International Journal of PharmTech Research
CODEN (USA): IJPRIF, ISSN: 0974-4304
Vol.8, No.3, pp 330-339, 2015

Formulation of Telmisartan HCL Fast Disintegrating Tablets by Sublimation Technique

B.Ramu[1]*, N.Ramakrishna[2], Meruva sathish[3], D.Anoosha[4]

[1,3 ,4]K.V.K College Of Pharmacy , Department Of Pharmaceutics, JNTUH Hyderabad India.
[2]Avanthi institute of pharmaceutical sciences, Department of Pharmaceutics, India.

Abstract: In the present work, an attempt has been made to develop fast disintegrating tablets of Telmisartan HCl. In the present work sodium Primogel,Polyplasdone XL and Vivasol were employed as super disintegrating agents to enhance the solubility and dissolution rate of selected drug molecule. Camphor was employed as sublimating agent, due to presence of camphor maximum pores will be formed. As the numbers of pores were more the body fluid will penetrates more easily. All the formulations were prepared by direct compression method using 8mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed god flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F9 formulation showed maximum % drug release i.e., 110.4 % in 2 min hence it is considered as optimized formulation. The F9 formulation contains Vivasol as super disintegrate in the concentration of 20 mg.
Keywords: Telmisartan HCl , Sublimating agent , camphor, Primogel, Polyplasdone XL and Vivasol.

1. 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 a better understanding of the physicochemical and biochemical parameters pertinent to their performance.

Despite of tremendous advancements in drug delivery, the oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, ease of administration lead to high levels of patient compliance. It is always the aim of a scientist or a dosage form designer to enhance the safety of a drug molecule while maintaining its therapeutic efficacy. Recent advances in NDDS aim for the same by formulating a dosage form, convenient to be administered so as to achieve better patient compliance[1]. Mouth Dissolving Tablet (MDT) [2]is one among such approaches. Improved patient 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 oral route of administration is the most preferred route due to its many advantages like ease of administration, accurate dosage, self-medication, pain avoidance, versatility and patient compliance. Tablets

and capsules are the most popular dosage forms. Telmisartan is in a class of medications called angiotensin II receptor antagonists[8]. It works by blocking the action of certain natural substances that tighten the blood vessels, allowing the blood to flow more smoothly and the heart to pump more efficiently. fast disintegration tablets of telmisartan HCl immediately lowers the blood pressure ensuring the fast plasma drug concentration levels and plays a key role in treatment of hypertension .

Sublimation method:

In this method a subliming material like (Ammonium bicarbonate, Ammonium carbonate, Urea, Benzoic acid, Naphthalene, camphor) is removed by sublimation from compressed tablets and high porosity is achieved due to the formation of many pores. Where camphor particles previously existed in the compressed tablets prior to sublimation of the camphor[4]. A high porosity was achieved due to the formation of many pores where camphor particles previously existed in the compressed mannitol tablets prior to sublimation of the camphor. These compressed tablets which have high porosity (approximately 30%) rapidly dissolved within 15 seconds in saliva[6].

Advantage: Tablets dissolve in 10-20 sec. and exhibit sufficient mechanical strength[4].

Methodology

Materials used in the formulation:

Telmisartan Hcl pure drug was obtained as gift sample from hetero labs, primogel, polyplasdone, vivasol, camphor, magnesium sterate, talc, micro crystalline cellulose all of the analytical grade obtained from merck specialities pvt ltd,Mumbai, india.

Preparation of tablets:

Composition of Telmisartan HCL oro Dispersible Tablet by direct compression is shown in table 1. All the ingredients were weighed. Required quantity of drug and excipient mixed thoroughly in a polybag. The blend is compressed using rotary tablet machine-8 station with 8mm flat punch, B tooling. Each tablet contains 40 mg Telmisartan HCL and other pharmaceutical ingredients. Total weight of tablet was found to be 200 mg.

Table no 1.Composition of various tablet formulations

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Telmisartan HCL (mg)	40	40	40	40	40	40	40	40	40
Primogel (mg)	8	16	20	-	-	-	-	-	-
Polyplasdone XL(mg)	-	-	-	8	16	20	-	-	-
Vivasol (mg)	-	-	-	-	-	-	8	16	20
Camphor	40	40	40	40	40	40	40	40	40
Magnesium Stearate(mg)	2	2	2	2	2	2	2	2	2
Talc(mg)	2	2	2	2	2	2	2	2	2
MCC(mg)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Total wt(mg)	200	200	200	200	200	200	200	200	200

Preformulation Studies [9]:

The goals of the preformulation study are:

- To establish the necessary physicochemical characteristics of a new drug substance.
- To determine its kinetic release rate profile.
- To establish its compatibility with different excipients.

Construction of Telmisartan Hydrochloride calibration curve with phosphate buffer pH 6.8:

100mg of Telmisartan HCl was dissolved in 100ml of phosphate buffer pH 6.8 to give a concentration of 1mg/ml (1000µgm/ml). From the above standard solution (1000µgm/ml) 10 ml was taken and diluted to 100ml with phosphate buffer pH 6.8 to give a concentration of 100µgm/ml. From this stock solution aliquots of 0.2,0.4,0.6,0.8 and 1ml were pipette out in 10ml volumetric flask and the volume was made up to the mark with phosphate buffer PH 6.8 to produce concentration of 2,4,6,8 and 10 µgm/ml respectively. The absorbance (abs) of each conc. was measured at respective (λ_{max}) i.e., 244 nm.

Drug- excipient compatibility studies by FT-IR:

The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany(Alpha T).The potassium bromide pellets were prepared on KBr press by grounding the solid powder sample with 100 times the quantity of KBr in a mortar. The finely grounded powder was then introduced into a stainless steel die and was compressed between polished steel anvils at a pressure of about 8t/in^2. The spectra were recorded over the wave number of 8000 to 400cm^{-1}.

Flow properties:

Angle of Repose:

It is performed to determine the flow rate of powder done by the funnel method. The powder was poured into a funnel which is fixed from height of 2cm of the plane surface. Circumference was drawn with a pencil on the graph paper and the radius of base of a pile was measured at 5 different points and average was taken for calculating Angle of repose using following formula: $\Theta = \tan^{-1} H/R$

Θ=angle of repose

H=height of powder cone, R=radius of powder cone

Angle of Repose less than 30^0 shows the free flowing property of the material.

Table 2: Angle of Repose values (as per USP)

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Loose bulk Density (LBD):

Loose bulk density was obtained by dividing the mass of powder by the bulk volume in cm^3. The sample of about 50 cm^3 of powder, previously been passed through a standard sieve no. 20, was carefully introduced into a 100 ml graduated cylinder. The cylinder was dropped at 2 second intervals on to hard wood surface three times from a height of 1 inch. The bulk density of each formulation was then obtained by dividing the weight of sample in grams by the final volume in cm^3 of the sample contained in the cylinder. It was calculated by using equation given below:

Df = M /Vp
Where, Df = bulk density
M = weight of sample in grams
Vp = final volume of powder in cm^3

Tapped density (TD):

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times if the difference between these two volumes is less than 2%. If it is more than 2%, tapping was continued for 1250 times and tapped volume was noted. Tapping was continued until the

difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by

Do = M /Vp
Where,
Do = Tapped density,
M = weight of sample in grams
Vp = final volume of powder after tapping in cm^3

Carr's consolidation index:

The Carr index is an indication of the compressibility of a powder. This is calculated by the formula

$$C = \frac{(\rho b - \rho t)}{\rho b} \times 100$$

Where, ρ_b is the bulk density , ρ_t is the tapped bulk density

A Carr index greater than 25 is considered to be an indication of poor flowability, and below 15, of good flowability.

Table 3: Carr's index value (as per USP)

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
2 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

Hausner's ratio:

The Hausner ratio is a number that is correlated to the flowability of a powder or granular material. The Hausner ratio is calculated by the formula

$H= \rho_{b/} \rho_b$
Where,
ρ_b is the bulk density
ρ_b is the tapped bulk density

Hausner ratio greater than 1.25 is considered to be an indication of poor flowability.

Post Compression Parameters:

Evaluation of uncoated tablets [10]:

Shape and colour:

The tablets were examined under a lens for the shape of the tablet and colour by keeping the tablets in light.

Uniformity of thickness:

Randomly 10 tablets were taken from formulation batch and their thickness (mm) was measured using a Vernier callipers.

Hardness test:

The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in Kg/cm^2. Six tablets were randomly picked from each formulation.

Friability test:

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined by using Roche friabilator (Lab India, FT 1020). It is expressed in percentage (%). Ten tablets were initially weighed [$W_{(initial)}$] and transferred into friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. The tablets were weighed again [$W_{(final)}$]. The percentage friability was then calculated by,

$$F = \frac{[W(initial) - W(final)]}{W(initial)} \times 100$$

Weight variation test:

The tablets were selected randomly from each formulation and weighed individually to check for weight variation. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The % deviation in weight variation is shown in table.

Table no 4.Limits of Weight variation

Average Weight Of Tablet(mg)	%deviation
130mg or less	10
> 130or <324	7.5
> 324	5

Drug Content estimation:

The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch.

Four tablets were weighed and crushed in the mortar. The powder equivalent to 1.25 mg of the drug were weighed and dissolved in 100ml phosphate buffer pH 6.8 to give a concentration of 12.5 µg/ml. 2ml of this solution was taken and diluted to 10ml to give a concentration of 2.5µg/ml. The absorbance of the prepared solution was measured at 244nm using UV Visible spectrophotometer (Lab India, UV-3200).

***In -vitro* dissolution studies [11]:**

In-vitro release studies were carried out using a modified USP XXIII dissolution test apparatus (Lab India, DS-800).

The dissolution fluid was 500ml of phosphate buffer pH 6.8 at a speed of 50rpm at a temperature of 37^0c were used in each test. Samples of dissolution medium (5ml) were withdrawn for every 2min and assayed for Telmisartan HCl by measuring absorbance at 244 nm. For all the tests 5ml of the test medium were collected at specified time intervals and replaced with same volume of phosphate buffer pH 6.8.

Application of Release Rate Kinetics To Dissolution Data [12]:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release rate kinetics:

To study the zero–order release kinetics the release rate data ar e fitted to the following equation.

$F = K_o t$

Where, 'F' is the drug release at time't', and 'K_o' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics: The release rate data are fitted to the following equation

Log (100-F) = kt

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

F = k t1/2

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model:

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$M_t/ M_\infty = K\ t^n$

Where, M_t/ M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport), n=1; and for supercase II transport, n > 1. In this model, a plot of log (M_t/ M_∞) versus log (time) is linear.

Hixson-Crowell release model:

$(100\text{-}Q_t)^{1/3} = 100^{1/3} – K_{HC}.t$

Where, k is the Hixson-Crowell rate constant.

Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets).

Results and Discussion

Standard Calibration curve of Telmisartan HCl:

Table 5 : Concentration and absorbance obtained for calibration curve of Telmisartan HCl In pH 6.8 Phosphate buffer

S. No.	Concentration (µg/ml)	Absorbance* (at 244 nm)
1	2	0.107
2	4	0.215
3	6	0.299
4	8	0.402
5	10	0.507

It was found that the estimation of Telmisartan HCl by UV spectrophotometric method at λ_{max} 244 nm in pH 6.8 Phosphate buffer had good reproducibility and this method was used in the study. The correlation

coefficient for the standard curve was found to be closer to 1, at the concentration range, 2- 10µg/ml. The regression equation generated was y = 0.049x + 0.009, R^2 = 0.998.

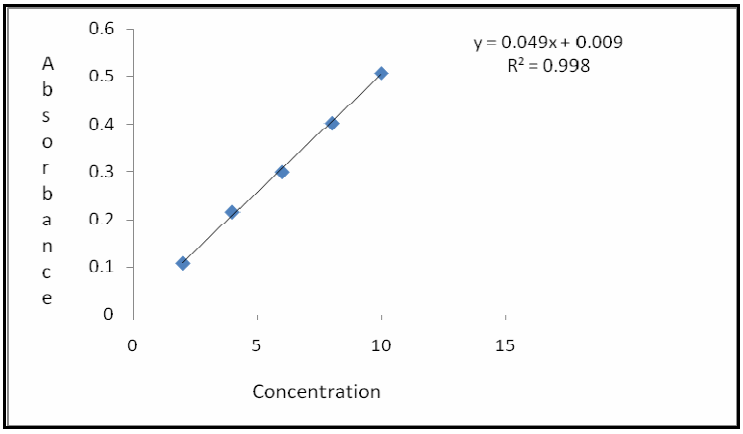

Fig 1: Standard graph of Telmisartan HCl in pH 6.8 Phosphate buffer

Fourier Transform-Infrared Spectroscopy:

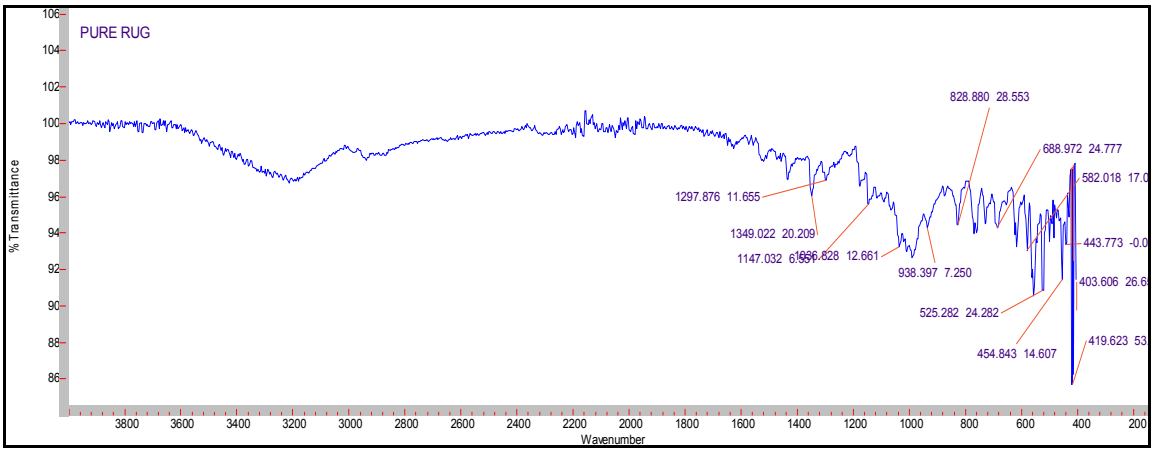

Figure 2: FT-TR Spectrum of Telmisartan HCl pure drug.

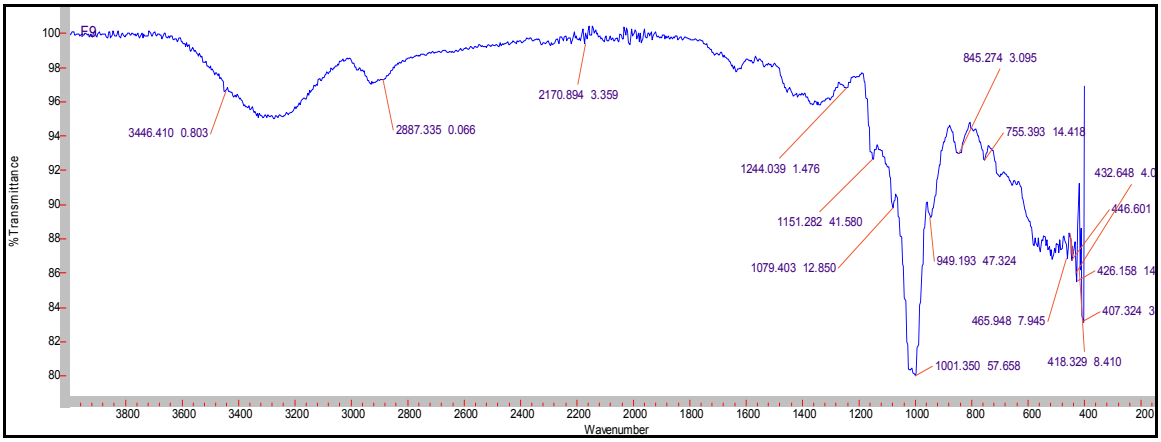

Figure 3 : FT-IR Spectrum of Optimized Formulation

From the FTIR data it was evident that the drug and super disintegrates, other excipients doses not have any interactions**.** Hence they were compatible.

Evaluation Parameters for Fast Dissolving Tablets of Telmisartan HCl :

Pre-compression parameters:

The data's were shown in Table 6.The values for angle of repose were found in the range of 25°-30°. Bulk densities and tapped densities of various formulations were found to be in the range of 0.41 to 0.50 (gm/cc) and 0.50 to 0.58 (gm/cc) respectively. Carr's index of the prepared blends fall in the range of 13.06% to 18.18%. The Hausner ration fall in range of 1.14 to 1.22. From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.'

Table 6 : Pre-compression parameters

Formulations	Bulk Density (gm/cm^2)	Tap Density (gm/cm^2)	Carr's Index (%)	Hausner ratio	Angle Of Repose(Ɵ)
F_1	0.45	0.55	18.18	1.22	27.91
F_2	0.47	0.55	14.54	1.17	28.23
F_3	0.50	0.58	13.79	1.16	29.34
F_4	0.46	0.55	16.36	1.19	26.71
F_5	0.50	0.58	13.79	1.16	29.34
F_6	0.47	0.55	14.54	1.17	28.23
F_7	0.50	0.58	13.79	1.16	29.34
F_8	0.41	0.50	18	1.21	26.78
F_9	0.41	0.50	18	1.21	26.78

Post compression Parameters:

Weight variation test:

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 7. The average weight of the tablet is approximately in range of 207 to 198.5, so the permissible limit is ±7.5% (>120mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test:

Hardness of the three tablets of each batch was checked by using Monsanto hardness tester and the data's were shown in Table 7. The results showed that the hardness of the tablets is in range of 2.5 to 3.00 kg/cm^2, which was within IP limits.

Thickness:

Thickness of three tablets of each batch was checked by using Vernier Caliper and data shown in Table-7. The result showed that thickness of the tablet is raging from 3.56 to 3.64.

Table. 7.Post-Compression parameters:

Formulation code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Disintegration Time (sec)	Friability (%)	Assay (%)
F1	205	2.5	3.59	20.33	0.43	97.23
F2	204	2.6	3.64	22.66	0.34	98.55
F3	200	2.5	3.59	30.33	0.49	98.16
F4	199	2.6	3.58	19.00	0.47	99.34
F5	201	2.3	3.59	30.33	0.49	98.16
F6	202	2.7	3.64	22.66	0.34	98.55
F7	200	2.5	3.59	30.33	0.49	98.16
F8	207	2.6	3.56	17.00	0.34	99.25
F9	202	2.5	3.56	17.00	0.34	99.25

Friability:

Tablets of each batch were evaluated for percentage friability and the data's were shown in the Table 7. The average friability of all the formulations lies in the range of 0.30 to 0.51% which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

In vitro disintegration time:

Tablets of each batch were evaluated for in vitro disintegration time and the data's were shown in the Table 7. The results showed that the disintegration time of prepared tablets were in the range of 12.66 to 30.33 seconds.

Assay:

Assay studies were performed for the prepared formulations. From the assay studies it was concluded that all the formulations were showing the % drug content values within 97.23 -99.2%.

In vitro Dissolution studies:

Invitro dissolution studies were carried out by using 500ml of pH 6.8 Phosphate buffer in USP dissolution apparatus by using paddle method. The dissolution studies were carried out for about 30 min. The dissolution data for all the formulations were given in the Table 8.

Table: 8. Invitro dissolution studies of all formulations

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
2	25.4	30.8	45.72	24.3	31.7	48.3	28.4	39.5	110.4
4	39.6	36.72	66.16	31.6	34.5	82.9	35.2	76.3	110.3
6	48.6	56.16	101.16	49.3	41.9	98.7	48.9	96.2	
8	64.3	87.4		58.3	62.4		66.8	99.7	
10	76.4	98.5		74.3	89.1		78.1		
15	97.6			88.1	99.5		86.4		
20	97.1			94.6			100.3		
25				98.1					
30									

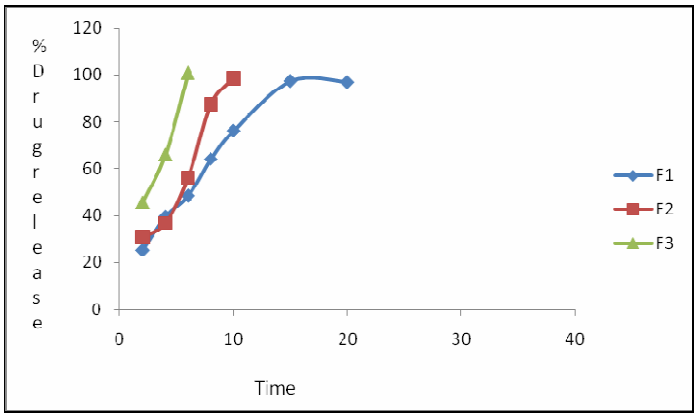

Fig 4 . Dissolution profile of formulations prepared with Primogel as super disintegrate

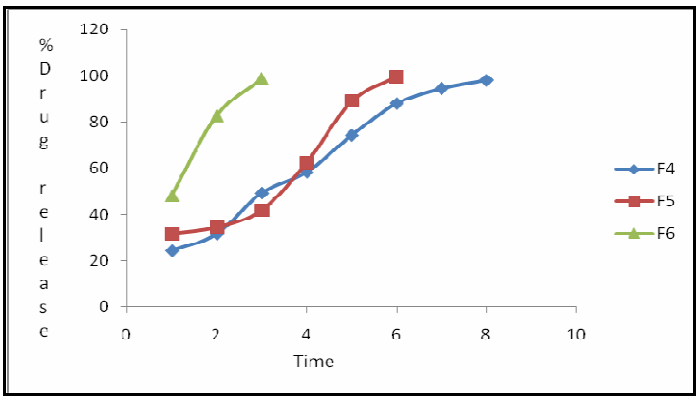

Fig 5: Dissolution profile of formulations prepared with Polyplasdone XL as super disintegrate

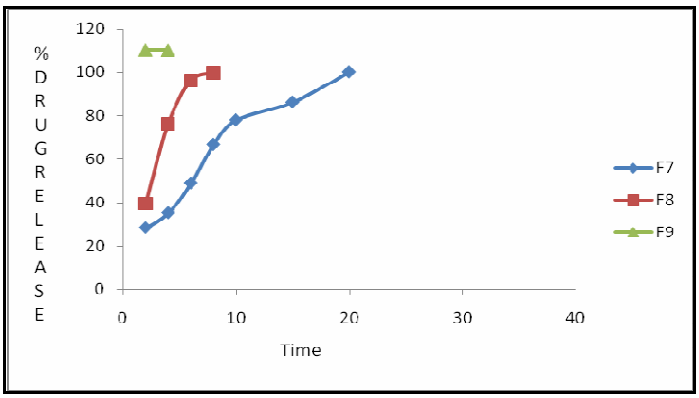

Fig 6: Dissolution profile of formulations prepared with Vivasol as super disintegrate

From the tabular column 7.4 it was evident that the formulations prepared with super disintegrate Vivasol showed maximum % drug release in 2 min i.e.110.96% (F9 formulations and the concentration of super disintegrate was 20 mg). So the principle of super disintegrates was found to be useful to produce oro dispersible tablets. F9 formulation was considered as optimized formulation. The formulation followed zero order release mechanism. As the time increases the percentage drug release was increased.

Conclusion

In the present work, an attempt has been made to develop fast disintegrating tablets of Telmisartan HCl. In the present work Primogel,Polyplasdone XL and Vivasol were employed as super disintegrating agents to enhance the solubility and dissolution rate of selected drug molecule. Camphor was employed as sublimating agent, due to presence of camphor maximum pores will be formed. As the number of pores was more the body fluid will penetrates more easily. All the formulations were prepared by direct compression method using 8mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed god flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F9 formulation showed maximum % drug release i.e., 110.4 % in 2 min hence it is considered as optimized formulation. The F9 formulation contains Vivasol as super disintegrate in the concentration of 20 mg.

References

1. Kaur T, Bhawandeep G, Sandeep K, and Gupta GD. Mouth dissolving tablets: a novel approach to drug delivery. Int J Curr Pharm Res. 2011; 3(1): 1-7.
2. Chein YW. Oral Drug Delivery and Delivery Systems. 2nd Ed. New York: Marcel Dekker; 1992.
3. Kaur T, Bhawandeep G, Sandeep K, Gupta GD. Mouth dissolving tablets: a novel approach to drug delivery. Int J Curr Pharm Res. 2011; 3(1): 1-7.

4. Augsburger LL, Stephen WH. Orally disintegrating tablets. Pharmaceutical dosage forms: tablets. Infroma Healthcare Publication, 3rd ed., 2; 293-312.
5. Schwartz BJ, Connor RE. Optimization technique in pharmaceutical formulations and processing. Modern Pharmaceutics. 3rd ed. Marcel Dekker Inc. New York; 1996; 607-24.
6. Simone S, Peter CS. Fast dispersible ibuprofen tablets. Eur J Pharmaceut Sci. 2002 Feb 1; 15: 295–305.
7. Nishant V, Vikas R. Preparation and optimization of mouth/orally dissolving tablets using a combination of glycine, carboxymethyl cellulose and sodium alginate, a comparison with superdisintegrants. Pharmaceut Dev Tech. 2008; 13: 233–43.
8. Goodman and Gilman, the pharmalogical basis of therapeutics, Joel G. Hardman editior, 10th ed., Mc Graw Hill publication; 1250-56.
9. Jain CP, Naruka PS. Formulation and evaluation of fast dissolving tablets of valsartan. Int J Pharm Pharmaceut sci. 2009 July-Sep; 1(1): 219-26.
10. Lachman L, Liberman HA and Kanig JL. Theory & practice of industrial pharmacy. 3rd ed. Mumbai:Varghese publishing house; 1991: 296-302.
11. Indian pharmacopoeia, Govt. of India, ministry of health and family welfare. New Delhi: The controller of publications; 1996.
12. Jinichi F, Etsue Y, Yasuo Y, Katsuhide T. Evaluation of rapidly disintegrating tablets containing glycine and carboxymethylcellulose. Int J Pharm. 2006; 310: 101-09.

*****