T. S. N. S. Varalakshmi et al. / Journal of Pharmacy Research 2015,9(2),139-144

Research Article
ISSN: 0974-6943

Available online through
www.jprsolutions.info

Formulation and evaluation of solid dispersions of valsartan for dissolution rate enhancement

T. S. N. S. Varalakshmi*, Ch. Siva Ramesh, I. Jyothi, Y. Jyothi, G. Bharathi, P. Chinni Babu
Department of Pharmaceutics, Adarsa College of Pharmacy, G. Kothapalli, E.G.Dt, Andhrapradesh, India

Received on:18-12-2014; Revised on: 25-01-2015; Accepted on:13-02-2015

ABSTRACT

Objective: The objective of the study was to formulate solid dispersions of Valsartan using hydrophilic carriers in different concentrations and to determine their effect on solubility of drug.**Methods:** Solid dispersions of Valsartan were prepared using urea, PEG4000 as carriers in different drug: carrier ratios of 1:1, 1:2, and 1:4 by employing solvent evaporation method. Physical mixtures were also prepared for the above ratios. The prepared physical mixtures and solid dispersions were evaluated for flow properties, solubility studies, drug content and *In-vitro* dissolution studies.**Results:** The prepared physical mixtures and Solid dispersions of Valsartan showed good flow property and uniformity in drug content. From the saturated solubility studies and *In-vitro* dissolution studies it was observed that there was increase in solubility of drug and enhanced dissolution rate in solid dispersions compared to physical mixtures respectively. Formulation containing 1:4 ratio of drug: PEG4000 is considered as best formulation as it has shown highest drug release in short time i.e. 99.86 % in 20min. **Conclusion:** Our studies showed that the solubility of the drug can be significantly enhanced with solid dispersions of the studied polymers. With increase in the carrier content there is increase in the solubility resulting in enhanced dissolution rate.

KEYWORDS: Valsartan, hydrophilic carriers, Urea, PEG4000, solvent evaporation method.

INTRODUCTION

The oral route of drug administration is the most common and preferred method of drug delivery due to convenience and ease of ingestion. Poorly water soluble drugs having slow drug absorption leads to inadequate and variable bioavailability and gastrointestinal mucosal toxicity. This poor oral bioavailability of the drug is the major challenging task for the designing the oral dosage forms. The poor oral bioavailability of the drug is due low solubility, low dissolution of the drug rather than permeation of the drug through epithelia of gastrointestinal tract[1].

There are various techniques available to improve the solubility of poorly soluble drugs, such as micronization, nanosuspension, modification of the crystal habits, eutectic mixtures, solid dispersions, micro emulsions, self micro emulsifying drug delivery systems, cyclodextrin inclusion and lipid based delivery systems etc[2].

The most promising method for promoting dissolution is the formation of solid dispersion in a proper carrier. The term solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix in solid state prepared by melting (fusion), solvent, or melting solvent method. Solid dispersions (SDs) have traditionally been used as an effective method to improve the dissolution properties and bioavailability of poorly water-soluble drugs. In solid dispersion systems, a drug may exist as an amorphous form in polymeric carriers, and this may result in improved solubilities and dissolution rates as compared with crystalline material. Drugs molecularly dispersed in polymeric carriers may achieve the highest levels of particle size reduction and surface area enhancement, which result in improved dissolution rates[3].

Valsartan is angiotesin II receptor antagonist, widely used in the management of hypertension to reduce cardiovascular mortality in patients with left ventricular dysfunction, and in the management of heart failure. This drug is a BCS class II drug with poor aqueous solubility. Valsartan is rapidly absorbed ofter oral dose with bioavailability of about 23%. Peak plasma concentration occur within 2-4 hrs and its plasma half life 5-7 hrs after oral dose[4,5]. In the present study an attempt will be made to to improve solubility and dissolution rate of Valsartan through solid dispersion technique using water soluble carriers. Solid dispersions of Valsartan were prepared using urea, PEG4000 as carriers in different drug: carrier ratios of 1:1, 1:2,

***Corresponding author.**
T.S.N.S Vara lakshmi
Assistant professor
Adarsa College of Pharmacy
G.Kothapalli, E.G.Dt
Andhrapradesh, India

and 1:4 by employing solvent evaporation method.

MATERIALS & METHODS:

Materials

Valsartan was obtained as a gift sample from Mylan, Hyderabad, Andhra Pradesh, India.All solvents and chemicals were used of analytical grade and were obtained from S.D. Fine-Chem Ltd, Mumbai, India.

Method of estimation of Valsartan:

The standard stock solution was prepared by taking 100mg of valsartan into 100ml volumetric flask which was dissolved in methanol and volume made up to the mark using pH 6.8 phosphate buffer solution to get 1000µg/ml solution and was used as a stock solution.

From the above stock solution 10ml was pipette out and taken into another 100ml volumetric flask and was further diluted up to the mark to get working standard solution I containing 100 µg/ml solution. From the working standard solution I 0.1, 0.2, 0.3, 0.4 and 0.5 ml were taken and diluted to 10ml with pH 6.8 phosphate buffer to get a concentration of 10,20,30,40 and 50 µg/ml solutions respectively. The absorbance of these solutions was measured at 250 nm against blank (pH 6.8 phosphate buffer).The absorbance values thus obtained were plotted in a graph of concentration versus absorbance[6].

Preparation of Physical mixtures of Valsartan:

Physical mixtures were prepared by mixing accurate weight of drug with carrier in different proportions i.e, 1:1, 1:2, 1:4 (drug:carrier) and triturated in glass mortar and pestle for 30 minutes and then passed through 60 mesh sieve size.

Table 1: Composition of Valsartan Physical mixtures & Solid Dispersions

S.no	Formulation	Composition	Drug
1	PMU1	Valsartan+Urea	1:1
2	PMU2	Valsartan+Urea	1:2
3	PMU4	Valsartan+Urea	1:4
4	PMP1	Valsartan+PEG 4000	1:1
5	PMP2	Valsartan+PEG 4000	1:2
6	PMP4	Valsartan+PEG 4000	1:4
7	SDU1	Valsartan+Urea	1:1
8	SDU2	Valsartan+Urea	1:2
9	SDU4	Valsartan+Urea	1:4
10	SDP1	Valsartan+PEG 4000	1:1
11	SDP2	Valsartan+PEG 4000	1:2
12	SDP4	Valsartan+PEG 4000	1:4

Preparation of Solid Dispersions of Valsartan:

Solvent Evaporation Method:

Solid dispersion is one of the most commonly used techniques to improve the solubility of water insoluble drugs which in turn improves the bioavailability. Valsartan solid dispersions were prepared by using carriers (i.e. Mannitol, Urea and PEG 4000) in proportions viz. 1:1, 1:2 and 1:4 (Drug: Carrier) by solvent evaporation method.Methanol was added to the mixture of drug and carrier and triturated in dry mortar until the solvent evaporated and a clear film of drug and carrier was obtained. The resultant solid dispersion was scraped out with a spatula. Dispersions were pulverized in a mortar and pestle and passed through a sieve no 60. Then the prepared formulations were stored in a desiccator until further use[7].

CHARACTERIZATION OF SOLID DISPERSION:

Solubility Studies of Valsartan Solid Dispersion

Solubility measurements of Valsartan were performed according to a published method[12]. Solid dispersions equivalent to 100 mg of valsartan was shaken with 10ml distilled water in stoppered conical flask in an orbital shaker for 24 hours at room temperature. Subsequently, the solutions were filtered through a Whatman filter paper no 1. Filtered solution was diluted properly with pH 6.8 phosphate buffer. The diluted solutions were analyzed for the Valsartan in UV 250 nm[8].

Drug Content

Solid dispersions equivalent to 10 mg of Valsartan were weighed accurately and dissolved in the 10 ml of methanol. The solution was filtered, diluted suitably and drug content was analyzed at 244 nm by UV spectrophotometer. The Actual Drug Content was calculated using the following equation:

% Drug content = (Actual amount of drug in solid dispersion/Theoretical amount of drug in solid dispersion) X100

Determination of Flow Properties: [9,10,11]

Bulk density and Tapped density

Accurately weighed amount of solid dispersions were transferred to a 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 of powder/Bulk volume of the powder= M/V_b

Tapped Density= Mass of powder/Tapped volume of the powder =M/V_t

Carr's index and Hausner's ratio:

Carr's index and hausner's ratio are calculated by using following formulae.

Carr's index = [(Tapped density – Bulk density)/Tapped density] * 100

Hausner's Ratio = Tapped density / bulk density

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 Solid dispersions were 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

q = **$\tan^{-1}$ (h/r)**

Where h = Height of the heap

r = Radius of the heap

***In vitro* Release Studies**[12]

In vitro dissolution studies were performed for prepared solid dispersion. The following conditions were maintained for the dissolution process:

Instrument: LABINDIA DS-8000 Dissolution test apparatus.
Apparatus: Paddle type.
Temperature: 37±0.5°C
RPM: 50
Dissolution medium: 6.8 Phosphate buffer
Volume of medium: 900 ml.
Sampling intervals: 5, 10, 15, 20, 30, 45, 60, and 90 min.
Sample volume: 5 ml withdrawn at fixed time intervals and replaced with 5 ml of pH 6.8 phosphate buffer.

RESULTS AND DISCUSSION:

Standard Curve of Valsartan:

The UV spectrum of the drug in the range of 200-400nm on UV-visible spectrophotometer revealed that wavelength of maximum absorption (?max) of Valsartan was 250nm. From the graph of absorbance vs. concentration for pure Valsartan it was observed that the drug obeys beer's law in concentration range of 10-50 µg/ml (r= 0.997) at 250nm (Table 2, Figure 1).

Table 2: Standard plot data of Valsartan

S.No	Concentration (µg/ml)	Absorbance
1	10	0.232
2	20	0.421
3	30	0.643
4	40	0.802
5	50	0.981

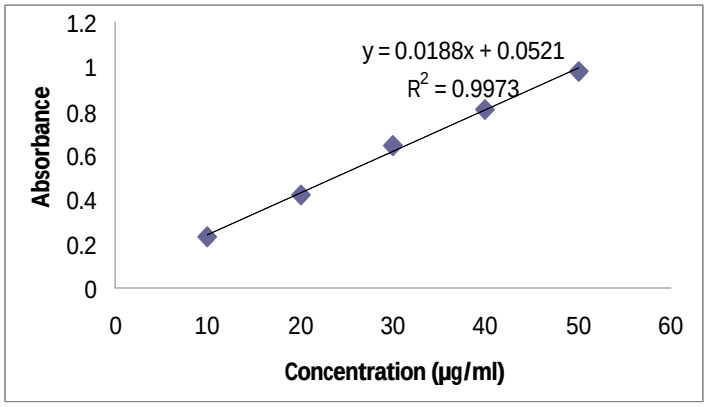

Figure 1: Standard plot of Valsartan in pH 6.8 phosphate buffer

Solubility Studies of Physical mixtures and Solid Dispersions of Valsartan:

Saturation solubility analysis was carried out for pure drug, prepared physical mixtures and solid dispersions. (Table 3). From the results of saturation solubility studies it was observed that there was increase in solubility of drug in solid dispersions compared to physical mixtures. With increase in the concentration of carrier solubility of drug increased and the solid dispersions containing PEG 4000 in the ratio of 1:4 (drug to carrier) had increased the solubility almost 5 fold compared to that of pure drug. (Figure 2).

Table 3. Solubility Studies of Valsartan

Sample	Carrier Solution	Solubility mcg/ml
PD	Pure drug in water	20.3
PMU1	Valsartan+Urea (1%)	54.31
PMU2	Valsartan+Urea (2%)	57.45
PMU4	Valsartan+Urea (4%)	63.84
PMP1	Valsartan+PEG 4000(1%)	69.82
PMP2	Valsartan+PEG 4000(2%)	74.18
PMP4	Valsartan+PEG 4000(4%)	81.24
SDU1	Valsartan+Urea(1:1)	69.81
SDU2	Valsartan+Urea(1:2)	72.5
SDU4	Valsartan+Urea(1:4)	77.54
SDP1	Valsartan+PEG 4000(1:1)	82.52
SDP2	Valsartan+PEG 4000(1:2)	88.15
SDP4	Valsartan+PEG 4000(1:4)	96.97

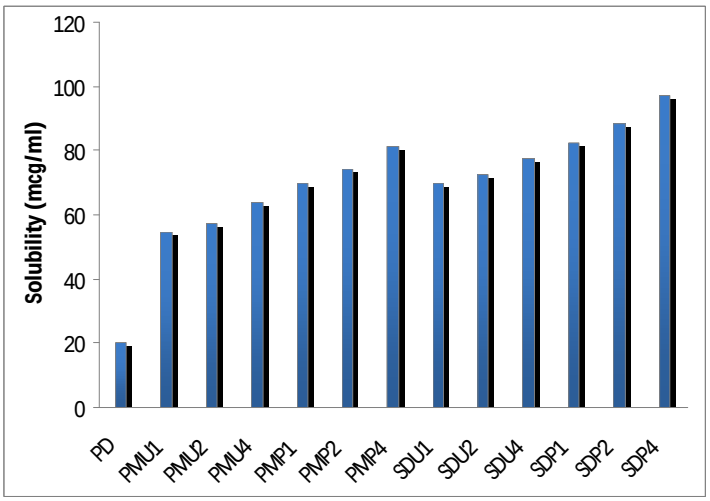

Figure 2: Solubility Studies of Valsartan

Drug Content:

Actual drug content of all twelve formulations were shown in (Table 4). The drug content of the prepared SDs was found to be in the range of 97.1 - 99.4 % indicating good uniformity in drug content in all the formulations.

Table 4: Estimation Drug Content of Solid Dispersions of Valsartan

S.no	Formulation	Drug: carrier	(%) Drug content
1	PD		100
2	PMU1	1:1	97.3
3	PMU2	1:2	99.4
4	PMU4	1:4	98.6
5	PMP1	1:1	99.2
6	PMP2	1:2	98.3
7	PMP4	1:4	98.7
8	SDU1	1:1	98.9
9	SDU2	1:2	97.1
10	SDU4	1:4	97.6
11	SDP1	1:1	98.8
12	SDP2	1:2	98.5
13	SDP4	1:4	98.6

Micromeritic studies:

Flowability of Valsartan (Pure drug) and its solid dispersions was assessed by determination of Carr's index (CI), Hausner's ratio (HR) and Angle of repose. Micormeritic behaviors of the untreated Valsartan powder and all prepared solid dispersions are listed in Table 5. The results shows that the flowability represented in terms of Carr's index, Hausner's ratio and angle of repose was much improved compared to those of original powders (untreated Valsartan). In case of pure Valsartan, powder could not pass through the funnel during the angle of repose experiment. The poor flow of Valsartan could be due to the irregular shape and high fineness of the powder, which posed hurdles in the uniform flow from the funnel. These results are significantly different from those of untreated Valsartan.

Table 5: Flow properties of Valsartan and its Physical mixtures and Solid dispersions

Sample	Carr's index	Hausner's ratio	Angle of repose(°)
Pure drug	38.37	1.62	45
PMU1	14.94	1.176	27.09
PMU2	15.69	1.186	26.52
PMU4	15.51	1.184	28.41
PMP1	14.76	1.173	26.47
PMP2	15.19	1.179	27.31
PMP4	14.9	1.175	25.49
SDU1	15.22	1.179	30.03
SDU2	14.20	1.165	29.56
SDU4	14.15	1.164	27.47
SDP1	14.29	1.166	26.56
SDP2	14.10	1.164	24.54
SDP4	13.83	1.16	22.68

***In Vitro* Dissolution Studies:**

Dissolution studies were performed to compare the drug release from the solid dispersions, Physical mixtures to that of the pure drug. The dissolution test was carried out for a period of 90min in pH 6.8 Phosphate buffer. All the experiments were carried out in duplicate and the results were shown in table 6. The drug release profiles were shown in figure 5 & 6 respectively.

Table 6. Cumulative %Drug Release of Valsartan Solid Dispersions

Time	PD	PMU1	PMU2	PMU4	SDU1	SDU2
5	9.88	15.38	18.25	23.25	25.13	28.25
10	16.68	20.34	24.35	28.38	31.01	35.03
15	19.52	28.07	30.49	33.16	39.31	48.98
20	24.88	32.48	39.15	46.59	51.65	63.12
30	26.52	40.78	45.49	58.48	63.06	71.34
45	29.48	47.42	58.27	64.17	76.27	81.45
60	34.43	54.07	65.58	75.61	83.64	89.83
90	38.26	62.69	77.42	82.19	95.91	97.42

Time	SDU4	PMP1	PMP2	PMP4	SDP1	SDP2	SDP4
5	32.50	26.50	29.13	34.13	35.50	45.38	85.13
10	49.68	31.52	35.66	46.06	48.82	59.13	92.47
15	65.08	35.57	42.73	51.69	53.09	71.45	99.86
20	72.31	41.02	47.09	62.85	66.51	84.97	
30	81.59	51.24	59.48	72.57	74.75	93.56	
45	98.60	62.63	65.89	87.66	89.34	98.45	
60		71.29	76.43	101.08	96.56		
90		85.88	89.58				

From Figures 3 & 4 it was clear that solid dispersions showed enhanced dissolution rate compared to physical mixtures and pure drug. The order of release is solid dispersions > physical mixtures > pure drug. As concentration of carrier increases dissolution rate of Valsartan has also increased. Solid dispersions increased the solubility by maximizing the surface area of the drug that comes in contact with the dissolution medium. This might be due to the surface tension lowering effect of polymer to the medium, resulting in the wetting of hydrophobic drug of crystalline surface, which can be attributed to the reduction of crystallinity of drug, and therefore improved release profile. From the *in vitro* drug release profile, it can be seen that formulation SDP4 containing drug and PEG 4000 in the ratio of 1:4 shows higher dissolution rate compared to other formulations i.e., 99.86 % drug release in 20 min. The increase in dissolution rate is in the order of SDP4 > SDP2 > SDU4 > PMP4 > SDP1 > SDU2 > PMP2 > PMP1 > PMU4 > PMU2 > PMU1 > PD.

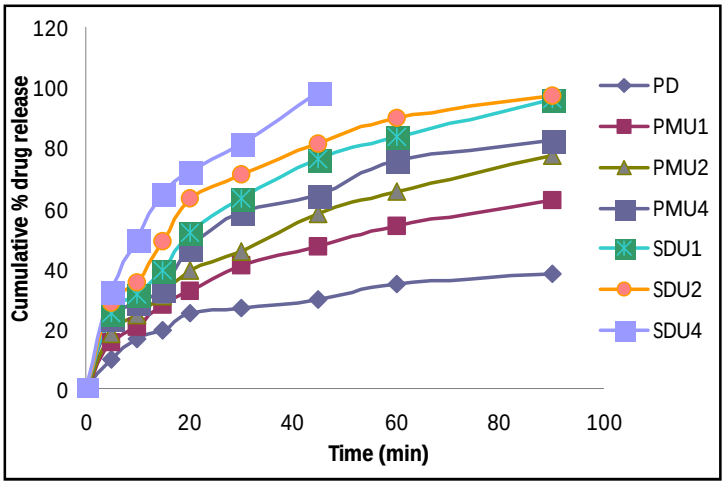

Figure 3. Comparision of Dissolution Profiles of Pure drug, Physical mixtures & Solid dispersions of Urea and Pure Drug

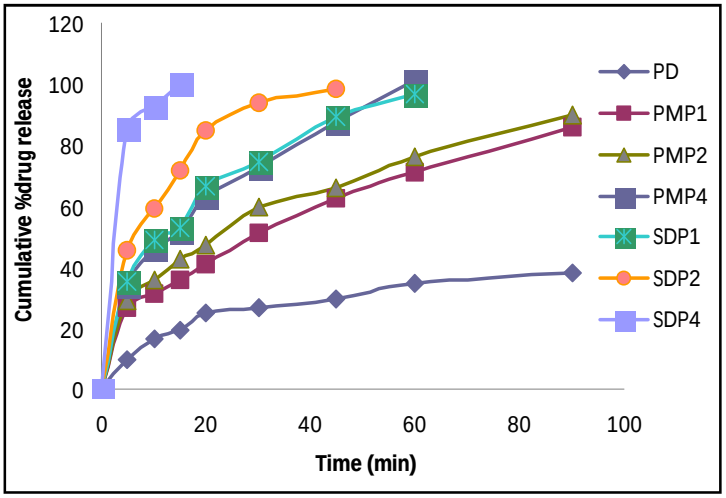

Figure 4 Comparision of Dissolution Profiles of Pure drug, Physical mixtures & Solid dispersions of PEG 4000 and Pure Drug

CONCLUSION:

From the results of the present study it can be concluded that the solubility of the drug can be significantly enhanced with the polymers used. With increase in the carrier content there is increase in the solubility resulting in enhanced dissolution rate.

The order of increase in dissolution rate was found to be SDP4 > SDP2 > SDU4 > PMP4 > SDP1 > SDU2 > PMP2 > PMP1 > PMU4 > PMU2 > PMU1 > PD

Formulation containing 1:4 ratio of drug: PEG4000 is considered as best formulation as it has shown highest drug release in short time i.e. 99.86 % in 20min. Therefore PEG 4000 can be successfully employed for developing solid dispersions of poorly soluble drugs like Valsartan.

ACKNOWLEDGEMENT:

The author wishes Mylon laboratories pvt.Ltd, Hyderabad, AP, India for sample of Valsartan drug and the management of Adarsa college of pharmacy, G. kothapalli, Gokavaram, East Godavari, AP, India for providing all the support and encouragement to carry out this study.

REFERENCES:

1. Amidon GL, Lennernas H, Shah VP and Crison JRTheoretical basis for a biopharmaceutical drug classification: the correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. *Pharm Res.*, (1995)**12**(3): 413-420.
2. Batra V, Shirolkar VS, Mahaparale PR, Kasture PV, Deshpande AD. Solubility and Dissolution Enhancement of Glipizide by Solid Dispersion Technique. Indian JPharm Educ Res 2008; 42(4):373-378.
3. Chiou WL and Riegelman S. Pharmaceutical Applications Of Solid Dispersion Systems. J Pharm Sci.1971;60:1281-1302
4. Valsartan, en.wikipedia.org/wiki/valsartan.(date at 22nd Oct.2010)
5. Valsartan ,www.medicinescomplete.com (date at 25th July.2010)
6. Pradhan kishanta kumar, mishra uma Shankar; stress degradation studies on valsartan and valsartan and development of a validated method by UV spectrophotometric in bulk and pharmaceutical dosage form: JPBMS, 2011, 8(02).
7. Jain R, Jani K, Setty C Et Al. Preparation And Evaluation Of Solid Dispersions Of Aceclofenac. *Int.J.Pharm Sci And Drug Research.* 2009; 1(1):32-35.
8. Dhirendra K, Lewis S, Udupa N Et Al. Solid Dispersions: A Review. *Pak. J. Pharm. Sci.* 2009; 22(2):234-246.

9. Hausner HH. Friction Conditions In A Mass Of Metal Powder. Int J Metall. 1967; 3:7–13.
10. Carr RL. Evaluating Flow Properties Of Solids. Chem Eng. 1965; 72:163–8.
11. Aulton ME. 3rd Ed. New York: Churchill Livingstone; Pharmaceutics: The Science Of Dosage Form Design; 1988, Pp. 605–13.
12. Leon Lachman, Herbert A, Liberman and Joseph L Karnig. The theory and practice of industrial pharmacy. 3rd ed. Lea and Febigen, Philadelphia, 1986; 301-302.

Source of support: Nil, Conflict of interest: None Declared