ORIGINAL ARTICLE

Formulation and evaluation of multiparticulate drug delivery systems comprising telmisartan

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Telmisartan is poorly soluble in water, and the rate of dissolution, as well as bioavailability, is less. In the present study, an attempt has been made to improve the dissolution of the drug by coating the drug and carrier over sugar pellets. The solubility promoters such as alkalizes, binders and surfactants were selected to make the drug solution. The prepared pellets were evaluated for their physicochemical properties and *in-vitro* dissolution. The drug release rate was found to be more from the pellets coated with the coating solution containing the sodium hydroxide, Tween 80 and hydroxypropyl methylcellulose. The optimized pellet formulation was selected for stability study, and the *in-vitro* dissolution study showed that was no difference in percent of drug released between initial and 6th month sample.

Key words: *Alkalizers, in-vitro dissolution, multiparticulate, telmisartan*

INTRODUCTION

Telmisartan is angiotensin II receptor antagonist, which is used in the prevention and treatment of hypertension. Telmisartan (TLM) belongs to class II drug in BCS classification, that is, the low solubility and high permeability. One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration. TLM is practically insoluble in water.[1] Absolute bioavailability of the TLM was 42–58% and the biological half-life are only 24 h that results into poor bioavailability after oral administration. Poor solubility of TLM leads to poor dissolution and hence variation in bioavailability. Thus increasing aqueous solubility and dissolution of TLM is of therapeutic importance. TLM is readily ionizable drug having pH-dependent solubility. The solubility of ionizable TLM was dependent on pH and was high in strong acidic or basic conditions, but very low under neutral conditions. Interestingly, incorporating 1% alkalizers greatly increased drug solubility compared to the addition of acidifiers.[2] For this reason, alkalizers were selected as pH modifiers to increase the dissolution rate of ionizable TLM. Further, literature survey revealed various techniques like preparation of solid dispersions,[3-10] cyclodextrin complexation,[11-12] preparation of fast dissolving tablets[13-15] and preparation of nanodispersion by spray drying[16] for the improvement of solubility of TLM. The aim of the present work was to develop TLM pellets to improve its water solubility, dissolution and bioavailability.

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MATERIALS AND METHODS

Materials

Telmisartan was obtained from Aescul Pharma, Ongole, India. All other chemicals and reagents used were of analytical grade.

Selection of suitable components

Preliminary study trials were carried out for the formulation of TLM pellets using different solvents, different surfactants, different alkalizers and different binders.

The solubility of TLM in various solvents (0.1N HCL, pH 4.5 acetate buffers, pH 7.5 phosphate buffer and distilled water), surfactants (0.5, 1, 1.5 and 2% w/v concentrations of Tween 80, Tween 20 and sodium lauryl sulfate), alkalizers (1% w/v solution of aqueous sodium hydroxide, potassium hydroxide and sodium

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bicarbonate) and binders (2% w/v solutions of hydroxypropyl methylcellulose 5cps, hydroxyl ethyl cellulose and polyvinyl pyrrolidone) was measured. Five milliliter of each solution was taken in test tubes, and an excess amount of TLM was added to obtain saturated solutions. The solutions were kept aside for 24 h, centrifuged, and the supernatant liquid was collected, analyzed at 296 nm by using UV-visible spectrophotometer. The experiment was repeated in triplicates. Results were represented as mean values (mg/ml ± standard deviation).

Preformulation studies

Compatibility

Accelerated storage test (40 ± 2°C/75 ± 5% RH and 60 ± 2°C/80 ± 5% RH).

Duplicates of drug and excipients mixture were taken in the amber colored bottle; these mixtures were kept in the accelerated storage condition in which one bottle is closed with aluminum foil and other one in an open condition. After 2–4 weeks, the mixtures were observed for any physical change.

Infrared red spectrum

The physicochemical compatibility between TLM and the excipients used in research was tested by infrared (IR) spectroscopy using Bruker Fourier transform IR spectrophotometer. The samples were scanned under diffuse reflectance mold directly. The spectra were recorded in the wave number region between 4400/cm and 400/cm. The individual spectra obtained for TLM pure drug and excipients were compared with the spectra of the prepared TLM pellets.

Preparation of telmisartan loaded pellets

Powder layering technique was used to prepare TLM loaded pellets. TLM and selected alkalizer, surfactant and binder were dispersed in distilled water according to the quantities mentioned in Table 1 and was used as coating solution. Sugar pellets were loaded into the coating pan and when the temperature of the coating pan reached about 70°C spraying of the drug solution was started. The pressure was adjusted to 0.1 atm and the spray rate was maintained at 0.1 ml/min and the pan speed was maintained at 15 rpm. The coating process was continued till all the drug solution was deposited on the sugar pellets. The solvent evaporates by leaving the drug on sugar pellets. They were dried in hot air oven at 70°C for 30 min.

Evaluation of telmisartan loaded pellets

Yield of pellets

The yield of the spheroids was determined as a percentage of the ratio of the final weight obtained after the production processes and the initial weight of the powder blend.

Moisture content

One gram of pellets were weighed and kept in an oven at 70°. Its weight was noted as initial weight (W_1). They were removed from the oven after regular tine intervals of 15 min and weighed. Loss in weight of pellets was noted. After attaining a constant weight, it was noted as final weight (W_2) and percent moisture content was calculated.

Friability

Roche friabilator was used to determine the friability. Preweighed pellets were placed in friabilator and rotated at a speed of 25 rpm for 4 min or up to 100 revolutions. The pellets were then reweighed after removal of fines and the percentage of weight loss was calculated.

Angle of repose, bulk and tapped density

Angle of repose was determined by two-sided open end cylinder method; bulk density and tapped density were determined by tapping methods.

Estimation of drug loading efficiency

One hundred milligram of pellets were taken in a mortar, crushed and mixed thoroughly with 10 ml of methanol, the solution was filtered and the filtrate was collected. It was suitably diluted with water, and absorbance was noted at 296 nm using a UV-visible spectrophotometer. The amount of the drug present in pellets was calculated from the calibration curve.

In-vitro dissolution studies

In-vitro dissolution studies for various formulations were performed in triplicate in dissolution rate testing apparatus (Electrolab) at 37 ± 0.5° employing USP apparatus type II at 75 rpm. Pellets equivalent to 40 mg of the drug were weighed and kept in the dissolution bowel containing

Table 1: Composition of telmisartan loaded pellets

Ingredients	Quantity (mg)									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Telmisartan	40	40	40	40	40	40	40	40	40	40
Sodium hydroxide	20	40	20	40	20	40	20	40	30	30
Tween 80	20	20	80	80	50	50	50	50	20	80
HPMC 5cps	50	50	50	50	20	20	80	80	20	20
Sugar pellets (18#20)	200	200	200	200	200	200	200	200	200	200
Water	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS
Total	330	350	390	410	330	350	390	410	310	370

HPMC: Hydroxypropyl methycellulose, QS: Quantity sufficient

900 ml of dissolution media (pH 7.5 phosphate buffer). Percent drug released was determined by taking an aliquot of 5 ml at different time intervals (5, 10, 15 and 20 min). An equal volume of the fresh dissolution medium was replaced to maintain the original volume. The samples were suitably diluted for estimating percent released and analyzed at 296 nm using UV-visible spectrophotometer.

Stability study

Stability study was conducted as per International Conference on Harmonization guidelines. The selected formulation was subjected to real-time (25 ± 2°C/60 ± 5% RH) and accelerated stability (40 ± 2°C/75 ± 5% RH) test. After specified period of time (1, 2, 3, 4, 5, 6 month), samples were withdrawn and *in-vitro* dissolution study was conducted.

Powder X-ray diffraction

To evaluate the changes in the crystallinity of the components of formulation prepared, the powder X-ray diffraction (XRD) study was carried out by using X-ray diffractometer. The samples of pure TLM drug and prepared TLM pellets were taken and irradiated with monochromatized CuK radiation and analyzed between from 5° to 50°.

RESULTS AND DISCUSSIONS

Solubility studies were aimed at identifying suitable excipients for the development of the TLM pellets. The solubility of TLM in various solvents, surfactant solutions, alkalizer solutions and binder solutions were presented in Table 2. Based on the solubility, sodium hydroxide, Tween 80 and hydroxypropyl methylcellulose 5cps were selected for the development.

The accelerated storage test showed that there were no physical changes (color and appearance) in the mixture after 2 and 4 weeks.

The IR spectrums of TLM pure drug and TLM loaded pellets were presented in Figures 1 and 2. There was no appearance or disappearance of peaks in the spectrum of TLM pellets when compared to pure TLM drug spectrum in the IR study. These show that there was no interaction between drug and excipients used in the formulation.

From the physical properties and flow properties of the TLM loaded pellets presented in Tables 3 and 4, it was revealed that all the pellets exhibited good flow properties, and the drug loading efficiency was also good. The results obtained in the *in-vitro* drug release for the formulations F1 to F10 and TLM pure drug were showed in Figure 3. The drug release from all the formulations F1 to F10 was

Table 2: Solubility data of telmisartan in various solvents and excipient solutions

Excipient solution	Solubility (µg/ml)
Distilled water	0.41±0.03
pH 0.1N HCL	4.1±0.02
pH 4.5 acetate buffer	2.01±0.01
pH 7.5 phosphate buffer	2.63±0.02
Tween 80 (0.5%)	0.738±00.031
Tween 80 (1%)	1.15±0.02
Tween 80 (1.5%)	1.4±0.01
Tween 80 (2%)	1.7±0.042
Tween 20 (0.5%)	0.42±0.02
Tween 20 (1%)	0.96±0.033
Tween 20 (1.5%)	1.19±0.011
Tween 20 (2%)	1.41±0.052
Sodium lauryl sulfate (0.5%)	0.395±0.011
Sodium lauryl sulfate (1%)	0.570±0.021
Sodium lauryl sulfate (1.5%)	0.620±0.045
Sodium lauryl sulfate (2%)	0.99±0.032
Sodium hydroxide	16.96±0.3
Potassium hydroxide	8.72±0.45
Sodium bicarbonate	1.80±0.011
HPMC 5cps	0.092±0.0011
Polyvinyl pyrrolidone	0.020±0.0025
Hydroxy ethylcellulose	0.0045±0.0037

HPMC: Hydroxypropyl methycellulose

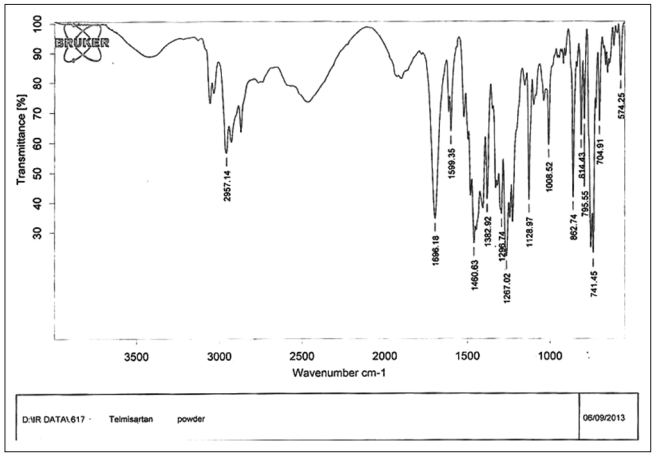

Figure 1: Fourier transform-infrared spectrum of telmisartan pure drug

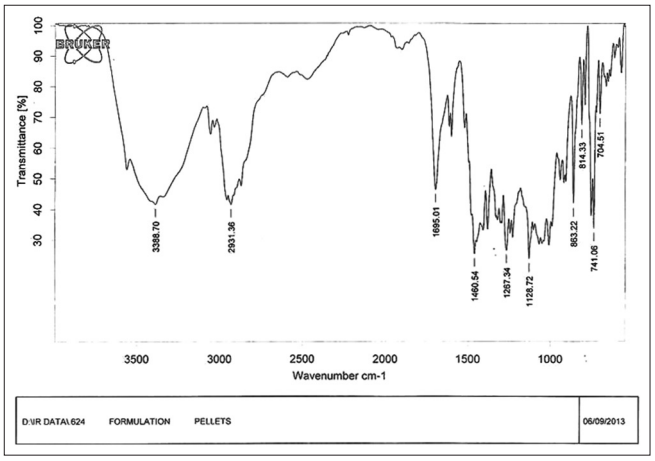

Figure 2: Fourier transform-infrared spectrum of telmisartan loaded pellets

higher compared to TLM pure drug. Formulations F2 and F9 showed highest percent of drug release (97.55%) by the end of 20 min. However, F9 showed faster dissolution compared to F2 by the end of 15 min. The dissolution rate from the formulations followed first order kinetics and the drug release rate, the dissolution efficiency, the time required to dissolve 50% and 90% of the labeled claim values were calculated and presented in Table 5. The *in-vitro* dissolution parameters are treated statistically with one-way ANOVA and the results indicated that the differences in dissolution rate are statistically significant. Among the prepared formulations, the formulations containing the high amount of alkalizing agent, low concentration of surfactant and binder offered rapid dissolution rate.

Table 3: Physical properties of telmisartan loaded pellets

Formulation	Yield of pellets (%)	Drug loading efficiency (%)	Friability (%)	Moisture content (%)
F1	93.11	89.02	0.47	1.1
F2	87.03	98.04	0.36	1.7
F3	94.26	88.01	0.51	1.5
F4	96.00	89.14	0.40	1.4
F5	88.43	93.27	0.71	1.4
F6	98.07	98.01	0.12	1.7
F7	95.51	80.72	0.36	1.6
F8	87.03	95.16	0.33	1.7
F9	96.11	97.04	0.82	1.3
F10	85.23	89.05	0.90	1.9

Table 4: Flow properties of telmisartan loaded pellets

Formulation	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Angle of repose (θ)
F1	0.515	0.608	26.4
F2	0.520	0.606	26.9
F3	0.526	0.617	26.7
F4	0.526	0.624	25.8
F5	0.532	0.633	27.5
F6	0.537	0.613	25.1
F7	0.543	0.611	25.5
F8	0.510	0.599	25.7
F9	0.515	0.610	25.1
F10	0.510	0.623	27

Formulation F9 was selected for stability study. *In-vitro* dissolution results of 6th month stability sample showed that there was no significant change in drug release between initial sample (97.55% drug release), real-time sample (95.64% drug release) and accelerated study sample (94.37% drug release). The results indicated the formulations were stable under the tested conditions of storage.

X-ray diffraction patterns of TLM and its pellets were shown in Figure 4. The diffraction pattern of TLM revealed several sharp high-intensity peaks suggesting that the drug existed as crystalline material.

The XRD pattern of TLM pellets revealed few characteristic peaks of TLM with a considerable reduction in the peak intensity. This diminished peak suggests conversion of the drug into amorphous form. This marked reduction in peak intensities provides an explanation for the significant increase in the dissolution rate.

CONCLUSION

Telmisartan pellets were formulated by coating the TLM on sugar pellets using a conventional coating pan. Various evaluation tests like yield, drug loading efficiency, moisture content and flow properties were performed on the TLM loaded pellets. All the pellets exhibited good flow properties and the drug loading efficiency was also good.

Infrared study revealed the compatibility of the drug with excipients. XRD diffractogram of the pellets revealed a decrease in crystallinity of the drug reflecting the amorphization of the drug. Stability studies revealed that the product does not undergo degradation on storage and hence expected to maintain the integrity during storage with reasonable shelf life.

Table 5: *In-vitro* dissolution kinetics of telmisartan pellets formulated F1-F10

Formulation	T_{50} (min)	T_{90} (min)	DE_{15} (%)	Correlation coefficient values			K (/min)
				Zero	First	Hixson-Crowell cube root	
F1	6.8	22.5	62.74	0.7323	0.9120	0.8576	0.1022
F2	3.5	11.5	74.91	0.5675	0.9053	0.7896	0.2002
F3	6.4	21.4	59.17	0.7173	0.9096	0.8514	0.1077
F4	5.1	16.8	61.90	0.8166	0.9374	0.8989	0.1369
F5	5.1	17.0	61.43	0.8172	0.9372	0.8595	0.1352
F6	6.3	20.8	58.69	0.7531	0.9385	0.8867	0.1108
F7	8.4	27.6	51.30	0.7646	0.9096	0.8658	0.0827
F8	4.5	14.9	68.46	0.6650	0.9299	0.8489	0.1547
F9	3.2	10.6	70.72	0.8141	0.9849	0.9436	0.2175
F10	5.4	18.0	61.07	0.7960	0.9021	0.8661	0.1277

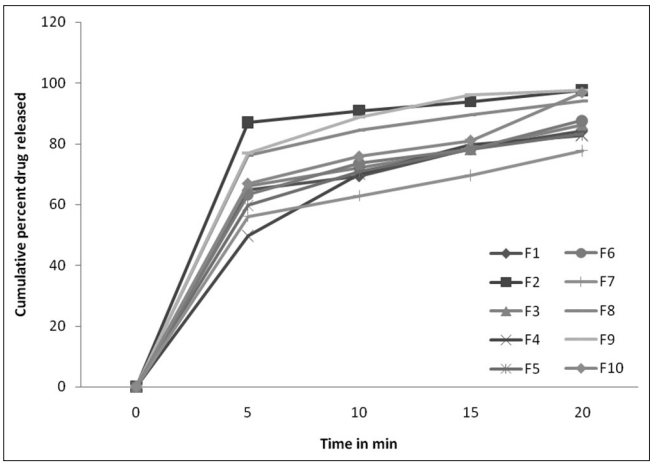

Figure 3: *In-vitro* drug release profiles of telmisartan loaded pellets

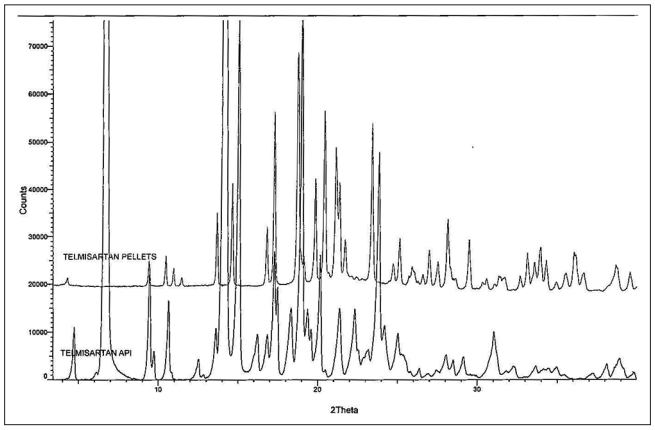

Figure 4: X-ray diffraction pattern of telmisartan pure drug and telmisartan pellets

REFERENCES

1. Sekar V, Chellan VR. Immediate release tablets of telmisartan using superdisintegrant-formulation, evaluation and stability studies. Chem Pharm Bull (Tokyo) 2008;56:575-7.
2. Tran PH, Tran HT, Lee BJ. Modulation of microenvironmental pH and crystallinity of ionizable telmisartan using alkalizers in solid dispersions for controlled release. J Control Release 2008;129:59-65.
3. Kothawade SN, Kadam NR, Aragade PD, Baheti DG. Formulation and characterization of telmisartan solid dispersions. Int J PharmTech Res 2010;2:341-7.
4. Bhise S, Mathure D, Patil MV, Patankar RD. Solubility enhancement of antihypertensive agent by solid dispersion technique. Int J Pharm Life Sci 2011;2:970-5.
5. Kausalya J, Suresh K, Padmapriya S, Rupenagunta A, Senthilnathan B. Solubility and dissolution enhancement profile of telmisartan using various techniques. Int J PharmTech Res 2011;3:1737-49.
6. Niranjan C, Sidharth P, Jagadish S, Anuradha C. Formulation and optimization of Telmisartan solid dispersions by Box-Behnken design. Int J Pharm Sci Health Care 2012;2:33-47.
7. Kothawade PC, Belgamwar VS, Deshmukh S. Solid dispersions of telmisartan for enhancing solubility, dissolution rate and oral bioavailability. Indo Am J Pharm Res 2013;3:7035-45.
8. Singh R, Jain DA. Formulation and characterization of telmisartan using solid dispersion techniques. Int J PharmTech Res 2013;5:516-25.
9. Chaudhary A, Sangra M, Kumar S. Formulation design and optimization of mouth dissolving tablets of telmisartan using solid dispersion technique. World J Pharm Res 2014;3:1318-33.
10. Vyas M, Jaiswal A, Upadhyay N, Behera AK. Formulation and development of solubility improvised complex of telmisartan using various techniques. Int J Univers Pharm Bio Sci 2014;3:311-26.
11. Murthy TE, Purna TS, Vijayakumar G. Studies on dissolution rate enhancement of telmisartan with hydroxypropyl-β-cyclodextrin complexes. Asian J Pharm Sci 2011;1:73-85.
12. Shashikant ND, Bhanudas SK. Comparative study of antihypertensive activity of telmisartan with telmisartan-hydroxypropyl-β-cyclodextrin inclusion complexes. Int J Compr Pharm 2011;2:1-5.
13. Bhowmik D, Jayakar B, Kumar KS. Design and characterization of fast dissolving tablet of telmisartan. Int J Pharm Recent Res 2009;1:31-40.
14. Dhiman V, Jain G, Jagtap V, Sheorey RV. Formulation and *in-vitro* evaluation of fast dissolving tablets of telmisartan. Int J Pharm Life Sci 2012;3:2159-64.
15. Patel K, Rajendra A. Design and evaluation of mouth dissolving tablets of anti hypertensive drug telmisartan. Int J Pharm Tech Res 2012;4:715-24.
16. Gaja JB, Sayyad FJ. Enhancement of solubility and dissolution rate of telmisartan by spray drying technique. Indo Am J Pharm Res 2013;3:1732-45.

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