Journal of Pharmaceutical Research Vol. 11, No. 2, April 2012 : 92-99.

FORMULATION DEVELOPMENT AND EVALUATION OF FAST DISSOLVING TABLETS OF TELMISARTAN

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Received on : 26.06.2012 Revised : 29.06.12 Accepted : 19.07.12

ABSTRACT

Present investigation was undertaken with a view to develop fast dissolving tablets of Telmisartan which offers a new range of product having desired characteristics and intended benefits. Fast dissolving tablets of Telmisartan using various superdisintegrants such as Sodium Starch Glycolate (SSG), Crosspovidone (CP) and Crosscarmellose sodium (CCS) were formulated by direct compression method and evaluated for physicochemical parameters, content uniformity, i*n vitro* release and stability studies. All the formulation batches showed drug release in the range of 98.6% - 100.6% within 20 min. Disintegration time of all batches was less than 1 min. The best formulation F6 containing 5% CP and 2.5% â-cyclodextrin exhibited 98.8% drug release within 15 min and disintegration time of 13 sec. The formulation F6 was found to be stable at accelerated conditions of temperature and humidity (40^{o}C and 75% RH). Fast dissolving tablets containing crosspovidone (5%) was found to give best results for *in vitro* disintegration and dissolution. Moreover, addition of â-cyclodextrin (2.5% w/w) might have enhanced swelling of tablet, thereby decreasing the disintegration time and increased wettability and dispersability of tablets leading to improved dissolution.

Key words: *Crosscarmellose sodium; Crosspovidone; sodium starch Glycolate; â-Cyclodextrin; direct compression.*

INTRODUCTION

Although various novel and advanced drug delivery systems have been introduced for therapeutic use, the popularity of oral dosage forms particularly tablets have not been eclipsed, because of its numerous advantages[1]. Two widely faced drawbacks in oral drug delivery are dysphagia and delivery of unpalatable drugs, which may be a problem for mainly geriatric, pediatric, bedridden, nauseous or non-compliant patients[2]. Therefore, emphasis is laid on the development of viable dosage alternatives that has led to exploration of oral mucosal route as a substitute delivery approach for systemic action. The highly vascularised nature and rich blood supply in oral mucosa provide faster onset of action of drugs. Moreover several constraints such as difficulty in swallowing in case of paediatrics and geriatrics patients, nausea and vomiting experienced with certain drugs when released in stomach, degradation and metabolism of susceptible drugs in GIT are avoided through oromucosal delivery of drugs[3]. It is estimated that 50% of the population is affected by this problem which results in a high incidence of noncompliance and ineffective therapy[2]. Traditional tablets and capsules administered with 250 ml of water may be inconvenient or impractical for such population. Hence, fast dissolving/disintegrating tablets (FDDTs) are a perfect fit for them. FDDTs dissolves or more commonly disintegrate rapidly in the saliva without the aid of water[4]. For this reason the development of mouth dissolving or rapidly disintegrating tablets (RDT) with proper taste masking are among recent trends in pharmaceutical market[2]. The fast dissolving/ disintegrating dosage forms are well established in the management of pain, inflammation, vomiting, headache and hypertension. Valuable research reports for formulation of rapidly disintegrating tablets are available; also various technologies for improving dissolution property of poorly water soluble drugs have been documented to enhance bioavailability following oral absorption[5]. Telmisartan is a promising drug candidate to formulate fast dissolving tablet (FDT). Telmisartan is an angiotensin II receptor antagonist (ARB) used in the management of hypertension with half-life of approximately 24 hours. The bioavailability of Telmisartan is poor (about 45 to 60%) which is due to extensive first pass metabolism. Conventional Telmisartan tablet available in market are not suitable where quick onset of action is required[6]. Present work reports preparation of fast dissolving tablets of Telmisartan using superdisintegrants such as Crosscarmellose sodium, Crosspovidone and Sodium starch glycolate and evaluated for their physiochemical parameters, *in vitro* dissolution and content uniformity and stability studies.

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MATERIALS AND METHODS

Telmisartan was procured from Sequel Pharmaceuticals Ltd. India. Avicel 112, Mannitol 400DC, Crosscaromellose Sodium, Crosspovidone and Sodium Starch Glycolate were purchased from Signet Chemical Corporation, Mumbai, India. â-cyclodextrin and Aspartame was kindly gifted by Ontop Pharmaceutical Pvt. Ltd. Bangalore. All other chemical used were of analytical grade.

METHODS

Preformulation studies

Melting point of drug

Melting point of drug was done by the capillary tube method using melting point apparatus (Servewell Instrument Pvt. Ltd.). Pure drug was filled into the capillary tube and capillary tube was kept in apparatus melting point seat at 260ÚÆC and capillary tube was observed till drug was melted. The temperature at this point was noted as melting point of drug.

FTIR of drug & excipient

FTIR spectrum was recorded of pure drug and excipients. The samples were analyzed by KBr pellet method using FTIR spectroscopy.

Drug Excipient compatibility

Pure drug and various excipients were mixed in equal amounts and the mixtures were kept for 3 days and then analyzed by FTIR spectroscopy for any interaction between drug and excipient.

Preparation of Fast Dissolving Tablets by Direct Compression Method

The critical parameters to formulate a fast dissolving tablet are choice of superdisintegrant and optimization of concentration of superdisintegrant. Fast dissolving tablet of Telmisartan were prepared by direct compression method using different superdisintegrants like Sodium Starch Glycolate, Crosscarmellose Sodium, Crosspovidone. Telmisartan (pure drug) was first converted into granulated form by adding PVP K-30 as binder using isopropyl alcohol as solvent and mixing by mechanical stirrer. The pure wet drug mass was sieved through # 12mm mesh and dried in hot air oven at a temperature of 45-55ºC for 2h, till the moisture content of dried mass of drug was 1-2%. High temperatures lead to change in color of drug, so low temperature range and longer period was preferred. The dried drug mass was further sieved through # 60 mesh. The granular drug was mixed with other ingredients (Sodium Starch Glycolate, Crosscarmellose Sodium, Crosspovidone, Avicel 112, Mannitol, â-cyclodextrin) and the active mass blend was passed through # 60 mesh (to get uniform size powder blend) and again mixed for 15 min in poly bag. Lubricating agent like talc, magnesium stearate and Aerosil, Raspberry flavour (passed through # 60 mesh) were added at last to the mixture and thoroughly mixed just before compression. The active drug blend was evaluated for flow properties and tablets were then compressed using 8mm flat punches in 8 station tablet machine. The composition of various batches is shown in Table 1.

Table 1: *Composition of various formulation batches (F1-F12)*

Formulation Code/ Ingredients*	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Telmisartan	20	20	20	20	20	20	20	20	20	20	20	20
Sodium Starch Glycolate	10	–	–	10	–	–	10	–	–	10	10	–
Cross Carmellose Sodium	–	10	–	–	10	–	–	10	–	10	–	10
Cross Povidone	–	–	10	–	–	10	–	–	10	–	10	10
â-Cyclodextrin	–	–	–	5	5	5	20	20	20	–	–	–
Avicel PH	102	102	102	97	97	97	82	82	82	92	92	92
Mannitol 400DC	55	55	55	55	55	55	55	55	55	55	55	55
Aspartame	8	8	8	8	8	8	8	8	8	8	8	8
Raspberry flavor	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75
Talc	1	1	1	1	1	1	1	1	1	1	1	1
Magnesium Stearate	2	2	2	2	2	2	2	2	2	2	2	2
Aerosil	1	1	1	1	1	1	1	1	1	1	1	1
PVP K30	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Isopropyl Alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total weight	200	200	200	200	200	200	200	200	200	200	200	200

**all quantities are expressed in mg.*

Evaluation of pre-compression parameters

Bulk Density

It was determined by Tap density tester (Electrolab-ETD-1020) by pouring a weighed quantity of blend into graduated cylinder and measuring the volume and weight[7].

BD = Weight of the powder / initial Volume

Tapped Density

It was determined by Tap density tester (Electrolab-ETD-1020) by placing a graduated cylinder, containing a known mass of drug-excipients blend. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10 cm at 2 second intervals. The tapping was continued until no further change in volume was noted.

TBD = weight of the powder / volume of the tapped packing

Angle of Repose

Angle of repose was determined by using funnel method. The accurately weighed blend was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of blend. The drug (as solid dispersion)-excipient blend was allowed to flow through the funnel freely on to the surface[7]. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

Tan □ = h/r

Where h and r are the height and radius of the powder cone.

Hausner's Ratio

Hausner's ratio is an indirect index of ease of powder flow. It was calculated by the following formula:

Hausner's ratio = D_t / D_b

Where, D_t is the tapped density; D_b is the bulk density. Lower Hausner's ratio (<1.25) indicates better flow properties.

Carr's Index

It indicates compressibility characteristics of powder. It is expressed in percentage and is given by

$I = \{(D_t - D_b)/ D_t\} * 100$

Where, D_t is the tapped density and D_b is the bulk density of the powder.

Evaluation of post compression parameters:

Weight variation

Twenty tablets were randomly selected from each formulation and weighed using a Shimadzu digital balance (AX200). The mean SD values were calculated[8].

Hardness

Hardness or tablet crushing strength (the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester[5]. It is expressed in kg/cm^2.

Tablet Thickness

Ten tablets from each formulation were taken randomly and their thickness was measured with Vernier Calipers[8]. The mean SD values were calculated.

Tablet Diameter

Diameter of tablet was measured by using Vernier Calipers. Three tablets were selected at random from each batch [8]. It is expressed in mm.

Friability test

The friability of a sample of 20 orally disintegrating tablets was measured utilizing a USP-type Roche friabilator (Electro Lab Ef- 2 USP). Preweighed tablets were placed in a plastic chambered friabilator attached to a motor evolving at a speed of 25 rpm for 4 minutes[9]. The tablets were then dedusted, reweighed, and percentage weight loss (friability) was calculated.

$\% \text{ Friability} = [(W_1 - W_2) * 100]/W_1$

Where, W_1 is the weight of tablet before test; W_2 is the weight of tablet after test.

Wetting Time

Five circular tissue papers were placed in a petri dish of 10-cm diameter. Ten milliliters of water containing 0.5% eosin, a water-soluble dye, was added to the petri dish. The dye solution was used to identify complete wetting of the tablet surface. A tablet was carefully placed on the surface of the tissue paper in the Petri dish at 25°C. The time required for water to reach the upper surface of the tablets and to completely wet them was noted as the wetting time. These measurements were carried out in replicate of six. Wetting time was recorded using a stopwatch [10].

Water Absorption Ratio

A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of distilled water. A tablet was put on the paper and the time required for complete wetting of the tablet was measured[11]. The wetting tablet was then weighed. Water absorption ratio "R" was determined using the equation as follows:

$R = (W_a/W_b) \times 100$

Where W_b is weight of tablet before water absorption & W_a is weight of tablet after water absorption.

In vitro disintegration test

The USP disintegration test apparatus was used to determine disintegration time. 6 tablets from each formulation were tested in 900 ml water at 37°C. The study was done in triplicate.

In vitro dissolution studies

In vitro drug release from all formulation batches (F1-F12) was carried out using USP II dissolution apparatus. All the formulations were subjected to *in vitro* dissolution studies by using 900 ml of 0.1N HCl kept at 37°C and rotated at a speed of 75rpm. The aliquots were collected at specified time intervals (5, 10, 15, 20, 25 min) and analyzed by liquid chromatography. Percent drug release was then calculated. The study was done in triplicate. *In vitro* drug release was also determined for marketed formulation and compared with that of optimum batch. HPLC conditions followed were as specified in official standards[12].

Column: Stainless steel column 15 cm x 4.6mm, packed with octadecylsilane bonded to porous silica (5 ì m) (Such as Inertsil ODS-3); Mobile phase: a mixture of 60 volumes of buffer solution prepared by dissolving 2.72 g of potassium dihydrogen phosphate in 1000ml of water, add 2ml with orthophosphoric acid and 40 volume of acetonitrile; Flow rate: 1ml per minute; Detector: UV detector at absorption maxima of 298 nm; Injection volume: 20 ì l.

Drug Content Uniformity

Drug Content was determined by the assay method as specified in IP 2010[12].

Accelerated Stability Testing

The accelerated stability studies of selected tablet batch F6 were carried out in stability chamber (Thermo Lab) kept at 40°C and 75% RH conditions for three months. The effects of temperature and time on the physical characteristics of the tablet were evaluated for assessing the stability of the prepared formulations. The tablets were examined for their physical changes, drug content and *in vitro* dissolution after interval of 15 days, 1 month, 2 month and 3 months.

RESULTS AND DISCUSSION

Preformulation studies

Melting point:

The melting point of pure drug was in the range of 260°C to 262°C.

FTIR of drug & excipient

The FTIR spectra of pure drug and various excipients are shown in Figure (1 - 8). The IR spectra of drug showed characteristic peaks of drug as given in Table 2.

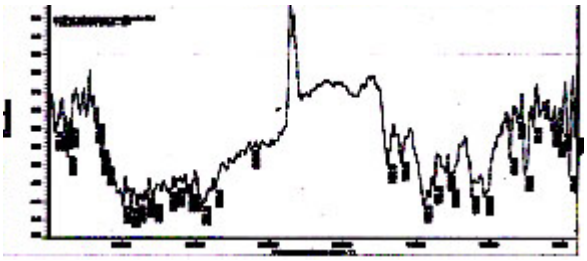

Fig. 1: *FTIR Spectra of pure drug Telmisartan*

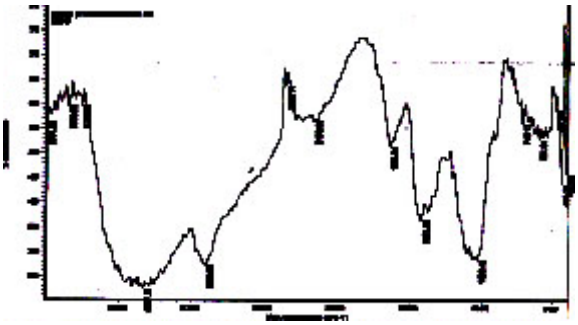

Fig. 2: *FTIR Spectra of Avicel -112*

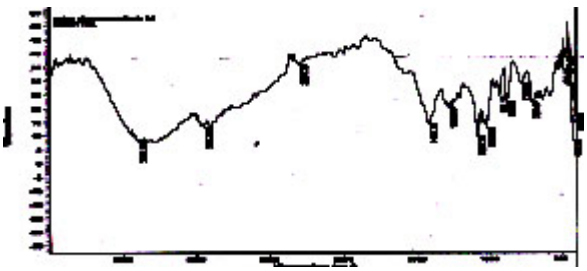

Fig. 3: *FTIR Spectra of Mannitol*

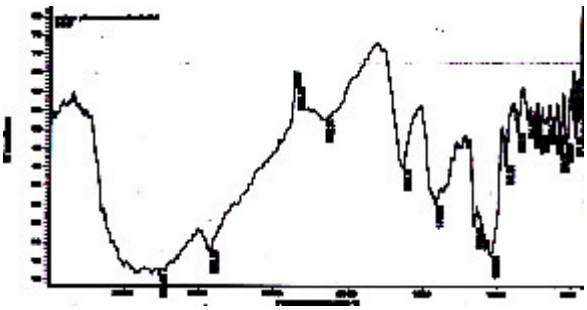

Fig. 4: *FTIR Spectra of □-Cyclodextrin*

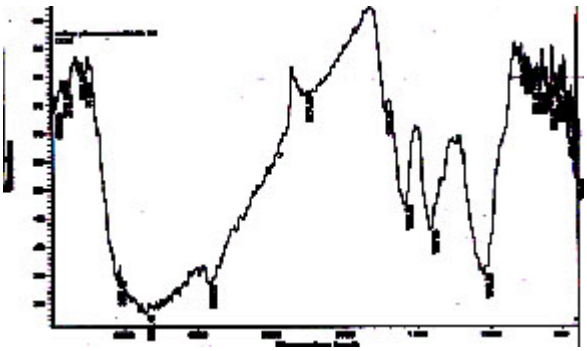

Fig. 5: *FTIR Spectra of Crosscarmellose Sodium*

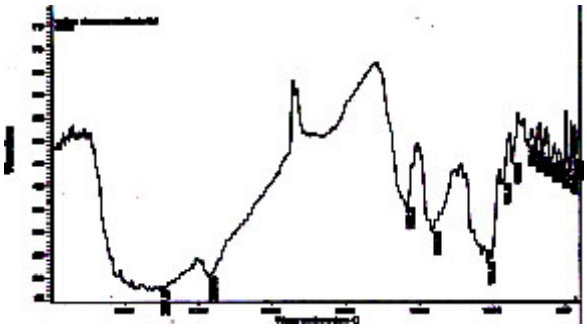

Fig. 6: *FTIR Spectra of Sodium Starch Glycolate*

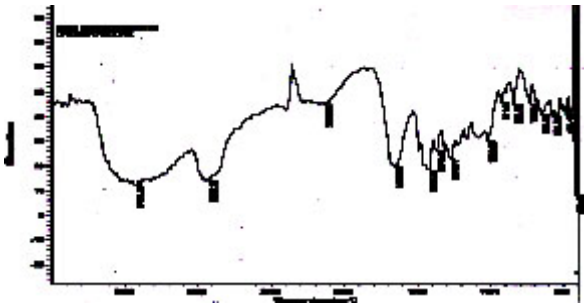

Fig. 7: *FTIR Spectra of Crosspovidone*

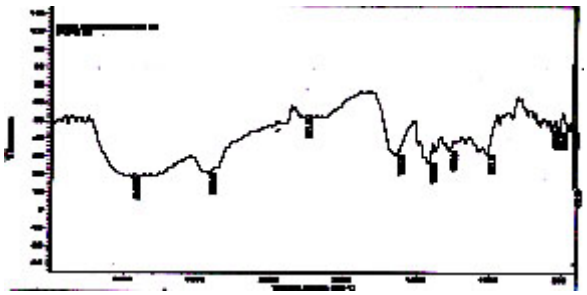

Fig. 8: *FTIR Spectra of PVP-K30*

Table 2: *Standard band frequency of drug Telmisartan*

Wave Number (cm^{-1})	Fuctional group
3392	O-H (H- Bonded)
3680	O-H Free
1640	C=N(imines and Oximes)
1453	C-H(CH_3 bend)
639	C-H(Alkenes out of plane bent)

Drug - excipient compatibility study

The IR spectrum of various mixtures (drug with various excipients) is shown in Figure 9-15. Presence of characteristic peaks of drug in IR spectra indicates no interaction of drug with excipients was observed.

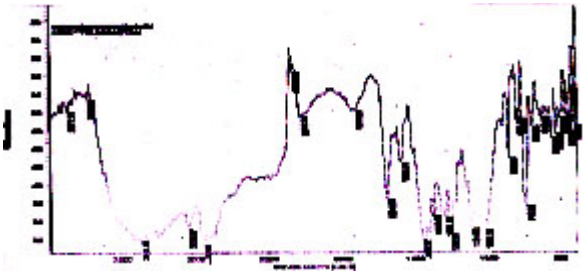

Fig. 9: *FTIR Spectra of mixture of Avicel 112- Telmisartan*

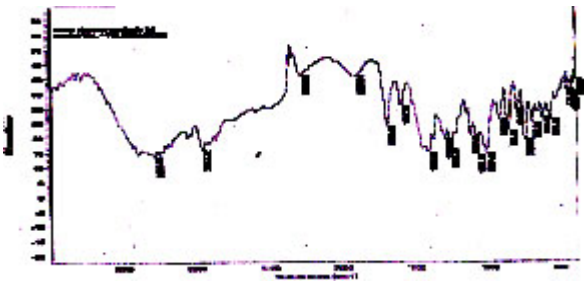

Fig. 10: *FTIR Spectra of mixture of Mannitol- Telmisartan*

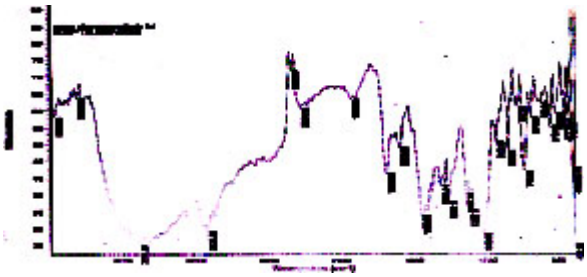

Fig. 11: *FTIR Spectra of mixture of □-Cyclodextrin and Telmisartan*

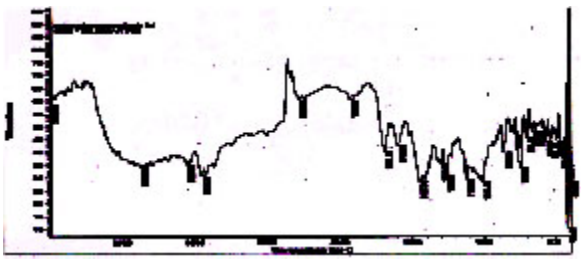

Fig. 12: *FTIR Spectra of mixture of CCS and Telmisartan*

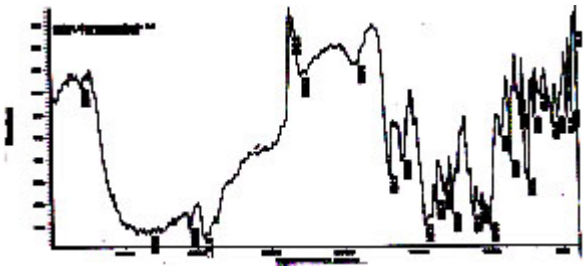

Fig. 13: *FTIR Spectra of mixture of SSG and Telmisartan*

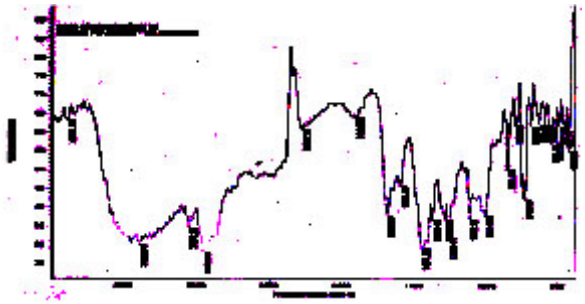

Fig. 14: *FTIR Spectra of mixture of Crospovidone and Telmisartan*

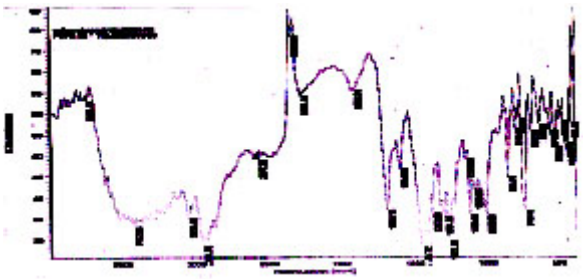

Fig. 15: *FTIR Spectra of mixture of PVP k-30 and Telmisartan*

Evaluation of Precompression Parameters

The results of precompression studies are given in Table 3. The results of bulk density and tapped density ranged from (0.475±0.024 to 0.556±0.043) and (0.545 ±0.021 to 0 .632 ±0.019) respectively. The results of angle of repose (23.34 ±0.24 to 29.17 ±0.25) indicated good flow properties which were further supported by Carr's index values (12.02 to 16.09) and Hausner's ratio data (1.13 to 1.19).

Table 3: *Evaluation of Precompression parameters of various batches (F1-F12)*

Formulation Code	Bulk density (g/ml)	Tapped density(g/ml)	Angle of repose	Hausner's ratio	Carr's Index (%)
F1	0.496 ±0.023	0.588 ±0.013	27.23 ±0.31	1.18	15.65
F2	0.478 ±0.014	0.545 ±0.021	23.42 ±0.13	1.14	12.29
F3	0.475 ±0.024	0.556 ±0.020	25.35 ±0.25	1.17	14.57
F4	0.503 ±0.028	0.598 ±0.009	28.75 ±0.32	1.19	15.89
F5	0.498 ±0.031	0.586 ±0.018	27.13 ±0.08	1.18	15.02
F6	0.501 ±0.029	0.583 ±0.021	24.75 ±0.15	1.16	14.06
F7	0.497 ±0.025	0.588 ±0.015	27.45 ±0.22	1.18	15.48
F8	0.556 ±0.043	0.632 ±0.019	23.34 ±0.24	1.13	12.02
F9	0.521 ±0.009	0.613 ±0.023	28.23 ±0.09	1.18	15.01
F10	0.527 ±0.021	0.621 ±0.026	27.72 ±0.32	1.18	15.14
F11	0.511 ±0.032	0.609 ±0.031	29.17 ±0.25	1.19	16.09
F12	0.507 ±0.017	0.601 ±0.031	27.68 ±0.09	1.18	15.64

Evaluation of Post Compression Parameters

The physical properties of different formulation batches are given in Table 4. Tablet mean thickness was almost uniform in all formulations. All tablet batches passed weight variation test as % weight variation was within pharmacopoeial limits of (±7.5%) of weight. The prepared tablets from all formulations possessed good mechanical strength with sufficient hardness in the range of (2.5 ±0.4 to 2.8 ±0.4). Friability values below 1% are good indication of good mechanical resistance of tablets. The wetting time values for all the batches

lie between (23 ±3 sec to 66 ±2 sec). A significant low value of wetting time (23 and 25 sec) was observed in batches containing crosspovidone (F3 and F6) indicating porous nature of superdisintegrant. Wetting time was also less (35 sec) in batches F11 and F12 (Containing combination of CP with SSG and CCS respectively). Comparatively higher values in F11 and F12 batches may be due to higher viscosity due to higher concentration of superdisintegrants (5% + 5%) in these batches. Water absorption ratio was more than 100% for all formulations. The *in vitro* dispersion time for all the twelve formulations ranged between (38 ±2 to 66 ±4 sec) with the least value (38 sec) observed in batch F6. All the formulation batches showed disintegration time (DT) value of less than 1 min. Significant decrease in DT was observed in batch F3 containing crosspovidone which was further decreased (slight) by addition of â-Cyclodextrin 2.5% (F6 batch) whereas higher concentration of â-Cyclodextrin (10%) enhanced DT value (F9 batch). The wetting time, *in vitro* dispersion time and disintegration time of the tablets were significantly reduced in tablets containing crospovidone which may be attributed due to the wicking type of disintegrants (crosspovidone) formed thus facilitating faster disintegration. Due to porous network of tablet, water uptake was increased and disintegration facilitate. Moreover, addition of â-Cyclodextrin also leads to increased disintegration characteristics (F6 batch) which may be due to increased swelling of tablet due to increased absorption of medium in which studies are carried out. However, higher concentrations of â-Cyclodextrin (F9 batch) rather increase the disintegration time which may due to formation of viscous plugs at higher concentrations. Thus porous structure of tablet, wicking and swelling effects in combination made the tablets more rapidly disintegrating as supported by literature[13,14].

Drug Content Uniformity

The percentage drug content of all the batches was found to be between 99.1 to 100.5% of Telmisartan which was within acceptable limits.

In vitro drug release studies

All the formulation batches exhibited 100% release within 20 min (Figure 16). More than 85% drug release within 15 min was observed in all formulation batches (F1-F12) with maximum dissolution rate (98.8% in first 15 min) in batch F6 which may be attributed to highly porous network, rapid capillary activity (achieved with crosspovidone) which leads to pronounced hydration thereby enhancing drug dissolution (also supported by disintegration data). Moreover, addition of â-Cyclodextrin enhanced the dissolution characteristics which may be due to increased wettability which is attributed to increased surface area available for dissolution due to reduction in interfacial tension between drug and dissolution media. Higher concentrations of â-Cyclodextrin did not retard dissolution behavior as the case with disintegration studies. Figure 17 indicated comparative release profile of best batch F6 with that of marketed product. Drug release of 7.6% was observed within first 5 min in case of marketed conventional tablet which is significantly less than that of batch F6 (92.1%).

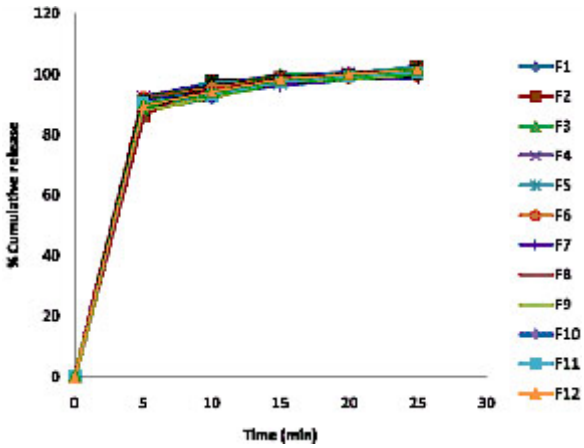

Fig. 16: *Comparative in vitro dissolution profile of various batches (F1-F12)*

Table 4: *Evaluation of post compression parameters of various formulation batches (F1-F12)*

Code	Weight variation (mg)	Tablet Thickness (mm)	Tablet diameter (mm)	Hardness (Kg/cm^2)	Wetting time (Sec)	Water absorption ratio (%)	Friability (%)	Disintegration time (Sec)	Dispersion time (Sec)
F1	200.19	3.45±0.04	8.08±0.02	2.80±0.3	49±2	134.23	0.5±0.03	32 ±2	54±2
F2	199.75	3.53±0.04	8.08±0.02	2.80±0.4	41±2	162.72	0.13 ±0.04	34 ±3	52 ±2
F3	200.46	3.59±0.03	8.08±0.01	2.85±0.2	23 ±3	117.11	0.64 ±0.03	18 ±2	44±3
F4	198.86	3.47 ±0.03	8.07 ±0.02	2.76±0.3	54 ±3	134.23	0.19±0.03	38 ±2	53 ±2
F5	200.37	3.46±0.04	8.07 ±0.02	2.74±0.3	57 ±2	127.46	0.21 ±0.04	36 ±2	57 ±2
F6	199.26	3.52±0.03	8.05±0.02	2.80±0.3	25 ±2	106.85	0.27±0.03	13 ±2	38 ±2
F7	197.47	3.34±0.04	8.07 ±0.02	2.80±0.3	66 ±2	104.49	0.19±0.03	44±3	52 ±3
F8	199.47	3.47 ±0.03	8.07 ±0.01	2.5 ±0.4	48 ±3	129.90	0.13±0.04	54 ±2	57 ±3
F9	199.6	3.50±0.03	8.07 ±0.02	2.6 ±0.3	51 ±3	102.60	0.07 ±0.03	19 ±2	46 ±2
F10	199.01	3.47 ±0.4	8.07 ±0.02	2.6 ±0.4	43 ±2	177.48	0.06 ±0.04	38 ±2	66 ±4
F11	199.70	3.55±0.03	8.07±0.02	2.5±0.3	35±4	137.79	0.1±0.05	29±2	46±3
F12	199.07	3.54±0.03	8.08±0.01	2.6±0.4	35±3	177.22	0.093±0.05	33 ±2	50 ±3
Telma -20	136.02	2.86±0.03	7.04±0.02	1.81±0.2	115± 5	7.7	0.58 ±0.04	240± 0.5	352 ±4

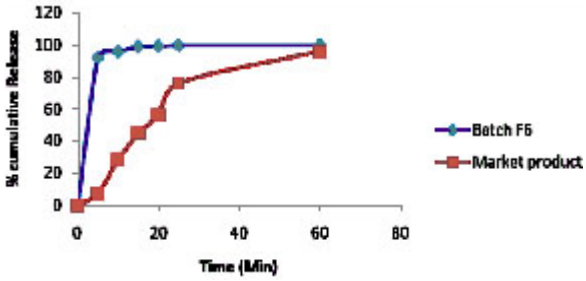

Fig. 17: Comparison of dissolution profile of optimum batch F6 with marketed product

Accelerated stability studies

Stability studies performed on batch F6 as per ICH guidelines for 90 days at 40°C / 75% RH. The results showed no remarkable changes in the physical properties of the tablets as well as no remarkable changes in the drug content (Table 5) and the release profile (Figure 18) indicated good stability of the formulation even after stressed conditions.

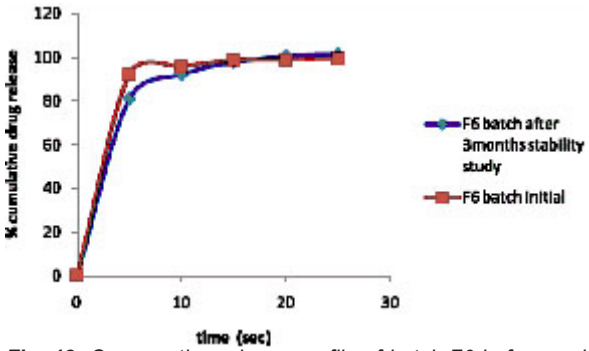

Fig. 18: Comparative release profile of batch F6 before and after stability studies

CONCLUSION

Faster disintegration characteristics of crosspovidone as compared to other superdisintegrants can be exploited to formulate FDT of various drugs which can lead to better management of various diseased conditions. It can be concluded that fast dissolving tablets of telmisartan containing crosspovidone and â-Cyclodextrin can be prepared to obtain faster action of the drug with enhanced solubility characteristics for the effective treatment of hypertension. This approach is effective, economical and industry feasible compared with the use of more expensive adjuvants in the formulation of mouth dissolving tablets.

ACKNOWLEDGEMENT

The authors are grateful to Dr. Madhu Chitkara, Vice Chancellor, Chitkara University, Punjab, India; Dr. Ashok Chitkara, Chancellor, Chitkara University, Punjab, India; Dr. Sandeep Arora, Director, Chitkara College of Pharmacy, Chitkara University, Punjab, India; for general support. Mr. J.S. Parmar, Executive Director, Ontop Pharmaceutical Pvt. Ltd. for technical support and laboratory facilities.

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***Table 5:** Physicochemical parameters of formulation F6 stored at Accelerated Condition (40°C and 75% RH)*

Parameter → Time ↓	Weight variation (mg)	Tablet Thickness (mm)	Tablet diameter (mm)	Hardness (Kg/cm²)	Wetting time (Sec)	Friability (%)	Disintegration time (Sec)	Dispersion time (Sec)	Assay %
15 days	199.46	3.54±0.03	8.07±0.02	2.51±0.3	26±2	0.13±0.07	13±2	34±2	99.5
30 days	199.51	3.56±0.04	8.08±0.02	2.47±0.3	25±2	0.27±0.04	12±3	37±2	99.1
60 days	199.76	3.66±0.06	8.14±0.014	2.45±0.3	26±3	0.65±0.04	12±2	37±3	98.9
90 days	200.00	3.69±0.03	8.14±0.02	2.42±0.2	24±3	0.19±0.03	12±2	36±2	98.8

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