

PREPARATION AND *IN VITRO* CHARACTERIZATION OF VALSARTAN SOLID DISPERSIONS USING SKIMMED MILK POWDER AS CARRIER

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ABSTRACT : Solubility 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, Valsartan 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 behavior and improved drug release. Formulation containing drug:polymer ratio of 1:9 showed the best release with a cumulative release of 81.60% as compared to 34.91 % 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.

Key-words: Solid Dispersion, Skimmed milk powder, solubility, Valsartan, Dissolution

INTRODUCTION

The formulation of poorly soluble drugs for oral delivery now presents one of the major challenges to formulation scientists in the industry¹⁻⁴. Various formulation parameters that play a crucial role for successful formulation are aqueous solubility, stability at ambient temperature and humidity, photo stability, 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 classification⁵. As per recent report⁶, 46% of the total NDAs filed between 1995 to 2002 were BCS class IV, while only 9% 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-solvents⁷, Milling techniques⁸, super critical processing⁹, Solid

dispersions¹⁰ including complexation¹¹, and precipitation techniques¹².

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. Valsartan is 3-methyl-2-[pentanoyl-[[4-[2-(2H-tetrazol-5-yl) Phenyl] methyl] amino]- butanoic acid. It is white fine powder having poor aqueous solubility. The present study is an attempt to overcome the poor aqueous solubility of VALSARTAN by solid dispersion technique using skimmed milk powder (SMP) as carrier.

MATERIALS & METHODS

Valsartan was obtained as gift sample from Rubicon Research limited, Mumbai, Skimmed milk powder

(SMP) was obtained from Himedia Laboratories, 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 μ m) filter paper and the filtrate was diluted. The absorbances were measured in spectra at 250 nm. From the absorbance the solubility of the drug were calculated.

Preparation of Solid dispersions:

Four formulations of Solid dispersions containing Valsartan 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. Valsartan 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 at -1kg/cm^2 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 250 nm. From the absorbance total drug content in the batches was calculated and given in table 4.

Dissolution studies¹⁶

The *in vitro* dissolution study was performed in USP XIX Dissolution rate test apparatus (Cmpbell, Mumbai) using 900 ml of Phosphate buffer pH 6.8. Amount of SD & PM equivalent to 80 mg 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 250 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 Valsartan (pure drug) and solid dispersions equivalent to 40 mg of the drug were separately introduced into 25- ml stoppered 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- μ m membrane filter and the filtrate was suitably diluted and analyzed on a UV Spectrophotometer at 250 nm. The same procedure was followed for Valsartan physical mixture and absorbance was taken at 250 nm.

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 study²²:

All the selected formulations and pure drug were subjected to X-ray diffraction study. The XRD patterns were recorded on a PW1729, Philips diffractometer (Eindhoven, The Netherlands) using Ni-filtered, $\text{CuK}\alpha$ radiation, a voltage of 40kV and a 25-mA current. The scanning rate employed was 10 min^{-1} over the 10 to 30° 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 Chloroform : Ethyl acetate : Acetic acid. The spots were visualized under UV scanner at 248nm 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 Spectrophotometer (Shimadzu, Japan) by scanning from 200-400nm and the λ max was found out.

RESULTS & DISCUSSIONS

The objective of this work is an attempt to increase the aqueous solubility and dissolution rate of Valsartan by solid dispersion techniques²³ using skimmed milk powder as hydrophilic carrier.

Phase solubility study:

Phase solubility study of Valsartan was conducted as per the method reported by M. Cirri *et al*¹³. Table: 1 gives the phase solubility data. The solubility of Valsartan 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 solubilization effect of the carrier on the drug.

Drug Content of Solid dispersions and Physical mixtures:

Valsartan 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 $\pm 5\%$ of the theoretical amount indicating the method used for formulation was suitable and reproducible in nature.

In vitro Release studies¹⁶:

Valsartan – SMP Solid dispersions¹⁴.

Table: 2 show the release data and profile of Valsartan–SMP Solid dispersions. The interpretation of the data and the profile showed that the percentage cumulative release (%CR) from Valsartan-SMP Solid dispersion was higher than pure drug. It was also postulated that batch SD4 showed a CR of 81.6% where as pure drug gave CR of 34.92%. The CR from the batches was also found to be increased on increasing the concentration of the carrier incorporated in formulations.

Valsartan-SMP Physical mixtures¹⁵:

The release data and profiles of Valsartan-SMP Physical mixture were given in Table: 2 The batch PM4 showed CR of 69.80% much more higher than other formulations indicating that PM4 was the best releasing batch in the formulation.

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. Valsartan was found to have saturation solubility of 0.0278 mg/ml. Batches SD4 and PM4 gave a solubility value of 0.0419 mg/ml and 0.0387 mg/ml respectively. The results proved that the carriers SMP was able to enhance the solubility of Valsartan in water.

Wettability studies:

The Buchner funnel method and water absorption method of Valsartan 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 80 minutes and 3.904 respectively its indicating poor wettability of the drug. The wetting time of samples was found to be very less (62 min) and water absorption ratio was more (17.28 min) than pure drug. This behavior 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 Valsartan from Solid dispersions.

XRD analysis²²

XRD analysis of the pure drug and selected batches were performed at CECRI, Karaikudi. 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. The observations were reported by Yuichi Tokuza *et al* and Center for Computational Project.

XRD Patterns of Valsartan and selected formulations were given in Fig: 2 XRD pattern of Valsartan 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:

I R Studies:

The I.R Spectrum of Valsartan 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 Valsartan 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 λ_{\max} of the sample and pure drug was found to be similar proving that no interaction between drug and carriers. (Data not shown)

CONCLUSION

The objective of the present study was to improve the solubility and dissolution behaviour of the poorly soluble drug, Valsartan 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 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, Valsartan can be improved markedly by using solid dispersion technique and the carrier PGS has increased the dissolution of the drug without any interaction.

Table: 1 Phase solubility data of Valsartan with SMP

Temp °C	Slope	Intercept	Ka	ΔG kJ/mol	ΔH kJ/mol	ΔS kJ/mol
25	32.911	-0.646	1.596	-12.22	-12.22	-12.18
37	47.482	-0.850	1.202	-8.571	-8.57	-8.543

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

Sample	D:C	%CR 10	%CR 30	%CR 60	%DE 60	MDT 60	T50
Pure Drug	-	2.878	22.163	34.919	16.50	31.65	63.6
Solid Dispersions	1:1	30.322	39.636	49.212	35.51	16.70	73.0
	1:3	45.501	48.162	54.383	45.23	10.09	31.8
	1:5	47.034	52.021	55.822	47.55	8.89	19.00
	1:9	56.693	68.846	81.604	63.37	13.40	6.3
Physical mixtures	1:1	28.789	36.861	42.641	32.52	14.23	132.9
	1:3	43.125	47.833	52.277	43.69	9.86	44.2
	1:5	44.658	47.963	52.529	44.53	9.14	38.2
	1:9	54.317	60.067	69.880	56.14	11.80	6.2

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

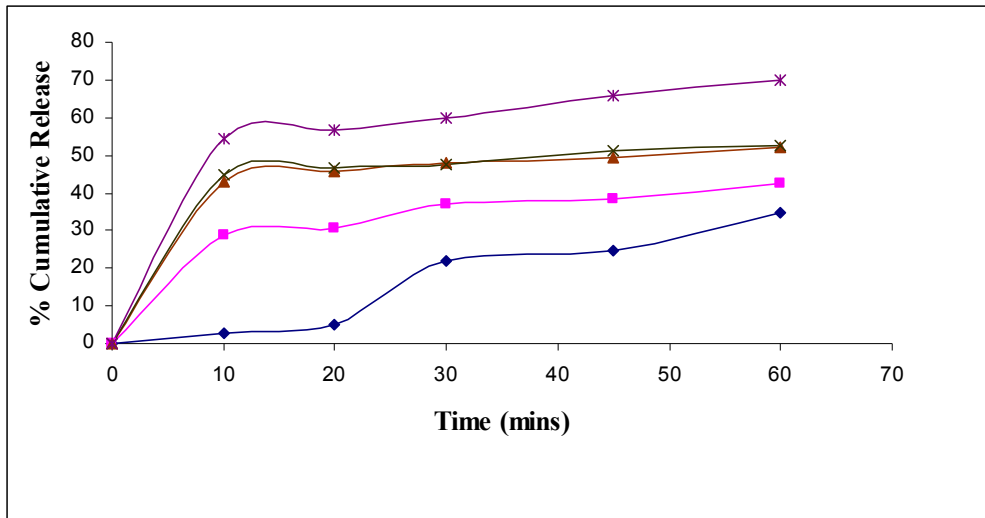
TABLE: 3. Selection Parameters for Formulations

Formulation	Drug Content (%)	Solubility (mg/ml)	Rf Values
Pure Drug	100.00	0.0278	0.51
SD4	100.36	0.0418	0.59
PM4	99.40	0.0387	0.56

Table 4: Wettability & Permeability Analysis

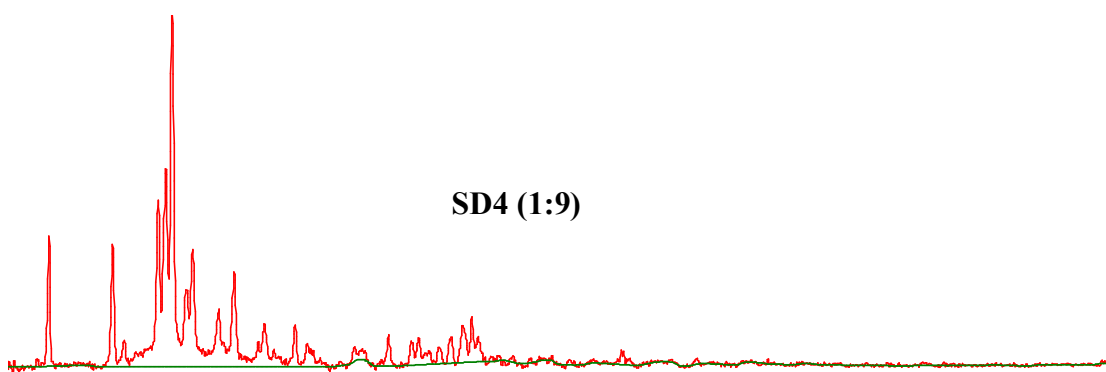
Formulation	Permeability (mg/ml/hr)		Wettability	
	Egg Membrane	Cellulose Nitrate Membrane	Buchner Funnel Method (Min)	Water absorption Method (R)
Pure Drug	0.0030	0.0137	80	3.904
SD4	0.0093	0.0294	62	17.28
PM4	0.0075	0.0249	69	13.45

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



◆-VALSARTAN; ■-SD(1:1); ▲- SD (1:3); ×- SD (1:5); *- SD (1:9)

Fig. 2 XRD Pattern of SD and PM compared with pure drug.



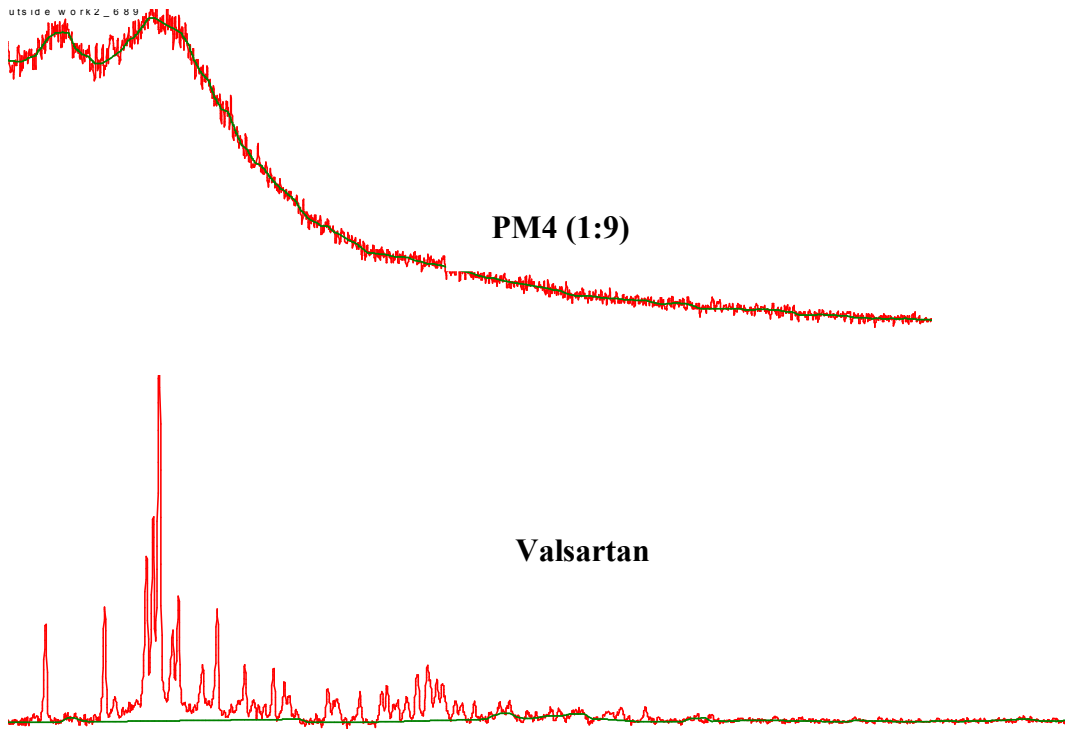
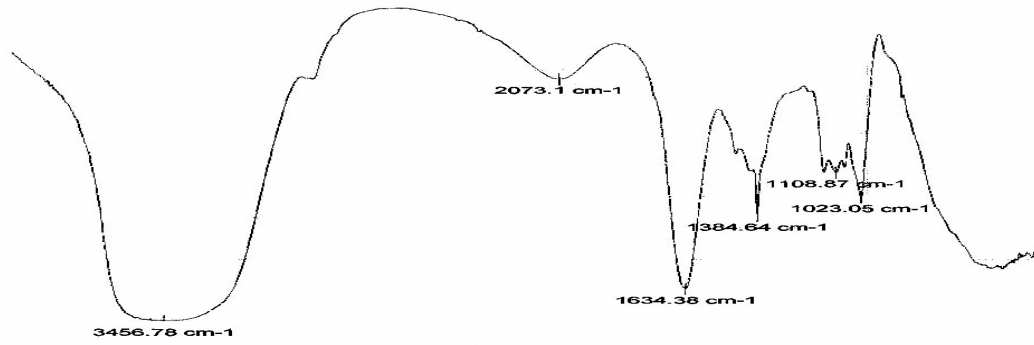
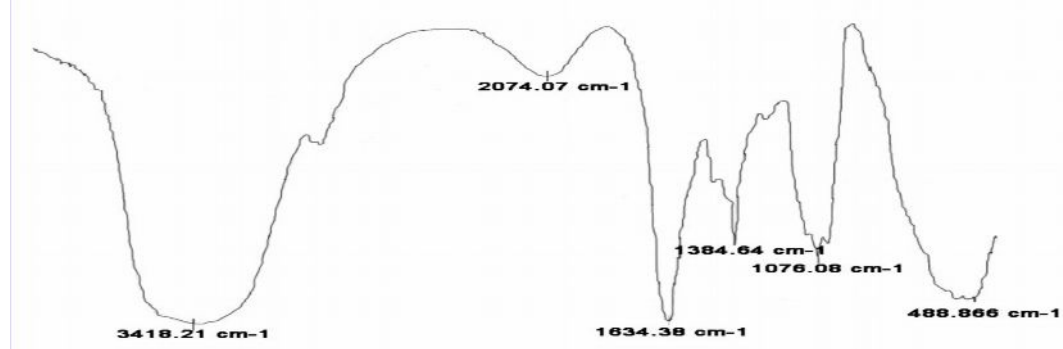


Fig: 3. IR Spectrum of SD and PM compared with pure drug

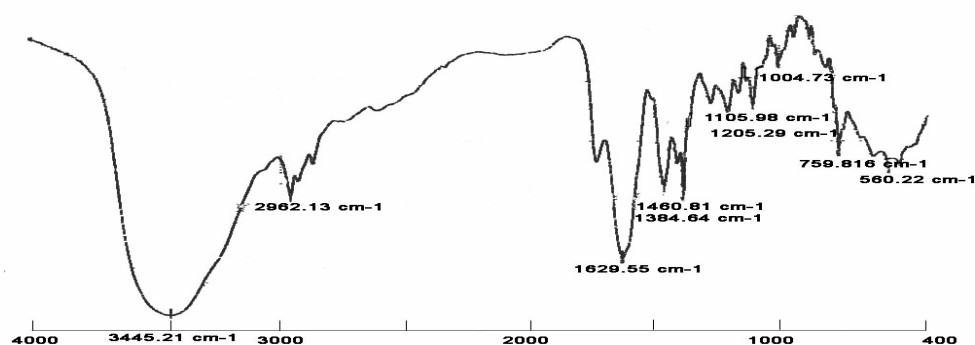
SD4 (1:9)



PM4 (1:9)



VALSARTAN



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