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FORMULATION AND EVALUATION OF TELMISARTAN FLOATING DRUG DELIVERY SYSTEM

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ABSTRACT

The present research work was an attempt to formulate and evaluate tablet containing Telmisartan in the form of tablet to prolong the release of orally administer. Telmisartan in the floating tablets by using different Grade of hydroxypropylmethylcellulose (HMPC). Citric acid, sodium bicarbonate as gas generating agent. Different viscosity grade polymer of HPMC k4 M, HPMCK100M were used a floating polymer. It was observed that different viscosity not only influence the drug release from hydrophilic matrix but they also affect the floating properties of tablets. Telmisartan is an anti-hypertensive drug under the class of angiotensin II receptor blocker. The bioavailability of Telmisartan is range between 42%-58%. Preformulation studies for drug excipient compatibility is done by FTIR spectroscopy it was observed that there was no compatibility problem with they are used in study. The tablets were characterized for the pre and post compression parameters such as friability, hardness, thickness, drug content, weight variation, in-vitro buoyancy studies and in-vitro drug release studies and the results were within the limits. The in vitro drug release studies were carried out in an USP type II apparatus in 0.1N HCL.

KEYWORD: Telmisartan HPMC K4M, HPMC K100M, gastric residence time, Floating tablets.

1. INTRODUCTION

'Floating systems or dynamically controlled systems are low-density systems that have sufficiently buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. This results in an

increased gastric retention time and a better control of the fluctuations in plasma drug concentration.''

Floating drug delivery system (FDDS) have a bulk density less than gastric fluid and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug the residual system is emptied form the stomach. This results in an increased GRT and a better control of the fluctuation in plasma drug concentration. FDDS is one approaches for improving the bioavailability of drug via floating the tablets instantly depend upon is interacting with gastric fluid.

Telmisartan is an anti-hypertensive drug under the class of selective angiotensin II receptor blocker. It is a class II drug according to biopharmaceutical classification system (BCS); with poor solubility and high permeability. TEL shows the low dissolution rate in GIT media and poor bioavability it has dose dependent bioavailability .which is ranging between 42% and 58% according to its own doses of 40mg to 160mg respectively. In anthor word TEL has high absorption rate with peak plasma concentration of 44.7µg/L. It is practically insoluble in water (7µg/mL).

2 METHODOLGY

2.1 Material

Telmisartan, HPMCK4M, HPMCK100M, Microcrystalline cellulose, Sodium bicarbonate, Polyvinylpyrrolidone, Magnesium Stearate, and Talc were used to formulate floating tablets. All the reagents were used of analytical grades.

2.2 Preparation of TEL Floating Tablet

Floating matrix tablets containing Telmisartan were prepared by wet granulation technique using varying concentrations of different grades of polymers with sodium bicarbonate. Polymers and Telmisartan were mixed homogeneously using glass mortar and pestle. Isopropyl alcohol was used as granulating agent. Granules were prepared by passing the wet coherent mass through a # 8 sieve. The granules were dried in hot air oven at a temperature of 60^0c. Dried granules were sieved through # 22 sieves and lubricated with magnesium stearate and talc just 4-5 min before compression. Lubricated granules were compressed into tablets using Rolex tablet machine to obtain tablets of desired specifications.

Table No. 1: Composition of Telmisartan Floating Tablets.

Ingredients(mg.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Telmisartan	40	40	40	40	40	40	40	40	40
HPMC K4M	20	20	20	25	25	25	30	30	30
HPMCK100M	60	75	90	60	75	90	60	75	90
Sod. Bicarbonate	20	20	20	20	20	20	20	20	20
Citric Acid	10	10	10	10	10	10	10	10	10
PVP K30M	20	20	20	20	20	20	20	20	20
Mg stearate	10	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5	5
MCC	185	200	215	190	205	215	190	210	225
Total	350	350	350	350	350	350	350	350	350

3. RESULTS AND DISCUSSION

3.1 Preformulation Study

3.1.1 Characterization Study: In the present study, an attempt was made to formulate floating tablets of Telmisartan by using HPMC K4M, HPMCK100 M as polymer. the characterization done by the UV, FTIR Spectroscopy.

3.1.2 Description: white to off-white crystalline powder.

3.1.3 Determination of melting point

The melting point of Telmisartan was found to be in the range of 260°C to 269°C. the reported melting point for telmisartan is of 265°C to 272°C. Hence, experimental value are in good agreement with official value.

3.1.4. Solubility: Practically insoluble in Water and 0.1N HCL, Telmisartan is freely soluble in Ethanol and dichloromethane. Springly soluble in methanol.

3.1.5. Preparation of Standard Curve of Telmisartan

Accurately weighed 50 mg of drug was dissolved in ethanol and then made up to a volume of 50ml with 0.1 N HCL it gives 1000µg/ml ppm concentration stock solution. From the stock solution different concentration (10, 20, 30, 40, 50, and 60 µg/ml) were prepared. TEL at the λ_{Max} of the drug, the absorbance was measured & plotted against the respective concentration.

Table No 2: Calibration curve of Telmisartan.

Sr. No.	Concentration (µg/ml)	Absorbance in 0.1N HCl
1	10	0.044
2	20	0.087
3	30	0.133
4	40	0.170
5	50	0.218
6	60	0.266

3.2 Pre-compression Evaluation

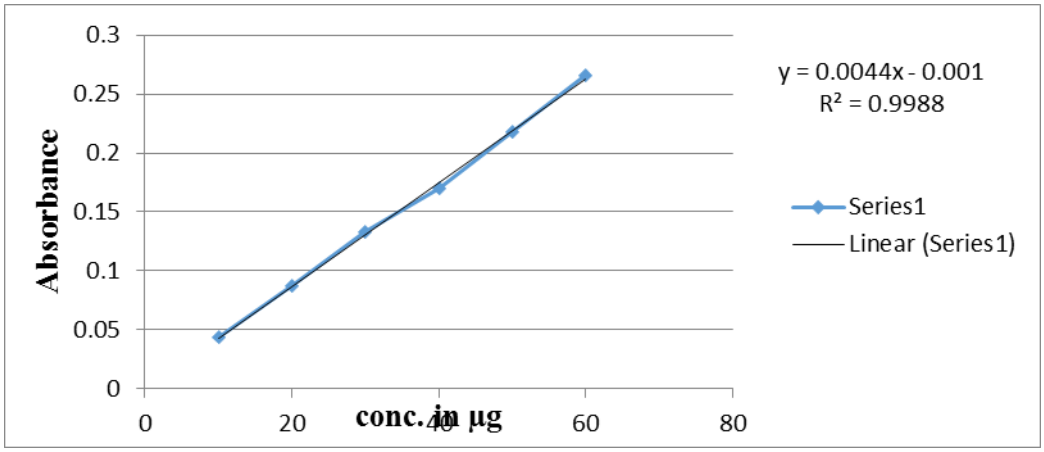

Fig no 1: Standard calibration curve of Telmisartan.

1. Angle of Repose (θ)

The angle of repose of powder blend was determined by the funnel method. A clean and dry funnel was taken and attached to burette stand. A white paper site was placed 5cm below the tip of the funnel in a dry plat form. Gently this sample was pore in to the funnel. Using a pencil circle was drawn around the tip of powder. The height of the hip also measured.

Angle of Repose $(\theta) = \tan^{-1} h/r$

Where, h= height of the powder cone and r= radius of the powder cone.

2. Bulk density (Db.)

Both loose bulk density (LBD) and tapped bulk density (TBD) was determined.

a) Loose Bulk Density (LBD)

An accurately weighed quantity of 10 gm. of powder was transferred to 10ml measuring cylinder and the volume occupied by the powder in terms of ml was recorded. LBD and TDB were calculated using the following equations.

LBD = Weight of powder in gram
Untapped volume of the packed in ml

b) Tapped bulk density (TBD)

Loosely packed powder in the cylinder was tapped 100 times on plan hard surface and volume occupied in ml.

TBD = Weight of powder in gram
Tapped Volume of the packing in ml

2. Compressibility index

The compressibility index is measure of the capacity of a powder to be compressed. The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down. The formula for Carr's Index is as below:

$$\text{Carr's index} = \frac{\text{TBD- LBD} \times 100}{\text{TBD}}$$

4. Hausner's ratio (HR)

This was calculated as the ratio of tapped density to bulk density of the sample

$$\text{HR} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Table No 3: Scale of Flow ability.

Sr.No	Hausner ratio	Compressibility Index (%)	Angle Of Repose (θ)	Properties
1	1.00 – 1.11	< 10	25-30	Excellent
2	1.12 – 1.18	11-15	31-35	Good
3	1.19-1.25	16-20	36-40	Fair
4	1.26-1.34	21-25	41-45	Passable
5	1.35-1.46	26-31	46-55	Poor
6	1.46-1.59	32-37	56-65	Very Poor
7	>1.60	>38	>66	Very ,very Poor

Table No 4: Micrometric properties of powder blend.

Batch Code	Angle of repose (θ)	Bulk density (gm./cm3)	Tapped density (gm./cm3)	Hausner ratio (HR)	Carr index (IC)
FT-1	24.22	0.37	0.44	1.18	15.09
FT-2	24.44	0.36	0.40	1.11	10.00
FT-3	26.67	0.34	0.38	1.10	9.52
FT-4	24.30	0.37	0.42	1.11	10.638
FT-5	25.19	0.35	0.39	1.10	9.580
FT-6	26.56	0.33	0.385	1.15	13.065
FT-7	25.11	0.36	0.42	1.15	13.095
FT-8	25.9	0.34	0.39	1.15	13.66
FT-9	27.75	0.31	0.35	1.13	11.98

3.4 Post-compression evaluation of Telmisartan floating tablets

1. Weight variation test

To study weight variation 10 tablets of the formulation were weighed using an electronic balance and the test was performed according to the official method. 10 tablets were selected randomly from each batch and weighed individually to check for weight variation.

$$\text{Percentage Deviation (PD)} = \frac{W_{avg}-W_{initial}}{W_{avg}}$$

Where, WAvg = average weight and

WInitial =initial weight

Acceptance Criteria for tablet weight variation (USP29-NF34)

Table No 5: Weight variation tolerance for uncoated tablets.

Average weight of Tablet (mg)	% difference allowed
130 or less than	±10
130-324	±7.5
More than 324	±5

2. Drug content

Five tablets were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was dissolved in 0.1N HCL. The drug content was determined measuring the absorbance at 272 nm after suitable dilution using a Jasco V-630 UV- Visible double beam spectrophotometer.

3. Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm2. Three tablets were randomly picked and hardness of the tablets was determined.

4. Thickness

The thickness of the tablets was determined by using Vernier calipers. Five tablets were used, and average value was calculated.

5. Friability Test

The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Five tablets were initially weighed and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again. The % friability was then calculated by-

$$\text{Percentage Friability} = \frac{W\text{-}W_0}{W} \times 100$$

Where,

W0= initially weight

W= weight after friability

Percentages Friability of tablets less than 1% are considered acceptable.

6. Tablet density

Tablet density is an important parameter for floating tablets. The tablet will float when its density is less than that of 0.1N HCL (1.004).

The density was determined using following formula

$v = \pi r2h$

d = m/v

Where, v = volume of tablet (cc)

r = radius of tablet (cm)

h = crown thickness of tablet (cm)

m = mass of tablet.

Table No 6: Evaluation of physical parameters of Telmisartan floating tablets.

Batch Code	Weight variation Average wt. in (mg) ±SD	Hardness (kg/cm2) ±SD	Thickness (mm) ±SD	Friability (%)	Drug Content Uniformity (%)±SD	Tablet Density
FT-1	349.7±0.53	4.22±0.22	5.10±0.10	0.87	97.66±0.57	0.78
FT-2	348.9±0.55	4.68±0.38	5.10±0.20	0.81	96.66±1.52	0.87
FT-3	348.8±0.56	4.50±0.27	5.16±0.05	0.92	96.66±2.08	0.85
FT-4	349.2±0.61	4..46±0.20	5.23±0.11	0.83	97.66±0.57	0.85

FT-5	348.8±0.56	4.66±0.25	5.30±0.10	0.99	98.66±0.57	0.84
FT-6	348.4±0.54	4.42±0.45	5.06±0.15	0.90	94.66±0.57	0.88
FT-7	345.6±0.84	4.36±0.41	5.13±0.15	0.82	97.00±0.57	0.86
FT-8	348.3±0.87	3.64±0.20	5.13±0.11	0.79	96.66±0.57	0.87
FT-9	348.7±0.33	4.12±0.31	4.93±0.15	0.89	94.66±2.08	0.90

7. In vitro buoyancy studies

The in vitro buoyancy was determined by floating lag time method described by Dave B.S. The tablets were placed in 100 ml beaker containing 0.1 N HCl. The time required for the tablets to rise to the surface and float was determined as floating lag time. The time between introduction of dosage form and its buoyancy in 0.1 N HCl and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

8. Swelling index of Telmisartan floating tablets

The swelling index of tablets was determined by using 0.1 N HCl (pH 1.2) at room temperature. The swollen weight of the tablets was determined at predefined time intervals. The swelling index was calculated by the following equation:

$$\text{Swelling Index (SI)} = \frac{Wt - Wo}{Wo} \times 100$$

Where,

Wt. = Weight of tablet at time t.

W0 = Initial weight of tablet

Table No 7: Floating Profile of Telmisartan tablets.

Formulation code	Floating lag time (sec)	Total Floating time (hours)	Swelling Index (%)
F1	48	6	85.25
F2	37	6	89.22
F3	50	4	83.42
F4	20	8	87.21
F5	16	10	98.62
F6	45	10	96.32
F7	56	10	89.42
F8	80	12	92.43
F9	95	12	88.66

9. In Vitro drug release studies of Telmisartan floating tablets

The release rate of from floating tablets was determined using The United States Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37 ± 0.5°C and 50 rpm. A sample (5ml) of the solution was withdrawn from the dissolution apparatus hourly for 12h, and the samples were replaced with fresh dissolution medium. The samples diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 272nm using a Jasco UV-Vis double beam spectrophotometer. Cumulative percentage of drug release was calculated using the equation obtained from a standard curve.

Table No 8: In-Vitro Drug Release Data of Telmisartan batch F1-F9.

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1	9.881	14.784	20.913	13.150	10.698	7.838	21.322	16.419	12.333
2	14.022	24.264	27.159	19.761	16.887	12.785	29.204	21.005	20.165
3	21.046	29.302	36.298	25.590	25.561	21.028	36.721	31.336	27.223
4	28.926	36.410	41.810	36.355	32.648	31.359	45.095	38.047	35.545
5	36.440	41.922	49.804	46.362	41.000	36.844	50.655	46.428	44.730
6	46.038	50.324	55.797	52.337	50.215	43.993	57.879	53.220	51.105
7	56.506	60.814	59.779	59.162	52.533	46.685	61.055	56.780	55.470
8	66.213	70.544	63.373	66.431	65.271	51.026	65.881	62.401	59.450
9	75.564	78.692	69.845	75.373	79.066	58.250	71.141	67.643	63.042
10	78.964	84.431	76.760	80.277	84.964	84.878	74.386	71.687	63.791
11	84.737	86.565	79.625	85.614	90.737	88.654	77.237	73.299	68.629
12	89..766	88.945	81.321	93.753	99.736	89.325	85.006	78.187	72.675

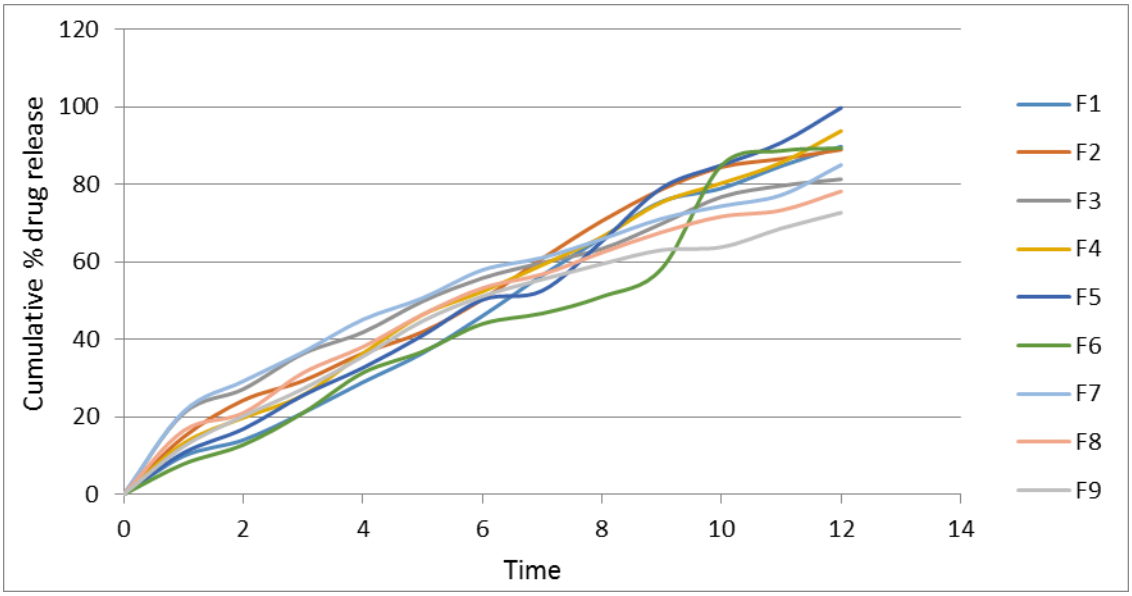

Fig No 2: In vitro Release Profile of Clarithromycin all Formulation.

CONCLUSION

From the present study, the following conclusions were observed:

- Gastric Floating Drug Delivery (GFDD) systems of Telmisartan with shorter lag time can be prepared by wet granulation method using HPMC K4M, HPMC K100 and NaHCO3, Citric acid as gas generating agent
- All the prepared tablet formulations were found to be good without capping and chipping.
- The in vitro dissolution profiles of all the prepared GFDDS formulations of Telmisartan were found to extend the drug release over a period of 10 to 12 hours and the drug release rate decreased with increase in polymer concentration.
- IR spectroscopic studies indicate no drug-excipients interaction in the prepared formulations. Comparing the all formulations, GFDDS formulation of F5 was considered as an ideal formulation which exhibited 99.73% of drug release in 12 hours, and floating lag time of 16 second with a total floating time of 12 hours.

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