

# Solid Dispersion (Kneading) Technique: A Platform for Enhancement Dissolution Rate of Valsartan Poorly Water Soluble Drug

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## ABSTRACT

The objective of this study was to the enhancement of dissolution rate of Valsartan. Using a solid dispersion (kneading) method with Kollidon and Povidone K30 as a carrier. Eight different drugs: Carrier ratios were prepared. Using factorial design taking 3 factors i.e., the concentration of Valsartan (x1), Kollidon (x2), and Povidone K30(x3). The enhancement of dissolution depends on the amount of carrier and an increase in the concentration of carrier. Enhancement of dissolution rate depends on reduce particle size of drug place on the surface of carrier and increased wettability of drug particle by carrier. Solid Dispersions prepared with Kollidon as a carrier in ratio 1:4 shows the enhancing dissolution in 30 mins to drug and Physical Mixture. Formulation evaluated by fourier-transform infrared spectroscopy, differential scanning colorimetry, X-ray diffraction, Scanning Electron Microscopy.

**Keywords:** In-vitro dissolution Kollidon, Povidone K30, Solid Dispersion, Valsartan.

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## INTRODUCTION

Poorly water-soluble drug for oral route formulation is an ongoing challenge for formulation.<sup>1</sup> The bioavailability of drugs depends on the dissolution rate and solubility of drug. These are rate-determining steps for therapeutic activity. The SDs show the best result in enhancement of solubility, wettability, dissolution, and bioavailability.<sup>2</sup> On the surface of carrier deposition of drug lead to reducing in particle size of drug that enhancement of dissolution rate. Larger the surface area of inert carrier that better is release rate.<sup>3</sup> A technique used to the enhancement of solubility, dissolution rate, and bioavailability of poorly water-soluble drug.<sup>4,5</sup> Valsartan is angiotensin II, receptor antagonist. These effectively use in the treatment of hypertension. Valsartan is poorly water solubility but showing high membrane permeability. Valsartan are considered as class II of drug biopharmaceutical classification system.<sup>6</sup> Improvement in its solubility and dissolution rate leads to the enhancement of bioavailability. Studies on solid dispersion of valsartan have been done using various carriers such as soluplus, gelucire-50/13, cyclodextrin, HPMC, PVP K30, and skimmed milk powder. This main study objective is an enhancement of solubility, the dissolution rate of poorly water-soluble valsartan by using various hydrophilic carriers.

The SDs are prepared by Kneading technique by using various drug: carrier ratios.

## MATERIAL AND METHOD

### Material

Valsartan are obtained by a sample from Ranbaxy laboratory; Kollidon was purchased for Research lab chem. Industries, India. Povidone K30 purchased from Pallav chemical Pvt. Ltd, India.

### Physical Mixture Prepare (PM)

A physical mixture of Valsartan with Kollidon/Povidone K30 in 1:1 ratio was prepared by mixing of drug and carrier by using mortar and pestle. This mixture passed through mesh no 40. Store in 48h in desiccators.<sup>7</sup>

### Solid Dispersion Preparation (SD)

Preparation of solid dispersion use kneading technique. Different eight ratio of drug and carrier 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8 were used. V1 to V8 correspond to preparations containing Kollidon, and V9 to V16 corresponds to preparations containing Povidone K30. Valsartan and Kollidon or Povidone K30 are weighed according to ratio. These are kneaded for 30 minutes using small volume of methanol to give paste, and

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dried at 40°C in oven. These dried mass through sieve no. 30 and store in desiccators 48 hours.<sup>8</sup>

#### Determination of Solubility:

The excess quantity of drug and solid dispersion weighs, and these are put in conical flasks. Flasks are containing 25 mL of phosphate buffer pH 7.4. Sample place in rotary flask shaker for 24 hours. After equilibrium is achieved, solution is diluted. These solutions analyzed by Ultra violet spectroscopy at 250 nm.<sup>9</sup>

#### Fourier Transforms Infrared Spectroscopy (FTIR)

Structural changes and interaction between carrier and drug in the solid dispersions was studied using FTIR spectroscopy. IR spectra of carrier, drug, physical mixture, and SDs were recorded using an FTIR spectrophotometer [Thermo Nicolet 380, USA]. Sample are scanned frequency range 400–4000 cm<sup>-1</sup>.<sup>10</sup>

#### Dissolution Studied

*In vitro* dissolution studies carried out using Type II dissolution test apparatus, using pH 7.4 phosphate buffers as dissolution media, at a temperature of 37 ± 0.5°C. Speed maintain at 50rpm.<sup>11</sup>

#### Differential scanning calorimeter

Melting behavior of carrier, drug, and SDs was determine by using Differential scanning calorimeter instrument (Mettler Tolado).<sup>12</sup>

#### Powder X-ray Diffraction Studies

Using of XRD patterns were recorded using BRUKER-axs D8-ADVANCE, model generator Powder, X-ray diffraction patterns, were used to determine intensities and position of diffraction peaks were considered for comparison and identification of crystallinity of the drug or carrier.<sup>13,14</sup>

#### Scanning Electron Microscopy

Using scanning electron microscopy to determine the external morphology of pure drug and solid dispersion. Solid dispersion was coated with gold-palladium alloy using coat ion sputter.<sup>15,16</sup>

## RESULTS AND DISCUSSION

#### Preparation Solid Dispersion of Valsartan and Physical Mixture (PM)

Three different factors selected that is amount of drug and (Kollidon and Povidone K30) were prepared at two levels, and sixteen batches (F1-F16) of solid dispersion were formulated using factorial design in Table 1.

#### Solubility Studies

Figure 1 represents an increase in drug solubility of SDs over pure drug in phosphate buffer (pH 7.4). Solid dispersion containing Kollidon showed solubility (0.356 mg/mL), a 10 fold increase in solubility as compared to pure drug (0.0050 mg/mL) and Povidone K30 in Figure 2. This may be due to

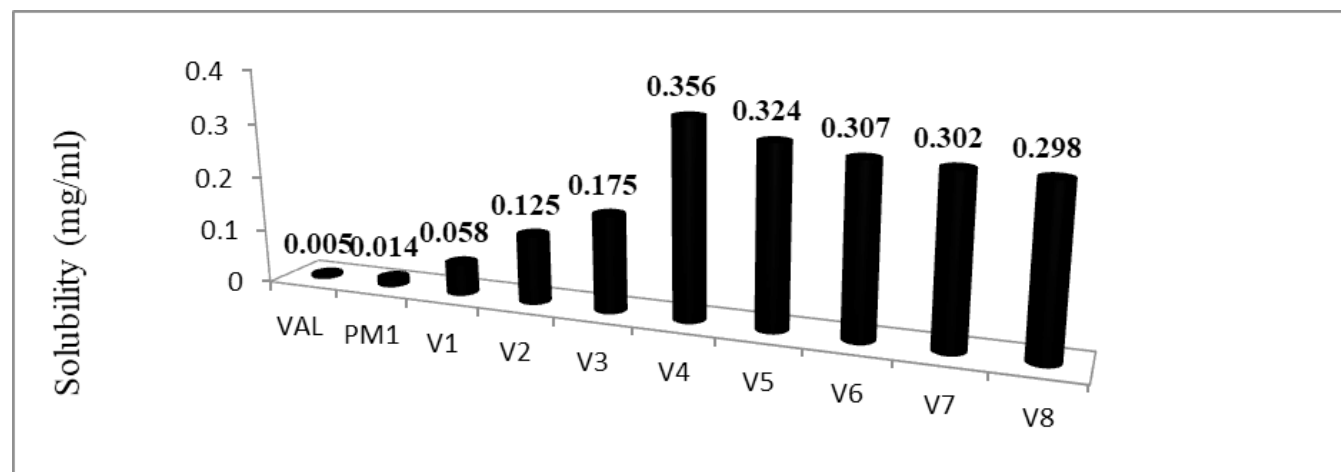


Figure 1: Solubility of Valsartan, PM1, SDs- Kollidon

Table 1: Formulation of solid dispersion

Valsartan - Kollidon			Valsartan - Povidone K30		
Formulation code	Polymer	Drug: Polymer ratio	Formulation code	Polymer	Drug: Polymer ratio
PM1	Kollidon	1:1	PM2	Povidone K30	1:1
V1	Kollidon	1:1	V9	Povidone K30	1:1
V2	Kollidon	1:2	V10	Povidone K30	1:2
V3	Kollidon	1:3	V11	Povidone K30	1:3
V4	Kollidon	1:4	V12	Povidone K30	1:4
V5	Kollidon	1:5	V13	Povidone K30	1:5
V6	Kollidon	1:6	V14	Povidone K30	1:6
V7	Kollidon	1:7	V15	Povidone K30	1:7
V8	Kollidon	1:8	V16	Povidone K30	1:8

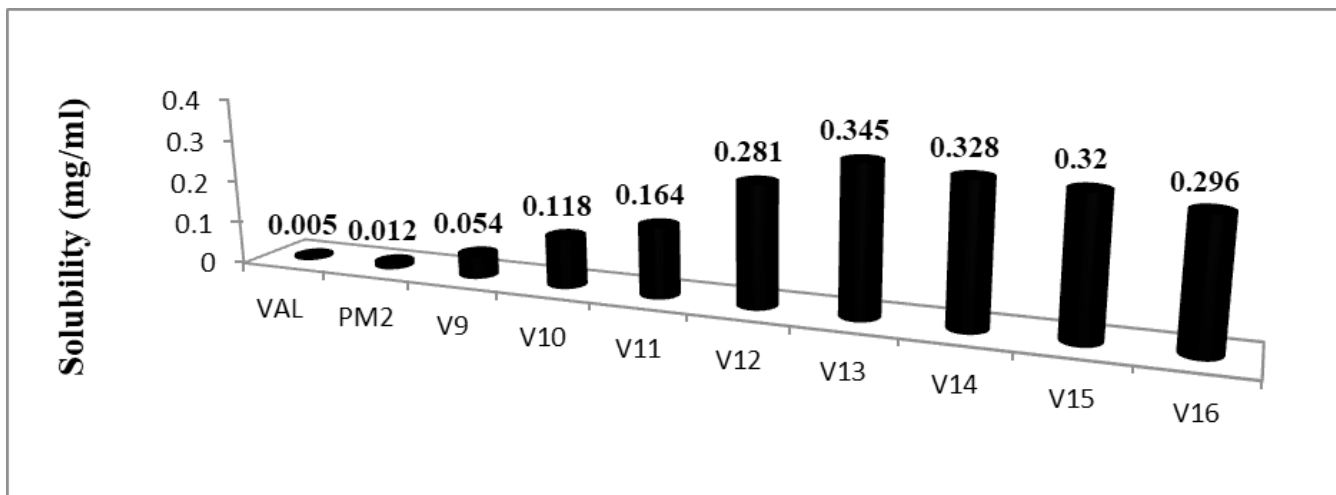


Figure 2: Solubility of Valsartan, PM2, SDs- Povidone K30

either the reduction in the crystallinity of drugs or improved wetting of the drug particles.

**Fourier Transforms Infrared Spectroscopy**

FTIR spectrum of valsartan showed its characteristic IR absorption peaks at 1732, 1601, 1470, 1456, 1270, 1202, 1162, 995, 978, 778, 762, 738, 682 and 672 cm<sup>-1</sup>. Kollidon showed characteristic absorption peaks at 3918, 3902, 3890, 3869, 3863, 3613, 3566, 1683, 1541.1762, 1507, 666, 643 and 616 cm<sup>-1</sup>. Povidone K30 showed characteristic absorption peaks at 1646, 1457, 1519, 1540, 1418, 1285, 837, 742, 680 and 613 cm<sup>-1</sup>. Whereas SDs V4 peaks were observed at 3902, 3864, 3838, 3749, 3648, 3566, 1716, 1697, 1541, 1507, 1456, 1418, 708 and 604 cm<sup>-1</sup>. And SDs V13 peaks were observed at 1660, 1651, 1273, 665, 650, 639, 629, 615 and 607 cm<sup>-1</sup> (Figure 3). These spectrum observations indicated no interaction between the drug and carrier used in solid dispersion.

**In vitro dissolution studies**

All the carriers selected showed rapid and higher dissolution of valsartan as compared to pure drug. The dissolution rate

observed with various carriers were in following increasing order: Kollidon > Povidone K30. Tables 2 and 3 show the

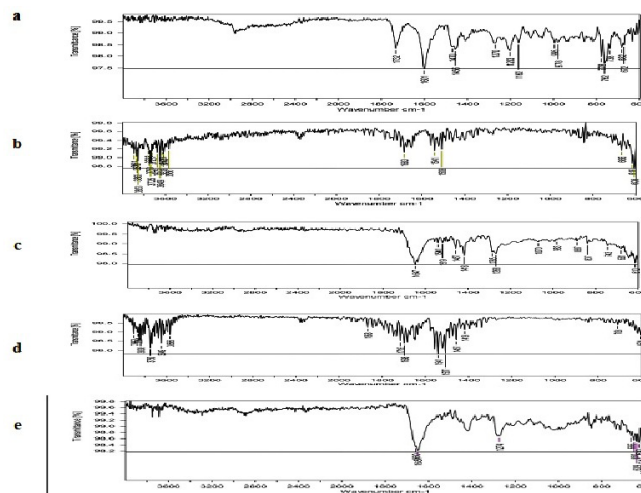


Figure 3: FTIR spectra a) Valsartan b) Kollidon c) Povidone K30 d) SDs V4 e) SDs V13

Table 2: Dissolution profile of Valsartan, PM1, and SDs- Kollidon

Time	Val	PM1	V1	V2	V3	V4	V5	V6	V7	V8
0	0	0	0	0	0	0	0	0	0	0
5	17.62	19.23	40.9	41.12	41.44	49	45.5	45.21	45.76	45.76
10	25.31	28.17	45.98	46.21	46.52	52.44	47.48	47.44	47.12	50.63
15	32.17	36.23	59.1	59.3	59.61	63.7	59.37	63.55	63.11	64.43
20	35.13	39.12	70.82	71.08	71.38	78.12	75.5	75.32	75.61	75.56
25	38.12	50.17	85.4	85.61	85.95	90.28	87.88	87.67	87.12	90.32
30	39.97	59.24	92.02	92.33	92.56	97.89	96.06	95.63	95.87	95

Table 3: Dissolution profile of Valsartan, PM2 and SDs- Povidone K30

Time	Val	PM2	V9	V10	V11	V12	V13	V14	V15	V16
0	0	0	0	0	0	0	0	0	0	0
5	17.62	18.24	34.74	34.67	34.78	35.22	42.92	42.12	41.6	41.44
10	25.31	28.32	42.21	43.08	43.28	43.64	47.72	46.43	45.92	45.12
15	32.17	35.76	55.32	55.65	55.84	56.21	61.34	58.82	58.45	58.13
20	35.13	39.34	65.78	67.14	67.32	67.69	74.12	71.45	70.56	70.28
25	38.12	50.11	81.9	82.25	82.44	82.79	86.97	85.12	84.78	84.4
30	39.97	58.72	89.97	91.12	91.33	91.66	96.21	95.65	95.45	95.02

comparison of the dissolution profile of different formulations of solid dispersions. The aqueous dissolution profile of the SDs of valsartan: Kollidon with different carriers in the ratio of 1:8 is shown in Figure 4 and valsartan: Povidone K30 ratio of 1:8 is shown in Figure 5. SDs of drug with Kollidon as the carrier showed almost 97.89% drug release in 30 mins whereas Povidone K30 as the carrier showed 96.21% drug release, indicating that Kollidon is the most suitable carrier giving better dissolution profile than Povidone K30. Kollidon has a very fine particle size, hence a large surface area. The surface area available for adsorption of drug crystals increases with an increase in the concentration of carrier, leading to an increase in the interfacial area of contact between the drug particles and dissolution media.

### Differential Scanning Colorimetry

DSC of valsartan, Carriers, PM, and SDs prepared are shown in Figure 6. Thermogram of drug showed a single sharp endothermic peak at 103.39°C, corresponding to its melting point indicating the crystalline nature of the drug. Kollidon showed an endothermic peak at 104.19°C, whereas SDs with Kollidon as the carrier showed an endothermic peak at 87.39°C. The absence of a melting peak of a drug in the solid dispersion indicated that the drug is entrapped by the carrier, thereby reducing the overall crystallinity of the system. Change in the crystalline structure of drugs in the solid dispersion increased solubility of the drug, which is reflected by the enhanced dissolution rate of the drug from solid dispersion.

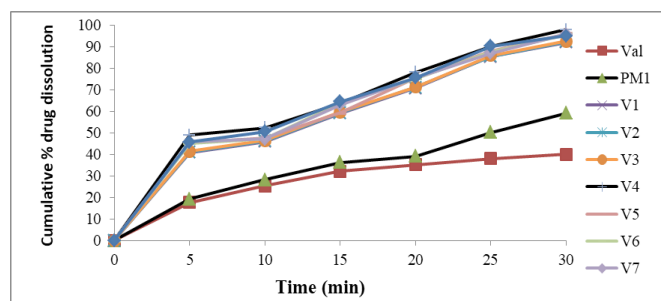


Figure 4: In-vitro drug dissolution of Valsartan, PM1 and SDs Val-Kollidon

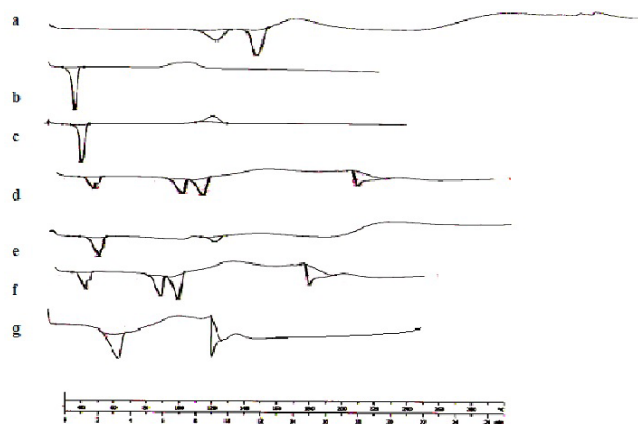


Figure 6: DSC thermogram a) Valsartan b) Kollidon c) Povidone K30 d) PM1 e) PM2 f) SDs V4 g) SDs V13

### X-Ray Diffraction (XRD)

XRD patterns of pure drug, carriers, PM, and solid dispersions are depicted in Figure 7. The diffraction pattern of pure drug valsartan showed a highly crystalline nature, indicated by numerous distinctive peaks at a diffraction angle of  $2\theta$  (17.92°, 31.66°, 45.52°) throughout the scanning range. XRD of solid surface dispersions showed the disappearance of sharp distinctive peaks at a diffraction angle of  $2\theta$  (17.78°, 31.73°, 45.42°). The diffraction patterns of the physical mixture and SD indicated changes in the crystalline nature of the drug. The relative  $2\theta$  angle of valsartan peaks remained unchanged, but the relative intensity of the peaks was decreased. Thus, the relative reduction in the diffraction intensities in the solid dispersions can be attributed to the change in orientation during the crystal growth phase.

### Scanning Electron Microscopy (SEM)

The electron microphotographs of pure valsartan and SDs are shown in Figure 8. Figure (a) shows the large smooth surface crystals of pure valsartan. Figure (c) shows SDs of irregular

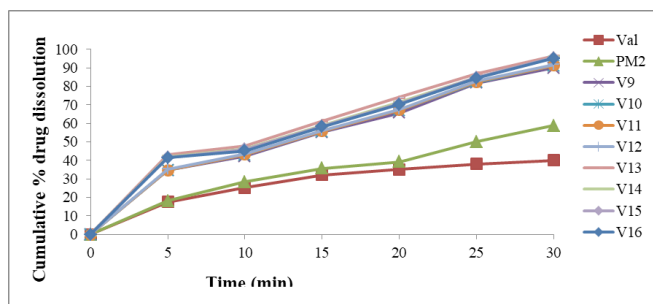


Figure 5: In-vitro drug dissolution of Valsartan, PM2 and SDs Val-Povidone K30.

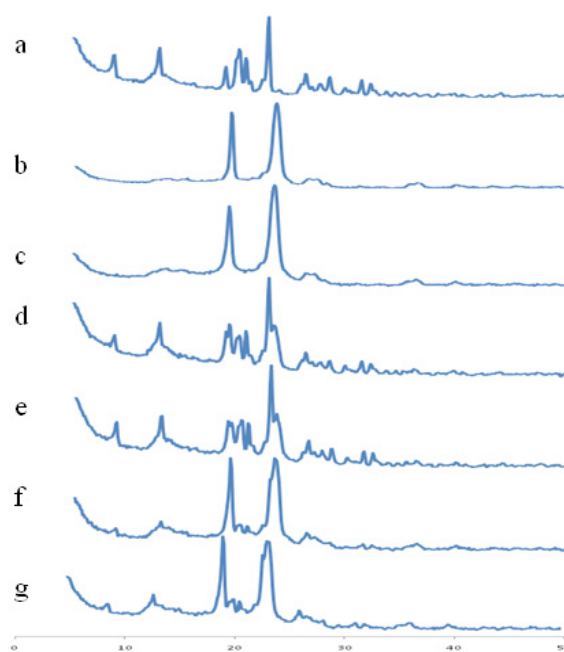
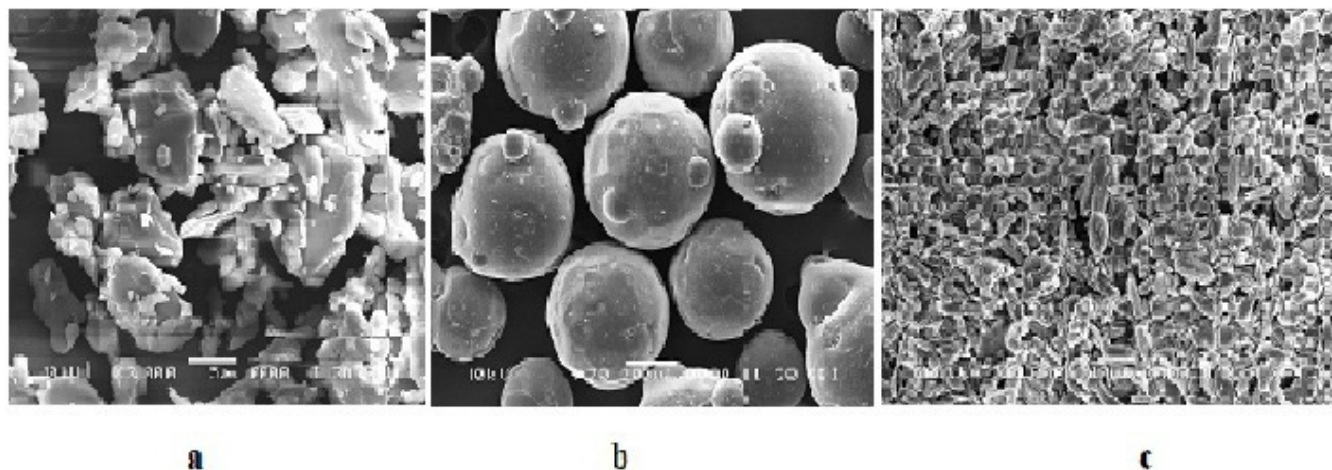


Figure 7: XRD spectra a) Valsartan b) Kollidon c) Povidone K30 d) PM1 e) PM2 f) SDs V4 g) SDs V13



**Figure 8:** SEM microphotographs of Drug valsartan, Kollidon, and solid dispersion V4.

matrices due to the porous nature of the carrier with fine particles of the drug deposited on it. SEM studies explained the surface morphological properties of the SD, indicating that the solid dispersion is in the amorphous state.

### CONCLUSION

Solid dispersion (Kneading) technique was successful in improving the dissolution rate of poorly water-soluble drugs like valsartan. SDs V4 of drug with kollidon as the carrier showed significantly higher dissolution rate as compared to pure drug and physical mixture. The nature and amount of carrier used played an important role in the enhancement of dissolution rate. FTIR and DSC studies showed no evidence of interaction between the drug and carrier.

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### REFERENCES

1. Kiran T, Shastri N, Ramakrishna S, Sadanandam M. Surface solid dispersion of glimepiride for enhancement of dissolution rate. *Int J Pharm Tech Res.* 2009 Jul;1(3):822-831.
2. Yang KY, Glemza R, Jarowski CI. Effects of amorphous silicon dioxides on drug dissolution. *Journal of pharmaceutical sciences.* 1979 May;68(5):560-565.
3. Barzegar-Jalali Enhancement of dissolution rate and anti-inflammatory effects of piroxicam using solvent deposition technique *Drug Dev. Ind Pharm.* 28(6); 2002, 681-686.
4. Taylor LS, Zografi G, Spectroscopic characterization interactions between PVP and Indomethacin in amorphous molecular dispersions, *Pharm. Res.* 1997;14: 1691-1698.
5. Yamashita K, Nakate T, Okimoto O. Establishment of new preparation method for solid dispersion formulation of tacrolimus, *Int. J. Pharm.* 2003;267: 79-91.
6. Seth NS, "Formulation and evaluation of solid dispersion of olanzepine," *Int. J. Pharm. Sci. Res.* 2011;2(2):691-697.
7. Chavan S, Patel K, Shelar D, Vavia P. Preparation of Oxcarbazine Solid Dispersion by Hot Melt Extrusion for Enhanced Dissolution: Downstream Processing to tablets. *Am. J. PharmTech Res,* 2013; 3 (1).
8. Nagender Reddy CH, Anil Reddy T, Srinivasan S. Review on: Better solubility enhancement of poorly water soluble drugs. *International Journal of Inventions in Pharmaceutical Sciences,* 2013; 1 (4):267- 273.
9. Valizadeh H, Nokhodchi A, Qarakhani N, Zakeri-Milani P, Azarmi S, Hassanzadeh D, and Lobenberg R. Physicochemical characterization of solid dispersions of indomethacin with PEG 6000, Myrj 52, Lactose, Sorbitol, Dextrin, and Eudragit E100. *Drug Dev. and Ind. Pharm.* 30 (3):303-317 (2004).
10. Winters S, York P, and Timmins P. Solid state examination of a gliclazide: beta-cyclodextrin complex. *Eur. J. Pharma. Sc.* 5:209-214 (1997).
11. Prajapati ST, Gohel MC, Patel LD. Studies to Enhance Dissolution Properties of Carbamazepine. *Indian J Pharm Sci* 2007;69:427-430.
12. Price JC, Polyethylene glycol, in: A. Wade, P.J. Weller (Eds.), *Handbook of Pharmaceutical Excipients*, American Pharmaceutical Association/The Pharmaceutical Press, Washington, DC/London, 1994; pp. 355-361.
13. Prajapati ST, Gohel MC, Patel LD. Studies to Enhance Dissolution Properties of Carbamazepine. *Indian J Pharm Sci* 2007;69:427-430.
14. Swarbrick J, Boylan J C; *Encyclopedia of Pharmaceutical Technology*; 2nd edn, 2002, 2458-2479.
15. Lawrence M J, Rees G D; *Microemulsions based media as novel drug delivery systems*, *Adv. Drug. Del. Rev.*, 2000; 45: 89-121.
16. Jain P, Yalkowsky S H; Solubilization of poorly soluble compounds using 2 pyrrolidone, *Int J of Pharmaceutics,* 2007;35:223-227.