World Inventia Publishers

Journal of Pharma Research

http://www.jprinfo.com/

Vol. 7, Issue 7, 2018 ISSN: 2319-5622 USA CODEN: JPROK3

Research Article

DEVELOPMENT OF VALSARTAN SOLID DISPERSION TO ENHANCE AQUEOUS SOLUBILITY USING KNEADING METHOD

Harshvardhan Chouhan *, Madhavi Kasturi Arti J. Majumdar, Neelesh Malviya

Department of Pharmaceutics, Smriti College of Pharmaceutical Education, Indore, Madhya Pradesh, INDIA.

Received on: 24-06-2018; Revised and Accepted on: 07-07-2018

ABSTRACT

Objective: *The main objective of the current research is to formulate and evaluate solid dispersion of valsartan to enhance aqueous solubility of BCS Class II antihypertensive drug valsartan by the application of kneading technique.* ***Method:*** *In this study, the solid dispersions of valsartan were prepared using synthetic hydrophilic polymers like PEG-4000, PEG-6000 and Poloxamer - 407 using kneading method. The drug and polymer were mixed in the ratio 1:1, 1:5 and 1:10, to which small amount of solvent was added to form thick paste. They were further dried at room temperature and sieved to obtain solid dispersions.* ***Results:*** *Total 9 formulations of valsartan solid dispersions were prepared, out of which SD 09 formulation containing PEG 6000 showed higher aqueous solubility with the solubility enhancement ratio of 8.5. All the formulations were subjected to various evaluation tests such as saturation solubility, flow property, percent yield, drug content as well in vitro drug release. Among all the formulations, SD 09 was optimized based on solubility and drug release behavior. The optimized formulation did not show any drug- excipient interaction which was revealed from DSC and FTIR studies. The solid state characterization of SD 09 using SEM analysis showed conversion of crystalline form of drug to amorphous form.* ***Conclusion:*** *Successfully solid dispersions of valsartan were developed showing significant enhanced aqueous solubility behavior compared to that of pure drug.*

KEYWORDS: *Valsartan, Solid Dispersion, Solubility Enhancement.*

INTRODUCTION

Solid dispersion technique can be used to enhance the solubility, dissolution rate and absorption of several insoluble drugs [1]. Poor aqueous solubility and bioavailability were the two major problems that hinder drug absorption after administration and faced by various pharmaceutical companies. Solid dispersion is one of the techniques used to increase the dissolution rate of the lipophilic drugs [2-4]. Solid dispersion is one of such methods and it involves a dispersion of one or more active ingredients in an inner carrier or matrix in the solid state prepared by melting, dissolution in a solvent or melting-solvent method [5]. Solid Dispersion technology has been successfully been used for improving the solubility of the drugs and hence bioavailability [6]. There was tremendous improvement in solubility and bioavailability of poorly soluble drug by use of hydrophilic polymers like PEG-4000, PEG-6000 and Poloxamer – 407. Valsartan, BCS class II drug is an angiotensin II receptor blocker and is widely used for the treatment of hypertension. It is selected as a model drug in the present work because of its relatively poor aqueous solubility and bioavailability (25%) [7]. Thus solid dispersions of valsartan were prepared using predetermined drug polymer ratio with hydrophilic polymers like PEG-4000, PEG-6000 and Poloxamer - 407 using kneading technique.

***Corresponding author:**

Harshvardhan Chouhan

Department of Pharmaceutics,

Smriti College of Pharmaceutical Education,

Indore, Madhya Pradesh, INDIA.

** E-Mail: harshcures1992@gmail.com*

DOI: https://doi.org/10.5281/zenodo.1308511

MATERIALS AND METHODS

Materials:

Valsartan was obtained from Hetero Drugs, Hyderabad, India. Hydrophilic polymers PEG (Polyethylene Glycol) 4000, PEG (Polyethylene Glycol) 6000 were obtained from Loba Chemie, Mumbai and Poloxamer - 407 was obtained from Chemdyes Corporation Rajkot Ahmedabad, India. All other chemicals used were of analytical grade.

Experimental Methods:

Preparation of calibration curve of valsartan in 7.4 pH phosphate buffer:

Accurately weighed 10 mg of valsartan was dissolved in 2ml of 7.4 pH phosphate buffer and volume was made upto 10 ml with phosphate buffer. From the stock solution, 1ml of sample was taken and volume was made upto 10 ml with buffer. From this various dilutions were prepared with concentration range of 5, 10, 15, 20, 25, 30, 40, 50, 60 and 70µg/ml and absorbance was measured at 250 nm usig UV-VIS spectrophotometer.

Preparation of valsartan solid dispersions by kneading technique:

Precalculated quantities of valsartan and polymers were weighed accurately and added to mortar and pestle. Then to this mixture 5ml of methanol was added and mixed for 45 minutes until thick paste was obtained. It was further dried at room temperature, grounded to fine powder and then passed through sieve no # 44. The prepared solid dispersions were stored in desiccator for further studies [8].

Evaluation of valsartan solid dispersions:

Saturation Solubility studies of valsartan solid dispersions:

Saturation solubility studies of valsartan were performed using flask shaker or shake flask method. Excess amount of each valsartan solid dispersion was introduced into 25ml conical flask, containing each 10 ml of distilled water and then shaken in an orbital

shaker(100rpm) for 24 hrs at room temperature until equilibrium was achieved. The contents of each bottle were filtered through Whatman filter paper (No.1). The filtrate was then diluted accordingly and analysed at 250 nm spectrophotometrically.

Rheological properties of valsartan solid dispersions:

The flow properties of valsartan solid dispersions were characterized in terms of Tapped density, Bulk density, Angle of repose, Carr's index and Haussner ratio. Angle of repose (q) was measured using fixed funnel method and tapped density was determined using bulk density apparatus [5].

Table No. 1: Formulation of valsartan solid dispersions using different polymeric carriers

Formulation Code	Drug	Poloxamer - 407	PEG - 4000	PEG - 6000
SD 01	40	40	-	-
SD 02	40	200	-	-
SD 03	40	400	-	-
SD 04	40	-	40	-
SD 05	40	-	200	-
SD 06	40	-	400	-
SD 07	40	-	-	40
SD 08	40	-	-	200
SD 09	40	-	-	400

Percent practical yield:

It was calculated to know about the percent yield which usually helps in the selection of an appropriate method for production. The valsartan solid dispersions were collected and weighed to determine the practical yield which was calculated by following equation.

$$\text{Percent Practical Yield} = \frac{\text{Practical mass} \times 100}{\text{Theoretical mass}}$$

Drug content analysis:

Solid dispersion of weight equivalent to 80 mg of Valsartan was weighed accurately and then dissolved in 100 ml of methanol. The solution was then filtered, diluted suitably with buffer and drug content was analyzed at ƛmax 250 nm against blank by UV-VIS spectrophotometer. The drug content was calculated using the following equation.

$$\text{\% Drug Content} = \frac{\text{Actual weight of drug in solid dispersion} \times 100}{\text{Theoretical weight of drug in solid dispersion}}$$

***In-vitro* drug release studies:**

In-vitro release studies of prepared valsartan solid dispersions were conducted using USP Type II Apparatus (paddle type). Dissolution studies of solid dispersions were performed using 900 ml Phosphate buffer at pH-6.8 as dissolution medium at 37± 0.5ºC with 50 rpm speed. Samples of each preparation was equivalent to 40 mg drug were added to dissolution medium. Samples of 5ml aliquots were withdrawn periodically at 5, 10, 15, 30, 45, and 60 min time intervals and then filtered through 0.45µ membrane filter. The withdrawn sample was replaced every time by the same quantity of fresh dissolution medium. The filtered solutions were diluted suitably and samples were analyzed for drug content by using UV spectrophotometer at ƛmax of 250 nm [9].

Characterization of optimized valsartan solid dispersion:

Valsartan solid dispersion having maximum saturated solubility and drug release was optimized and characterized by DSC, FTIR, SEM analysis and compared with the pure drug.

Differential Scanning Calorimetry (DSC):

Thermal analysis of pure drug valsartan and optimized solid dispersion formulation was recorded with Netzsch DSC – 200PC (Germany). Accurately weighed samples were placed on the aluminum plate, sealed with aluminum lids and heated at a constant rate of 5ºC/min, over a temperature range of 0 to 250ºC [10]. Aluminium pan here was used as reference cell and calibrated by Indium.

Fourier Transform Infrared Spectroscopy (FT-IR):

Fourier Transform Infrared (FT - IR) spectral measurements for valsartan, PEG – 6000 and optimized solid dispersion formulation were recorded using Shimadzu – IR Affinity – 1 spectrophotometer. The solid dispersions were first finely grounded with KBr to prepare pellets and then background spectrum was collected under identical conditions. The average scans were collected in the range of 4000 – 400 cm^{-1} at the spectral resolution of 2 cm^{-1}.

Scanning Electron Microscopy (SEM):

The shape as well surface morphology of valsartan and optimized solid dispersion formulation prepared by kneading method was examined using ZEISS scanning electron microscope (Germany).

RESULTS AND DISCUSSION

Preparation of calibration curve of valsartan in 7.4 pH phosphate buffer:

The calibration curve of valsartan was plotted in 7.4 pH phosphate buffer and the results were illustrated in Table 2.

Table No. 2: Calibration curve of Valsartan in Phosphate Buffer pH-7.4

S. No	Concentration (µg/ml)	Absorbance
1	5	0.0943
2	10	0.1047
3	15	0.1571
4	20	0.2312
5	25	0.2581
6	30	0.3168
7	40	0.4048
8	50	0.4936
9	60	0.5504
10	70	0.6454

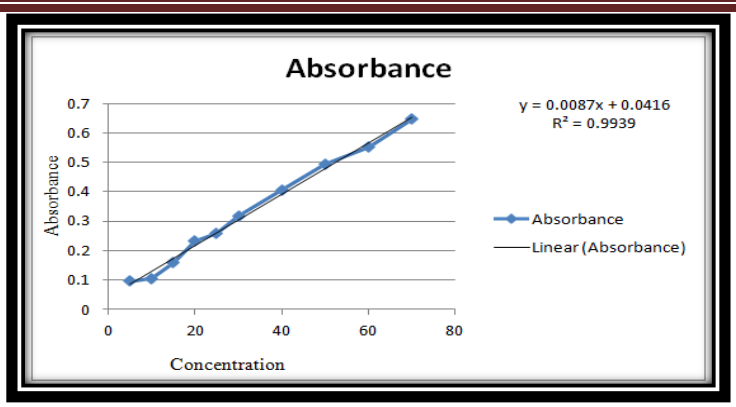

Fig. 1: Calibratiion curve of Valsartan in pH-7.4 phosphate buffer

Evaluation of valsartan solid dispersions:

Saturation solubility studies of valsartan solid dispersions:

The aqueous solubility of valsartan was found to be enhanced in solid dispersion formulation. These formulations were prepared with polyethylene glycol-4000, propylene glycol-6000 and poloxomer - 407 using kneading technique. The solubility enhancement ratio was determined by the following formula:

Enhancement ratio = Solubility of solid dispersion in distilled solvent / Solubility of drug in distilled water

The solubility of pure drug valsartan in water is 0.021mg/ml Results revealed that the solubility enhancement was observed best in formulation SD 09 which is of 8.5.

Table No. 3: Solubility studies of valsartan solid dispersions in water

Formulation Code	Solubility in water (mg/ml)	Solubility enhancement
SD 01	0.082	3.9
SD 02	0.095	4.5
SD 03	0.103	4.9
SD 04	0.107	5.1
SD 05	0.116	5.5
SD 06	0.128	6.1
SD 07	0.143	6.8
SD 08	0.166	7.9
SD 09	0.179	8.5

Table No. 4: Flow properties of solid dispersions of valsartan

Formulation Code	Angle of Repose	Bulk Density	Tapped Density	Carr's Index	Hausner's Ratio
SD01	27	0.74	0.85	14.9	1.15
SD02	27	0.72	0.83	15.3	1.15
SD03	24	0.71	0.81	14.0	1.14
SD04	28	0.74	0.84	15.3	1.14
SD05	24	0.72	0.83	15.3	1.15
SD06	24	0.7	0.79	12.9	1.13
SD07	25	0.69	0.76	10.1	1.10
SD08	26	0.71	0.78	9.85	1.10
SD09	22	0.71	0.79	11.2	1.11

Rheological properties of valsartan solid dispersions:

Various flow properties such as Bulk density, Tapped density, Angle of repose, Carr's index and Hausner's ratio were determined. Among all, SD 09 formulation showed good flow properties.

Percent Practical Yield:

The percent practical yield of valsartan solid dispersions was calculated using following equation:-

% Practical Yield = Practical yield (Solid Dispersion)/ Theoretical yield (drug + polymer)

The results of % practical yield of all formulations of solid dispersions were observed to be in the range of 65.00% - 103.6% and were shown in Table 5.

Drug Content analysis:

The drug content analysis was done for all valsartan solid dispersions. Obtained results indicated that all formulations have uniform drug content that ranged between 96.5% to 98.8% when analysed spectrophotometrically at λmax 250 nm and the results were given in Table 6.

***In – vitro drug* release studies:**

To compare the release profile of various batches of the valsartan solid dispersions, the *in-vitro* release study for drug was carried out by using USP II type apparatus. *In-vitro* dissolution studies revealed dissolution of drug increased with the increase in carrier concentration. The results of the drug release from valsartan solid dispersions were shown in fig. 2 and the formulation SD 09 showed higher drug release compared to others.

Characterization of optimized valsartan solid dispersion:

Among all formulations SD09 was found to be optimized as it showed better solubility as well as drug release profile. DSC and FTIR studies were performed to detect any drug- excipient interaction in valsartan solid dispersions.

The solid dispersions of valsartan did not show any drug-polymer interactions which could be accessed from the peaks in DSC thermograms. Endothermic peak of solid dispersion SD 09 was observed to be 67°C, whereas endothermic peak of pure drug.

Valsartan was shown to be 108.42°C. Absence of melting peak of drug in valsartan solid dispersion was shown to be entrapped by carrier thus reducing overall crystallinity of system.

FTIR graph indicates no interaction between the drug and polymer as peaks of pure drug were also found in FTIR spectra of SD 09 formulation. The FTIR studies did not show any other additional peak, significant shift as well disappearance of characteristics peak in the formulation. Peak corresponding functional groups of valsartan and PEG 6000 excipient were observed to be observed SD 09 formulation.

Scanning Electron Microscopy (SEM):

SEM photographs for the pure drug and SD 09 formulation were shown in fig. 5, the drug crystal seemed to be crystalline, white to off – white coloured, smooth surfaced, regular shaped and size. Solid dispersions were appeared as homogeneous and uniformly mixed mass with slightly wrinkled surface. Drug crystals also appeared to be incorporated into polymeric particles. The results attributed amorphous nature of the drug present in molecularly dispersed state inside dry mass of the polymer.

Table No. 5: Practical yield of solid dispersions of valsartan

Formulation code	Practical Yield (%)
SD 01	102.5%
SD 02	79.09%
SD 03	93.57%
SD 04	70.83%
SD 05	65.00%
SD 06	86.19%
SD 07	96.66%
SD 08	103.6%
SD 09	88.33%

Table No. 6: Drug Content of solid dispersions of valsartan

Formulation	Percent Drug Content
SD 01	96.5
SD 02	96.6
SD 03	96.9
SD 04	97.1
SD 05	97.2
SD 06	97.7
SD 07	97.5
SD 08	97.6
SD 09	98.8

Table No. 7: *In vitro* drug release profile of solid dispersions

Time (min)	Percent Cumulative drug release								
	SD 01	**SD 02**	**SD 03**	**SD 04**	**SD 05**	**SD 06**	**SD 07**	**SD 08**	**SD 09**
00	0	0	0	0	0	0	0	0	0
05	17.43	20.65	24.78	27.78	29.55	31.67	34.88	34.98	35.11
10	24.76	29.66	34.66	39.66	42.23	46.54	48.55	50.66	53.44
15	32.66	39.32	42.54	44.54	49.43	51.87	53.66	58.75	61.32
30	48.44	54.65	57.22	59.22	63.15	65.88	67.89	69.54	74.34
45	58.56	64.71	68.54	69.54	71.97	75.43	79.54	80.43	82.51
60	68.74	74.52	76.31	79.31	82.76	83.22	85.64	87.43	89.77

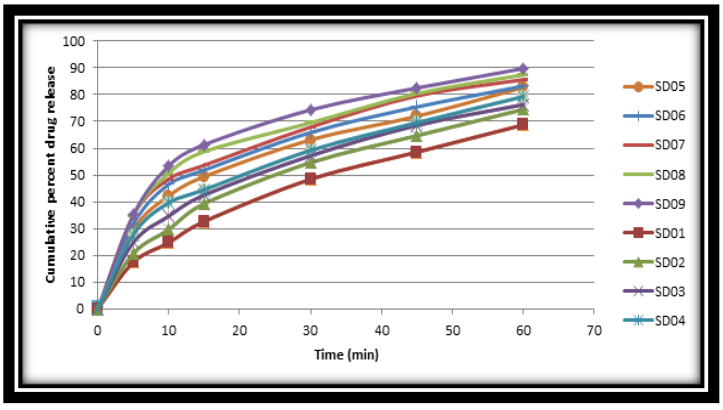

Fig. 2: Graph representing *in – vitro* drug release of valsartan solid dispersions

Differential Scanning Calorimetry (DSC):

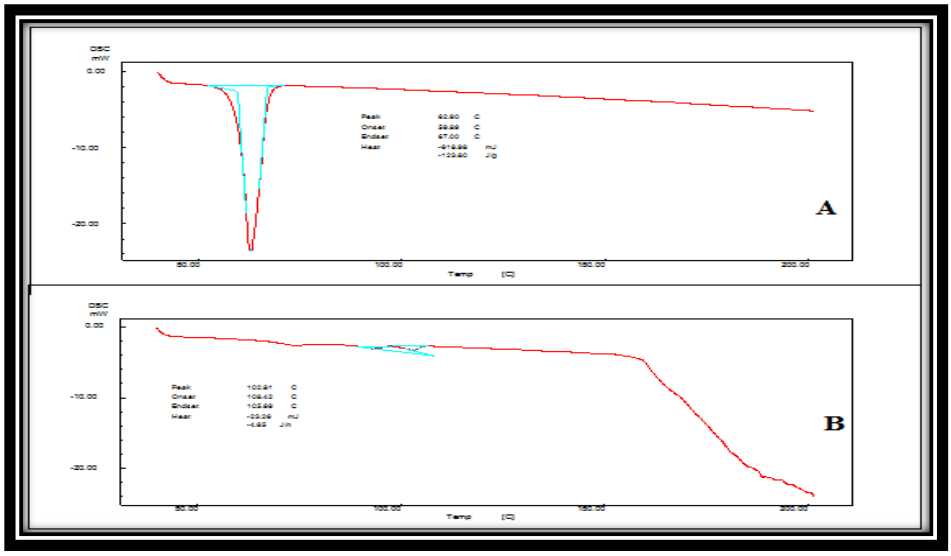

Fig. 3: DSC of (A) valsartan pure drug and (B) SD 09 solid dispersion

Fourier Transform Infrared Spectroscopy (FT-IR):

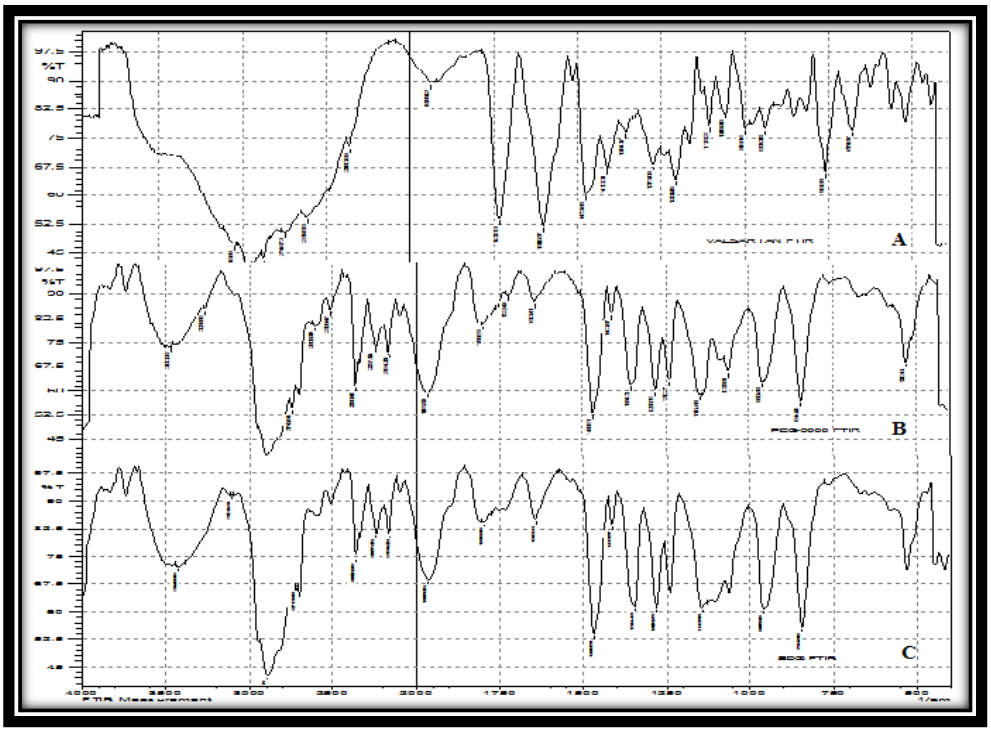

Fig. 4: FTIR spectra of (A) valsartan pure drug (B) PEG 6000 and (C) SD 09 solid dispersion

Table No. 8: Comparison of FT-IR graph peaks of valsartan, PEG – 6000 and SD 09 formulation

S.No	Peak of Valsartan	Peak of PEG - 6000	Peak of SD 09 Formulation	Group
1	678.97	-	630.44	Aromatic rings
2	939.36	-	958.65	Aromatic rings
3	-	1147.88	1143.83	Aldehyde group
4	-	1280.78	1280.78	C=O group
5	1354.07	1354.07	1344.43	Alcohol group
6	1600.97	1643.41	1643.41	Aldehyde, ketone
7	-	2237.50	2237.50	Aliphatic chain
8	2360.95	2360.95	2360.95	Alkyl group

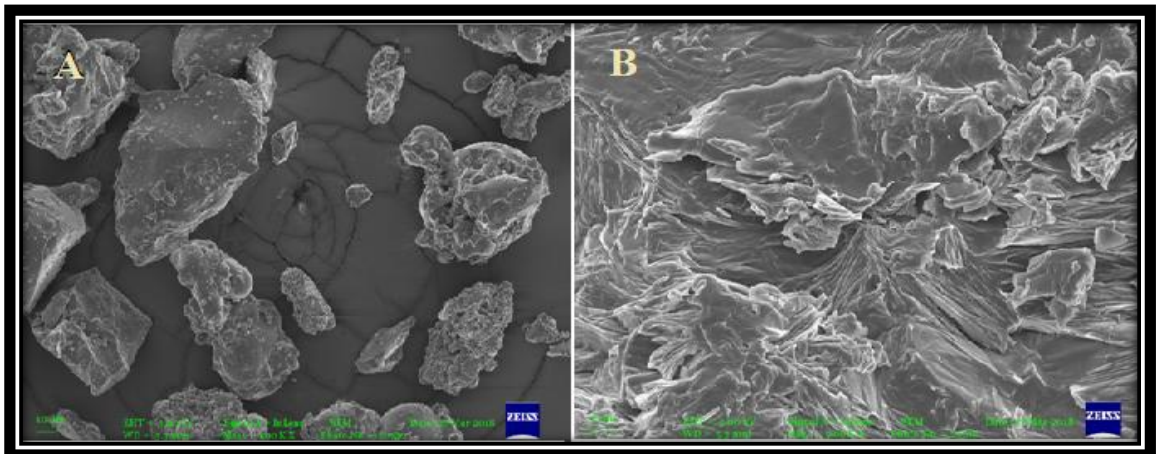

Fig. 5: SEM images of (A) Valsartan pure drug (B) SD 09 solid dispersion

CONCLUSION

Successfully solid dispersions of valsartan were prepared with enhanced aqueous solubility. From the research work, we conclude that the solid dispersions of valsartan showed higher dissolution profiles when compared with that of pure drug by the use of hydrophilic polymers like PEG-4000, PEG-6000 and Poloxamer – 407 with the application of kneading method. Among three polymers used, PEG – 6000 showed the highest enhancement in the dissolution rate as well efficiency of aqueous solubility of valsartan in 1:10 ratio.

REFERENCES:

1. Mayer Sohn M, Gibaldi M. J Pharm Sci **1996**;55:1323.
2. Arias MJ, Gines JM, Moyano JR, Rabasco AM. J Drug Target **1994**;2(1):45-51.
3. Lee S, Nam K, Kim MS, Jun SW, Park JS, Woo JS, Hwang SJ. Arch Pharm Res **2005**;28(7):866-874.
4. Palmieri GF, Cantalamessa F, Di Martino P, Nasuti C, Martelli S. Drug Dev Ind Pharm **2002**;28(10):1241-1250.
5. Balakrishnaiah M, Rama Mohan Gupta V. Indo Am J Pharm Sci **2016**;3(12):1581-1592.
6. Chaulang G, Patel P, Hardikar S, Kelkar M, Bhosale A, Bhise S. Trop J Pharm Res **2009**;8(1):43-51.
7. Gupta A. Int J Pharm Biol **2010**;1(1):1-10.
8. Lalit J, Tapar KK. Int J Pharm Sci Res **2011**;2(10):2623-2628.
9. Ketan S, Chauhan CS, Dumaniya D, Patel B. J Pharm Sci Bio-Sci Res **2013**;3(2):77-90.
10. Jambarapu PK, Ramarao T, Jayaveera KN, Dvrn B, Yamsani MR. Int J Drug Del **2014**;6(1):14.

How to cite this article:

Harshvardhan Chouhan, et al. DEVELOPMENT OF VALSARTAN SOLID DISPERSION TO ENHANCE AQUEOUS SOLUBILITY USING KNEADING METHOD. J Pharm Res 2018;7(7):120-125. **DOI:** https://doi.org/10.5281/zenodo.1308511

Conflict of interest: The authors have declared that no conflict of interest exists.

Source of support: Nil