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Design and Characterization of Fast Melt Tablets of Telmisartan

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ABSTRACT

Telmisartan is an angiotensin II inhibitor used in the treatment of hypertension. Development of an FMT of telmisartan and to evaluate the effect of co-processed superdisintegrants on its disintegration time and release profile was the prime objective of this research work. Tablets were prepared by direct compression using two different superdisintegrants crospovidone and sodium starch glycolate in combination by co-processing technique. Co-processing is done by two methods namely physical mixing and solvent evaporation. Crospovidone and sodium starch glycolate were used in the different ratios (1:2, 1:3 & 1:4). The drug and excipients were characterized using FT-IR spectroscopy. The developed superdisintegrants were evaluated for angle of repose, Carr's index and Hausner's ratio. Fast dissolving tablets of telmisartan were evaluated for pre-compression and post compression parameters.

Keywords: Telmisartan, Superdisintegrants, Co-processing, Fast dissolving tablet.

INTRODUCTION

The aim and objective of the present study is to develop and evaluate FMT of telmisartan and enhance the onset of action of telmisartan and also to study the influence of excipients. Telmisartan is the model drug which is used in the treatment of the hypertension. The study was intended to select the best possible diluents and the superdisintegrants combination to formulate the dispersible tablets among all the diluents and disintegrants used. The basic approach in the development of the fast dissolving tablet is by using co-processed superdisintegrants. Crosspovidone and sodium starch glycolate are the superdisintegrants used in this formulation (Sekhar *et al*., 2008). Co-processed superdisintegrants were prepared by both physical mixing and solvent evaporation methods in different combinations of 1:2, 1:3 and 1:4. In this study the above mentioned superdisintegrants are selected and best combination one (1:4) is selected for further studies. Therefore it was decided to adopt the Direct Compression Technique to prepare FDT in an easy and comfortable way.

MATERIALS AND METHODS:

Materials:

Telmisartan (Aurobindo Pharma Ltd., Hyderabad), Crospovidone (S.D. Fine Chem Ltd., Mumbai), Sodium starch glycillate (Loba Chem Pvt. Ltd., Mumbai), Talc (S.D. Fine Chem Ltd., Mumbai), Ethanol (Merck Pvt. Ltd., Mumbai), Sodium sachharin (S.D. Fine Chem Ltd., Mumbai). All other reagents used were of AR grade and procured locally.

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Preparation of Telmisartan fast dissolving tablets

In the present study, first microcrystals of telmisartan were prepared by *in situ* micronization technique, in which the optimized formulation has been selected. Telmisartan fast dissolving tablets were prepared by direct compression method using telmisartan and HPMC inclusion complex prepared by *in situ* micronization technique (Rasenack *et al*., 2002). Co-processed Superdisintegrants used which were prepared by solvent evaporation and physical mixing methods. The amount of complex equivalent to 40 mg of drug per tablet were taken and mixed with directly compressible diluents and co-processed superdisintegrants in a mortar with the help of pestle. The powder blend was then compressed using 8 mm round faced punch under tablet punching machine. The total weight of tablet was 150 mg. The formula included variable amounts of all excipients are shown in the table no 2.

Coprocessing of superdisintigrants

Co-processed superdisintegrants were prepared by solvent evaporation and physical mixing methods. In physical mixing a blend of crospovidone and Sodium

starch glycolate (in the ratio of 1:2, 1:3 & 1:4) were taken and mixed well in a mortar with pistle. In solvent evaporation method a blend of crospovidone and Sodium starch glycolate (in the ratio of 1:2, 1:3 & 1:4) was added to 10 ml of ethanol. The contents of the beaker (250 ml capacity) were mixed thoroughly and stirring was continued till most of ethanol evaporated. The wet coherent mass was passed through # 44 mesh sieve. The wet granules were dried in a hot air oven at 60º C for 20 minutes. The dried powder mass was sifted through # 44mesh sieve. (Sekhar *et al*., 2008)

Evaluation of Telmisartan Fast Dissolving Tablets

A) Pre compression evaluation tests

a) Angle of repose

The angle of repose of powders was determined by the funnel method. Accurately weighed powders were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powders. The powders were allowed to pass through the funnel freely onto the surface. The diameter and height of the powder cone was measured and angle of repose was calculated by using the given formula. The effect of angle of repose on flow property of powders was listed in Table No. 3 and the results were tabulated in Table No. 5.

$$\tan\theta = \frac{h}{r}$$

Where,

h = height of the powder cone

r = radius of the powder cone

b) Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) of powders were determined. A quantity of 2 gms of powder from each formula was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was tapped continuously until no further change in volume was observed. Then LBD and TBD were calculated by using the given formula and the results were tabulated in Table No. 5.

$$LBD = \frac{\text{Weight of the powder}}{\text{Volume of the packing}}$$

$$TBD = \frac{\text{Weight of the powder}}{\text{Tapped volume of the packing}}$$

c) Carr's index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the loose bulk density and tapped bulk density of a powder and the rate at which it is packed down. The effect of carr's index on flow property of powders was listed in Table No. 4. The formula for Carr's Index is given below and the results were tabulated in Table No. 5.

$$\text{Carr's index } (\%) = \frac{TBD - LBD}{TBD} \times 100$$

d) Hausner's ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. It is calculated by using the given formula and the effect of hausner's ratio on flow property of powders was listed in Table No. 4. The results were tabulated in Table No. 5.

$$\text{Hausner's ratio} = \frac{TBD}{LBD}$$

FT-IR Spectroscopy

Fourier Transform Infrared (FT-IR) spectral measurements for prepared powders were recorded using Thermo-IR 200 FT-IR spectrophotometer. Potassium bromide pellet method was employed. The powders were finely ground with KBr to prepare the pellets under a hydraulic pressure of 600 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}. The results were shown in Figure no 3, 4, and 5.

b) Post compression evaluation tests for fast dissolving tablets

1) Thickness

Tablet thickness can be measured using a simple procedure. 5 tablets were taken and their thickness was measured using a digital vernier calipers at different places of each tablet and calculate the average thickness for each tablet.

2) Hardness

It is the force required to break a tablet by compression in the radial direction, it is an important parameter in formulation of mouth dissolve tablets because excessive crushing strength significantly reduces the disintegration time. In the present study the crushing strength of the tablet was measured using Pfizer hardness testers. An average of three observations is reported.

3) Uniformity of weight

I.P. procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity.

4) Disintegration time

The test was carried out on 6 tablets using the apparatus specified in I.P.-1996 distilled water at 37ºC ± 2ºC was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds.

5) *In-vitro* drug release

The development of dissolution methods for ODTs is comparable to the approach taken for conventional tablets, and is practically identical. Dissolution conditions for drugs listed in a pharmacopoeia monograph, media saliva simulated fluid of pH 6.8 is used for ODT. The USP 2 Paddle apparatus is used for this purpose which is the most suitable and common choice for orally-disintegrating tablets, with a

paddle speed of 75 rpm commonly used. Typically the dissolution of ODT is very fast when using USP monograph conditions; hence slower paddle speeds may be utilized to obtain a profile. For every 2 minutes 1 ml of sample was collected and diluted suitably with buffer 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.

6) Friability test

Friability of the tablets was determined using Roche friability (Electrolab, Mumbai). This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Pre-weighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were de dusted using a soft muslin cloth and reweighed.

The friability (f) is given by the formula.

$$f = (1- W_0 / W) \times 100$$

Where,

W_0 is weight of the tablets before the test and

W is the weight of the tablet after the test.

7) *In-vitro* dispersion time test

To determine dispersion time 10 ml measuring cylinder was taken in which 6 ml distilled water was added and tablet was dropped in it. Time required for complete dispersion was determined.

8) Wetting time

Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. Ten millimeters of water-containing Eosin, a water-soluble dye, is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

9) Water absorption ratio

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper & the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio (R), was determined using following equation,

$$R = 10 (W_a / W_b)$$

Where,

W_b is weight of tablet before water absorption

W_a is weight of tablet after water absorption.

10) Accelerated Stability study

The Orally disintegrating tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.

(i) 40 ± 1 °C

(ii) 50 ± 1°C

(iii) 37 ±1°C and Relative Humidity= 75% ± 5%.

The tablets were withdrawn after a period of 15 days and analyzed for physical characterization (Visual defects, Hardness, Friability, Disintegrations, and Dissolution and drug content). The data obtained is fitted into first order equations to determine the kinetics of degradation. Accelerated stability data are plotting according arrhenius equation to determine the shelf life at 25°C.

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.

RESULTS AND DISCUSSION

The bulk density of all formulations powder blend containing co-processed excipients was found to be in the range of 0.41 to 0.57 gm/ml, whereas the tapped density was observed between 0.46 to 0.63 gm/ml. From the values of bulk density and tapped density the values for Compressibility index and Hausner's ratio were calculated. The values for Compressibility index were found between 11.50 to 14.05 %. The values for Hausner's ratio were found to be less than 1.12 to 1.17. All these values are within the specified limits which indicate good flow properties. Angle of repose was found to be less than 30 which indicate good flow of powder. Overall these values indicate good flow properties of powder blend, uniform die fill and better compression ability. Therefore, from this data so obtained, it was decided to go for direct compression of tablets from the powder blends (Table.5).

The weight variation of all formulations was found to be in the range of less than 2%. None of the tablet was found to deviate from the average weight of tablets (variation with deviation less than ± 7.5, which complies with I.P specification) signifies that there is uniformity in flow of powder blend which leads to uniform die fill. Hardness test for all formulations was carried out and observations obtained were in the range of 3.0 to 4.0 kg/cm^2. Hardness for all formulations was observed to be proper, which signify that tensile strength of all formulations was maintained after direct compression. Test for friability was conducted for all formulations, % friability was found to be in the range of 0.6 to 1.3 (Table.6).

Friability test for all formulations indicated that % friability was less than 1%, which compiles the I.P specification and reveals that all formulations have possessed good physical strength and can withstand the mechanical shocks that can be observed during handling, shipping and transportation. The thickness of all formulations was found to be uniform as it was obtained in the range of 2.45 to 2.74 mm. The values for thickness and diameter signify uniformity and it was due to uniformity in die fill, good flow properties, uniform pressure and appropriate punch movement.

All the six formulations gave a significant improvement in the porosity. The concentration of superdisintegrants (1:2, 1:3 and 1:4) changes for each

formulation which needs to be optimized. The optimized ratio was found to be 1:4 for F6 formulation. From the above results it is observed that F6 formulation shows decrease in wetting time, disintegration time, in vitro dispersion time and more water absorption ratio. It indicates that high capillary action of sodium starch glycolate and high swelling action of crospovidone combination improves the wicking and swelling action tablets (Table.7).

Co-processing by solvent evaporation gives more synergy between the superdisintegrants than physical mixing. F6 formulation shows better results due to solvent evaporation of superdisintegrants. The mouth feel of the tablets also good due to mannitol and sweetening agent masks the bitter taste of telmisartan. Wetting time of tablets is found in the range of 28 to 35 sec. and the water absorption ratio was found in the range of 84.26 to 96.44 %. As the porosity of formulation is increased by the superdisintegrating agents and water uptake is increased due to increased capillary action, the formulation is showing less wetting time. The less wetting time helps in the quick dispersion of the formulation when come in contact with the saliva and having linear relationship with disintegration time.

Disintegration time for all formulations was found to be in the range of 19 to 29 sec. Disintegration study explained that there was decrease in disintegration time with successive increase in concentration of sodium starch glycolate but comparatively solvent evaporation co-processed formulations take least time for disintegration with respect to their physical mixture formulations. Such a difference in disintegration time between both of these formulations indicates that in solvent evaporation co-processed formulation there might be increase in capillary action of Superdisintegrants which might have led to improved water uptake. *In vitro* dispersion time indicates complete dispersion of formulation in the saliva and it was found to be in the range of 21sec to 32sec and it is due to more porosity of superdisintegrant. Quick dispersion of formulation favours fast disintegration of formulation. Drug content of all formulations was observed in between 94.39 to 97.74. Drug content for all formulations shown uniformity indicating that there was a uniform flow and uniform distribution of drug.

The highest drug release from F6 formulation is due to presence of increased concentration of solvent evaporation treated sodium starch glycolate which favours the more capillary action and more water absorption and favours the maximum drug release. Solvent evaporation treated superdisintegrants are better than physical mixing superdisintegrants. Solvent evaporation develops more synergy between the superdisintegrants than physical mixture and it is due to in presence of a solvent the superdisintegrants are undergone a homogenous distribution (Table.8).

Table.1 Different ratios of co-processed superdisintegrants

S.No	Formulation code	Method of co- processing	Ratio of Crospovidone : SSG
1	F1	Physical mixing	1:2
2	F2	Physical mixing	1:3
3	F3	Physical mixing	1:4
4	F4	Solvent evaporation	1:2
5	F5	Solvent evaporation	1:3
6	F6	Solvent evaporation	1:4

Table.2 Composition of fast dissolving tablets of telmisartan

Ingredients	F1	F2	F3	F4	F5	F6
Drug complex (mg) (Drug equivalent weight)	40	40	40	40	40	40
Crospovidone and Sodium starch glycolate (mg)	6	6	6	6	6	6
Mannitol (mg)	100	100	100	100	100	100
Talc (mg)	3.5	3.5	3.5	3.5	3.5	3.5
Sodium saccharin (mg)	0.5	0.5	0.5	0.5	0.5	0.5
Total weight (mg)	150	150	150	150	150	150

Table.3 Effect of Angle of repose on Flow property of Powders

Angle of Repose	Type of Flow of powder
< 20	Excellent
20-30	Good
30-34	Passable
≥35	Very poor

Table.4 Effect of Carr's Index and Hausner's Ratio on Flow property of Powders

Carr's Index (%)	Type of Flow of powder	Hausner's Ratio
< 10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34

26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
≥ 38	Extremely poor	≥1.60

Table.5 Physical parameters of powder blend

S.No	Formulation code	Bulk density	Tapped density	Carr's index	Hausner's ratio	Angle of repose (^{0})
1	F1	0.49	0.57	14.05	1.16	25.3
2	F2	0.41	0.46	11.5	1.15	25.1
3	F3	0.57	0.63	15.1	1.17	22.1
4	F4	0.54	0.61	13.5	1.17	21.4
5	F5	0.48	0.51	13.9	1.15	21.6
6	F6	0.42	0.49	12.2	1.12	20.2

Table.6 Physical parameters of tablets

S.No	Formulation code	Hardness (kg/cm^2)	Thickness (mm)	% Friability	% Weight variation
1	F1	3.9	2.66	0.9	1.61
2	F2	3.7	2.73	1.3	0.94
3	F3	3.7	2.74	0.7	1.26
4	F4	3.5	2.56	0.6	2.01
5	F5	3.9	2.45	0.8	1.21
6	F6	3.6	2.59	1.2	1.32

Table.7 Evaluation tests for fast dissolving tablets of telmisartan

S.No	Formulation code	Wetting time (sec)	*In vitro* dispersion time (sec)	Disintegration time (sec)	Water absorption ratio	% Drug yeild	% Drug content	Mouth feel
1	F1	35	32	29	84.26	97.74	94.34	Good
2	F2	34	30	27	86.35	96.29	94.27	Good
3	F3	35	28	28	87.53	97.84	96.85	Good
4	F4	31	27	26	87.98	96.37	94.39	Good
5	F5	29	20	20	91.23	98.02	97.75	Good
6	F6	28	21	19	96.44	97.22	96.64	Good

Table.8 Comparative Dissolution studies of fast dissolving tablets of telmisartan

S.No	Time (min)	Formulation Code						
		Pure drug	F1	F2	F3	F4	F5	F6
1	2	4.65±0.62	49.4±0.34	50.2±1.34	50.8±0.53	52.31±0.93	54.25±0.37	54.98±0.59
2	4	9.87±0.31	56.7±0.65	59.3±0.65	61.3±0.42	58.74±0.29	61.34±0.97	63.43±0.47
3	6	18.43±1.02	69.5±0.32	71.3±0.98	74.8±0.89	71.51±0.76	73.38±0.56	76.85±0.49
4	8	21.67±0.76	75.4±0.68	76.7±1.22	79.3±1.02	79.43±1.02	80.27±0.38	82.53±0.79
5	10	28.76±1.12	79.6±0.87	82.8±0.82	84.3±0.63	81.34±0.87	85.83±0.65	89.33±0.83
6	12	35.23±0.45	82.2±0.45	84.3±0.52	87.5±0.49	86.54±0.27	91.23±0.86	**95.25±0.48**

Table.9 Release kinetics of fast dissolving tablets

Kinetic model		F1	F2	F3	F4	F5	F6
First order	r	0.996	0.987	0.979	0.986	0.982	0.979
	k	0.017	0.035	0.055	0.027	0.041	0.061
Hixon-crowell	r	0.992	0.976	0.958	0.973	0.972	0.961
	k	0.025	0.050	0.0074	0.040	0.057	0.081
Zero order	r	0.980	0.940	0.896	0.944	0.929	0.892
	k	1.532	2.770	3.762	2.267	3.080	3.999
Higuchi	r	0.994	0.997	0.984	0.999	0.995	0.982
	k	7.051	9.460	10.892	8.181	10.03	11.32
Peppas	r	0.927	0.926	0.924	0.927	0.96	0.925
	k	0.388	0.233	0.151	0.285	0.203	0.135

Erosion	r	0.992	0.976	0.958	0.973	0.972	0.961
	k	0.005	0.010	0.016	0.008	0.012	0.017
Baker-Lonsdale	r	0.987	0.993	0.994	0.999	0.994	0.989
	k	0.0012	0.0024	0.004	0.001	0.003	0.005
Weibull	r	0.959	0.970	0.976	0.980	0.971	0.966
	k	0.371	0.636	0.902	0.491	0.722	0.993
DE 30		20.14	33.96	44.71	28.48	37.45	47.24
DE 60		32.92	48.83	60.30	41.88	52.82	63.01
T 50		51.11	26.32	16.34	36.04	20.09	15.01

Figure.1 Dissolution profile of fast dissolving tablets of telmisartan

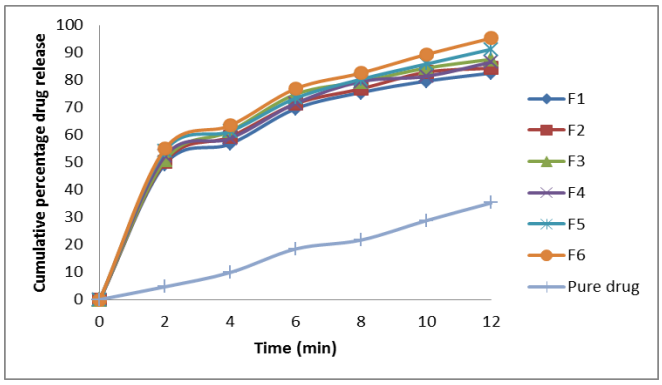


Figure.2 Release kinetics of fast dissolving tablets

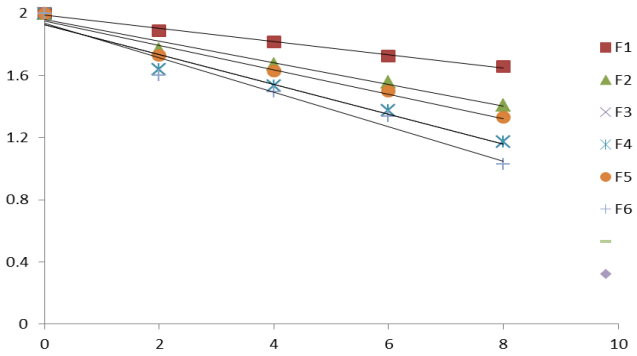


Figure.3 FT-IR spectrum of telmisartan

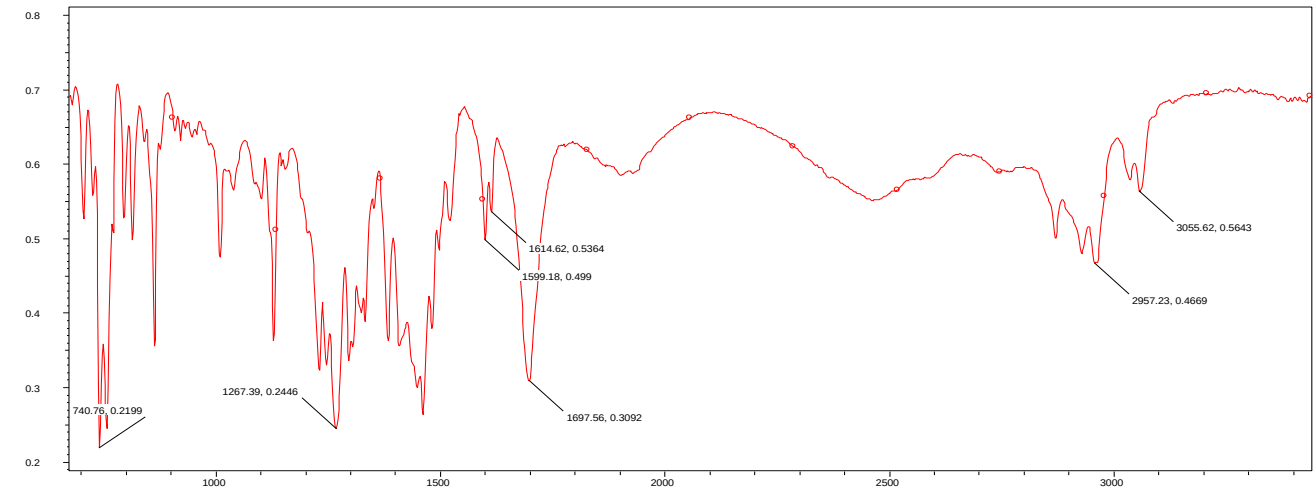


Figure.4 FT-IR spectrum of telmisartan with crosspovidone

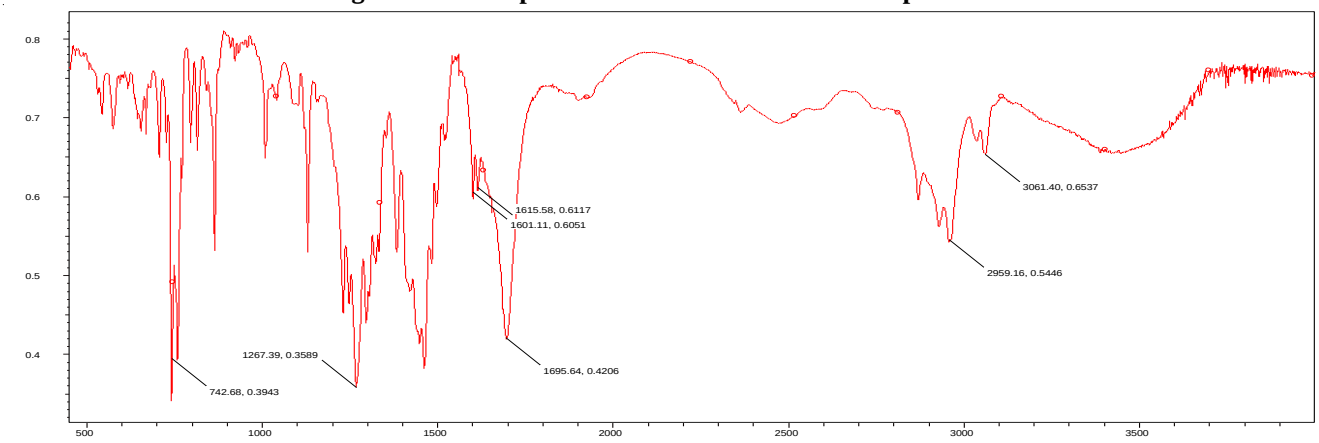
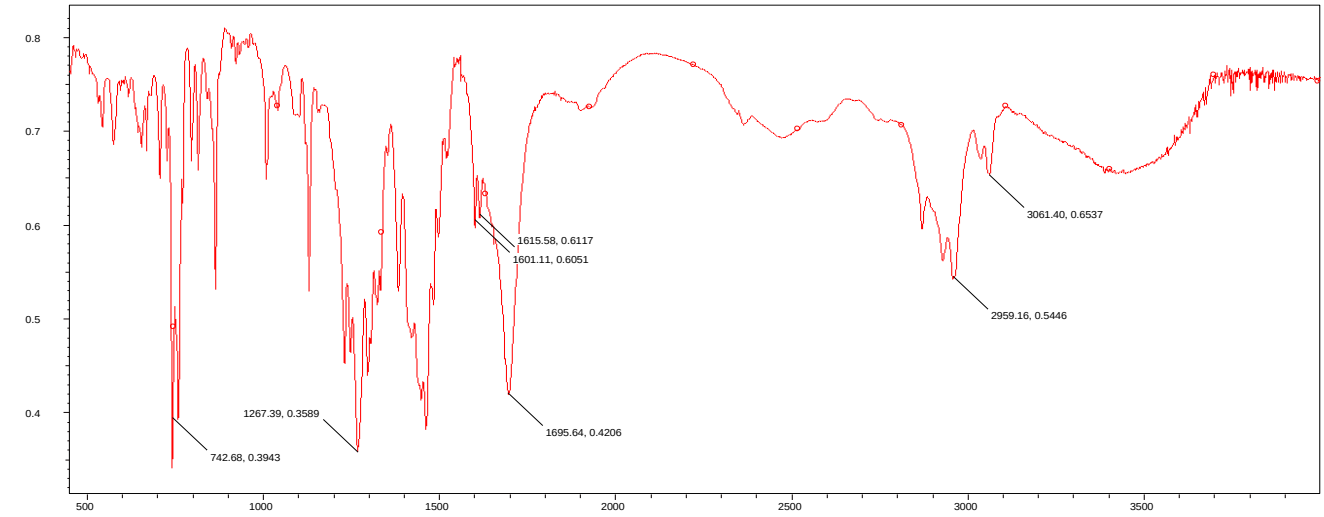


Figure.5 FT-IR spectrum of telmisartan with sodium starch glycolate



CONCLUSION

Fast melt tablets (FMT) of telmisartan were successfully prepared by using direct compression method. From the present work it concludes that the co-processing of excipients could lead to the formation of excipients with superior properties such as better flow, low moisture sensitivity, superior compressibility and rapid disintegrating ability. Among the various formulations of fast dissolving tablet of telmisartan, the formulation containing solvent evaporation treated co-processed superdisintegrants crospovidone and sodium starch glycolate in 1:4 Proportion (F6) is the best formulation having 95.25% drug release within 12 min and the least time for tablet disintegration. Thus from the present work it reveals that the solvent evaporation of co-processing gives the better results than the physical mixng. Increasing the concentration of sodium starch glycolate there is decrease in disintegration time of tablet. FT-IR study reveals that their no interaction between drug and excipients and can be used for preparation of fast dissolving tablets of telmisartan.

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