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DESIGN AND EVALUATION OF MOUTH DISSOLVING TABLETS OF TELMISARTAN BY USING DIFFERENT SUPER DISINTEGRANTS

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ABSTRACT

The present research was carried out to develop mouth dissolving tablets using superdisintegrants and improve the solubility ultimately bioavailability of Telmisartan by encapsulating it inside the cavity of β-cyclodextrin. Mouth dissolving tablets improve the oral bioavailability by enhancing the drug disintegration and release of drug particles from the dosage form, which enable quick and direct delivery into the circulatory system by avoiding first pass metabolism. Total nine batches of mouth dissolving tablets were prepared using superdisintegrants like Crosscarmellose sodium (CCS), Sodium Starch Glycolate (SSG) and Crosspovidone (CP) by direct compression method. Precompression parameters (Angle of repose, Carr's index and Hausner ratio) were in acceptable range as per the specifications given in IP. Prepared tablets were evaluated for thickness, uniformity of weight, hardness, friability and the results were well within IP limits. Out of the nine formulations developed, the F7 – F9 formulations containing CP as super disintegrant had exhibited the gratifying results when compared with the other two. The results conclude that F9 is the best formulation containing 40 mg of CP. It showed the superlative results in terms of disintegration time, wetting time and *In vitro* drug release. F9 had low wetting time 8.22 sec, low *in vitro* disintegration time (5 sec), high water absorption ratio (180%) and highest drug release profile (99.81%) which releases the drug within 12 minute. The different kinetic models revealed that drug release followed zero order and diffusion mechanism. It was concluded from the results that prepared mouth dissolving tablets might decrease dosing frequency, enhance bioavailability, improves patient compliance, rapid onset of action and avoid first pass metabolism, which was the objective of the present work.

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INTRODUCTION

Hypertension is one of the most important modifiable risk factors for coronary heart diseases (CHD) in Western and Asian population. Recently, estimated total number of people with hypertension in 2000 was 972 million and this is projected to increase by 60% to a total of1.56 billion by 2025 i.e., 29% of the worldwide adult population1. Recent advances in Novel Drug Delivery Systems (NDDS) aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance2. Through many marketed drugs are available as conventional solid dosage forms for the treatment of hypertension, it is found inconvenient to swallow for children and elders leading to patient noncompliance. This problem can be addressed through the development of mouth dissolving dosage forms with the prime objective of enhancing the drug efficacy pertaining to complete disintegration and thus the release of drug particles from the dosage form which enable quick and direct delivery into the circulatory system by avoiding first pass metabolism. These formulations are particularly beneficial for the hypertensive patient, as in such type of patient immediate treatment is required to prevent them from cardiac arrest, heart attack etc. So there is a need to develop a mouth dissolving tablet containing anti-hypertensive drug with immediate response to reduce morbidity, escape from first pass metabolism with reduced manufacturing difficulties and cost effectiveness[2].

Telmisartan is an angiotensin II receptor antagonist used in the management of hypertension. It belongs to BCS class II where the drugs show high permeability and low solubility[3]. Telmisartan has oral bioavailability of about 42% due to its first pass metabolism. To improve its solubility and bioavailability the rationale to formulate mouth dissolving tablets of Telmisartan was attributed to the fact that clinical studies have proven that these formulations can improve patient compliance, provide a rapid onset of action and may further increase dissolution and hence potential bioavailability of drug. Mouth dissolving tablets can offer an attractive alternative route of administration. The advantage of the mouth dissolving drug delivery is that the drug can be directly absorbed into systemic circulation bypassing enzyme degradation in the gut and liver[4].

Therefore in the present study was aimed towards the fabrication and evaluation of mouth dissolving tablets (MDT) by direct compression technology using telmisartan as model drug and sodium starch glycolate, crosscarmellose sodium and crosspovidone as super disintegrates at different concentrations.

MATERIALS

Telmisartan was gift sample by Optimus Pharma Limited, Hyderabad. Sodium Starch Glycollate, Croscarmellose sodium, Crospovidone were purchased by Loba Chemie, Mumbai. Microcrystalline Cellulose was puchased by S.D. Fine Chem. Ltd, Mumbai and all other ingredients used were of analytical grade.

METHODS

A. PREFORMULATION STUDIES:

Solubility Analysis:

Pre-formulation solubility analysis was done using the suitable solvent system to dissolve the drug as well as various excipients.

Melting Point Determination:

Melting point determination was done as a first indication of purity of the drug sample. The presence of relatively small amount of impurity can be detected by lowering as well as widening in the melting point range.

Identification of Pure Drug:

FTIR spectroscopy was used for identification of pure drug.

Determination of λ_{max}:

Stock solution was prepared by taking accurately weighed 10 mg of Telmisartan was transferred in a 100 ml volumetric flask. To the flask phosphate buffer was added in small proportion so as to dissolve Telmisartan. The volume was made up to 100 ml with phosphate buffer pH 6.8 to get a concentration of 100 µg/ml. 20 µg/ml solution of Telmisartan was prepared in dilution which was subjected to UV-Vis spectrophotometer from 400- 200 nm to determine the λ_{max}.

Drug Excipients Compatibility Studies:

Infra-red spectroscopy (Brooker FTIR Tokyo, Japan) analysis was performed to check the excipients compatibility with the drug[5].

Construction of calibration curve:

Primary stock solution was prepared by dissolving 100 mg of Telmisartan in small quantity of methanol and final volume (100 ml) was made by adding pH 6.8 phosphate buffer solution. 1 ml of this stock solution was diluted again with phosphate buffer upto 100 ml. From this stock solution different concentration (2, 4, 6, 8 and 10 µg/ml) of working standard solutions were prepared by taking 2, 4, 6, 8 and 10 ml respectively and final volume to 10 ml were made with phosphate buffer solution. Absorption of each sample was measured at 296 nm using UV-Vis spectrophotometer and pH 6.8 phosphate buffer as blank. The graph was plotted by taking concentration on X-axis and absorption on Y-axis. The plot appeared as a straight line & the linearity was determined by using y= mx +c formula. The method obeyed Beers law in concentration range from 2-10 µg/ml. Reproducibility of method was tested by analysing separately weighed samples of Telmisartan.

B. PREPARATION OF TELMISARTAN MOUTH DISSOLVING TABLETS:

1. Preparation of Drug & Carrier Complexes:

These were prepared by using solvent casting method. Telmisartan was dissolved in 3 ml of 0.1N Sodium hydroxide and stirred intensively then β-cyclodextrin (1:1 molar ratio) was added to obtain semi solid mass which was kept in the oven for drying at 50^0C for 1-2 hr and the dried mass was scratched and passed through mesh #100 and was kept in dessicator for further use[6].

2. Preparation of Mouth Dissolving Tablets:

Tablets containing 20 mg of Telmisartan were prepared by direct compression technique. In the formulation, each super disintegrant was employed in three concentrations (20, 30 and 40 mg). The composition of MDT of Telmisartan is shown in Table No: 1.The drug and all other excipients, except magnesium sterate and talcum powder were previously sieved through 60 mesh were thoroughly mixed for 15 min by using a poly bag. The resulting mixture was mixed with the mixture of magnesium sterate and talcum powder for up to 5 min. Powder blend was then directly compressed using 8 mm, round-shaped tooling in an 10 station tablet compression machine[7].

Table No - 1: Formulation of Telmisartan MDT`s.

S.NO.	Ingredients	F_1 (mg)	F_2 (mg)	F_3 (mg)	F_4 (mg)	F_5 (mg)	F_6 (mg)	F_7 (mg)	F_8 (mg)	F_9 (mg)
1	Telmisartan&β-cyclodextrin	40	40	40	40	40	40	40	40	40
2	CroscarmelloseSodium	20	30	40	---	---	---	---	---	---
3	Sodium Starch Glycolate	---	---	---	10	15	20	---	---	---
4	Crosspovidone	---	---	---	---	---	---	10	15	20
5	Sucrose	5	5	5	5	5	5	5	5	5
6	Microcrystalline Cellulose	50	40	30	50	40	30	50	40	30
7	Mannitol	25	25	25	25	25	25	25	25	25
8	Talc	5	5	5	5	5	5	5	5	5
9	Mg. Stearate	5	5	5	5	5	5	5	5	5
	Total Weight	150	150	150	150	150	150	150	150	150

C. PRECOMPRESSION PARAMETERS:

The prepared blend was evaluated for following parameters before the compression

Bulk Density:

Apparent bulk density was determined by pouring the 5 gm of powder into a 100 ml graduated cylinder. The bulk volume (V) of the poured drug was determined and the bulk density was calculated using the formula[8].

$$D_b = M / V_b$$

Where ; D_b is bulk density, M is weight of the powder and V_b is bulk volume of the powder.

Tapped Density:

Measuring cylinder containing known mass (5 gm) of powder was tapped for 100 times. The minimum volume (Vt) occupied was measured. The tapped density was calculated using following formula[8].

$$Dt = M / Vt$$

Where; M is the mass of powder and Vt is the tapped volume of the powder

Carr`s Index:

It indicates powder flow properties. It is expressed in percentage and is given as

$$I = D_t - D_b / D_t \times 100$$

Where; Dt is the tapped density, Db is the bulk density of the powder

HausnerRatio:

Hausner ratio is an indirect index of ease ofpowder flow. Hausner ratio is the ratio oftapped density to bulk density. Lower thevalue of Hausner ratio better is the flowproperty. Powderwith Hausner ratio less than1.18, 1.19, 1.25, 1.3- 1.5 and greater the 1.5indicate excellent, good, passable, and verypoor, respectively. It was calculated bythe following formula[8].

$$\text{Hausner ratio} = D_t / D_b$$

Where; D_t is the tapped density and D_b is the bulk density

Angle of repose:

The angle of repose was determined using funnel method. Funnel was kept vertically with stand at 6.3 cm. height. The opening end of funnel was closed with thumb and 5 gm of powder was poured into funnel until a maximum cone height (h) was obtained vertically. Radius of the heap (r) was measured and the angle of repose (θ) was calculated using the formula[8].

$$\theta = \mathrm{Tan}^{-1}(h / r)$$

Where; θ= Angle of Repose, h = height of the cone and r = radius of the cone

D. POST FORMULATION STUDIES

Average 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[8].

Thickness:

Tablet thickness can be measured using a simple procedure. 5 tablets were taken and their thickness was measured using Vernier calipers[8].

Hardness:

It is the force required to break a tablet by compression in the radial direction, it is an important parameter in formulation of ODTs 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[8].

Disintegration Time:

The process of breakdown of a tablet into smaller particles is called as disintegration. One tablet in each of the 6 tubes of the basket is to be placed and the apparatus subjected to run. The assembly should be raised and lowered between 50 cycles per minute. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded[8].

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 he tablets at a height of 6 inches in each revolution. Preweighed sample of tablets was placed in the friabilator and were subjected to100 revolutions. Tablets were de dusted using a soft muslin cloth and reweighed. The friability (f) is given by the formula[8].

$$\% \text{ Friability} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

Drug Content Uniformity Test:

The tablets were weighed and powdered. An amount of powder equivalent to 150 mg of Telmisartan was dissolved in 100 ml of phosphate buffer pH 6.8, filtered, diluted suitably and analyzed for drug content at 296 nm using UV-Visible spectrophotometer. From the absorbance values, amount of drug present in the given tablet was calculated.

Wetting Time:

Five circular tissue papers of 10 cm diameter were placed in a petridish with a 10 cm diameter. Ten milliliters of water-containing Eosin, a water-soluble dye, is added to petridish. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet was noted as a wetting time[9].

Water Absorption Ratio:

A piece of tissue paper folded twice was placed in a small Petridish (internal diameter = 6.5 cm)containing 6 ml of water. A tablet was placed on the paper and time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio (R) was determined using following equation[9,10].

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

Where; Wa - Weight of tablet after water absorption**,** Wb - Weight of tablet before water absorption

***In Vitro* Dissolution Studies:**

In vitro drug release studies for the mouth dissolving tablets of Telmisartan was studied using dissolution test apparatus (II USP XXVII model) Paddle type, for the fabricated batches with therotation speed of 50 rpm using phosphate buffer pH 6.8 as the dissolution medium maintained at a temperature of 37 ± 0.5°C. Samples were withdrawn at predetermined time interval and filtered through whatman filter paper, diluted suitably and analyzed at 296 nm for cumulative drug release using double beam UV-Visible spectrophotometer. The dissolution experiments were conducted in triplicate[8,11].

***In Vitro*Dispersion Time:**

In vitro dispersion time was measured by dropping a tablet in a measuring cylinder containing 6 ml of phosphate buffer pH 6.8 (simulated saliva fluid). The time for the tablet to completely disintegrate into fine particles was noted. Three tablets from each batch were randomly selected and *in vitro* dispersion time was performed[8,11,12].

Drug Release Kinetics:

In order to investigate the mechanism of release of drug from the tablets, the release data was analyzed with the following mathematical release models[8]:

Model		Equation
Zero order kinetics	:	$Q = Q_o - K_o t$
First order kinetics	:	$Q = Q_o (1 - e^{-K1t})$
Higuchi square root model	:	$Q_t = K_H t^{1/2}$
Hixson-Crowell's cube root model	:	$\sqrt[3]{Q_o} - \sqrt[3]{Q_t} = K_{HC}{}^t$
Korsmeyer-peppas model	:	$\frac{Q_t}{Q\infty} = K_k t^n$

Where, Q_t– amount of drug release at time t, Q_o– initial amount of drug and K_o, K_1, K_H, K_{HC} and K_K are the coefficients of the equations.

RESULTS & DISCUSSION

A. PREFORMULATION STUDIES:

Solubility Analysis:

Telmisartan is freely soluble in dichloromethane, methanol, absolute ethanol and chloroform, practically insoluble in water.

Melting Point Determination:

The melting point of the pure drug was determined at 262°C

Identification of Pure Drug:

FT-IR spectroscopy was used to determine the functional group present in the pure drug sample. The FTIR spectrum of pure Telmisartan was showed the characteristic peaks at 740 cm-1, 1128 cm-1, 1268 cm-1, 3057 cm-1, 1695 cm-1 & 862 cm-1 were due to aromatic C-H binding, C-N stretching, C=N stretching, aromatic C-H stretching , C=O stretching and O-H stretching respectively. IR spectra of Telmisartan as follows:

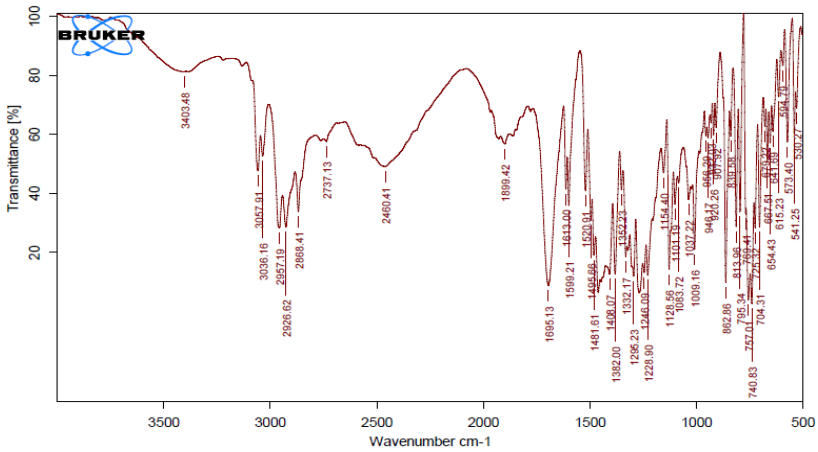


Figure No - 1: FT-IR Spectra for the Pure Telmisartan.

D. Determination of λ_{max}:

The Telmisartan solution was scanned in UV-Vis spectrophotometer from 400- 200 nm to determine the λmax. The λmax was found to be at 296 nm, so the calibration curve of Telmisartan was developed at this wavelength.

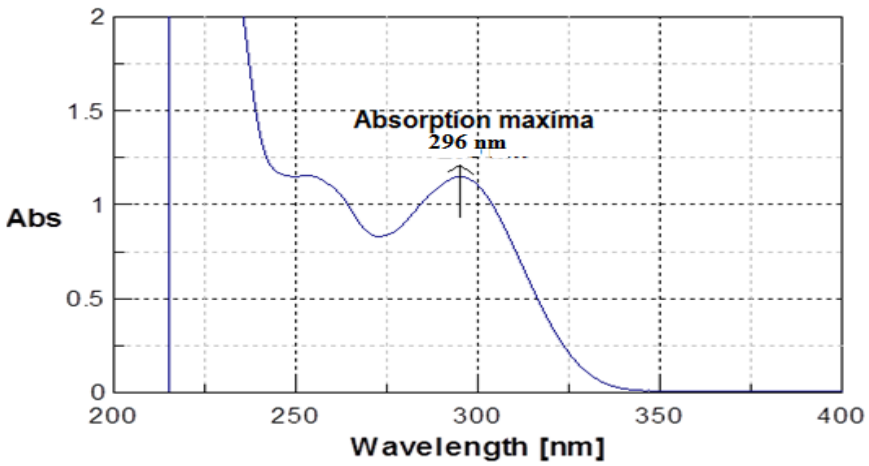


Figure No - 2: λ max of Telmisartan.

Drug excipients compatibility studies:

The interaction studies were carried out to ascertain any kind of interaction of drug with the excipients used in the preparation of tablets. The samples of pure drug and formulas were dispersed in KBr powder and compressed into pellets at a pressure of 6000 kg/cm^2 and analyzed. Spectral measurements were obtained by powder diffuse reflectance on a FT-infrared spectrophotometer.

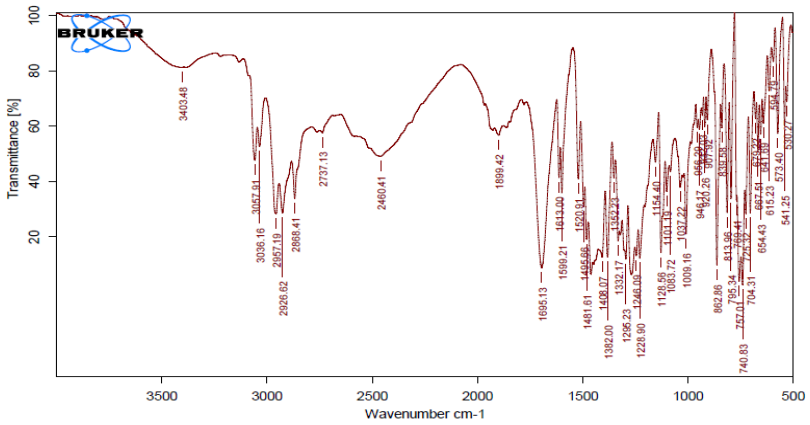


Figure No - 3: FT-IR Spectra for the Pure Telmisartan.

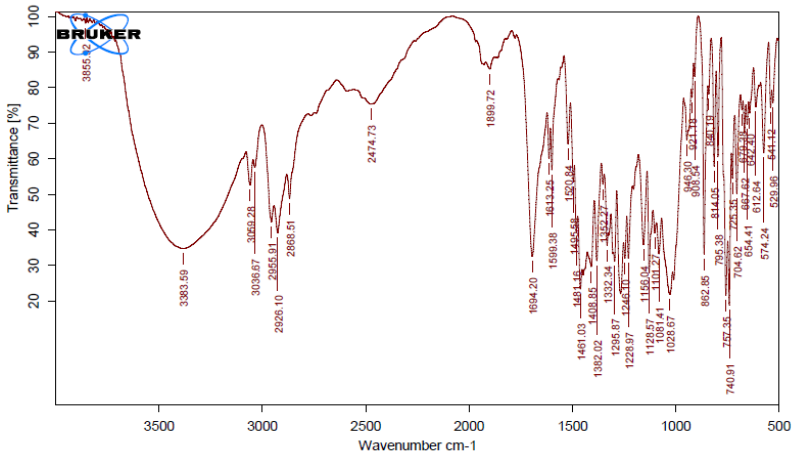


Figure No - 4: FT-IR Spectra for the Mixture of Drug and β-Cyclodextrin.

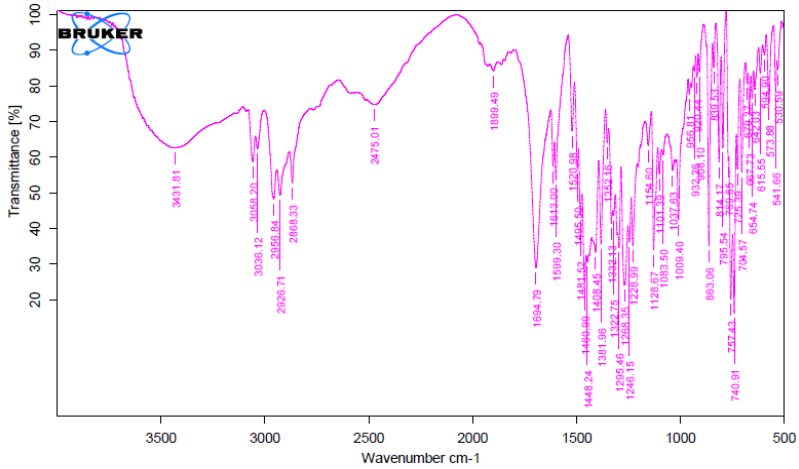


Figure No - 5: FT-IR Spectra for the Mixture of Drug and Crosscarmellose Sodium.

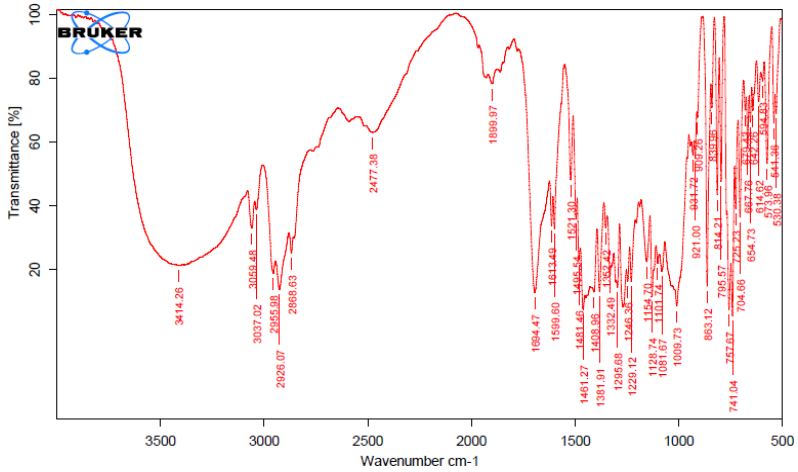


Figure No - 6: FT-IR Spectra for the Mixture of Drug and Sodium starch glycolate.

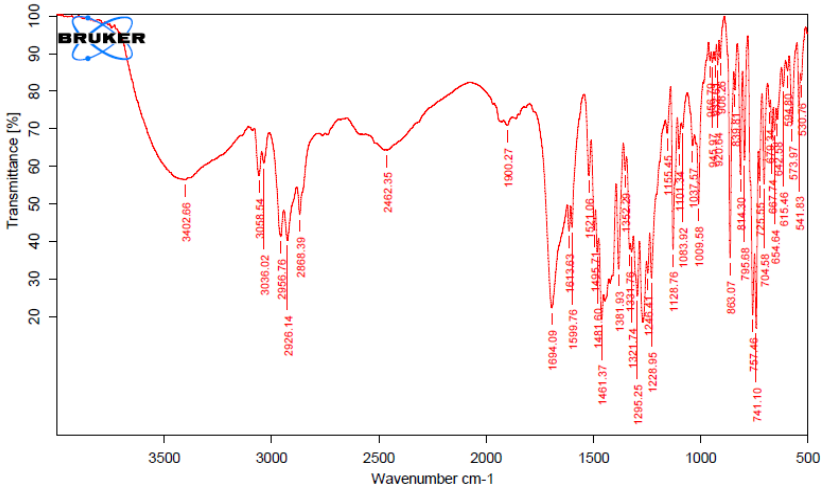


Figure No - 7: FT- IR Spectra forthe Mixture of Drug and Crosspovidone.

Inference:

The FTIR spectra of the pure drug and tablet formulations were shown in Figures 3 -7.The spectra of drug and super disintegrants employed were showed a broad peak at the same place of the peak observed at the spectrum of pure drug has been observed, which indicated that there was no chemical interaction with the polymers.

Standard Graph of Telmisartan:

The construction of standard curve of Telmisartan was done by using pH 6.8 PBS as the medium. Telmisartan was found to have the maximum absorbance at 296 nm. The standard graph of Telmisartan in pH 6.8 PBS was constructed by making the concentrations of 2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml, 10 µg/ml solutions. The absorbance of solutions was examined under UV-spectrophotometer at an absorption maximum of 296 nm. The standard graph was constructed by taking the absorbance on Y-axis and concentrations on X-axis. The standard calibration curve of Telmisartan in pH 6.8 PBS was shown in Fig No - 8. Drug concentration and absorbance followed linear relationship. The curve obeyed Beer-Lambert's law and the correlation coefficient value (R^2) of buffer was 0.999.

Table No – 2: Standard Calibration Curve of Telmisartan in pH 6.8 PBS.

S. No.	Concentration(µg/ml)	Absorbance in pH 6.8 PBS
1	0	0.000
2	2	0.066
3	4	0.123
4	6	0.184
5	8	0.244
6	10	0.313

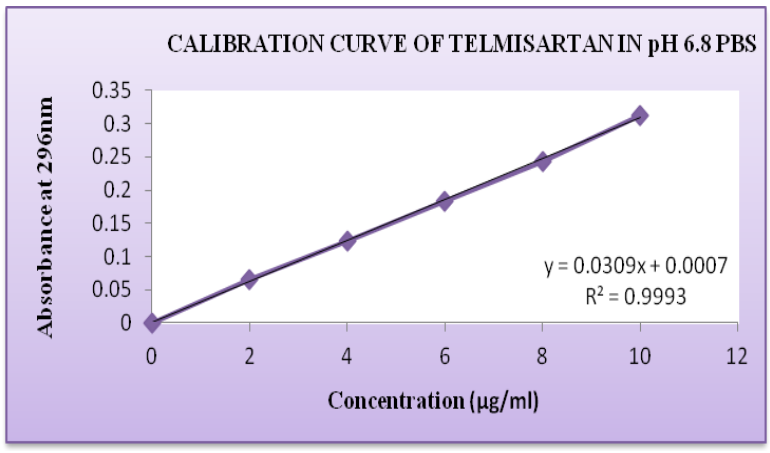


Figure No - 8: Calibration Curve of Telmisartan in pH6.8 PBS.

B. PREPARATION OF TELMISARTAN MDT`s:

Preparation of Drug:

Carrier Complex:

Telmisartan and β-cyclodextrin complex with 1:1 molar ratio was prepared by using solvent casting method.

Preparation of Mouth Dissolving Tablets

Tablets containing 20 mg of Telmisartan were prepared by direct compression technique.By using this technique all the formulations of Telmisartan were prepared to achieve desirable disintegration time of the tablets. Nine Different formulations of Telmisartan MDTs were prepared with 40 mg of Telmisartan & β-cyclodextrin complex and different concentration of Sodium Starch Glycolate, Crosscarmellose sodium and crosspovidone as superdisintegrants, the Microcrystaline cellulose as bulking agent, Sucrose as sweetening agent, Magnesium steatare as lubricant, talc as glidant specified in Table No -9. Each super disintegrant was used in 3 different concentrations (20, 30, and 40 mg) and keeping the all other ingredients at constant.

There are three super disintegrants, each one of it has 3 formulations and overall 9 formulations of Telmisartan MDTs were prepared and these are assigned with formulation codes from F1 to F9.

C. PRECOMPRESSION PARAMETERS:

Bulk Density & Tapped Density:

The powdered blends of all the formulations were evaluated for bulk density and tapped density by using bulk density apparatus and the results were shown in Table No - 3. The bulk density was found in the range of 0.392±0.29 - 0.514±0.34gm/cm^3. The tapped density ranged between 0.439±0.25 - 0.672±0.29gm/cm^3. Which indicate that powder is loosely packed. These values were further used for calculating Carr's index and Hausner ratio to check its flow ability of powder.

Table No -3: Bulk Density &Tapped Density of all the Formulations F1 - F9.

S. No	Formulation Code	Bulk Density (Gm/Cm$^{3)}$	Tapped Density (Gm/Cm$^{3)}$
1.	F1	0.457±0.26	0.586±0.31
2.	F2	0.392±0.29	0.439±0.25
3.	F3	0.484±0.14	0.546±0.26
4.	F4	0.414±0.17	0.530±0.18
5.	F5	0.432±0.14	0.573±0.28
6.	F6	0.464±0.36	0.591±0.32
7.	F7	0.514±0.34	0.672±0.29
8.	F8	0.460±0.39	0.563±0.33
9.	F9	0.461±0.25	0.581±0.35

Carr's Index & Hausner's ratio:

The Compressibility index of all the formulations exists in the range between12.06±0.27–13.54±0.29. The result of the Hausner's ratio of all the formulations is between 1.014±0.25–1.152±0.16.These values indicate that the prepared blends possessed minimum interparticulate interactions and good flow property which is preliminary requirement for formulating the tablets.

Table No - 4: Carr's Index and Hausner'sRatio.

S.No	Formulationcode	Carr's Index	Hausner's Ratio
1.	F1	12.21±0.31	1.014±0.25
2.	F2	12.32±0.37	1.062±0.26
3.	F3	12.86±0.41	1.121±0.24
4.	F4	12.06±0.27	1.028±0.26
5.	F5	12.69±0.26	1.049±0.13
6.	F6	13.20±0.27	1.152±0.16
7.	F7	12.39±0.19	1.116±0.21
8.	F8	13.54±0.29	1.054±0.19
9.	F9	13.28±0.23	1.039±0.13

Angle of Repose:

The prepared powder blends of all the formulations were evaluated for the flow properties (Table No- 5).Resistance offered to the movement of particle can be judged by angle of repose. It provides qualitative and quantitative assessment of internal cohesive and frictional force under low level of external load applied during mixing and tableting. The angle of repose of all the formulations was within the range of 19^0 -21^0. These values indicate that the powder blend had exhibited good flow properties.

Table No - 5: Angle of Repose.

S. No	Formulation	Angle Of Repose
1.	F1	19.35±0.14
2.	F2	20.61±0.26
3.	F3	21.02±0.23
4.	F4	19.69±0.25
5.	F5	20.7.±0.42
6.	F6	21.20±0.18
7.	F7	20.80±0.51
8.	F8	19.61±0.32
9.	F9	19.89±0.35

C. POST FORMULATION STUDIES:

All the formulations were prepared under similar conditions and the tablets exibited white color, convex in shape with smooth surface. The hardness for the tablets of all formulations was adjusted to 3–3.5 Kg/cm^2 so that the effect of superdisintegrant on the dissolution rate could be evaluated accurately. The friability of all the formulated tablets was within 1%, which is an indication of good mechanical resistance of the tablet. The drug content varied between 96.04%±0.41 to 98.60%±0.34 for all the formulations. The thickness was measured for the tablets of all formulations and was found to be within the acceptable range. The weight of the tablet varied between 150.1±0.62 to 152.2±0.98mg for all the formulations. The variation in weight was within the range of ± 7.5% complying with pharmacopoeial specification.

Table No - 6: Evaluation Parameters of Telmisartan MDT`s.

Formulation Code	Hardness (Kg/Cm^2)	Friability (%)	Weight Variation (Mg)	Thickness (Mm)	Drug Content (%)
F1	3.2±0.23	0.262±0.001	151.3±0.48	3.2±0.007	96.12%±0.61
F2	3.0±0.21	0.389±0.002	150.1±0.62	3.4±0.001	96.54%±0.22
F3	3.1±0.16	0.475±0.007	150.7±0.13	3.3±0.003	98.24%±0.32
F4	3.2±0.14	0.346±0.005	150.3±0.64	3.7±0.005	97.20%±0.71
F5	3.4±0.21	0.521±0.001	150.6±0.26	3.5±0.002	98.12%±0.15
F6	3.2±0.22	0.589±0.004	152.1±0.31	3.5±0.008	98.60%±0.34
F7	3.5±0.14	0.60±0.008	150.6±0.42	3.4±0.001	98.23%±0.23
F8	3.2±0.16	0.421±0.002	152.2±0.98	3.5±0.005	96.04%±0.41
F9	3.1±0.15	0.398±0.008	150.3±0.16	3.4±0.004	97.01%±0.26

Wetting Time:

It is major importance in selection of the best MDT formulation among all the 9 formulations. For all the formulations, with increase in the superdisintegrant concentration from 20-40 mg, the wetting time was decreased accordingly. It is clear from the results that the formulation containing SSG had shown more wetting time than CCS and CP. This may be due to the fact that SSG is disintegrated by swelling mechanism leading to longer wetting time and lesser water absorption ratio. The formulations that contain Crosspovidone have the shortest wetting time, which may be attributed to the strong wicking action of this super disintegrant. So it was selected as the best superdisintegrant and used 20 mg, 30 mg, 40 mg in formulations F7 – F9 to investigate other formulation variables.

The wetting time was noted visually and the results are given in Table No -7.The wetting time was in the range of 8 seconds to 80.56 seconds. The result shows that all the formulations pass the test and the formulation F9 showed minimum wetting time of 8 seconds.

Table No - 7: Wetting time of Telmisartan MDT`s.

S. No	Formulation Code	Wetting Time (Sec)
1	F1	80.56
2	F2	44.20
3	F3	28.30
4	F4	63.30
5	F5	39.40
6	F6	31.00
7	F7	18.48
8	F8	12.12
9	F9	8.22

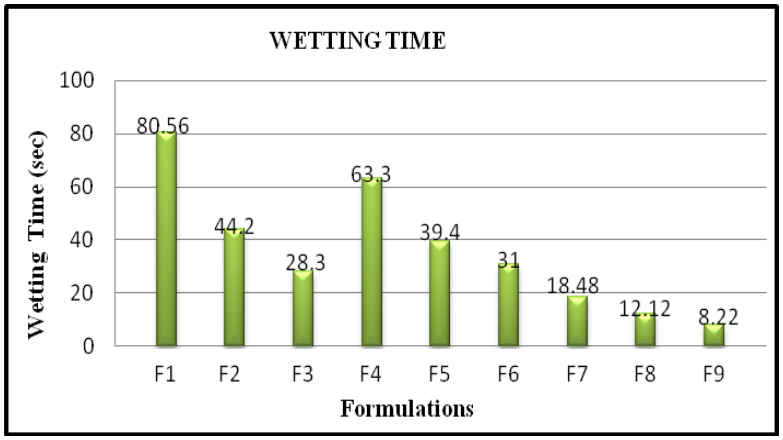


Figure No - 9: Comparison of Wetting Time of Formulations F1 – F9.

Water Absorption Ratio:

Water absorption ratio (R) value increased with increase in concentration of super disintegrant (from 20-40 mg). This increase is due to the water up taking ability of the super disintegrants. More is the superdisintegrant concentration, greater is the water uptake and thereby increase in the "R" value is observed. This pattern followed in case of all the 3 super disintegrants used in total 9 formulations of Telmisartan MDTs.Augmentation of water absorption ratio may lead to decreased wetting time as well as disintegration time, thus decreasing the absorption time of the drug from the formulation. The formulation F9 containing 40 mg of Crosspovidone showed maximum water absorption value (180±0.56) compared to other formulations.

Table No - 8: Water Absorption Ratio of Telmisartan MDT`s.

S. No	Formulation Code	Water Absorption Ratio
1.	F1	102±0.24
2.	F2	141±0.92
3.	F3	162±0.48
4.	F4	47±0.92
5.	F5	87±0.95
6.	F6	90±0.24
7.	F7	102±0.40
8.	F8	155±0.85
9.	F9	180±0.56

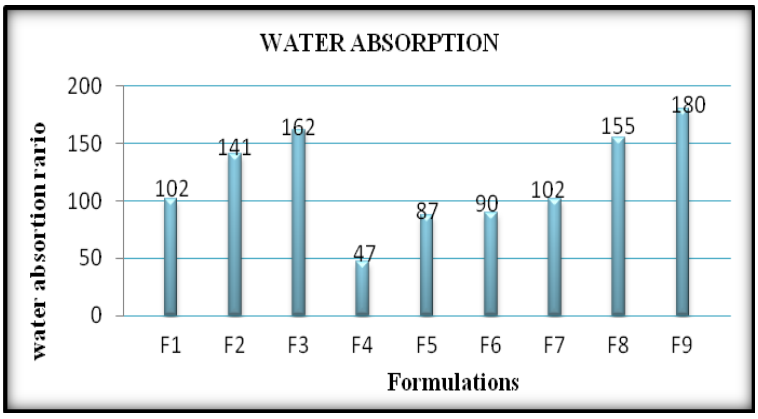


Figure No - 10: Comparison of Water Absorption Ratio of Formulations F1– F9.

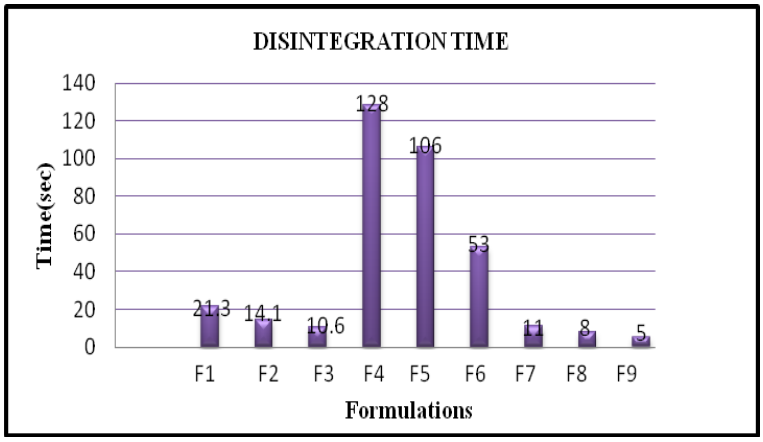
Disintegration & Dispersion Time:

Disintegration time is very important for mouth dissolving tablets which are desired to be less than 60 seconds. This rapid disintegration plays a role in drug absorption in buccal cavity, which promotes the bioavailability of the drug. The *in vitro* disintegration time of prepared tablets (F1 – F9) was present between 5 to 128 sec. respectively. Out of all the formulations, the tablets prepared using 40 mg of CP showed rapid disintegration in 5 sec. It was clear that the disintegration time of CP containing tablets were comparatively lower than tablets containing CCS and SSG. This may be due to its rapid capillary activity and pronounced hydration with little tendency to form gel when comes in contact with buffer and water.

In vitro dispersion time indicates complete dispersion of formulation in the saliva and it was found to be in the range of 12.8 sec to 163 sec and it is due to more porosity of superdisintegrant. Quick dispersion of formulation favours fast disintegration of formulation. Out of all the formulations, the tablets prepared using 40mg of CP showed rapid dispersion in 12.8 sec. It was clear that the disintegration time of CP containing tablets were comparatively lower than tablets containing CCS and SSG.

Table No – 9: *In-Vitro* Drug Disintegration& Dispersion Time Studies.

Formulation Code	*In-Vitro* Dispersion Time (Seconds)	*In-Vitro* Disintegration Time (Seconds)
F1	29.3	21.3
F2	20.3	14.1
F3	14.5	10.6
F4	163.0	128
F5	120.6	106
F6	80.0	53
F7	24.6	11
F8	14.2	08
F9	12.8	05



FigureNo-11: Comparison of Disintegration Time of Formulations F1 – F9.

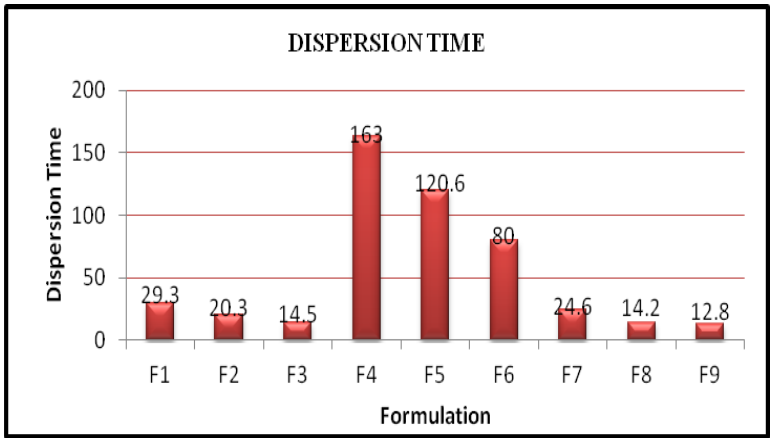


Figure No - 12: Comparison of Dispersion Time of formulations F1 – F9.

***Invitro* Release Studies:**

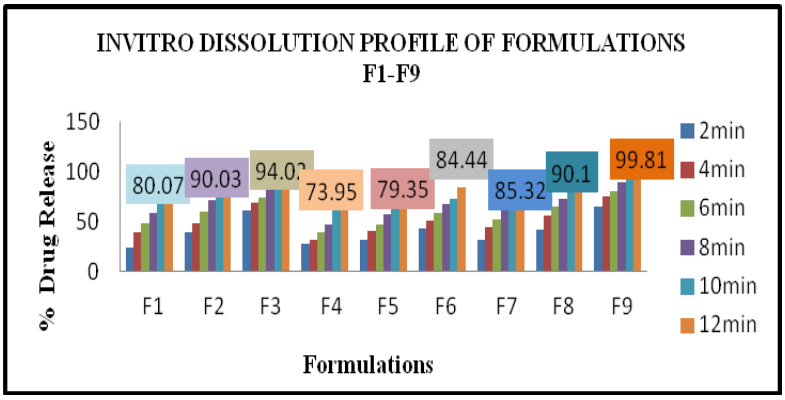
The release profiles of the formulations were determined using USP dissolution apparatus XXIV-Type II. The MDTs were placed in dissolution flask contain pH 6.8 PBS solution. Then the paddle was rotated at 50 rpm, and immediately aliquots of 5 ml sample were withdrawn at every two minute over a period of 12 minutes. The drug content was determined at 296nm by using UV spectrophotometer. The *In vitro* drug release studies were performed to evaluate the release of MDTs. The cumulative percentage release in pH 6.8 PBS for all the formulations was recorded and the formulation F3, F6 and F9 showed higher drug release, respectively94.02%, 84.44% and 99.81% within 12 minutes. The higher drug release from these formulations was possible due to presence of higher concentration of the super disintegrant. The cumulative amounts of drug released from the formulations are shown in Table No – 10. The drug releases of nine formulations were compared with each other and the results are represented diagrammatically and it was shown in Fig No: 13**.** The tablets formulated with CP (F9) showed greater rate of dissolution when compared to the tablets formulated with CCS and SSG. In formulation F9 containing 30 mg of MCC along with 40 mg of CP showed better dissolution rate than those of all other formulations. This might be because of its high disintegrating nature.

The results of dissolution studies of formulations F1 – F9 in Table No: 10 indicate that the dissolution rate is in the following order

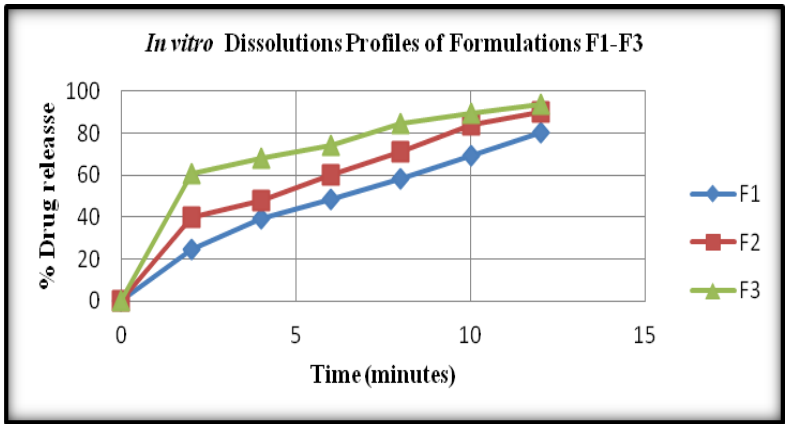
F9> F3 > F2> F8> F7> F6> F1 > F5> F4

Table No – 10: Cumulative Percent Drug Release of Telmisartan MDT`s.

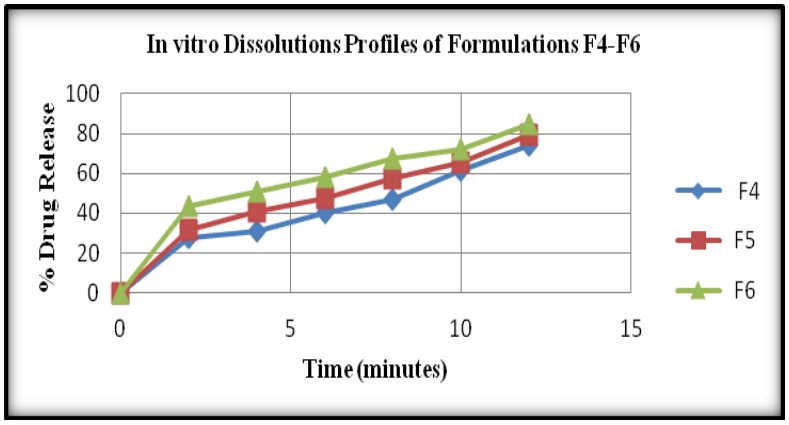
Time	% Drug Release								
(min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
2	24.47	39.89	60.9	27.63	31.44	43.68	31.25	41.39	65.54
4	39.50	48.05	68.31	31.09	40.89	50.55	44.65	56.43	75
6	48.68	59.9	74	39.91	47.23	58.04	52.7	64.9	80.7
8	58.04	70.89	84.31	46.77	57.49	67.68	64.61	72.63	89.63
10	69.40	83.75	89.66	61.25	65.62	72.24	76.11	85.71	94.49
12	80.07	90.03	94.02	73.95	79.35	84.44	85.32	90.1	99.81



FigureNo-13: Comparative Dissolution Profiles of the Formulations F1-F9.



FigureNo-14: Comparative Dissolution Profiles of the Formulations F1-F3.



FigureNo-15: Comparative Dissolution Profiles of the Formulations F4-F6.

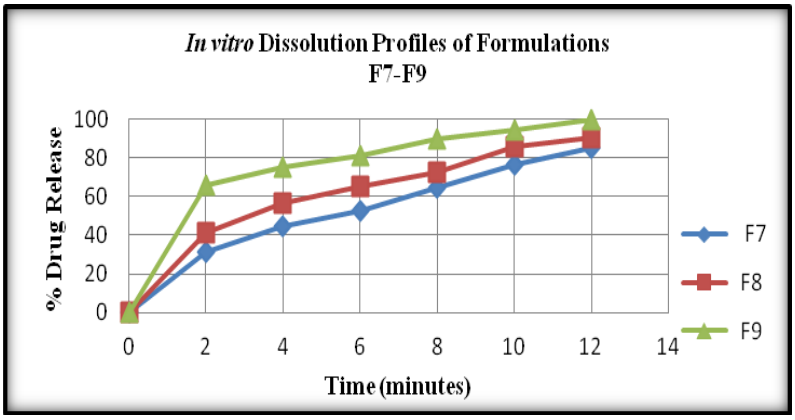


Figure No - 16: Comparative Dissolution Profiles of the Formulations F7 – F9.

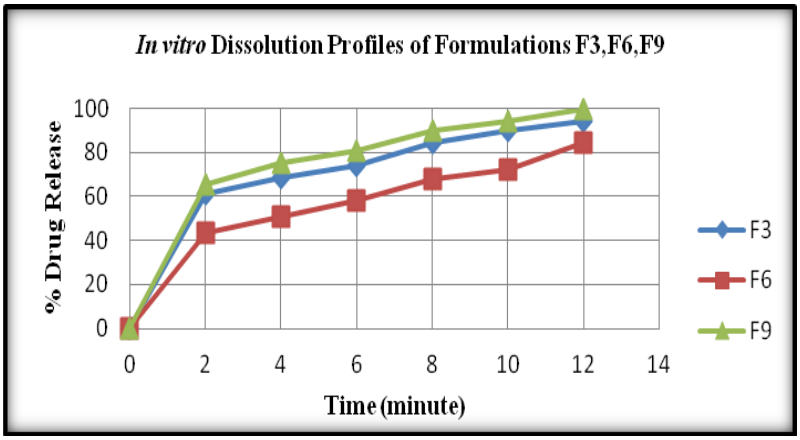


Figure No - 17: Comparison of Dissolution Profiles of Formulations F3, F6, F9.

KINETIC MODELING OF DRUG RELEASE

In order to describe the release kinetics of all nine formulations the corresponding dissolution data was fitted in various kinetic models like Zero order, First order, Higuchi, Hixon Crowell and Peppas. The kinetic data obtained from formulation F9 was mentioned in Table No: 11. These values were compared with each model and drug equation. Here the formulation F9 followed first order kinetics and drug release described by dissolution and will vary with the change in surface area and diameter of the tablet.

Table No – 11: Kinetic Modeling of Drug Release from F9.

S.No	Time (min)	Log T	Square root of Time	% CR	% Drug Remaining	Log % CR	Log % Drug Remaining	Square root of % Drug Remaining
1	2	0.3010	1.4142	65.54	34.46	1.8165	1.5373	5.8702
2	4	0.6020	2	75	25	1.8750	1.3979	5
3	6	0.7781	2.4494	80.7	19.3	1.9068	1.2855	4.3931
4	8	0.9030	2.8284	89.63	10.37	1.9524	1.0157	3.2202
5	10	1	3.1622	94.49	5.51	1.9753	0.7411	2.3473
6	12	1.0791	3.4641	99	1	1.9956	0	0.4358

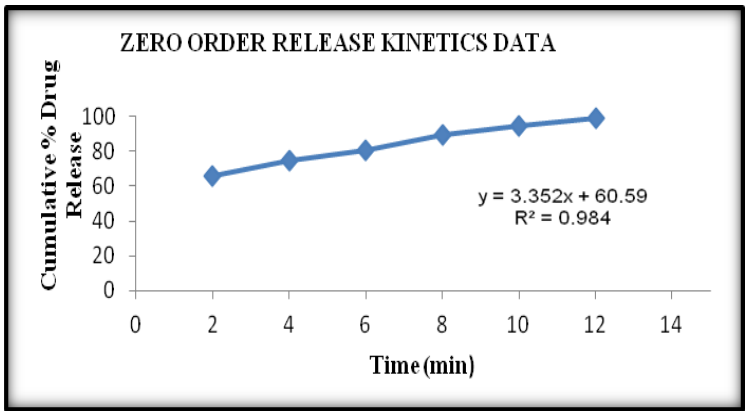


Figure No - 18:Zero Order Release Kinetics Data.

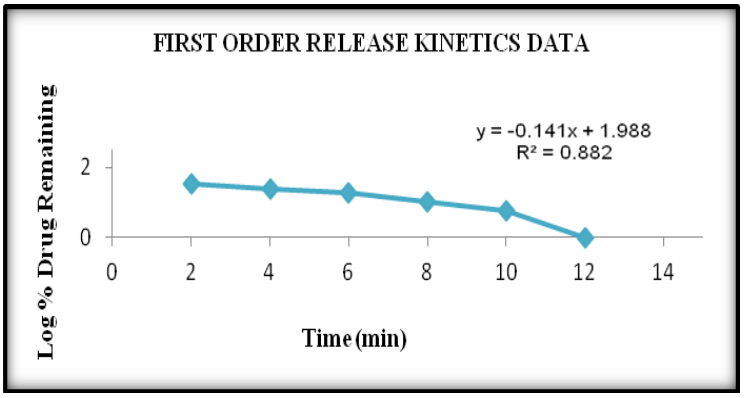


Figure No - 19: First Order Release Kinetics Data.

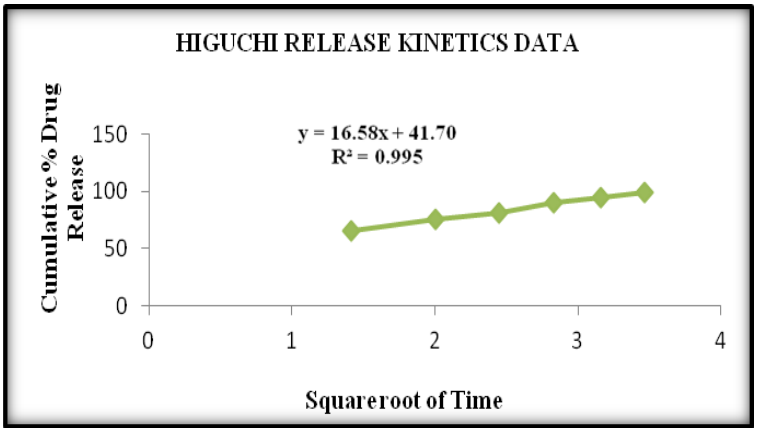


Figure No - 20: Higuchi Release Kinetics Data.

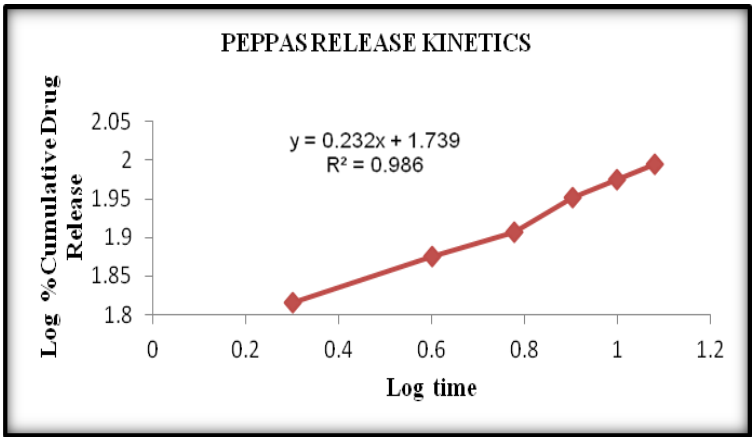


Figure No - 21: Peppas Release Kinetics.

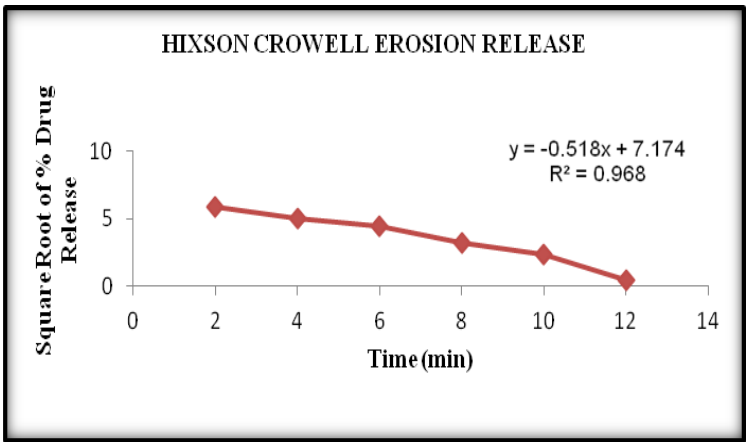


Figure No - 22: Hixson Crowell Erosion Equation.

Inference:

Hixon Crowell cube root law and Higuchi's models were applied to test the release mechanism. From the above plots it was concluded that optimized formula showed zero order release and drug release described by diffusion mechanism.

CONCLUSION

Telmisartan (BCS class II drug) is an angiotensin II receptor antagonist (ARB) used in the management of hypertension, it is extremely unstable in the acidic condition of gastric fluid. An attempt has been made to overcome the problem by developing a mouth dissolving tablet of Telmisartan by direct compression method using CCS, SSG & CP as super disintegrants. Out of the nine formulations developed, the F7 – F9 formulations containing CP as super disintegrant had exhibited the gratifying results when compared with the other two. The results conclude that F9 is the best formulation containing 40 mg of CP. It showed the superlative results in terms of disintegration time, wetting time and *In vitro* drug release. It was concluded from the results that prepared mouth dissolving tablets might decrease dosing frequency, enhance bioavailability, improves patient compliance, rapid onset of action and avoid first pass metabolism, which was the aim of the present work.

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