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Formulation and Evaluation of Valsartan Fast Disintegrating Tablets Using Solid Dispersion Technique

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ABSTRACT

Recent developments in fast disintegrating /dissolving tablets have brought convenience in dosing to elderly and children who have trouble in swallowing tablets. The main objective of the present study was to formulate and evaluate the fast disintegrating tablet of Valsartan. As precision of dosing and patient's compliance become important prerequisite for a long term Antihypertensive treatment, there is a need to develop a formulation for this drug which overcomes problems such as difficulty in swallowing, inconvenience in administration while travelling and patient's acceptability. Hence, the present investigation was undertaken with a view to develop a fast disintegrating tablet of Valsartan which offers a new range of product having desired characteristics and intended benefits. Valsartan is practically insoluble in water therefore to enhance the solubility and dissolution rate of drug, solid dispersions of Valsartan were prepared using mannitol as carrier by kneading method. The additions of different concentrations of superdisintegrants such as sodium starch glycolate, crospovidone were studied. U.V. Spectrophotometric method was selected for assay as well as in-vitro dissolution studies. The FTIR and DSC were used to characterize the solid state of solid dispersions. A marked increase in dissolution rate was observed with all solid dispersions, among that the optimized solid dispersion was selected for tablet formulation. The tablets prepared by direct compression technique on rotary tablet machine. The tablets were evaluated for pre-compression and post-compression parameters. Among all tablet formulations, F7 containing solid dispersion of valsartan and crospovidone as a superdisintegrant showed least disintegration time and faster dissolution.

Keywords: Valsartan, Superdisintegrants, Fast disintegrating tablets.

INTRODUCTION

Fast disintegrating tablets, disintegrate or dissolve quickly in the oral cavity, or swallowed without the need of water for the administration. As the tablet disintegrates in mouth, this enhances the clinical effects of drug through absorption from mouth, pharynx and esophagus leading to an increase in bioavailability by avoiding first pass liver metabolism. Fast disintegrating tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people. Fast disintegrating tablets are also called as mouth-dissolving tablets, melt-in mouth tablets, rapimelts, porous tablets, quick dissolving etc. Recent developments in fast-dissolving tablets (FDT) provide a convenient solution for patients who have difficulties in swallowing conventional solid dosage forms. These FDT turns into a soft paste or liquid form for easy swallowing and thus it is free of suffocation risk (Fu Y *et al*., 2004; Bogner RH *et al*., 2002). The primary beneficiaries for FDTs are pediatric and geriatric patients, bedridden or developmentally disabled patients. The key properties of FDTs are fast absorption of water in to the core of the tablets and disintegration of associated particles into individual components for fast dissolution (Chang RK *et al*., 2000; Dobetti L, 2001).Valsartan (Anonymous 1) (*S*)-3-methyl-2-(*N*-{[2'-(2*H*-1,2,3,4-tetrazol-5-yl)biphenyl-yl]methyl} pentanamido) butanoic acid], is an oral Antihypertensive & Angiotensin-II receptor blocker used for the treatment of Hypertension.Valsartan is practically insoluble in water, the dissolution rate can be increased by increasing the surface area of available drug by various methods like Micronization, Complexation and Solid dispersions (Martin A, 1993) (SDs). Hence present study was carried out to enhance solubility and dissolution properties of Valsartan through the preparation of Solid Dispersions (SDs) using Mannitol (Raymond C Rowe *et al*., 2003; Arias MJ *et al*., 1995) as

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carrier at various proportions (1:1,1:2,1:3,&1:4) by using different techniques like Physical mixtures, SD's by kneading method and the addition of different concentration of superdisintegrants such as Sodium starch glycolate (Raymond C *et al*., 2003), Crospovidone (Raymond C Rowe *et al*., 2003) were studied. U.V. Spectrophotometric method was selected for assay as well as in-vitro dissolution studies. The FTIR and DSC were used to characterize the solid state of solid dispersions. A marked increase in dissolution rate was observed with all solid dispersions among that the optimized solid dispersion was selected for tablet formulation. The tablets prepared by direct compression technique on rotary tablet machine. The tablets were evaluated for pre-compression and post-compression parameters. Among all tablet formulations, F7 which containing solid dispersion of valsartan and Crospovidone as a superdisintegrant showed least disintegration time and faster dissolution.

MATERIALS AND METHODS

Valsartan, Sodium starch glycolate,& Crospovidone were obtained as gift sample from Matrix pharma Pvt. Ltd., Nasik, Methanol, Mannitol, Microcrystalline cellulose, Sodium saccharin, Magnesium stearate, Mint flavour were procured from S.D Fine Chemicals, Mumbai.

PREPARATION OF PHYSICAL MIXTURES AND SOLID DISPERSIONS OF VALSARTAN

Preparation of physical mixtures

Accurately weighed quantities of Valsartan and mannitol in the ratios of (1:1, 1:2, 1:3 and 1:4) were weighed and taken in a glass mortar, were mixed thoroughly. The resultant mixture was passed through sieve number 100 # and stored in a dessicator for the complete removal of moisture.

Preparation of Solid Dispersions

Kneading Method

The accurately weighed amount of Valsartan and mannitol (1:1, 1:2, 1:3 and 1:4) were taken in a glass mortar and triturated by adding small volume of methanol to get smooth moist mass. The mass was kneaded for 45 minutes and then dried in an oven at 35ºC till the constant weight is reached. The dried mass was pulverized and sifted through #100. The obtained product was stored in a dessicator.

Evaluation of Valsartan Solid Dispersions

Estimation of Drug Content

A quantity, which was equivalent to 100 mg of drug, was accurately weighed and transferred to 100ml volumetric flask. Then the volume was made up with, pH-6.8 phosphate buffer and shaken for 10 min to ensure complete solubility of the drug. Then the solution was filtered and filtrate was diluted suitably and Assayed for drug content at 251 nm by using UV-Visible spectrophotometer.

In vitro dissolution study

filtered. Filtrate was diluted suitably and assayed for drug

The prepared solid dispersions were subjected to *in vitro* dissolution. Dissolution test was carried out using USP23 basket method [apparatus 1]. The stirring rate was 50 rpm, pH-6.8 phosphate buffer was used as dissolution medium and dissolution medium was maintained at 37±1^{o}C. Samples of 5 ml was withdrawn at regular intervals of time, filtered and replaced with 5 ml of fresh dissolution medium, dilutions were made and analyzed for Valsartan at 251 nm by using UV-visible spectrophotometer.

Fourier Transform – Infra Red Spectroscopy

FT-IR spectra were recorded on samples prepared in potassium bromide disks using thermon electron FTIR. Samples were prepared in potassium bromide discs by means of a hydrostatic press. The scanning range was 400 to 4000 cm^{-1} and the resolution was 4 cm^{-1}.

Differential Thermal Analysis (DTA)

DTA patterns of samples were obtained with Schimadzu DTA -50 instrument using vented aluminium pans. For DTA analysis each sample of 5-10 mg weight was taken in hermetically sealed flat-bottomed aluminium pans. The sample was heated over a temperature of range 30-300^{0}C in nitrogen atmosphere (30ml/min) at constant rate of 10^{0}C. The instrument was calibrated with standard medium.

Method of preparation of tablets by direct compression

Tables were prepared by using the selected SD i.e. Valsartan: Mannitol (1:4 KM), which showed best dissolution profile among all the solid dispersions prepared. All the ingredients were passed through mesh # 30 and the drug complex was passed through mesh #40. All the ingredients, MCC, SSG, Crospovidone and mint flavour were load into the polyethylene bag and mixed for 10 min. To this drug complex was added and mixed for 10 min. The blend was compressed using 12 stationary rotary punching machines until desired hardness was obtained.

Evaluation of the tablets of Valsartan:Mannitol solid dispersions

Compressed tablets were then evaluated for hardness (Bankar GS *et al.,* 1991), disintegration (Pharmacopoeia of India, 1996), Friability (Pharmacopoeia of India, 1996) and drug content. Hardness was measured by Monsanto type hardness tester. For disintegration one tablet was placed in each tube of disintegration apparatus (USP/IP standard). The test was carried out using distilled water as a disintegration media at 24^{o}C±2^{o}C. Friability was determined in friabilator (model Ef- 2, electro lab), by taking 10 tablets. For drug content analysis 20 tablets were accurately weighed and finely powdered. The quantity of powder equivalent to 100 mg of Valsartan was taken into a 100ml volumetric flask and volume adjusted to 100 ml with pH-6.8 phosphate buffer and content at 251nm, using double beam U V/ Visible

spectrophotometer (Shimadzu, model -1700). The drug content of the tablets was found to be in range of 97.05% to 99.05%.

In vitro dissolution study of tablets

In-vitro dissolution study of the tablets (Pharmacopoeia of India, 1996; USP, 2000) was conducted using USP dissolution. Apparatus - 2, at 50 rpm using pH-6.8 phosphate buffer as a dissolution media, at 37°C±0.5°C. Samples were withdrawn at various time intervals and filtered through a 0.45 micron whatman filter paper, diluted, and assayed at 251nm using UV / Visible double beam spectrophotometer.

Stability study of F7

In order to determine any change in *in-vitro* drug release profile on storage. Stability of F7 was carried out at 40°C and 75%RH in stability chamber [Thermolab]. The formulation was withdrawn after 4 weeks. And evaluated for change in *in-vitro* drug release pattern, hardness and disintegration time.

RESULT AND DISCUSSION

All the Solid dispersions (SD_S) were found to be free flowing, Low values of C.V (<1.0%) in percent drug content indicated uniformity of drug content in each batch of solid dispersions. The dissolution profiles of various physical mixtures and sold dispersions were shown in Fig.1,2. All the Physical mixtures and solid dispersions showed rapid dissolution of Valsartan as compared to pure drug. The dissolution rate of Valsartan increases with Increase in Mannitol, up to 1:4 ratio of drug; mannitol this increase in dissolution rate may be due to improved wettability by the carrier. The dissolution rates of solid dispersions prepared by Kneading Method were greater than PM and pure drug. The order of dissolution rates are SD>PM>Pure drug. In each case the dissolution was found to obey First order kinetics (R>0.9924).The dissolution rate constant (K_1) was calculated from the slope of the first order linear plots of the dissolution data. The dissolution efficiency ($DE_{15\%}$) value based on the dissolution data were calculated according to Khan (Khan KA, 1975). T_{50} (time taken for 50 % dissolution) values were recorded from the dissolution profile. The dissolution parameters of pure drug, PM and SDs were shown in Table.1. It is indicated that The Valsartan: mannitol. 1:4 Kneading method shown maximum dissolution efficiency $DE_{(15\%)}$ and low $t_{1/2}$. It was converted to cost effective tablet formulation. Different concentrations of super disintegrants such as sodium starch glycolate and crospovidone were used. Formulae of the tablets were shown in table.2. Among all tablet formulations prepared, F7 which containing solid dispersion of valsartan:mannitol 1:4 ratio and Crospovidone 6% as a superdisintegrant showed least disintegration time and faster dissolution rate than the tablets prepared according to other formulae. The dissolution profile of tablets shown in Fig.3,4. The results of mean hardness, disintegration, the friability, Wt.Variation, and assay of prepared tablets were shown in Table.3. The % Dissolution in 10min, T_{50} and dissolution efficiency (DE_{15},r^2,$t_{1/2}$) values of tablets were shown in Table.4. FT-IR spectroscopy was used to study the possible interaction between Valsartan and mannitol in SDs the spectra showed the characteristic peaks corresponding to the drug and carrier used was unchanged showing no significant interaction between drug and carrier shown in Fig.5,6,7,8,9,10. The obtained DSC thermogram corresponding to the melting point of Valsartan and mannitol indicated that SDs was stable and absence of any additional peak indicated no interaction between drug and carrier, shown in Fig.11,12,13,14. In order to determine the change in the *in-vitro* release profile on storage stability study of F7 was carried out at 40°c and 75% RH for one month, there is no significant change in Dissolution profile and no visible physical changes were observed in the formulation.

Fig.1 Dissolution profiles of Valsartan from Mannitol Solid Mixtures prepared by Physical mixing

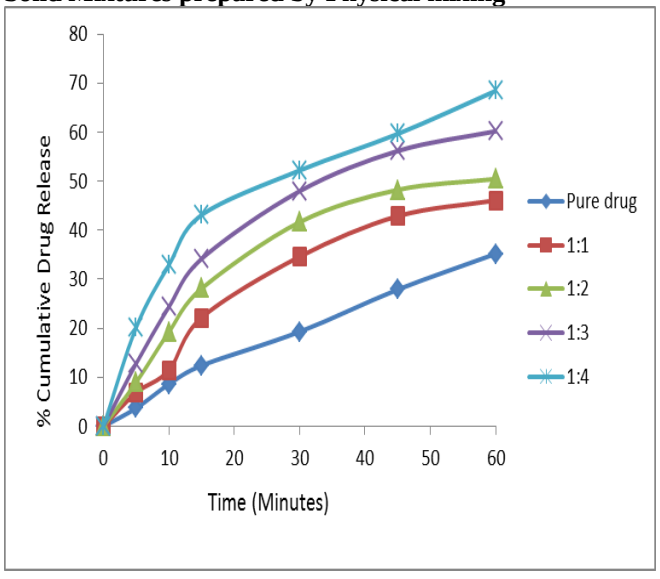


Fig.2 Dissolution profiles of Valsartan from Mannitol Solid Mixtures prepared by Kneading Method

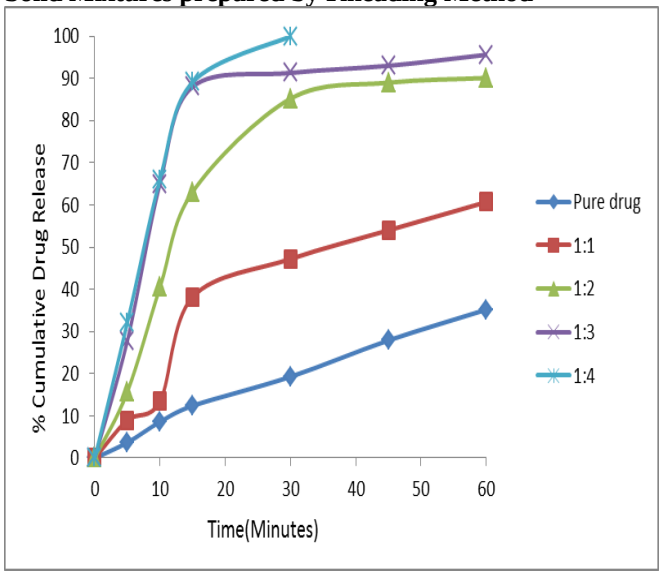


Fig.3 Dissolution profiles of VAL and VAL: Mannitol (1:4) (KM) Tablets from F1-F4

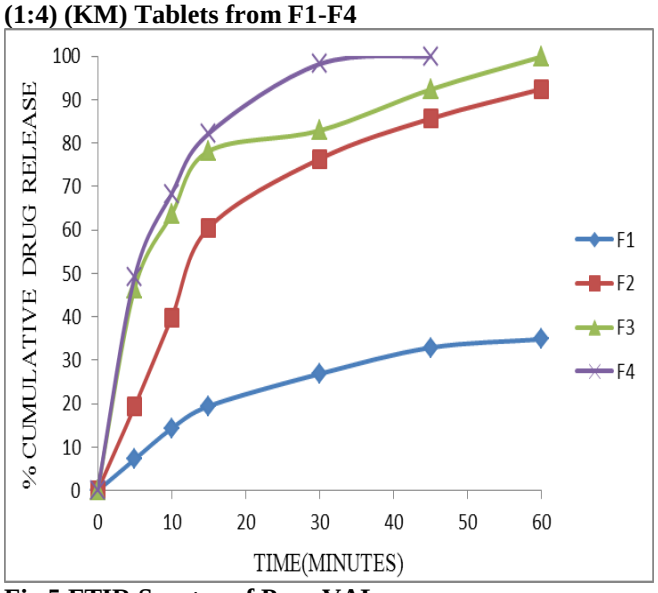


Fig.4 Dissolution profiles of VAL and VAL:Mannitol (1:4) (KM) Tablets from F5-F7

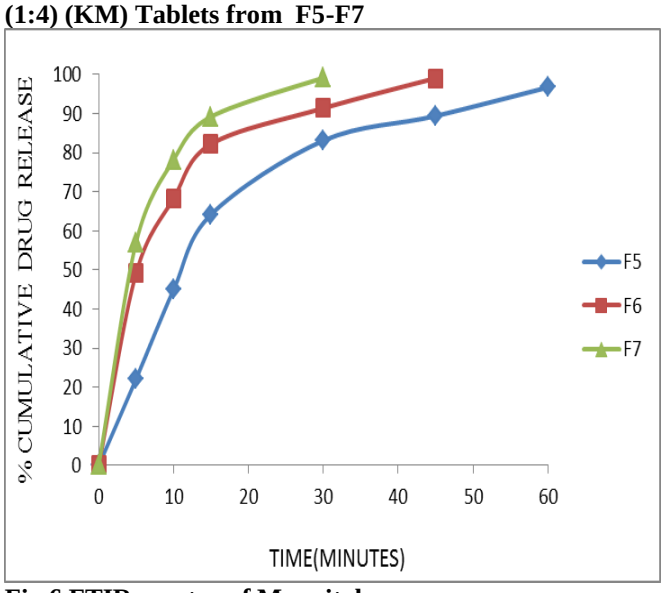


Fig.5 FTIR Spectra of Pure VAL

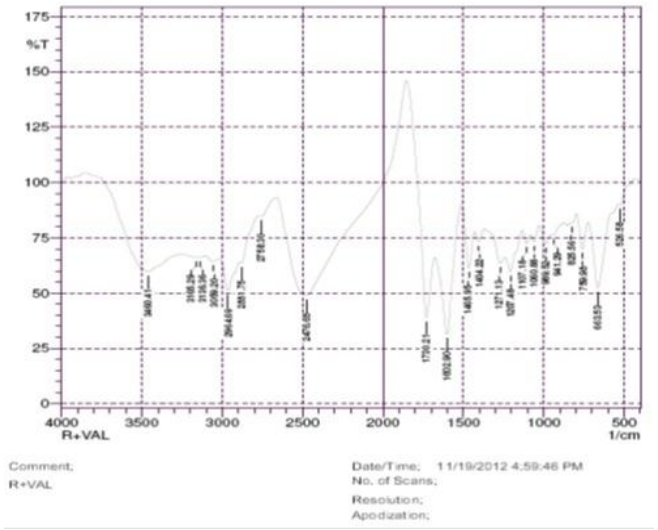


Fig.6 FTIR spectra of Mannitol

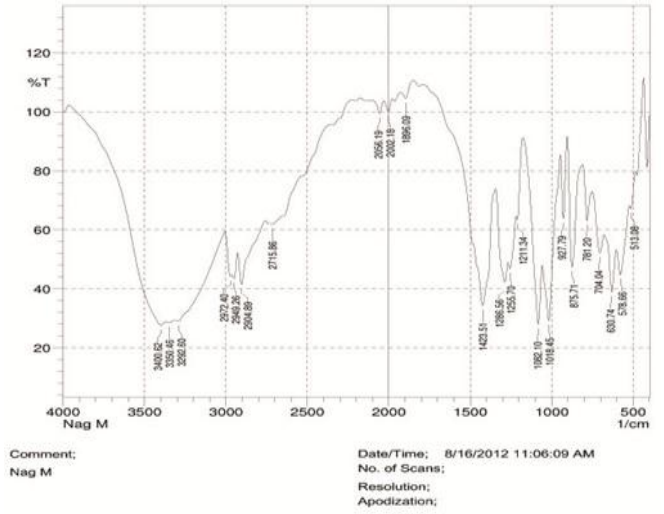
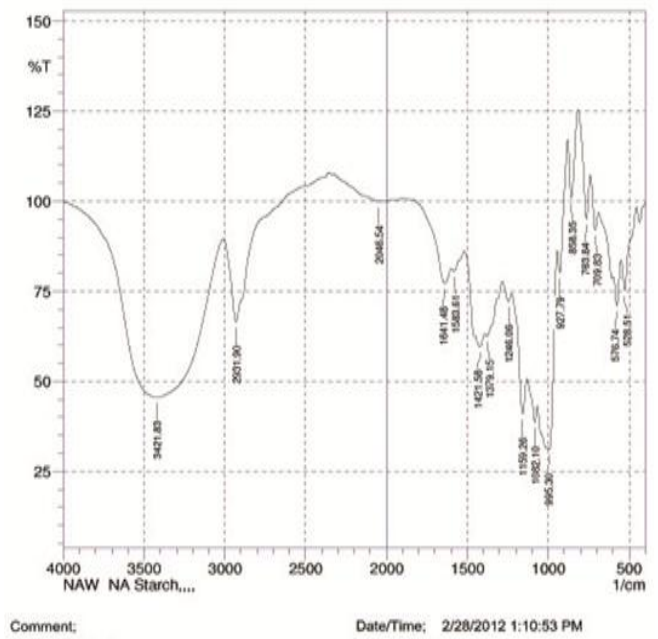


Fig.7 FTIR spectra of sodium starch glycolate

Fig.8 FTIR spectra of crospovidone



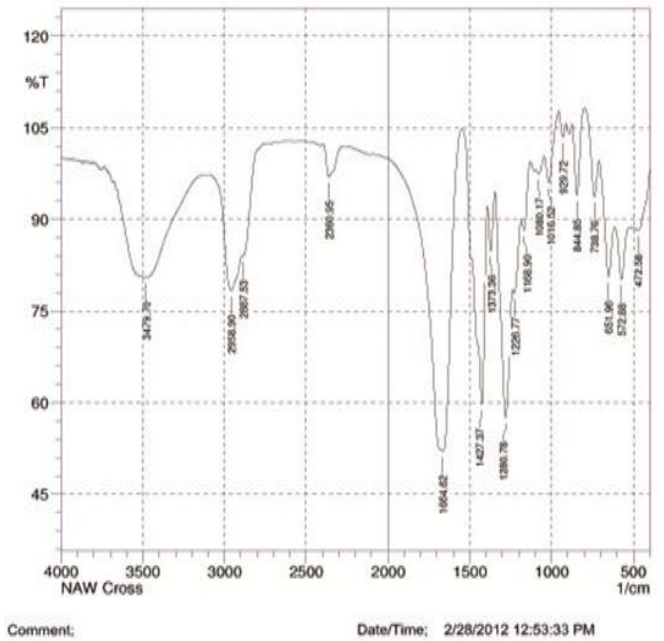


Fig.9 FTIR spectra of VAL: Mannitol (1:4) KM

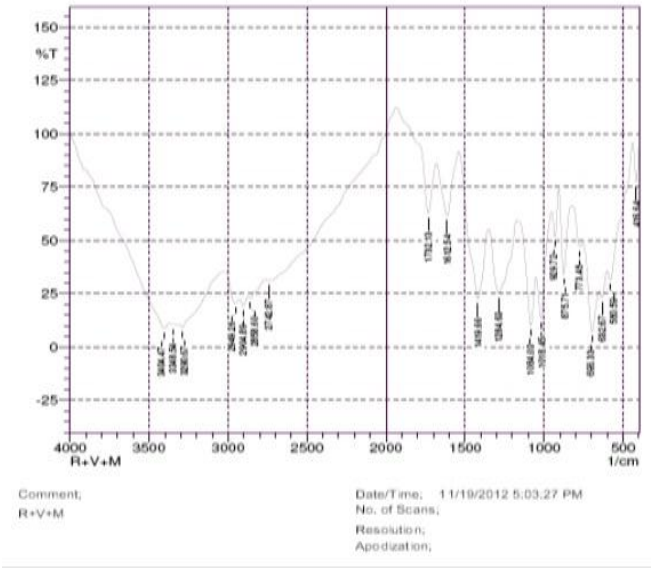


Fig.10 FTIR spectra of Formulation F7

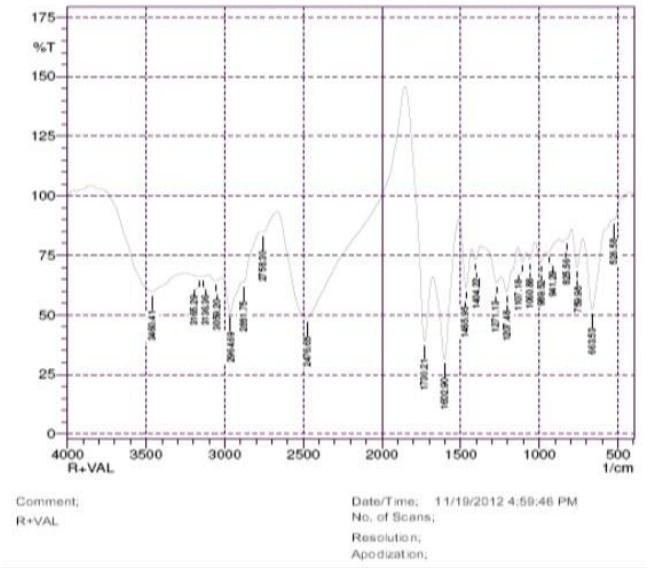


Fig. 11 DSC pattern of pure VAL

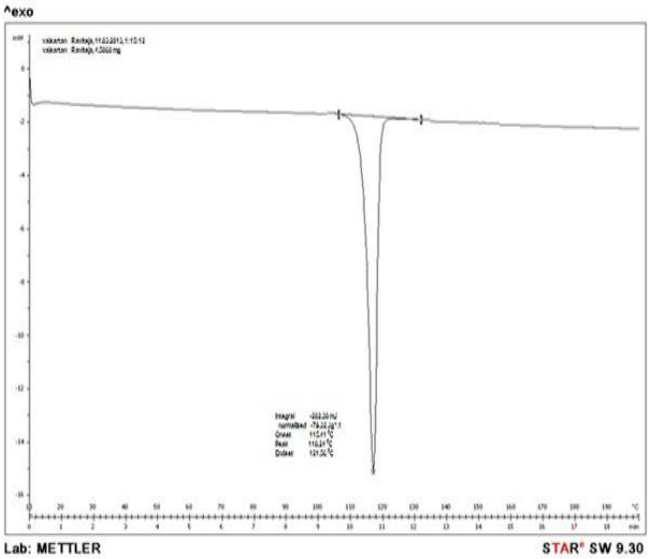


Fig.12 DSC pattern of pure Mannitol

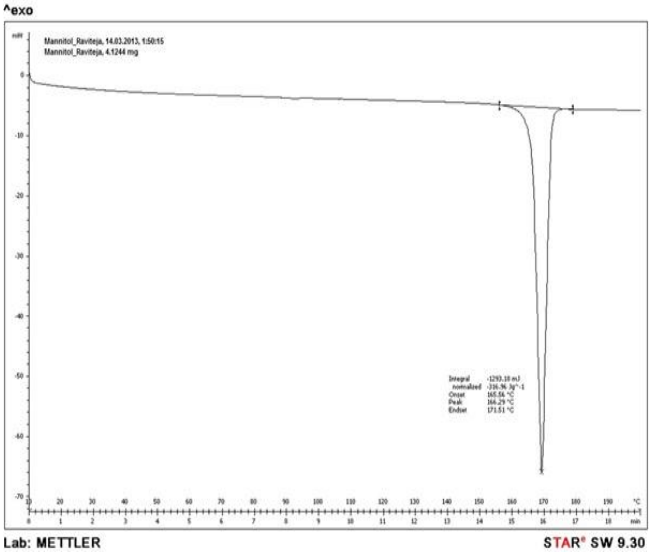


Fig.13 DSC pattern of VAL:Mannitol(1:4) KM

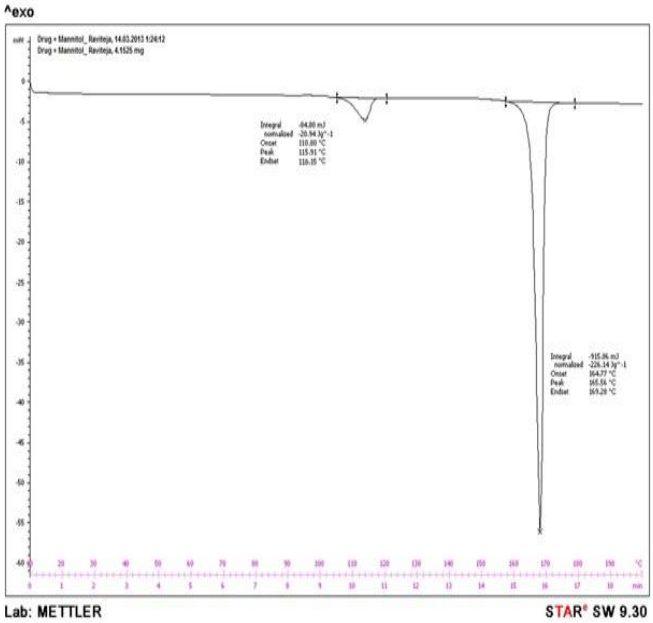


Fig.14 DSC pattern of VAL:Mannitol(1:4) KM with CP

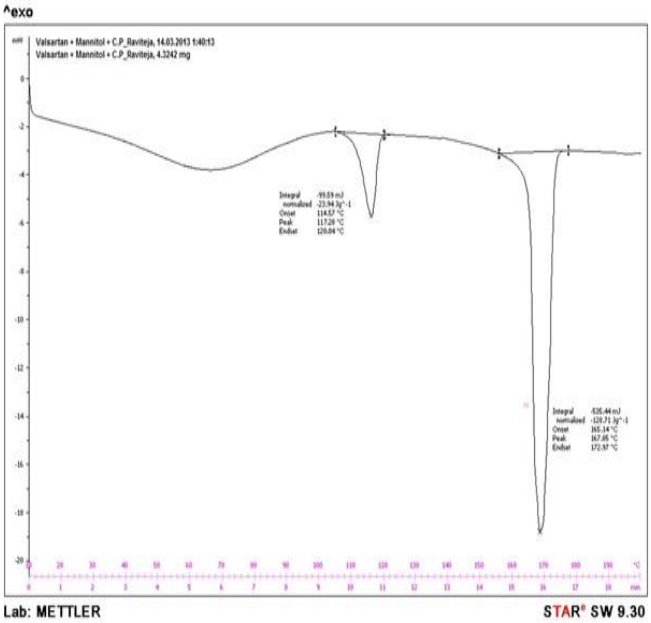


Table.1 Dissolution parameters of various Valsartan:Mannitol solid dispersions

Product	% Dissolution In 10 min	T_{50} min	DE_{20} (%)	R^2	$t_{1/2}$
Valsartan	8.6	>60	6.16	0.992	>60
PM					
1:1	11.42	>60	9.79	0.948	>60
1:2	19.22	59	14.0	0.910	>60
1:3	24.33	33	17.86	0.933	50.15
1:4	32.88	27	24.86	0.983	42.98
KM					
1:1	9.0	33	13.86	0.920	50.2
1:2	15.7	14	29.2	0.906	16.9
1:3	27.82	8	45.6	0.811	14.4
1:4	32.18	6	47.6	0.983	4.1

Table.2 Composition for the preparation of tablets: (per tablet)

Sl. No	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7
1	VAL	80	---	---	---	---	---	---
2	VAL : MANNITOL (1:4)KM	---	400	400	400	400	400	400
3	SSG	---	10	20	30	---	---	---
4	CP	---	---	---	---	10	20	30
5	MCC	403	73	63	53	73	63	53
6	Sodium Saccharin	1.5	1.5	1.5	1.5	1.5	1.5	1.5
7	Mint Flavour	0.5	0.5	0.5	0.5	0.5	0.5	0.5
8	Magnesium Stearate	10	10	10	10	10	10	10
9	Talc	5	5	5	5	5	5	5
	TOTAL	500	500	500	500	500	500	500

Table.3 Evaluation of Post-Compression parameters of Tablets

Formula	F1	F2	F3	F4	F5	F6	F7
Hardness (Kg/cm2±S.D) *	4.3±0.5	3.8±0.35	4.0±0.25	4.2±0.26	3.5±035	3.81±0.12	4.0±0.42
D.T(Sec)	42	40	37	34	30	28	20
Wt.Variation (%)*	98.04±0.05	99.02±0.12	98.05±0.15	97.05±0.35	99.05±0.25	98.01±0.25	99.04±0.25
Drug Content (%)±S.D*	98.84±0.06	98.15±0.28	99.10±0.12	98.27±0.26	98.24±0.18	99.12±0.10	99.49±0.10
Friability (% w/w)	0.82	0.78	0.72	0.68	0.65	0.64	0.48
Uniformity of dispersion	Pass	Pass	Pass	Pass	Pass	Pass	Pass

*n=3

Table.4 Dissolution parameters of formulated Tablets

Product	% Dissolution In 10 min	T_{50}	DE_{15} (%)	R^2	$t_{1/2}$
F1	14.42	>60	10.3	0.934	>60
F2	39.88	12.5	29.8	0.881	25.0
F3	36.58	11	49.7	0.896	13.6
F4	68.36	5.1	52.8	0.992	5.0
F5	44.98	11	33.09	0.968	12.5
F6	68.32	6	54.9	0.984	7.3
F7	78.22	4.8	59.97	0.999	4.1

CONCLUSION

From the above investigations it was concluded that the solid dispersion technique could be successfully used to improve the water solubility of Valsartan using mannitol as carrier and the tablets prepared from solid dispersion of Valsartan: Mannitol 1:4 ratio prepared by Kneading method,containing 6% Crospovidone as a superdisintegrant i.e. F7 shown promising improvement in the dissolution characteristics and thus there is possible enhancement in the bioavailability of Valsartan.

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