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DESIGN AND CHARACTERIZATION OF FAST DISSOLVING FILMS OF TELMISARTAN SOLID DISPERSIONS

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ABSTRACT

The major problem in formulation of oral films of telmisartan is that it belongs to BCS Class II moiety. Pharmacologically telmisartan is an angiotensin II receptor antagonist which has high affinity towards the type I (AT1) angiotensin receptor. Telmisartan is absorbed over 4 hours, and its bioavailability is only 25%. Hence there is a need to increase the oral bioavailability of telmisartan by formulating it in to solid dispersions and incorporating the same in to the formulation of fast dissolving films which gives fast onset of action. Six formulations (FT1-FT6) of telmisartan films were prepared and evaluated for their physical characteristics such as thickness, tensile strength, weight variation, folding endurance, drug content uniformity and surface pH and gave satisfactory results. The compatibility of the drug in the formulation was confirmed by FTIR studies. The formulations were subjected to disintegration, *in vitro* drug release studies and formulation FT5 was found to be best formulation which contain HPMC+ Maltodextrin as film forming polymers along with telmisartan solid dispersion with polyvinyl pyrrolidone K30 at weight ratio of 1:4 showed excellent film forming characteristics such as disintegration time of 57 sec and percentage drug release 90.34% within 10 minutes.

KEY WORDS

Telmisartan, Solid dispersions, Fast is dissolving film, Maltodextrin and HPMC.

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INTRODUCTION

Recently fast dissolving drug delivery systems have started gaining popularity and acceptance as new drug delivery systems which aim to enhance safety and efficacy of a drug molecule by formulating into a convenient dosage form for administration and to achieve better patient compliance. They undergo rapid disintegration in the salivary fluids of the oral cavity in less than a minute, where they release the drug¹. Most of the drug is swallowed orally with the

saliva and the absorption of drug takes place in the gastro-intestinal tract. The fast dissolving dosage forms are referred by various names by researchers like quick disintegrating, orally disintegrating, rapidly disintegrating, mouth dissolve or melt in mouth dosage forms². Telmisartan is an Angiotensin II Receptor Antagonist, which is used in the prevention and treatment of Hypertension. Telmisartan belongs to class II drug in BCS classification the major problems with it is its low solubility in biological fluids, which results into poor bioavailability after oral administration and late onset of action. In order to enhance the solubility of Telmisartan and subsequently dissolution and absorption, Solid dispersions of Telmisartan were prepared by kneading technique at different drug carrier (PVP) weight ratios and were evaluated^{3, 4}. The optimized formulation of solid dispersions, TEL PVP was selected and used in the preparation of TEL films by solvent casting method, which offers superiority over other practicing methods. The casted films were evaluated and *in vivo* therapeutic efficacy was assessed by comparing with that of conventional formulation.

Advantages of telmisartan fast dissolving film include⁵

- Patient of increases Hypertension not capable to swallow large quantities of water.
- In case of high blood pressure quick onset of action required because uncontrolled high blood pressure create Strokes, Heart attack, Kidney Problem.
- Hypertension markedly reduces functional ability and extremely restlessness in such cases rapid onset of action required.
- No Marketed Telmisartan film available in India.
- Specially intended to geriatric patients who have problem of swallowing.

MATERIALS AND METHOD

Materials

Telmisartan was obtained as a gift sample from Aurobindo Pharma Ltd, Hyderabad, Maltodextrins from Loba Chem Pvt. Ltd., Mumbai, Hydroxypropyl methylcellulose (HPMC-K4M) from S.D. Fine

Chem Ltd., Mumbai and polyvinyl pyrrolidone (PVP) were procured from Merck Pvt, Ltd. Mumbai. All other chemicals used were of analytical grade.

METHODOLOGY

Standard Curve of Telmisartan

Telmisartan is a white fine powder which is practically insoluble in water. Though several methods are reported for its estimation, the UV spectrophotometric method is employed in the study. Telmisartan shows maximum absorbance at 290 nm in phosphate buffer of 7.5 p^H. Based on this information, a standard graph was constructed (Figure No.1).

Preparation of telmisartan solid dispersions

Using solvent evaporation method

Telmisartan solid dispersions were prepared by solvent evaporation method using polyvinyl pyrrolidone (PVP K30) as carrier in different proportions 1:1, 1:2, 1:3 and 1:4 (drug : carrier) as shown in (Table No.2). The drug and carrier were dissolved in chloroform in a china dish and the mixture was heated until the solvent gets evaporated and a clear film of drug and carrier was obtained. Dispersions were pulverized in a mortar and pestle and passed through a sieve no: 10 before packing in an airtight container.

Characterization of solid dispersions

% Practical Yield

Percentage practical yield is calculated to know about percent yield, thus its help in selection of appropriate method of production. Solid dispersions were collected and weighed to determine practical yield (PY) from the following equation (Figure No.2).

$$\text{Percentage of practical yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

Drug content

10 mg of solid dispersions were weighed accurately and dissolved in 10 ml of methanol. The solution was filtered, diluted suitably and drug content was analyzed at 216nm by UV spectrophotometer. Each sample analyzed in triplicate (Figure No.3). Actual drug content was calculated for all batches using the equation as follows.

$$\text{Percentage of drug content} = \frac{\text{Observedvalue}}{\text{Actualvalue}} \times 100$$

In vitro drug release studies

The release profile of an entrapped drug predicts how a delivery system might function and gives valuable insight into its *in vivo* behaviour. *In vitro* release profile for each solid dispersion as well as pure drug was performed using USP XXII type2 dissolution apparatus. Sample equivalent to 10 mg of Telmisartan was added to 900ml of phosphate buffer of p^H 7.5 at 37±0.5°C and stirred at 75 rpm (Table No.3). Aliquot of 5 ml was withdrawn at time intervals of 15, 30, 45 and 60 min. The withdrawn volume was replenished with the same volume of dissolution medium in order to keep the total volume constant. The absorbance of the samples was measured at λ_{max} 290 nm after suitable dilution if necessary, using appropriate blank. Results of *in vitro* drug release studies obtained from absorbance data were shown graphically as cumulative percentage drug released versus time (Figure No.4).

PREPARATION OF FAST DISSOLVING FILMS

Accurately weighed quantities of film forming polymers such as HPMC of various grades, plasticizers, salivary stimulating agent and flavoring agent were dissolved in distilled water and resulting dispersion was stirred for 60 min at 70°C. Then the final solution was casted into a petri dish (area of 38.46 cm²) and it was dried at the room temperature. In initial attempts placebo films were prepared by omitting TEL. Later, the optimized TEL: PVP solid dispersion (1:4 ratio) with equivalent weight 20 mg of TEL was added to the formulation to obtain FDF of TEL (Table No.4). After sufficient drying, film was cut into 2×2 cm square strips. The prepared square thin film strips were stored in a desiccator for further studies.

Evaluation of fast dissolving films

Tackiness, folding endurance and thickness

Six films of final formulations were randomly selected. Each of the strips was pressed against the fingertips and tackiness was recorded. Results were

noted in qualitative terms as tack and non-tacky. Folding endurance of prepared films was determined by repeatedly folding a small strip of film (2 × 2 cm²) at the same place until it breaks, was noted as the folding endurance value. The test was conducted for six film strips. Films were measured for their thickness using micro screw-gauge at different strategic locations. Thickness test was to ascertain uniformity in the thickness of the prepared film, as thickness is proportional to the accuracy of dose in the strip.

Weight variation

Ten films were randomly selected and their average was calculated. Individual films were weighed and compared with the average weight for the deviation and reported.

Disintegration studies

Petri dish method

The time for films (for six strips) to dissolve was recorded using modified disintegration method. In this disintegration test, a petri dish was filled with 2 mL of distilled water and the film strip was carefully placed on the surface of water and the time is recorded until the oral film was dissolved completely.

Drug content

Drug content determination of the film was carried out by dissolving the film of 2 cm² in 100 ml of pH 6.8 phosphate buffer using magnetic stirrer for 1 hour. The drug concentration was then evaluated spectrophotometrically at λ_{max} of 290 nm (Table No.5). The determination was carried out in triplicate for all the formulations and average with standard deviation was recorded and reported.

Surface p^H

The surface pH was found to be in the range of 6.11 to 6.88, which is closer to neutral pH indicating that FDFs may have less potential to irritate the sublingual mucous and hence, more acceptable by the patients.

In-vitro dissolution studies

The dissolution studies were conducted using simulated salivary fluid (SSF) consisting of each film strip (containing drug equivalent to 20 mg) was then submerged into the dissolution medium. The

dissolution study was carried out using dissolution test apparatus USP type-I at 37°C, at 50 rpm, using 900 ml phosphate buffer saline (pH 6.8) as a dissolution medium (Table No.6). Test samples were withdrawn at different time intervals and analyzed spectrophotometrically at 290 nm. The absorbance values were transformed into concentration using standard graph (Figure No.5).

RESULTS AND DISCUSSION

Among the four formulations of solid dispersions i.e. F1, F2, F3 and F4, the optimized formulation is F4 which shows maximum drug content and percentage drug release compared to other formulations (Figure No.4). These optimized Telmisartan Polyvinyl pyrrolidone solid dispersions (TEL: PVP) at weight ratio of 1:4 prepared by solvent evaporation method was selected for this study. It is proposed to formulate and develop the fast dissolving films of above solid dispersions to evaluate the efficacy of PVP solid dispersions in the FDF formulation. The formulated FDFs were appeared to be clear, homogeneous, some are transparent and some are partially transparent. They were found to be physically flexible, non-tacky and dry. The folding endurance was measured manually, by folding the FDF repeatedly at a point till it broke. The breaking time was considered as the end point. Folding endurance was found to be highest for FT3 and lowest for FT1. It was found that the folding endurance of the FDF was affected with increase of carrier concentration. The folding endurance values of the FDF were found to be optimum and therefore, the FDFs exhibited the good physical and mechanical properties. The folding endurance of films was found to be in the range of 75 to 90 (Table No.5). As all the formulations contain different amount of polymers, the thickness was gradually increased with the amount of polymers. All the film formulations were found to have thickness in the range of 0.198 to 0.261 mm and were observed within the limits.

Weight variation and surface pH

The randomly selected film strips about 1×1 cm² area were cut at different places from the casted film and weight was measured. Weight of film strip units varies from 192.02 to 202.54 mg. The results indicated that selected carriers, solvent used in method of solid dispersion preparation, proportion of carrier used have reduced the variation and improved the uniformity of the distribution in casted films (Table No.5). The surface pH was found to be in the range of 6.15 to 6.85, which is closer to neutral pH indicating that FDFs may have less potential to irritate the sublingual mucous and hence, more acceptable by the patients.

Disintegration time

It was observed that *in vitro* dissolving/disintegration time varies from 54 to 87 sec for all the formulations (Table No.5). *In vitro* disintegration time of FDFs was affected by polymers viz. HPMC K4M and malt dextrin. This is due to polymer's high water absorption and retention capacities.

Drug content

The prepared film formulations were assayed for their drug content. Results showed the more uniformity of the drug in the film strips and indicated the less drug loss in formulations as shown in (Table No.5).

In vitro dissolution studies

The *in-vitro* drug release profiles of the formulations in SSF pH 6.8 show differences depending on their composition. The rate of drug release from the HPMC K4M films was significantly lower than the films containing Maltodextrin along with the HPMCK4M (Figure No.5). This is due to the swelling of the high viscosity HPMC K4M upon contact with the dissolution medium, resulting in the formation of a thick matrix gel, thereby hindering the release of the drug from the film which shows the dissolution of 70% at the end of 10 min whereas FT5 films containing combination of HPMC and Maltodextrin as hydrophilic polymers shows high percentage of drug release (90%) within 10 minutes compared to that of films containing HPMCK4M alone as a polymer.

FTIR STUDIES

FT-IR spectra of pure telmisartan, maltodextrin, HPMC, PVP K30 and their combinations were shown in the (Figure No.6-12). Pure telmisartan showed principal absorption peaks at 1697.56 cm⁻¹ (C=O stretching), 1614.62 cm⁻¹ (C=C aromatic stretching), 740.76 cm⁻¹ (C-H aromatic bending), 2957.23 cm⁻¹ (C-H stretching), 1599.18 cm⁻¹ (C-C

bending), 3055.62 cm⁻¹ (C-H aromatic stretching), and 1267.39 cm⁻¹ (C-O stretching). Same peaks of C=O, C=C, C-H, and C-C bonds were present as that of pure drug without much shifting in the spectra of telmisartan along with the polymers. This suggested no chemical interaction between the drug and polymers.

Table No.1: Standard curve of telmisartan in phosphate buffer of p^H 7.5

S.No	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.05
3	4	0.18
4	6	0.27
5	8	0.36
6	10	0.40

Table No.2: Formulation plan of Telmisartan solid dispersions

S.No	Formulation	Drug: Polymer (mg)
1	F1	1:1
2	F2	1:2
3	F3	1:3
4	F4	1:4

Table No.3: In-vitro drug release data of solid dispersions

S.No	Time	Percentage cumulative drug release				
		Pure drug	1:1	1:2	1:3	1:4
1	15	17.1	25.20	37.62	49.14	59.76
2	30	38.2	41.90	50.10	61.47	71.67
3	45	42.5	51.49	60.17	72.61	80.47
4	60	45.9	58.80	71.92	81.65	92.07

Table No.4: Formulation plan of Telmisartan fast dissolving films

S.No	Ingredients	FT1	FT2	FT3	FT4	FT5	FT6
1	TEL:PVP(equivalent to 20mg of Tel)	37.26	37.26	37.26	37.26	37.26	37.26
2	HPMCK4M	100	120	---	---	50	60
4	Maltodextrin	---	---	100	120	50	60
5	Propylene glycol	40	30	40	30	40	30
6	Citric acid	20	10	20	10	20	10
7	Water up to (ml)	20	20	20	20	20	20

Table No.5: Evaluation data for fast dissolving films

S.No	Formulation code	Weight variation	Thickness	Folding endurance	%Drug content	Disintegration time
1	FT1	175.01±0.25	0.250±0.81	75±1.78	65.43±0.66	90±0.78
2	FT2	152.52±0.96	0.261±0.67	87±1.26	62.66±0.87	87±0.82
3	FT3	167.61±0.35	0.198±1.02	90±1.07	67.42±0.73	85±0.62
4	FT4	195.73±1.06	0.252±1.05	82±0.76	58.32±0.84	70±0.56
5	FT5	192.02±1.24	0.185±0.92	85±0.78	85.76±0.72	66±0.91
6	FT6	202.54±0.93	0.201±0.87	79±1.56	75.94±1.03	57±0.78

Table No.6: In-vitro drug release data of fast dissolving films

S.No	Time(min)	Percentage drug released					
		FT1	FT2	FT3	FT4	FT5	FT6
1	2	15.13	25.34	26.42	27.56	28.87	28.97
2	4	20.35	30.23	33.47	35.18	45.46	48.46
3	6	40.67	49.21	54.96	43.27	60.56	75.18
4	8	62.50	65.22	77.81	54.91	80.12	80.21
5	10	70.12	78.34	80.26	77.06	90.56	87.57

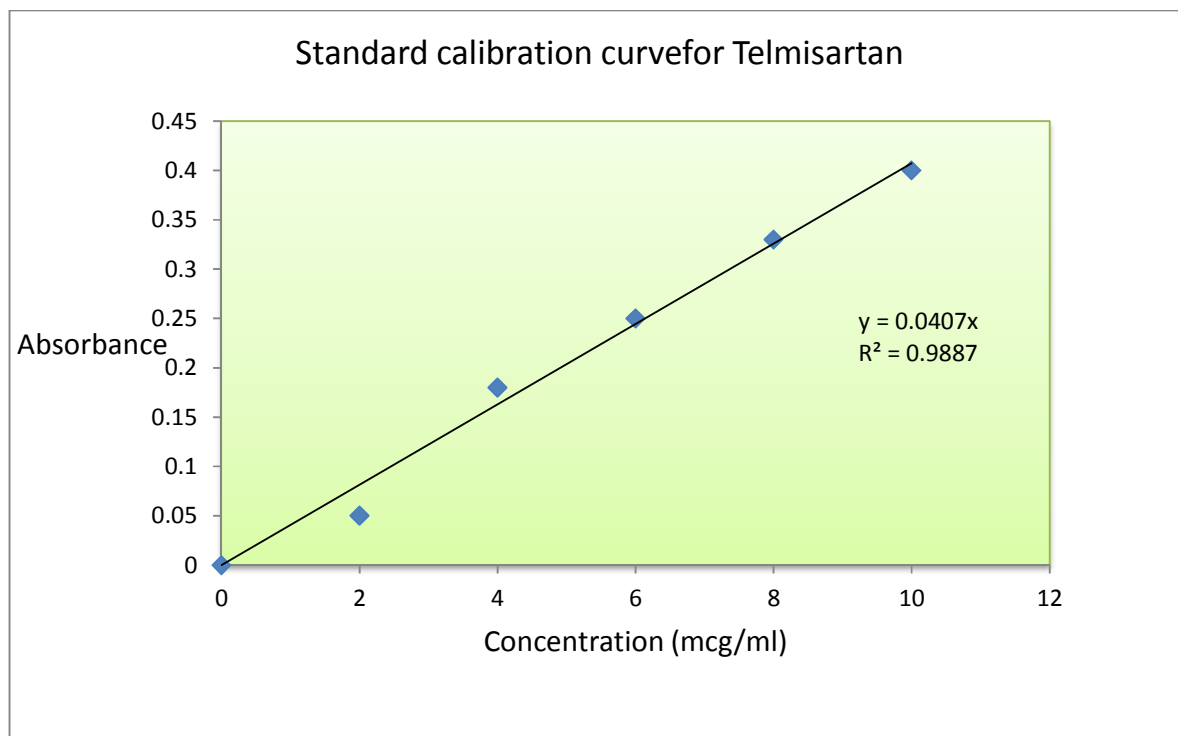


Figure No.1: Standard plot of telmisartan in phosphate buffer

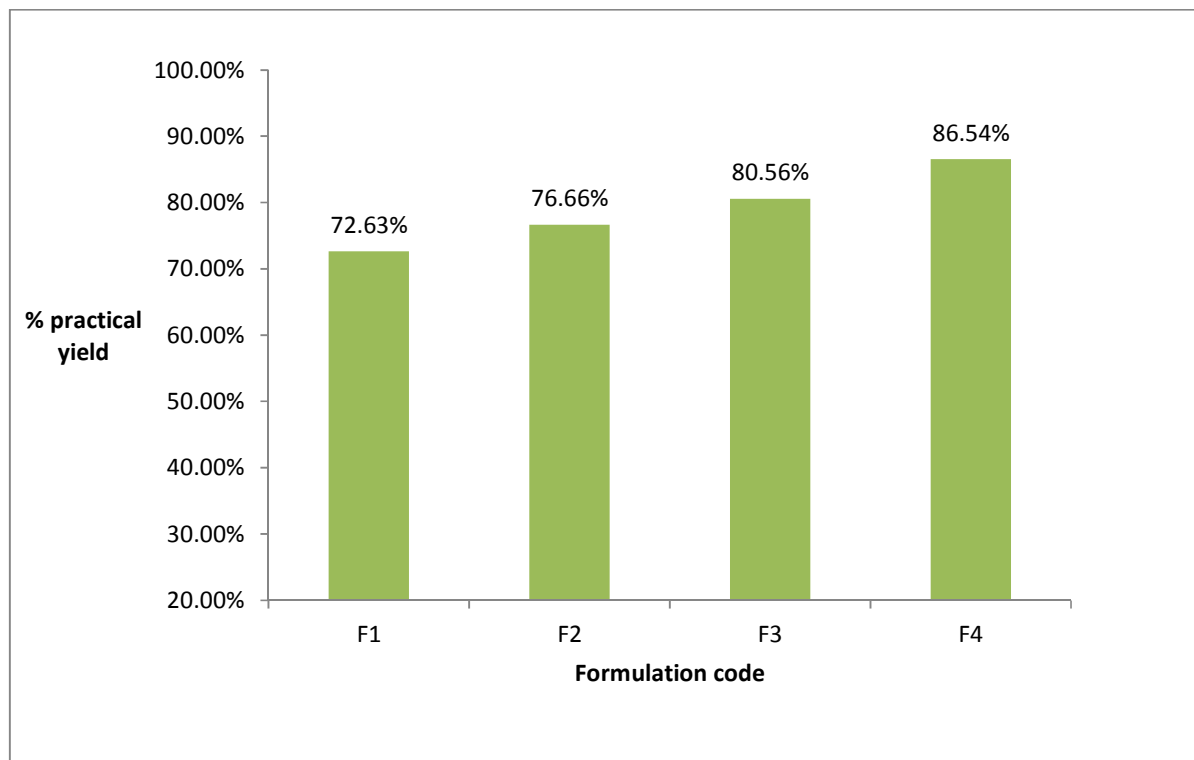


Figure No.2: Percentage practical yield of solid dispersions

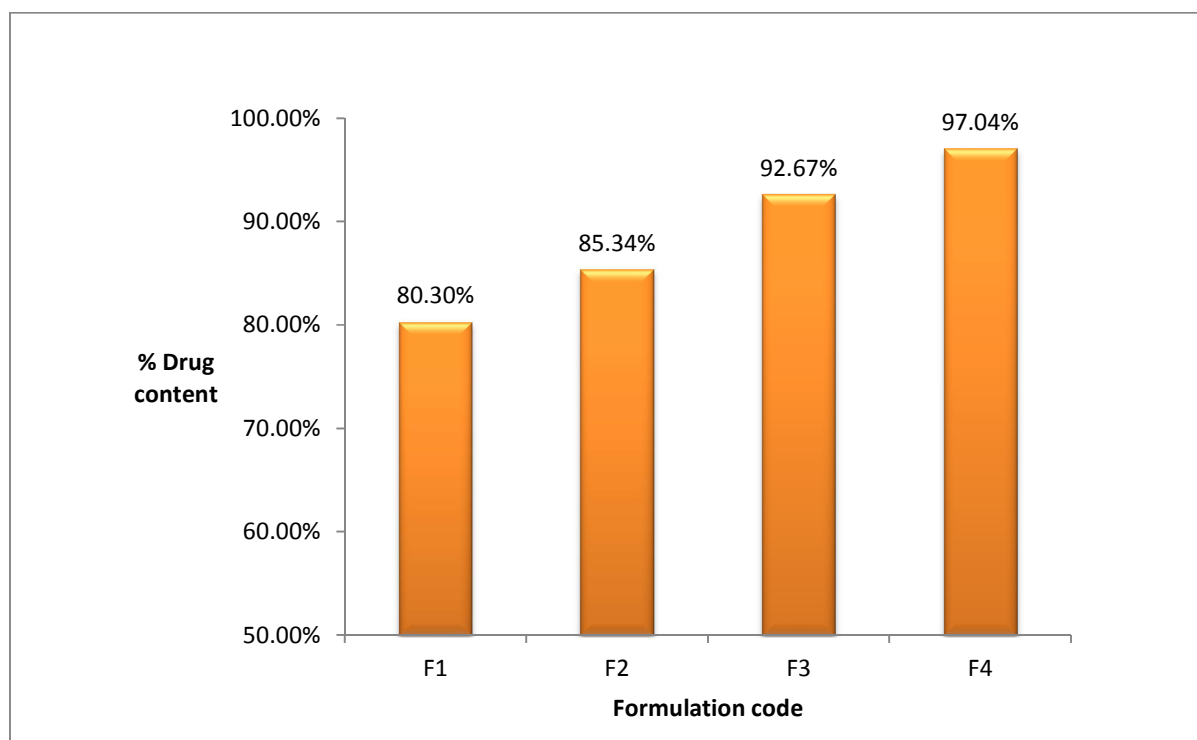


Figure No.3: Percentage drug content of solid dispersions

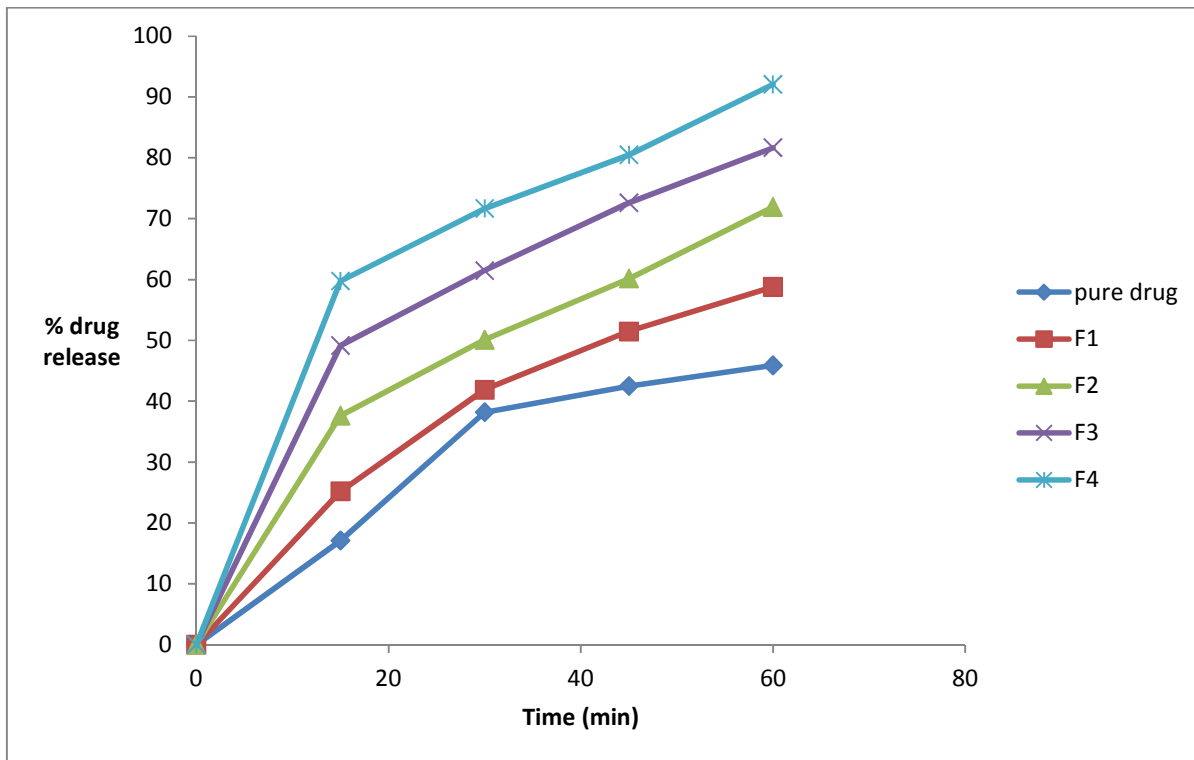


Figure No.4: Dissolution profile of solid dispersions of telmisartan

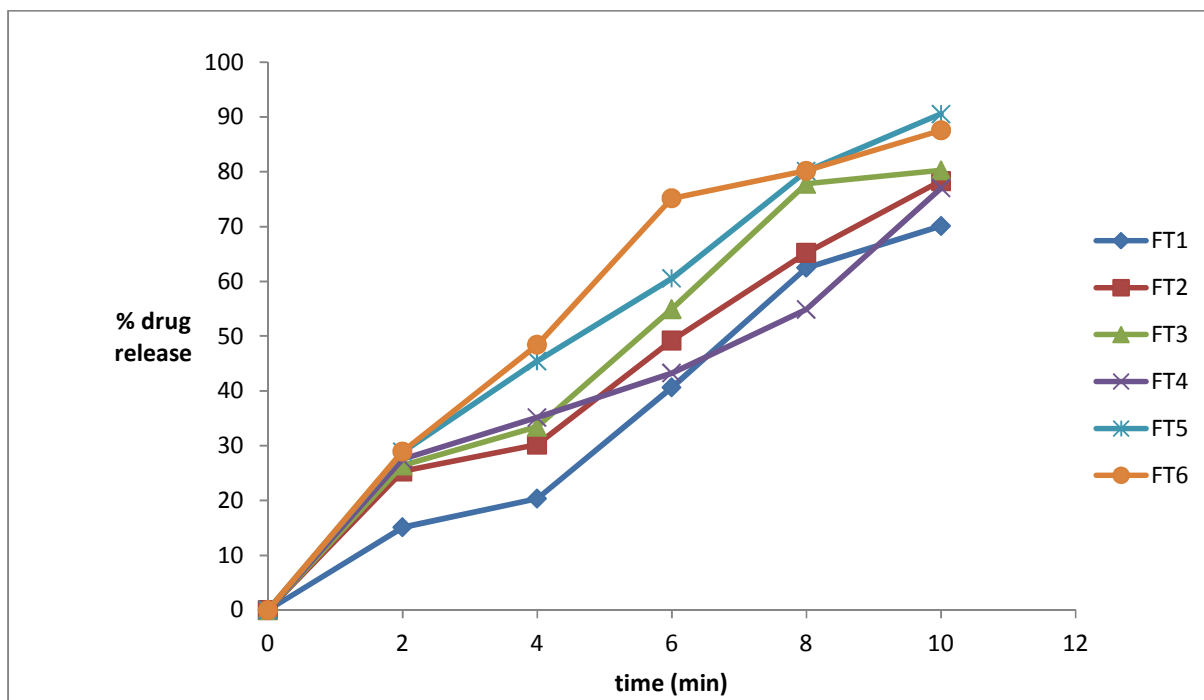


Figure No.5: Dissolution profile of fast dissolving films

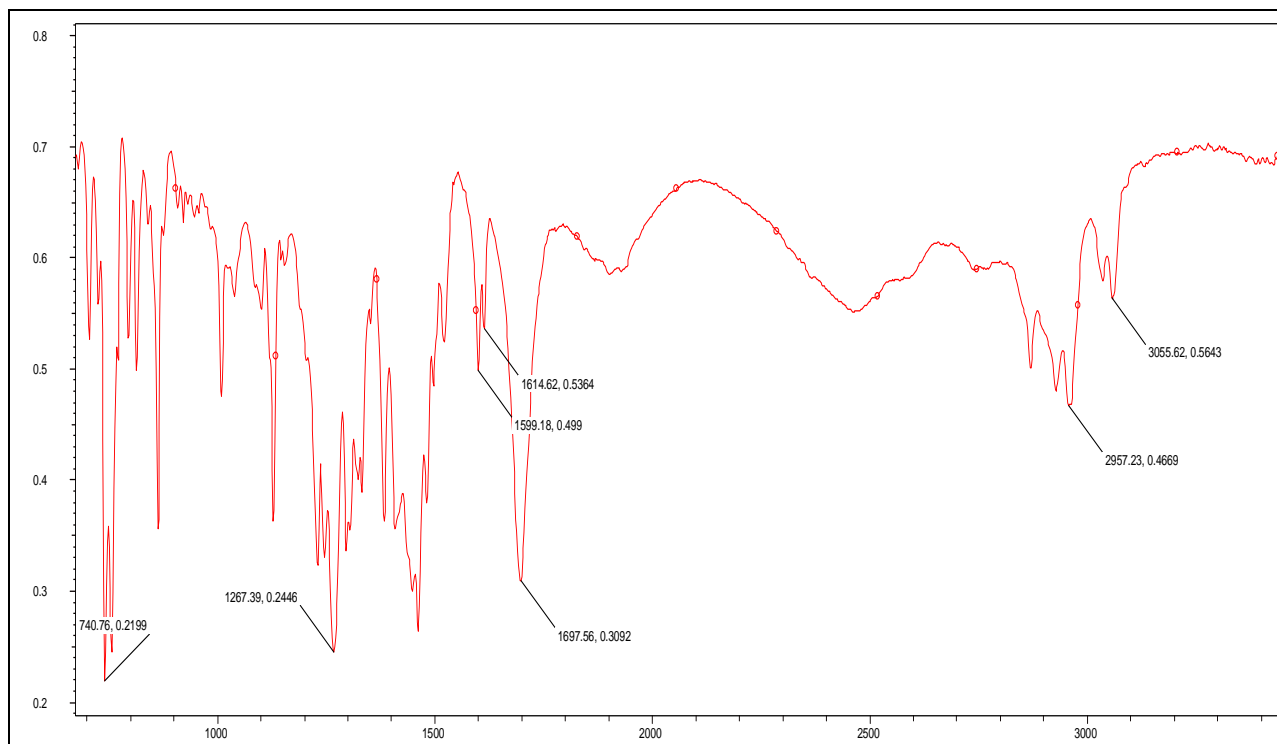


Figure No.6: FT-IR spectrum of telmisartan

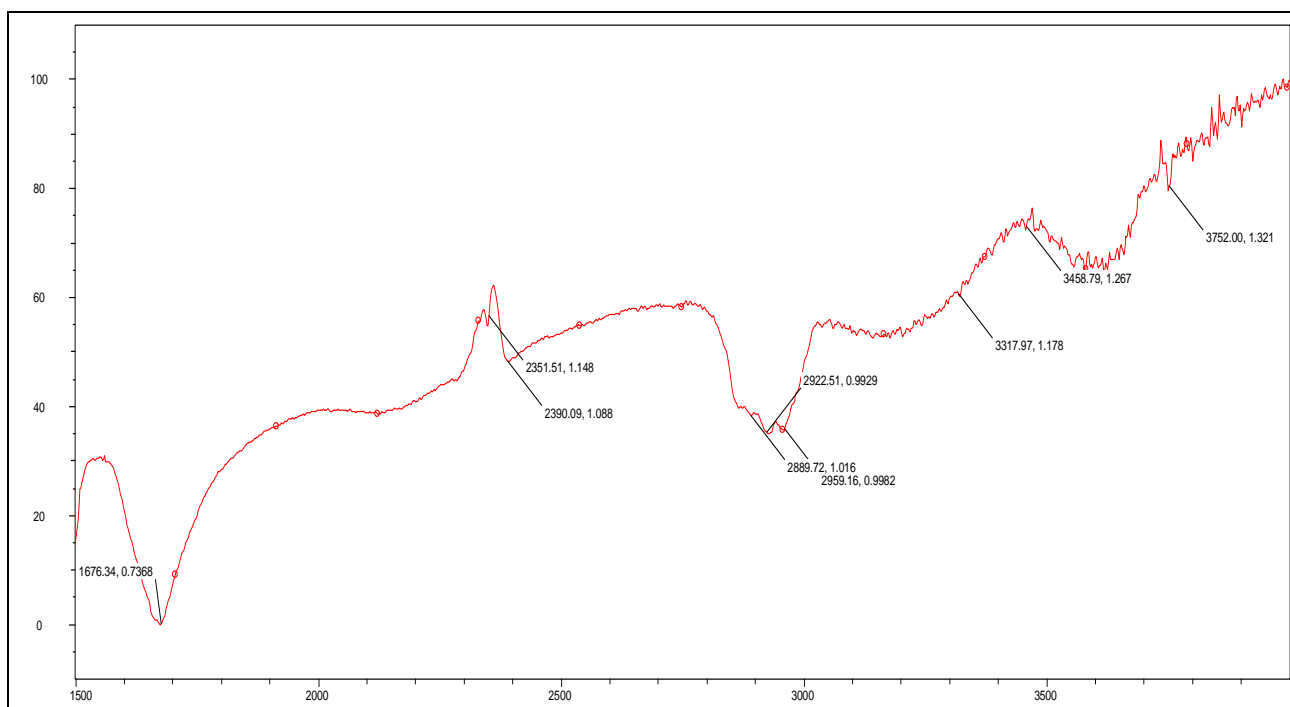


Figure No.7: FT-IR spectrum of PVP K30

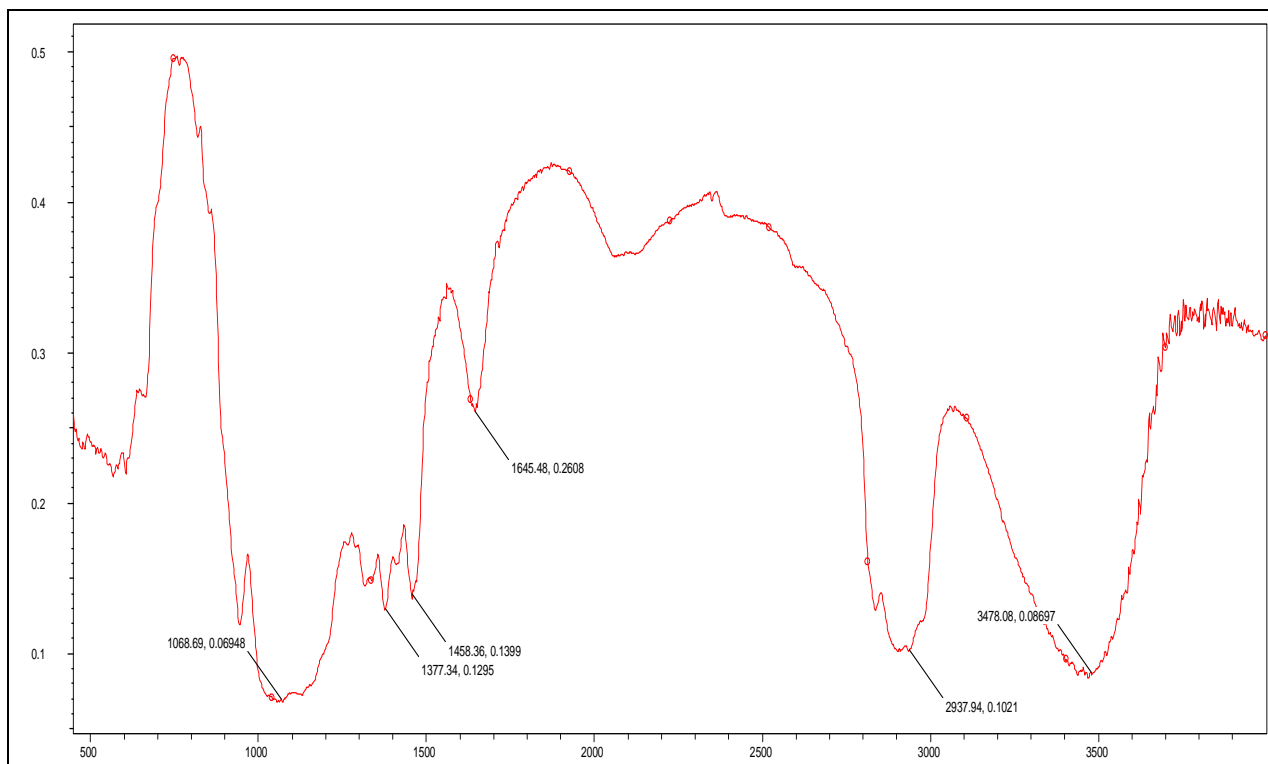


Figure No.8: FT-IR spectrum of HPMC

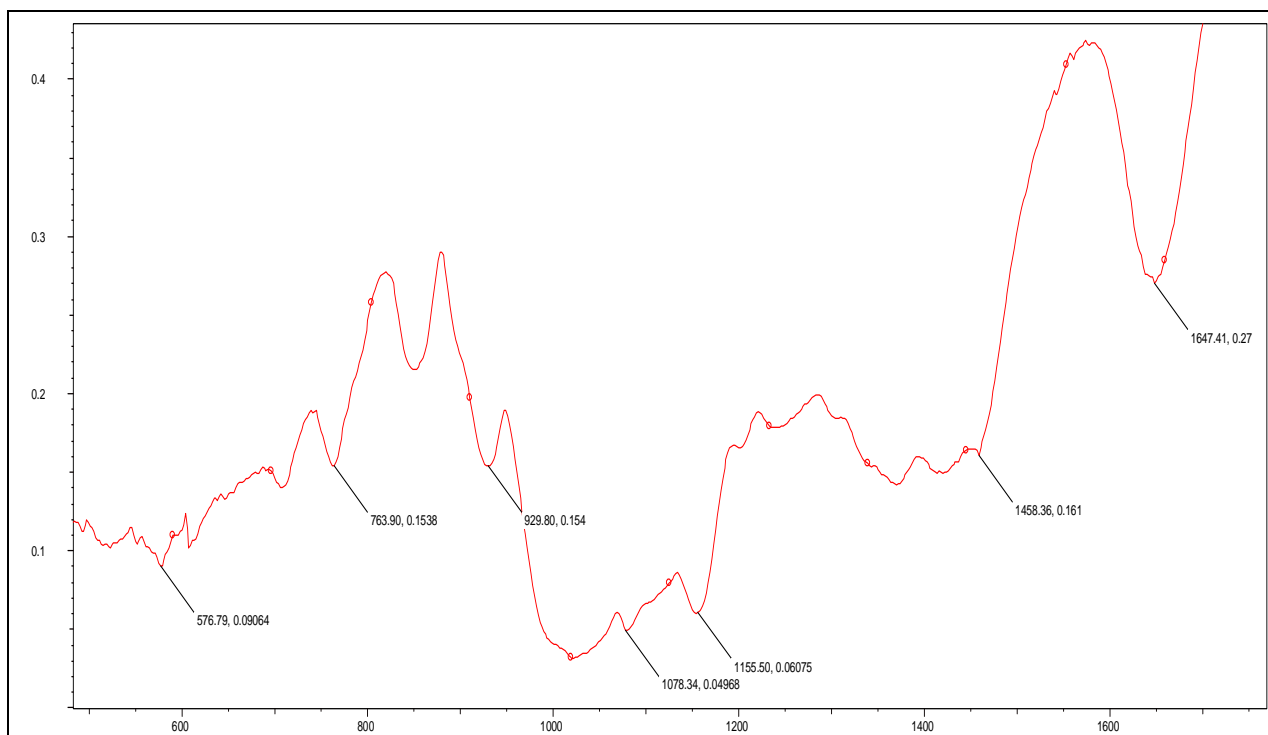


Figure No.9: FT-IR spectrum of Maltodextrin

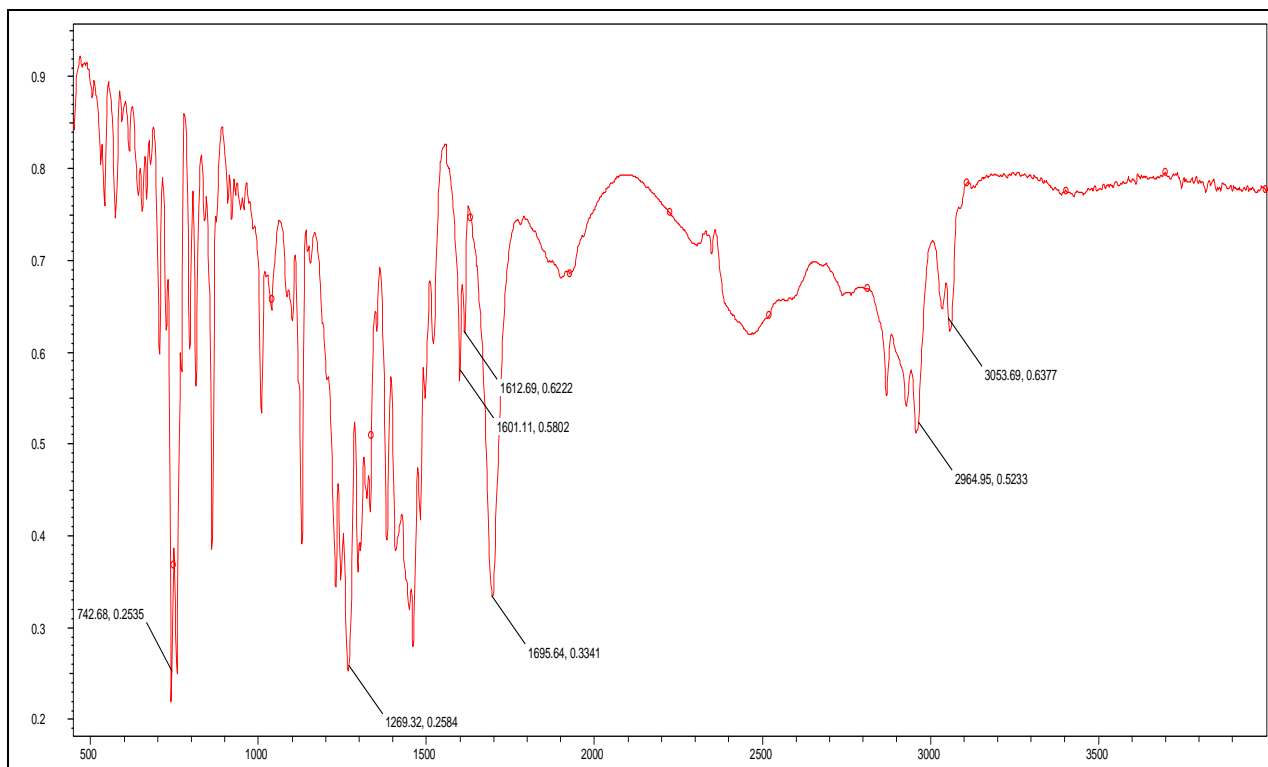


Figure No.10: FT-IR spectrum of telmisartan with maltodextrins

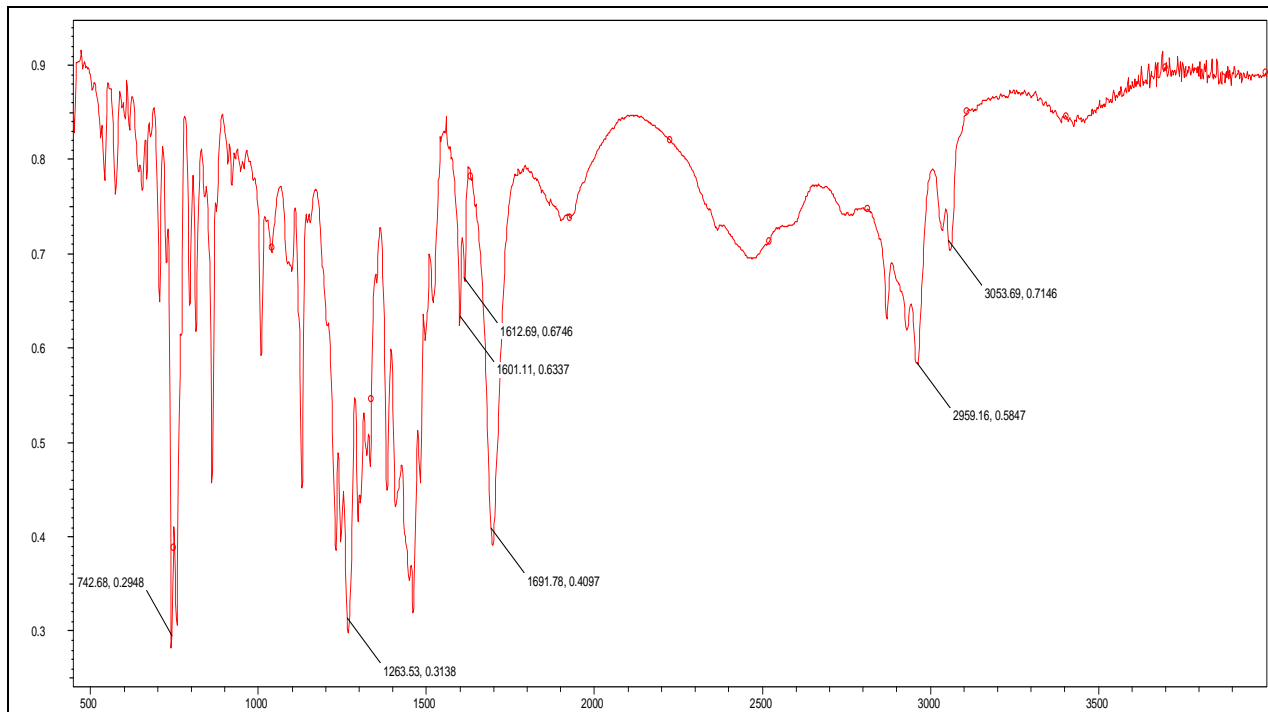


Figure No.11: FT-IR spectrum of telmisartan with HPMC

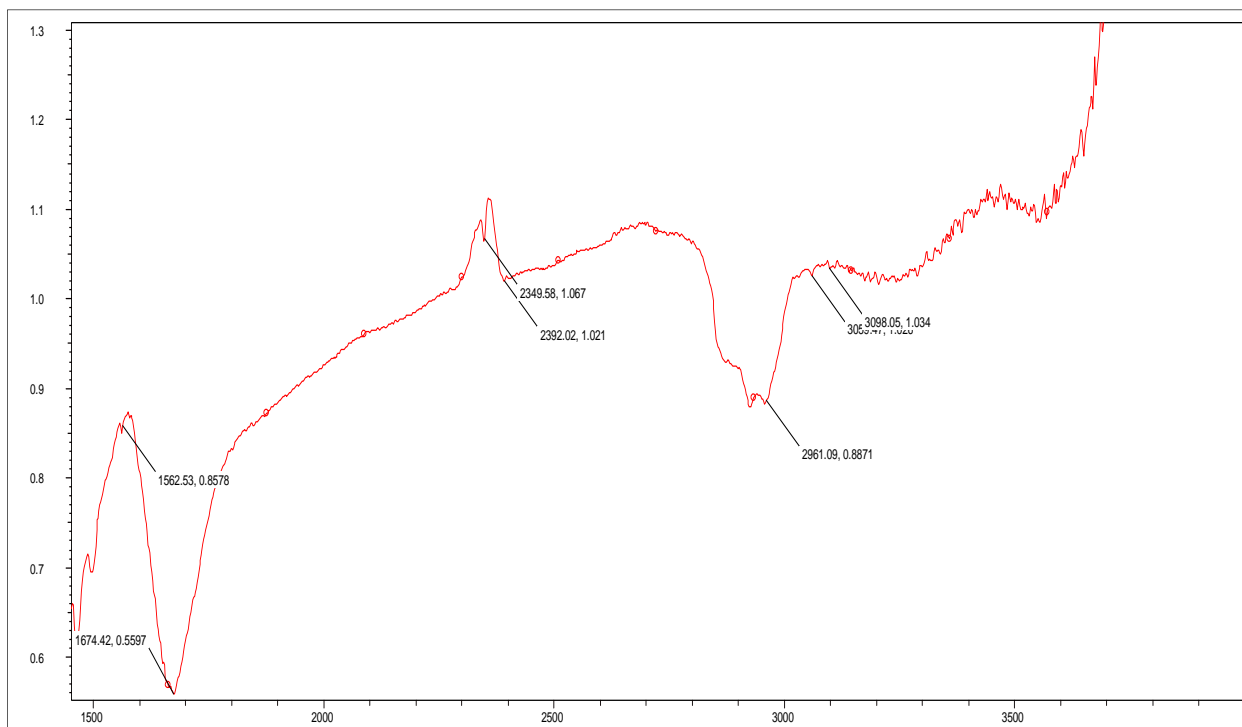


Figure No.12: FTIR spectrum of telmisartan with PVP K30

CONCLUSION

Fast dissolving oral films or melt in mouth films constitute an innovative dosage form and are having great importance during the emergency cases such as allergic reactions and asthmatic attacks whenever immediate onset of action is desired. In the present study, Telmisartan solubility was enhanced by the solid dispersion technique using carrier like PVP K30 and the optimized F4 formulation was incorporated in to the fast dissolving film. Among all the formulations telmisartan oral fast dissolving films containing combination of HPMC and Malt dextrin as hydrophilic polymers shows high percentage of drug release within 10 minutes compared to that of films containing HPMC alone as a polymer. Present study reveals that fast dissolving films can be a potential novel drug delivery system for geriatric, pediatric and also for general population.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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