International Journal of PharmTech Research
CODEN (USA): IJPRIF, ISSN: 0974-4304
Vol.9, No.1, pp 28-34, 2016

Improvement of aqueous solubility and In-vitro drug release rate of Telmisartan using hydrophilic base by various dispersion techniques

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Abstract: Telmisartan is angiotensin-II receptor blocker used as antihypertensive agent in the treatment of hypertension. This drug belongs to BCS class II i.e. low solubility and high permeability. The low aqueous solubility and low dissolution results in poor bioavailability which leads to low therapeutic response. In present investigation an attempt was made to overcome this problem by enhancing aqueous solubility. In present study solid dispersions of telmisartan were prepared by different methods, i.e. kneading, solvent evaporation and fusion methods using PEG 8000 as hydrophilic carrier. The prepared solid dispersion was evaluated and characterised by different techniques, which includes solubility determination, in-vitro dissolution, UV, FTIR, DSC and XRD analysis. Enhancement of aqueous solubility and dissolution of telmisartan was observed with solid dispersion of drug using carrier PEG 8000 by kneading method. Formulation containing 1:4 ratio of drug: PEG 8000 exhibited the highest aqueous solubility almost eight times greater than the pure drug and best cumulative release of 97.80 % as compared to 45.90 % for the pure drug.

1. Introduction

Telmisartan is angiotensin-II receptor blocker (ARB) used as antihypertensive agent in the treatment of hypertension. It binds to the angiotensin II type one (AT1) receptors with high affinity, leads to inhibition of the action of angiotensin II on vascular smooth muscle, which causes a reduction in arterial blood pressure [1].Telmisartan is 2-(4-{[4-methyl-6-(1-methyl-1H1,3-benzodiazol-2-yl)-2-propyl-1H-1,3-benzodiazol1yl] methyl} phenyl) benzoic acid, structure is shown in fig.1 [2]. This drug belongs to BCS class II. It is practically insoluble in water. The low aqueous solubility and poor dissolution results in poor bioavailability [3].The reported solubility of telmisartan in distilled water is 0.0067mg/ml. normal dose of telmisartan is 20,40,80 mg once in a day [4]. Solid dispersion is one of the solubility enhancement technique in which drug is incorporated in water soluble carrier. Different solid dispersion methods were used to prepare solid dispersion likewise physical mixing, solvent evaporation, fusion, kneading melts extrusion [5-7]. Different solid dispersion methods were reported enhancement in aqueous solubility of telmisartan which include solvent evaporation, kneading, physical mixing by using different polymer like PVPK30, β-cyclodextrin and PEG 4000[8]. In present work solid dispersion of telmisartan were prepared using three methods which are kneading, solvent evaporation and fusion method. Here PEG 8000 is used as hydrophilic carrier for preparing solid dispersion in various drugs: polymer ratios. All solid dispersion batches were evaluated for practical yield, drug content, solubility determination, *in-vitro* dissolution, UV, FTIR, DSC and XRD analysis.

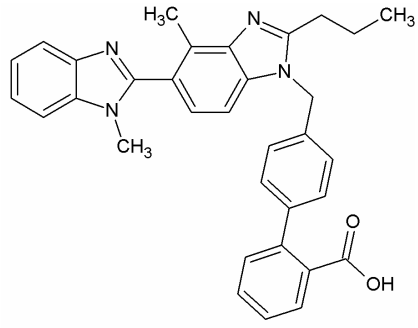

Figure 1: Chemical structure of Telmisartan

2. Materials and Methods

2.1Materials: Telmisartan was obtained as a gift sample from Micro lab Pvt. Ltd. Bangalore, Polyethylene glycol 8000 (PEG8000) and Hcl were purchased from SD-Fine Chem. Mumbai, (India) and all other chemicals and reagents were of analytical grade.

2.2 Methods: Solid dispersions of telmisartan were prepared by following methods.

2.2.1 Kneading method [9]: In present work the drug and carrier was used in different ratios [1:2, 1:4, 1:6]. Both drug and carrier was triturated using mortar by adding small volume of distilled water to give a thick paste, which was kneaded up to 60 minutes and kept in oven for drying at room temperature. Then the dried mass was pulverized, sifted through sieve no.60 and stored in desiccator for further studies. The formulations were coded as K1, K2 and K3for drug- polymer ratios 1:2, 1:4 and 1:6 respectively.

2.2.2 Solvent evaporation method [10]: In present work drug and carrier was used in different ratios [1:2, 1:4, 1:6]. The respective amount of carrier and drug was dissolved in methanol. The solvent was then removed by evaporation. The prepared dispersions were pulverized, sifted through sieve no. 60 and stored in desiccator for further studies. The formulations were coded as S1, S2 and S3 for drug- polymer ratios 1:2, 1:4 and 1:6 respectively.

2.2.3 Fusion method [11]: In present work the drug and carrier was used in different ratios [1:2, 1:4, 1:6]. The respective amount of polymer [PEG 8000] was placed in a china dish and allowed to melt by heating up to its melting point. To the molten mass, an appropriate amount of telmisartan was added and stirred constantly until homogenous dispersion was obtained. The mixture was cooled rapidly by placing the dish in an ice bath for 5 min to solidify. The solid mass was pulverized, sifted through sieve no. 60 and stored in desiccator for further studies. The formulations were coded as F1, F2 and F3 for drug- polymer ratios 1:2, 1:4 and 1:6 respectively.

2.3 Evaluation of solid dispersion:

2.3.1 Percentage practical yield: The prepared solid dispersions were weighed accurately and it was taken as theoretical yield. Then the percentage practical yield was calculated by using the formula as follows:

$$\% \text{ of practical yield} = \frac{\text{Practical mass (Solid dispersion)}}{\text{Theorotical mass (drug + polymer)}} \times 10_0$$

2.3.2 Drug content: Solid dispersions equivalent to 10 mg telmisartan was weighed accurately and dissolved in methanol. The solution was filtered by Whatmann filter paper no. 0.45, diluted and analysed at 291 nm by UV spectrophotometer. Actual drug content was calculated for all batches using the equation as follows:

$$\text{Drug content (\%)} = \frac{\text{Actual amount of TEL in SD}}{\text{Theoretical amount of TEL in SD}} \times 10_0$$

2.3.3 Saturation solubility study: Solubility studies were conducted by taking the excess amount of pure telmisartan and solid dispersion formulations containing equivalent amounts of drug were placed in a flask with

glass stopper containing distilled water. The samples were placed on a magnetic stirrer at 100 rpm for 24 h at 37±0.5^{0}C until equilibrium was achieved and the aliquots were filtered through 0.45 µm filter. The filtered samples were diluted and assayed at 291 nm using an UV visible spectrophotometer against blank. Samples were analysed in triplicate.

2.3.4 In-vitro dissolution [12]: *In-vitro* dissolution studies of pure telmisartan and solid dispersion formulations were conducted in 900 ml 0.1 N Hcl at 50 rpm maintained at 37 ± 0.5°C using USP type-I dissolution apparatus. 40 mg of telmisartan and equivalent amount of solid dispersions were added to dissolution medium and 5 ml aliquots were withdrawn at 5, 10, 15, 30, 45 and 60 minutes time intervals. The volume was maintained by adding 5 ml of fresh dissolution medium to maintain sink condition. The withdrawn samples were assayed for telmisartan content at 291 nm using a UV visible spectrophotometer. Percent of telmisartan dissolved at various time intervals was calculated.

2.4 Fourier transforms infrared spectroscopy (FTIR): FT-IR spectra of telmisartan and solid dispersion of drug were carried out to check compatibility of drug with polymer. Pure drugs and solid dispersion were mixed with potassium bromide (KBr) of IR grade in the ratio of 1:100. The mixtures were then scanned using FT-IR Spectrophotometer (Shimadzu DR-8031, Japan). The scanning range was 400-4000 cm^{-1}. The FT-IR spectrum of solid dispersion was compared with that of the FT-IR spectra of pure drug for studying interaction.

2.5 Differential scanning calorimeters (DSC): DSC studies of telmisartan and solid dispersion of drugs with polymer was performed to access change in thermal behaviour of pure telmisartan and prepared solid dispersion. DSC thermo gram was obtained using DSC (Diamond DSC, Perkin Elmer) at heating rate of 10^{0}C/min from temperature 0-300^{0}C.

2.6 X-ray diffraction studies (XRD): XRD studies of telmisartan and solid dispersion of drugs with polymer performed to access the changes in the crystallinity, when drug was mixed with polymer. XRD patterns were recorded using (Miniflex II, Rigaku) with Cu-kαradiation. The scanning angle ranged from 10° to 50° of 2θ.

2.7 Stability study: The optimised solid dispersion batch was kept for accelerated stability study for 90 days in oven at temperature about 40°C± 2°C and 75%RH according to ICH guideline Q1A.

3. Results and Discussion:

3.1 Calibration curve of telmisartan in 0.1 N Hcl*:* Various concentrations (2-10µg/ml) of telmisartan were prepared in 0.1 N Hcl and the UV absorbance were measured at 291 nm using UV visible spectrophotometer. The results of calibration curve are shown in Table 1 and fig. 2.

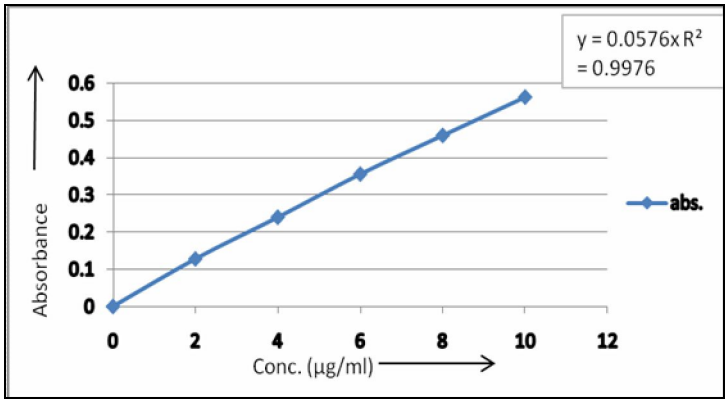

Figure 2: Calibration curve of Telmisartan in 0.1N Hcl

Table 1: Standard calibration curve of Telmisartan in 0.1N Hcl

Sr. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.128
3	4	0.240
4	6	0.356
5	8	0.460
6	10	0.563

3.2 Percentage practical yield: The % practical yield of all solid dispersion formulations was found in range of 90-95%.

3.3 Drug content: The % drug content of all solid dispersion formulations was found in range of 97-99%.

3.4 Saturation solubility study: Solubility study of all solid dispersion formulations was determined. It was found that increase in aqueous solubility of telmisartan using PEG 8000 as hydrophilic carrier as shown in table 2.The highest aqueous solubility was found by kneading method. Formulation K2 shows highest solubility (0.0490mg/ml) as compared to pure telmisartan (0.0067 mg/ml). Kneading method shows highest solubility because water soluble carrier PEG8000.

Table 2: Percentage practical yield, % Drug content and Solubility

Sr. no.	Formulation code	% Practical yield	% Drug content	Solubility (mg/ml)	Increase in solubility compare to drug(fold)
1.	K1	92.21	97.52%	0.0270	4.02
2.	K2	94.86	98.77%	0.0490	7.31
3.	K3	93.52	97.95%	0.0428	6.38
4.	S1	91.32	98.01%	0.0216	3.22
5.	S2	90.88	97.59%	0.0330	4.92
6.	S3	94.74	97.92%	0.0278	4.14
7.	F1	93.72	98.67 %	0.0200	2.98
8.	F2	91.58	98.23%	0.0328	4.89
9.	F3	90.94	98.90%	0.0303	4.52

3.5 In-vitro dissolution studies: The results of *in-vitro* dissolution studies are shown in Table 3 and fig. 3. It was found that the kneading method shows enhanced dissolution compared to fusion and solvent evaporation method. The formulation K2 shows highest dissolution of 97.80 % as compared to pure drug.

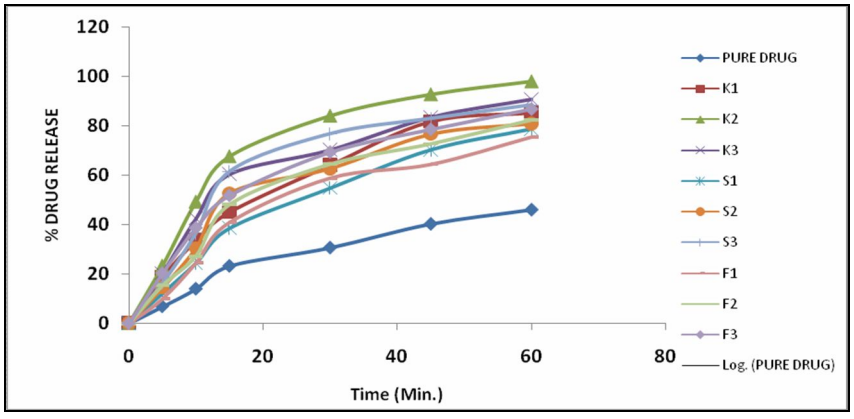

Figure 3: % Drug release profile

Table 3: *In-vitro* dissolution studies of solid dispersion

Time (min)	% Drug release									
	P.D.	K1	K2	K3	S1	S2	S3	F1	F2	F3
0	0	0	0	0	0	0	0	0	0	0
5	6.84± 1.65	18.76± 0.33	23.30± 1.96	20.24± 0.86	12.26± 1.05	14.50± 0.64	16.42± 0.62	10.38± 1.63	15.45± 1.73	20.28± 1.03
10	13.95 ±1.09	33.64± 0.78	49.16± 1.44	42.34± 0.64	24.42± 0.7	30.46± 0.96	36.56± 0.84	24.52± 2.48	27.38± 0.94	38.66± 0.23
15	23.18 ±1.44	45.14± 0.47	67.49± 0.87	60.28.± 0.94	38.52± 0.88	52.68± 0.74	61.42± 1.28	40.88± 0.24	48.22± 1.33	51.80± 0.82
30	30.58 ±1.79	64.14± 1.98	83.90± 0.64	70.12± 1.08	54.72± 0.48	62.60± 1.12	76.68± 1.40	58.80± 0.92	64.54± 1.43	69.34± 1.10
45	40.16 ±0.99	81.78± 0.16	92.54± 0.79	83.32± 0.82	70.20± 0.9	76.45± 0.38	82.84± 0.86	64.32± 0.78	72.46± 0.82	78.56± 0.98
60	45.90 ±0.18	85.34± 0.56	97.80± 0.07	90.58± 0.15	78.60± 1.10	80.74± 0.08	88.30± 1.08	75.36± 0.60	82.38± 0.70	86.77± 0.89

P.D.-pure drug

3.6 FT-IR studies: The FTIR spectra of telmisartan and solid dispersion are shown in fig.4. The characteristic peaks observed are shown in Table 4. From these observations it was found that there was no interaction between drug and polymer. FT-IR study shows that drug and polymer were compatible with each other.

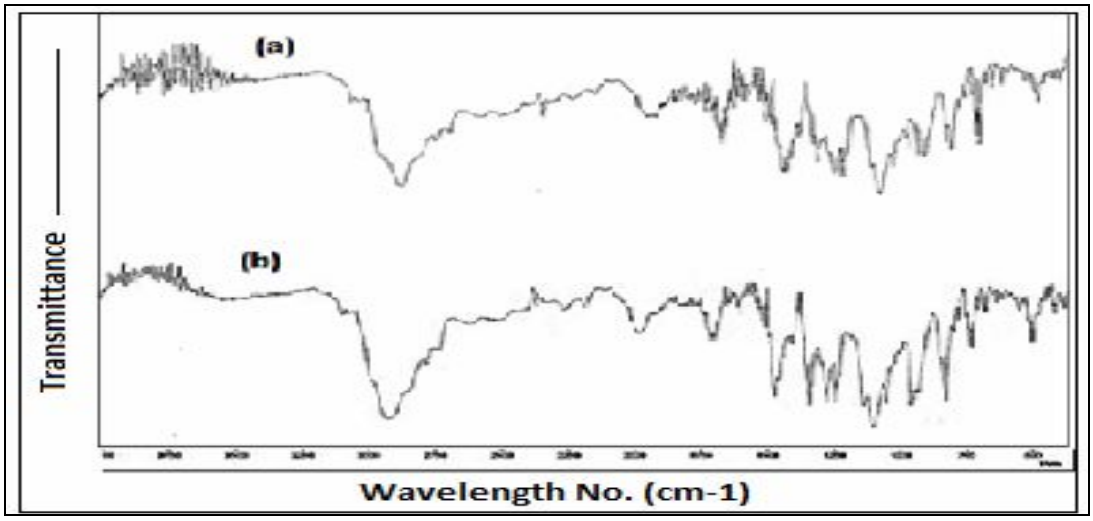

Figure 4: FT-IR spectra of a) Telmisartan b) solid dispersion.

Table 4: Principle FT-IR peaks of pure Telmisartan and solid dispersion

Functional group	Range(cm^{-1})	Pure drug(cm^{-1})	Solid dispersion(cm^{-1})
O-H Stretching	3000-3700	3059.10	3057.17
C=Stretching	1600-1900	1693.50	1693.50
C-N Stretching	1180-1360	1278.81	1276.88
CH_3 Bending	1300-1500	1342.46	1342.46

3.7 DSC studies: DSC thermograms of pure telmisartan as well as their solid dispersions prepared by kneading method are shown in fig. 5. Pure telmisartan exhibited a characteristic sharp endothermic peak at 269.06^{0}C which is associated with the melting point of the drug and sharpness of the peak indicates crystalline nature of the drug. However, the characteristic, endothermic peak corresponding to drug melting was broadened and shifted towards a lower temperature (264^{0}C) with reduced intensity in solid dispersions. This could be

recognized to higher polymer concentration and uniform distribution of drug in the polymer, resulting in complete miscibility of drug in polymer and conversion of crystalline to amorphous form.

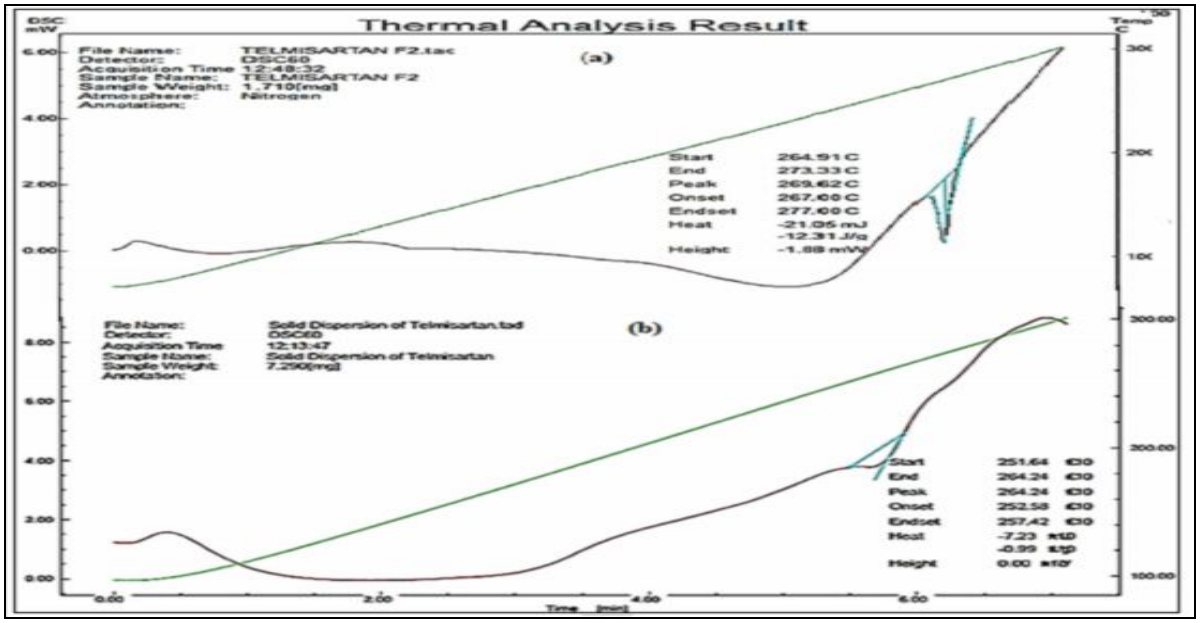

Figure 5: DSC Thermograms of a) Telmisartan, b) solid dispersion.

3.8 X-Ray Diffraction Studies (XRD): The X-ray diffract gram of puretelmisartan and formulation are shown in fig. 6. XRD pattern of pure telmisartan shows characteristic diffraction and intense peak at 19.0° and 23.0° indicating crystalline nature of telmisartan,while XRD pattern of solid dispersion exhibited decrease in peak intensity at the same point due to decrease in crystallinity. Reduced peak intensity of solid dispersion may be due to dispersion of drug in polymer.

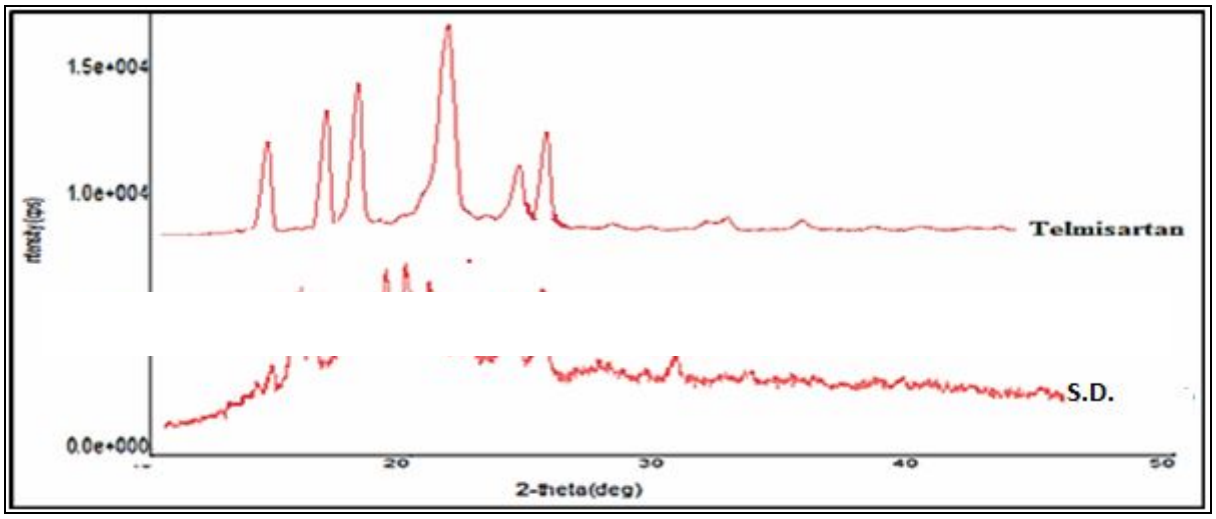

Figure 6: XRD of a) Telmisartan b) solid dispersion

3.9 Stability study: After 90 days all solid dispersion formulations were evaluated for drug content, *in –vitro* drug release, solubility study. From study it was found that all formulations did not shows any characteristic changes.

4. Conclusion

On the basis of obtained results it can be concluded that the solubility and dissolution rate of telmisartan was increased by solid dispersion technique using PEG8000 as hydrophilic carrier and all three methods exhibited enhancement of aqueous solubility and dissolution rate, out of these methods kneading method was found to be best method among studied.

Conflict of Interests

The authors declare that there is no conflict of interests in the publication of the paper.

Acknowledgement

Authors are grateful to Micro lab. Pvt. Ltd. Bangalore, India for providing the gift sample of the pure drug of telmisartan. The authors are also grateful to the Director, School of Pharmacy, S. R. T. M. University, Nanded, for providing research facilities.

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