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Research Article

PREPARATION & EVALUATION OF EPROSARTAN MESYLATE SOLID DISPERSIONS

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Abstract

The aim of the present study was to improve the solubility and bioavailability of a poorly water-soluble drug in human body, using a solid dispersion technique. Solubility and dissolution rate is an important physicochemical factor affecting absorption of drug and its therapeutic effectiveness. Consequences of poor aqueous solubility would lead to failure in formulation development. The poor solubility of drug substances in water and their low dissolution rate in aqueous G.I.T fluid often leads to insufficient bioavailability. In the present investigation, an attempt was made to improve the solubility and dissolution rate of a poorly soluble drug, Eprosartan by solid dispersion method using skimmed milk powder as carrier. Four different formulations were prepared with varying drug:carrier ratios viz.1:1, 1:3, 1:5 and 1:9 and the corresponding physical mixtures were also prepared. The formulations were characterized for solubility parameters, drug release studies and drug-polymer interactions by using phase solubility studies, dissolution studies; XRD analysis, FTIR spectrum, TLC analysis and UV overlay spectra. All the formulations showed marked improvement in the solubility behaviour and improved drug release. Formulation containing drug: polymer ratio of 1:9 showed the best release with a cumulative release of 82.67 % as compared to 6.919 % for the pure drug. The interaction studies showed no interaction between the drug and the carrier. It was concluded that skimmed milk powder as a carrier can be very well utilized to improve the solubility of poorly soluble drugs.

Keywords: Solid Dispersion, Skimmed milk powder, solubility, Eprosartan, Dissolution.

Introduction

The formulation of poorly soluble drugs for oral delivery now presents one of the major challenges to formulation scientists in the industry[1-4]. Various formulation parameters that play a crucial role for successful formulation are aqueous solubility; stability at ambient temperature and humidity, photostability, compatibility with solvents and excipients etc. of these, solubility is the most important property for developing formulations. Compounds exhibiting dissolution rate limited bioavailability are considered class II according to BCS classification[5]. As per recent reports, 49 % of the total NDAs filed between 1995 to 2010 were BCS class IV, while only 8 % were BCS class I drugs, revealing that a majority of approved new drugs were water insoluble. There are drug candidates that have poor solubility in water but can be dissolved by suitable conventional formulation strategies which include, Co-solvents[7], Milling techniques[8], super critical processing[9], Solid dispersions[10] including complexation[11], and precipitation techniques[12]. Solid dispersion technique has often proved to be the most commonly used in improving dissolution and bioavailability of poorly soluble active pharmaceutical ingredients because it is simple, economic and advantageous. In solid dispersion technique, water soluble carriers are used to improve dissolution characteristics of poorly water soluble drugs. Eprosartan is a nonpeptide angiotensin II receptor antagonist approved in more than 20 countries (e.g. US, UK, Germany) for the treatment of patients with hypertension. The drug is orally active and has a distinct non-biphenyl, non-tetrazol chemical structure. Pharmacokinetic studies of eprosartan have been conducted in healthy volunters, patients with hypertension and in special patient populations.

Eprosartan plasma concentrations peak at 1 to 3 hours after an oral dose in the fasted state. Administering eprosartan with food delays absorption, and causes variable changes (< 25%) in Cmax and AUC values which do not appear clinically important. Plasma concentrations of eprosartan increase in a slightly less than dose-proportional manner over the 100 mg to 800 mg dose range. The mean terminal elimination half-life of eprosartan following multiple oral doses of 600 mg was approximately 20 hours. Absolute oral bioavailability was calculated to be approximately 13% in a study of 17 healthy volunteers who received the commercially available oral tablet as well as an intravenous formulation of eprosartan tract. The low oral bioavailability of eprosartan may be the result of incomplete absorption due the physico-chemical properties of the drug. Eprosartan exhibits pH-dependent aqueous solubility and lipophilicity which may result in variable absorption as the compound passes through the gastrointestinal tract. Because the variable and mean absolute bioavailability of eprosartan is only 13%, doses as high as 800 mg per day may be required for an effective treatment of hypertension, congestive heart failure and renal failure. Additionally, since the commercial form of the drug is its mesylate salt, high dose tablets (e.g., 600 mg tablets weigh 1,000 mg) may be difficult to swallow. The oral bioavailability of eprosartan is limited by the solubility, rather than the metabolism within cytochrome P450 in the liver. Therefore, there is a need for a formulation that enhances the bioavailability of eprosartan. Eprosartan mesylate is Monomethane sulfonate of 4-({2-butyl-5-[2-carboxy- 2- (thiophen-2-ylmethyl) eth-1-en-1-yl] -1H-imidazol-1-yl}methyl) benzoic acid. It is white fine powder having poor aqueous solubility. The present study is an attempt to overcome the poor aqueous solubility of eprosartan by solid dispersion technique using skimmed milk powder (SMP) as carrier.

Materials and Methods

Eprosartan Mesylate was obtained as gift sample from Life Care Laboratories Pvt. Ltd. Hyderabad, Skimmed milk powder (SMP) was obtained from SD Fine Limited, Mumbai. All other solvents and reagents used were of analytical grade.

Methods

Phase Solubility Study

Phase Solubility study was conducted as per the method reported by M. Cirri et.al[13].Drug and carrier as per the specified drug: carrier ratio were weighed accurately and added to pure drug with 25 ml of water in screw capped bottles. All the bottles were shaken in Remi orbital incubator shaker at 37°C and 24°C for 24 h. The container with drug and water was used as control. After 24 h the solutions were filtered using (0.4 nm) filter paper and the filtrate was diluted. The absorbances were measured in spectra at 232 nm. From the absorbance the solubility of the drug were calculated.

Preparation of Solid dispersions

Four formulations of Solid dispersions containing Eprosartan with skimmed milk powder (SMP) as carrier in ratios of 1:1, 1:3, 1:5 and 1:9 were prepared by Dispersion method as proposed by K.P.R.Chowdary et.al[14]. The drug and carrier were weighed accordingly to the specified drug: carrier ratio. Eprosartan was dissolved in ethanol and the carrier was taken in mortar. The carrier was triturated slowly with ethanol i.e. drug solution and it was dispersed till a porous mass was formed. The mass was dried in Vacuum oven maintained at1kg/cm2 at room temperature. Solid mass was pulverized and passed through sieve no.80 to get uniform sized particles.

Preparation of physical mixture

The drug and carrier were weighed accordingly to the specified drug: carrier ratio as reported by Sudha. R. Vippagunta et.al[15]. The physical mixture was prepared by mixing of drug and carrier in a mortar. Solid mass was pulverized and passed through sieve no.80 to get uniform sized particles.

Estimation of Drug content

The Physical mixture & Solid dispersions equivalent to 50 mg of model drug was taken and dissolved separately in 50 ml of 0.1N NaOH. The solution was filtered and was further diluted such that the absorbance falls within the range of standard curve. The absorbances of solutions were determined at 233 nm. From the absorbance total drug content in the batches was calculated and given in Table 3.

Dissolution studies[16]

The in vitro dissolution study was performed in USP Dissolution rate test apparatus type-II (LABINDIA Nasik) using 900ml of 0.2M Phosphate buffer PH 7.5 Amount of SD & PM equivalent to 400mg of the solid dispersions and physical mixtures were weighed and kept in the dissolution flask. Samples were withdrawn at pre determined time interval and the same volume was replaced immediately to maintain sink condition. The withdrawn samples were suitably diluted and the absorbance of the solution was determined at specified wavelength of 233 nm.

Saturation solubility study

The Solid dispersions, Physical mixtures and pure drug Saturation solubility study was performed as reported by J.Hecq et.al[17]. Weighed amount of Eprosartan (pure drug) and solid dispersions equivalent to 40 mg of the drug were separately introduced into 25- ml stoperred conical flasks containing 10 ml of distilled water. The sealed flasks were agitated on a rotary shaker for 24 h at 27° C and equilibrated for 2 days. An aliquot was passed through 0.45-µm membrane filter and the filtrate was suitably diluted and analyzed on a UV Spectrophotometer at 233 nm. The same procedure was followed for Eprosartan physical mixture and absorbance was taken at 233nm**.**

Wettability study

The pure drug and formulations were subjected to wettability studies by Buchner funnel method as proposed by M.C. Gohel et.al[18] and Water absorption method as per the method reported by Sunil Kumar Battu et.al[19].

Permeation study

The permeation study of the pure drug, solid dispersions and the physical mixtures were carried out using two different membranes viz .Egg membrane and Cellulose nitrate membrane. The diffusion of the drug through the membranes was analyzed in a diffusion cell and the procedure was followed as proposed by Mehdi Ansari et.al[20] for egg membrane and Giovanna Corti et.al[21] for cellulose nitrate membrane.

X-ray Diffraction study[22]

All the selected formulations and pure drug were subjected to X-ray diffraction study. The XRD patterns were recorded on a PW1729, Philips diffractometer (Institute of chemical technology Mumbai.) using Ni-filtered, CuKα radiation, a voltage of 40kV and a 25-mA current. The scanning rate employed was 10 min-1 over the 10 to 300 diffraction angle (2θ) range.

Drug-Polymer Interaction analysis

The drug-polymer interaction studies were performed with IR study, TLC analysis and UV overlay spectra. IR spectrum of pure drug, solid dispersions and physical mixtures were taken in Double beam IR spectrophotometer (Shimadzu, Japan) using KBr pellet technique. TLC analysis was done by applying the test solution and the reference solution (both 20mg/5ml) on the plate coated with silica gel and allowing the mobile phase containing Benzene: Methanol: Formic acid. The spots were visualized under UV scanner at 254 nm and the Rf values were calculated. The overlay spectra of pure drug and the formulations dissolved in 0.1N Sodium hydroxide were taken in UV-Visible Spectrphotometer (Shimadzu, Japan) by scanning from 200-400nm and the λ max was found out.

Results and Discussion

The objective of this work is an attempt to increase the aqueous solubility and dissolution rate of Eprosatan Mesylate by solid dispersion techniques[23] using skimmed milk powder as hydrophilic carrier.

Phase solubility study

Phase solubility study of Eprosartan was conducted as per the method reported by M. Cirri et.al[13]. Table 1 gives the phase solubility data. The solubility of Eprosartan was found to be increasing constantly on increasing the concentration of the carrier (SMP) when physically mixed with the drug. The negative ΔG, ΔH, ΔS values of the formulations indicate the spontaneity of the process at low temperature. The thermodynamic Parameters results proved the solublization effect of the carrier on the drug.

Drug Content of Solid dispersions and Physical mixtures

Eprosartan assay data was given in Table 3. From the data it was clearly evident that the assayed drug content in the formulated solid dispersions and physical mixtures was found to be within the range of +5% of the theoretical amount indicating the method used for formulation was suitable and reproducible in nature.

***In vitro* Release studies[16]**

Eprosartan – SMP Solid dispersions[14] Table 2 and fig 1 show the release data and profile of Eprosartan– SMP Solid dispersions. The interpretation of the data and the profile showed that the percentage cumulative release (%CR) from Eprosartan-SMP Solid dispersion was higher than pure drug. It was also postulated that batch SD4 showed a CR of 82.67 % where as pure drug gave CR of 6.919 % The CR from the batches was also found to be increased on increasing the concentration of the carrier incorporated in formulations. Eprosartan-SMP Physical mixtures[15]: The release data and profiles of Eprosartan-SMP Physical mixture were given in Table 2 The batch PM4 showed CR of 69.88 % much more higher than other formulations indicating that PM4 was the best releasing batch in the formulation.

Table: 1 Phase solubility data of Eprosartan with SMP

Temp °C	Slope	Intercept	Ka	ΔG kJ/mol	ΔH kJ/mol	ΔS kJ/mol
25	31.09	-0.546	1.498	-11.18	-11.19	-11.18
37	46.442	-0.750	1.132	-7.473	-7.58	-7.554

Table: 2. *In vitro* Drug release parameters for Eprosartan- SMP Solid dispersions and Physical mixtures

Sample	D:C	%CR 15	%CR 30	%CR 60	%DE 60	MDT 60	T50
Pure Drug		2.478	4.54	6.919	2.50	36.65	>150
Solid Dispersions	1:1	24.412	26.545	30.212	35.51	16.70	<150
	1:3	42.248	49.162	57.376	45.23	10.09	<120
	1:5	48.034	52.021	67.822	47.55	8.65	<80
	1:9	59.683	69.846	82.674	63.37	13.52	<10
Physical mixtures	1:1	22.767	24.067	28.880	56.14	11.63	<170
	1:3	39.65	44.833	50.274	41.69	9.55	<140
	1:5	44.638	47.963	52.529	44.53	9.55	<60
	1:9	54.677	60.067	69.880	56.14	11.43	<20

(%CR – cumulative release, %DE – Dissolution efficiency, MDT – Mean dissolution time)

Table: 3. Selection Parameters for Formulations

Formulation	(%) Drug Content	Solubility (mg/ml)	R f Values
Pure Drug	100.00	0.0298	0.60
SD4	100.48	0.0519	0.65
PM4	99.32	0.0487	0.59

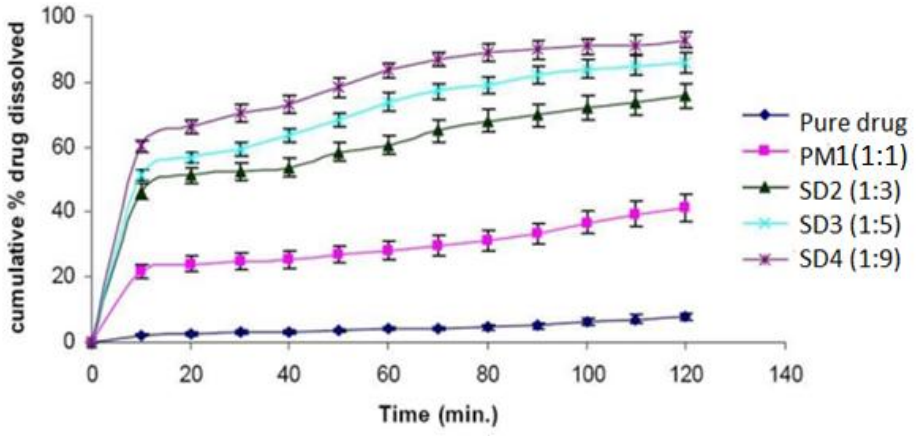


Fig: 1 *In vitro* release pattern of Solid dispersions and pure drug

Saturation solubility studies

Saturation solubility studies were conducted as per the method reported by J.Hecq et.al[17] and was shown in Table 3. Eprosartan was found to have saturation solubility of 0.0298 mg/ml. Batches SD4 and PM4 gave a solubility value of 0.0519 mg/ml and 0.0487 mg/ml respectively. The results proved that the carriers SMP was able to enhance the solubility of Eprosartan in water.

Wettability studies

The Buchner funnel method and water absorption method of Eprosartan and selected batches were investigated as per the method reported by M .C. Gohel et.al[18] and Sunil Kumar et.al[19] respectively and findings are shown in Table 4. The wetting time and water absorption ratio of the pure drug was found to be 90 minutes and 4.904 respectively its indicating poor wettability of the drug. The wetting time of samples was found to be very less (58 min) and water absorption ratio was more (18.22min) than pure drug. This behaviour may be attributed to increased wettability by the action of hydrophilic carrier used in the formulation.

Permeation study

Permeation study through Egg membrane was done as per the method reported by Mehdi Ansari et.al[20] and Giovanna Corti et.al[21]. The data for Egg membrane and Cellulose nitrate membrane was given in the Table 4. It was observed that the amount of drug permeated from selected batches in both membranes was found to be higher than pure drug. Permeation through Cellulose nitrate membrane shows better result when compared with Egg membrane. The results can be considered as the evident for increase in release rate of Eprosartan from Solid dispersions.

XRD analysis[22]

XRD analysis of the pure drug and selected batches were performed at Institute of chemical technology Mumbai. It is generally stated that if three consecutive Relative intensity percentage values in XRD pattern decreases it can be confirmed as decrease in crystallinity had occurred in samples. The base foot of the peak and the FWHM (Full Width Half Maximum) values of the intense peaks are compared with that of the standard patterns. If the base of the peaks is broader in nature and its FWHM values decreases it indicates significant reduction in crystallinity. XRD Patterns of Eprosartan and selected formulations were given in Fig 2 XRD pattern of Eprosartan showed numerous sharp, narrow and intense peaks, claiming its

high crystallinity. The patterns of formulations showed no/little peaks indicating its amorphous nature. On comparison of selected samples patterns with that of pure drug, it was observed that the number and intensity of peaks were found to be less in samples, and Relative Intensity Percentage values were also found to be well correlating with interpretation guidelines. The bases of peaks in the sample were broader in nature confirming the reduction in crystallinity in samples. The decreased FWHM value of intense peaks in the samples than pure drug also confirms the reduction in crystallinity in samples. These observations from comparison of XRD pattern can be treated as confirmation tool for reduction in crystallinity and phase transition (from crystalline to amorphous form) had occurred in the samples.

Interaction Analysis

IR Studies

The I.R Spectrum of Eprosartan along with selected formulations was taken and the characteristic peaks were shown below in Fig 3. The characteristic peaks were noted down and positions of the peaks were compared with the I.R spectrum of the selected samples. The results of the I.R analysis revealed that no interaction between drug and carriers.

TLC data

Rf values of Eprosartan and formulations are shown in the Table 3. It was noticed that there was no significant change in Rf value of pure drug and selected samples. The results of the TLC analysis revealed that no interaction between drug and carriers.

UV-Visible Spectroscopy

The λmax of the sample and pure drug was found to be similar proving that no interaction between drug and carriers.

Conclusion

The objective of the present study was to improve the solubility and dissolution behaviour of the poorly soluble drug, Eprosartan by solid dispersion technique using SMP as carrier. The dispersion method of preparing solid dispersions was found to be satisfactory as it produced good product with high drug content. Out of the four formulations prepared formulation SD4 showed marked increase in the

Table 4: Wettability & Permeability Analysis

Formulation	Permeability (mg/ml/hr)		Wettability	
	Egg Membrane	Cellulose Nitrate Membrane	Buchner Funnel Method (Min)	Water absorption Method (R)
Pure drug	0.0020	0.0155	90	4.904
SD4	0.0096	0.0299	58	18.22
PM4	0.0085	0.0239	60	12.35

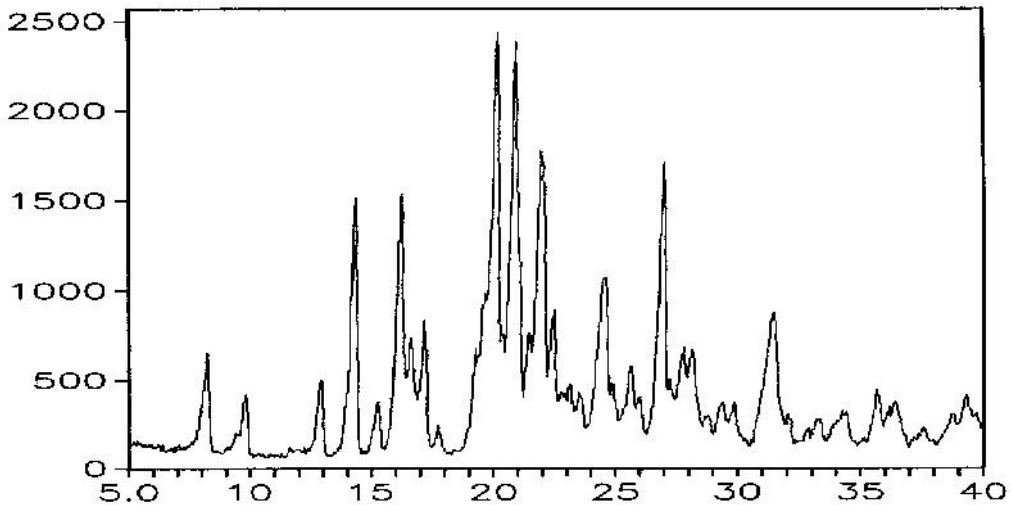
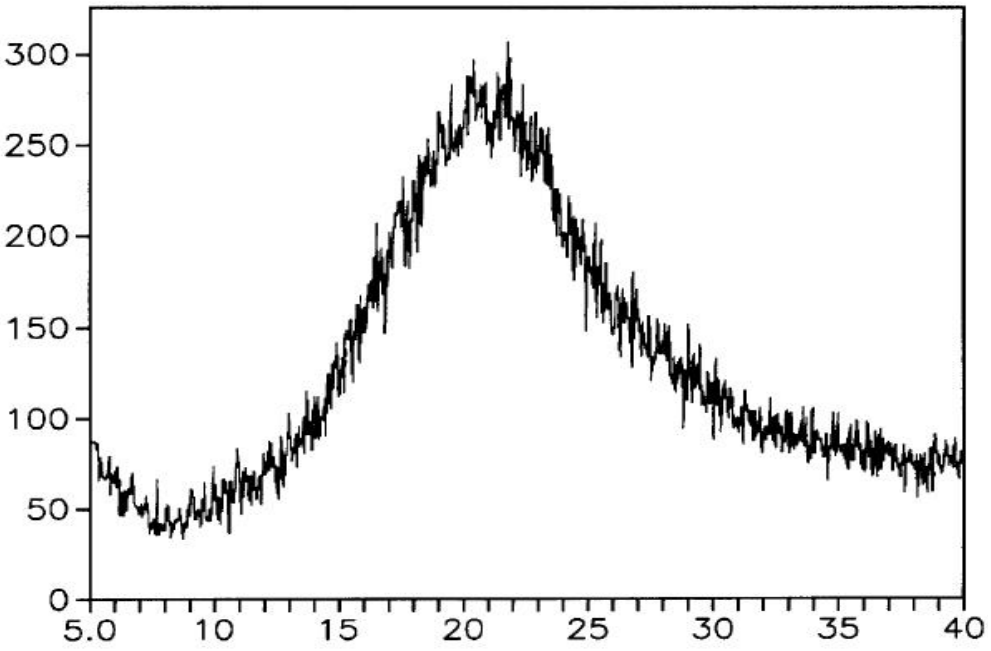
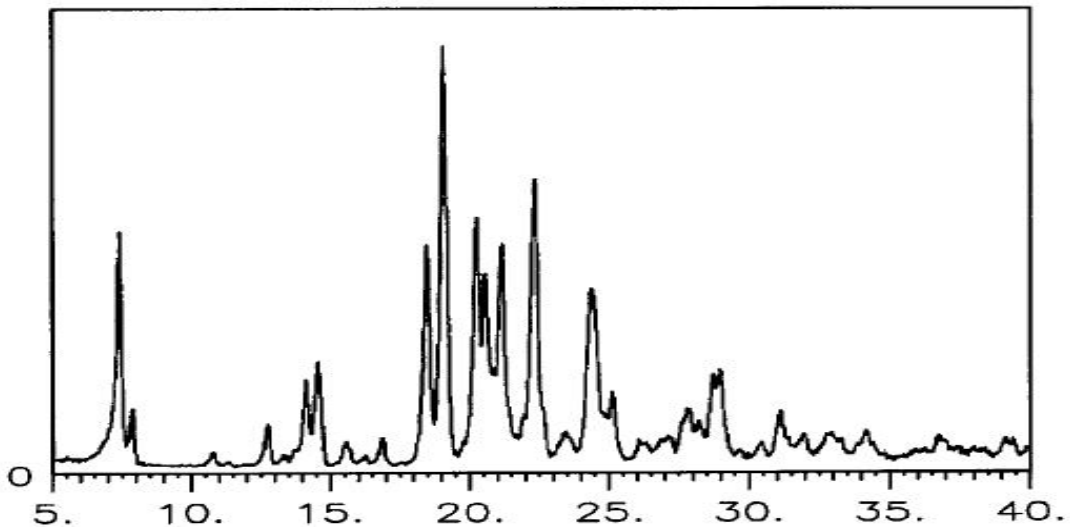


Fig: 2 XRD Pattern of SD and PM compared with pure drug. SD4 (1:9)



PM4 (1:9)



EPROSATAN

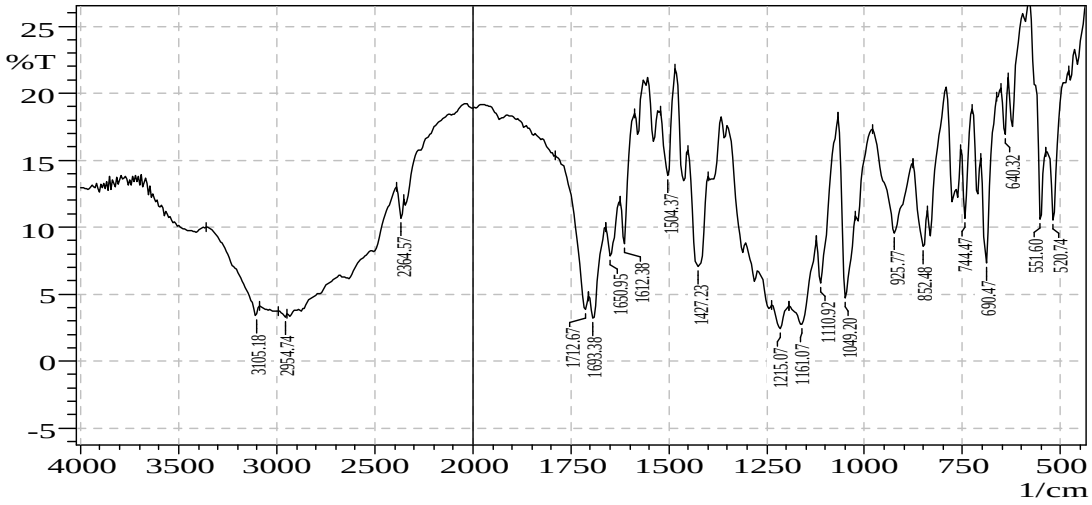
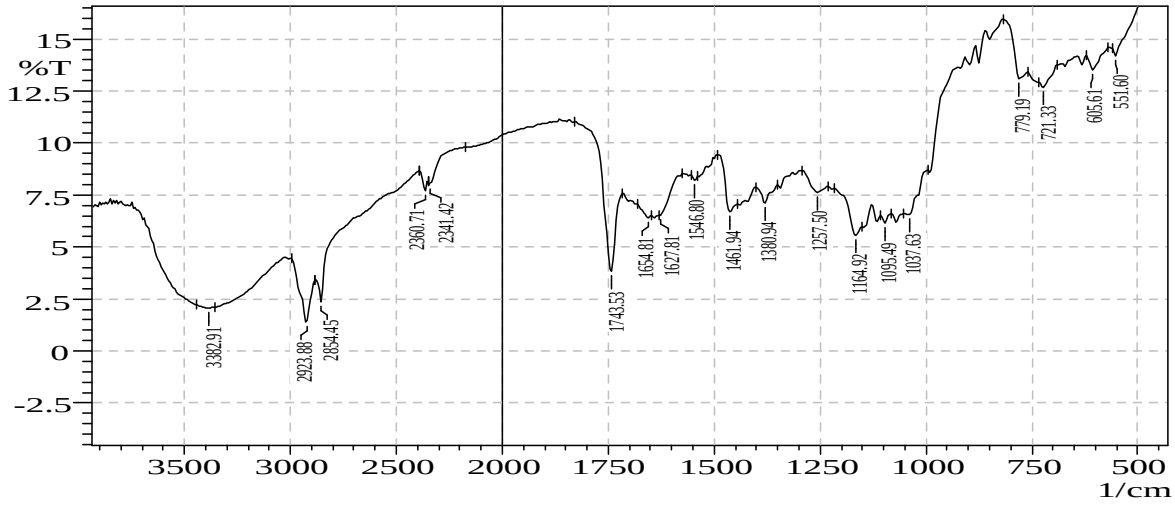


Fig: 3. IR Spectrum of SD and PM compared with pure drug EPROSARTAN



PM4 (1:9)

solubility as well as the dissolution when compared to pure drug. The IR study, TLC analysis and the UV overlay spectra of the formulations showed no signs of interactions of the drug with the carrier. Further the XRD analysis showed that there was a considerable decrease in the crystallinity of the drug which increases the surface area thereby increasing the dissolution. Thus it can be concluded that the solubility of the poorly soluble drug, Eprosartan can be improved markedly by using solid dispersion technique and the carrier PGS has increased the dissolution of the drug without any interaction.

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