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Design and Evaluation of Mouth Dissolving Tablets of Anti Hypertensive Drug Telmisartan

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Abstract: Telmisartan (TLM) is an angiotensin II receptor antagonist used in the treatment of hypertension. TLM mouth dissolving tablets were prepared using skimmed milk powder (SMP) and poloxamer-188 (PXM-188) as carriers and crosspovidone as super disintegrant. Mouth dissolving tablets should give fast disintegration, dissolution, ease of swallowing, quick on set of action. The prepared formulations were subjected to FTIR, DSC and XRD studies. The result indicated no interaction between drug and carriers. The XRD results showed that the drug was converted into amorphous form and uniformly dispersed throughout the carriers.
Key words: Telmisartan, skimmed milk powder, poloxamer-188, crosspovidone, kneading method, mouth dissolving tablets.

INTRODUCTION

Oral formulation has been the preferred and most common route of drug delivery around the globe. The popularity of this dosage form is owing to its ease of administration and good patient compliance. Mouth dissolving tablets will avoid missing out of dose even during traveling or other situations where there is no access to water.[1]

Telmisartan is chemically described as 4'-[(1,4'-dimethyl-2'-propyl [2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-[1,1'-biphenyl]-2-carboxylic acid. TLM is practically insoluble in water and in the pH range of 3 to 9, sparingly soluble in strong acid (except insoluble in hydrochloric acid), and soluble in strong base.[2] TLM is an angiotensin II receptor antagonist and is widely used in the management of hypertension to reduce cardiovascular motility in patients with left ventricular dysfunction following myocardial infraction and in the management of heart failure.[3,4]

The present investigation deals with the development of an effective and stable mouth dissolving tablet of TLM having adequate hardness, low disintegration time. Mouth dissolving tablets can be prepared by various conventional methods like direct compression, wet granulation, moulding, spray drying, freeze drying and sublimation. Mouth dissolving tablets disintegrate and/or dissolve rapidly in the saliva without need for water, releasing the drug. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form.[5]

In the present work an attempt is done to prepare solid dispersion of drug with SMP and PXM-188 using kneading method. The best solid dispersion will be incorporated in to mouth dissolving tablet using super disintegrant crosspovidone.

EXPERIMENTAL

Materials and Methods

Telmisartan was obtained as a gift sample from Unichem Laboratories Ltd, Raigad. Skimmed milk powder was obtained from Amul Sagar, Gujarat. Poloxamer-188 and Crosspovidone was obtained from Amneal Pharmaceuticals, Ahmedabad. Lactose and Magnesium stearate was obtained from SD-fine chemicals, Mumbai.

Preparation of telmisartan solid dispersions

Solid dispersion were prepared by kneading method. Prepared the different ratio SD of drug with SMP and PXM-188, 1:2, 1:4, 1:6, 1:8 and 1:10 respectively in a mortar with methanol and water mixture (1:1, by volume). Then kneaded the wet mixture thoroughly with a pestle to obtain a paste like consistency. The paste was then dried under vacuum at room temperature, pulverized by passing through sieve no. 80 and stored in a dessicator till further use.[6]

Evaluation parameters for solid dispersion

Fourier Transform infrared spectroscopy (FTIR):
The drug-carrier mixtures of telmisartan were prepared in the form of KBr pellets and subjected for scanning from 4000 cm-1 to 400 cm-1 using FTIR spectrophotometer.

Differential scanning calorimetry (DSC):
Approximately 2 mg of telmisartan or drug-carrier mixture was taken in aluminium pan, sealed with aluminium cap and kept under nitrogen purging (atmosphere). Both the samples were scanned from 50-400 °C with the scanning rate of 10 °C rise/min using differential scanning calorimeter (DSC-60, Shimadzu, Japan).

Powder X-Ray Diffraction studies (XRD):
The powder XRD of the telmisartan and solid dispersion formulations were recorded using an X-ray diffractometer. The scanning rate was 5º/min and diffraction angle (2θ) was 0 to 50ºC.

Drug content
Equivalent to 20 mg of the drug was weighed accurately, dissolved in 0.1 N NaOH and suitably diluted with phosphate buffer solution of pH 6.8. The content of Telmisartan was determined spectrophotometrically at 292 nm against blank using UV-visible spectrophotometer (1601, Shimadzu, Kyoto, Japan).

***In vitro* dissolution studies of Solid Dispersion**
The quantity of solid dispersion equivalent to 20 mg of telmisartan was placed in dissolution medium. The dissolution study of solid dispersion was conducted using dissolution testing apparatus II (paddle method) in 500 ml of phosphate buffer solution of pH 6.8 at 37ºC and at a speed of 50 rpm. Aliquots of 5 ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain a constant volume after each sampling and analyzed spectrophotometrically at 292 nm against suitable blank using UV-visible spectrophotometer (1601, Shimadzu, Kyoto, Japan).

Solubility analysis
Excess amount drug and solid dispersion (equivalent to 20 mg drug) was added to 100 ml conical flask containing 25 ml distilled water. The system was agitated on a rotary shaker for 24 h at 100 rpm maintained at room temperature and filtered. The filtrate was suitably diluted and analyzed on a UV-Spectrophotometer at 292 nm.

Preparation of mouth dissolving tablets
Solid dispersion of telmisartan with skimmed milk powder and poloxamer-188 equivalent to 20 mg of drug prepared by kneading method were taken and mixed with directly compressible diluent, superdisintegrant. Powder blend were directly compressed using 10.05 mm, round-shaped flat punch in a single station tablet compression machine (Cadmach, Ahmedabad, India). The weight variation, hardness, disintegration tests, friability and drug content of the prepared tablets were tested according to USP.

Evaluation Parameters for Mouth Dissolving Tablets of Telmisartan
The tablets were evaluated for hardness, weight variation, friability, wetting time, disintegration and *in vitro* drug dissolution. The crushing strength of the tablets was measured by a Monsanto hardness tester, and friability by Roache Friabilator with 10 tablets.

***In vitro* dissolution studies of prepared tablets formulations**
In-vitro dissolution study was performed by using USP dissolution testing apparatus II (Paddle

method) using 500 ml of phosphate buffer solution of pH 6.8 as dissolution medium. Temperature of the dissolution medium was maintained at 37°C, A series of triplicate samples (5 ml) were withdrawn at every 5 min interval and filtered. The absorbance of filtered solution was measured by UV spectrophotometric method at 292 nm and concentration of the drug was determined from calibration curve equation.

Table 1: Formulation of telmisartan mouth dissolving tablets prepared by solid dispersion method

Ingredient (mg)	F1	F2	F3	FS	F4	F5	F6	FP
SD TLM-SMP	120	120	120	120	---	---	---	---
SD TLM-PXM-188	----	----	----	----	200	200	200	200
Lactose	132	129	125	137	52	49	46	57
Crosspovidone	5.6	8.4	11.2	0	5.6	8.4	11.2	0
Mg stearate	3	3	3	3	3	3	3	3

Table 2: Evaluation parameters for mouth dissolving tablets of telmisartan

Formulation code	Weight variation (mg)	Friability (%)	Hardness (kg/cm^2)	Wetting time (sec)	Disintegration time (sec)	Drug content (%)
F1	260.63±1.70	0.384	3.50±0.36	21±1.00	35±1.00	100.28±2.70
F2	259.16±1.23	0.772	3.20±0.26	13±1.00	24±3.05	98.70±3.92
F3	260.03±1.86	0.461	3.56±0.35	16±1.15	30±2.50	99.16±1.28
FS	259.56±2.28	0.424	3.73±0.20	53±3.60	232±2.51	99.85±4.96
F4	259.36±0.90	0.579	4.00±0.20	23±1.52	39±3.05	96.50±2.29
F5	260.60±0.81	0.810	4.16±0.30	18.1.52	34±1.52	98.90±2.10
F6	260.53±1.84	0.557	4.33±0.15	19.2.08	33±3.00	99.60±2.39
FP	259.76±3.14	0.926	4.36±0.15	60.3.00	479±3.60	98.18±2.38

Table 3: Dissolution parameters of mouth dissolution tablets of telmisartan with different formulations in the phosphate buffer solution pH 6.8 as dissolution medium.

Formulation Code	Dissolution efficiency		Mean Dissolution Time(min)	$t_{50\%}$ (min)	$t_{90\%}$ (min)
	15min	30min			
TLM	71.87	63.90	11.74	ND	ND
F1	72.28	71.31	14.56	12.28	40.24
F2	72.05	67.84	13.15	10.9	34.2
F3	70.64	65.92	10.22	8.72	28.13
FS	64.87	67.38	20.11	17.55	56.38
F4	71.44	69.59	15.15	13.14	46.42
F5	70.96	70.28	9.89	7.85	25.32
F6	67.42	71.10	8.66	6.86	22.4
FP	67.71	68.85	18.71	16.38	57.47

*pure drug dissolution with 1% SLS, ND-Not Determined

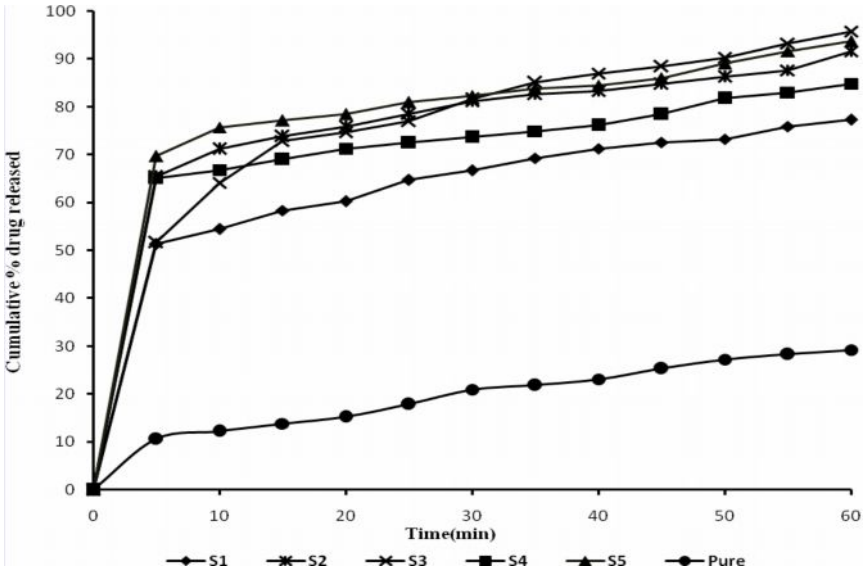

Figure 1: *in vitro* drug release profile of TLM and its solid dispersion with SMP by kneading method

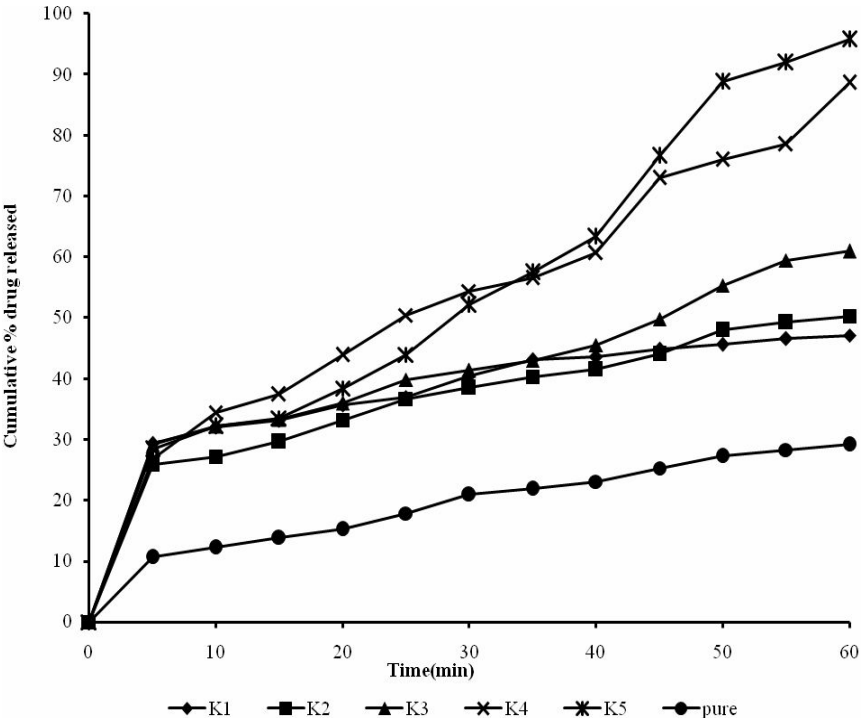

Figure 2: *In vitro* drug release profile of TLM and its solid dispersion with PXM-188 by kneading method

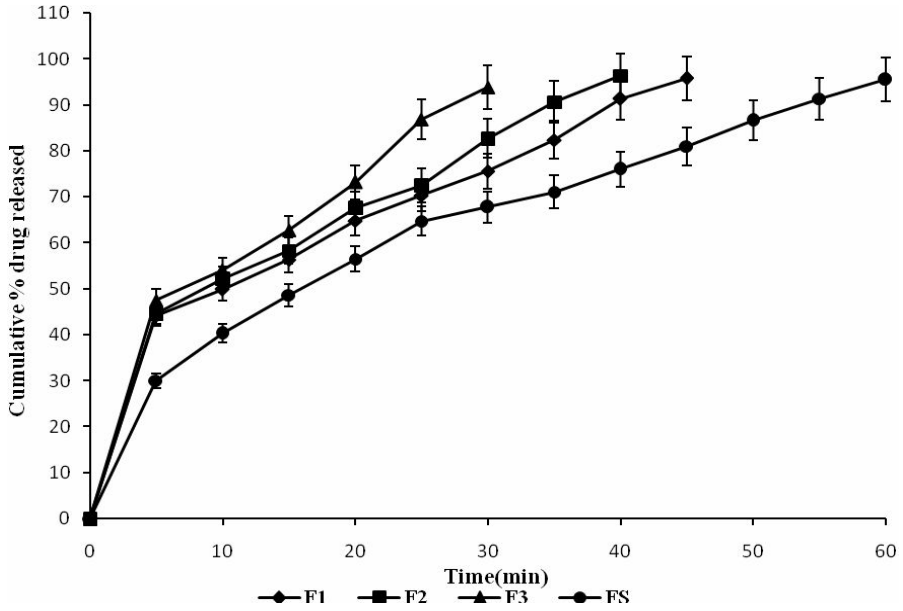

Figure 3: *In vitro* drug release profile of formulations F1, F2, F3 and FS by using different concentration of superdisintegrants

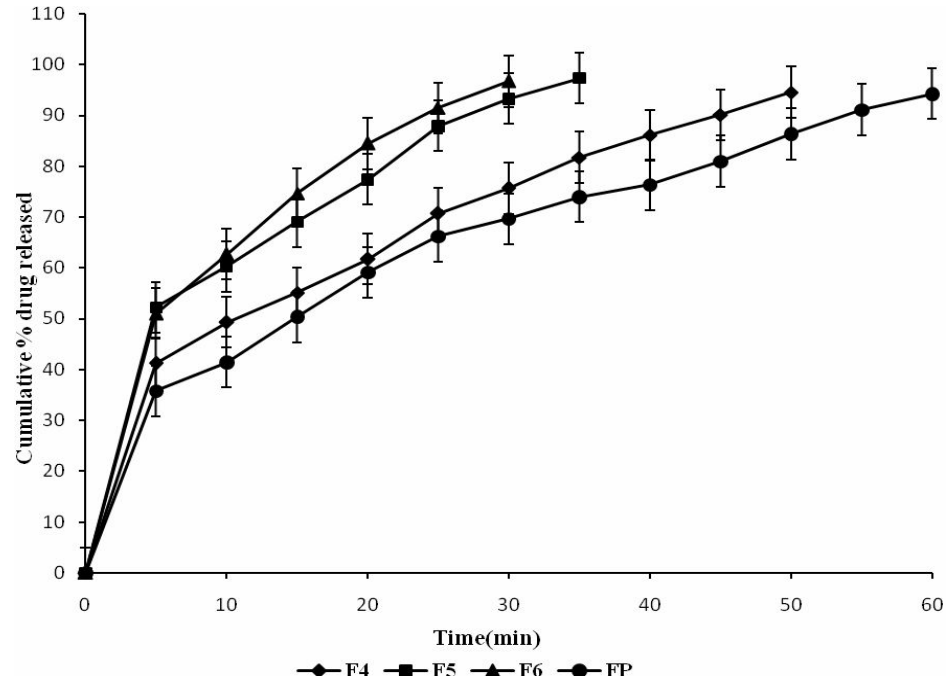

Figure 4: *In vitro* drug release profile of formulations F4, F5, F6 and FP by using different concentration of superdisintegrants

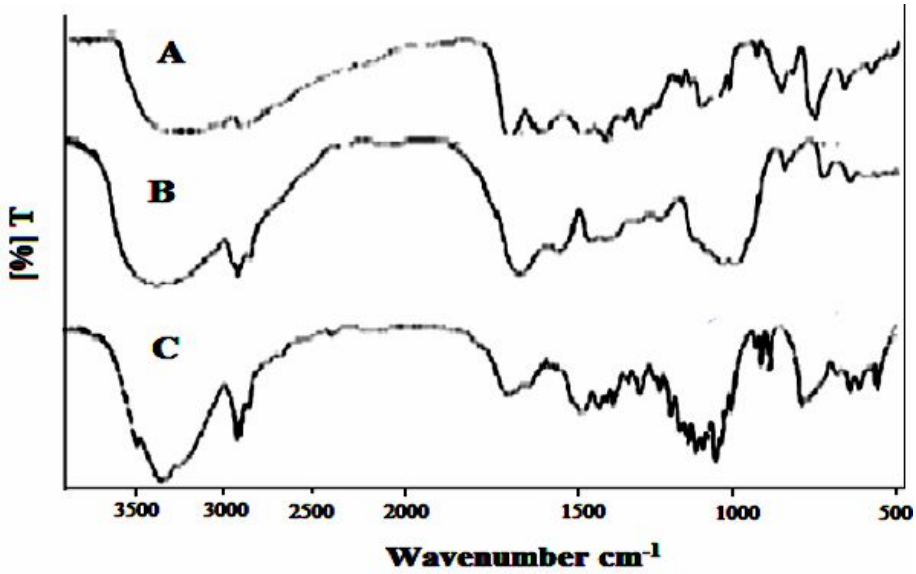

Figure 5: FTIR spectra of pure Drug (A), SMP (B), and Solid dispersion (C)

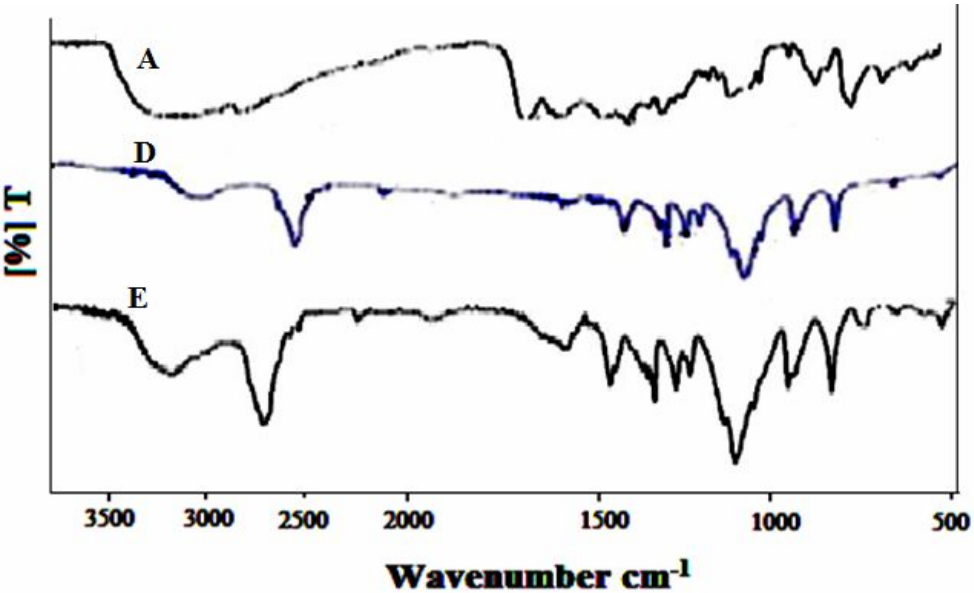

Figure 6: FTIR spectra of pure Drug (A), PXM-188 (D), and Solid dispersion (E)

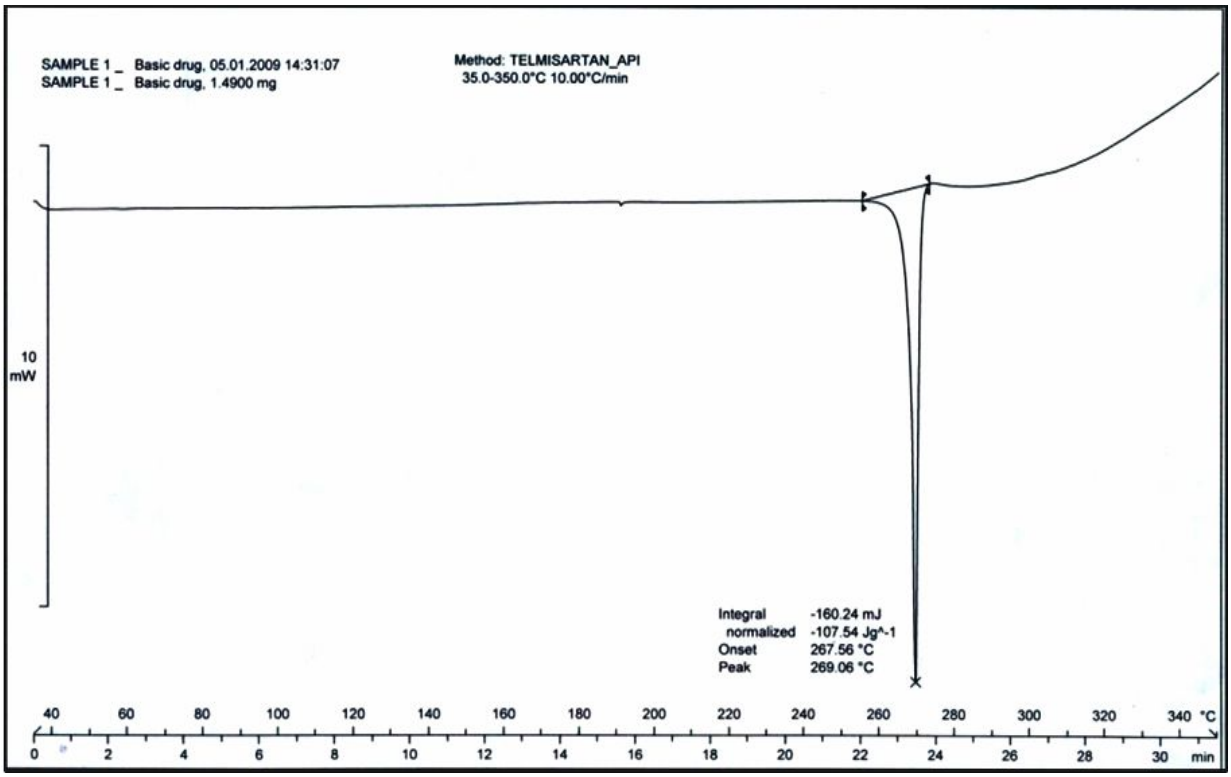

Figure 7: DSC thermogrames of the pure telmisartan

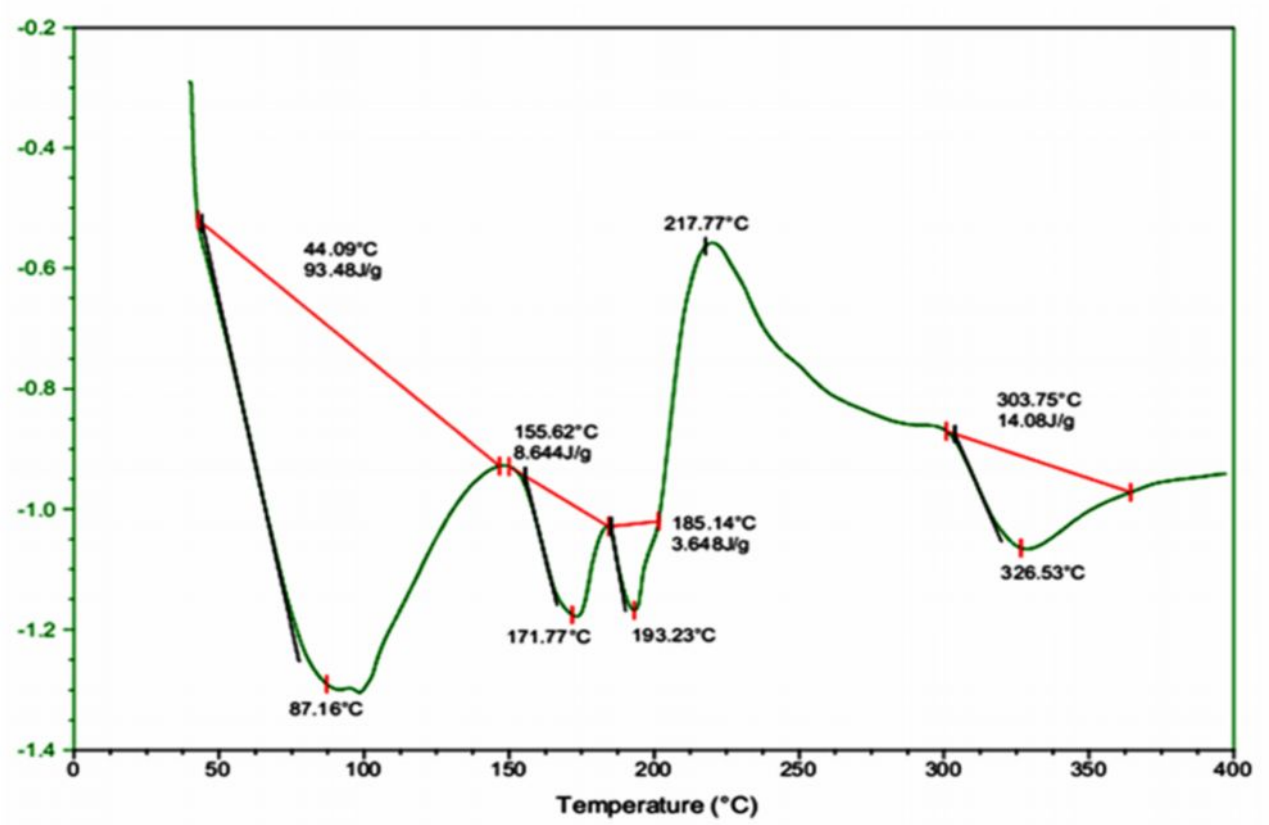

Figure 8: DSC thermogrames of pure SMP

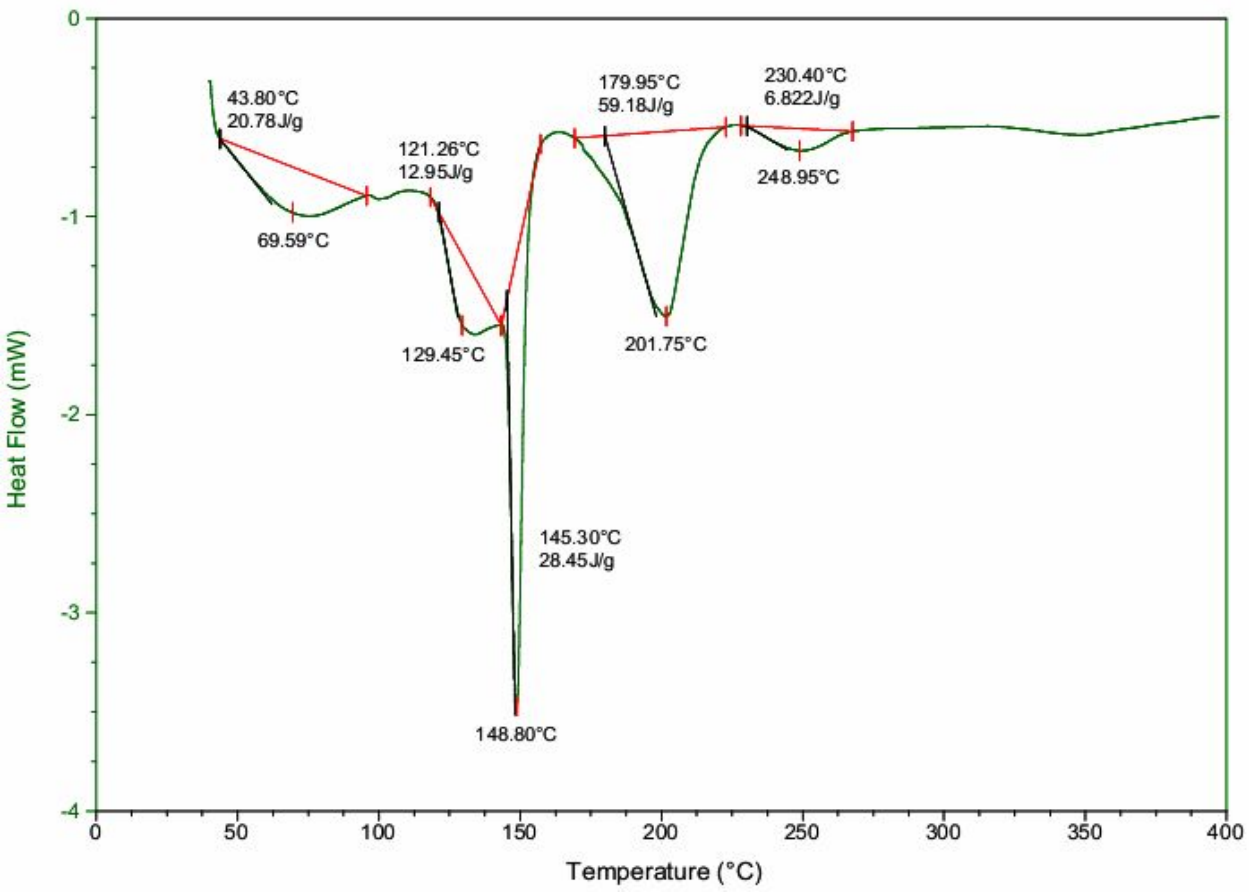

Figure 9: DSC thermogrames of solid dispersion with SMP by kneading method

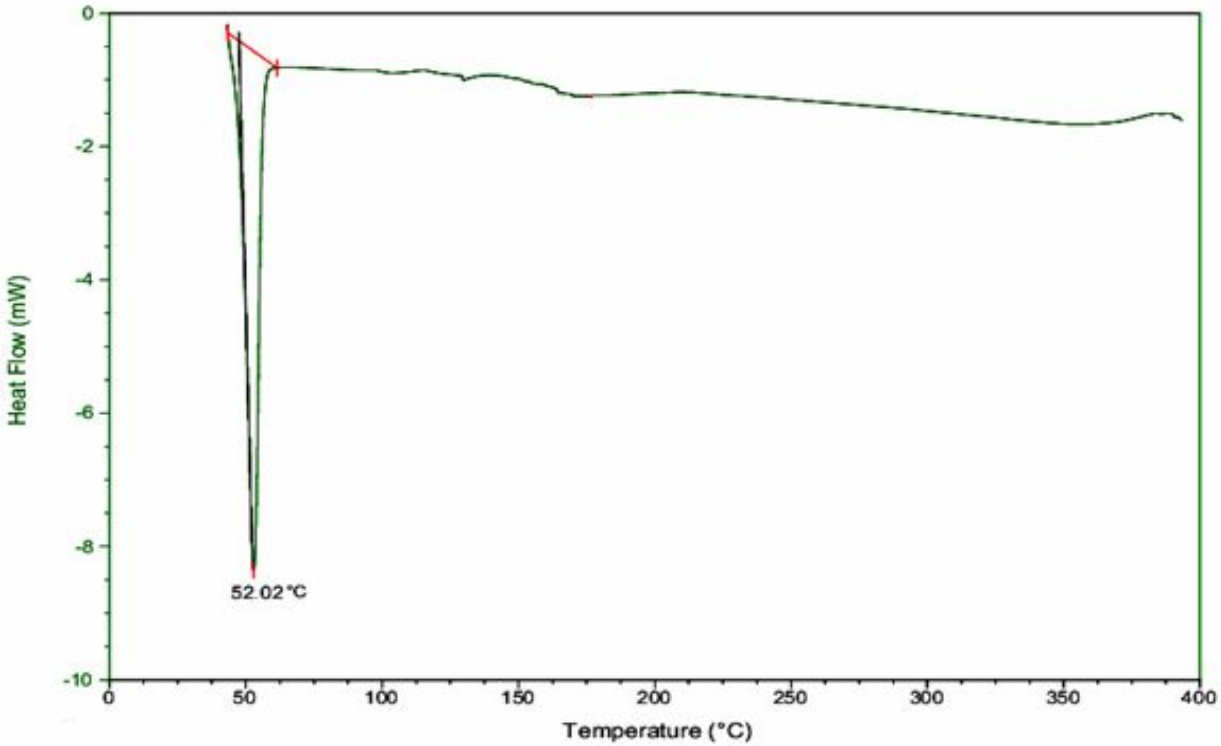

Figure 10: DSC thermogrames of pure PXM-188

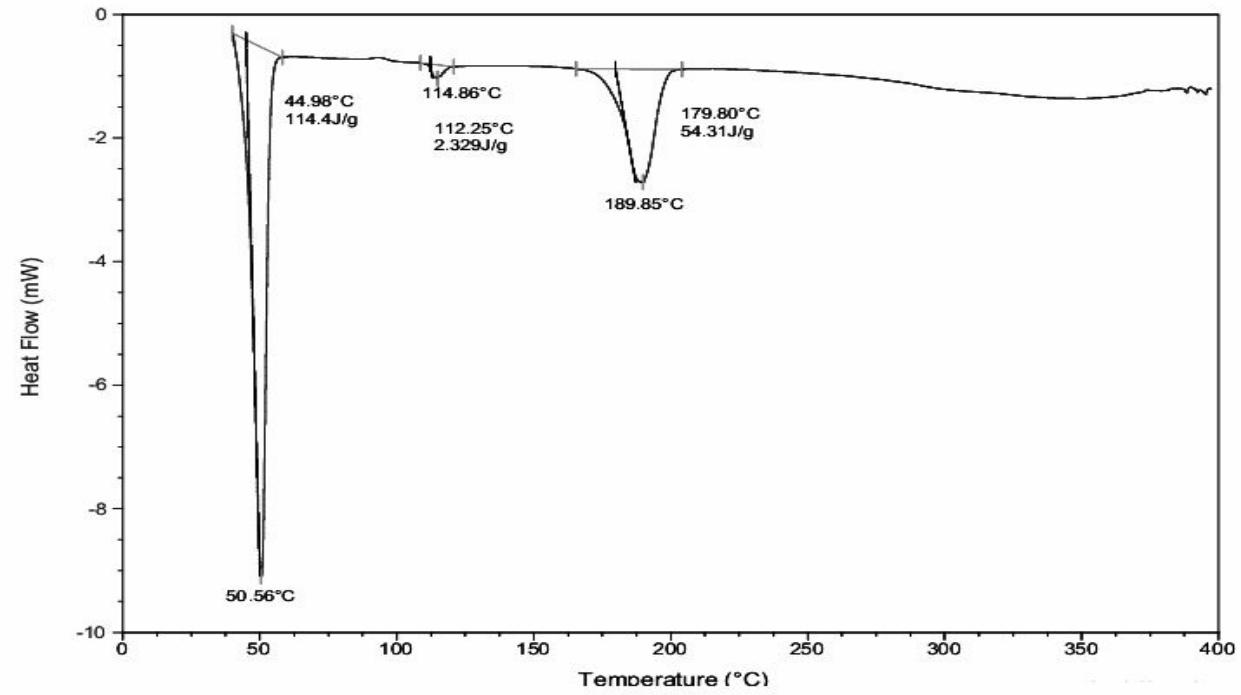

Figure 11: DSC thermogrames of solid dispersion with PXM-188 by kneading method

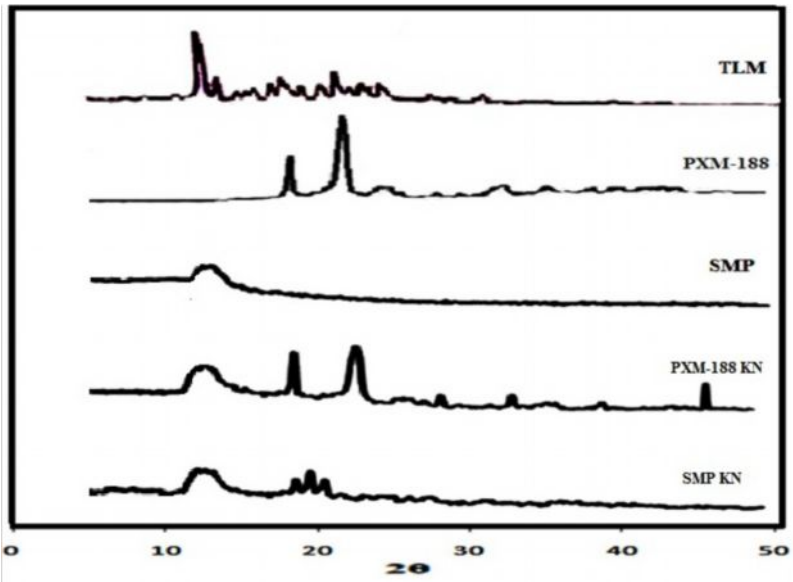

Figure 12: XRD spectra of pure TLM, SMP, PXM-188 and solid dispersion formulations kneading method with SMP and PXM-188

RESULTS AND DISCUSSIONS

Fourier Transform infrared spectroscopy (FTIR): Infrared spectrum of pure telmisartan is shown in figure 2. The following characteristic peaks were observed in IR spectra of telmisartan and its solid dispersion with SMP and PXM-188 (figure 5and 6). The characteristic absorption peak of TLM was obtained at 2957 cm^{-1} due to C-H stretching vibration of aromatic group. Other characteristic peaks were obtained at 2871 cm^{-1} due to C-H stretching of aliphatic group, -OH bending and –C=O stretching of – COOH acid at 1388 cm^{-1}, C=C stretching of aromatic group at 1599 cm^{-1} and functional group of (-COOH) at 1667 cm^{-1}.

By comparing the FTIR spectrum of TLM and its solid dispersion with SMP and poloxamer-188 it can be seen that all the characteristic absorption bands of TLM were retained so it can be concluded that there was no chemical interaction between TLM and polymers.

Differential scanning calorimetric (DSC) study:
DSC was used to assess the thermal behavior of the drug (TLM) and its solid dispersion prepared. In figure 4, DSC thermogram of telmisartan shows a single sharp characteristic endothermic peak (Tpeak = 269.06°C) corresponding to its melting, indicating its crystalline nature and a single peak indicates that the drug sample is free from impurities.
However, the characteristic endothermic peak corresponding to drug melting was broadened and shifted toward lower temperature with reduced intensity in the solid dispersion prepared by kneading method (Figures 8-11). This could be attributed to higher polymer concentration and uniform distribution of drug in the crust of carrier, resulting in complete miscibility of drug in the carrier.

Powder X-Ray Diffraction studies
XRD patterns of TLM, SMP, PXM-188 and its solid dispersion prepared by kneading method is shown in Figure 12. The diffraction pattern of telmisartan revealed several sharp high intensity peaks at diffraction angles (2θ) of 6.8, 9.7, 14.23, 14.2, 15.1, 16.2, 18.3, 20.7, 22.3, and 25.1 suggesting that the drug existed as crystalline material.
The XRD pattern of TLM and its solid dispersion with SMP and PXM-188 prepared by kneading method. The few characteristic peaks of telmisartan with considerable reduction in the peak intensity. This diminished peak suggests conversion of drug into amorphous form. This marked reduction in peak intensities provides an explanation for the significant increase in the dissolution rates by solid dispersion preparation.

Evaluation of tablets:
The hardness of the tablets was measured by using Monsanto hardness tester and was ranged between 3.20±0.26 to 4.36±0.15 Kg/cm^2. The weight variation of all the formulation was passed within Pharmacopoeial limit of ±5% of the weight. The test for friability of all the tablets formulation lies in the range of 0.38 % to 0.92 % (less than 1 %) indicating good mechanical strength of tablets. The average wetting time of all the formulations was obtained in the range of 13 to 23 sec. Disintegration time of all the formulations was obtained in the range of 24±3.05 to 39±3.05 sec.

Drug content uniformity
Drug content uniformity study data is shown in the Table 2. The content uniformity for all the formulations prepared by using different concentration of superdisintegrant was found to be in the range of 96.50±2.29 % to 100.28±2.70 % which showed that there was uniform distribution of the drug in tablets of all formulations.

***In vitro* drug dissolution studies**
Finally, the tablets were evaluated for *in vitro* dissolution studies in phosphate buffer solution pH 6.8. The formulation FS and FP prepared without superdisintegrant showed about 95 % and 94 % of drug release within 60 min respectively. The average dissolution study data of all the formulations prepared by using different concentration of superdisintegrant. Among all the formulations F1 to F3 prepared with different concentration of superdisintegrant showed 93.83±1.96 % to 96.31±0.99 % drug release within 45 min and F4 to F6 prepared with different concentration of superdisintegrant showed 94.51±2.09 % to 97.30±1.49 % drug release within 50min respectively. This result suggests a direct relationship of concentration of superdisintegrants with drug release. As the amount of superdisintegrant increases in the acceptable range, the drug release also increases.

Model independent kinetic parameters:
The dissolution efficiency for all formulations in 15 min ranged from 64.87 to 72.28% and mean dissolution time ranged from 8.66 min to 20.11 min. Among formulation F1, F2, F3 and FS, formulation F2 showed higher dissolution efficiency 72.05% in 15 min and disintegration time of 24±3.05 sec. Among formulations F4, F5, F6 and FP, formulation F5 showed good dissolution efficiency in 15 min 70.69% and disintegration time of 33±3.00 sec. Hence formulation F2 and F5 were selected as optimized formulations.

CONCLUSION:

The concepts of formulating mouth dissolving tablets of telmisartan offers a suitable and practical approach in serving desired objectives of faster disintegration and dissolution characteristics.
In the present work, Mouth dissolving tablets of telmisartan were prepared by direct compression technique using SMP and PXM-188 as a solubilizing agents, Crosspovidone as Superdisintegrant.
In the kneading method using hydrophilic carriers such as SMP and PXM-188 were employed to enhance solubility and dissolution rate. The evaluated parameters showed decrease in crystallinity of TLM. The solid dispersion prepared

by kneading method showed a most effective method showing a better solubility and dissolution rate compared to other methods.
Finally, we can conclude that, among various formulations prepared, the mouth dissolving tablets prepared by kneading method using SMP and PXM-188 contained crosspovidone (6%) F2 and F5 disintegrated rapidly and gave highest dissolution of Telmisartan within a short period of time.

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