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Preparation, Characterization and Optimization of Poloxamer Solid Dispersions of a Poorly Water Soluble Drug Aprepitant

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Authors' contributions

This work was carried out in collaboration between all authors. Author RD wrote the protocol, managed the literature searches, performed the experiments including analyses and wrote the first draft of the manuscript. Author RO managed the HPLC analysis of the study. The study was designed by author NB. All authors read and approved the final manuscript

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Original Research Article

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ABSTRACT

Aim: The aim of the present investigation was to enhance the dissolution rate of a poorly water soluble drug, aprepitant, by preparation of solid dispersion with hydrophilic carrier, poloxamer 188, using solvent evaporation method.
Place and Duration of Study: Department of Pharmaceutical Sciences and Department of Emerging Life Sciences, Guru Nanak Dev University, Amritsar, Punjab, between

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August 2012 and July 2013.
Study Design: Designs of experiments were carried out with two input variables, drug to carrier ratio (X_1) and amount of solvent (X_2). A total of 7 experiments were performed (4 factorial runs and 3 centre points) as per full factorial design. Percent dissolution efficiency at 60 min (DE_{60}) was selected as the response variable. Pareto chart along with half probability plot were studied for determining the most significant process variables, which were modelled using ANOVA.
Methodology: Solid dispersions of aprepitant with poloxamer 188 were prepared using the solvent evaporation method and studied systematically using an optimization technique. A 2^2 full factorial design approach was used for the optimization of process variables on dissolution characteristics. The optimized solid dispersion was characterized by dissolution studies, Fourier Transform Infrared Spectroscopy, Differential Scanning Calorimetry, X-ray powder Diffraction studies and Scanning Electron Microscopy.
Results: The results of the experimental study confirm that the factors like drug to carrier ratio and solvent amount significantly influence the dependent variable DE_{60}. A high level of drug to carrier ratio and low level of solvent amount were found to be suitable for maximum DE_{60}. The use of factorial design approach helped in the optimization of the solid dispersion. The characterization of optimized solid dispersion (F5) demonstrated that the decrease in crystallinity of aprepitant and poloxamer 188 might be responsible for the enhanced dissolution rate. Analysis of dissolution data indicated the best fitting with first-order model.
Conclusion: Dissolution enhancement of aprepitant was successfully obtained by preparing its solid dispersion with poloxamer 188 using solid evaporation method.

Keywords: Aprepitant; poloxamer 188; factorial design; dissolution efficiency; solid dispersion; solvent evaporation.

1. INTRODUCTION

Emesis is primarily recognized as a protective reflex occurring in response to ingestion of hazardous compounds or medical interventions, which may create major problem during surgical procedures or in anticancer therapy [1]. Aprepitant (APT) is a potent and orally active antiemetic drug approved for the treatment of chemotherapy induced nausea and vomiting (CINV) and post-operative nausea and vomiting (PONV) [2]. APT acts centrally to block the activation of G-protein coupled NK-1 receptors in vomiting centres within the central nervous system [3,4]. Aprepitant is a basic compound with a pKa value of 9.7. The drug is lipophilic and crosses the blood brain barrier. However, it is poorly water soluble (3-7 µg/ml) and belongs to BCS Class II [1,2]. The low aqueous solubility of APT and consequently the dissolution results in erratic bioavailability. This is because the active drug substance should be in solution in the aqueous environment of the intestine in order to cross the luminal wall to achieve a desirable therapeutic effect [5]. Thus; enhancement of dissolution of APT is useful for acceptable bioavailability.

There is a great interest to develop efficient, reliable, economical and scalable method to increase the oral bioavailability of poorly water soluble drugs. Common approaches to tackle this challenge are optimization of chemical properties of active pharmaceutical ingredients (APIs) (as salt formation), particle size reduction which includes microsizing and nanosizing [6], solubilization, complexation with beta cyclodextrins and solid dispersions [7]. The preparation of solid dispersions in pharmaceutically acceptable water-soluble carriers

has been shown to be particularly effective in enhancing the rate of dissolution and the oral bioavailability. This may be attributed to the increase in the solubility along with maximizing the surface area of the amorphous drug that comes in contact with the dissolution medium as the carrier dissolves [8,9].

Poloxamers are polyoxyethylene-polypropylene block co-polymer non-ionic surfactants [10] that have been successfully used as solubilizing and wetting agents in the preparation of solid dispersions of several poorly water-soluble drugs such as meloxicam [11], rofecoxib [12,13] and also herbal medicines [14].

In the present investigation, solid dispersions of poloxamer 188 (PXM) and APT were prepared using the solvent evaporation method and studied systematically using an optimization technique. A 2^2 full factorial design approach was used for the optimization of process variables on dissolution characteristics. The objective of the current work was to evaluate the feasibility of formulating a solid dispersion of APT with enhanced solubility/dissolution rate and concomitantly bioavailability. The joint influence of the independent variables, amount of solvent and drug to carrier ratio was studied on the dependent variable DE_{60} (dissolution efficiency at 60 min). Differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), x-ray powder diffraction (XRPD), scanning electron microscopy (SEM) and dissolution tests were employed to characterize the prepared solid dispersions.

2. MATERIALS AND METHODS

2.1 Materials

Aprepitant was kindly provided as a gift sample by Hetero Labs Limited, Baddi, India. PXM and sodium lauryl sulphate (SLS) were purchased from HiMedia Laboratories Pvt. Ltd., Mumbai, India. Acetonitrile and ortho-phosphoric acid were purchased from SD Fine-Chem. Pvt. Ltd., Mumbai, India and Fischer Scientific, Mumbai, India, respectively. All chemicals used were of analytical grade. Double distilled water and triple distilled water were used throughout the studies.

2.2 Methods

2.2.1 Solubility determination in different media

Solubility of the aprepitant was determined in different media i.e. distilled water, 0.1N hydrochloric acid, 0.1% SLS and 0.5% SLS. In this study, excess known amount of drug i.e. 10 mg of aprepitant was added to a conical flask containing 5mL of medium and kept for 48 hours on water bath shaker (Narang Scientific Works Pvt. Ltd, New Delhi) at room temperature (25±0.5℃) at 100 rpm. All flasks were stoppered and sealed with parafilms to avoid solvent loss. The content of each conical flask was filtered through a 0.2 µm membrane filter (Millipore). Subsequently, the filtrates were analyzed using the optimized HPLC method [15].

2.2.2 Phase-solubility studies

Solubility determinations were performed in triplicate according to the method reported by Higuchi and Connors [16]. An excess amount of APT (10 mg) was added to 5 mL of distilled

water containing increasing concentrations of PXM (PXM) (i.e., 0.1%, 0.25%, 0.5%, 0.75% and 1% w/v). The flasks were sealed and shaken at room temperature (25±0.5℃) for 48 hours on a shaker at 100 rpm. After attainment of equilibrium, the samples were filtered through a 0.2 µm membrane filter. The solubilised amount was determined using the optimized HPLC method.

2.2.3 Preparation of physical mixtures and solid dispersions

Physical mixtures were prepared by mixing accurate weight of aprepitant with PXM in drug to carrier ratio of 1:1, 1:2 and 1:3 (PM1, PM2 and PM3, respectively). The mixture was pulverized and then mixed thoroughly in a mortar with a pestle until homogenous mixture was obtained (around 30 minutes). The mixture was passed through sieve #200, collected and stored in an amber coloured vial away from light and humidity until use in a dessicator.

Solid dispersions were prepared by the solvent evaporation method [17]. Solid dispersions of aprepitant in PXM containing three different drug to carrier ratios (1:1, 1:2 and 1:3) and using three different volumes of solvent (10 mL, 20 mL and 30 mL) to be used, thereof nine combinations (SD1 to SD9), were prepared. PXM was dissolved in ethanol with constant stirring until a clear solution was obtained, followed by APT addition and stirring using magnetic stirrer (IKA, S22) for 45 minutes. The solvent was evaporated at 50℃ under vacuum in a rotary evaporator (Heidolph 2 Laborota 4001). The resultant solid dispersions were stored in a desiccator at room temperature for 24 hours, pulverized and sieved through sieve# 200.

2.2.4 High-performance liquid chromatography (HPLC)

The samples obtained from phase-solubility and dissolution tests were quantitatively analysed for drug concentration using a reverse phase column based on high-performance liquid chromatographic method (Shimadzu Nexera Highest Pressure UHPLC). The LC system consisted of a pump configured to Lab Solutions software with auto sampler. The UHPLC was equipped with a column oven and the analytical column used was Enable C - 18-G (4.6 mm X 150 mm, 5µ). The mobile phase was a mixture of acetonitrile and 0.1% ortho-phosphoric acid (50:50) at a flow rate of 1 mL min^{-1}. The OPA solution was filtered through 0.2 µm membrane filter prior to mixing with ACN. After mixing, the solution was again filtered through 0.2 µm membrane filter and degassed in a sonicator for 10 min. The injection volume was 5µL with run time of 16 min and the detection was done at 210 nm. The column was equilibrated to at least 30 min prior to the injection of the drug solution. The retention time was found to be 11.7 min.

2.2.5 *In vitro* dissolution studies

Drug, physical mixtures and solid dispersions equivalent to 100 mg of aprepitant were used for studying the rate and extent of drug dissolution. The study was performed using USP Type II (Paddle type) Apparatus (Lab India Dissolution Test Apparatus, DISSO 2000, India) maintained at 37±0.5℃ at 75 rpm, using 900 mL of 0.5% w/v SLS as a dissolution medium. Sampling (3mL) was done at intervals of 5, 10, 15, 30, 45, 60, 90, 120, 150 and 180 minutes [2]. An equal amount of dissolution medium containing 0.5% SLS was replaced immediately after withdrawal of the test sample to maintain the sink condition. Test samples were filtered through 0.2 µm membrane filter and analysed using HPLC method.

Percent Dissolution Efficiency (DE) for each formulation was computed as percent ratio of area under the dissolution curve up to the time, *t*, to that of the area of the rectangle described by 100% dissolution at the same time [18].

$$DE = \left(\frac{\int_0^t y.dt}{y100.t}\right)100$$

For these formulations, DE_{30} and DE_{60} were calculated. Other dissolution parameters such as T_{60}, DP_5, DP_{30} and DP_{180} were also calculated. T_{60} is the time taken to release 60% of the drug. DP is the percent drug released at a particular time.

2.2.6 Fourier transform infrared (FT-IR) spectroscopy

FT-IR spectra of different samples that is, aprepitant, PXM, physical mixture and the optimized solid dispersion (F5) were recorded with FT-IR Spectrophotometer (Perkin Elmer). FT-IR study was done using KBr pellets as blank by using completely dried KBr powder and then samples were analysed in the range of 4000- 450 cm^{-1}.

2.2.7 Differential scanning calorimetry(DSC)

Thermal analysis was done using differential scanning calorimeter with auto sampler (Mettler Toledo). Thermal data analysis of the DSC thermogram was conducted using STARe SW 9.01 software. Approximately 5 mg of APT, PXM, physical mixtures and optimized solid dispersion (F5) was placed in a sealed aluminium pan and heated at a scanning rate of 2ºC/ min from 20℃ to 250℃.

2.2.8 X-ray powder diffraction measurements (XRPD)

X-ray powder diffraction studies were performed using X-ray Diffractometer (Bruker D8 Focus) under the following conditions: CuK‰ line (λ=0.154 nm), voltage 40 kV and current 35 mA at ambient temperature. XRPD patterns were recorded using OriginPro 8.5 software for powder diffractometry. The samples were analysed over the 2- theta range from 15° to 80°.

2.2.9 Scanning electron microscopy (SEM)

The scanning electron microscopy (SEM) analysis was carried out to study the surface morphology of aprepitant, PXM, physical mixture and the optimized solid dispersion (F5) using Carl Zeiss EVO LS10 scanning electron microscope. The samples were mounted on the stubs using double-sided adhesive tape and analysed.

2.2.10 Mathematical modelling of release kinetics

The *in- vitro* drug release data of the optimized solid dispersion (F5) was fitted to various release kinetic models viz. zero-order, first-order, Higuchi, Hixson-Crowell cube root and Korsemeyer-Peppas model employing the following set of equations [12,19-22].

Zero- order kinetic model

$$M_0 - M_t = k_0 t$$

First- order model

$$\ln(M_0/M_t) = k_1 t$$

Higuchi model

$$M_t = K\sqrt{t}$$

Hixoson- Crowell cube root model

$$(W_{0)}^{1/3} - (W_t)^{1/3} = k_{1/3}\, t$$

Korsemeyer- Peppas model

$$M_t / M_\infty = kt^n$$

where, M_0, M_t and M_∞ correspond to the drug amount taken at time equal to zero, dissolved at a particular time, t, and at infinite time, respectively. The terms W_0 and W_t refer to the weight of the drug taken initially and at time t, respectively. Various other terms viz. k, k_0, k_1, $k_{1/3}$ and K refer to the release kinetic constants obtained from the linear curves of Korsemeyer–Peppas, zero-order, first-order, Hixson-Crowell cube root law and Higuchi model, respectively.

2.2.11 Micromeritic properties

Flowability of aprepitant and its solid dispersion was assessed by determination of Carr's index (CI), Hausner's ratio (HR) and angle of repose.

Accurately weighed amount of drug/solid dispersion was transferred to a 100 ml graduated cylinder to measure the apparent volumes or bulk volume (V_b). The measuring cylinder was tapped for a fixed period of time and tapped volume (V_t) occupied in the cylinder was measured. The bulk density and tapped/true density were calculated in gram per milliliter by the following formula:

Bulk Density= Mass/Volume= M/V_b
Tapped Density= Mass/Tapped volume =M/V_t.

Carr's index and Hausner's ratio were calculated by using following formulae:

Carr's index = [(Tapped density–Bulk density)/Tapped density] $\times$ 100
Hausner's Ratio = Tapped density / bulk density

2.3 Angle of Repose

A funnel was fixed in a stand in such a way that the top of the funnel was at a height of 6 cm from the surface. The pure drug/optimized solid dispersion was passed from the funnel so that they formed a pile. The height and the radius of the heap were measured and the angle of repose was calculated using the equation:

$\theta = \tan^{-1}(h/r)$
h = Height of the heap
r = Radius of the heap

3. RESULTS AND DISCUSSION

3.1 Solubility Determination in Different Media

The values of saturation solubility in different media are shown in (Fig. 1). From the results, it is evident that the maximum solubility of aprepitant was achieved in 0.5% SLS (pH=7.3).

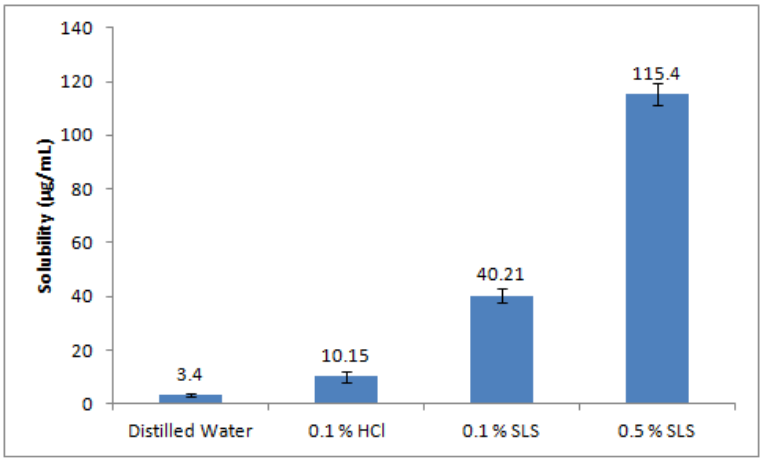


Fig. 1. Saturation solubility of aprepitant in different media

3.2 Phase-solubility Studies

Phase-solubility studies suggested that the solubility of APT increased with the increase in carrier concentration which shows a linear increase in drug solubility with increased carrier level, giving A_L type solubility diagram (Fig. 2). Similar results have been reported for many drugs using hydrophilic carriers, due to formation of soluble complexes between the drug and the carrier [11,23].

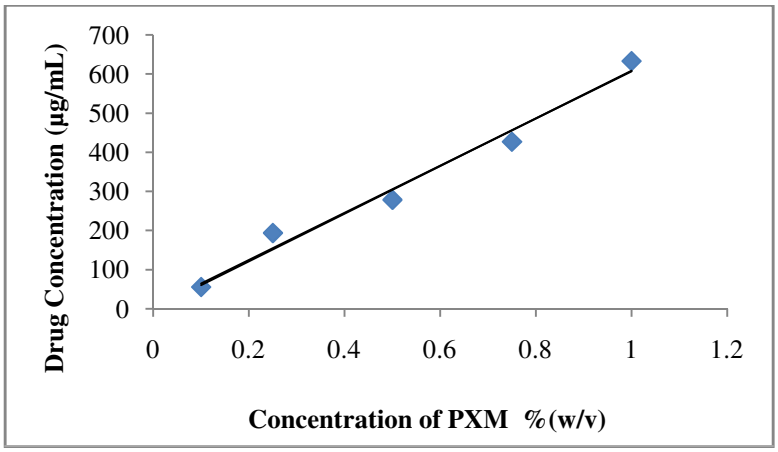


Fig. 2. Phase-solubility diagram for aprepitant in the presence of different concentrations of PXM

3.3 *In vitro* Drug Dissolution Studies

Aprepitant was dissolved by 7.74% and 15.49% in 5 minutes and 3 hours, respectively, suggesting a strong need to enhance the dissolution of aprepitant. Compared with the pure drug, the presence of PXM increased the dissolution of aprepitant from the physical mixtures, which increases the dissolution rate. In the case of PM1 and PM2, the drug was

dissolved in 3 hours by 51.43 % and 48.48%, respectively. The rate of dissolution was found to be highest in the physical mixture PM3 i.e. 55.75% in 3 hours (Fig. 3). The dry mixing in physical mixtures has been reported to bring drug in close contact with the hydrophilic carriers and the increased dissolution rate can thus be explained as a result of increased wettability and dispersibility of aprepitant [24]. Solid dispersions showed further enhancement in dissolution as shown in (Table 1). This effect can be attributed to the lack of crystallinity of aprepitant and poloxamer, i.e. amorphization, increased wettability, dispersibility and particle size reduction of the drug [25].

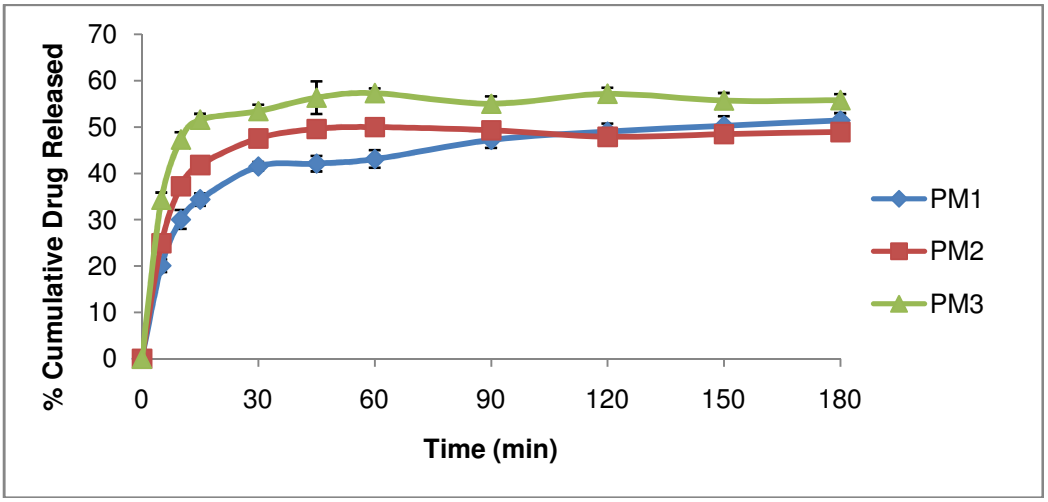


Fig. 3. Dissolution curves of physical mixtures of aprepitant and poloxamer-188

It is evident from the data in (Table 1) that solid dispersions SD6, SD8 and SD9 show fairly good enhancement in the dissolution rate with DE_{60} of 65.66, 67.10 and 66.63, respectively. Also the time taken to dissolve 60% of drug i.e. T_{60} for SD6, SD8 and SD9 was found to be lesser i.e. 11.49 min, 11.46 min and 9.30 min, respectively, as compared to the rest. However, a formulation was required to be optimized for further enhancement in the dissolution rate. Preliminary studies for preparation of solid dispersions have indicated that factors like carrier ratio and solvent amount are effective variables for the *in vitro* dissolution so were selected for further systematic studies. Hence, factorial design approach was used for optimization wherein the drug/carrier and the solvent amount were selected as independent variables and the dissolution efficiency at 60 min was selected as the dependent variable.

3.4 Experimental Design

Design of experiments (DOE) were carried out with two input variables, drug to carrier ratio (1:1.5 and 1:4.5) and amount of solvent (15 mL and 45 mL). A total of 7 experiments were performed (4 factorial runs with 3 centre points) as per full factorial design. Percent dissolution efficiency at 60 min (DE_{60}) was taken as the response variable. The composition of the factorial design batches F1 to F7 are shown in (Table 2).

Pareto chart (Fig. 4) indicated highly significant interaction term for carrier ratio and solvent amount followed by individual significance of carrier ratio and solvent amount. Although, solvent amount have marginally significance level in the model but this has to be included to

make the model hierarchal. The fitted ANOVA model (Table 3) was significant at *P-value=0.0038* (F=57.09, d*f*=3) and model lack of fit was not significant (*P=0.624*) as shown in (Table 3), which indicated that model noise is not significant as compared to signal and model can be navigated in the design space. Contour plot that presents the effect of carrier ratio and solvent amount on DE_{60} is shown in (Fig. 5). Analysis of interaction plot (Fig. 6) indicated that lower side carrier ratio favoured the increment of DE_{60}. As carrier ratio is increased from 1: 1.5 to 1: 4.5, there was decrease in DE_{60} at 15 mL solvent amount. But, an opposite effect was seen when solvent amount was taken as 45 mL.

Table 1. Dissolution parameters of solid dispersions of aprepitant and PXM

Solid dispersion	Drug to carrier ratio	Solvent amount (mL)	Dissolution efficiency		Time taken to release 60% drug (min)	Percent drug released at particular time		
			DE_{30}	DE_{60}	T_{60}	DP_5	DP_{30}	DP_{180}
SD1	1:1	10	38.84	46.18	61.60	28.09	52.23	73.07
SD2	1:2	10	36.78	45.62	65.83	31.38	51.20	69.65
SD3	1:3	10	36.77	46.41	50.21	29.16	45.17	69.03
SD4	1:1	20	38.70	48.65	48.79	39.10	52.60	78.76
SD5	1:2	20	27.19	37.95	100.34	15.46	42.96	42.41
SD6	1:3	20	60.98	65.66	11.49	51.15	75.68	67.43
SD7	1:1	30	47.39	59.52	20.09	47.97	65.10	79.87
SD8	1:2	30	62.45	67.10	11.46	62.75	68.51	78.82
SD9	1:3	30	59.17	66.63	9.30	46.00	71.48	76.87

Table 2. Factorial design for optimization of solid dispersion

Batch code	Type	Carrier ratio (1:x) (A)		Solvent amount (mL) (B)		DE_{60}
		Actual values	Coded values	Actual values	Coded values	
F1	Centre	3	0	30	0	68.33
F2	Centre	3	0	30	0	66.63
F3	Factorial	4.5	+1	15	-1	58.8
F4	Centre	3	0	30	0	65
F5	Factorial	1.5	-1	15	-1	83.02
F6	Factorial	1.5	-1	45	+1	60.28
F7	Factorial	4.5	+1	45	+1	67.43

Table 3. Analysis of variance for selected factorial design

Source	Sum of Squares	d*f*	Mean Square	F Value	*p-value* Prob> F	
Model	368.6	3	122.9	57.1	0.0038	Significant
A-carrier ratio (1:x)	72.8	1	72.8	33.8	0.0101	
B-solvent amount (mL)	49.8	1	49.8	23.1	0.0171	
AB	246.0	1	246.0	114.3	0.0017	
Residual	6.5	3	2.2			
Lack of Fit	0.911	1	0.911	0.329	0.624	Not significant
R^2= 0.982				Adj. R^2= 0.965	Pred. R^2= 0.887	

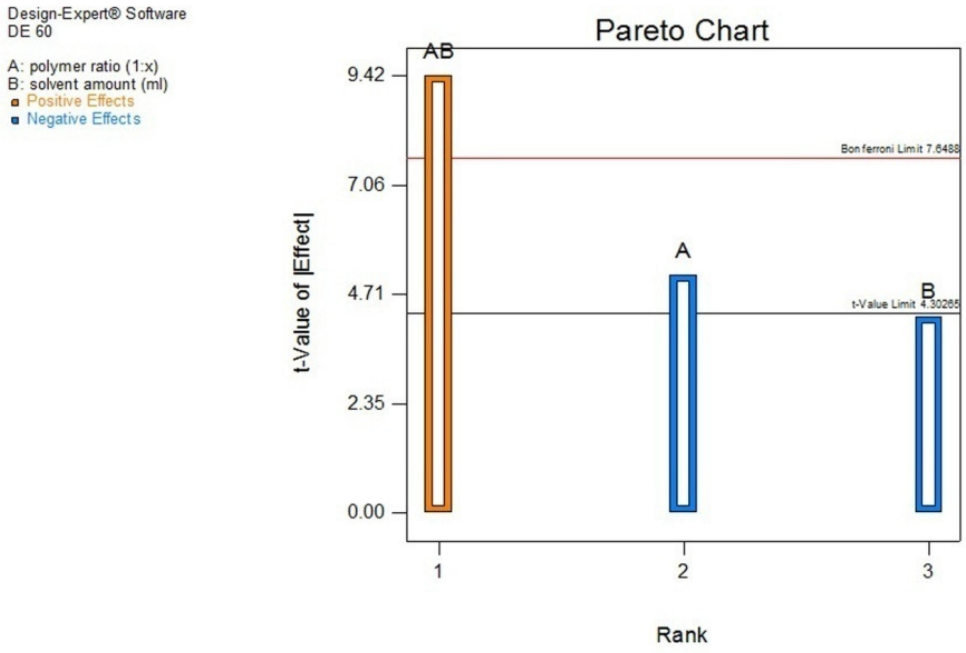


Fig. 4. Pareto chart showing relative importance of input variable polymer ratio and solvent amount

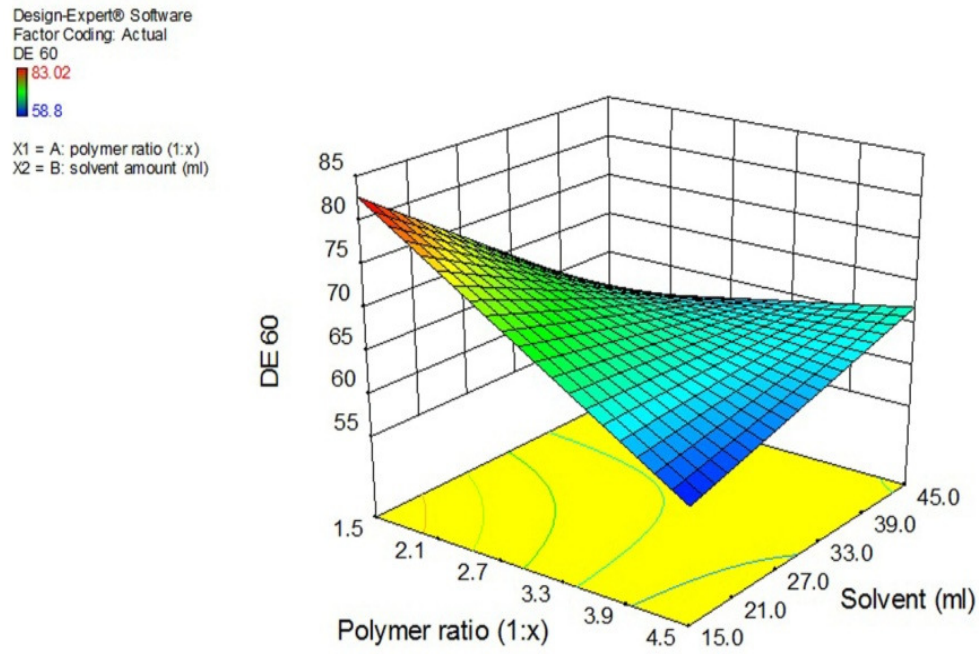


Fig. 5. 3D Contour plot showing the effect of polymer ratio and solvent amount vs. dissolution efficiency at 60 min (DE_{60})

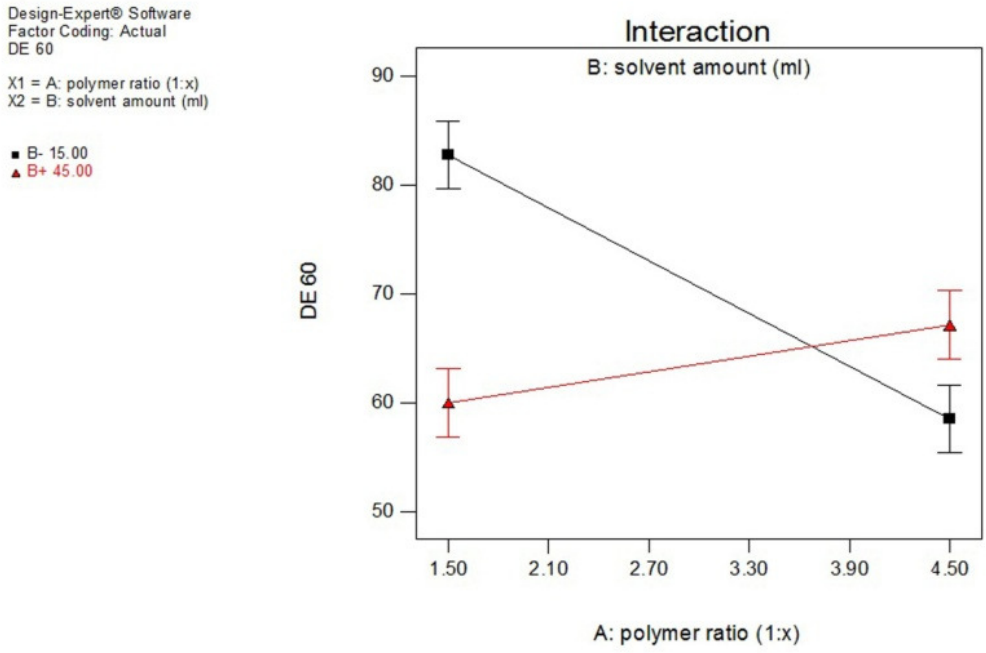


Fig. 6. Interaction plot showing the interaction between the input variables- polymer ratio and solvent amount

The model equations for coded and actual factors are given as Equation (1) and Equation (2), respectively.

Final equation in term of coded factors:

$$DE_{60} = + 67.07 - 4.27\ A - 3.53\ B + 7.84\ A \times B \quad (1)$$

Where A = carrier ratio (1: x) and B= solvent amount are in coded form.

Final equation in terms of actual factors:

$$DE_{60} = + 114.03000 - 13.30167\ A - 1.28083B + 0.34856\ A \times B \quad (2)$$

Where A = carrier ratio (1: x) and B= solvent amount (mL) are in actual values.

The proposed model predicted maximum DE_{60} of 83.02% from solid dispersion F5 having drug and carrier in the ratio of 1:1.5 and prepared using solvent amount 15mL. The drug release profiles of aprepitant and the optimized solid dispersion (F5) in 0.5% SLS is shown in (Fig. 7).

3.5 Mechanism of Dissolution

(Table 4) lists the regression parameters obtained after fitting various release kinetic models to the *In- vitro* dissolution data. The goodness of fit for various models investigated for binary systems were in the order of first-order >Korsemeyer> Higuchi > Hixson-Crowel> zero-order.

The first-order model describes drug release kinetics in the most benefitting manner. This suggests that the drug is released in a way that it is proportional to the amount of drug remaining in the dispersion, in such a way that the amount of drug released by unit of time diminishes [26].

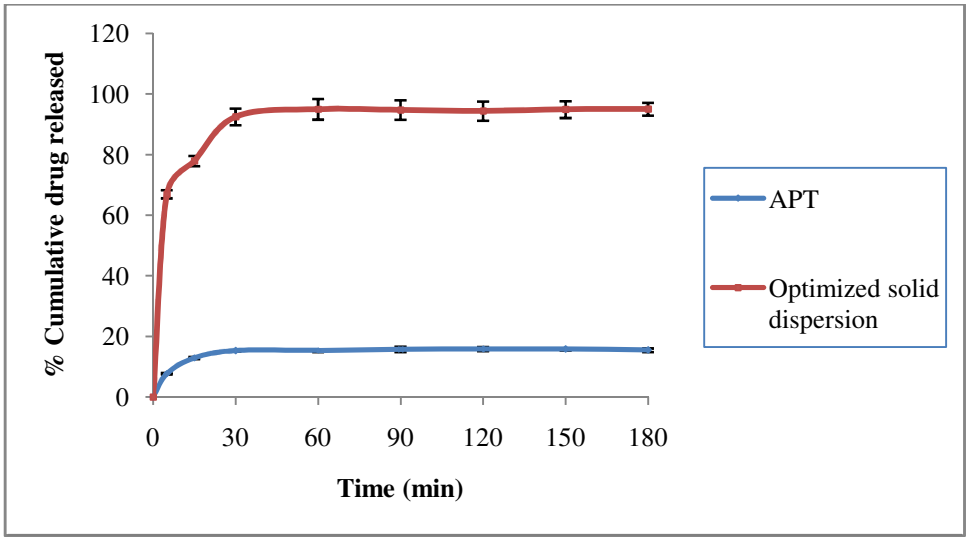


Fig. 7. Drug release profiles of aprepitant and the optimized solid dispersion (F5) in 0.5%SLS medium

Table 4. Fitting of drug release from optimized solid dispersion (F5) to various release kinetic models

Zero-order		First-order		Higuchi		Hixson-crowell		Korsemeyer-peppas	
Slope	r^2	Slope	r^2	Slope	r^2	Slope	r^2	Slope	r^2
0.1149	0.49	0.0077	0.8334	2.134	0.6612	0.0067	0.5404	.0942	0.8239

3.6 Micromeritic Properties

Micromeritic properties of aprepitant and optimized solid dispersion are presented in (Table 5).

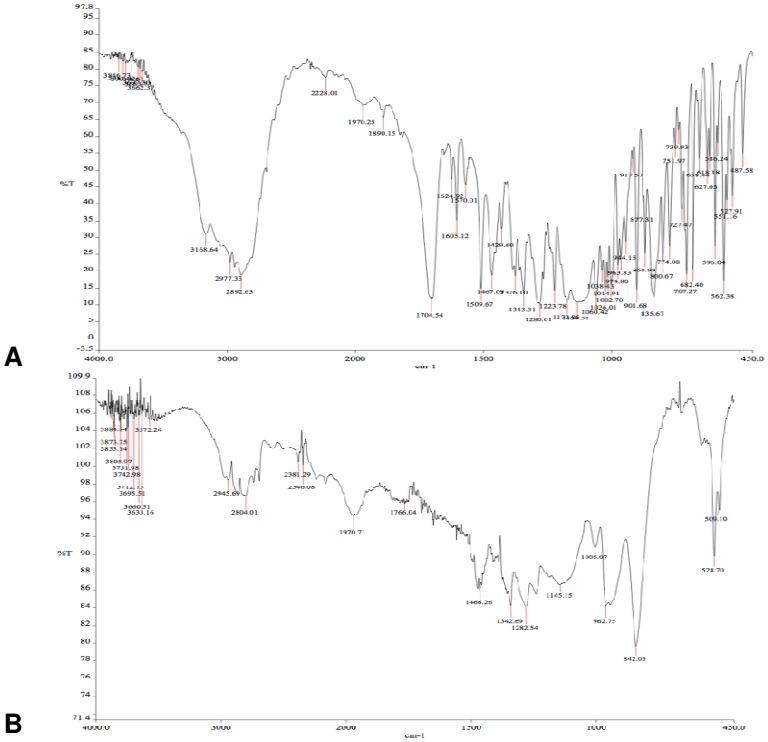
Table 5. Micromeritic properties of aprepitant and the optimized solid dispersion

Sample	Carr's Index	Hausner's ratio	Angle of repose (°)
Aprepitant	49.09±0.61	1.96±0.07	47±0.57
Optimized solid dispersion	14.10±0.23	1.16±0.11	23.15±0.36

(Table 5) shows that the flowability represented in terms of Carr's index, Hausner's ratio and angle of repose was much improved in optimized solid dispersion as compared to pure drug aprepitant.

3.7 Fourier Transform Infrared Spectroscopy

(Fig. 8) shows the spectra of APT, PXM, physical mixture and the optimized solid dispersion (F5). The IR spectrum of aprepitant is characterized by the presence of bands at 2977 cm $^{-1}$ and 2892 cm $^{-1}$(CH stretch),1704 cm^{-1}(C=O stretch),1605 cm^{-1} (C=C stretch), 1467 cm^{-1} (CH_2 bend), 1376 cm^{-1} (C-F stretch), 1342 cm^{-1} (CH_3 bend), 1280 cm^{-1} (C-O stretch) and 1172 cm^{-1} (C-N stretch). PXM exhibits characteristic peaks at 3458 cm^{-1} (O-H stretch), 2945 cm^{-1} and 2804 cm^{-1} (CH stretch), 1280 cm^{-1} (C-O stretch) 1466 cm^{-1} (CH_2 bend) and 1342 cm^{-1} (CH_3 bend).The IR spectrum of the physical mixture of aprepitant with PXM showed intense peaks at 2880 cm^{-1}, 1704 cm^{-1}, 1604 cm^{-1}, 1466 cm^{-1}, 1375 cm^{-1}and 1172 cm^{-1} corresponding to C-H, C=O, C=C, CH_2, C-F, C-O and C-N stretches, respectively. The spectrum of the optimized solid dispersion (F5) of aprepitant with PXM is characterized by the band at 3493 cm^{-1} (NH stretch), 2888 cm^{-1} (CH stretch), 1704 cm^{-1} (C=0 stretch), 1605 cm^{-1} (C=C stretch), 1467 cm^{-1} (CH_2 bend), 1375 cm^{-1} (C-F stretch), 1342 cm^{-1} (CH_3 bend), 1280 cm^{-1} (C-O stretch) and 1172 cm^{-1} (C-N stretch). In the spectrum of the optimized solid dispersion, OH and NH stretch can be seen as a merged broad band at 3493cm^{-1}. It was observed that the characteristic peaks of the pure drug were also present in the spectrum of the optimized solid dispersion, revealing the inert nature of the carrier used showing the absence of incompatibility between the drug and the carrier [11]. Further, the spectra peaks of drug are almost unchanged in the optimized solid dispersion indicating that the overall symmetry of molecule is not significantly affected [27].



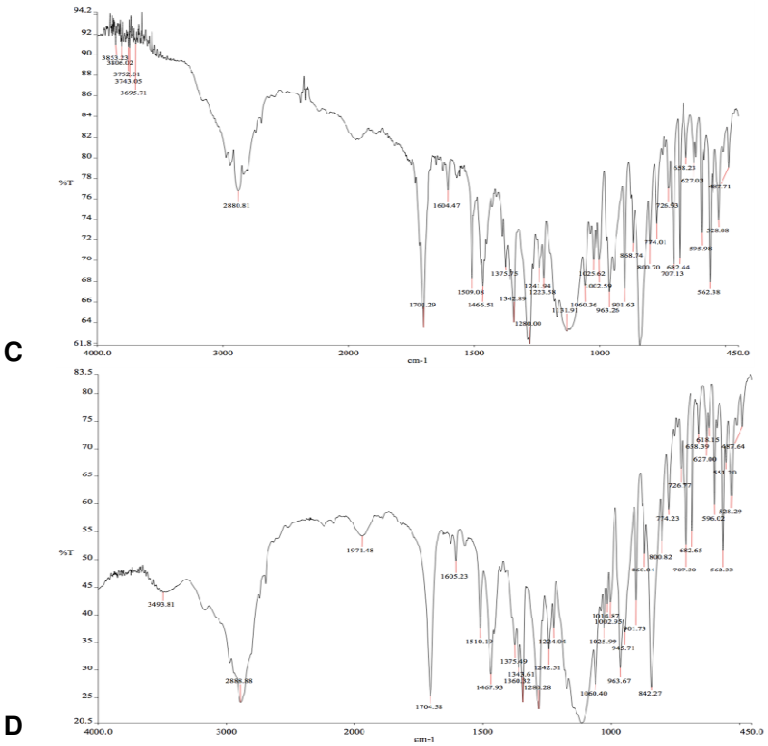


Fig. 8. Fourier transform infrared images of; A: aprepitant; B: poloxamer; C: physical mixture and D: optimized solid dispersion (F5)

3.8 Differential Scanning Calorimetry (DSC)

The DSC endotherms of aprepitant, PXM, physical mixture and the optimized solid dispersion (F5) are given in (Fig. 9). Aprepitant shows endothermic peak at 255.65℃. In the thermogram of PXM, a sharp peak was observed at 61.74℃ which was associated with melting endotherm of PXM. The physical mixture and solid dispersion show endothermic peaks at 59.13℃ and 56.92℃, respectively. The endothermic peak corresponding to melting point of aprepitant is absent in the DSC thermograms of both the physical mixture and the solid dispersion. This might be due to the presence of amorphous form of aprepitant in the physical mixture and the solid dispersion revealing their amorphous nature.

3.9 X-ray Powder Diffraction Measurements

The diffractograms of aprepitant, PXM, physical mixture and the optimized solid dispersion (F5) are shown in (Fig. 10).

In the X- ray diffractogram of aprepitant, sharp peaks were observed at a diffraction angle (2θ) of 15.31°, 16.61°, 17.09°, 17.67°, 18.59°, 19.39°, 20.57°, 22.01°, 22.91°, 23.65°, 24.84° and 25.78° with intensities of 113.28, 88.60, 134.30, 206.39, 63.05, 87.14, 424.43, 127.82, 69.10, 189.10, 281.28 and 91.48, respectively. This indicates the presence of crystalline drug. In the case of PXM, the characteristic peaks were observed at 19.11° and 23.29° with intensities of403.50 and 572.85, respectively. The XRPD of the physical mixture exhibits peaks at 15.36°, 17.69°, 16.64°, 17.12°, 19.13°, 20.56°, 22.01°, 23.30° and 24.79° with

intensities of 64.65, 135.23, 68.94, 76.92, 254.26, 197.13, 107.94, 353.27 and 92.16, respectively. For the solid dispersion, peaks were observed at 15.25°, 16.59°, 16.99°, 17.59°, 19.06°, 20.69°, 22.05°, 23.33° and 24.67° with intensities of 57.21, 60.48, 64.12, 96.33, 246.43, 137.52, 85.53, 310.87 and 62.36, respectively. It can be observed that for the physical mixture and solid dispersion, the typical drug crystalline peaks were still detectable with reduced intensity and less number. Also, the physical mixture and solid dispersion exhibited the characteristic peaks of PXM, but with lower intensities. This indicates the formation of amorphous drug within crystalline carrier matrix [14]. It also confirms the presence of a little amount of crystalline drug in the physical mixture and the solid dispersion despite the disappearance of its melting peak in the corresponding DSC curves [11,28]. Moreover, the XRPD patterns of the physical mixture/solid dispersion exhibited peaks less than the sum of the number of peaks of aprepitant and PXM in their pure forms. This suggests that crystallinity of both drug and carrier is reduced in the physical mixture and solid dispersion. Decrease in crystallinity of the drug and carrier might also be contributed to the enhancement of dissolution of the drug [14].

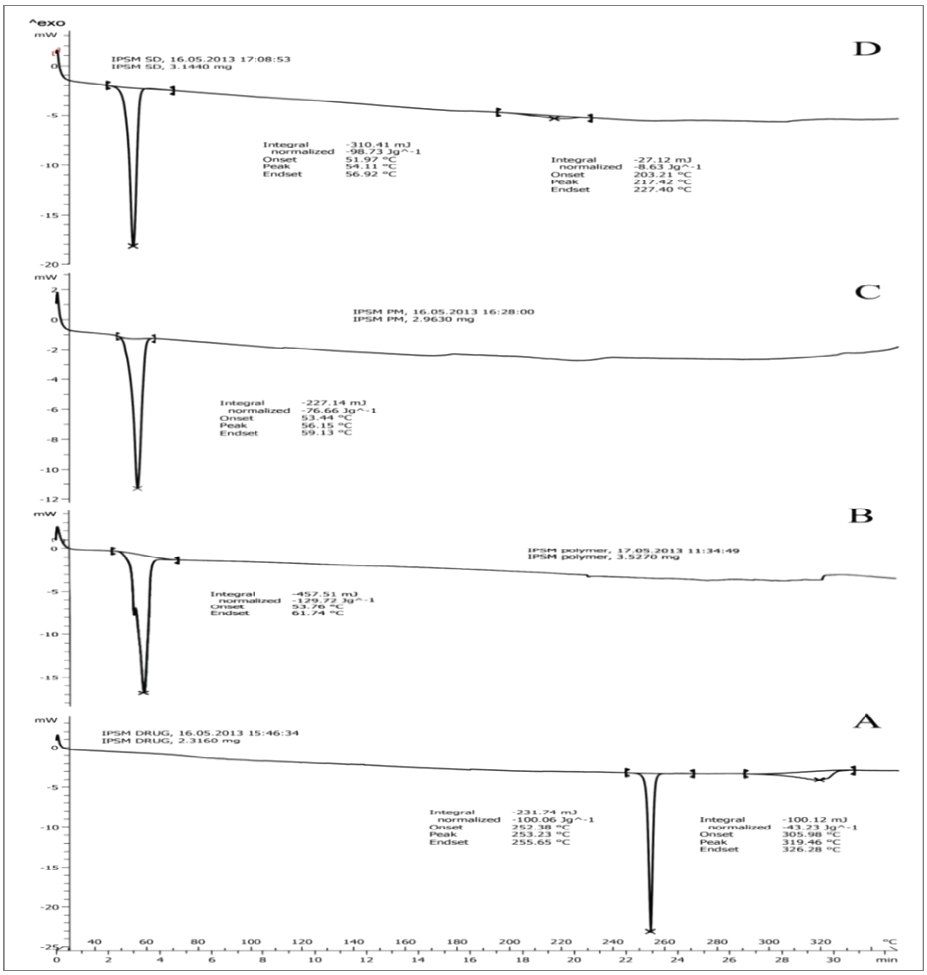


Fig. 9. Differential Scanning Calorimetry thermograms of; A: aprepitant; B: poloxamer; C: physical mixture and D: optimized solid dispersion (F5)

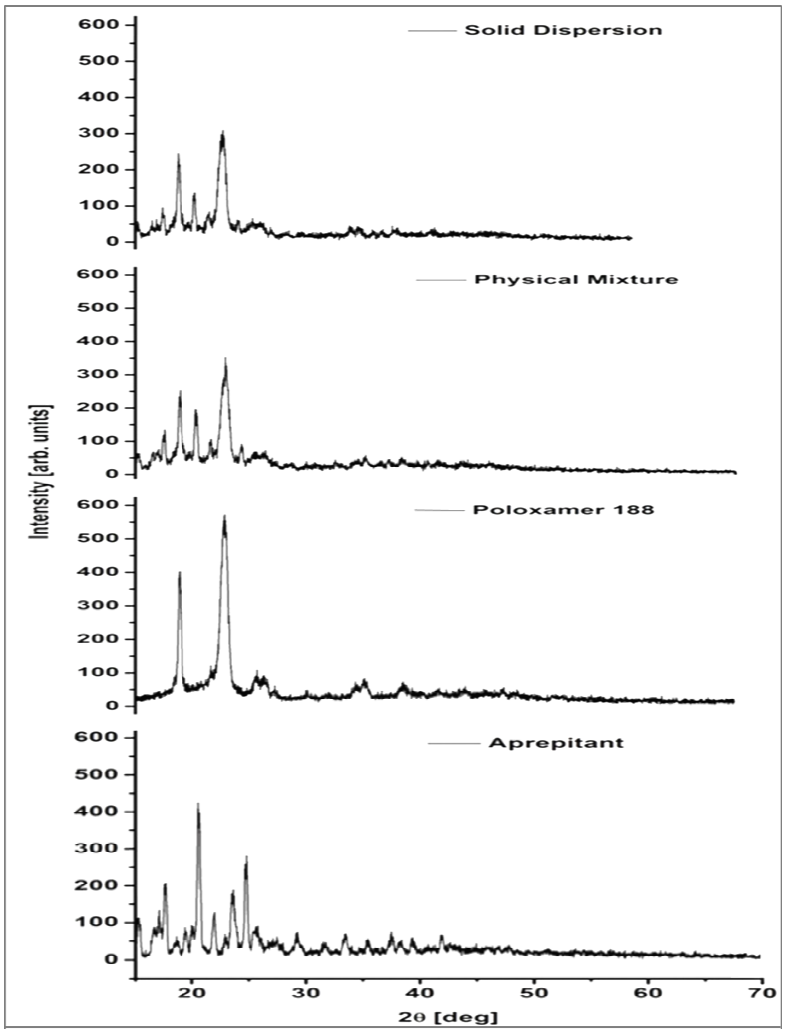


Fig. 10. X-ray diffraction spectra of; A: aprepitant; B: poloxamer; C: physical mixture and D: optimized solid dispersion (F5)

3.10 Scanning Electron Microscopy (SEM)

The SEM images of aprepitant, PXM, physical mixture and the optimized solid dispersion (F5) are given in (Fig. 11). The scanning electron micrographs showed that aprepitant existed as crystals with particle size of 2 µm while PXM existed as spherical particles with smooth surface and larger size. In the physical mixture, the characteristic aprepitant crystals, which were mixed with PXM particles or adhered to their surface, were clearly detectable, thus confirming the presence of cyrstalline drug. In the solid dispersion, the surface is slightly rougher compared to PXM and the particle size is much bigger than aprepitant but similar to that of PXM, suggesting that the surface morphology of solid dispersion is much similar to the surface morpholgy of PXM. It can be concluded that the increased surface area and the close contact between the hydrophilic carrier and the drug might be responsible for the enhanced dissolution of the solid dispersion [29].

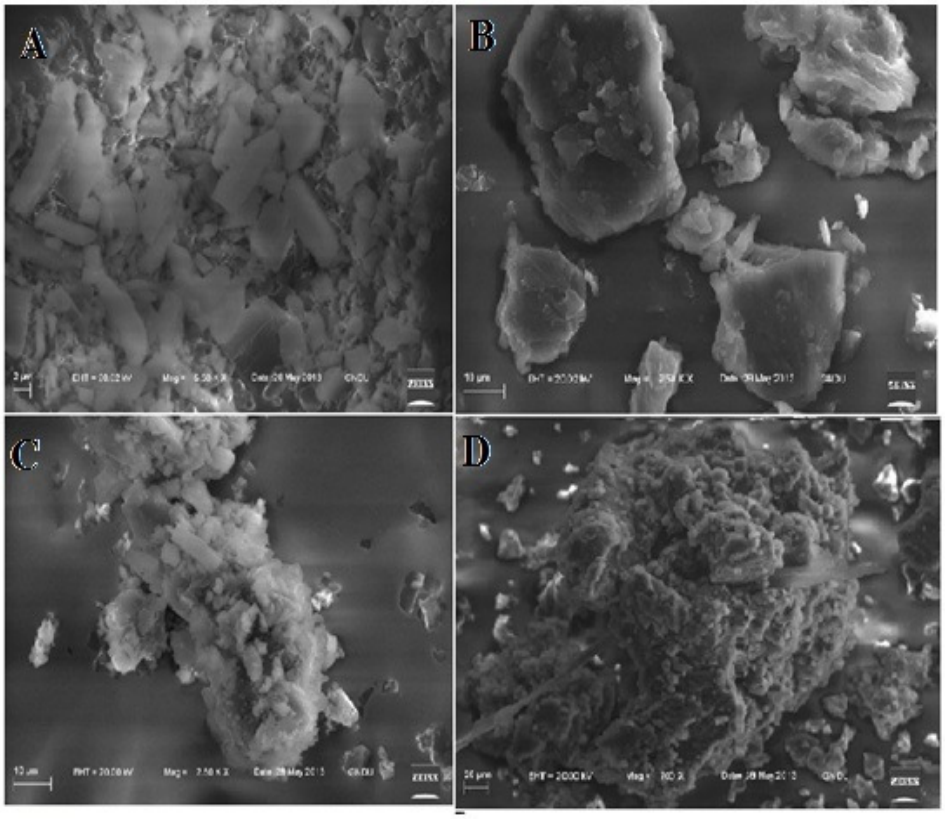


Fig. 10. Scanning electron microscopy images of; A: aprepitant; B: poloxamer; C: physical mixture and D: optimized solid dispersion (F5)

4. CONCLUSION

The results of the experimental study confirm that the factors like drug to carrier ratio and solvent amount significantly influence the dependent variable DE_{60}. Characterization studies revealed that solid dispersion of APT-PXM showed enhancement of APT dissolution due to the conversion of APT into a less crystalline and/or amorphous form. The application of experimental design techniques for optimization of formulation helped in reaching the optimum point in the shortest time with minimum efforts. The work can be further extended by conducting plasma level studies of the optimized solid dispersion in test animals for determination of various pharmacokinetic parameters, hence aiming at bioavailability enhancement of aprepitant.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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