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Fabrication and Evaluation of Sublingual Tablet of Telmisartan Using Different Superdisintegrants

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ABSTRACT

Telmisartan (BCS class II drug) is an angiotensin II receptor antagonist (ARB) used in the management of hypertension. Hypertension is one of the most important modifiable risk factors for CHD in Western and Asian population. The aim of the present research work was to improve the solubility ultimately bioavailability of Telmisartan by encapsulating it inside the cavity of β-cyclodextrin. Formulation of drug, β-cyclodextrin and excipients were used to develop sublingual tablets. Sublingual routes are one of the most promising strategies to improve the oral bioavailability by enhancing the drug efficacy pertaining to complete disintegration and thus the release of drug particles from the dosage form would enable quick and direct delivery into the circulatory system by avoiding first pass metabolism. Sublingual tablets (6 batches) using polymers like CP, SSG and CCS by employing direct compression method. The results of pre-compression 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 results are well within IP limits. Out of 6 formulations, the tablets which contain 5% of CP (F6) had shown low wetting time 30.26, low in vitro disintegration time 26.08 sec, high water absorption ratio 95.66% and highest drug release profile i.e. 80.33% which releases the drug within 3 minute. The different kinetic models revealed that drug release followed non-fickian diffusion mechanism. The stability studies of the optimized batch were subjected by storing at 40°C±2°C / 75%±5% RH up to 90 days. After 90 days, the tablets were again analyzed and there was no significant change observed.

INTRODUCTION

Hypertension is one of the most important modifiable risk factors for coronary heart diseases (CHD) in Western and Asian population[1]. Recently, estimated total number of people with hypertension in the 2000 was 972 million and this is projected to increase by 60% to a total of 1.56 billion by 2025 i.e., 29% of the worldwide adult population[2].

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. 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 compliance[3]. This problem can be addressed through the development of sublingual 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 would enable quick and direct delivery into the circulatory system by avoiding first pass metabolism. Additionally, abundance of blood supply at the sublingual region allows excellent drug penetration to achieve high plasma drug concentration with rapid onset of an action. These formulations are particularly beneficial for the hypertensive patient, as in such type of patient immediate treatment have to be required to prevent them for cardiac arrest, heart attack etc. So there is a need to develop a sublingual tablet containing anti-hypertensive drug with immediate response to reduce morbidity, escape from first pass metabolism, reduced manufacturing difficulties and cost effectiveness[4]. Especially, in case of management of hypertension, Sublingual tablets provide effective and easier way of medication.

Telmisartan is an angiotensin II receptor antagonist (ARB) used in the management of hypertension. It belongs to BCS class II in which high permeability and low solubility occurred[5]. It has oral bioavailability of about 42% due to its first pass metabolism. To improve its solubility drug was encapsulated inside the cavity of β-cyclodextrin. The rationale to formulate Sublingual 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.

To make an effective Sublingual formulation, careful consideration is necessary on all the ingredients as well as on formulation parameters (*in vitro* dispersion time, water absorption ratio, wetting time, hardness, pharmacotechnical evaluation parameters) used in the formulation. Sublingual administration can offer an attractive alternative route of administration. The advantage of the sublingual drug delivery is that the drug can be directly absorbed into systemic circulation bypassing enzyme degradation in the gut and liver[6-7].

Therefore in the present work, it was proposed to formulate sublingual tablets of Telmisartan. Telmisartan is an antihypertensive drug which is practically insoluble in water, which ultimately affects its bioavailability. So, the aim of present work is to improve its solubility by encapsulating inside the cavity of β-cyclodextrin and preparing its Sublingual tablets by direct compression method.

MATERIALS AND METHODS

A. Materials

Telmisartan and β-cyclodextrin was procured as gift sample from Morepen Pvt. Ltd., Baddi and was used without further purification. Microcrystalline cellulose was procured from Thomas Baker Pvt. Ltd., Mumbai whereas Mannitol, Crospovidone, Croscarmellose sodium, Sodium starch glycolate, Dry Maize starch, Aerosil and Magnesium sterate from Qualikems Fine chemicals Pvt. Ltd., New Delhi. All other solvents and reagents were of analytical grade.

B. Preparation

1) *Method of Preparation of Drug: Carrier Complexes:* Telmisartan was dissolved in 3 ml of 0.1N Sodium hydroxide and stirred intensively then β-cyclodextrin (1:1 molar ratio) was added and semi solid mass was obtained which was kept in the oven for drying at 50^{0}C for 1-2 hr and dried mass was scratched and sifted through mesh #100 and kept in dessicator for further use.

2) *Preparation of formulation blend:* All the ingredients (Mannitol granules, magnesium stearate, talc, and aerosil) were sifted individually through sieve no. 40 to break up the lumps and to get uniformity in particle size for the ease of mixing and to ensure proper flow. The weighed ingredients were then transferred to a laboratory mixer in a sequential manner. Telmisartan & β-

cyclodextrin complex was mixed with the bulking agent i.e.1/2 portion (of mannitol granules) to ensure the uniformity of active medicament throughout the blend and then other excipients were added. Talc and magnesium stearate were added few minutes before the start of compression. Finally tablets were prepared by direct compression.

3) *Preparation of tablets:* Traditionally, pharmaceutical formulations developed by "Hit & Trial" method which requires an imaginative effort. It is widely used classical technique to develop an ideal formulation. Following formula for formulations were derived with same classical technique.

Table I. Sublingual tablets of Telmisartan were formulated by direct compression methods described below

Ingredients	**F1 (mg) CCS 3%**	**F2 (mg) CCS 5%**	**F3 (mg) SSG 3%**	**F4 (mg) SSG 5%**	**F5 (mg) CP 3%**	**F6 (mg) CP 5%**
	(Weight in mg)					
Telmisartan	20	20	20	20	20	20
β-cyclodextrin	20	20	20	20	20	20
Sodium hydroxide	1	1	1	1	1	1
Microcrystalline cellulose	42	42	42	42	42	42
Mannitol granules	90.8	86.8	90.8	86.8	90.8	86.8
Croscarmellose sodium	6	10	-	-	-	-
Crospovidone	-	-	-	-	6	10
Sodium starch glycolate	-	-	6	10	-	-
Aerosil	2	2	2	2	2	2
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.7	1.7	1.7	1.7	1.7	1.7
Dried maize starch	15	15	15	15	15	15
Total wt. (mg)	200	200	200	200	200	200

C. Pre-compression Evaluation of Blends of Telmisartan

1) Drug excipient compatibility studies: FTIR studies were performed on drug, physical mixture and treated samples. Compatibility studies of drug with various excipients were done to check any chemical interaction between them. IR spectra were recorded in IR spectrophotometer with KBr pellet method.

In this method, potassium bromide and drug sample were mixed and grounded to fine powder. The powder was then punched to produce a disc which was then inserted into the IR sample holder and the spectrum was run. The physical mixtures of drug and treated sample were also subjected to same treatment. The spectrum was scanned over a frequency range 4000-400 cm^{-1} with a resolution of 4 cm^{-1} and was compared with the reference spectrum of the drug.

1) Manual assessment: Manual assessment was done by visual inspection to check any change in color and flow of the prepared treated samples.

2) Angle of Repose (θ): For determination of angle of repose (θ), the blend were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The blends were poured till the time when upper tip of the pile surface touched the lower can be measured by angle of repose.

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

Where, θ = the angle of repose, h = height of pile, r = radius of the base of pile[8]

3) Bulk Density (Db): Apparent bulk density (g/ml) is determined by pouring bulk powder into a graduated cylinder via a large funnel and measuring the volume and weight. Bulk density can be calculated by the following formula:-

$$Db = \frac{M}{Vb}$$

Where, Db = Bulk density, M = Mass of the powder, Vb = Bulk volume of the powder.

4) Tapped density (Dt): Tapped density was determined by placing a graduated cylinder containing a known mass of powder on a mechanical tapping apparatus, which is operated for a fixed number of taps (100) or until the powder bed volume has reached a minimum. The tapped density is computed by taking the weight of drug in cylinder and final volume. It is calculated according to the following formula:-

$$Dt = \frac{M}{Vt}$$

Where, Dt = Tapped density, M = mass of the powder, Vt = bulk volume of the powder

5) Compressibility Index (Carr's Consolidation Index): Another indirect method of measuring powder flow form bulk densities was developed by Carr. The percentage compressibility of a powder is a direct measure of the potential powder arch or bridge strength and stability. It is calculated according to the following formula:-

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

Where, Dt = Tapped density of the powder, Db = Bulk density of the powder

6) Hausner's Ratio: Hausner's Ratio is an indirect index of ease of powder flow. If the hausner ratio of powder is near to 1.25, indicates better powder flow. It is calculated by the following formula:

$$\text{Hausner ratio} = \frac{Db}{Dt}$$

Where, Dt = Tapped density of the powder, Db = Bulk density of the powder

C. Evaluation of Compressed Tablets

1) Thickness: Thickness of tablets (n=5) was determined using vernier caliper. A single tablet was taken and put between the two knobs of vernier caliper and reading was noted.

2) *Hardness:* Hardness of tablets (n=5) was determined by using Monsanto hardness tester.

3) Friability: Average weight of tablets (n=6) was noted using an electronic balance. The tablets were placed in Roche friabilitor and were rotated at 25 rpm for 4 min. Final weight of tablets was recorded after 4 min. Percent friability was calculated using the below mention equation.

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

4) *Weight variation:* Twenty tablets from each formulation were selected randomly and weighed individually average weight was determined. Individual tablets weighed were then was compared with average weight. The Indian Pharmacopoeia allows a little variation in the weight of a tablet. In all the formulations the tablet weight was more than 80 mg and less than 250 mg, hence 7.5% maximum difference allowed.

5) Drug content: Ten tablets from each formulation of Sublingual tablets were powdered finely. An amount equivalent to 22 mg of Telmisartan was weighed and dissolved in 50 ml methanol. The solution was filtered through Whatmann filter paper (No.41), suitably diluted to 100 ml with pH 6.8 phosphate buffer in volumetric flasks and assayed at 296 nm, using a UV-Visible spectrophotometer. The same procedure was repeated thereby for remaining formulations.

6) *Wetting time:* A piece of tissue paper folded twice was placed in a small (internal diameter 6.5cm) petri dish containing 10 ml of pH 6.8 phosphate buffer, a tablet was put on the paper, and the time for complete wetting was measured.

7) *Water Absorption Ratio:* A piece of tissue paper folded twice was kept in a petri dish (internal diameter 6.5 cm) containing 6 ml of purified water. The tablet was placed on the tissue paper and allowed to wet completely. The wetted tablet was removed and again weighed. Water absorption ratio, R was determined according to the following formula:

$$R = \frac{Wa - Wb}{Wb} \times 100$$

Where, R= water absorption ratio, Wb and Wa are the weight before and after water absorption.

8) In vitro 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.

9) *In vitro Dispersion Time:* Tablet was added to 10 ml of phosphate buffer solution, pH 6.8 at 37±0.5°C. Time required for complete dispersion of a tablet was measured.

10) *Dissolution Studies and its Data analysis:* In the present study the drug release was determined by USP type 2 dissolution apparatus (maintained at 37°C ± 5°C). The dissolution medium was prepared by using 900 ml 6.8 pH phosphate buffer at temperature and rotated at 70 rpm, Out of this material 10 ml of the sample was withdrawn by using syringe fitted with prefilter at known interval of time and replaced with fresh same quantity of dissolution medium and the λ_{max} was noted at 296 nm.

11) *Kinetic Models:* Drug release kinetics can be analyzed by various mathematical models, which were applied considering the amounts of drug released from 0 to 30 minutes[9]. Depending on these estimations, suitable mathematical models to describe the dissolution profiles were determined. The following plots were made:

- % drug release versus time (zero-order kinetic model)
- % log drug unreleased versus time (first-order kinetic model)
- % drug release versus square root of time (Higuchi model)
- log % drug release versus log time (Krosmeyer Peppas equation)

Table II. Equations of release kinetic models

Kinetics	**Equation**
Zero order	$M_o - M_t = k_o t$
First order	$\ln(M_o/M_t) = k_1 t$
Krosmeyer Peppas	$M_t/M_\infty = kt^n$
Higuchi	$M_t = K\sqrt{T}$

Where, M_o, M_t and M_∞ correspond to the drug amount taken at time equal to zero, dissolved at a particular time t, and at infinite time, the terms W_o and W_t refer to the weight of the drug taken initially and at time t, respectively. Various other terms viz. k, k_o, k_1, and K refer to the release kinetic constants obtained from the linear curves of Korsemeyer–Peppas, zero order, first order, and Higuchi model, respectively.

12) Accelerated Stability Studies on Optimized Telmisartan Formulations: In the present study, the optimized formulations were packed suitably and kept in stability chamber under the following conditions for a period as prescribed by ICH guidelines for accelerated studies. 40 ± 1^0C and RH 75% ± 5%. The samples were analyzed at 30, 60 and 90 days intervals for different physiochemical and *in vitro* drug release profile.

RESULTS AND DISCUSSION

The batches of tablets were prepared according to Table no. III by direct compression method. The values of results obtained before and after the compression are given below in the following tables along with their discussion

Table III. Pre-compression parameters of Tablets of F1 to F6 formulation

Formulation Code	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner ratio	Angle of repose (θ)
F1	0.48±0.02	0.57±0.01	15.78±0.02	1.19±0.02	27.44±0.02
F2	0.47±0.01	0.56±0.03	16.07±0.03	1.19±0.01	29.01±0.03
F3	0.47±0.02	0.57±0.03	17.5±0.02	1.21±0.02	26.45±0.02
F4	0.47±0.02	0.56±0.03	16.07±0.01	1.19±0.03	27.52±0.03
F5	0.48±0.03	0.56±0.02	14.2±0.01	1.16±0.02	29.45±0.02
F6	0.48±0.03	0.56±0.01	14.2±0.01	1.16±0.01	30.14±0.02

A. Discussion of evaluation of powder blends

The formulated powder blend evaluated and results were shown in Table no. III.

1) *Bulk density and Tapped density:* Bulk density and the tapped density of all the prepared formulation (F1 to F6) was found in the range of 0.47-0.48 g/ml and 0.56-0.57 g/ml respectively, which indicated that powder is loosely packed. These values were further used for calculating Carr's index and Hausner ratio to check its flow ability as given table no. III.

2) *Carr's Consolidation Index (Carr's index %):* The compressibility index of all the prepared formulation lies in the range of 14.20% - 17.50 % inferring the mixture possessed a good flow in all formulations F1 to F6. Hence the prepared blends possessed minimum interparticulate interactions and good flow property which is preliminary requirement for formulating the tablets.

3) *Hausner Ratio:* The Hausner ratio of all the prepared formulations were in the range of 1.16 - 1.21 revealing good flow ability. If the value of Hausner ratio is less than (<1.25) reveals better flow properties indicating decreased weight variation among the tablets and enhances uniformity in the drug content in tablets.

4) *Angle of repose:* 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 prepared formulations were in the range of 26°.45' to 30°.14' indicating that powder have smooth surfaced particles leading to increased flow of powder in all batches.

5) *FTIR Spectroscopy:* FTIR spectrum of Telmisartan showed a peaks at 749 cm^{-1} , 1127 cm^{-1}, 1269 cm^{-1}, 3060 cm^{-1}, 1697 cm^{-1} & 861 cm^{-1} were due to aromatic C-H binding, C-N stretching, C=N stretching, aromatic C-H stretching , C=O stretching , O-H stretching respectively. It was clear from the spectra that there was no appreciable change in the positions of the characteristic bands of the drug when compared with other excipients. None of the functional groups of drug have undergone any chemical reaction with other components. Hence, it was confirmed that

there was no chemical interaction amongst any of the components so these components were compatible with drug, therefore, used for formulation studies.

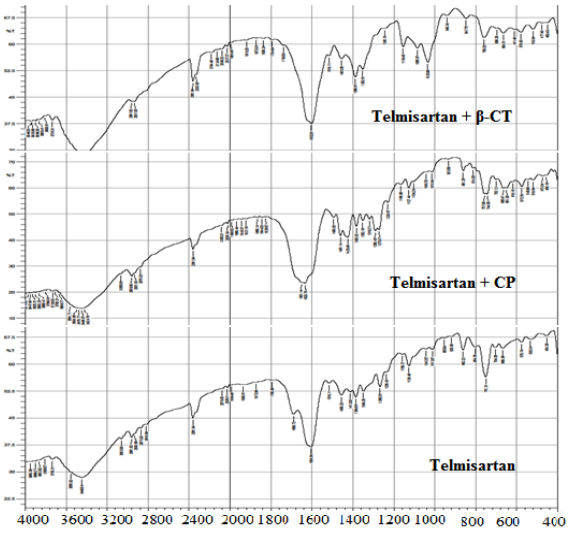

Figure I: FTIR spectra of Telmisartan + β-CT, Telmisartan + CP and Telmisartan alone

6) *Result of manual assessment:* Results of treated samples showed that there was no physical change in colour as well as in flow properties of drug when compared with physical mixture.

Table IV. Post Compression Parameters of Tablets of Formulations F1 to F6

Post compression parameters	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Weight variation (mg)	199.23± 0.02	198.11±0.03	198.02±0.01	198.02±0.02	202.01±0.02	201.02±0.03
Thickness (mm) mean (n=5) ± S.D	2.82± 0.02	2.81±0.03	2.79±0.10	2.80±0.02	2.82±0.03	2.84±0.04
Hardness ($kg/cm^{2)}$ mean (n=5) ± S.D	4.11±0.08	3.63±0.07	4.22±0.06	4.51±0.03	3.82±0.05	3.33±0.04
Friability (%) mean (n=6) ± S.D	0.35±0.02	0.42±0.03	0.51±0.05	0.49±0.03	0.39±0.02	0.49±0.03
Water absorption ratio (%) ± S.D	70.23±0.02	82.00±0.03	65.42±0.11	58.12±0.12	81.25±0.11	95.66±0.14
Wetting time (sec) ± S.D	39.15±0.06	33.15±0.03	45.20±0.03	41.13±0.03	36.45±0.04	30.36±0.05
In vitro disintegration time (sec) ± S.D	50.11±0.12	47.15±0.10	59.23±0.12	91.18±1.11	38.11±0.12	26.08±0.11
Percent drug content (%) w/w	99.52± 0.03	101.3± 0.2	101.4± 0.2	98.7± 0.3	99.22± 0.05	98.4± 0.2

B. Discussion of evaluation of prepared tablets

Five tablets from each batch were evaluated and their results were complied in Table IV.

1) *Weight variation, thickness & hardness:* All the prepared Sublingual tablets of Telmisartan (200 mg) were evaluated for weight variation and found that all the tablets were within the permitted limit of ±7.5% as per IP whereas the thickness was found to be within the range of 2.79 to 2.84 mm. The thickness was almost uniform for all the tablets. The hardness of all the tablets F1, F2, F3, F4, F5 and F6 was found to be 4.1, 3.6, 4.2, 4.5, 3.8 and 3.3 kg/cm^2, respectively. From the table, it was clear that with increased in concentration of superdisintegrant, the hardness decreases in all the batches. If lesser the value of hardness, lesser will be its wetting time which ultimately affects the dissolution that is prerequisite for the Sublingual tablets. On comparing the results, hardness value was found to be less for the 5% CP 3.3 kg/cm^2.

2) *Friability:* Calculated percent loss in weight checked by Roche Friabilator tester was in permitted range as given in IP (1%). The lower values of percent loss ensure that tablets were mechanically stable which determines of durability of tablets at the time of production. In the present work, different superdistintegrants (Croscarmellose sodium, sodium starch glycolate and Crospovidone) were used in ratios (3% and 5%) to check their effect on dissolution profile and wetting time and also to select the best formulation by comparing their outcomes.

3) Water absorption ratio (WAR): The water absorption ratio for the tablets were computed using formula given in equation results indicated that WAR varied between 58.12 to 95.66% for F1 to F6 batches. The water content was observed maximum (95.66%) for the formulation CP 5% and minimum (58.12%) for SSG 5%. It was noticed that water absorption ratio increased with increased concentration of superdisintegrant. 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.

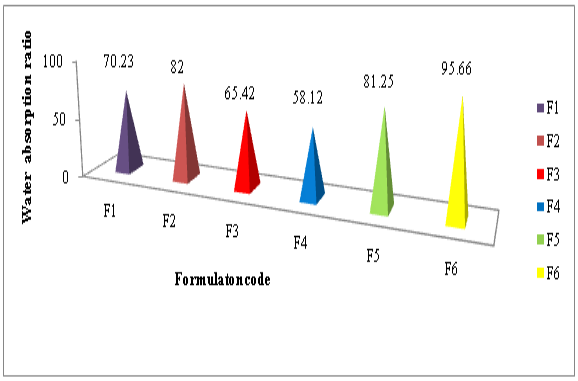

Figure II. Water absorption ratio profile of Telmisartan formulations F1-F6

4) *Wetting time:* Wetting time gives an idea about the enhancement of the tablet disintegration in buccal mucosal drug delivery system. The wetting time for prepared F1, F2, F3, F4, F5, and F6 was 39.15, 33.15, 45.20, 41.13, 36.45 and 30.36 sec respectively. 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. This concludes that the wetting is associated to the inner structure of the tablets and hydrophobicity of the components. The value of wetting time, it required more time to disintegrate the tablet.

Among the three superdisintegrant used the tablet prepared F6 using 5% of CP was voluntarily wetted having the wetting time 30.36 sec. This minimum wetting time may be due to the higher percentage of water absorption ratio and lesser hardness value.

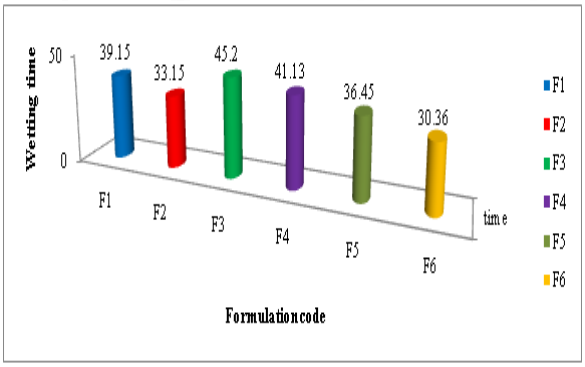

Figure III. Wetting time profile of Telmisartan formulations F1-F6

5) *In vitro disintegration time:* Disintegration time is very important for Sublingual 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 F1, F2, F3, F4, F5, F6 was 50.11, 47.15, 59.23, 91.18, 38.11 and 26.08 sec. respectively. Out of all the formulations, the tablets prepared using 5% of CP showed rapid disintegration in 26 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. Whereas CCS and SSG may have high gelling tendency which cause swelling of tablets mass with subsequently retardation of disintegration. It was observed from the table that disintegration time of the tablets decrease with increase in the concentration of CCS and CP. Whereas disintegration time increased with increase in the concentration of SSG, the probable reason may be due to blockage of capillary pores in tablet mass as result of formation of viscous plugs by SSG, which subsequently prevented free access of fluid into tablet.

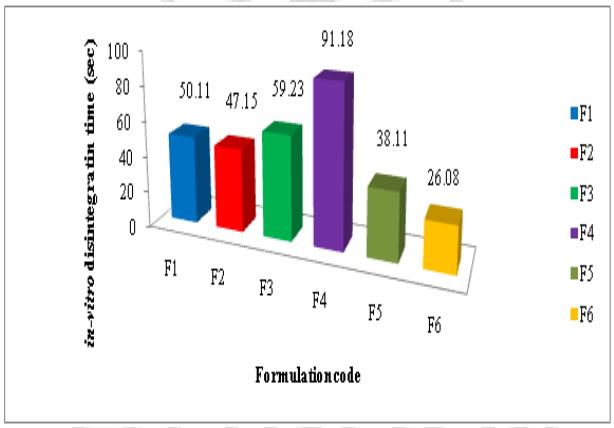

Figure IV. *In vitro* disintegration time profile of Telmisartan formulations F1-F6

6) *Drug content uniformity:* The percentage drugs content of the tablets were found to be in the range of 98.40% to 101.4% for Telmisartan that indicated drug was present uniformly in the tablets.

7) *In vitro Dissolution Studies: In vitro* dissolution studies of the prepared Sublingual tablets were preformed in pH 6.8 phosphate buffer. The dissolution was found to be increased linearly with increasing concentration of superdisintegrant. Formulations F1, F2, F3, F4, F5 and F6 was released in 3 minutes, respectively and shown in figure V. In comparative study of the formulations F1, F2, F3, F4, F5 and F6 showed 73.16%, 75.55% 72.36%, 70.48%, 77.42% and

80.33% drug release respectively in 3 minutes. The relative efficiency of different superdisintegrants to improve the dissolution rate of tablets was in order, CP> CCS >SSG. By increasing the concentration of SSG may leads to decrease dissolution which may be due to the formation of viscous plugs inside the tablets thus retarding its dissolution. Among the various formulations prepared, the tablet containing 5% CP (F6) had showed 80.33% drug release in 3 minutes. This increased drug release may be due to the higher percentage of water absorption ratio, lesser wetting time and lesser *in vitro* disintegration time.

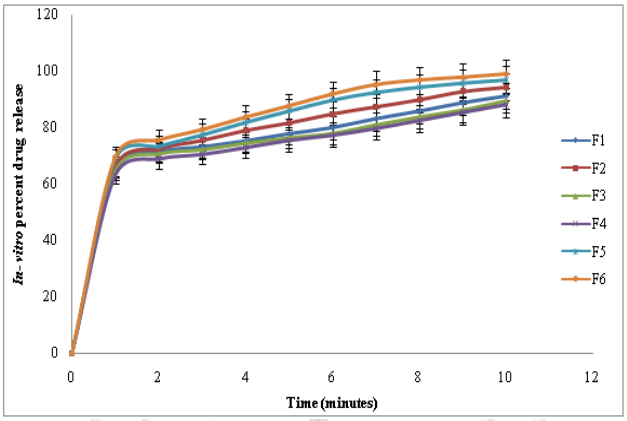

Figure V. Comparative release kinetics of batch F1-F6 in pH 6.8 phosphate buffer

8) *In vitro dispersion:* Out of all the formulations, prepared by using different superdisintegrants, CP 5% containing tablets have highest dissolution profile, low wetting time, high water absorption ratio, high drug content, so it was selected for further studies and figure (VI) show dispersion time of (F6) formulation.

Figure VI. *In vitro* dispersion of tablets prepared by direct compression method

9) *Discussion of drug release kinetics:* Finally *in vitro* dissolution release data (F6) formulations were subjected to goodness of fit test by linear regression analysis according to Zero order model, first order model, Higuchi's model and Krosmeyer-Peppas model to ascertain the mechanism of drug release. Value of Regression parameter (R^2) of formulation (F6) containing CP 5% after fitting the data to various model & the kinetic data of best formulation were computed.

Table V. Regression parameters of formulation (F6) containing Crospovidone 5% obtained after fitting the data to various models.

	Models	Zero Order	First Order	Higuchi Equation	Korsemeyer Pappas
Sr. No	Batches	R^2	R^2	R^2	R^2
1.	F6	0.9548	0.9651	0.9879	0.9864

Table V enlist that among the regression correlation co-efficient(R2) values of First order equation was found to be higher, similarly among the Higuchi's equation and Krosmeyer Peppas equation, the (R^2) values of Higuchi's equation was found to be higher. Hence the drug release followed the First order release kinetics with non-fickian diffusion mechanism.

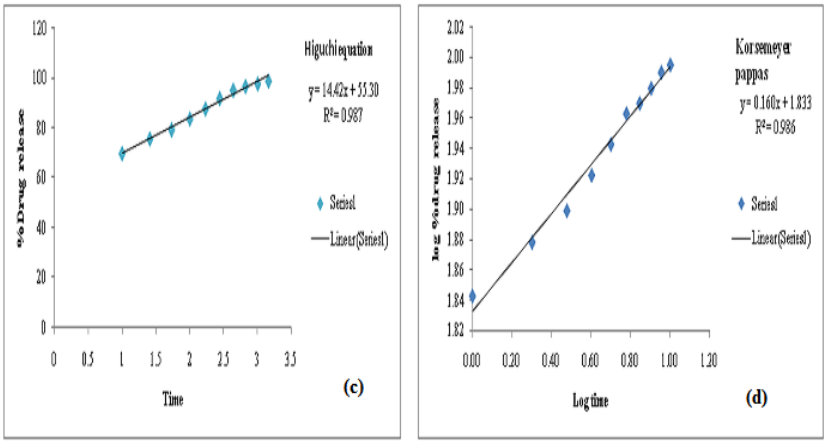

Figure VII. Regression parameters of formulation F6

10) *Stability study of optimized Formulation (F6):* The optimized formulations were subjected to accelerated stability study by storing the formulations at 40^{o}C±2 ^{o} C/75%±5% RH up to 90

days. After 30, 60 and 90 days the tablets were again analyzed for the appearance, hardness, friability, average weight, and disintegration time and dissolution studies. There were no significant changes observed even after 90 days in the above parameters, but only small change in the average weight and disintegration time was observed. This may be due to slightly increase in the hardness and friability of the tablets during storage. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light and enables recommended storage conditions, re-test periods and shelf lives to be established.

Table VI. Release kinetics data of optimized batch (F6) after 30, 60, & 90 days

PARAMETERS	TIME			
	0 Days	**30 Days**	**60 Days**	**90 Days**
Appearance	No change	No change	No change	No change
Average weight (mg)	200	201	202	202
Hardness (kg/cm^2)	3.3	3.3	3.4	3.4
Disintegration time(seconds)	26	26	27	27
Percent friability	0.4960	0.4960	0.5109	0.5809

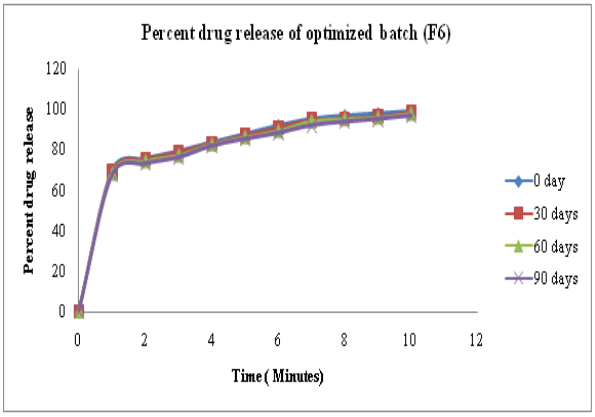

Figure VIII. Release profile of optimized formulation (f6) after 30, 60, & 90 days in 6.8 pH phosphate buffer

CONCLUSION

The Sublingual tablets of Telmisartan were prepared by direct compression method using three different superdisintegrants in different ratio 3% and 5% respectively. Post-compression studies of the prepared tablets were subjected to different evaluation parameters such as hardness, friability, weight variation, drug content uniformity, wetting time, water absorption ratio, *in vitro* dispersion time, *in vitro* dissolution studies and accelerated stability studies. The percent loss in weight checked by Roche Friabilator was in permitted range as given in IP (1%). The lower values of percent loss ensure that tablets were mechanically stable which determines the durability of tablets at the time of production[10]. It was concluded from the results that prepared Sublingual tablets might decrease dosing frequency, enhance bioavailability, improves patient compliance, low dosing, rapid onset of action, fast disintegration, low side effect and good stability, which was the aim of the present work.

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