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Formulation and Characterization of Telmisartan Microcrystals by *In Situ* Micronization Technique

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ABSTRACT

Telmisartan is an BCS class II drug which is having more absorption and poor solubility and used in the treatment of hypertension. Due to poor solubility it is showing less bioavailability (36%) and less therapeutic effectiveness. In order to increase the solubility of telmisartan *in situ* micronization technique is employed by using the stabilizing agents like guar gum, maltodextrins, and HPMC. The particle size of the telmisartan is decreased and crystal morphology is altered by the preferential adsorption of stabilizing agent onto the specific faces of drug. Among all formulations F9 formulation containing HPMC as stabilizing agent at 0.1% w/v concentration with 1:6 ratio of solvent to anti-solvent (v/v) showed the highest percentage drug release of 95.32% within 60 min. The release kinetics of all formulations are obeying 1st order kinetics and drug release is increased along with the time. The characterization studies like SEM analysis, DSC, XRD and FT-IR studies were done and the drug and stabilizing agents were proved to be compatible.

Keywords: Telmisartan, *In situ* micronization, Stabilizing agent, HPMC, Particle size.

INTRODUCTION

In the absorption of drugs solubility and dissolution rate are the important factors and effective action of drug is depended on these factors. Telmisartan is an selective angiotensin II blocker and used in the treatment of hypertension. Telmisartan is showing less solubility so that less bioavailability (36%) will be observed. By using different stabilizing agents like guar gum, maltodextrins and HPMC in *in situ* micronization technique the solubility of telmisartan is increased. In *in situ* micronization technique different solvent-anti solvent ratios 1:2, 1:4 and 1:6 were used and methanol is used as solvent (Mosharaaf *et al*., 1995). Poor wettability can be increased through adsorption of hydrophilic stabilizing agent onto the surface of telmisartan and it is clear that precipitation in the presence of stabilizing agent can have a positive effect on dissolution rate.

MATERIALS AND METHODS

Materials

Telmisartan (Aurobindo Pharma Ltd., Hyderabad), Guar gum (S.D. Fine Chem Ltd., Mumbai), Maltodextrin (Loba Chem Pvt. Ltd., Mumbai), HPMC (S.D. Fine Chem Ltd., Mumbai), Methanol (Merck Pvt. Ltd., Mumbai). All other reagents used were of AR grade and procured locally.

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Preparation of Telmisartan Microcrystals

First, an organic solution of the drug was prepared by dissolving 0.3 gms of drug in 10 ml of methanol. Then measured quantity of aqueous solution containing 0.1% w/v of stabilizing agent (antisolvent to the drug solution) was added rapidly under stirring to the drug solution. This caused super saturation with respect to the drug and subsequent nucleation and crystal growth. The 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 excipient and dried in an oven at 45^0C for 2 hrs (Nighute *et al*., 2009). In this way, formulations from F1-F9 were prepared (Table.1) by changing the solvent to anti-solvent ratios as listed in Table.2.

Evaluation of Telmisartan Microcrystals

Percentage Crystal Yield

Percentage crystal yield was calculated by comparing the practical yield and theoretical yield to know about efficiency of any method and thus its help in selection of appropriate method of production. The final

weights of the microcrystals were taken and percentage crystal yield was calculated by using the formula as follows.

$$\% \text{ Crystal yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

Drug Content

Equivalent weight of prepared microcrystals containing 10 mg drug were taken and transferred into 10 ml methanol. Then take 1 ml from above solution and diluted up to 10 ml methanol and repeat the same again with 1 ml from above solution. The resulting solutions were filtered through a 0.45µ membrane filter and diluted accordingly. The absorbance of the solutions was measured at 296 nm. Percentage of drug content was calculated by using the given formula.

$$\% \text{ Drug content} = \frac{\text{Observed value}}{\text{Actual value}} \times 100$$

Mean Crystal Size

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 crystal size.

***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 900 ml saliva simulated fluid buffer of pH 6.8 as dissolution medium at 37±0.5°C with 75 rpm speed (Kausalya *et al*., 2011). Samples of each preparation equivalent to 100 mg of drug were added into the dissolution medium. The sample of 1ml aliquots were withdrawn periodically (15, 30, 45 and 60 min) and filtered through 0.45µ membrane filter. The withdrawn sample was replaced every time with same quantity of fresh dissolution medium. The filtered solutions were diluted suitably and the samples were analyzed for their drug content by using UV spectrophotometer at wavelength of 296 nm. Percentage of drug dissolved at various time intervals was calculated by plotting time on X- axis against percent cumulative drug release on Y-axis.

Drug Release Kinetics

To investigate the possible mechanisms of drug release by telmisartan microcrystals, the drug release data were fitted to various models such as zero-order, first-order, hixson crowell, higuchi, erosion model, baker-lonsdale, weibull and korsmeyer's peppas kinetics.

Characterization of Microcrystals

FT-IR Spectroscopy

Fourier Transform Infrared (FT-IR) spectral measurements for telmisartan and their microcrystals were recorded using Thermo-IR 200 FT-IR spectrophotometer. Potassium bromide pellet method was employed. The microcrystals were finely ground with KBr to prepare the pellets under a hydraulic pressure of 3000 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}.

Differential Scanning Calorimetry (DSC)

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/min was employed over a temperature range of 0- 350^{0}C with nitrogen purging. The sample was weighed into an aluminium pan was used as reference.

X-Ray Diffraction Study (XRD)

X-Ray diffraction spectra of telmisartan and their microcrystals were recorded on a Seifert 303, Germany X-Ray diffractometer with Ray-flex software using Ni-filtered, Cu-K-α-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 10-70°C at step time of 0.5 seconds. The relative intensity I/I_0 and the interplanar distance (d) corresponding to the 2-θ value were reported and compared.

Scanning Electron Microscopy (SEM)

Scanning electron micrographs of telmisartan microcrystals and pure drug 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.

RESULTS AND DISCUSSION

Percentage Crystal Yield

From the results, it was observed that there was no significant loss of drug during the preparation of microcrystals by rapid solvent change method (Table.3).

Drug Content Estimation

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 (Table.4).

***In Vitro* Dissolution Studies**

From the results, it was found that the percentage drug release of pure telmisartan was very low and only 36.26% dissolved in 60 minutes. Out of nine formulations, F9 formulation showed the highest percentage drug release i.e., 95.23% within 60 minutes when compared to that of pure drug. However all the nine formulations gave a significant improvement in the solubility (Table.5 and Figure.1).

Drug Release Kinetics

From the results, it was found that the drug release patterns of microcrystals of telmisartan have found to be followed the first-order kinetic model predominantly and followed by zero-order and Hixson Crowell's cube root model as well. This release patterns are evident with the correlation coefficient 'r' values which were nearer to 1 (Table.6).

FT-IR Spectroscopy

FT-IR spectra of pure telmisartan, guar gum, maltodextrin and HPMC and its microcrystals prepared by rapid solvent change method. Pure telmisartan showed principal absorption peaks at 1693.48 cm^{-1} (C=O stretching), 1604.24 cm^{-1} (C=C aromatic stretching), 743.47 cm^{-1} (C-H aromatic bending), 2957.84 cm^{-1} (C-H stretching), 1520.89 cm^{-1} (C-C bending), 3059.94 cm^{-1} (C-H aromatic stretching), and 1266.93 cm^{-1} (C-O stretching). Same peaks of C=O, C=C, C-H, and C-C bonds were present as that of pure drug without much shifting in the spectra of telmisartan microcrystals suggested no chemical interaction between the drug and stabilizing agent (Figure.2, 3, 4 and 5).

Table.1 Composition of different formulations of Telmisartan microcrystals

S. No.	Ingredients	Formulation code								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Telmisartan (gms)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
2	Guar gum (gms)	0.02	0.04	0.06	---	---	---	---	---	---
3	Maltodextrin (DE<20) (gms)	---	---	---	0.02	0.04	0.06	---	---	---
4	HPMC (gms)	---	---	---	---	---	---	0.02	0.04	0.06
5	Solvent (methanol) (ml)	10	10	10	10	10	10	10	10	10
6	Anti-solvent (water) (ml)	20	40	60	20	40	60	20	40	60

Table.2 Solvent to anti-solvent ratios of different formulations of Telmisartan microcrystals

S. No.	Formulation code	Solvent to anti-solvent ratio (v/v)
1	F1	1:2
2	F2	1:4
3	F3	1:6
4	F4	1:2
5	F5s	1:4
6	F6	1:6
7	F7	1:2
8	F8	1:4
9	F9	1:6

Table.3 Percentage crystal yield of Telmisartan microcrystals

S. No.	Formulation code	% Crystal yield
1	F1	93.25
2	F2	95.55
3	F3	96.30
4	F4	92.69
5	F5	94.44
6	F6	96.70
7	F7	91.57
8	F8	95.55
9	F9	96.15

Table.4 Percentage drug content of Telmisartan microcrystals

S. No.	Formulation code	% Drug content
1	F1	86.31
2	F2	91.63
3	F3	94.99
4	F4	86.87
5	F5	92.03
6	F6	95.36
7	F7	85.70
8	F8	90.22
9	F9	96.60

Table.5 Dissolution data of microcrystals of Telmisartan

S. No.	Time (min)	% Cumulative drug release (mean± S.D.)								
		Pure drug	TEL : Guar gum			TEL : Maltodextrin			TEL : HPMC		
			F1	F2	F3	F4	F5	F6	F7	F8	F9
1	15	6.80 ± 0.36	26.81± 1.21	28.38± 0.92	30.01± 0.76	26.98± 1.21	28.32± 0.98	29.03± 1.34	29.18± 0.91	31.32± 0.93	39.62± 0.83
2	30	15.18± 0.82	39.30± 0.67	41.67± 0.76	45.98± 1.34	41.32± 1.13	44.19± 0.67	45.02± 1.17	43.30± 1.11	47.03± 0.48	53.18± 1.43
3	45	25.36± 0.94	56.67± 1.35	62.38± 1.23	68.32± 1.41	59.13± 0.94	61.13± 0.82	64.32± 0.98	61.78± 0.86	64.29± 0.89	74.12± 1.14
4	60	36.26± 0.54	67.39± 0.98	74.13± 1.32	80.23± 0.78	74.01± 0.76	78.67± 0.92	83.93± 0.89	78.13± 0.96	84.12± 0.45	**95.32± 0.65**

Table.6 Correlation coefficient(r) & rate constant (k) values of telmisartan microcrystals

Kinetic model		F1	F2	F3	F4	F5	F6	F7	F8	F9
First order	r	0.996	0.987	0.979	0.986	0.982	0.979	0.996	0.987	0.978
	k	0.017	0.035	0.055	0.027	0.041	0.061	0.009	0.031	0.049
Hixon-crowell	r	0.992	0.976	0.958	0.973	0.972	0.961	0.997	0.977	0.960
	k	0.025	0.050	0.0074	0.040	0.057	0.081	0.014	0.045	0.067
Zero order	r	0.980	0.940	0.896	0.944	0.929	0.892	0.997	0.947	0.906
	k	1.532	2.770	3.762	2.267	3.080	3.999	0.880	2.481	3.470
Higuchi	r	0.994	0.997	0.984	0.999	0.995	0.982	0.973	0.998	0.988
	k	7.051	9.460	10.892	8.181	10.03	11.32	5.422	8.855	10.46
Peppas	r	0.927	0.926	0.924	0.927	0.96	0.925	0.929	0.924	0.918
	k	0.388	0.233	0.151	0.285	0.203	0.135	0.537	0.259	0.169
Erosion	r	0.992	0.976	0.958	0.973	0.972	0.961	0.996	0.977	0.960
	k	0.005	0.010	0.016	0.008	0.012	0.017	0.003	0.009	0.014
Baker-lonsdale	r	0.987	0.993	0.994	0.999	0.994	0.989	0.966	0.993	0.995
	k	0.0012	0.0024	0.004	0.001	0.003	0.005	0.0006	0.002	0.004
Weibull	r	0.959	0.970	0.976	0.980	0.971	0.966	0.935	0.972	0.977
	k	0.371	0.636	0.902	0.491	0.722	0.993	0.996	0.987	0.978

Figure.1 Dissolution profile of Telmisartan microcrystals

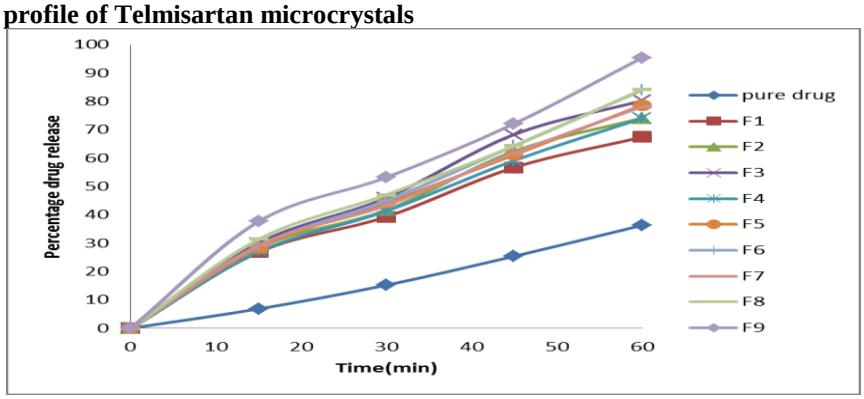


Figure.2 FT-IR spectrum of telmisartan

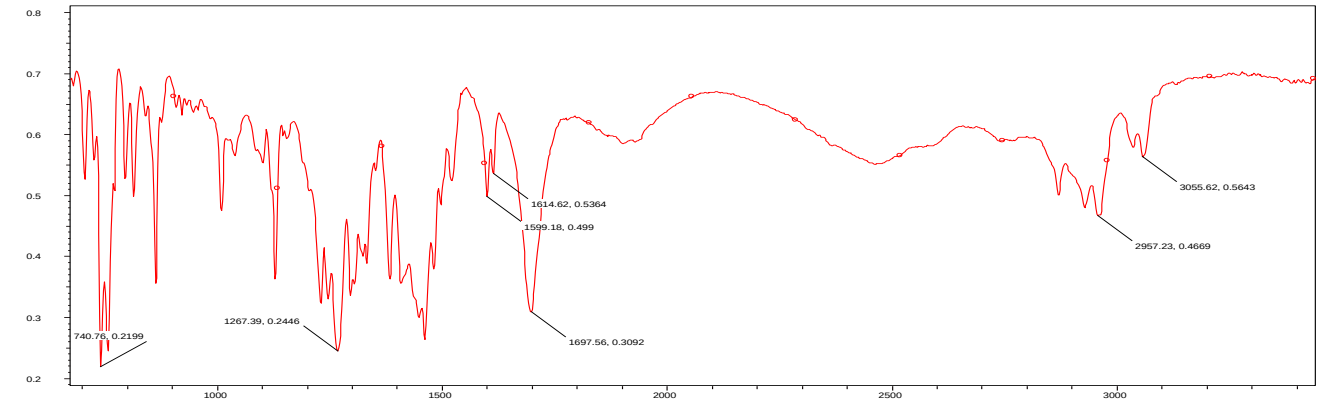


Figure.3 FT-IR spectrum of telmisartan microcrystals containing guar gum

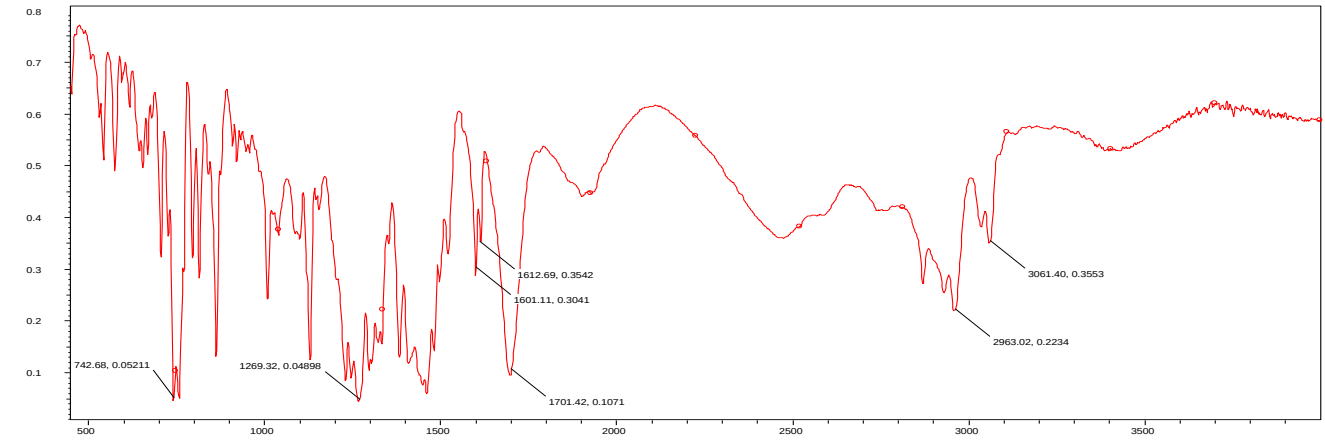


Figure.4 FT-IR spectrum of telmisartan microcrystals containing HPMC

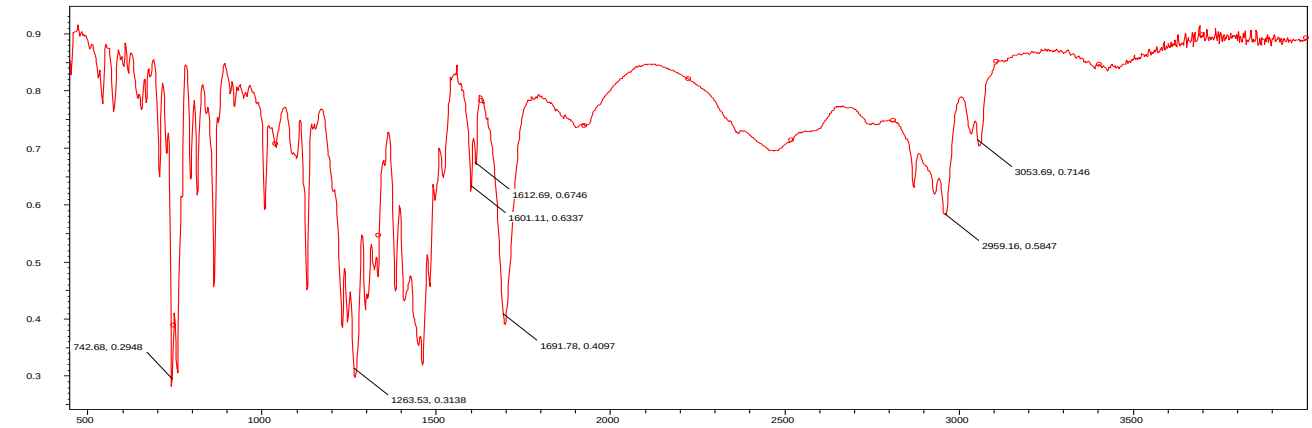


Figure.5 FT-IR spectrum of telmisartan microcrystals containing maltodextrins

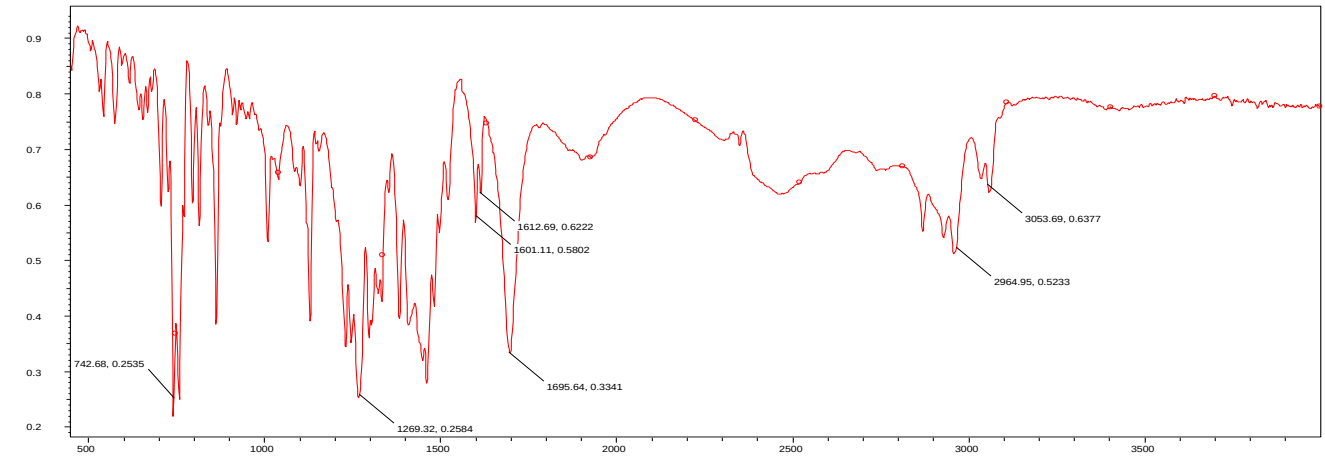


Figure.6 Scanning electron micrograph of telmisartan

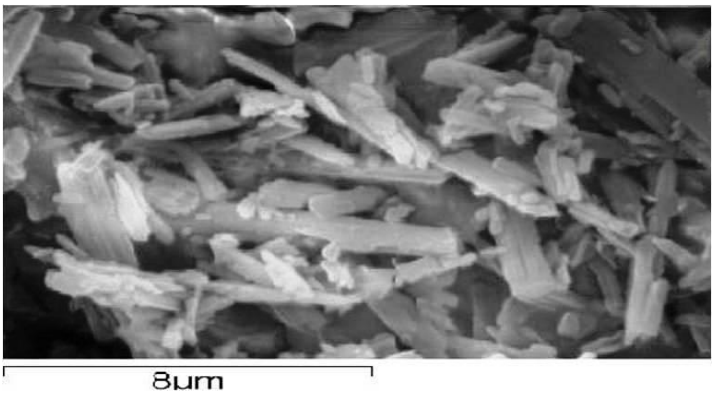


Figure.7 Scanning electron micrograph of F9 formulation

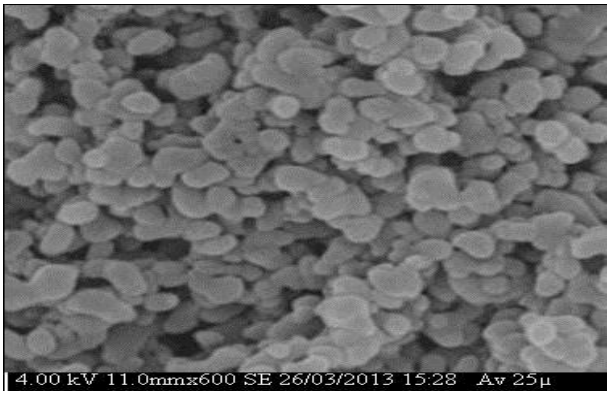


Figure.8 DSC of Telmisartan

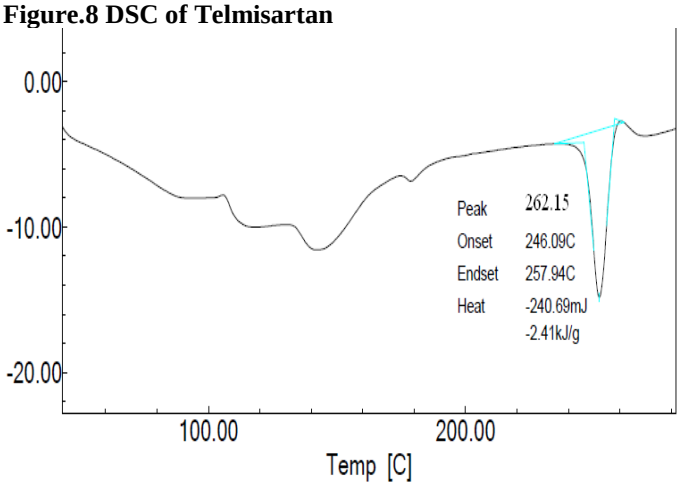


Figure.9 DSC of optimized formulation

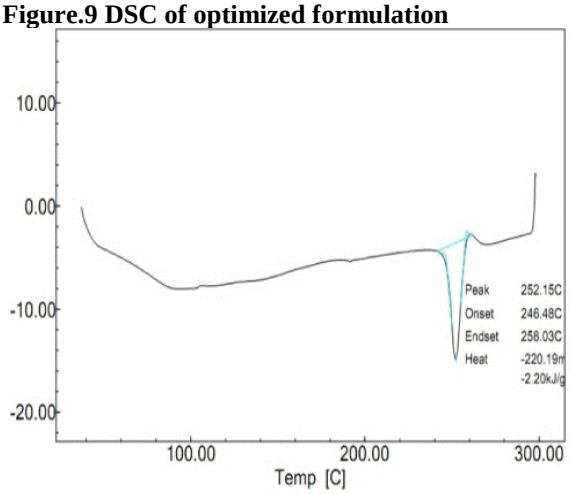


Figure.10 XRD of telmisartan

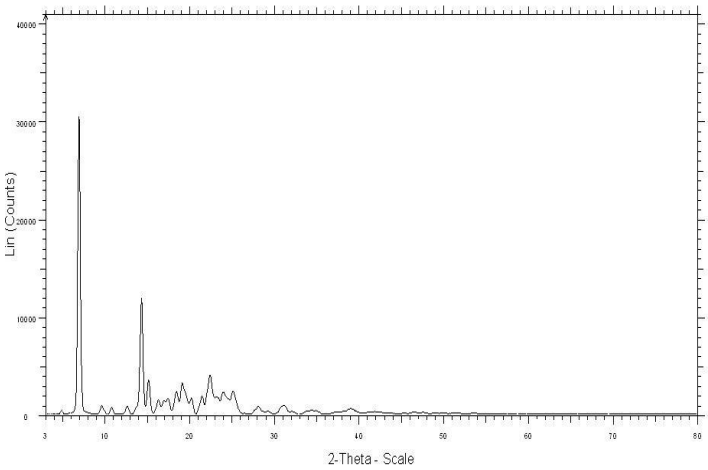
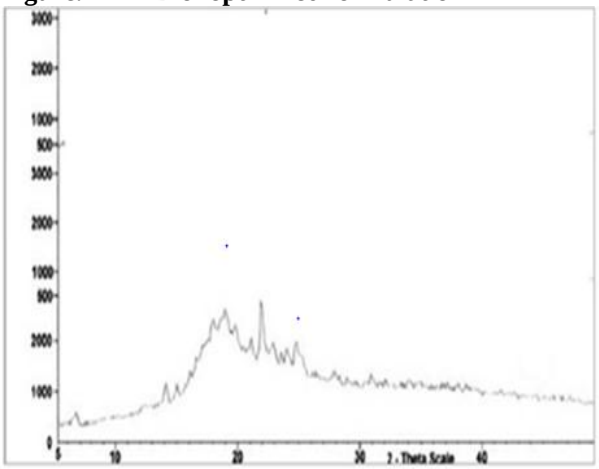


Figure.11 XRD of optimized formulation



Scanning electron microscopy (SEM)

Pure drug showed large needle like shaped crystal habit with particle size of 100µm diameter. Microcrystals containing HPMC as stabilizing agent at 0.1% w/v concentration with 1:6 ratio of solvent to anti-solvent (v/v) respectively (F9 formulation) showed small round shaped crystals with particle size of 25µm diameter (Figure.6 and 7). From the results, it was observed that the particle size of drug decreases three folds by *in situ* micronization technique. This may be due to face specific adsorption of stabilizing agent alters the growth rate of the crystal faces where adsorption takes place and thus changes the morphology of the crystal. Modification of crystal habit can improve the dissolution rate by promoting the growth of more hydrophilic faces or inhibiting the growth of more hydrophobic faces.

CONCLUSION

Preparation of telmisartan microcrystals was successfully done by in situ micronization technique using the stabilizing agents like guar gum, maltodextrins and HPMC. The formulation containing HPMC as stabilizing agent at 0.1% w/v concentration with 1:6 ratio of solvent to anti-solvent (v/v) showed the highest percentage drug release of 95.32% within 60 min. Microcrystals showed narrow particle size distribution and change in the crystal habit from rod type to round shaped crystals. 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 SEM analysis results proved that reduced particle size and adsorption of stabilizing agent onto the surface of telmisartan showed the better dissolution than pure drug. The present study proved that in situ micronization technique is better for improving the solubility of poor soluble drugs.

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