ISSN: 0976-4607
Research Article

International Journal of Innovative Pharmaceutical Research

Journal homepage: www.ijipr.com

Design and Characterization of Microcrystals for Enhanced Dissolution Rate of Telmisartan

V. Vijayakumar Reddy*, M. Aswini[1], P. Harini[1], B. Prathyusha[1], and M. Sai Sreevani[1]

[*,1]Department of Pharmaceutics, Sri Padmavathi School of Pharmacy,
Vaishnavi Nagar, Tiruchanoor (Po), Tirupati, Andhra Pradesh, India-517503.

ABSTRACT

Poor aqueous solubility and bioavailability of the drugs are important factors affecting absorption of drug and its therapeutic effectiveness. Telmisartan is a well-known and widely used anti-hypertensive drug and it belongs to biopharmaceutical classification system (BCS) class II drug with low solubility and high permeability. the present study was aimed to prepare and characterize microcrystals of telmisartan, employing *in situ* micronization technique by rapid solvent change approach to enhance the solubility and dissolution rate and to optimize the solvent and anti-solvent ratio (v/v) using constant stabilizer concentration in the formulation of telmisartan microcrystals. The prepared formulations were characterized for Percentage crystal yield, Mean particle size (µm), Drug content, *In vitro* dissolution studies. amongst the formulations prepared (F1-F6), F3 formulation consisting of solvent ratio (methanol/water) 1:6 and 0.1% PVP considered as optimized formulation in which % drug release was found to be 96.37% within 60 min in comparison with that of pure drug dissolution of 38.36% within 60 min. also FT-IR spectroscopy, Differential scanning calorimetry (DSC), X-ray diffraction studies (XRD), Scanning electron microscopy (SEM) studies were carried out in order to characterize the drug and microcrystals, results showed that there is no chemical interaction between the drug and the stabilizer, and crystalline habit modification has occurred in the microcrystals without any polymorphic changes.

Keywords: Microcrystals, *In situ* micronization, Telmisartan.

INTRODUCTION

Formulation of poorly soluble compounds for oral delivery now presents one of the most frequent and greatest challenges to formulation scientists in pharmaceutical industry (Sharma Daisy, 2009). Telmisartan is an Angiotensin II Receptor Antagonist, which is used in the prevention and treatment of Hypertension (Gosse P, 2006). One of the major problems with it is its low solubility in biological fluids, which results into poor bioavailability after oral administration (42%) and late onset of action. It also shows high first pass metabolism which further reduces the oral bioavailability. *in situ* micronization has been used to has been used to increase the solubility, dissolution and consequently the bioavailability of much poorly water soluble drugs (Wienen W *et al*., 2000). *in situ* micronization is used to reducing the average diameter of the solid material's particles (Chaumeil JC *et al*.,1998). Particle size reduction is achieved because adsorption of stabilizing agent (which limits the size of the particles generated) onto the particle surface that inhibits particle growth. Crystal morphology may be altered by preferential adsorption of stabilizing agent onto specific faces of the growing crystal which can help in increasing its dissolution rate (Russell Thiering *et al*., 2011). This technique is a rapid, easy to handle, needs only common equipment and direct process.

***Corrosponding author**

V. Vijayakumar Reddy
Email id: vvkreddy92@gmail.com

MATERIALS AND METHODS

MATERIALS

Telmisartan (Aurobindo Pharma Ltd., Hyderabad), PVP K30 (S.D. Fine Chem Ltd., Mumbai), methanol (S.D. Fine Chem Ltd., Mumbai).

Preparation of Microcrystals (Nighute A.B *et al*., *2009*, Sekhon B.S., 2009)

First, an organic solution of the drug was prepared by dissolving 0.3 gm of drug in 10 ml of methanol. Then measured quantity of aqueous solution containing 0.1% w/v of carrier (antisolvent to the drug solution) was added rapidly under stirring to the drug solution. This causes super saturation with respect to the drug and subsequent nucleation and crystal growth. The

Table.1 Composition of Different Formulations of Microcrystals

S.No.	Ingredients	F1	F2	F3	F4	F5	F6
1	Telmisartan (gms)	0.3	0.3	0.3	0.3	0.3	0.3
2	PVP K30 (gms)	0.02	0.04	0.06	0.08	0.10	0.12
3	Solvent volume (ml)	10	10	10	10	10	10
4	Anti-solvent volume (ml)	20	40	60	20	40	60

Table.2 Solvent and Anti-solvent ratios of Different Formulations of Microcrystals

S.No	Formulation Code	Solvent and Anti-solvent ratios (v/v)
1.	F1	1:2
2.	F2	1:4
3.	F3	1:6
4.	F4	1:8
5.	F5	1:10
6.	F6	1:12

mixture was stirred for 60 min by using magnetic stirrer. The crystals were collected by filtration using whatman filter paper (grade 1, 90 mm diameter) followed by three consecutive washings with 10 ml of cold water to remove any non-adsorbed excipients and dried in an oven at 45^0C for 2 hrs. In this way, formulations from F1-F6 were prepared by changing the solvent to anti-solvent ratios as listed in Table.1.

EVALUATION OF TELMISARTAN MICROCRYSTALS

1. PERCENTAGE CRYSTAL YIELD

Percentage crystal yield was calculated to know about percent yield or efficiency of any method and thus its help in selection of appropriate method of formulation. The final weights of the prepared microcrystals were taken and percentage crystal yield was calculated with the following equation and the results are tabulated in Table.3.

$$\% \text{ crystal yield} = \frac{\text{Practical yield}}{\text{Theoritical yield}} \times 100$$

2. MEAN PARTICLE SIZE (µm)

The eye piece micrometer was calibrated by using a standard stage micrometer at 45X. Samples were taken and the suspension was prepared by using propylene glycol and the prepared suspension was mounted on a slide and placed on a mechanical stage. The size of particles was estimated with the help of eye piece micrometer. Around 100 particles were counted to estimate the true mean and the results are tabulated in Table.4.

3. DRUG CONTENT

Equivalent weight of prepared microcrystals containing 10 mg of drug were taken and transferred into 100 ml standard flask and volume was made up to 100 ml with methanol. The resulting solutions were filtered through a 0.45µ membrane filter and suitably diluted. The absorbance of the solutions was measured at 296 nm. Percentage of drug content was calculated by using the given formula and the results are tabulated in Table.5.

$$\% \text{ of Drug Content} = \frac{\text{Observed value}}{\text{Actual Value}} \times 100$$

4. *IN VITRO* DISSOLUTION STUDIES

In vitro dissolution studies of pure telmisartan and microcrystals were conducted with the USP type II apparatus (paddle type). The dissolution studies were performed using phosphate of pH 7.4 buffer as dissolution medium at 37±0.5°C with 75 rpm speed. Samples of each preparation equivalent to 10 mg of drug were added into the dissolution medium. The sample of 5ml aliquots were withdrawn periodically (5, 10, 15, 30, 45 and 60 min) and filtered through 0.45 µ membrane filter. The withdrawn sample was replaced every time with same quantity of fresh dissolution medium. The filtered solutions were diluted suitably. Samples were analyzed for their drug content by using UV spectrophotometer at wavelength of 296 nm. Percent of telmisartan dissolved at various time intervals was calculated and plotted against time. The results are shown in Table.6 and Figure.1.

CHARACTERIZATION OF MICROCRYSTALS

1. FT-IR Spectroscopy

Fourier Transform Infrared (FT-IR) spectral measurements for telmisartan, PVP K30, and their microcrystals were recorded using Thermo-IR 200 FTIR spectrophotometer. Potassium bromide pellet method was employed. The microcrystals were finely ground with KBr to prepare the pellets under a hydraulic pressure of 600 psi and background spectrum was collected under identical conditions. Each spectrum was derived from 16 single average scans collected in the range of 4000-400 cm^{-1} at the spectral resolution of 2 cm^{-1}(Ruchi Tiwari *et al*., 2009).The results are presented in Table.11 and Figure.2, 3 and 4.

2. DSC Thermal Analysis

Thermal analysis of telmisartan and their microcrystals were recorded with Netzsch DSC 200PC (Netzsche, Selb, German). The temperature axis and cell constant of DSC were previously calibrated with Indium.

A heating rate of 5^0C/min was employed over a temperature range of 25-200^{0}C with nitrogen purging. The sample was weighed into an aluminum pan was used as reference (Seemanchala *et al*., 2009). The results are presented in Figure.5 and 6.

3. X-Ray Diffraction Study (XRD)

X-Ray diffraction spectra of telmisartan, PVP K30 and their microcrystals were recorded on a Seifert 303, Germany X-Ray Diffractometer with Reflex software using Ni-filtered, CuKα-radiation, a voltage of 40 kV and a current of 25 mA. The instrument was operated in the continuous scan mode over a 2-θ range of 10 to 70° at step time of 0.5 seconds. The relative intensity I/I_0 and the inter-planar distance (d) corresponding to the 2-θ value were reported and compared (J Kausalya *et al., 2011)*. The results are depicted in Figure.7 and 8.

4. Scanning Electron Microscopy (SEM)

Scanning electron micrographs of telmisartan microcrystals and pure drug powder were taken using a scanning electron microscope (Philips, Philips XL 30 ESEM, Japan). Samples were fixed on an aluminum stub with conductive double-sided adhesive tape and coated with gold in an argon atmosphere (50 Pa) at 50mA for 50 sec (Patel Bhumika *et al*., 2012) shown in Figure.11 and 12.

RESULTS AND DISCUSSION

1. PERCENTAGE CRYSTAL YIELD

Six formulations of surface microcrystals of telmisartan were prepared and weighed accurately. Then the percentage practical yield was calculated by using the formula as follows

$$\text{Percentage of crystal yield} = \frac{\text{Practical yield}}{\text{Theoritical yield}} \times 100$$

When compared to other formulations, F3 formulation showed highest Percentage practical yield i.e., 93.15% shown in table.3.

Table.3 % Crystal Yield of telmisartan microcrystals Containing PVP K30

S. No.	Formulation Code	% Practical yield
1	F1	84.57
2	F2	87.22
3	F3	93.15
4	F4	83.01
5	F5	80.22
6	F6	75.47

Table.4 Mean particle size of telmisartan microcrystals Containing PVP K30

S. No.	Formulation Code	Mean particle size (µm)
1	F1	24.01
2	F2	21.33
3	F3	16.34
4	F4	18.17
5	F5	21.21
6	F6	23.06

Table.5 % Drug Content of telmisartan Microcrystals Containing PVP K30

S. No.	Formulation Code	% Drug content
1	F1	85.70
2	F2	91.53
3	F3	94.60
4	F4	93.22
5	F5	92.45
6	F6	90.11

Table.6 Dissolution data of microcrystals of telmisartan

S. No.	TIME (min)	% CUMULATIVE DRUG RELEASE						
		Pure	F1	F2	F3	F4	F5	F6
1	5	3.95	7.51	9.38	12.54	14.54	17.68	16.54
2	10	6.48	11.82	16.82	22.15	21.67	23.29	24.83
3	15	11.16	14.87	21.39	32.43	35.48	39.48	42.16
4	30	17.49	27.37	39.86	65.86	58.57	56.39	53.37
5	45	25.87	39.48	54.58	84.53	78.45	69.86	67.29
6	60	38.36	63.45	74.95	96.37	84.31	81.63	78.53

2. Mean Particle size

The mean particle size of untreated telmisartan powder was 300 µm while particles precipitated in the presence of 0.1% w/v of PVP was less than 25 µm. No

important disparity was achieved in particle size values among the different methanol/water ratio. This was might be because of the fact that constant concentration (0.1 %) of PVP was used in optimization of methanol/ water ratios. The results were tabulated in Table.4.

3. % Drug Content Estimation

The percent drug content of telmisartan microcrystals containing PVP K30 as stabilizing agent was in the range of 85.70-94.60 as shown in Table.5. It was low for F1 and the high for F3. The results revealed that the ratios and carriers used to prepare formulations have shown no effect on the drug content and uniformity of the microcrystals. In the preparation of microcrystals, the solvent used has no effect on results.

4. *In vitro* Dissolution Studies

From the results, it was found that the percentage drug release of pure telmisartan was very low and only 38.36% dissolved in 60 minutes. Out of four formulations, F4 formulation showed the highest percentage drug release i.e., 96.37% within 60 minutes when compared to that of pure drug. However all the four formulations gave a significant improvement in the solubility as compared to that of the pure drug shown in Table.6 and Figure.1.

Figure.1 *In vitro* dissolution profiles of telmisartan microcrystals

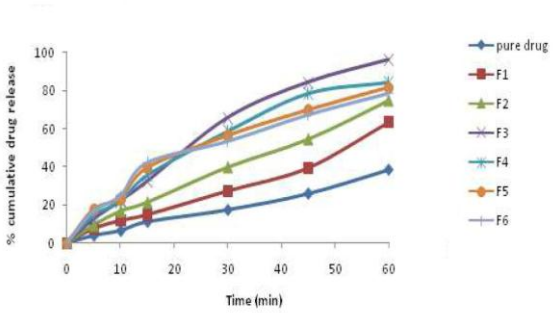

Figure.2 FT-IR spectra of Telmisartan

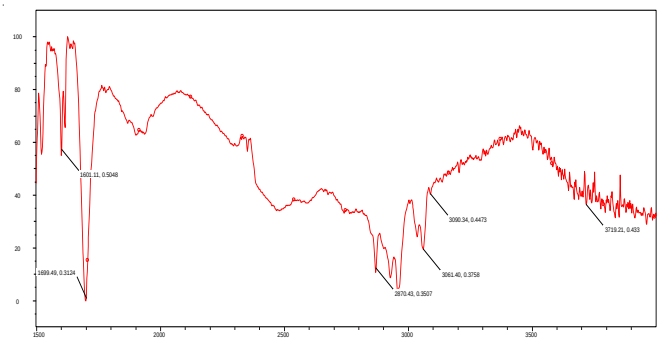

Figure.3 FT-IR spectra of PVP K30

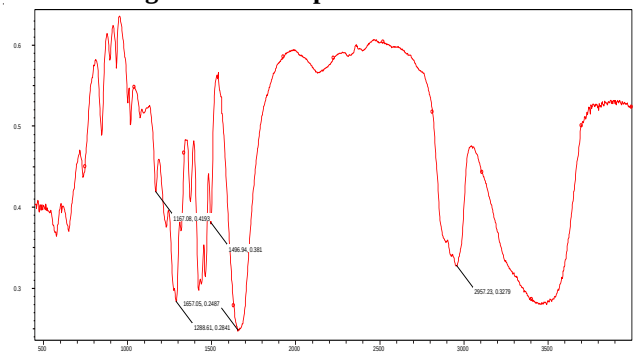

Figure.4 FT-IR spectra of Formulation

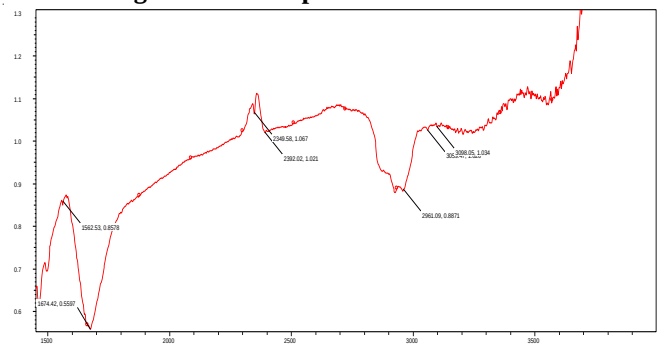

Figure.5 DSC of Telmisartan

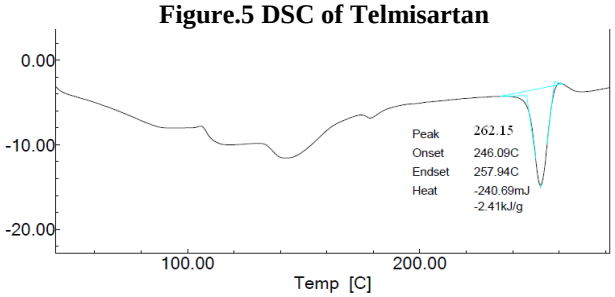

Figure.6 DSC of F3 formulation

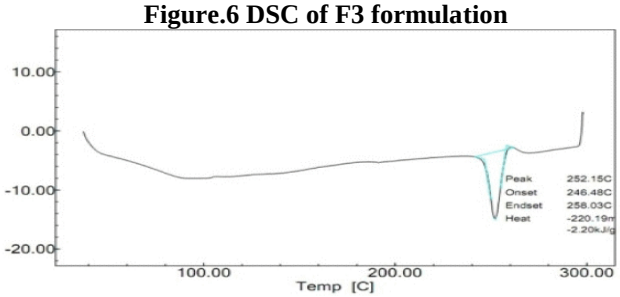

Figure.7 XRD of telmisartan

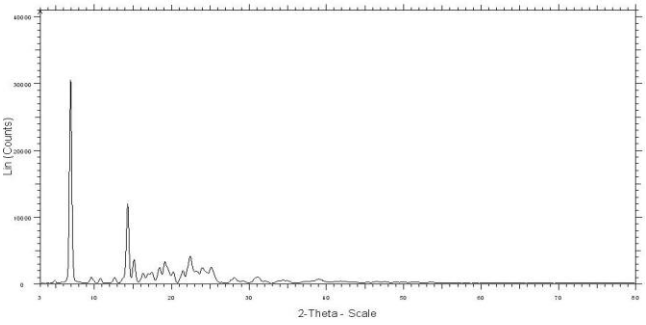

Figure.8 XRD of PVP K30

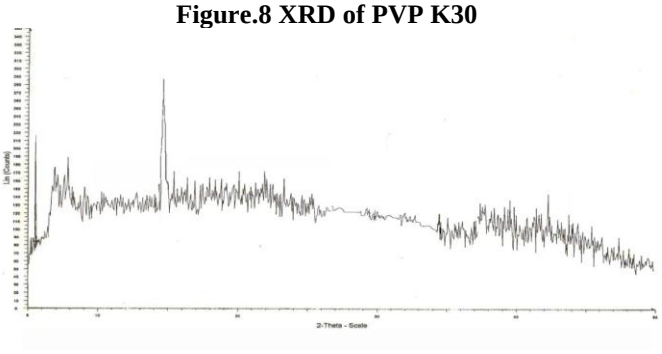

Figure.9 XRD of F3 formulation

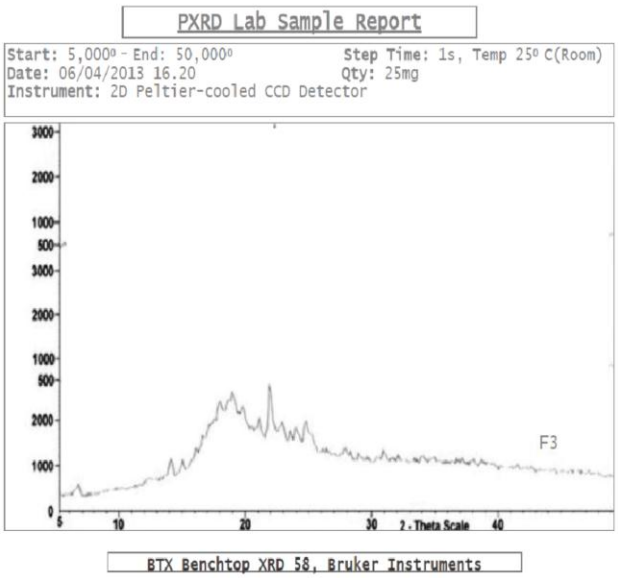

Figure.10 Size distribution of Formulation

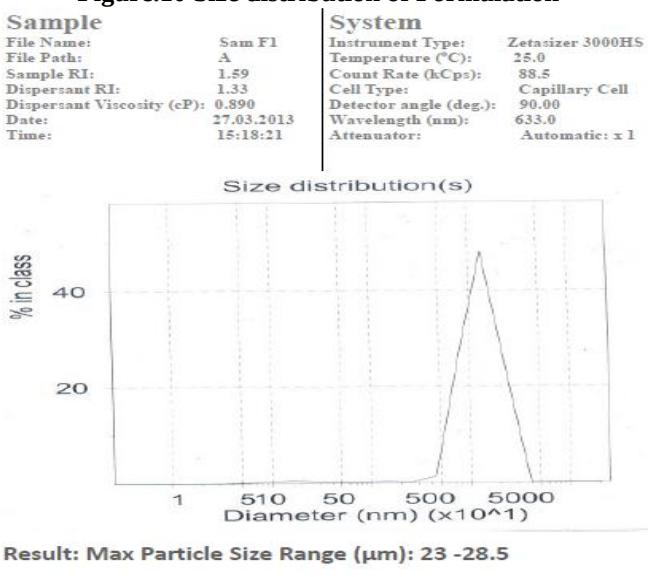

Figure No.11: SEM of Pure telmisartan

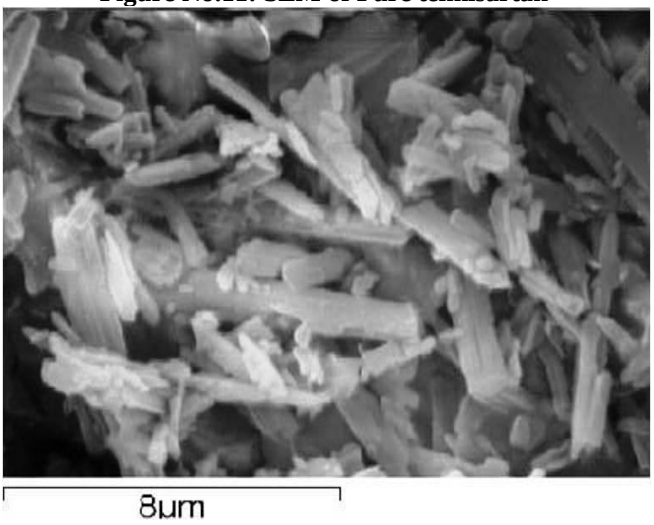

Figure No. 12: SEM of F3 formulation

CHARACTERIZATION OF MICROCRYSTALS

1. FT-IR SPECTROSCOPY

From the FTIR data, it was found that there were no new bands observed in the spectrum, which confirms that no new chemical bonds were formed between the drug and the excipients. The FTIR spectra were shown in figure.2, 3 and 4.

2. Differential Scanning Calorimetry

From DSC thermograms the melting point of pure drug telmisartan was found to be 262.15°C which the value reported in literature hence the procured drugs are pure forms and were shown in Figure.4. The microcrystals of DSC thermograms of telmisartan indicate that there are no interaction between the drugs and excipients which can be accessed from the peaks in the DSC thermograms (Figure.5 and 6).

3. X-Ray diffraction studies

Characteristic peaks appeared in the XRD for TEL showed high intensity peaks at 2θ values of 6.856, 14.253, 15.082, 19.065 and 22.35 as shown in Figure.7. In case of microcrystals, intensity peaks were exhibited at 7.003 and 22.487 were shown in Figure.9. The lack of numerous distinctive peaks of the drug in case of microcrystals demonstrated that high concentration of the drug was dissolved in the solid-state carrier matrix in an amorphous structure suggesting the transformation of crystalline form of Telmisartan to amorphous form in the microcrystals.

4. Scanning electron microscopy (SEM)

Face specific adsorption of stabilizing agent alters the growth rates of the faces where adsorption takes place and thus changes the morphology of the crystal. Modification of crystal habit can improve the dissolution rate by promoting growth of more hydrophilic faces, or inhibiting growth of more hydrophobic faces. Scanning electron micrographs of Pure TEL drug powder and TEL microcrystals were shown in Figure.10&11. Pure TEL powder showed large needle like shaped crystal habit and microcrystals prepared using 0.1 % PVP (F3 formulation) showed small round shaped crystals.

CONCLUSION

Telmisartan microcrystals were prepared by solvent change method using PVP as a hydrophilic stabilizing agent. Solvent ratio (methanol/water) 1:6 and 0.1% PVP were optimum parameters for micro-crystallization of telmisartan. Microcrystals produced using PVP showed narrow particle size distribution and change in the crystal habit from rod type to small plate type. The FTIR, DSC, and XRD results showed no chemical interaction between the drug and the stabilizer, and crystalline habit modification has occurred in the microcrystals without any polymorphic changes. The XRD revealed that crystallinity was reduced significantly in microcrystals. The enhanced dissolution rates attributed to the reduction of the particle size, change in crystal habit, formation of hydrophilic surface and the increased wettability due to adsorption of PVP and reduction in crystallinity of telmisartan during micro-crystallization. In conclusion, the above mentioned technique is a promising tool for effective microcrystal formation during pharmaceutical development in order to increase dissolution rate of poorly water soluble active ingredient.

REFERENCES

Chaumeil JC. Micronization: a method of improving the bioavailability of poorly soluble drugs. *International Journal of pharmacy and Pharmaceutical sciences*. 1998;20(3): 211-5.

Gosse P. A review of Telmisartan in the treatment of Hypertension: Blood pressure control in the early morning hours. *Vascular Health and Risk Management*. 2006;2:195-201.

Kausalya J and K Suresh. Solubility and dissolution enhancement profile of telmisartan using various techniques. *International journal of pharm tech research*. 2011;3(3): 1737-1749.

Nighute AB and Bhise SB. Enhancement of dissolution rate of Rifabutin by preparation of micro crystals using solvent change method. *International journal of Pharm Tech research*. 2009;1(2):142-148.

Patel Bhumika and RH Parikh. Enhancement of dissolution of telmisartan through use of solid dispersion technique. *Journal of pharmacy and bio allied sciences*. 2012;1(2): 250-258.

Ruchi Tiwari and Gaurav Tiwari. Solid Dispersions: An overview to modify bioavailability of poorly water soluble drugs. *International Journal of Pharm Tech Research*. 2009;1(4): 1338-1349.

Russell Thiering, Fariba Dehghani and Neil R. Foster. Current issues relating to anti-solvent micronization techniques and their extension to industrial scales. *Journal of Supercritical Fluids*. 2011;2(3): 159–177.

Seemanchala Rath and Bijan Kumar Guptha. Formulation and optimization of Immeadiate release Telmisartan tablets using full factorial design. *International journal of applied pharmaceutics*. 2009;3(1): 2170-2176.

Sekhon BS. Pharmaceutical co crystal a-review. *Pharmaceutical*. 2009;1(3): 2120-2127.

Sharma Daisy. Solubility Enhancement-Eminent Role in Poorly Soluble Drugs. *Research Journal of Pharrmacy and Technology*. 2009;2:220-224.

Wienen W, Entzeroth M, Jacobus CA, Stangier J, Busch U and Ebner T. A Review on Telmisartan: A novel long acting angiotensin II-receptor antagonist. *Cardiovascular Drug Reviews*. 2000;18(2):127-154.