RESEARCH ARTICLE

DESIGN AND DEVELOPMENT OF FAST MOUTH DISSOLVING TABLET OF TELMISARTAN FOR ENHANCED BIOAVAILABILITY

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ABSTRACT

An ideal dosage regimen in the drug therapy of any disease is the one, which immediately attains the desire therapeutic concentration of drug in plasma (or at the site of action) and maintain constant for the entire duration of treatment. To fulfill these medical needs, Formulator have devoted considerable efforts for developing a novel type of dosage form for oral administration known as mouth dissolving tablets (MDT). It is define as "a tablet that disintegrates and dissolves rapidly in the saliva within a few seconds without the need of drinking water or chewing." A mouth dissolving tablet usually dissolves in the oral cavity within 15sec to 30sec Most of the MDTs include certain superdisintegrantsand taste masking agents. Telmisartan (TLM) is a non-peptide Angiotensin receptor II (Type- ATI) antagonist, that cause inhibition of action of Angiotensin II on vascular smooth muscle in the treatment of hypertension. The bioavailability of telmisartan is poor about 45% which is due to extensive first pass hepatic metabolism. The bioavailability can be increased by fast dissolving formulation. Conventional telmisartan tablets available in markets are not suitable were quick onset of action is required. In order for better patient compliance its better to develop a dosage form that can rapidly disintegrate and dissolve in saliva without need of water. The aim of present investigation was to prepare mouth dissolving tablet of an anti hypertensive drug telmisartan. The solubility of poorly soluble drug was enhanced by preparing inclusion complexes (solvent evaporation and kneading method) with β cyclodextrin and PEG 4000 in various concentrations. The optimized complexes (drug:βcyclodextrin, 1:2 ratio) were further kneaded with suitable proportion of superdisintegrant such as crosscarmellose, sodium starch glycolate and crosspovidone. Mouth dissolving tablets of Telmisartan was prepared by Direct compression method. The pre-compressive parameters for the blends and post compressive parameter for the prepared tablet were evaluated. All formulation showed desired pre and post-compressive characteristics. FTIR study showed no evidence of drug excipient interaction. The optimized formulation was found to be F6. It can be concluded that Mouth dissolving tablet of Telmisartan can be prepared by inclusion complexes with cyclodextrin and combination of superdisintegrants provide complete and better dissolution within in shorter period of time. Hypertensive treatment anywhere, and anytime particularly for ageriatric, pediatric, metally ill, bedridden and patients who do not easy access to water.

INTRODUCTION

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. DDS make a significant contribution to global pharmaceutical sales through market segmentation, and are moving rapidly. Drug delivery systems are becoming increasingly sophisticated as pharmaceutical scientists acquire better understanding of the physicochemical parameters pertinent to their performance. Despite of tremendous advancement in drug delivery, the oral route remains the perfect route for the administration of therapeutic agents because of low cost of therapy, ease of administration, accurate dosage, self medication, pain avoidance, versatility etc leading to high level of patient compliance. Tablets and capsules are

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the most popular dosage forms (Chein, 1992). But one important drawback of such dosage forms is 'Dysphagia' or difficulty of swallowing. This is seen to afflict nearly 35% of the general population. This disorder is also associated with a number of condition like:

1. Parkinsonism
2. Motion sickness
3. Unconsciousness
4. Elderly patients
5. Children
6. Mentally disabled persons
7. Unavailability of water

Improved patients compliance has achieved enormous demand. Consequently demand for their technologies is also increasing many folds. To develop a chemical entity, a lot of money, hard work and time are required. So focus is rather being laid on the

development of new drug. Delivery systems for already existing drugs, with enhanced efficacy and bioavailability, thus reducing the dose and dosing frequency to minimize the side effects. The aim of a scientist or a dosage form designer to enhance the safety of drug molecule while maintain its therapeutic efficacy. Recent advances in Novel Drug Delivery Systems (NDDS) aim for the same by formulating dosage form, convenient to be administered so as to achieve better patient compliance. Pharmaceutical technologists have put in their best effort to develop a Fast Dissolving Drug Delivery system, i e Mouth dissolving tablets.

Fast Mouth dissolving tablet (FMDT)

It's a tablet that disintegrates and dissolves rapidly in the saliva, within a few seconds without the need of drinking water or chewing. A mouth dissolving tablet usually dissolves in the oral cavity with in 15seconds to 30seconds. Most of the MDTs include certain super disintegrants and taste masking agents. United states food and drug administration (FDA) as "a solid dosage form containing medicinal substances or active ingredient which disintegrate rapidly usually within a matter of seconds when placed upon the tongue. Fast dissolving tablets are also known as mouth dissolving tablets, melt-in mouth tablets, orodispersible tablets, rapid melts, porous tablet, quick dissolving tablet. Fast dissolving tablets dissolve or disintegrate in the oral cavity without need of water. Most fast dissolving tablets must include substances to mask the bitter taste of active ingredient. This masked active ingredient is then swallowed by the patient's saliva along with a soluble and insoluble excipients. It has been concluded that faster the dissolution, faster the absorption (only the unionized form of drug) and onset of action. Some drugs are absorbed from the oral cavity, pharynx and esophagus as the saliva passes down to stomach. Thus the bioavailability of drug is significantly more than those observed from conventional tablets dosage form. The time for disintegration of fast disintegrating tablets is generally considered to be less than one minute. The fast dissolving solid dosage form turns in to a soft paste or liquid form for easy swallowing, and thus it is free of risk of choking. In recent years, a variety of improved methods for delivering drugs have been developed with the aim of improving bioavailability, convenience and patient compliance. Some tablets are designed to dissolve in saliva within a few seconds, and so called true fast-dissolving tablets (Chang et al., 2000).

Ideal properties of FMDT

A Mouth Dissolving Tablet should:

a. Not require water or other liquid to swallow.
b. Easily dissolve or disintegrate in saliva within a few seconds
c. Have a pleasant taste
d. Leave negligible or no residue in the mouth when administered.
e. Be portable and easy to transport
f. Be able to manufactured and in a simple conventional manner with low cost
g. Be less sensitive to environmental conditions like temperature, humidity etc.

Advantages of FMDT

a. No need of water to swallow the tablet.
b. Can be easily administered to pediatric, elderly and mentally disabled patients.
c. Accurate dosing as compared to liquids.
d. Dissolution and absorption of drug is fast, offering rapid onset of action.
e. Bioavailability of drugs is increased as some drugs are absorbed from mouth, pharynx and esophagus through saliva passing down in to stomach.
f. Advantageous over liquid medication in terms of administration as well as transportation.
g. First pass metabolism is reduced, thus offering improved bioavailability and thus reduced dose and side effects.
h. Free of risk of suffocation due to physical obstruction when swallowed, thus offering improved safety.
i. Suitable for sustained/controlled release activities.
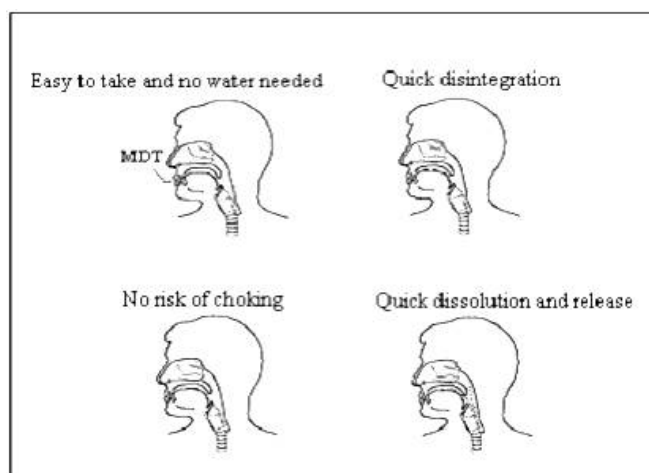j. Allow high drug loading (Kuchekar et al., 2005).

Figure 1. Advantages of FMDTs

Limitations of Mouth Dissolving Tablets

1. Mechanical strength of final product.
2. Drug and dosage form stability
3. Mouth feel.
4. Taste: the tablet may leave unpleasant taste and /or grittiness in mouth if not formulated properly.
5. Rate of dissolution of drug formulation in saliva.
6. Swallow ability.
7. Rate of absorption from the saliva solution and overall bioavailability.
8. Dryness of the mouth due to decreased saliva production may not be good candidates for these tablet formulations (Slowson and Slowson, 1985).

The need for development of fast mouth dissolving tablet

Patient factor: Fast dissolving dosage forms are suitable for those patients (particularly pediatric and geriatric patients) who are not able to swallow traditional tablets and capsules with an 8-oz glass of water. These include the following:

- Patients who have difficulty in swallowing or chewing solid dosage forms.
- Patients incompliance due to fear of choking (Indurwade et al., 2002).
- Very elderly patients of depression who may not be able to swallow the solid dosage forms.

- An eight-year old patient with allergies desires a more convenient dosage form than anti histamine syrup.
- A middle aged patient undergoing radiation therapy for breast cancer may be too nauseous to swallow her H2-blocker.
- A schizophrenic patient who may try to hide a conventional tablet under his or her tongue to avoid their daily dose of an atypical antipsychotic.
- A patient with persistent nausea, who may be journey, or has little or no access to water.

Effectiveness factor: Dispersion in saliva in oral cavity causes pre-gastric absorption of drug which dissolves. Buccal, pharyngeal and gastric regions are all areas of absorption for many drugs. Any pre-gastric absorption avoids first pass hepatic metabolism which increase the bioavailability. Furthermore, safety profiles may be improved for drugs that produce significant amounts of toxic metabolites mediated by first-pass liver metabolism and gastric metabolism and for drug that have a substantial fraction of absorption in the oral cavity and pre-gastric segments of GIT.

Manufacturing and marketing factors: As a drug nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. A new dosage form allows a manufacturer to extend market exclusivity, unique product differentiation, value-added product line extension, and extend patent protection, while offering its patient population a more convenient dosage form. This leads to increased revenue, while also targeting underserved and under-treated patient populations. As examples, Eisai Inc. launched Aricept FDT, a line extension of donepezil for Alzheimer's disease, in Japan in 2004 and in the U.S. in 2005 in response to a generic challenge filed in the U.S. by Ranbaxy. Merck's Japanese subsidiary launched Lipola M (simvastatin ODT), a line extension of its block-buster, Zocor®, a cholesterol-lowering drug, in response to seventeen generic registrations of simvastatin applied for in Japan in 2004. Marketers build a better brand and in this way company's reputation can be improved.

MATERIALS AND METHODS

Telmisartan, β-cyclodextrin, PEG 4000, Methanol, Cross carmellose sodium, Crospovidone, Sodium starch glycolate Distilled water from Yarrow chem product, Mumbai

Methodology

Preparation of calibration curve of telmisartan in phosphate buffer 6.8

Preparation of standard stock solution of Telmisartan in phosphate buffer (pH 6.8)

Standard stock solution of Telmisartan was prepared by dissolving accurately weighing 100 mg drug in little quantity of phosphate buffer (pH6.8) in 100ml volumetric flask. The volume was then made up to 100ml by using phosphate buffer (pH6.8) to obtain stock solution of 1000 μg/ml.

Preparation of calibration curve of Telmisartan

From stock solution (1000μg/ml), 1ml is diluted to 10ml using 6.8 pH phosphate buffer solution (100μg/ml). From this 1ml is diluted to 10 ml using 6.8 pH phosphate buffer solution (10μg/ml). To a series of 10 ml volumetric flask appropriate aliquots of the solution was taken to produce a concentration range of 2-10μg/ml. To each volumetric flask 1ml each of 0.5% (w/v) NQS reagent and 0.01M NaOH were added. The contents were shaken for a while and were placed in a water bath maintained at $50^0C \pm 2^0C$ for 10 minutes. The solution were allowed to cool at room temperature for a while and finally diluted up to the mark with water. Absorbance of the resulting brown coloured solution was measured at max 296 nm. This procedure was performed in triplicate to validate the calibration curve.

Solubility and dissolution enhancement using Cyclodextrin and peg

Preparation of physical mixture of β cyclodextrin and PEG 4000

Accurately weighed quantities of drug and carrier were weighed taken in a glass mortar were mixed thoroughly. The resultant mixture was passed through sieve number 100 # and was stored in desiccators for the complete removal of moisture and was tested for the content uniformity. Drug: polymer ratios of 1:1, 1:2 and 1:4 were prepared (Batr, 2008; Patel et al., 2008).

Preparation of inclusion complexes

 a. Solvent evaporation technique
 b. Kneading method

a. Solvent Evaporation Technique

The drug and carriers are used in different ratios [1:1, 1:2, 1:4]. The respective amount of carrier was dissolved in methanol (20ml) and Telmisartan was added in parts with continuous stirring. The solvent was then removed by evaporation. The prepared dispersions were pulverized and sifted through 100 # and stored in desiccators for further studies (Mohsen, 2002; Mourya, 2002; Modi and Tayade, 2006).

b. Kneading Method

In this method the drug and carriers are used in different ratios [1:1, 1:2, 1:4] Both drug and carrier was triturated by using a small volume of ethanol and water(1:1) to give a thick paste, which was kneaded up to 60 minutes and then kept for air dry. Then the dried mass was scratched and pulverized and sifted through 100# and stored in desiccators for further studies (Verheyen et al., 2002; Mohsen, 2002; JaniRupal, 2009).

Evaluation parameters for solubility enhancement

Practical Yield

Solid Dispersions were collected and weighed to determine practical yield (P1') from the followingequation (Rahamathulla et al., 2008; Lackman et al., 1991).

PY (%) =practical mass(mixture) **x**100
Theoreticalmass (drug+carrier)

Drug content

Weighed accurately 10 mg of the drug and dissolved in methanol and suitably diluted with phosphate buffer solution

of pH 6.8. The content of Telmisartan was determined spectrophotometrically at 296 nm against blank using UV-visible spectrophotometer

In Vitro Dissolution Studies of Solid Dispersions

The quantity of solid Dispersions equivalent to 40 mg of Telmisartan was placed in dissolution medium. The dissolution study or solid Dispersions was conducted using dissolution testing apparatus II (paddle method) in 900 ml of phosphate buffer solution of pH 6.8 at 37^0C and at a speed of 50 rpm. Aliquots of 5 ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintaine constant volume after each sampling and analyzed spectrophotometrically at 296 nm against suitable blank using UV-visible spectrophotometer .

Drug carrier compatibility study

Fourier Transform infrared spectroscopy (FTIR)

The drug-carrier mixture of Telmisartan were prepared in the form of KBr pellets and subjected for scanning from4000 cm-1 to 400 cm-1 using FTIR spectrophotometer.

Preparation of fast mouth dissolving tablet of telmisartan

The composition of preliminary trial batches of Mouth dissolving tablets of telmisartan were shown in table11. The inclusion complexes of Telmisartan, equivalent to 40 mg and mannitol were mixed thoroughly in glass motor, using a pestle. Crospovidone, crosscarmellose sodium, sodium starch glycolate were passed through sieve number 22, while talc and magnesium stearate were passed through sieve number 60. All the ingredients were mixed in mortar and pestle. Magnesium stearate and talc were finally added as lubricants. Tablets were prepared using 8mm round flat-faced punches of tablet punching mechine, compression force was kept constant for all formulation.

Evaluation parameters for mouth dissolving tablet of telmisartan

Pre-compression parameters

The prepared powder mixtures were evaluated for the blend property like bulk density, tapped density, carr's index, angle of repose and Hausner's ratio.

Post- compression parameter: The tablets after punching of every batch were evaluated for in-process and finished product quality control tests i.e thickness, hardness, weight uniformity test, friability, water absorption ratio:, wetting time, disintegration time, in-vitro dissolution.

Thickness

Thickness of tablets indicates the strength to withstand compression force applied during manufacturing process. Thickness of tablets was measured by micrometer screw gauge. Five tablets from each type of formulation were used and average value were calculate. It is expressed in mm.

Hardness test: The resistance of tablets to shipping, breakage, under condition of storage, transportation and handling before

usage depends on its hardness. For each formulations, the hardness of 6 tablets was determined using the Monsanto hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm^2. Then constant force was applied by rotating the knob until the tablet fractured.

Weight uniformity test: Twenty tablet were weighed individually and all together. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits (±7.5%).

Friability: Friability is the measured of tablet strength. Roche friabilator was used for testing the friability using the following procedure. A sample of pre weighed 6 tablet was placed in Roche friabilator which was then operated for 100 revolutions.ie. 4 minutes. At the end of test tablets were dusted and reweighed. A loss of less than 1% in weight is generally considered acceptable[106]. The loss in the weight of tablet is the measure of friability and is expressed in % as % friability = initial weight – final weight / initial weight×10

Wetting time

Simple tissue paper (12 cm×10.75) folded twice was placed in a small petri dish (internal diameter = 6.5 cm) containing 6ml of phosphate buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured.

Water absorption ratio

It was tested by using double folded tissue paper and the petri dish contains 6ml of saliva buffer pH 6.8. Firstly randomly taken tablets from the all formulation, weight was calculated it was denoted as Wb and then the tablets were allowed to place on the tissue paper. After completely wet of the tablet weight was calculated and denoted as Wa. And by using the following formula water absorption ratio (R) was measured.

$$R = 100\{(Wa- Wb) / Wb\}$$

Where,
Wb = weight of tablet before absorption.
Wa = weight of tablet after absorption.

Uniformity of drug content

Five tablet of each type of formulation were weighed and crushed in mortar and powder equivalent to 40 mg of Telmisartan was weighed and dissolved in 100 ml of phosphate buffer (pH6.8). This was the stock solution from which 1ml sample was withdrawn and diluted to 10 ml with phosphate buffer (pH 6.8). The absorbance was measured at wavelength 296nm using UV-visible spectrometer.

Content uniformity was calculated using formula

% purity = 10c (Au / As)

Where, C – concentration

Au and As – absorbance of unknown and standard respectively.

Disintegration time

Initially the disintegration time for orodispersible tablets was measured using the conventional test for tablets as described in the pharmacopoeia. Tablet required for complete disintegration that is without leaving any residue on the screen was recorded as disintegration time.

In-vitro drug release study of tablets

In- vitro release of the tablet was conducted using USP dissolution apparatus II at 75 rpm. Using 900 ml of phosphate buffer pH6.8 as a dissolution media maintained at 37± 0.5º. samples were withdrawn at various time intervals, filtered through filter paper, diluted and assayed at 296 nm, using UV spectrophotometer.

Calibration curve of telmisartan

Determination of max

The max of drug was found to be 296 nm

Concentration(µg/ml)	Absorbance(296nm)
0	0
2	0.132
4	0.253
6	0.384
8	0.513
10	0.643

STANDARD PLOT OF TELMISARTAN

$y = 0.128x + 0.000$
$R^2 = 0.999$
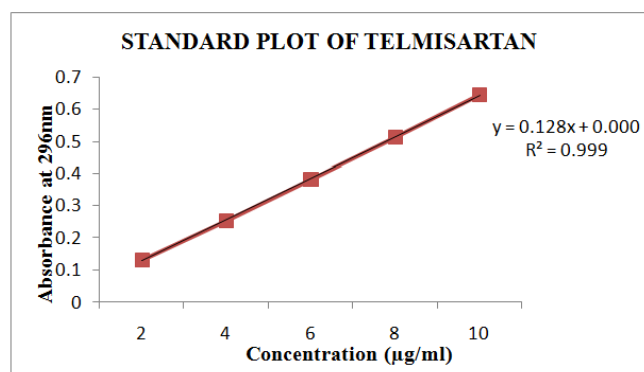
RESULTS

Standard curve of Telmisartan was prepared in pH 6.8 phosphate buffer, the r^2 and slope value were found to be 0.999 and 0,128 respectively, which shows a linearity of absorbance between 2-10µg/ml

Solubility enhancement

Preparation of physical mixture

Table 2. Formula for Telmisartan physical mixture

S.No.	Batch code	Composition	Ratio (drug:carrier)
1	P1	Telmisartan + β-cyclodextrin	1:1
2	P2	Telmisartan + β-cyclodextrin	1:2
3	P3	Telmisartan + β-cyclodextrin	1:4
4	P4	Telmisartan + PEG 4000	1:1
5	P5	Telmisartan + PEG 4000	1:2
6	P6	Telmisartan + PEG 4000	1:4

P1- P6 (physical mixtures with different ratios of carriers)

Formula for Telmisartan Inclusion complexes using solvent evaporation and kneading method

Table 3. Formula for Telmisartan inclusion complexes using solvent evaporation and kneading method

Polymers	Batch No:	Method	drug	β-cyclodextrin	PEG4000
β- cyclodextrin	A1	Solvent evaporation	100	100	
	A2		100	200	
	A3		100	400	
	A4	Kneading method	100	100	
	A5		100	200	
	A6		100	400	
PEG4000	B1	Solvent evaporation	100	-	100
	B2		100	-	200
	B3		100	-	400
	B4	Kneading method	100	-	100
	B5		100	-	200
	B6		100	-	400

A1- A3(cyclodextrin using solvent evaporation method)
A4-A6(cyclodextrin using kneading method)
B1-B3(PEG4000 using solvent evaporation method)
B4-B5(PEG4000 using kneading method)

Results

In the present investigation the solubility of poorly water soluble Telmisartan was enhanced by preparing inclusion complexes with β-cyclodextrin. The drug and carrier ratio of 1:1,1:2,1:4 were used for preparation of inclusion complexes by kneading method to enhance the solubility of Telmisartan.

Evaluation parameters for solubility enhancement

Table 4. Estimation of practical yield

S. No.	Formulation	% Practical yield of telmisartan
1	A1	82
2	A2	98
3	A3	92
4	A4	84
5	A5	97
6	A6	90
7	B1	78
8	B2	96
9	B3	90
10	B4	82
11	B5	95
12	B6	90

Results

The result indicate that;

i. Formulation (A2) prepared by solvent evaporation method shows better practical yield.
ii. Formulation (A5) prepared by kneading method shows better practical yield.
iii. Formulation (B2) prepared by solvent evaporation method shows better practical yield.
iv. Formulation (B5) prepared by kneading method shows better practical yield.

Result

The result indicate that,

1. Formulation (A2) prepared by solvent evaporation method shows 99.5% drug content.

2. Formulation (A5) prepared by kneading method shows 99.5% drug content.
3. Formulation (B2) prepared by solvent evaporation method shows 99.0% drug content.
4. Formulation (B5) prepared by kneading method shows 99.0% drug content.

Drug content

Table 5. Drug content of physical mixture of Telmisartan

S. No.	Formulations	% of Telmisartan present
1	P1	97.5
2	P2	98.5
3	P3	98.0
4	P4	97.5
5	P5	99.0
6	P6	98.5
7	A1	98.5
8	A2	99.5
9	A3	99.0
10	A4	98.0
11	A5	99.5
12	A6	98.5
13	B1	97.5
14	B2	99.0
15	B3	98.5
16	B4	98.5
17	B5	99.0
18	B6	98.5

(P1-P6)- physical mixture with different ratios
(A1-A6)- using cyclodextrin
(B1-B6)- using PEG

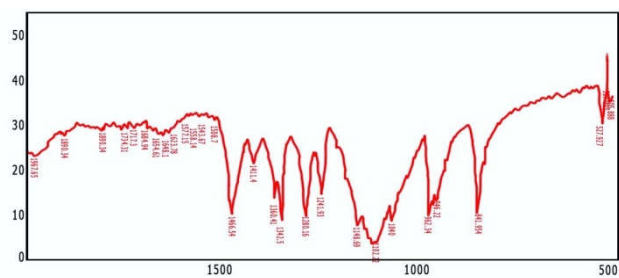## DRUG-EXCIPIENT COMPATIBILITY STUDIES
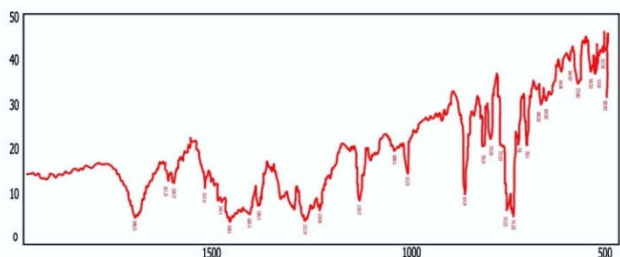
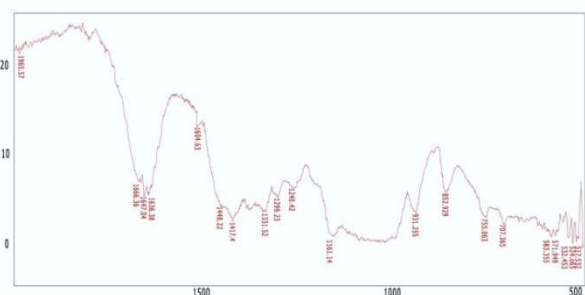
Figure 4. FTIR of Telmisartan

Figure 6. FTIR of PEG4000
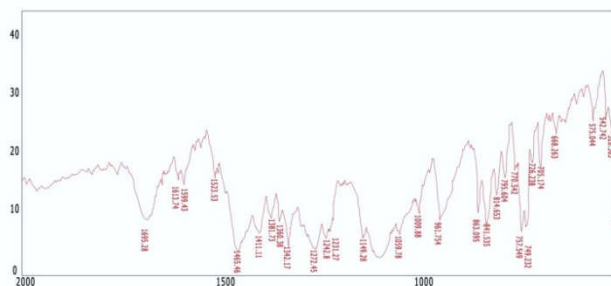

Figure 7. FTIR of β cyclodextrin

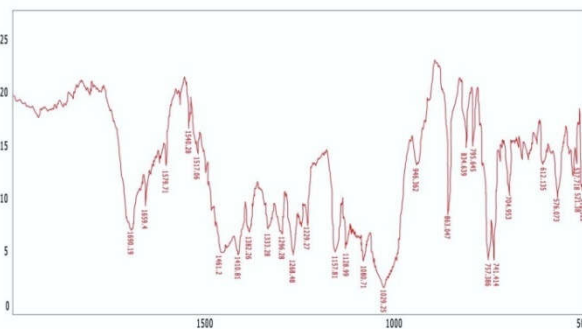**Figure 8. FTIR of Telmisartan+PEG4000**

Figure 8. FTIR of Telmisartan+β cyclodextrin

Result

A described in the methodology section the FTIR spectroscopy studied were carried out for pure drug alone, polymer alone, drug and polymer combination. IR spectrum of telmisartan alone and their physical mixture were shown in figure. From the result it was observed that, the characteristic peaks of telmisartan were not affected and prominently observed in IR spectrum of physical mixture of telmisartan and polymer. This indicate there is no interaction between telmisartan and polymer thus they are compatible with each other.

In-vitro dissolution profile of telmisartan

Table 6. Invitro dissolution profile of Telmisartan formulations

a)Physical mixture

S.No.	Time	Pure drug	Cumulative % release					
			P1	P2	P3	P4	P5	P6
0	0	0	0	0	0	0	0	0
1	10	9.25 ±0.33	23.56 ±0.32	25.12 ±0.68	22.65 ±0.14	22.56 ±0.12	31.82 ±0.54	19.95 ±0.34
2	20	13.77 ±0.42	32.45 ±0.45	33.12 ±0.61	34.54 ±0.45	30.35 ±0.25	38.75 ±0.45	24.35 ±0.54
3	30	17.73 ±0.52	42.56 ±0.44	46.14 ±0.51	41.39 ±0.51	40.56 ±0.52	45.15 ±0.33	36.96 ±0.65
4	40	24.45 ±0.12	58.65 ±0.54	59.65 ±0.64	49.26 ±0.65	57.33 ±0.41	59.43 ±0.12	41.12 ±0.45
5	50	29.68 ±0.56	66.45 ±0.33	67.32 ±0.63	56.21 ±0.56	66.57 ±0.51	69.92 ±0.48	44.12 ±0.14
6	60	35.42 ±0.12	73.52 ±0.25	74.25 ±0.35	64.55 ±0.36	72.45 ±0.56	73.54 ±0.32	48.32 ±0.63

Result

The result indicate that the,

1. The in vitro dissolution study of all formulations were having (P1-P6) shows the cumulative percentage of

drug release minimal 46.23 and maximum 74.25 at the end of 60 minutes.

2. The in vitro dissolution study of all formulations were having (B1-B3) shows the cumulative percentage of drug release minimal 48.50 and maximum 97.39 at the end of 60 minutes.

3. The in vitro dissolution study of all formulations were having (A1-A3) shows the cumulative percentage of drug release minimal 81.89 and maximum 93.45 at the end of 60 minutes.

4. The in vitro dissolution study of all formulations were having (B4-B6) shows the cumulative percentage of drug release minimal 49.86 and maximum 91.46 at the end of 60 minutes.

5. The in vitro dissolution study of all formulations were having (A4-A6) shows the cumulative percentage of drug release minimal 83.45 and maximum 99.89 at the end of 60 minutes.

As compared to other formulations, A2 given 57.45% drug release after first 20 minutes&99.89 % of drug release at the end of 60 minutes. All the formulations complies all evaluator parameters. Therefore the A2 formulations was chosen as the best formulations from all other batch.

From these evaluations the result is

From the in vitro drug release profile, it can be seen that formulations containing 1:2 ratio of β-cyclodextrin inclusion complexes by using kneading method showed higher dissolution rates when compared to 1:2 ratio of PEG 4000 by using solvent evaporation method. The significant improvement in dissolution characters of inclusion complexes in the dissolution medium, increased drug particle wettability and reduction of crystallinity degree of the product.

Result

1. The value for angle of repose were found in the range of 25.31 to 27.59°
2. Bulk density and tapped densities of the blend was found as 0.68 to 0.74 and 0.74 to 0.80(mg/ml) respectively.
3. Carr's index of the prepared blends falls in the range of 7.14 to 9.85% and this is also supported by Hausner's factor value which were in the range of 1.07 to 1.09, Hence the prepared blends possessed good flow properties and can be used for manufacturing of tablets by direct compression method.
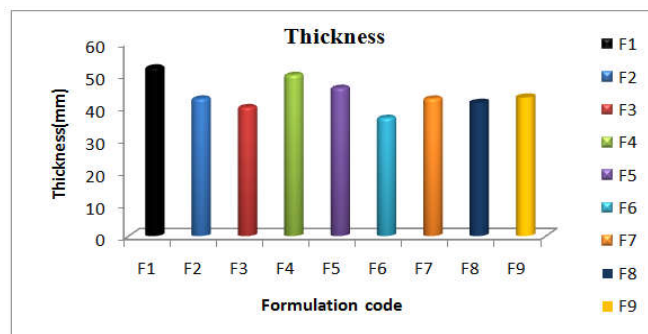

Figure 9. Evaluation of thickness uniformity of Telmisartan mouth dissolving tablets

Physical parameters of telmisartan mouth dissolving tablet Evaluation parameters thickness

Result

Thickness of telmisartan mouth dissolving tablet were evaluated with the use of screw gauge and was found to be in the range of 2.93-2.98mm. The thickness was found to be uniform within each formulation.

Formula for telmisartan mouth dissolving tablet

Table 7. Formula for mouth dissolving tablets of Telmisartan

Ingredients	Batches								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
SD.Eq.to 40mg TEL	120	120	120	120	120	120	120	120	120
Cross carmellose sodium	7.5	10	12.5	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	7.5	10	12.5	-	-	-
Cross povidone	-	-	-	-	-	-	7.5	10	12.5
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Aerosil	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Mannitol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Precompression parameter

Table 8. Precompression parameter of mouth dissolving tablet of Telmisartan

Batches	Bulk density (mg/ml)	Tapped density (mg/ml)	Hausner's ratio	Carr's index (%)	Angle of repose (degree)
F1	0.68	0.74	1.08	8.82	27.59
F2	0.71	0.78	1.09	9.85	25.74
F3	0.74	0.80	1.08	8.10	26.31
F4	0.70	0.75	1.07	7.14	25.85
F5	0.73	0.79	1.08	8.21	27.59
F6	0.74	0.80	1.08	8.10	26.71
F7	0.73	0.79	1.08	8.21	26.31
F8	0.71	0.77	1.08	8.45	25.74
F9	0.72	0.79	1.09	9.72	25.93

Table 9. Thickness uniformity of Telmisartan mouth dissolving tablet

Batches	Trial 1 mm	Trial 2 mm	Trial 3 mm	Mean mm	±	S.D
F1	2.94	2.93	2.93	2.9333	±	0.0058
F2	2.91	2.93	2.92	2.92	±	0.01
F3	2.93	2.92	2.93	2.9267	±	0.0058
F4	2.94	2.93	2.94	2.9367	±	0.0058
F5	2.96	2.96	2.95	2.9567	±	0.0058
F6	2.96	2.96	2.97	2.9633	±	0.0058
F7	2.98	2.97	2.99	2.98	±	0.01
F8	2.97	2.96	2.97	2.9667	±	0.0058
F9	2.98	2.99	2.98	2.9833	±	0.0058

Hardness

Table 10. Hardness of Telmisartan mouth dissolving tablet

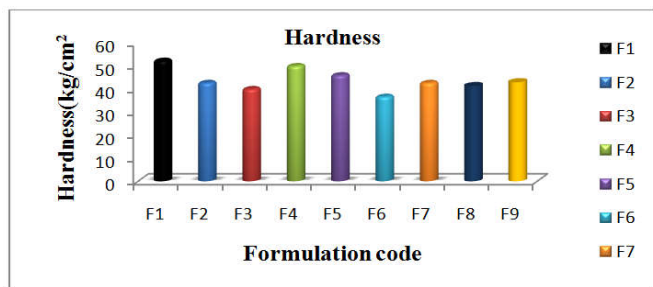| Batches	Trial 1 mm	Trial 2 mm	Trial 3 mm	Mean ± S.D mm		
F1	3.9	3.8	3.9	3.8667	±	0.0577
F2	3.8	3.8	3.7	3.7667	±	0.0577
F3	3.5	3.4	3.6	3.5	±	0.1
F4	3.3	3.2	3.3	3.2667	±	0.0577
F5	3.6	3.6	3.5	3.5667	±	0.0577
F6	3.5	3.4	3.7	3.5333	±	0.1528
F7	3.3	3.2	3.1	3.2	±	0.1
F8	3.2	3.1	3.3	3.2	±	0.1
F9	3.3	3.3	3.4	3.3333	±	0.0577

Figure 6.8: Evaluation of hardness of Telmisartan mouth dissolving tablet

Result

The hardness of tablet was found to be 3.2-3.9 kg/cm^2. The hardness of telmisartan mouth dissolving tablet was within the limit range.

Weight variation

Table 11. Weight variation of Telmisartan mouth dissolving tablet

Batches	Trial 1 mm	Trial 2 mm	Trial 3 mm	Mean ± S.D mm		
F1	149.8	149.6	149.9	149.77	±	0.1528
F2	149.9	149.8	149.7	149.8	±	0.1
F3	149.9	150	149.9	149.93	±	0.0577
F4	149.6	149.6	149.7	149.63	±	0.0577
F5	150.1	150	150.2	150.1	±	0.1
F6	150.1	150.2	150	150.1	±	0.1
F7	149.9	149.9	149.8	149.87	±	0.0577
F8	149.8	149.6	149.8	149.73	±	0.1155
F9	150.1	150.2	150.3	150.2	±	0.1

Result

All the formulation passes the weight variation test as all tablet within the range limit for weight variation.
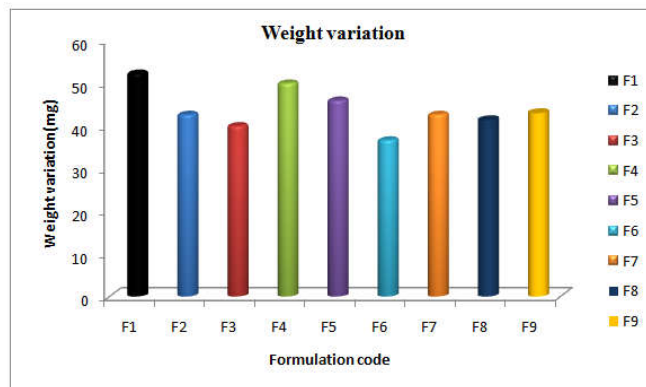

Figure 11. Evaluation of weight variation of Telmisartan mouth dissolving tablet

Friability

Table 12. Friability of Telmisartan mouth dissolving tablet

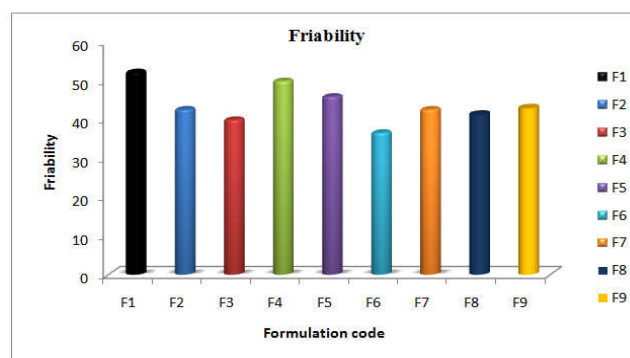| Batches	Trial 1 mm	Trial 2 mm	Trial 3 mm	Mean mm	±	S.D
F1	0.05	0.05	0.04	0.0467	±	0.0058
F2	0.05	0.04	0.05	0.0467	±	0.0058
F3	0.04	0.06	0.05	0.05	±	0.01
F4	0.08	0.08	0.09	0.0833	±	0.0058
F5	0.04	0.06	0.05	0.05		0.01
F6	0.05	0.04	0.06	0.05	±	0.01
F7	0.09	0.09	0.08	0.0867	±	0.0058
F8	0.09	0.08	0.09	0.0867	±	0.0058
F9	0.05	0.05	0.04	0.0467	±	0.0058

Figure 10. Evaluation of friability of Telmisartan mouth dissolving tablet

RESULT

All the tablet shows percentage friability in the range of 0.05-.09%. which is within the limit.

Wetting time

Table 13. Wetting time of Telmisartan mouth dissolving tablet

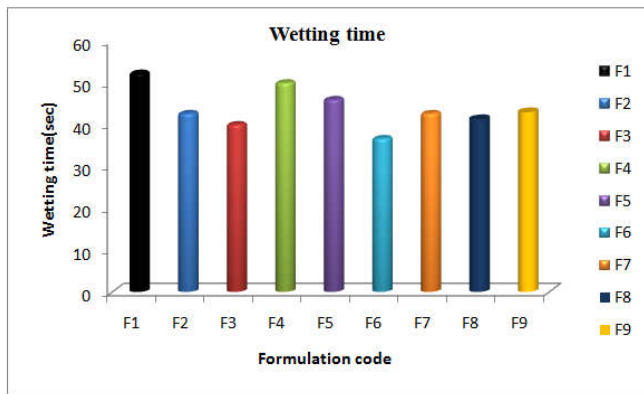| BATCHES	Trial 1 mm	Trial 2 mm	Trial 3 mm	Mean mm	±	S.D
F1	30	30	31	30.333	±	0.5774
F2	38	37	38	37.667	±	0.5774
F3	29	29	28	28.667	±	0.5774
F4	32	31	31	31.333	±	0.5774
F5	29	29	30	29.333		0.5774
F6	33	32	32	32.333	±	0.5774
F7	35	35	36	35.333	±	0.5774
F8	31	31	32	31.333	±	0.5774
F9	30	29	31	30	±	1

Figure 11. Evaluation of wetting time of Telmisartan mouth dissolving tablet

Result

It was observed that wetting time of tablet was in the range of 30-38 seconds. The wetting time was within the limit.

Water absorption ratio

Table 14. Water absorption ratio of Telmisartan mouth dissolving tablet

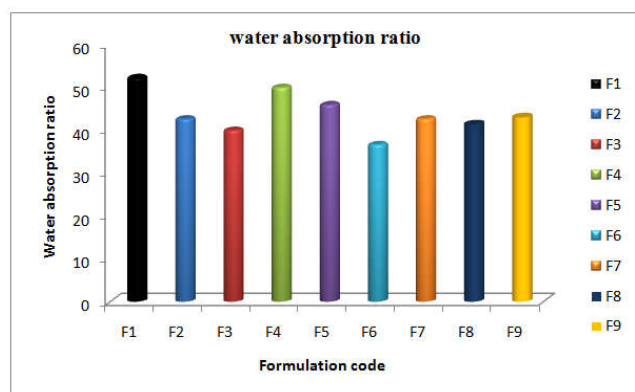| Batches	Trial 1 mm	Trial 2 mm	Trial 3 mm	Mean mm	±	S.D
F1	81.08	81.1	81.06	81.08	±	0.02
F2	85.04	85.02	85.06	85.04	±	0.02
F3	87.63	87.63	87.61	87.623	±	0.0115
F4	63.1	63.08	63.08	63.087	±	0.0115
F5	65.33	65.33	65.35	65.337	±	0.0115
F6	89.99	90.01	90.01	90.003	±	0.0115
F7	86.63	86.65	86.61	86.63	±	0.02
F8	83.02	83	83.04	83.02	±	0.02
F9	82.1	82.1	81.98	82.06	±	0.0693

Figure 12. Evaluation of water absorption ratio of Telmisartan mouth dissolving tablet

Result

The water absorption ratio of telmisartan mouth dissolving tablet within the range of 81.08-90.01.

Uniformity of drug content

Result

Assay for the prepared formulation was performed to determine drug content uniformity and it was found between 98.21-99.34%.

Table 15. Uniformity of drug content of Telmisartan mouth dissolving tablet

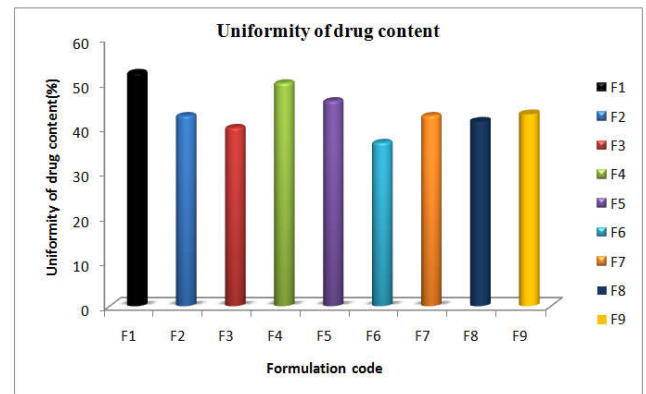| Batches	Trial 1 mm	Trial 2 mm	Trial 3 mm	Mean ± S.D mm		
F1	98.72	98.72	98.74	98.727	±	0.0115
F2	98.99	98.97	98.99	98.983	±	0.0115
F3	99.21	99.23	99.25	99.23	±	0.02
F4	99.06	99.07	99.09	99.073	±	0.0153
F5	98.23	98.24	98.26	98.243	±	0.0153
F6	99.34	99.35	99.32	99.337	±	0.0153
F7	98.72	98.75	98.77	98.747	±	0.0252
F8	98.23	98.24	98.21	98.227	±	0.0153
F9	98.9	98.7	98.88	98.827	±	0.1102

Figure 13. Evaluation of uniformity of drug content of Telmisartan mouth dissolving tablet

Disintegration time

Table 16. Disintegration of Telmisartan mouth dissolving tablet

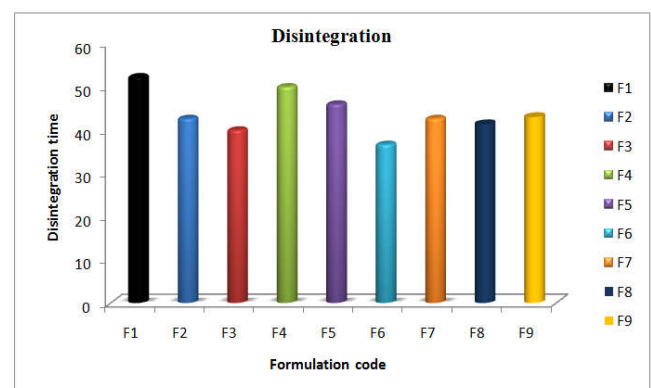| Batches	Trial 1 mm	Trial 2 mm	Trial 3 mm	Mean ± S.D mm		
F1	53	52	52	52.333	±	0.5774
F2	42	43	43	42.667	±	0.5774
F3	40	41	39	40	±	1
F4	49	50	51	50	±	1
F5	46	47	45	46	±	1
F6	37	36	37	36.667	±	0.5774
F7	43	43	42	42.667	±	0.5774
F8	42	41	41	41.333	±	0.5774
F9	42	44	43	43	±	1

Figure 14. Evaluation of disintegration time of Telmisartan mouth dissolving tablet

Result

The disintegration may assist quick swallowing and drug absorption in buccal cavity thus greater bioavailability of the drug. The disintegration time was found 37-53 sec.

In vitro release study of mouth dissolving tablet of telmisartan

Table 17. In-vitro release study of mouth dissolving tablet of Telmisartan

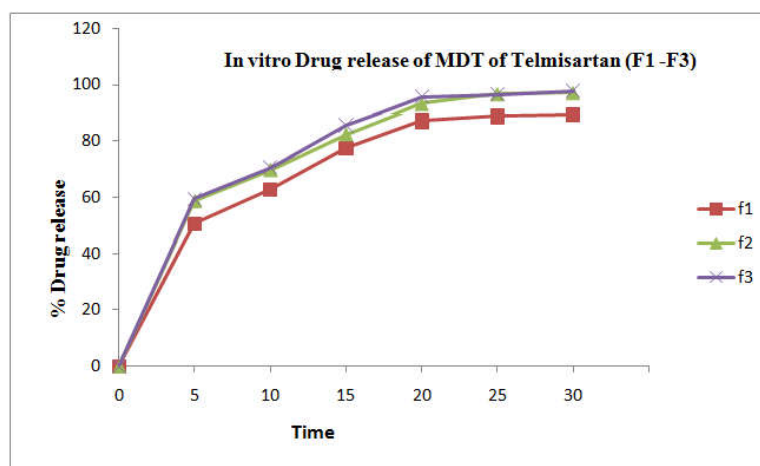| TIME (Sec)	% DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
00	00	00	00	00	00	00	00	00	00
05	50.92	58.71	59.43	51.48	57.62	62.25	54.87	56.03	57.07
10	63.04	69.75	70.57	65.09	70.29	70.95	68.10	68.92	70.24
15	77.81	82.37	85.55	80.45	84.62	85.77	81.71	82.31	85.06
20	87.14	93.18	95.65	90.88	95.03	97.02	87.42	88.84	92.74
25	88.78	96.58	96.58	92.58	96.18	98.17	88.90	89.89	93.45
30	89.39	97.02	97.84	92.69	96.68	98.78	89.56	90.00	95.26

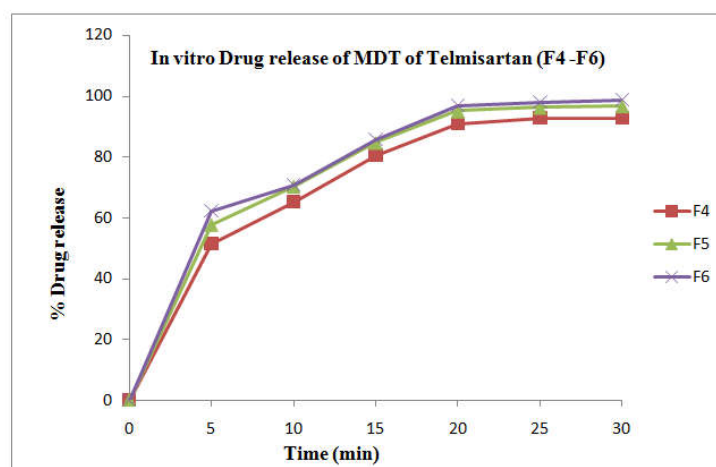**Figure 15. In- vitro drug release study of mouth dissolving tablets of Telmisartan (F1-F3)**

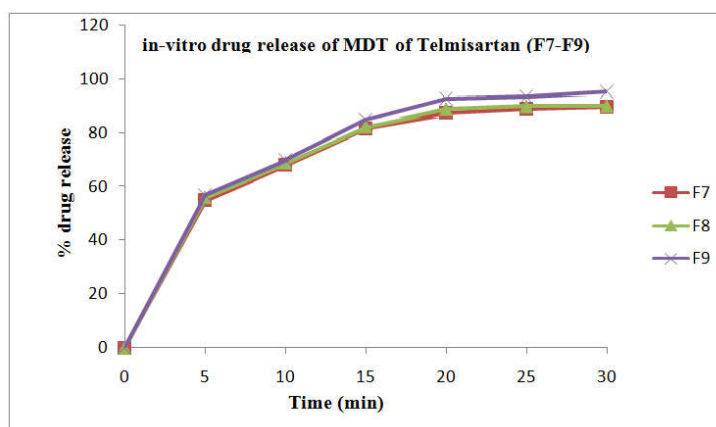**Figure 16. In-vitro drug release study of mouth dissolving tablet of Telmisartan (F4-F6)**

Figure 17. In-vitro drug release study of mouth dissolving tablet of Telmisartan(F7-F9)

Result

Finally, the tablets were evaluated for in vitro dissolution studies in phosphate buffer solution pH 6.8. Among all the formulation F1-F3 prepared with different concentration of super disintegrant(cross carmellose sodium)showed 89.39% to 97.84% drug release within 30 minute and F4 to F6 prepared with different concentration of super disintegrant (sodium starch glycolate) showed 92.69% to 98.78% drug release within 30 minutes and formulation F7 to F9 prepared with different concentration of super disintegrant(cross povidone) showed 89.56% to 95.26% drug release within 30 minutes respectively. This result suggests a direct relationship of concentration of super disintegrants with drug release. As the amount of super disintegrant increases in the acceptable range, the drug release also increases. Among all the formulation F6 showed maximum drug release 98.78%, prepared by using SSG as super disintegrant.

Conclusion

Telmisartan is non-peptide Angiotensin Receptor II (type-ATI) Antagonist, that cause inhibition of the action of Angiotensin II on vascular smooth muscle in the symptomatic treatment of Hypertension. The bioavailability of Telmisartan is poor about 45%, which is due to extensive first pass metabolism. The bioavailability can be increased by fast dissolving formulation. Conventional Telmisartan tablet available in market are not suitable where quick onset of action is required. To provide the patient with the most conventional mode of administration, there was a need to develop rapidly disintegrating dosage form, particularly one that disintegrate and dissolve or disperse in saliva and can be administered without need of water. Telmisartan solubility was enhanced by inclusion complexes method and the mouth dissolving tablet were prepared by direct compression method. Then the mouth dissolving tablet were subjected for following evaluation parameters. The results of the evaluation parameters were within the limit. In solubility enhancement of telmisartan, the in vitro drug release profile, it can be seen that formulations containing 1:2 ratio of β-cyclodextrin inclusion complexes by using kneading method showed higher dissolution rates when compared to 1:2 ratio of PEG 4000 by using solvent evaporation method. The significant improvement in dissolution characters of inclusion complexes in the dissolution medium, increased drug particle wettability and reduction of crystallinity degree of the product. Formulation of mouth dissolving tablet by using kneading method of Telmisartan is unique technique by which solubility of the drug can be enhanced which is most challenging aspects of the drug delivery. The technique adopted was found to be economical and industrially feasible. Thus, it can be concluded that combination of inclusion complexes and superdisintegrant is a promising approach to prepare efficient Mouth dissolving tablet of poorly water soluble drug i.e Telmisartan.

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