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FORMULATION AND EVALUATION OF SOLUBILITY ENHANCED FAST DISINTEGRATING TABLETS OF TELMISARTAN USING NATURAL SUPERDISINTIGRANTS

Y Sirisha*, A Srinivasa Rao, Mohd Abdul Hadi

Bhaskar pharmacy college, Yenkapally (V), Moinabad (M), R. R. District, Hyderabad, Andhra Pradesh, India

***Correspondence**

Y Sirisha

Bhaskar pharmacy college, Yenkapally (V), Moinabad (M), R. R. District, Hyderabad, Andhra Pradesh, India

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Abstract

Telmisartan (TLM) is an angiotensin II receptor antagonist used in the treatment of hypertension. According to biopharmaceutical classification system, telmisartan belongs to class II drug. It is practically insoluble in water and it shows low dissolution profile and poor absorption. In order to improve the solubility and dissolution rate of telmisartan, 6 inclusion complexes were prepared by both physical mixing and kneading methods in 1:1, 1:2 and 1:3 molar ratios of telmisartan and β-cyclodextrin. The complexes were tested for dug content and in-vitro drug release studies. Based on these parameters formulation KM3 was selected as best one for further studies as % drug content was 98.47% and in-vitro drug release was 76.991% in 45min. The tablets were formulated for the inclusion complex KM3 using two natural super disintegrants gum karaya and soy polysaccharides in three concentrations and were evaluated for % weight variation, hardness and disintegration time and in-vitro drug release studies. The % weight variation range was found to be between 508±0.57 to 524±0.34, the hardness range was found to be between 3.4±0.29 to 4.2±0.18 kg/cm2, the disintegration time ranges between 5min 20sec to 7min 25sec, in-vitro drug release shows that as concentration of super disintegrant increases rate of drug release increases. Among all the formulations, F3 shows best result with a disintegration time of 5min 30sec and drug release up to 92.555% in 45min.

Keywords: Telmisartan, Inclusion complexes, β-Cyclodextrins, Gum karaya, Soy polysaccharides.

INTRODUCTION

Cyclodextrins (CDS) were discovered approximately over 100 years ago and the first patent on CDS and their complexes were registered in 1953. Cyclodextrin (CDs) are cyclic oligosaccharides containing six (α-CD), seven (β-CD) or eight (γ-CD) α-1, 4-linked glycopyranose units, with a hydrophilic hydroxyl group on their outer surface and a hydrophobic cavity in the center. CDs are capable of forming inclusion complexes with many drugs by taking up a whole drug molecule or some part of it, into the cavity. Cyclodextrin have ability to alter their physical, chemical and biological properties of guest molecules by formation of inclusion complex. In the pharmaceutical industry CDS have mainly used as complexing agents to increase the aqueous solubility of poorly soluble drugs and to increase the bioavailability and stability. β- CD acts as safe excipient in pharmaceutical formulations. Its advantages are quick onset of action, reduces drug side effects, increases shelf life and reduction of toxicity. Telmisartan (TLM) is an angiotensin II receptor antagonist used in the treatment of hypertension. Inclusion complex can be prepared by various methods like kneading method, solvents evaporation method, physical mixing method, freeze drying method, neutralization method, spray drying method, co precipitation method, co evaporation method and co grinding method. Among these three methods are selected for increasing the solubility (kneading method, solvent evaporation method and physical mixing method). The main aim is to increase the solubility of drug by forming complex with β-cyclodextrin by using different methods and to test the effect of natural superdisintegrants on the release of drug from the inclusion complex in the tablet.

MATERIALS AND METHODS

Materials

Pure drug telmisartan was obtained as a gift sample from Aurobindo Pharma limited. Gum karaya, Soy polysaccharides were purchased from Rajesh chemicals, Mumbai. β-CD was purchased from Himedia laboratories Pvt. Ltd, Mumbai. Dibasic calcium phosphate, Magnesium stearate and talc were purchased from S.D. Fine Chem. Ltd, Mumbai. The chemicals and reagents used are of analytical grade.

Methods

Pre formulation Studies

Influence of pH of solvent on solubility of telmisartan

0.1N HCL, pH 4.5 acetate buffers, pH 6.8 phosphate buffers and distilled water were prepared. Five ml of each solvent was taken into four different test tubes. Excess quantity of the drug was added to each test tube to prepare the saturated solutions and kept aside for 24hrs. It was filtered through 0.23µm membrane filter and samples were suitably diluted and analyzed at 230nm by using UV-Visible spectrophotometer.[2]

Phase solubility studies with β-Cyclodextrin

An excess amount of drug was added to 15ml of β-Cyclodextrin aqueous solution (0- 15mmolL^{-1}) in boiling tubes and shaken at room temperature for about 30minutes. Then samples were filtered and analyzed for drug content at 230nm. The stability constant of complex (k_c) was calculated by employing the following formula[2].

$$K_C = \frac{Slope}{S_o(1 - Slope)}$$

Where S_o is solubility of telmisartan in the absence of CDs.

Preparation of β-cyclodextrin inclusion complexes

Inclusion complexes of telmisartan and cyclodextrins were formulated by using the following techniques and also shown in[2] Table 1.

Physical mixing method

To prepare telmisartan-β-cyclodextrin complexes with 1:1 molar ratio, 155.97mg of telmisartan and 344.02mg of Cyclodextrin were weighed accurately and mixed thoroughly by trituration in a mortar. Then complexes obtained were sieved by using sieve no #120.

Similarly, complexes at 1:2 and 1:3 molar ratios were also prepared.

Kneading method

Telmisartan β-cyclodextrin complexes were also prepared with 1:1 molar ratio by transferring 344.02mg of cyclodextrin in a mortar and wetted with a few drops of methanol/water mixture (1:1v/v). 155.97mg of telmisartan was added slowly and kneaded with addition of few drops of methanol/water mixture. Finally the wetted mass was dried at room temperature and sieved by using sieve no #120. Same procedure was also repeated to prepare the complexes of 1:2 and 1:3 molar ratios.

Evaluation of Inclusion Complexes

Evaluation of inclusion complexes was performed to select one method and one molar ratio from every set of complexes i.e., telmisartan-β-cyclodextrin complexes.

Determination of drug content in complexes

The drug content of complexes was determined by dissolving the 10mg of complex in 10ml of solvent phosphate buffer pH 7.5. Then the drug content was measured by filtering the samples and analyzed the drug at 230nm[2].

In vitro dissolution studies

Dissolution rate experiments were performed in pH 7.5 buffer at 37^0C±0.5°C, using USP TDT-08L (electro lab, Mumbai) with paddle stirrer rotating at speed 75rpm. The complexes containing equivalent to 40mg of telmisartan were subjected to dissolution studies. At fixed time intervals, samples were withdrawn and filtered through whatmann filter paper and samples are analyzed at 230nm using UV visible spectrophotometer.

Formulation of tablets by using direct compression technique

Complexation is prepared with β-CD by using different methods like physical mixing and kneading method. Among that kneading method (1:3) is selected as best method for formulation of tablets. The complex containing equivalent to 40mg of telmisartan were taken and then mixed with directly compressible diluents and super disintegrants shown in Table 2. Finally the lubricating agent was added and made into the blend. The resulting blend was compressed to form a tablet by using 9mm round shaped punches.

Micromeritic properties of the blend

Bulk density

Blend was weighed and transferred to a measuring cylinder. Then bulk volume was noted. Bulk density was calculated by using the following formula[3]

$$\text{Bulk density} = \frac{\text{mass of the powder}}{\text{bulk volume}}$$

Tapped density

Blend was weighed, transferred to a measuring cylinder and subjected to 100 tapings. Then volume was noted as tapped volume. Tapped density was measured by using the following formula.

$$\text{Tapped density} = \frac{\text{mass of the powder}}{\text{tapped volume}}$$

Carr's index

Carr's index was calculated by using the following formula.

$$\text{Carr's index} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100$$

Hausner's ratio

Hausner's ratio was calculated by using the following formula.

$$\text{Hausner's ratio} = \frac{\text{tapped density}}{\text{bulk density}}$$

Angle of repose

Required quantity of blend was taken and poured into a hollow cylinder which was placed on a graph sheet. Then the cylinder was slowly lifted. Then height and diameter of the heap formed were noted down. The angle of repose (θ) was calculated by the formula.

$$\text{Angle of repose, } \theta = \text{Tan}^{-1}\frac{h}{r}$$

Evaluation of Tablets

Weight variation test

Twenty tablets were collected and were weighed collectively and individually. From the collective weight, average weight was calculated. The percent weight variation was calculated using the formula[4]

$$\%\ \text{Weight variation} = \frac{(\text{Average weight} - \text{Individual Weight})}{\text{Individual Weight}} \times 100$$

Hardness test

Hardness of the tablet was determined using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The lower plunger was then forced against a spring by tuning threaded bolts until the tablet fractured. Then the final reading was recorded. The hardness was calculated by deducting the initial pressure from the final pressure.[5]

Disintegration Time

The disintegration time was determined in distilled water at 37±0.5^{0}C using disintegration test apparatus USP ED-2L (Electro lab, Mumbai).[6]

Table 1: List of inclusion complexes (telmisartan-β-Cyclodextrin) formulated by different methods at different molar ratios

Batch code	Method employed	Telmisartan-β-Cyclodextrin
PM1	Physical mixing	1:1
PM2	Physical mixing	1:2
PM3	Physical mixing	1:3
KM1	Kneading method	1:1
KM2	Kneading method	1:2
KM3	Kneading method	1:3

Table 2: Composition of telmisartan tablets with various super disintegrants

Ingredients	F_1(mg)	F_2(mg)	F_3(mg)	F_4(mg)	F_5(mg)	F_6(mg)
Telmisaratan-β-cyclodextrin complex batch KM3 equivalent to 40 mg of telmisartan	173.9	173.9	173.9	173.9	173.9	173.9
DCP	19.6	17.1	14.6	19.6	17.1	14.6
Gum karaya	2.5	5	7.5	_	_	_
Soy polysaccharides	_	_	_	2.5	5	7.5
Magnesium stearate	2	2	2	2	2	2
Talc	2	2	2	2	2	2
Total weight	200	200	200	200	200	200

Table 3: Influence of pH of solvent on solubility of telmisartan

Solvent	Solubility (mg/ml)
0.1N Hcl	0.0376
pH 4.5 Acetate Buffer	0.0433
pH 6.8 phosphate buffer	0.0507
pH 7.5 Phosphate Buffer	0.0878
Distilled Water	0.4356

Table 4: Phase solubility Data of telmisartan observed from solutions containing varying concentration of *β*-cyclodextrin

Concentration of *β*-cyclodextrin (mol/L)	Telmisartan solubility (mol/L) X 10^{-6}
0	1.0562
3	1.9788
6	2.4167
9	2.8713
12	3.342

Table 5: Drug content data observed from telmisartan β-cyclodextrin complexes prepared with different methods and different molar ratios

Method employed	Drug: complexin agent	Theoretical amount drug present	Amount of total drug present	% Drug content
Physical method	1:1	3.11	2.84	91.52±0.40
	1:2	1.84	1.71	93.47±0.56
	1:3	1.31	1.26	96.32±0.48
Kneading method	1:1	3.11	2.88	92.86±0.72
	1:2	1.84	1.75	95.58±0.66
	1:3	1.31	1.28	98.47±0.59

Table 6: Micromeritic properties of the blends containing telmisartan β-Cyclodextrin complex and the selected excipients

Formulation code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose (θ)
F1	0.367±0.12	0.396±0.44	7.94±0.28	1.07±0.19	27.64±0.55
F2	0.396±0.32	0.457±0.30	15.60±0.21	1.15±0.14	30.96±0.39
F3	0.429±0.19	0.490±0.16	14.33±0.36	1.14±0.10	28.81±0.46
F4	0.362±0.10	0.412±0.11	11.21±0.18	1.01±0.28	20.32±0.38
F5	0.312±0.09	0.341±0.20	10.91±0.17	1.09±0.22	25.14±0.52
F6	0.397±0.34	0.383±0.15	12.16±0.11	1.11±0.34	27.56±0.36

Table 7: Physical parameters of telmisartan tablets formulated with drug-βCD complex in presence of various excipients

Formulation code	Average Weight (mg±S.D)	Hardness (Kg/cm^2)	Friability (%)	Disintegration time (Sec)	Drug content (%)
F1	511.55±0.02	3.4±0.29	0.20±0.37	5mint 20 sec	97.25±0.79
F2	511±0.323	3.7±0.45	0.26±0.44	5mints 55 sec	94.60±0.86
F3	515±0.29	3.7±0.52	0.24±0.30	5mint 30sec	96.37±0.92
F4	512±0.33	3.9±0.22	0.25±0.29	7min 25sec	94.85±0.70
F5	508±0.57	4.2±0.18	0.31±0.38	6min 50 sec	95.67±0.8
F6	524±0.34	3.5±0.46	0.33±0.12	5min 35sec	96.28±0.64

Table 8: In vitro dissolution parameters of telmisartan tablets formulated by employing Telmisaratan-β-cyclodextrin complex batch KM3 along with different natural superdisintegrants

Formulation code	% Drug dissolved	$D.E_{40}$ (%)	K_1 (Min^{-1})	T_{50} (Min)	T_{90} (Min)
F1	74.450	31.25	0.0226	30.7	102.0
F2	85.019	36.41	0.0293	23.7	78.6
F3	92.555	41.87	-0.0387	17.9	59.5
F4	67.965	32.91	0.0211	32.8	109.0
F5	76.319	35.91	0.0253	27.4	91.0
F6	82.554	38.74	0.0296	23.4	77.8

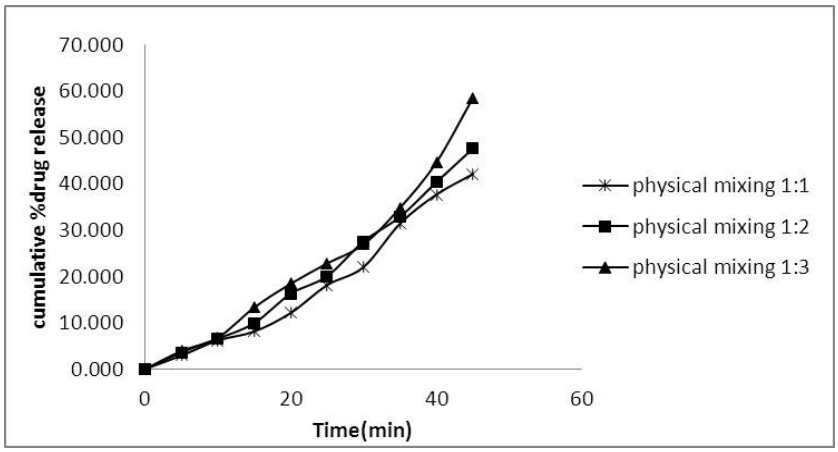

Figure 1: In-vitro dissolution profiles of telmisartan-β-Cyclodextrin Inclusion Complexes prepared with physical method

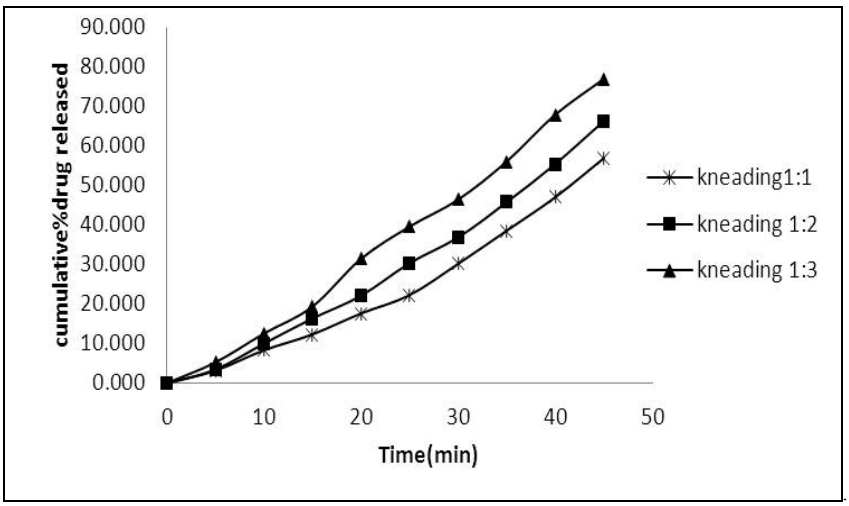

Figure 2: In-vitro dissolution profiles of telmisartan-β-Cyclodextrin Inclusion Complexes prepared with kneading method

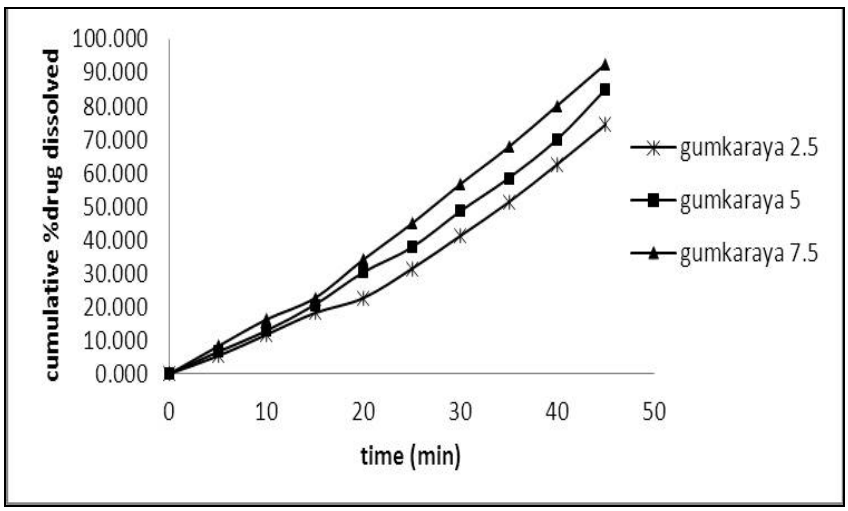

Figure 3: In-vitro dissolution profiles of telmisartan formulations prepared by using various concentrations of gumkaraya

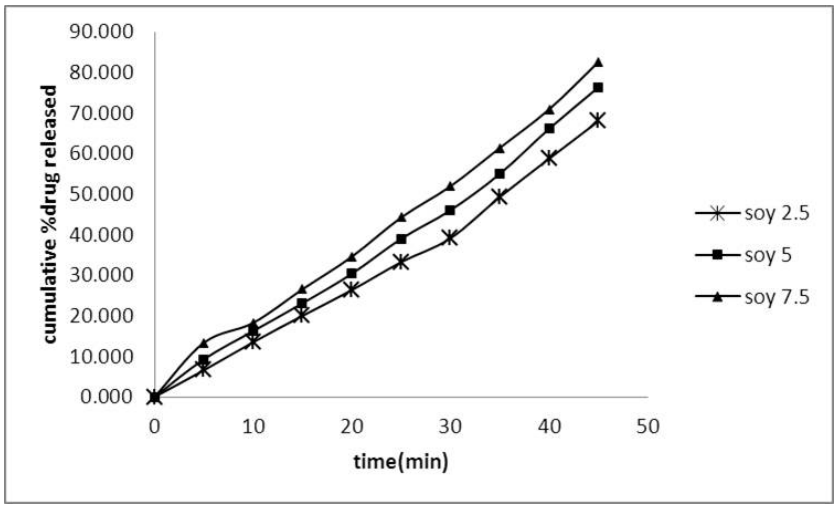

Figure 4: In-vitro dissolution profiles of telmisartan formulations prepared by using various concentrations of soy polysaccharides

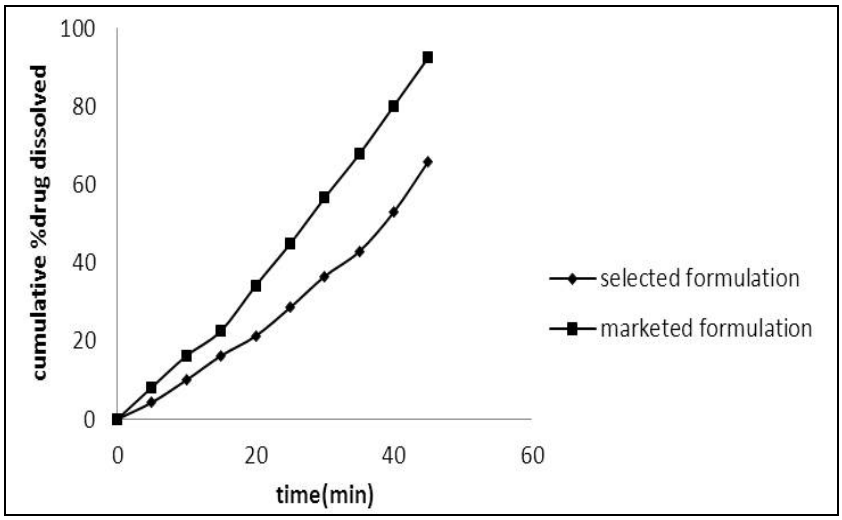

Figure 5: comparative in-vitro dissolution profile of selected and marketed formulation

Drug content determination

For determination of the drug content, a total 10 tablets were weighed and powdered. The powder equivalent to 40mg of telmisartan was weighed and dissolved in phosphate buffer 7.5:methanol (1:1) and then filtered through watt man filter paper and analyzed the drug content by measuring the absorbance at 230nm.[2]

In-vitro dissolution studies

In-vitro drug release is carried out using USP TDT-08L (Lab India, Mumbai) employing paddle method .The dissolution was performed in phosphate buffer pH 7.5 as a dissolution medium (900ml) and the temperature was maintained at 37 ± 0.5^0c. The speed of the paddle was adjusted at 75rpm. An aliquot of 5ml sample was withdrawn at every five minutes. The replaced samples were refreshed with fresh medium. Samples withdrawn were filtered through What Mann filter paper and analyzed at 230nm using UV–visible double beam spectrophotometer.[2]

RESULTS AND DISCUSSION

Influence of pH of solvent on solubility of telmisartan

Influence of pH on solubility of telmisartan was studied in four different solvents viz 0.1N HCL, pH 4.5 acetate buffer, pH 6.8 phosphate buffer, pH 7.5 phosphate buffer and distilled water. The solubility of telmisartan in these solvents is shown in Table 3. Telmisartan was more soluble in distilled water than other media.

Phase solubility studies with β-Cyclodextrin

The Complexation of telmisartan with β- CD was investigated by phase solubility studies. The phase solubility data for complex telmisartan - β-CD is presented in Table 4. According to Higuchi and Connors classification, it comes under A_L type curve. The solubility of drug is dependent on the concentration of complexing agent. The stability constant of complex (kc) was calculated and it was found to be $203M^{-1}$.

In-vitro dissolution studies of telmisartan-β-cyclodextrin complexes

The dissolution studies were conducted on telmisartan complexes prepared by different methods. The dissolution rate was found to be varied with the method of complexation and telmisartan-β-cyclodextrin molar ratio. Among all the complexes, faster dissolution rate was observed with the complex prepared by Kneading method at 1:3 molar ratios and shown in Figures 1-2.

Studies on tablets formulated with telmisartan β-CD complexes

The preliminary studies indicated that the telmisartan complexes formulated with β-CD by employing kneading method and having the drug: complexing agent 1:3 showed higher drug release compared to other complexing agent and other methods and ratios employed in present investigation. These complexes released drug 76.8 % label amount within 45min. So the tablets were formulated with the same complex. The complexes were subjected for drug content determination and the data is shown in Table 5. All the complexes have shown more than 90% of drug. The complex 1:3 prepared by kneading method has shown maximum drug content of 98.47%. As such the complex is not having the desired flow properties, so the tablets were formulated by employing direct compression technique. Micromeritic properties of the blend containing the complex along with direct compressible diluents were evaluated and shown in Table 6. All the formulations exhibited good flow properties and hence they are subjected to compression to prepare telmisartan tablets. Formulated tablets were subjected to various quality control tests and the results were shown in Table 7. All the tablets satisfied weight variation test and hardness was found to be in between 3.0-4.1Kg/cm^2 and the friability was found to be less than 1% indicating good mechanical strength to withstand transmission and storage.

Studies on effect of natural super disintegrants on dissolution rate of telmisartan

To study the influence of natural super disintegrants on dissolution rate of telmisartan, the tablets formulated with two different disintegrants such as karaya gum and soy polysaccharides. The formulated tablets were subjected to in-vitro dissolution studies in pH 7.5 phosphate buffer according to official medium. And the comparative dissolution profile was shown in Figure 3-4. The dissolution followed first order kinetics and in-vitro dissolution parameters such as T_{50} (time for dissolution of 50% drug), T_{90} (time for dissolution of 90%drug), DE (dissolution efficiency), rate constant K^{min-1} values was presented in Table 8. In the present study, it was observed that the tablets which when formulated by super disintegrant karaya gum F3 showed rapid dissolution in pH 7.5 buffer when compared to the tablets prepared by other natural super disintegrants. Among all formulations studied, formulation F3 was found best regarding drug release; it showed 92.555 % release of the drug within 40min. In addition this formulation showed shortest disintegration time of 5min 20sec and drug content is 94.68 %.

Comparative studies on the selected formulation and marketed formulation

The dissolution profile of tablets formulated with the telmisartan β-CD complex by using excipients like dibasic calcium phosphate, karaya gum and magnesium stearate and prepared by employing direct compression technique (F3) was compared with the dissolution profile of marketed telmisartan tablet (cresar). The dissolution media employed for comparative studies was 7.5 pH phosphate buffers. The comparative dissolution data of the marketed formulation were shown in Figure 5. The newly developed formulation from this investigation offered higher extent and rate of dissolution up to 90% compared to the marketed formulation up to 65%. Thus, the solubility and dissolution rate of telmisartan has been successfully enhanced by complexation with cyclodextrins and various natural super disintegrants.

CONCLUSION

As we have mentioned in the introduction that our main aim was to increase the solubility of drug by forming complex with β-cyclodextrin by using different methods and to test the effect of natural super disintegrants on the release of drug from the inclusion complex in the tablet. So, while performing the research we find among all the complexes, faster dissolution rate was observed with the complex prepared by Kneading method at 1:3 molar ratios. So, this complex was incorporated in tablets using natural super disintigrants. It was observed that the tablets which when formulated by super disintegrant karaya gum F3 showed 92.555 % release of the drug within 40min. In addition this formulation showed shortest disintegration time of 5min 20sec and drug content is 94.68 %.

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