-400.
5. Roila F, Herrstedt J, Aapro M, Gralla RJ and *et al.* Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. Ann Oncol. 2010; 21(5): 232-243.
6. Feyer P, Jordan K. Update, and new trends in antiemetic therapy: the continuing need for novel therapies. Ann Oncol. 2011; 22(1): 30-38.
7. Celio L, Ricchini F, De Braud F. Safety, efficacy, and patient acceptability of single-dose fosaprepitant regimen for the prevention of chemotherapy-induced nausea and vomiting. Patient Prefer Adherence. 2013; 7: 391-400.