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Evaluation Of Commercially Available Samples Of Fosaprepitant For Injection 150 Mg/Vial For Important Physico-Chemical Test Parameters

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ABSTRACT

Fosaprepitant Dimeglumine is commercially available in the market as a lyophilized dosage form in various geographies. However, no liquid composition of Fosaprepitant is available. The drug substance and the product are unstable in the aqueous dosage form. The drug substance undergoes degradation in the presence of water upon long storage. Hence, to overcome stability associated problems, an attempt of making simple liquid dosage form via non aqueous composition was attempted. It is also understood that the impurity levels of present research product is comparable to that of market available product which is lyophilized whereas the present research product is a liquid dosage form. It is also to be noted that the present research product and market available freeze-dried product is store refrigerated, hence there are advantages in the present research project. The overall results of this study revealed clearly that the Fosaprepitant Dimeglumine substance can be easily formulated as liquid. However, the formulation is as non-aqueous composition. Higher levels of impurities and also lower assay levels of aqueous based formulations was noticed during the initial time point analysis of all the three aqueous formulations. Hence, non-aqueous trials were evaluated. It is concluded that Fosaprepitant can easily be presented as nonaqueous formulation which would be a stable composition. The present research work aim was to develop a ready to dilute simple liquid injectable composition of anti-emetic drug candidate “Fosaprepitant”. Since, Fosaprepitant is very sensitive to heat and water hydrolysis, identifying suitable solvents was a challenging. During preformulation study, it was confirmed that the active substance is Fosaprepitant Dimeglumine. Based on the study outcome, It was concluded that, aqueous formulations was not possible due to severe degradation. However, the attempt of non-aqueous was able to give better results compared to aqueous compositions of Fosaprepitant. However, still there is a scope to work to fine tune non aqueous formulations of Fosaprepitant with respect to further control of impurities.

INTRODUCTION

Fosaprepitant is such one drug substance wherein the product made of it is being used to treat multiple myeloma. Overview of parenteral preparations, various types of vehicles and general guidance for developing injectable formulations. Fosaprepitant[1-4], which belongs to class of antiemetics and out of various antiemetics, Fosaprepitant is the chosen drug for present research based on the versatility of its nature. As a part of the assessment, drug's physical, chemical and biological properties have been covered. Also the brief details on the parenteral dosage form is covered in the introduction chapter. The literature review was able to interpret mainly on the formulations of Fosaprepitant Dimeglumine which have published in various patents and patent applications. Also, the literature review revealed that the active is highly unstable in aqueous and also sensitive to heat. Based on the literature survey carried, it is understood that there the currently available lyophilized drug product in the globe has shorter time period post primary and secondary dilution with compatible fluids. Hence, there was a need to attempt for the simple liquid and stable dosage form of Fosaprepitant. It was concluded that there is a need to develop a ready to dilute and a simple stable dosage form of anti-cancer drug called Fosaprepitant.

Need of the Study[5-10]:

From the literature review, it was understood that there is a need to work on presenting a simple, ready-to-dilute and stable dosage form of Fosaprepitant composition. Fosaprepitant Dimeglumine is available commercially in the global and local market as a freeze dried product. Commercially, there is no solution form of Fosaprepitant is available. Since the drug product is available as a lyophilized drug product, it would be having a shorter infusion/reconstitution time due to the instable nature of the active. Because of which, the product would tend to undergo degradation to form impurities and also drop in the potency of a drug product. Further, there is a difficulty to health care practitioner mainly during the emergency cases when the primary reconstitution needs to be done since there is a chance of dilution error. Also, the drug substance is highly sensitive to temperature and further degradation is pH dependent and also higher degradation is seen in an aqueous environment and hence it was challenging to optimize a suitable solvent and it's quantity in the present research work to make a stable liquid dosage form. Ready to dilute solution would help in ease of use and avoids one step of reconstitution. Also, present research work would be able to minimize/reduce the dosing errors resulting from

the reconstitution step. As the Lyophilized process or technique is a time-consuming process and also a tedious and requires considerable amount of energy during the process. Robust Freeze drying cycle development, optimization and further scaling up to commercial level is a big challenge and also offers cost involvement because of which the drug product becomes costlier. Hence, there was a need to develop a simple ready to dilute liquid formulation of Fosaprepitant and it was objective of current research product to focus on the same.

Market Available Formulation Evaluation[11-12]:

As a part of study objective, local market available three Indian market products were taken and subjected for evaluation to understand important physico-chemical test parameters. From the analytical evaluation of the three local market samples, it is understood that % content of known and unknown impurities is found comparable with the present research product [NFF1].It is learned that the proposed product is non-lyophilized and has various advantages.

Locally available 3 leading market products of Fosaprepitant for Injection were taken and evaluated for important analytical test parameters. Freeze Dried Drug product is available in the local market and the same was taken for characterization/evaluation.

Table No.:1. Pre-formulation Study Results

Sl. No.	Test parameter	Results
1	Description	White to off-white powder
2	Solubility	Freely soluble in water and in Dimethylsulfoxide.
3	Identification by IR	The sample spectrum exhibited maxima only at the same wavelength as that of standard spectrum of Fosaprepitant Dimeglumine
4	Melting Point	Between 205 and 210°C
5	Hygroscopic study	The material found hygroscopic.
6	XRD study	The result conformed material is crystalline
7	Water content	Not More Than 7.0%
8	pH	Between 6.5 and 8.0

Solubility: Found freely soluble in water, soluble in Dimethylsulfoxide and insoluble in n-Hexane.

Identification by IR

Fosaprepitant Dimeglumine drug sample exhibited characteristic peaks Having Fourier transform IR spectra with absorptions at about 1061,1133, 1170, 1281, 1450, 1509, 1678, 2525, 2858, 2937, and 3395 cm.

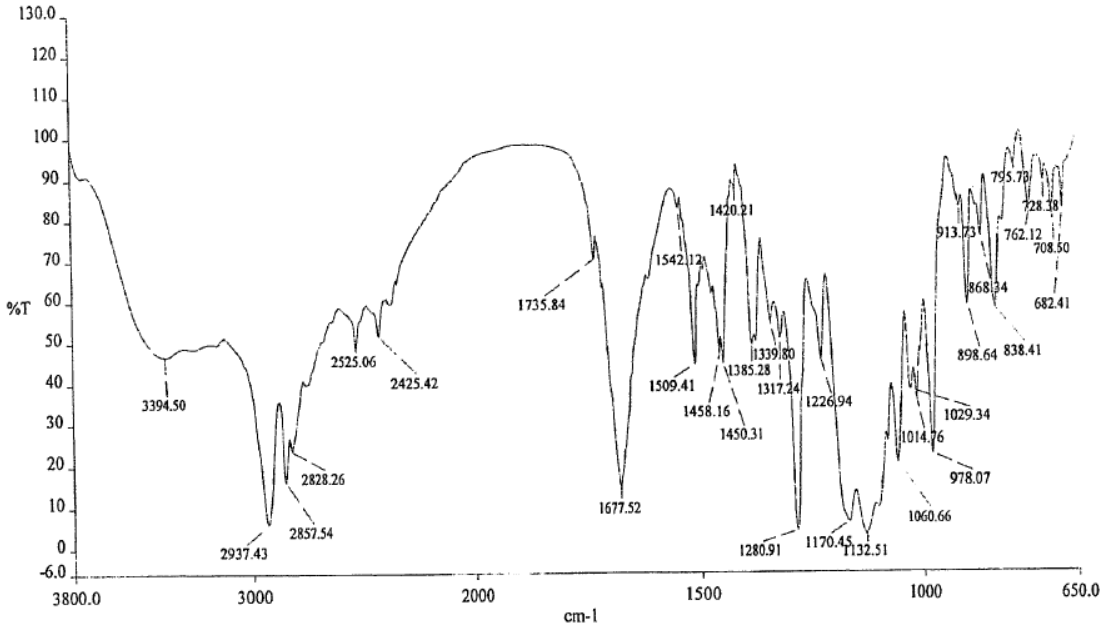

Figure No.1. IR Spectrum of Fosaprepitant Dimeglumine

Melting point by DSC chromatogram

By the onset of the DSC chromatogram, it showed a neutral form of Fosaprepitant characterized by a DSC thermogram with a sharp endotherm at 207^0C with onset at about 200.79^0C and end set at about 212.92°C.

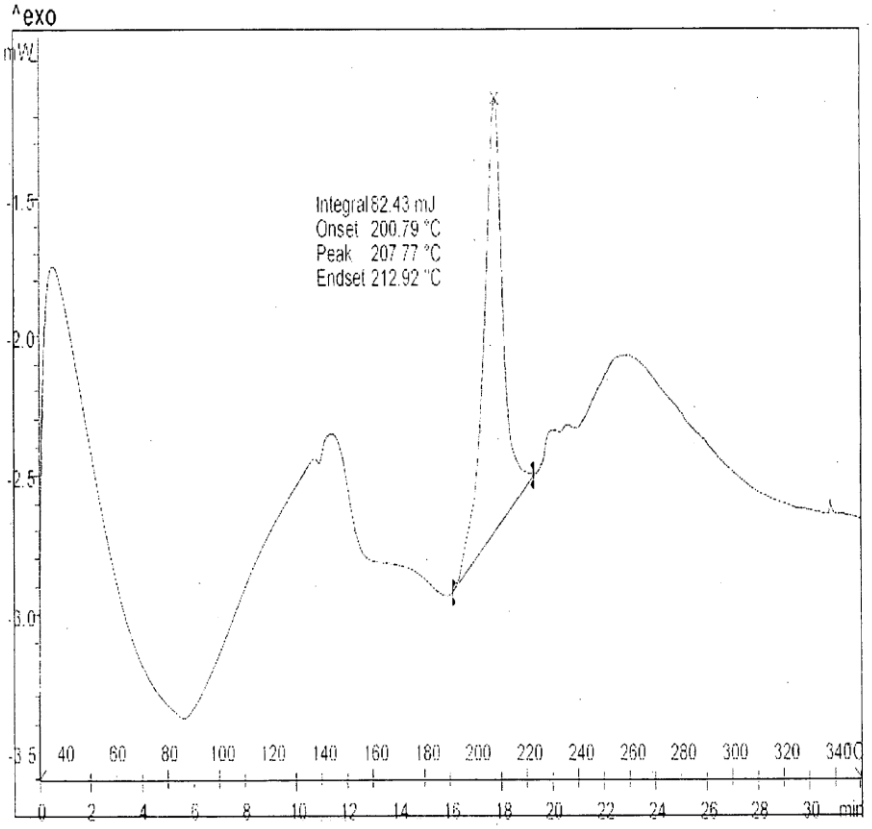

Figure No.: 2. DSC Theromgram of Fosaprepitant Dimeglumine

The drug substance is slightly hygroscopic in nature and environmental conditions such as temperature and humidity induce polymorphic conversions.

Table No.: 2. Hygroscopic Study Results.

API	**Weight (mg)**				**Weight Change (%)**			
	0 Day	7th Day	21st Day	28th Day	0 Day	7th Day	21st Day	28th Day
Fosaprepitant	300.00	305.1	308.7	313.5	Nil	1.7	2.9	6.27

The drug substance is found slightly hygroscopic in nature in high humidity condition. The drug substance has absorbed the moisture around 1.75% of its weight after 28 Days of exposure. Hence the substance is found slightly hygroscopic in nature.

XRD Chromatogram

Based on the XPRD diffractogram, it showed pattern with peaks at about 4.52, 8.29, 13.17, 17.23, 18.31, and 22.510.2°20.

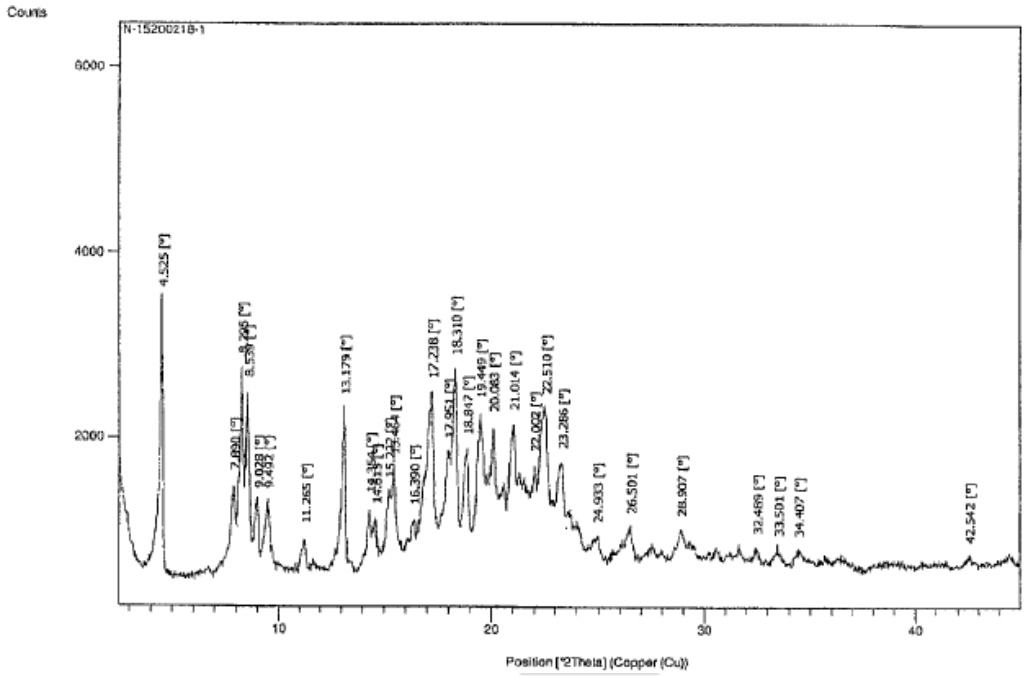

Fig No.:3. XRD diffractogram of Fosaprepitant Dimeglumine

Water Content: The water content of the drug substance Fosaprepitant was measured by using KF titrator and the result was 4.66%

pH: pH of the drug substance was measured using 1.0% of the concertation in carbon dioxide free water and the result is 7.53

Table No.: 3. Evaluation of Commercial Available at Local Market – Fosaprepitant for Injection 150 mg/vial.

Parameters	Market Sample-I	Market Sample-II	Market Sample-III
BRAND NAME	ABC	DEF	GHI
GENERIC NAME	Fosaprepitant for Injection 60 mg/vial.	Fosaprepitant for Injection 60 mg/vial.	Fosaprepitant for Injection 60 mg/vial.
MFG. DATE	Jan-2022	Oct-2021	Aug -2021
EXP. DATE	Dec-2023	Sep -2023	July-2023
PACK PROFILE	10 mL/20mm Clear vial individually packed in carton.	10 mL/20 mm Clear vial individually packed in carton.	10 mL/20 mm Clear vial individually packed in carton.
STORAGE CONDITION	Store refrigerated at 2 to 8^0C. Protect from light.	Store at 2 to 8^0C.	Store 2 to 8^0C with light protected.

Note: No brand names are disclosed due to unavailability of permission taken from the respective brand company. Therefore, abbreviation like ABC, DEF & GHI was assigned in the place of brand name & company name.

Evaluation: The local market available product of Fosaprepitant for Injection 150 mg/vial from three different manufacturers were evaluated comparatively for the Description, Water Content, pH, Assay & Related substances. The results were compiled in the results section.

Stability Study of Optimized Formulation:

Based on the outcome of all the trials made comprising aqueous and non-aqueous, it was learnt that the non-aqueous trail of NFF1code a better formulation based on the initial analytical characterization data. Though the analytical data of NFF1 was also comparative to NFF2 and

NFF3, however the controls of impurities in the code NFF1 was better and based on the data, it was proposed to adopt the NFF1 composition as an optimized one. Hence, it was decided to subject the formulation code of NFF1 to stability study to understand the overall behavior of the product when subjected to accelerated and long term stability conditions for 6 Months.

Table No.:4. Composition Details of the Optimized Formulation. [Reference Code of Formulation is NFF1]

Sl. No.	Ingredients	NFF1	Qty for 750 mL	Quantity Taken
1	Fosaprepitant Dimeglumine	25 mg/mL	30.6 G	30.727G
2	Dimethyl Sulfoxide	20 mg/mL	15.0 G	15.01 G
3	Soyabean Oil	300 mg/mL	225.0 G	225.02 G
4	Propylene Glycol	400 mg/mL	300.0 G	300.12 G
5	Sodium Hydroxide	Qs to pH	Qs to pH	Qs to pH
6	Hydrochloric Acid	Qs to pH	Qs to pH	Qs to pH
7	Poly oxy castor Oil 40	QS to 1 mL	Qs to 750 mL	Qs to 750 G

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

Note: 30.727 G Quantity of Fosaprepitant Dimeglumine is arrived based on the molecular weight and potency correction.

Brief Manufacturing Procedure of Stability Batch.

1. Dispensed the required quantity of ingredients as per the above composition table.

2. Dispensed quantity of Dimethylsulfoxide was collected into the beaker.

3. The drug was added into the above mixture and stirred for 10 minutes; a clear colour solution was obtained.

4. Weighed quantity of Sodium Hydroxide was added to the Propylene Glycol under stirring. Stirred for about 10 minutes. A clear solution was obtained. This solution was added to the above step under stirring. A clear solution was obtained.

5. Weighed quantity of Soybean oil was then added under stirring and stirred for 10 minutes. A clear solution was obtained.

6. The solution was finally made to 100% using polyoxy castor oil 40 under stirring and stirred for 5 minutes. A light yellow color solution was obtained. (pH of the solution (1:10 diluted with water) was recorded 8.18).

Stability Design: In any rational design and evaluation of dosage forms for the proposed research product, the stability of the active component must be a major criterion in determining their acceptance or rejection. Stability can be defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications. Or Stability of a drug can be defined as the time from the date of manufacture and the packaging of the formulation until its chemical or biological activity is not less than a pre-determined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously. The stability studies were carried as per ICH guidelines. The accelerated study was carried at temperatures of 25°C±2°C/60%±5% RH and real time condition was carried at temperatures of 5°C±3°Csample withdrawn at respective intervals of I, II, III & VI month at accelerated condition and III & VI month at real time condition for evaluation parameters such as Description, pH, Water Content, Assay and Related Substances test parameters.

Stability Design of Fosaprepitant Injection:

Table No.: 5. Stability Schedule of Accelerated Condition: 25ºC ± 2ºC/60% RH ± 5% RH &Real time Condition: 5ºC ± 3ºC.

S. No.	Tests	25ºC ± 2ºC/60% RH				5ºC ± 3ºC	
		1M	2M	3M	6 M	3M	6M
1	Description	@	@	@	@	@	@
2	pH	1	1	1	1	1	1
3	Water Content						
4	Assay By HPLC	1	1	1	1	1	1
5	Related Substances	1	1	1	1	1	1

@: The stability exposed vials of respective months for pH study shall be used for measuring the description.

Table No.:6. Evaluation of Indian Market Samples of Fosaprepitant Injection.

Sl. No.	Test Parameters	Results		
1	Brand names	**ABC**	**DEF**	**GHI**
2	Description	$	$	$
3	Reconstitution time	119seconds	98seconds	92seconds
4	pH [Reconstituted solution]	7.67	8.17	8.98
5	Water content by KF [% w/w]	2.13	2.86	3.01
6	Assay by HPLC	97.2%	96.3%	96.7%
7	Related substances by HPLC			
	Aprepitant Impurity	0.21	0.31	0.19
	N-benzyl Impurity A	0.17	0.19	0.24
	Desfluro Impurity B	0.23	0.18	0.21
	Dibenzylester Impurity C	0.18	0.24	0.19
	Fosaprepitant N-Oxide Impurity D	0.09	0.17	0.13
	Single Highest UK Impurity	0.18	0.12	0.24
	Total Impurities	1.18	1.45	1.39

$: A white to off white lyophilized powder

Evaluation Aquesous Fosaprepitant Formulations.

Table No.:7. 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% N-benzyl Impurity A: 0.38% Desfluro Imp B: 0.27% Dibenzyl ester Imp C: 0.31% Fosaprepitant N-Oxide Imp D: 0.38% Single Highest UNK Imp: 0.19% Total Imp: 3.42%
2	FF2	@	8.42	98.5	96.4%	Aprepitant: 0.92% N-benzyl Impurity A: 0.41% Desfluro Imp B: 0.23% Dibenzylester Imp C: 0.32% Fosaprepitant N-Oxide Imp D: 0.34% Single Highest UNK Imp: 0.21% Total Imp: 3.48%
3	FF3	@	8.59	99.4	95.9%	Aprepitant : 0.88% N-benzyl Impurity A: 0.44% Des fluoro Imp B: 0.25% Dibenzylester Imp C: 0.35% Fosaprepitant N-Oxide Imp D: 0.36% Single Highest UNK Imp: 0.23% Total Imp: 3.62%

ACF stands for Aqueous Fosaprepitant Formulations.

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

Table No.:8. Physical and Chemical Evaluation of Non-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% N-benzyl Impurity A: 0.13% Desfluro Imp B: 0.12% Dibenzylester Imp C: 0.09% Fosaprepitant N-oxide Imp D: 0.13% Single Highest UNK Imp: 0.08% Total Imp: 0.94%
2	NFF2	@	8.23	98.5	99.2%	0.53%	Aprepitant : 0.25% N-benzyl Impurity A: 0.17% Desfluro Imp B: 0.17% Dibenzylester Imp C: 0.13% Fosaprepitant N-oxide Imp D: 0.18% Single Highest UNK Imp: 0.13% Total Imp: 1.38%
3	NFF3	@	8.09	99.4	97.9%	0.51%	Aprepitant : 0.14% N-benzyl Impurity A: 0.18% Desfluro Imp B: 0.18% Dibenzylester Imp C: 0.13% Fosaprepitant N-oxide Imp D: 0.18% Single Highest UNK Imp: 0.11% Total Imp: 1.18%

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

NFF Stands for Non-Aqueous Fosaprepitant Formulations.

Stability Study of Fosaprepitant Optimized Formulation.

Table No.: 9. Stability Study of Optimized Fosaprepitant Formulation [Non Aqueous].

[Composition Reference. NFF2]

Sl. No.	**Test Parameters**	**Results**							
		25^{0}C/60% RH						**5 ±3^{0}C**	
		Initial		**1M**	**2M**	**3M**	**6M**	**3M**	**6M**
1	Description	$		$	$	$	$	$	$
2	pH	8.16		8.23	8.19	8.28	8.19	8.14	8.21
3	Water content by KF [% w/w]	0.52		0.58	0.49	0.51	0.58	0.47	0.54
4	Assay by HPLC [in %]	99.5		98.6	97.2	96.3	95.2	98.2	98.4
5	Related substances by HPLC [in %]	Aprepitant	0.21	0.25	0.26	0.28	0.41	0.19	0.23
		N-benzylImpurity A	0.15	0.22	0.29	0.36	0.43	0.13	0.16
		Desfluro Imp B	0.16	0.19	0.18	0.24	0.32	0.21	0.27
		Dibenzylester Imp C	0.07	0.13	0.15	0.19	0.24	0.10	0.11
		Fosaprepitant N-oxide Imp D	0.16	0.21	0.28	0.33	0.41	0.21	0.23
		Single Highest UK Impurity	0.14	0.17	0.18	0.24	0.31	0.13	0.18
		Total Impurities	0.99	1.29	1.48	1.78	2.31	1.07	1.38

@:A Clear yellow colour solution, UK: Unknown.

Table No.:10. Photostability Study of Optimized Formulation. [Optimized Batch of Composition Reference: NACF2]

Sl. No.	Condition	Description	pH	Water Content	Assay (in %)	Related Substances
1	Primary Pack	@	8.18	0.51	98.3	Aprepitant : 0.19% N-benzyl Impurity A: 0.21% Desfluro Imp B: 0.17% Dibenzylester Imp C: 0.16% Fosaprepitant N-oxide Imp D: 0.18% Single Highest UNK Imp: 0.14% Total Imp: 1.24%
2	Dark Control	@	8.29	0.49	99.7	Aprepitant : 0.18% N-benzyl Impurity A: 0.16% Desfluro Imp B: 0.11% Dibenzylester Imp C: 0.11% Fosaprepitant N-oxide Imp D: 0.12% Single Highest UNK Imp: 0.09% Total Imp: 0.93%
3	With Secondary Pack	@	8.33	0.53	99.2	Aprepitant : 0.14% N-benzyl Impurity A: 0.13% Desfluro Imp B: 0.14% Dibenzylester Imp C: 0.13% Fosaprepitant N-oxide Imp D: 0.14% Single Highest UNK Imp: 0.11% Total Imp: 0.89%

@: A Clear yellow colour solution.

Table No.:11. Evaluation of Indian Market Samples of Fosaprepitant Injection.

Sl. No.	**Test Parameters**	**Results**		
1	Brand names	**ABC**	**DEF**	**GHI**
2	Description	$	$	$
3	Reconstitution time	119seconds	98seconds	92seconds
4	pH [Reconstituted solution]	7.67	8.17	8.98
5	Water content by KF [% w/w]	2.13	2.86	3.01
6	Assay by HPLC	97.2%	96.3%	96.7%
7	Related substances by HPLC			
	Aprepitant Impurity	0.21	0.31	0.19
	N-benzyl Impurity A	0.17	0.19	0.24
	Desfluro Impurity B	0.23	0.18	0.21
	Dibenzylester Impurity C	0.18	0.24	0.19
	Fosaprepitant N-Oxide Impurity D	0.09	0.17	0.13
	Single Highest UK Impurity	0.18	0.12	0.24
	Total Impurities	1.18	1.45	1.39

$: A white to off-white lyophilized powder

Methodology:

The methodology aspects were focusing mainly on the aspects of aqueous and nonaqueous formulation trials. Also, the primary objective of the methodology was to arrive an optimized

trial with respect to quality and quantity of solvents/vehicles to arrive at a simple and stable formulation. The methodology aspects also covered the pre-formulation aspects which confirmed that the tested active pharmaceutical ingredient is Fosaprepitant dimeglumine. The various aspects of methodology are covered below.

Aqueous Formulations: Total of 3 formulations were prepared. The concentration chosen of Fosaprepitant is 25 mg/mL based on the solubility. During the developmental trials, the molecular weight correction was considered since the label claim is Fosaprepitant and input material is Fosaprepitant Dimeglumine. Initially, the drug substance was dissolved in water and one by one excipient was added and pH of the formulation was adjusted. Finally volume is made to 100% using water. Hydrochloric Acid and Sodium Hydroxide were used as acidifiers in the formulation.

The aqueous solubility of Fosaprepitant dimeglumine is pH dependent however the desired Fosaprepitant concentration could not be achieved by pH-control. Moreover, extreme lower pH levels [less than 3.0] were found to promote degradation and are thus unsuitable for administration. A clear colourless solution was observed from all the three formulations. 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 UV spectrophotometer at 650 nm. With respect to the chemical analysis of all three formulations, it was observed that all the three formulations has 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 related substances analysis, it was observed that all the 3 known formulations have higher amount of known and unknown impurities.

pH of the formulations is on alkaline side as the drug is stable in alkaline compared to 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 monophosphonate 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 assay in all the three formulations is around 95%. However,

with respect to impurities formation, all the known impurities such as Aprpitant, Impurity A, B, C and D impurity levels were found on higher side. It is also to be noted that % content of unknown impurity is on 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 with respect to lesser quantity of water so as 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 non aqueous Fosaprepitant was attempted.

Non Aqueous Formulations:

Based on the physicochemical data of aqueous formulations of Fosaprepitant, it was decided to attempt non-aqueous compositions to evaluate the overall nature of the drug substance when the composition is presented in non-aqueous formulations. Fosaprepitant Dimeglumine is freely soluble in DMSO solvent. As a part of assessment, total of 3 non-aqueous formulations was made. In non-aqueous composition also, the concentration chosen of Fosaprepitant was 25 mg/mL based on the solubility. Initially, the drug substance was dissolved in DMSO solvent, later on remaining solvents/excipient were added per composition table shown under non-aqueous formulation trials. Finally volume was made to 100% using polyoxy castor oil 40. Hydrochloric acid and Sodium Hydroxide were used as pH adjusting agent in the case of non-aqueous formulations.

A clear colourless to light yellow colour solution was observed in all the three formulations. pH of all 3 formulations were 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 the each of the formulations were transmitted through UV spectrophotometer at 650 nm. With respect to the chemical analysis of all the three formulations, it was observed that all three formulations have shown satisfactory assay levels. From the related substances analysis, it was observed that all the 3 known formulations have satisfactory levels of known and unknown impurities.

Market Available Formulation Evaluation:

As a part of study objective, local market available three Indian market products were taken and subjected to evaluation to understand important physico-chemical test parameters. From the analytical evaluation of the three local market samples, it is understood that % content of known and unknown impurities is found comparable with the present research product [NFF1].It is learnt that the proposed product is non-lyophilized and has various advantages as stated in the objectives chapter.

This chapter brings overall conclusion of the present research product. The overall results of this study revealed clearly that the Fosaprepitant Dimeglumine substance can be easily formulated as liquid. However, the formulation be as non-aqueous composition. Higher levels of impurities and also lower assay levels of aqueous based formulations was noticed during the initial time point analysis of all the three aqueous formulations. Hence, non-aqueous trials were evaluated. It is concluded that Fosaprepitant can easily be presented as nonaqueous formulation which would be a stable composition. The present research work aim was to develop a ready to dilute simple liquid injectable composition of anti-emetic drug candidate “Fosaprepitant”. Since, Fosaprepitant is very sensitive to heat and water hydrolysis, identifying suitable solvents was a challenging in the present research work was focused.

During preformulation study, it was confirmed that the active substance is Fosaprepitant Dimeglumine. Based on the study outcome, It was concluded that, aqueous formulations were not possible due to severe degradation. However, the attempt of non-aqueous was able to give better results compared to aqueous compositions of Fosaprepitant. However, still there is a scope to work to fine tune non aqueous formulations of Fosaprepitant with respect to further control of impurities.

Worldwide, Fosaprepitant Dimeglumine is commercially available in the market as a lyophilized dosage form in the various geographies. However, no liquid composition of Fosaprepitant is available. The drug substance and the product is unstable in the aqueous dosage form. The drug substance undergoes degradation in the presence of water upon long storage. Hence, to overcome stability associated problems, an attempt of making simple liquid dosage form via non aqueous composition was attempted. It is also understood that the impurity levels of present research

product is comparable to that of market available product which is lyophilized whereas the present research product is a liquid dosage form. It is also to be noted that the present research product and market available freeze-dried product is store refrigerated, hence there are advantages in the present research project.

The overall results of this study revealed clearly that the Fosaprepitant Dimeglumine substance can be easily formulated as liquid. However, the formulation is as nonaqueous composition. Higher levels of impurities and also lower assay levels of aqueous based formulations was noticed during the initial time point analysis of all the three aqueous formulations. Hence, non-aqueous trials were evaluated. It is concluded that Fosaprepitant can easily be presented as nonaqueous formulation which would be a stable composition. The present research work aim was to develop a ready to dilute simple liquid injectable composition of anti-emetic drug candidate "Fosaprepitant". Since, Fosaprepitant is very sensitive to heat and water hydrolysis, identifying suitable solvents was a challenging in the present research work was focused.

During preformulation study, it was confirmed that the active substance is Fosaprepitant Dimeglumine. Based on the study outcome, It was concluded that, aqueous formulations was not possible due to severe degradation. However, the attempt of non-aqueous was able to give better results compared to aqueous compositions of Fosaprepitant. However, still there is a scope to work to fine tune nonaqueous formulations of Fosaprepitant with respect to further control of impurities.

REFERENCES:

1. The package insert of Emend® approved by USFDA.
2. 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.
3. European Medicines Agency (2014) Ivemend® 150MG-EMEA/H/C/000743 -PSUV/0022. EPAR-Product information.
4. Feyer P, Jordan K (2011) Update and new trends in antiemetic therapy: the continuing need for novel therapies. Ann Oncol 22: 30-38.
5. 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.
6. Quinlan, Jeffrey D.; Hill, D. Ashley (1 June 2003). "Nausea and Vomiting in Pregnancy - American Family Physician". American Family Physician. 68 (1): 121–128. Retrieved 2015-10-09.

7. Schaefer, Christof; Scialli, Anthony; Rost van Tonningen, Margreet (2001). "Antiemetics and hyperemesis gravidarum". Drugs During Pregnancy and Lactation: Handbook of Prescription Drugs and Comparative Risk Assessment. Gulf Professional Publishing. ISBN 978-0-444-50763-1.
8. IV aprepitant (Cinvanti) for chemotherapy-induced nausea and vomiting. Med Lett Drugs Ther. 2018 Dec 03;60(1561):e200-e201.
9. Navari RM, Schwartzberg LS. Evolving role of neurokinin 1-receptor antagonists for chemotherapy-induced nausea and vomiting. Onco Targets Ther. 2018; 11:6459-6478.
10. Guan S, Zhang L, Zhong D, Ma Q, Meng F, Shao Y, Yu T, Liu X. [Curative Effect of Aprepitant Preventing CINV]. Zhongguo Fei Ai Za Zhi. 2018 Oct 20;21(10):800-804.
11. Zhang Y, Hou X, Zhang R, Chen G, Huang Y, Yang Y, Zhao Y, Fang W, Hong S, Kang S, Zhou T, Zhang Z, Chen X, Zhang L. Optimal prophylaxis of chemotherapy-induced nausea and vomiting for moderately emetogenic chemotherapy: a meta-analysis. Future Oncol. 2018 Aug;14(19):1933-1941.
12. Gilmore J, D'Amato S, Griffith N, Schwartzberg L. Recent advances in antiemetics: new formulations of 5HT3-receptor antagonists. Cancer Manag Res. 2018; 10:1827-1857.