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Dissolution Enhancement of Poorly Soluble Drug Aprepitant by Hot Melt Extrusion Method Using Hydrophilic Polymer: A Solid Dispersion Technique.

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ABSTRACT

The objective of this study was to develop a solid dispersion method for enhancing the aqueous solubility of aprepitant (BCS class II drug). In the present study a simplified definitive equivalent formulation is targeted by preparing a solid dispersion using hot melt extrusion. Model formulation isolated from a range of carrier-plastizer mixtures based on dissolution enhancements. Final choice was made with a combination of hydrophilic polymeric carrier hydroxyl propyl cellulose and a non ionic semisolid, hydrophilic–hydrophobic surfactant Tocophernasol having HLB-13. Aprepitant and hydroxyl propyl cellulose were granulated with hot tocophernasol and the prepared physical mixture was used for hot melt extrusion. The prepared solid dispersion evaluated for change of crystalline nature using Differential scanning calorimetry, FT-IR and Powder X-Ray diffraction. Further capsules formulations were developed using additives polyethylene glycol-4000, Sodium lauryl sulfate and Magnesium stearate. Formulations were evaluated for in vitro drug release in 2.2% SLS media and solubility improvement was assessed by using water as media. Prepared solid dispersion was shown dissolution equivalency in water media and the Formulations F7 and F8 were showed comparative dissolution with innovator formulation. The solid dispersion formulation by hot melt extrusion technique improved aqueous solubility of poorly-water soluble aprepitant and formulations are in vitro equivalent with innovator product.

Keywords: dissolution, polymer, solid dispersion

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INTRODUCTION

Oral drug delivery is the easiest and most convenient route for administering drugs. The oral bioavailability of a class II drugs having low solubility and high permeability it depends on its solubility therefore, an attempt to enhance the dissolution rate of drugs with limited water solubility is often required[1,2]. Beginning with polymorphic changes[3] and salt formation of an ionizable drug[4], co-solvency[5], solid dispersion [6], inclusion complex, [7,8] micronization [9], self-emulsifying delivery system[7,10], nanonization [11]etc, are widely explored techniques for solubility enhancement. Selection of solubilization method varies according to physicochemical property of drug and scale up feasibility of an individual technique.

Solid dispersions are one of the most successful methods and involve a mixture of a poorly water-soluble drug in one or more hydrophilic carriers in the solid state [12,13]. Solid dispersions can improve the dissolution rate of drugs by reducing their particle size, increasing the porosity and increasing their wettability of the final product. Mainly two methods reported for the preparation of solid dispersions are the melting method and the solvent evaporation method[13]. In the hot melt extrusion method, solid dispersions are prepared by melting the drug within a carrier, cooling the mixture and pulverizing the final product. The miscibility of the carrier among with drug molecules is the key factor to obtain an acceptable solid dispersion. In the method of solvent evaporation, the drug and the carrier are dissolved in a volatile solvent then the solvent is evaporated under a vacuum or an oven. Finally, the resulting film is pulverized.

Aprepitant(5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]e-thoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3-H-1,2,4-triazol-3-one; MK-0869; EMEND) is a potent and selective neurokinin 1 receptor antagonist, more effective in the treatment of chemotherapy-induced nausea and vomiting (CINV).Polymeric carriers have been the most successful carriers for solid dispersions because they can be used to prepare amorphous solid dispersions. Hydroxypropylcellulose (HPC) is water soluble and is widely used as a carrier for solid dispersions to increase the drug dissolution rate. Because of the high glass transition temperature (Tg) of HPC, its good solubility in most organic solvents including water , ethanol, methanol and chloroform makes it suitable for preparing solid dispersions Yuasa *et al*., carried out extensive studies of the influence of the chain length and proportion of HPC in the solid dispersion concluded that the release rates enhanced as the ratio of HPC was amplified and when lower Molecular weight HPCs were used as the carrier Literature suggests the usage of low viscous and suitable chain length products of HPC for solid dispersion formulation.

Therefore, the context of study was focused on exploring HPC-SL as a carrier and a suitable plasticizer from a group of components Vitamin-E.TPGS (Tocophernasol), Solutol HS 15, Gelucire 44/14 to increase the aqueous dissolution rate of aprepitant by developing a solid dispersion formulation.

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MATERIALS AND METHODS

Materials

Aprepitant sample was received as gift sample from MSN laboratories Ltd, Hyderabad. HPC-SL from Nippon, Vitamin-E.TPGS from BASF, Solutol HS 15 from BASF, Gelucire 44/14 from Gattefossae, PEG-4000 and PEG-8000 from clariant were samples supplied by vendors. Magnesium stearate, sodium lauryl sulphate and aerosol were procured from Ferro industries, India. All the other reagents were analytical grade used without further purification.

Solubility study

Table 1

S. No	Components	Solubility
	BCS Solubility in Buffers and selected media	
1	Aprepitant + Water	0.4mg/250mL
2	Aprepitant + 0.1 N HCl	10.8mg/250mL
3	Aprepitant + Acetate pH 4.5	0.4mg/250mL
4	Aprepitant + Sod. Phosphate pH 6.8	0.4mg/250mL
5	Aprepitant + 0.5% SLS in water	36.7mg/250mL
6	Aprepitant + 1% SLS in water	62.5mg/250mL
7	Aprepitant + 1.5% SLS in water	89.2mg/250mL
8	Aprepitant + 2% SLS in water	93.4mg/250mL
9	Aprepitant + 2.2 % SLS in water	124.8mg/250mL
	Solubility in Surfactants	
1	Aprepitant + Labrasol	35mg/gm
2	Aprepitant + Gelucire 44/14	30mg/gm
3	Aprepitant + PG	13mg/mL
4	Aprepitant + PEG 400	12mg/mL
5	Aprepitant + Capryol 90	19.6 mg/mL
6	Aprepitant + Capmul MCM	10mg/mL
7	Aprepitant + Tween 80	9.6mg/mL
8	Aprepitant + Poloxamer 407	10.3mg/mL
9	Aprepitant + Corn oil	8mg/mL
12	Aprepitant + Soyabean Oil	7.4mg/mL
13	Aprepitant + Castor oil	11mg/mL
14	Aprepitant + Peanut oil	10.8mg/mL
15	Aprepitant + Vitamin E TPGS	30.8mg/mL
19	Aprepitant + Cremephor EL	6mg/mL
20	Aprepitant + Lauroglycol	4mg/mL
21	Aprepitant + Cremephor RH 40	22.5mg/mL
22	Aprepitant + 50%Labrasol + 50% Gelucire 44/14	33.4 mg/gm
	Solubility in Solvents	
1	Aprepitant + Ethanol	50mg/mL
2	Aprepitant + Acetone	70mg/mL
3	Aprepitant + Isopropyl alcohol	15mg/mL
4	Aprepitant + 50%Acetone + 50% Ethanol	110mg/mL

BCS (Biopharmaceutical classification system) solubility study was carried out on Aprepitant. The saturated solubility of Aprepitant API (125mg) was determined in 250 ml of media (used medias are-water, buffers with pH 4.5, 6.0, and 0.5%, 1% and 2.2% SLS in water). The concentration of drug substance dissolved in each media was determined by

using assay method (By HPLC), based on the solubility data chosen the least soluble and release medias for aprepitant drug product dissolution evaluation.

The solubility of Aprepitant API evaluated in surfactants using forceful conditions like heat (Up to 40˚C) & sonication. Excess amount of Aprepitant API added to 5gm of surfactant mixed under forceful conditions for suitable period and centrifuged to obtain clear soluble portion, further analyzed the samples using assay method (by HPLC). The solubility of aprepitant API in solvents was determined by gradually adding (5/10 mg increments) the API into 1ml of solvent until the loss of solution clarity. Details of the solubility study are represented in table no: 1

Preparation and evaluation of carrier combinations

Table 2: Dissolution results of formulations in water media

S.No	Name (API + Exc.)	Description	Assay	Dissolution media –Water , 60minutes. % dissolution.
1	Aprepitant : HPC-SL(1:1.4) + vit. E tpgs 10%	Light yellow to off white hard granules	103.2	11.39
2	+ vit. E tpgs 20%	Light yellow to off white hard granules	102.5	10.26
3	+ vit. E tpgs 30%	Light yellow to off white oily solid mass	101.0	7.32
4	+ solutrol HS 10%	Light yellow to off white hard granules	100.5	6.05
5	+ solutrol HS 20%	Light yellow to off white hard granules	100.7	4.07
6	+ solutrol HS 30%	Light yellow to off white oily solid mass	104.4	4.29
7	+ Gelucirine 44/14 10%	Off white,hard crystals	102.4	3.52
8	+ Gelucirine 44/14 20%	Off white,hard crystals	106.5	3.72
9	Aprepitant : HPC-SL(1:1.2) + vit. E tpgs 15%	Light yellow to off white hard granules	101.1	8.96
10	Aprepitant : HPC-SL(1:1.4) + vit. E tpgs 15%	Light yellow to off white hard granules	99.4	11.52
11	Aprepitant : HPC-SL(1:1.6) + vit. E tpgs 15%	Light yellow to off white hard granules	99.6	11.13
12	Aprepitant : HPC-SL(1:1.8) + vit. E tpgs 15%	Light yellow to off white hard granules	100.5	10.97
13	Aprepitant : HPC-SL(1:2.0) + vit. E tpgs 15%	Light yellow to off white hard granules	101.6	11.37

Aprepitant: HPC-SL, drug polymer mixture prepared in 1:1.2 (125mg: 250mg) ratios in duplicate sets. Physical mixture was prepared by mixing respective amount of melted plasticizer (10%w/w, 15w/w, 20%w/w) with above drug, polymer mixture. Prepared physical mixtures were melted to glass transition temperature and melts were allowed to cool down at room temperature. Flakes were crushed and sifted through sieve ASTM # 30. Melt solid dispersion granules were evaluated for dissolution of aprepitant in water media (900mL) at 100RPM. 125mg equivalent aprepitant melt granules dispersed in 900ml of purified water at 100 rpm, Dissolution sample collected at 60 minutes period.

The above dissolution results showed a trend in formulations with improved dissolution results by increasing the concentration of plasticizer Vitamin-E.TPGS. At the optimal concentration of 15% w/w the dissolution results are good and satisfactory. Hence the same concentration used as optimized plasticizer concentration and polymer concentration further evaluated with 1:1.2,1:1.4,1:1.6,1:1.8 and 1:2 ratios in similar manner. Evaluated compositions were reported in table no : 2.

Preparation of hot melt extrudate

Identified ratio of Aprepitant, hydroxy propyl cellulose-SL 1:1.4 was mixed and melt granulated with Vitamin E TPGS (Tocophernasol). Prepared physical mixture extruded through twin screw hot melt extruder at temperature of zone 1:30˚C zone 2:70˚C, Zone 3-7: 140˚C and die at 145˚C with screw RPM 200. Extrudate was allowed to cool down at room temperature. Granules were made by crushing and sifted through Sieve ASTM # 30. Granules were characterized by DSC, FT-IR, and XRD techniques.

Preparation of solid dispersion formulations

Hot melt granules were pre-lubricated with polyethylene glycol (Respective amount of PEG used for pre lubrication of each batch).Final lubrication of granules was done with the components sodium lauryl sulfate or magnesium stearate in mentioned concentrations. Final equivalent weight of lubricated blend filled in size"00" capsules. Various formulation concentrations opted were shown in Table-3. Formulations were evaluated for dissolution of aprepitant in 2.2%SLS in water media.

Characterization of aprepitant solid dispersions

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry measurements were performed on aprepitant, HPC-SL, vitamin-E.TPGS and physical mixture and on solid dispersion using differential scanning calorimeter (METTLER TOLEDO with e STAR software). The samples were placed in a sealed aluminum crucible and evaluated with a heating rate of 10ºC/min at a temperature range of 30-350ºC.

X- Ray Powder Diffraction (XRD)

The powder crystallinity of the aprepitant and the aprepitant solid dispersions were determined using Bruker D8 Advance XRD with copper target instrument. The conditions were maintained at 40 Kv voltages, with 40 MA current at room temperature. The scanning rate employed was 0.1°/sec over a range of 2θ values from 4°to 40°.

FT-IR

An FTIR-8400S spectrophotometer (Shimadzu, Japan) was used to analysis of pure drug, physical mixtures of the drug with the excipients-FTIR with KBr disc. For each the spectrum, scans were obtained at a resolution of 4 cm-1 from a frequency range of 400-

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4000cm^{-1} . After running the spectra, significant peaks relating to major functional groups were identified; spectra of the subsequent sample of the same compound were compared with the original.

Scanning Electron Microscopy (SEM)

SEM was used to study the surface morphology of the extrudates and to examine the precipitation of drug from surface. Samples were mounted onto aluminum discs using double-sided adhesive copper mounting tape and placed in a dry atmosphere under vacuum overnight, prior to coating and analysis. Samples were subsequently coated with a thin film of gold (15 nm) using an Agar® Auto Gold Sputter Coater. SEM was performed using a JEOL 6500F (JEOL Ltd., Tokyo, Japan) field emission microscope operating at an accelerating voltage of either 2 or 5 kV with a 4 mA beam current emission. Images were captured using Jeol® software.

In vitro dissolution studies

Dissolution Studies

In vitro dissolution studies of Aprepitant and its dispersions were carried out by using dissolution apparatus with rotating paddles at 100rpm. Sample was added to 900 ml of 2.2% SLS media at 37±0.5.Dissolution sample collected at 10,15, 20, 30, 45 and 60minutes period. Best formulation dissolution compared with marketed formulation. Based up on the data obtained from the dissolution studies the *in vitro* kinetic modeling parameters such as zero order, first order, higuchi and peppa's model rate constants for solid dispersions were determined. The dissolution parameters were given in table-3

Table 3: Different formulations of aprepitant solid dispersions

S.No	Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Hot melt stage										
1	Aprepitant	125	125	125	125	125	125	125	125	125
2	Hydroxy propyl cellulose	175	175	175	175	175	175	175	175	175
3	Vitamin-E TPGS	45	45	45	45	45	45	45	45	45
Pre lubrication stage										
4	Polyethylene glycol-4000	100	--	150	150	150	150	150	150	150
5	Polyethylene glycol-8000	--	100	--	--	--	--	--	--	--
Lubrication stage										
6	Sodium lauryl sulfate	--	--	--	2.5	5.0	10	--	--	--
7	Magnesium stearate	--	--	--	--	--	--	1.25	2.5	5
Total weight:		445	445	495	497.5	500	505	496.25	497.5	500

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Data Analysis

Data are expressed as mean ± standard deviation, correlation coefficients (R2) and were processed using BCS software. The dissolution profiles of all the selected formulations for aprepitant were compared with the marketed formulation. Approach of similarity factor, *f2,* with all time points included in the *in vitro* dissolution studies. The equation for calculating similarity factor f_2 is defined by the following equation.

$$f_1 = n \Sigma n_{t=1} (R_t - T_t) / \Sigma R_t \times 100 \quad \text{----------} \quad (1)$$

$$f_2 = 50 \log \{[1+1/n \Sigma n_{t=1} (R_t - T_{t)2}]^{-0.5} \times 100\} \text{----------} \quad (2)$$

Where n is the number of dissolution time and R_t and T_t are the % dissolved at each tome point for reference and test dissolution values at time't'. If f_1 value was close to 0, and an f2 value was close to 100, the two curves were considered similar.

In general, if the *f1* value was less than 15 (0-15), and the *f2* value was greater than 50 (50-100), the dissolution profile of the two curves was considered similar[14].

Stability Studies

The prepared solid dispersions were further subjected to accelerated stability studies upto3 months at 25^0c with 60% RH, 30^0C with 75% and 40^0c with 75%, samples were withdrawn after one, two and three months and analyzed by HPLC method.

RESULTS AND DISCUSSION

In the present context of was made to improve the solubility and dissolution rate of aprepitant. The solid dispersions of aprepitant were prepared by hot melt extrusion method using HPC-SL as a carrier and vitamin-E.TPGS as a plasticizer

Solubility study

Solubility data of aprepitant in buffers, surfactants and solvents are showed in below table -3 Aprepitant showed poor solubility in Buffers, Surfactants. In the context of used surfactants Vitamin E TPGS, Gelucire 44/14, Solutol HS 15, Labrasol were shown good solubility and the solvent system 50-50 ratio of Acetone-Ethanol was shown highest solubility. From the buffer solubility data water was selected as discriminating media for solubility improvement and 2.2% SLS media was selected as formulation release media to know virtual formulation kinetics.

Characterization of Solid Dispersions:

DSC study

The DSC curve of aprepitant shown in fig.1 exhibited a sharp endothermic peak at 254.02^0 c. Which indicates the melting point of drug. In this scan no additional peaks present it indicates polymorphic forms of similar melting point. The DSC curve of HPC-SL shown in

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fig.2 a peak 45.11^{0}c which indicates the glass transaction of HPC-SL. The DSC curve of vitamin-E.TPGS shown in fig.3 a sharp 36.27 ^{0} c it indicates its melting point. The DSC curve Solid dispersion Drug and polymer (1:1.4) with vitamin-E.TPGS(15%w/w) shown in figure.4.The DSC curve of solid dispersion prepared by hot melt extrusion method showed the presence of small endothermic hump at 238.58°c. Change of melt character from sharp crystalline melting to small glassy transaction declares that miscibility of drug in carrier system (Polymer & Plasticizer) by reducing its crystalline nature and conversion to amorpous phase, In addition DSC curve notifies unique glass transaction endotherm of carrier components at 49.11^{0}c indicates purity of all three components. A new endothermic peak at approx 190^{0}c is the degradation/impurity of Vitamin E TPGS during DSC study.

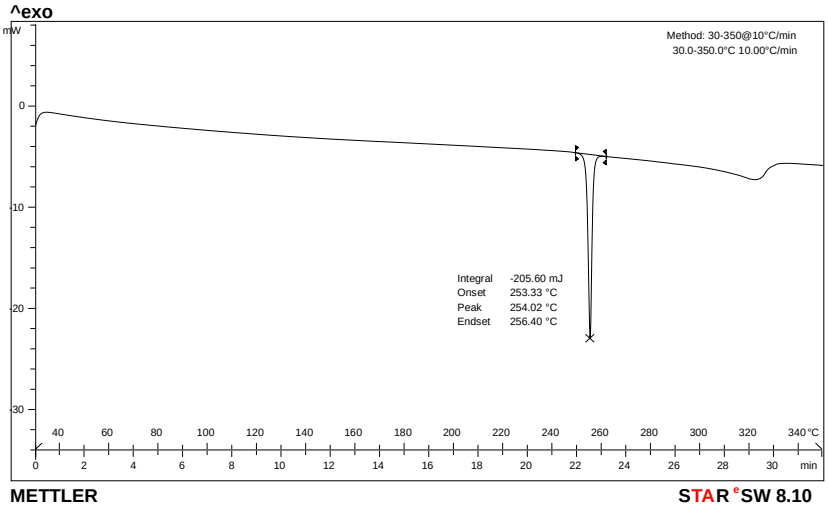

Figure 1: DSC curve of aprepitant

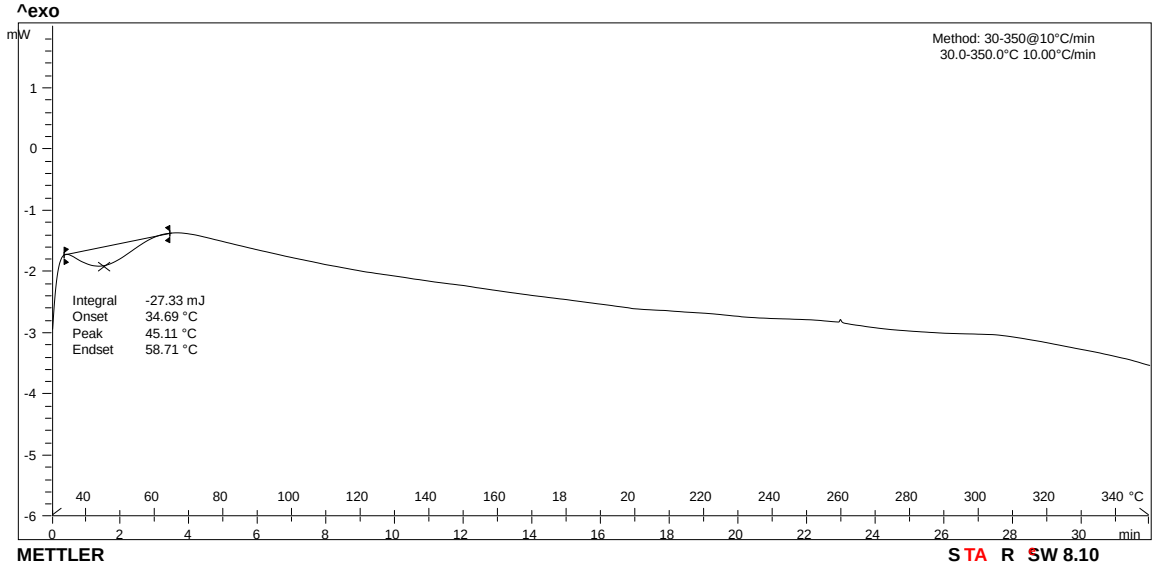

Figure 2: DSC curve of HPC-SL (carrier)

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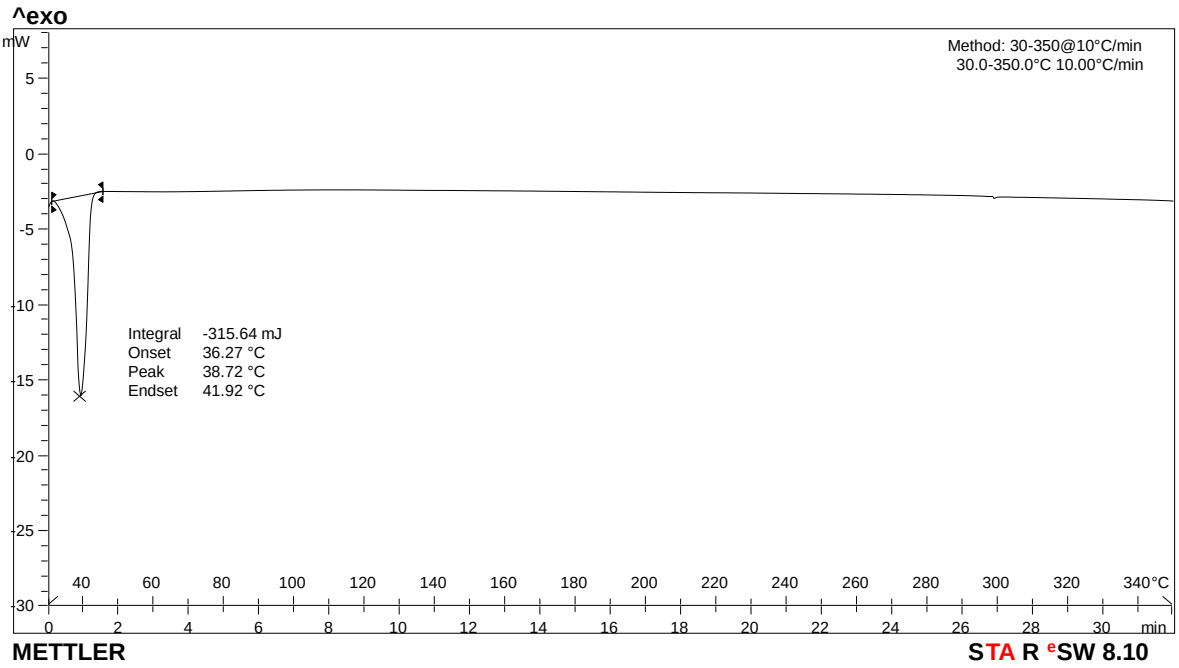

Figure 3: DSC curve of vitamin-E.TPGS (Plasticizer)

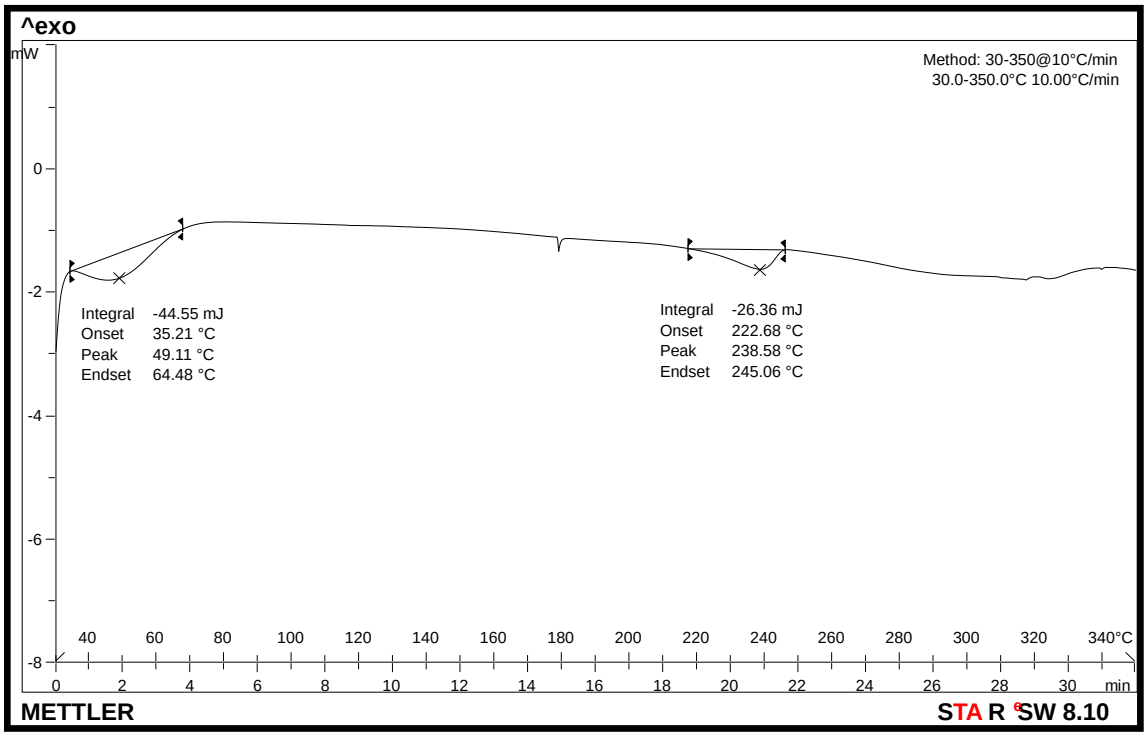

Figure 4: DSC curve of drug, polymer and vitamin-E.TPGS

XRD

The X- ray diffraction pattern of aprepitant displayed intense, sharp peaks (fig-5) indicating its crystalline nature. Aprepitant showed sharp peaks at a diffraction angle of(2θ) of 15.33^0,16.64^0,17.20^0,17.63^0,20.65° with high peak intensities while, the solid dispersions showed broaden peak at 20.66 ° with less intensity . This data reveals that typical drug

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crystalline peaks were still detectable and the diffraction pattern with reduced intensity and less number indicates reduced crystalline nature in solid dispersion (figure:6). Decrease in crystallinity of the drug in solid polymer dispersion contributes the enhancement of dissolution of the drug.

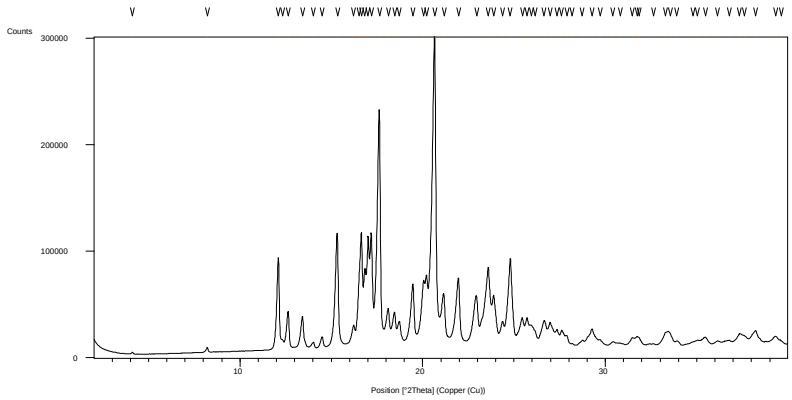

Figure 5: PXRD of pure aprepitant

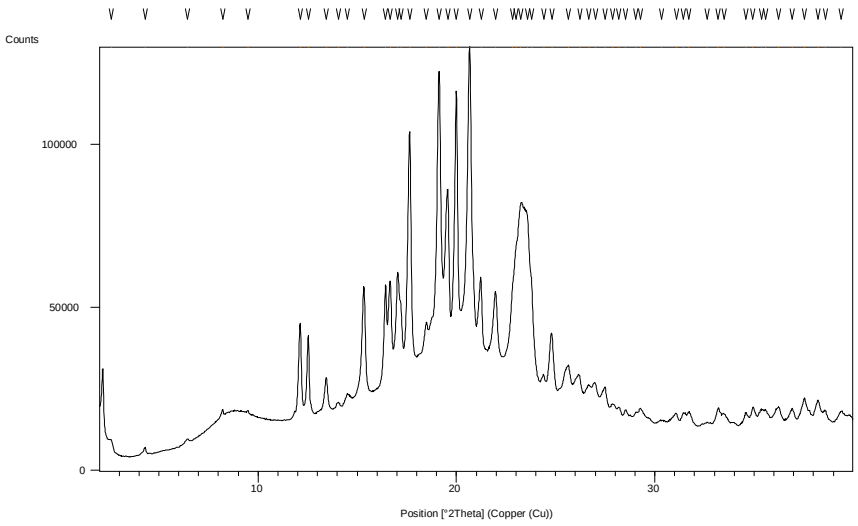

Figure 6: PXRD of Solid dispersion

FT-IR

Fourier transform infrared spectrometry (FTIR) spectra were recorded with FTIR-8400S spectrophotometer (Shimadzu, Japan) to evaluate the molecular states of pure drug: aprepitant; excipients: HPC-SL and vitamin-E, TPGS and physical mixture are shown in figures-7, 8, 9 and 10 respectively. Close agreement between the spectra of solid dispersion with FTIR of pure aprepitant declared that there were functional group H-H bond interactions of components with drug.

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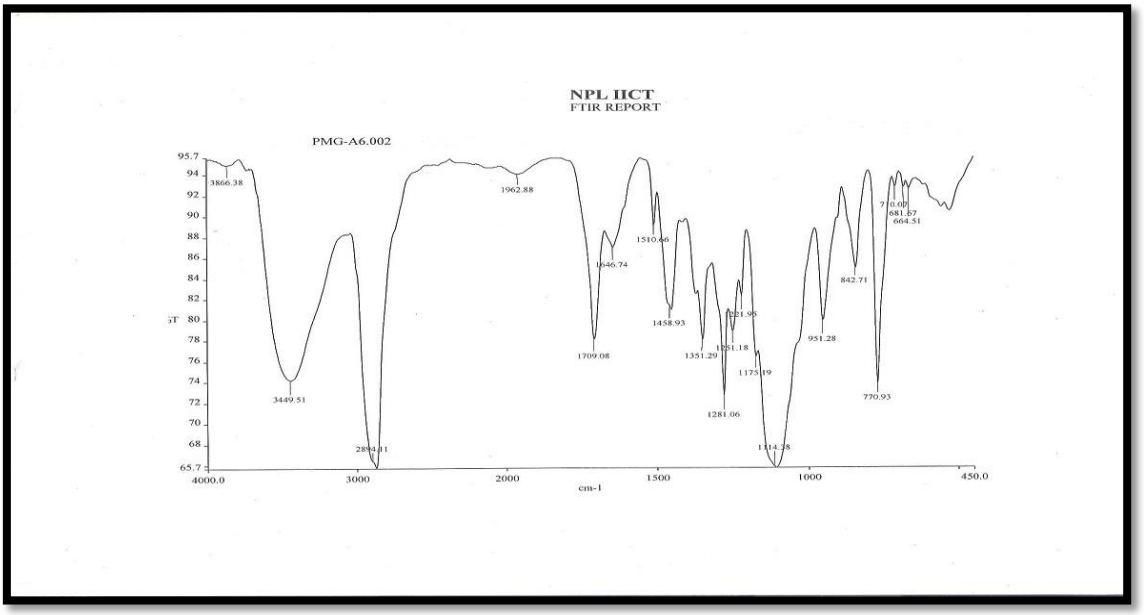

Figure-7: FTIR spectra of pure aprepitant

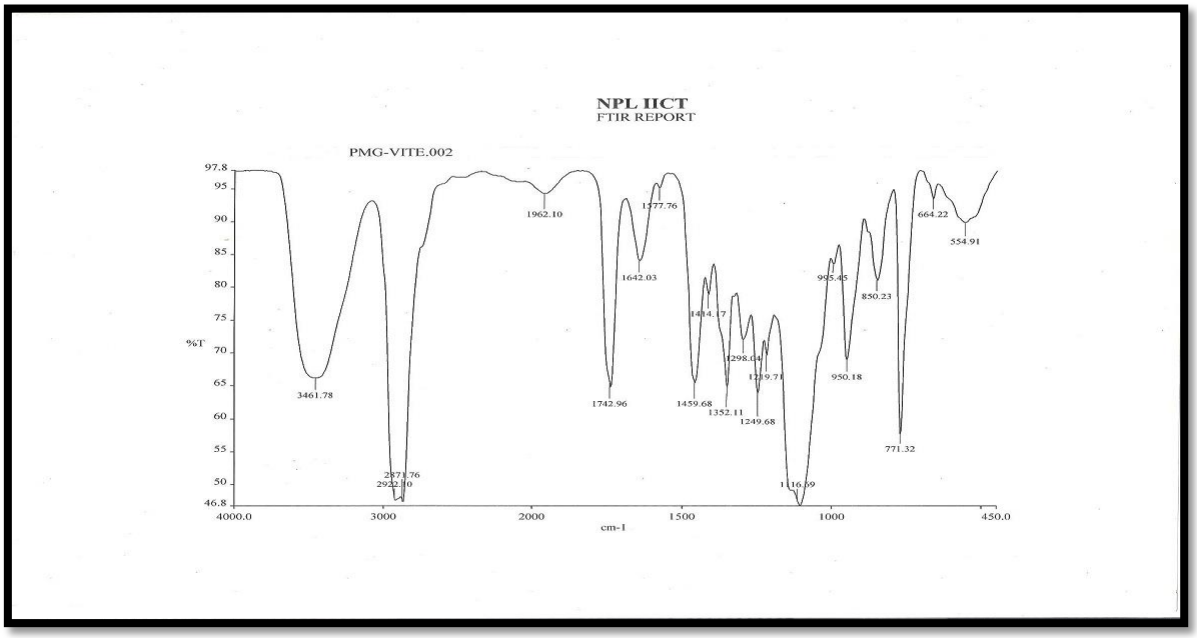

Figure 8: FTIR spectra of vitamin-E, TPGS

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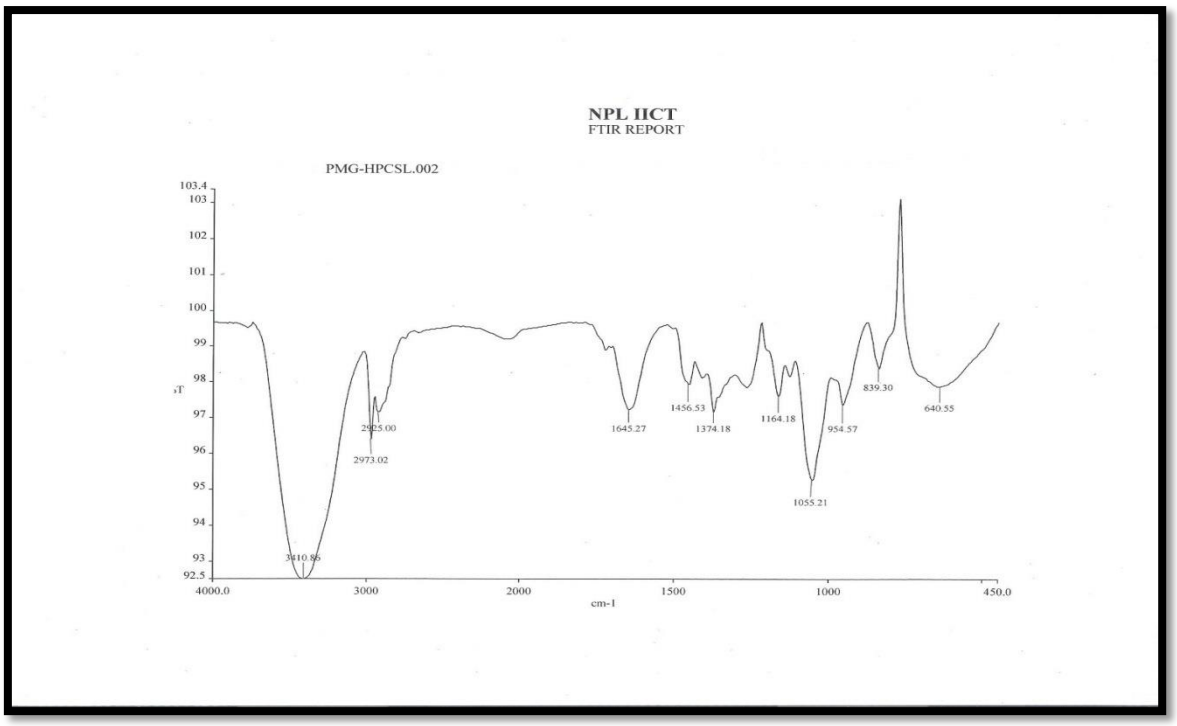

Figure-9: FTIR spectra of HPC-SL

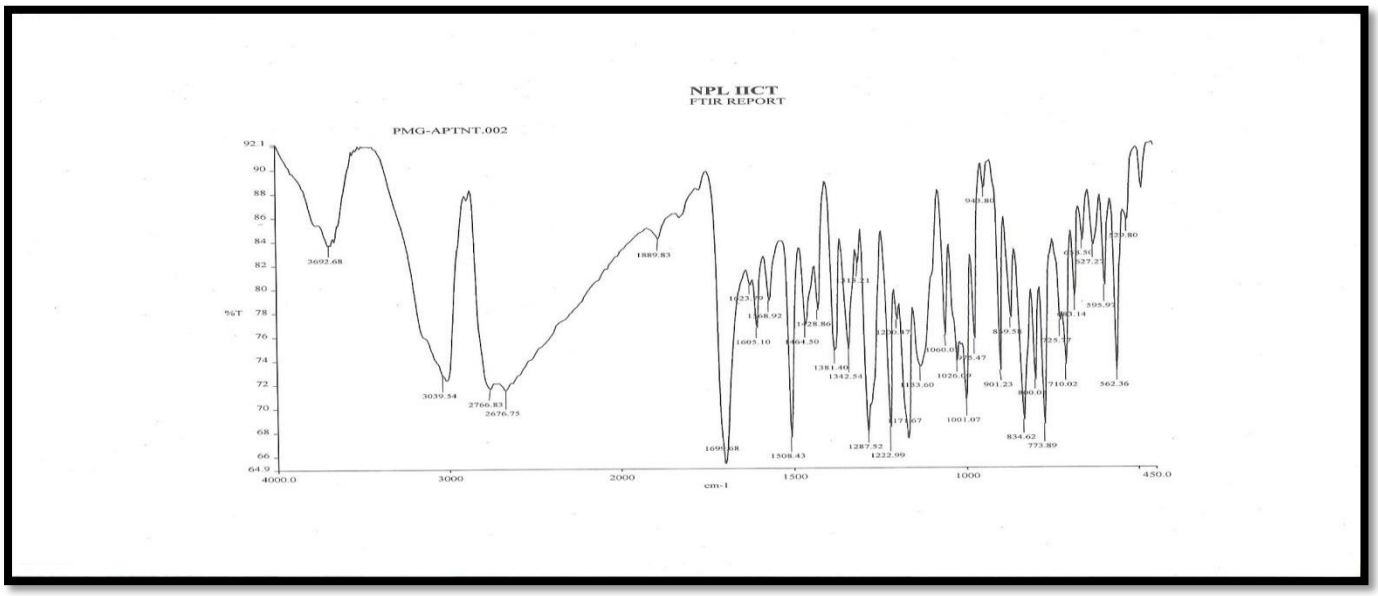

Figure 10: FTIR spectra of Solid Dispersion formulation of aprepitant

Scanning Electron Microscopy (SEM)

The surface morphology of the prepared solid dispersion and drug alone were examined by SEM analysis. Figure-11shows some selected SEM images of representative samples. The aprepitant crystals appeared as fine needles with smooth surfaces partially agglomerated in bundles. The SEM result shows that in the case of solid dispersion of aprepitant particles were in almost amorphous form, which indicates a reduction in particle size. This observation provides the evidence of solid dispersion formation.

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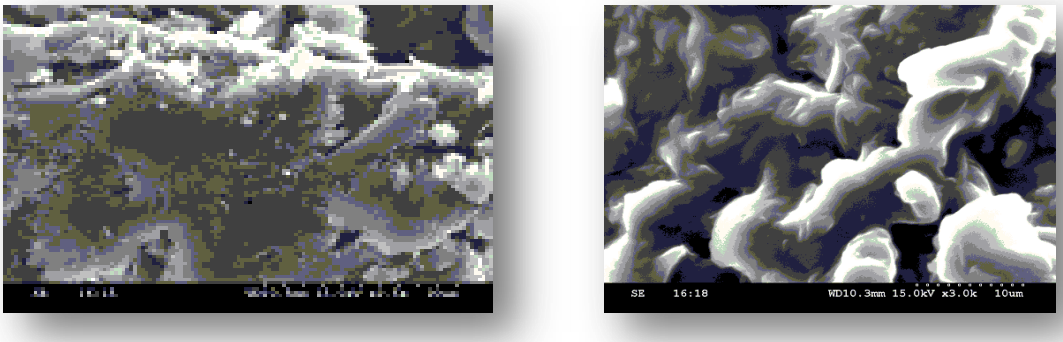

Figure 11: SEM image of Solid Dispersion of aprepitant

Dissolution studies

2.2% SLS media is FDA suggested comparative media for aprepitant. Aprepitant is poorly soluble drug; to attain the complete dissolution profile of aprepitant addition of surfactants was recommended. In 2.2% SLS media dissolution of aprepitant was slower in initial time points along with the level of surfactant initial dissolution decelerates due to immediate granular wetting and development of cohesiveness in granules in dissolution media. Same represents by %RSD variability. Formulations using lubricant magnesium stearate were shown uniform dissolution with low %RSD. Magnesium stearate due to it's hydrophobicity up to a concentration of 0.25%-0.5% shown comparable dissolution. A concentration of 0.5% yields comparable dissolution profile with reference formulation. Increase of magnesium stearate concentration to 1% was slower down the dissolution the dissolution due to impermeability to dissolution medium into the granules in capsule. The drug release rate at 10, 15, 20 30, 45 and 60 minutes and rate constants (K) values of the solid dispersions indicated their rapid drug dissolution F6, F7 and F8. The kinetics of drug release from all the solid dispersions follows first order. The dissolution profiles of aprepitant solid dispersions were compared with marketed tablet formulation of aprepitant. The similarity factors were calculated for these formulations. The similarity factor f2 values were 65,56,94,78 and F5, F6, F7 and F8 respectively shown in solid dispersions. All the results were calculated as mean± 3 S.D. Solid dispersions prepared by hot melt extrusion method were found to be suitable in increasing the dissolution rate of poorly soluble drug aprepitant. Dissolution of test formulation in 2.2%SLS media is comparable with reference, however comparison of formulation in aqueous media represents true picture of in-vivo performance capability of reference and test formulations. Evaluation in water media also represented in below table no: 6& Figure no 15.

Table 6: Dissolution release in water media

Time (Minutes)	5	10	15	20	30	45	60	Recovery
Reference	**3.2**	**5.9**	**10.1**	**6.9**	**7.8**	**6.0**	**6.4**	**6.9**
%RSD	*14.8*	*22.1*	*10.6*	*8.7*	*6.2*	*5.4*	*5.2*	7.1
As such drug	**0.1**	**0.4**	**0.4**	**0.4**	**0.4**	**0.4**	**0.5**	**0.4**
%RSD	*8*	*2.6*	*1.7*	*1*	*0.9*	*1*	*1.4*	*1*
Formulation F8	**9.6**	**8.5**	**8.5**	**9.4**	**8.7**	**13.7**	**13.3**	**10**
%RSD	21	7.7	7.4	10.4	8.9	10.9	8.9	10.7

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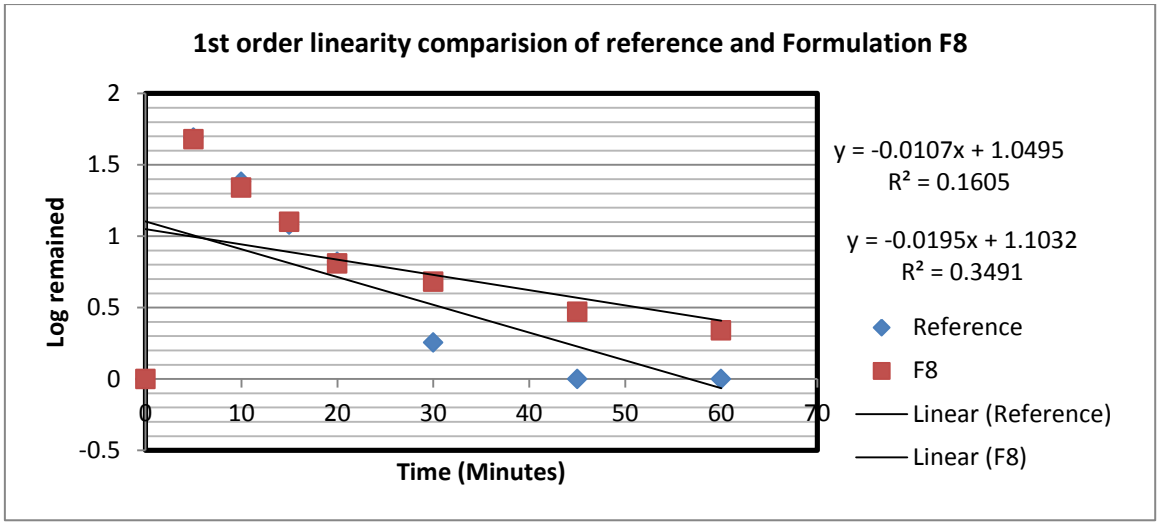

Figure 12: Comparative first order plots of reference formulation and formulation F8 in release media

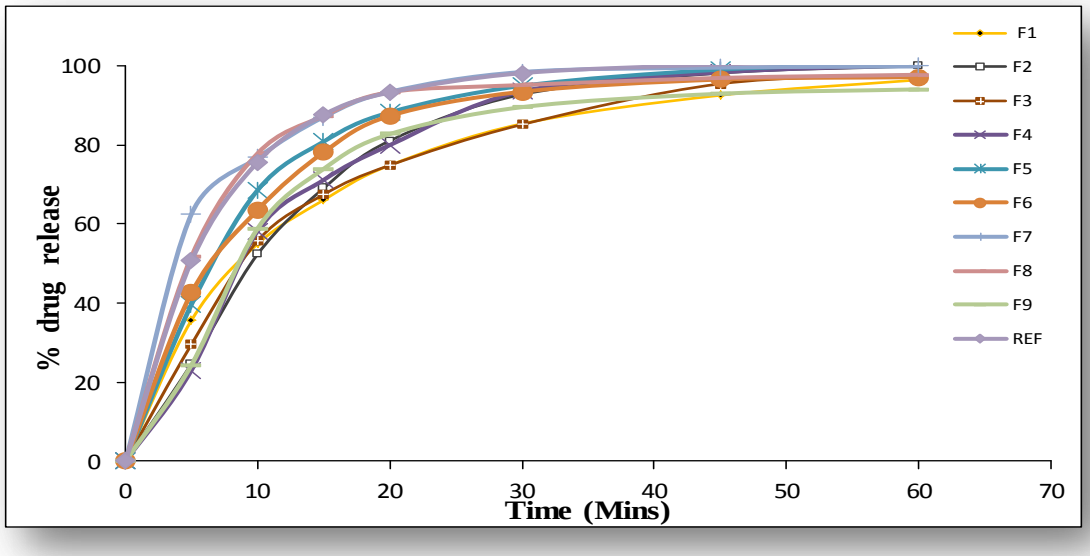

Figure 13: Cumulative % of drug release of different formulations

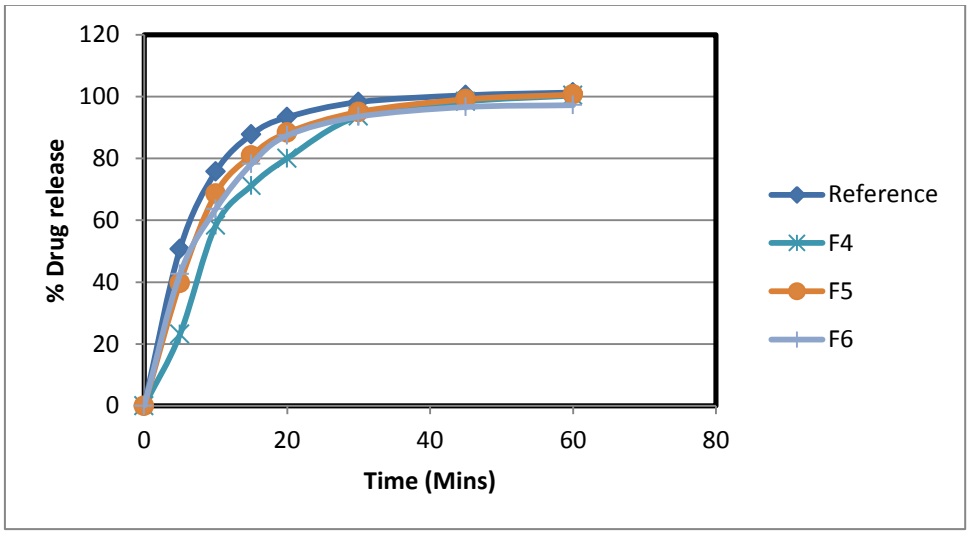

Figure 14: Cumulative % drug dissolution using SLS as lubricant

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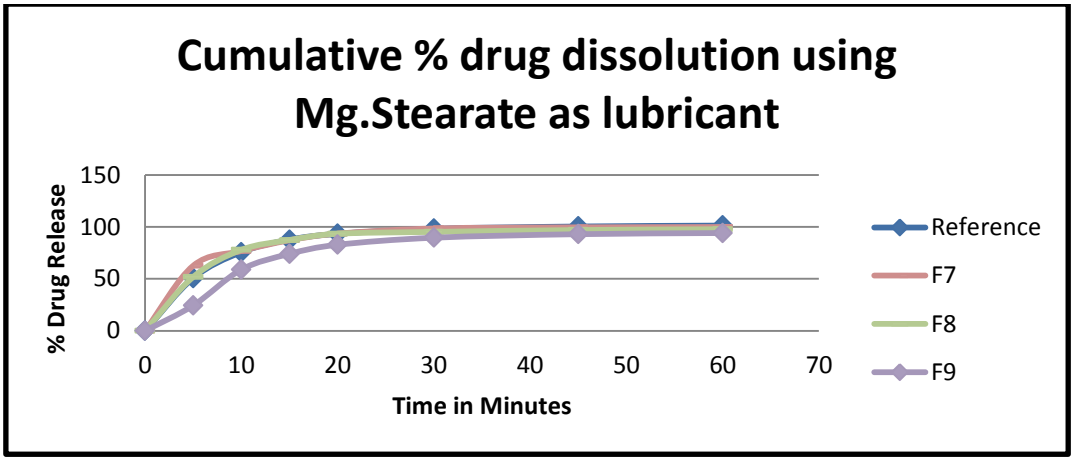

Figure 15: Cumulative % drug dissolution in 2.2% SLS media

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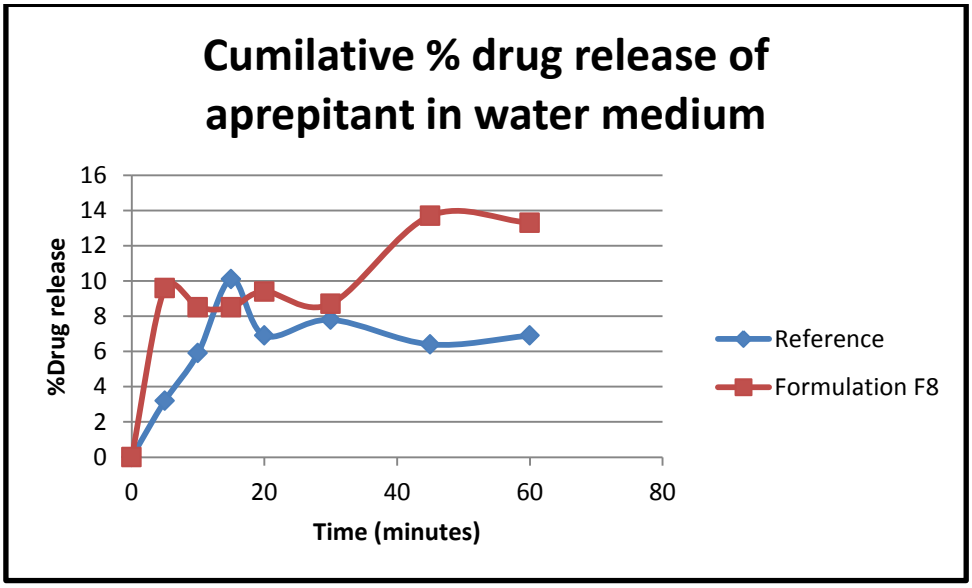

Figure 16: Cumulative % drug dissolution in water media.

Table 4: Dissolution results of formulations in 2.2% SLS media

S.No	Formulations	%Drug released at 15 mins	%Drug released at 30 mins	%Drug released at 60 mins	Zero order rate constant	First order rate constant K(min-1)	Peppas Model Constant	Higuchi Model Constant	F2 Value	F1 Value
1	Ref.	87.7	98.2	101.3	0.5296	0.9994	0.8264	0.8132	-	-
2	F1	66.1	85.4	96.5	0.7299	0.9908	0.9465	0.9427	40	15
3	F2	69.1	92.8	100	0.7276	0.995	0.8674	0.9204	43	11
4	F3	67.5	85.2	97.7	0.7402	0.9861	0.9034	0.9407	41	14
5	F4	71.2	93.6	100.3	0.7082	0.9902	0.8253	0.9081	47	10
6	F5	80.9	95	100.6	0.6093	0.9942	0.8389	0.8662	65	4
7	F6	78.2	93.5	97.2	0.6055	0.9912	0.8727	0.8667	56	7
8	F7	87.1	98.5	99.9	0.4809	0.9938	0.8894	0.776	94	7
9	F8	87.4	95.2	97.8	0.4831	0.9367	0.7771	0.7751	78	2
10	F9	74	89.6	94.1	0.6391	0.9775	0.7811	0.8665	47	11

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Table 5: Stability study of optimized formulation

Tests	Initial	1Month	2Month	3Month	3Month	1Month	2Month	3Month
		25*C/60% RH	25*C/60% RH	25*C/60% RH	30*C/75% RH	40*C/75% RH	40*C/75% RH	40*C/75% RH
Description	**Size '00" capsule with white to yellow colored granular powder**							
Assay (%)	100.3	100.5	99.6	99.1	98.3	98.1	98.3	98.6
Related substances:								
Impurity A	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Impurity B	ND	0.01	ND	ND	ND	ND	ND	ND
Impurity C	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10
Any un.known								
Total impurities	0.02	0.01	0.02	0.02	0.02	0.02	0.02	0.02
	0.21	0.21	0.21	0.22	0.21	0.22	0.21	0.21
Dissolution Q=80% in 45 minutes	99.9	98.6	100.5	97.4	99.2	99.1	99.6	98.2

Stability study

The results are appended in Table No-5. The effect of storage conditions on the dissolution behavior of the solid dispersions was evaluated. The representative dissolution profile of Aprepitant solid dispersion stored at 25 °C 60% RH for up to 3 months showed no significant change. Similar observation was obtained for dissolution of aprepitant solid dispersion at stored 40 °C 75% RH for 3 months (data not shown). It indicated that the aprepitant solid dispersion remained stable when stored at 25 °C, 30°C and 40 °C the same data depicted in table no : 5.

SUMMARY AND CONCLUSION

Aprepitant is a potent and selective neurokinin 1 receptor antagonist, more effective in the treatment of chemotherapy-induced nausea and vomiting drug has poor water solubility there by posing problems like absorption and bioavailability in their formulations. The oral route of drug administration is the most common method of delivery due to convenience and ease of ingestion but it is problematic if the drug is poorly water soluble. Among numerous ways of enhancing dissolution, solid dispersion of drug in a water soluble polymer or carrier is one of the promising techniques. The carrier used for the preparation of solid dispersion of aprepitant is HPC-SL and Vitamin-E, TPGS. Solid dispersion of aprepitant was prepared by hot melt extrusion method and evaluated for FT-IR, DSC, and Dissolution test, Kinetics of drug release and SEM. Among the different ratios of Aprepitant: HPC-SL, drug polymer ratio 1:1.4 shown consistent dissolution results up to 1:2 ratio. Hence 1:1.4 of drug to polymer concentration was selected for aprepitant solid dispersion formulations. The amount of plasticizer plays leading role in solubilization of aprepitant along with HPC-SL. The best suited Solubulizer & plasticizer is Vit.E.TPGS. The optimum concentration of Vitamin-E.TPGS requirement is evaluated by using 10%w/w, 15%w/w, 20% w/w concentration with finalized Drug: polymer combination. The dissolution results showed a trend in formulations that improved dissolution results with increasing concentration of plasticizer Vitamin-E.TPGS. The optimum concentration of 15%w/w.

showed good aqueous dissolution rates. Prepared solid dispersion characterization disclosed that the reduction of drug crystallinity, amorpous phase transformation of aprepitant. The SEM result shows that in the case of solid dispersion of aprepitant particles were in small dispersed clumps, which indicates the substitutional distribution drug particle size, which provides the evidence of solid dispersion formation.

Dissolution profile of aprepitant in release media shown immediate burst release and more than 85% release in 15 minutes, Due to which shows more linearity in first order rather than zero order. Release linearity of reference formulation and formulation F7 are closer. Dissolution results in aqueous media are comparable with innovator formulation. This indicates invitro equivalency of prepared solid dispersion formulation with innovator nano particle formulation.

REFERENCES

[1] Lindenberg M, Kopp S, Dressman JB. Eur J Pharm Biopharm, 2004; 58:265-278.
[2] Merisko-Liversidge E, Liversidge GG. Adv Drug Deliv Rev, 2011; 63:427-440.
[3] Murdande SB, Pikal MJ, Shanker RM, Bogner RH. Pharm Dev Technol ,2011; 16; 187-200)
[4] Serajuddin AT. Adv Drug Deliv Rev, 2007; 59:603-616
[5] Strickley RG. Pharm Res, 2004; 21:201-30.
[6] Chokshi RJ, Zia H, Sandhu HK, Shah NH, Malick WA. Drug Deliv ,2007; 14:33-45
[7] Vavia PR, Adhage NA. Drug Dev Ind Pharm, 1999; 25:543-545.
[8] Torne S, Darandale S, Vavia P, Trotta F, Cavalli R. Pharm Dev Technol, 2012.
[9] Leuner C, Dressman J. Eur J Pharm Biopharm, 2000; 50:47-60
[10] Patel AR, Vavia PR. The AAPS journal, 2007; 9: E344-52.
[11] Müller RH, Jacobs C,Kayser C. Adv Drug Deliv Rev, 2007; 47:3-19
[12] Challa R, Ahuja A, Ali J, Khar RK. AAPS Pharm SciTech, 2005; 6:E329-357.
[13] Vasconcelos T, Sarmento B, Costa P. Drug Discov Today, 2007; 12:1068-1075.