ISSN: 2321-3760

Research Article

International Journal of Current Trends in Pharmaceutical Research

IJCTPR, 2014, Vol. 2(6): 669-679

www.pharmaresearchlibrary.com/ijctpr

Formulation and Evaluation of Floating Matrix Tablets of Telmisartan

[1]U. Sambamoorthy[*], [1]D. Yashwant kumar, [2]G. Venkata Ramana, [3]K. Suresh, [4]J. Sunil

[1]SARC – (Scientific and Applied Research Center) Hyderabad
[2]Balaji institute of Pharmaceutical sciences, Narsampet, Warangal, Telangana.
[3]Pratishta Institute of Pharmaceutical Sciences, Durajpally Suryapet, Telangana.
[4]Geetanjali college of Pharmacy, keesara, Hyderabad, Telangana.

Received: 1 July 2014, Accepted: 21 September 2014, Published Online: 15 November 2014

Abstract

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids 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 from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. Telmisartan antagonizes the effect of angiotensin II (vasoconstriction and aldosterone secretion) by blocking the angiotensin II (AT_1 receptor) in vascular smooth muscle and the adrenal gland, producing decreased BP. In the present investigation telmisartan floating tablets were prepared by using different grades of polymers such as HPMC K4M, PEO WSR 303, and XANTHUM GUM. Formulated tablets showed satisfactory results for various Post compression evaluation parameters like: tablet thickness, hardness, weight variation, floating lag time,total floating time, content uniformity and *in vitro* drug release.the Physical parameters & floating characterstics were not good with the PEO AND XANTHUM GUM as CR polymers. HPMC K4M at Drug: Polymer ratio of 1:1.5 respectively showed better Sustained drug release of model drug. Formulation F6 gave better-controlled drug release and floating properties in comparison to the other formulations. The release pattern of the F6 formulations was best fitted to Korsmeyer-Peppas model, Higuchi and ZERO-order model and the release pattern from the formulation was non-Fickian diffusion or anomalous diffusion.

Keywords: Telmisartan, HPMC K4M, floating drug delivery, non-Fickian diffusion

Contents

***Corresponding author**
U. Sambamoorthy
SARC – (Scientific and Applied Research Center) Hyderabad
Manuscript ID: IJCTPR2259

PAPER-QR CODE

1. Introduction

Oral route is the most convenient and extensively used route for drug administration. This route has high patient acceptability, primarily due to ease of administration. Over the years, oral dosage forms have become increasingly sophisticated with major role being played by controlled release drug delivery systems (CRDDS) release drug at predetermined rate. Drug delivery technologies are advanced enough to design any dosage form that can deliver drugs at a constant rate for extended periods of time ranging from days to years and yet most oral controlled release dosage forms deliver drugs for only 12hrs. Oral delivery for 24 hrs is possible for some drugs; such are absorbed well throughout Gastro Intestinal Tract (GIT). Thus, the real issue in the development of oral controlled release dosage forms is how to extend the time for drug absorption from final intestine.

The development of oral CRDDS has been hindered by the inability to localize the system in the selected regions of the GIT. There has been considerable research over the last decade on the possibility of controlled and site specific delivery to the GIT by controlling the gastro intestinal transit of orally administered dosage forms using Gastro Retentive Drug Delivery Systems (GRDDS). Such GRDDS possess the ability of retaining the drug in GIT particularly in the stomach for long periods. The idea of gastro retention stems from the need to localize drugs at specific region of GIT such as stomach in the body. Often the extent of drug absorption is limited by the residence time of the drug at absorption site.

The transit time in GIT i.e., from the mouth to anus, varies from one person to another. It also depends upon the physical properties of the object ingested and the physiological conditions of the alimentary canal. In addition, the relatively brief G.I. transit time (8-12 hr) for most of the drugs impedes the formulation of once daily dosage form. Many drugs show poor bioavailability (BA) in the presence of intestinal metabolic enzymes like cytochrome P450 (CYP3A), abundantly present in the intestinal epithelium. Their activity decreases longitudinally along the small intestine, with levels rising slightly from the duodenum to the jejunum and declining in the ileum and colon. This nonuniform distribution of CYP3A causes regional variability in the absorption of drugs that are the substrates of those enzymes S. S.Davis 2005.

The therapeutic window of many drugs is limited by their short circulating half-life and absorption via a defined segment of the intestine. Such pharmacokinetic limitations lead in many cases to frequent dosing of these medications to achieve the required therapeutic effect. This results in "pill burden" and consequently decreased patient compliance. The phenomenon of absorption via a limited part of the GI tract has been termed the "narrow absorption window" once the dosage form passes the absorption window, the drug will be neither bioavailable nor effective. In extreme cases, drugs that are insufficiently absorbed due to narrow absorption cannot be delivered entirely, and are either given by a parental route or the development of Novel Techniques or by GRDDS. A rational approach to enhance bioavailability and improve pharmacokinetic and pharmacodynamic profiles is to retain the drug reservoir above its absorption area, i.e., in the stomach and to release the drug in a controlled manner, so as to achieve a zero order kinetics (i.e., "oral infusion") for a prolonged period of time. Various approaches have been pursued to increase the retention of an oral dosage form in the stomach [3, 4]. These systems include: Floating systems, bio adhesive systems, swelling and expanding systems, high density systems. Floating Drug Delivery System (FDDS) has a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate [5-7]. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This, results in an increase in the GRT and a better control of the fluctuations in the plasma drug concentration [8-10].

2. Materials and Methods

2.1 *Materials*

Telmisartan was obtained as a gift sample from pharmatrain. HPMC, PEO, PVPK30 and xanthum gum were supplied by colorcon. Avicel from FMC Biopolymer Mumbai, NaHco3 from SD Fine chemicals Mumbai, and magnesium state Evonik India, and Talc from SD Fine chemicals Mumbai and All other chemicals and reagents were of analytical grade.

2.2 Determination of λ_{Max} of Telmisartan in 0.1N HCL:

Procedure:

Working standard:50mg of Model drug was weighed and dissolved in 50ml 0.1N HCL and then made up to a volume of 50ml with0.1N HCL it give 1000µg/ml ppm concentrated stock solution. **Dilution 1**:From the working standard solution 1ml was diluted to 100ml with 0.1NHcl it will give 10 µg/ml concentrated solution. This solutions was scanned at range of 190-400nm wavelength light corresponding scan spectrum curve was noted .the corresponding wavelength having highest absorbance is noted as λ_{max}

2.3 Construction of calibration curve of Model drug in 0.1N HCL:

Procedure:

Working standard: 50mg of Model drug was weighed and dissolved in 50ml 0.1N HCL and then made up to a volume of 50ml with0.1N HCL it give 1000µg/ml ppm concentrated stock solution. From the stock solution different concentrations were prepared. The absorbance of the samples was measured at 248nm, using UV spectrometer with 0.1N HCl as blank.

2.4 Formulation of gastro retentive floating tablets by direct compression

Processing steps involved in Direct Compression:

The matrix tablets were prepared by following the General Methodology as given below:

All ingredients were weighed accurately and co sifted by passing through #40 sieve, blended in a Poly Bag for 5 min. The above granules were lubricated with # 60 Sieve passed Magnesium stearate & talc. The final blend was then compressed into tablets using 16 station tablet compression machine with an average hardness of 4.0KP,by using 9mm die.

Table 1: Preparation of different batches of floating matrix tablets of Telmisartan

Ingredients	F1	F2	F3	F4	F5	F6
TEMISARTAN	40	40	40	40	40	40
XANTHUM GUM	40	60	-	-	-	-
PEO WSR 303	-	-	40	60	-	-
HPMC K4M	-	-	-	-	40	60
MCC102	233	213	233	213	233	213
NAHCO3	20	20	20	20	20	20
PVPK30	15	15	15	15	15	15
Mg STEARATE	1	1	1	1	1	1
TALC	1	1	1	1	1	1

3. Results and Discussion

Evaluation of Tablets

The formulated tablets were evaluated for the following Pre, post compression quality control studies & In vitro Buoyancy studies and dissolution studies

A) Pre Compression studies:

1. Angle of Repose:

It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. Angle of Repose of granules was determined by the funnel method. Accurately weighed powder blend was taken in the funnel. Height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured and angle of repose was calculated using the following equation[17].

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

Where:

θ = angle of repose

h = height in cms

r = radius in cms

The angle of repose has been used to characterize the flow properties of solids. It is a characteristic related to inter particulate friction or resistance to movement between particles.

Flow Properties and Corresponding Angles of Repose

Table 2: Angle of Repose Limits

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair aid not needed	36–40
Passable may hang up	41–45
Poor must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	>66

2. Density:

a). Bulk density (BD): It is the ratio of total mass of powder to the bulk volume of powder Weigh accurately 25 g of granules, which was previously passed through 22 # sieve and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume. Calculate the apparent bulk density in gm/ml by the following formula [18].

Bulk density = weight of powder / Bulk volume.

$$\mathbf{D_b} = \frac{M}{V_0}$$

M = mass of the powder

V_0 = bulk volume of the powder.

b). Tapped density (TD): It is the ratio of total mass of powder to the tapped volume of powder**.** Weigh accurately 25 g of granules, which was previously passed through 22# sieve and transferred in 100 ml graduated cylinder of tap density tester which was operated for fixed number of taps until the powder bed volume has reached a minimum, thus was calculated by formula [18] .

Tapped density = Weigh of powder / Tapped volume

Dt = (*M*) / (*V* $_f$).

M = mass of the powder

V_f = tapped volume of the powder.

3. Carr's Index:

Compressibility index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down[19]. The formula for Carr's index is as below:

$$\textbf{Compressibility index} = 100 \times \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}}$$

4. Hausner's Ratio:

Hausner's Ratio is a number that is correlated to the flow ability of a powder [19] .

$$\textbf{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Scale of Flow ability (USP29-NF34)

Table 3: Compressibility Index Limits

Compressibility Index (%)	Flow Character	Hausner's Ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very Poor	1.46-1.59
> 38	Very, very Poor	> 1.60

B) Post compression studies:

1. General appearance: The formulated tablets were assessed for its general appearance and observations were made for shape, colour, texture and odour.

2. Average weight/Weight Variation: 20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to assure whether it was within permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for 300 mg tablets and none by more than double that percentage.

$$\textbf{Average weight} = \frac{\text{weight of 20 tablets}}{20}$$

$$\textbf{\%weight variation} = \frac{\text{average weight - weight of each tablet}}{\text{Average weight}} \times 100$$

Acceptance criteria for tablet weight variation (USP 29-NF 34)

Table 4: 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

Thickness: Thickness of the tablets (n=3) was determined using a Vernier calipers

4. Hardness test: Hardness of the tablet was determined by using the Monsanto hardness tester (n=3) the lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

5. Friability test: This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting.

Initial weight of 20 tablets is taken and these are placed in the Friabilator, rotating at 25rpm for 4min. The difference in the weight is noted and expressed as percentage. It should be preferably between 0.5 to 1.0%.

$$\%\text{Friability} = [(W_1-W_2)/W_1] \text{ X } 100$$

Where, W_1 = weight of tablets before test,
W_2 = weight of tablets after test

6. Assay Procedure:

Weigh and finely powder not less than 20 tablets. Transfer an accurately weighed. Portion of the powder equivalent to about 10mg of model drug a 10 ml volumetric. Flask. Add approximately 6ml of 0.1N HCl and shake and sonicate for 10 min to complete the extraction. Dilute the methanol to volume and mix. Pipette 1ml aliquot into a 10ml volumetric flask, dilute with mobile phase to volume, mix and filter. From it withdraw take 1ml aliquot and make up to mark with buffer. Calculate the quantity in mg of model drug. Hydrochloride in the portion taken by the formula

Assay = test absorbance/standard absorbance*standard concentration/sample concentration*purity of drug/100*100

7. In vitro Buoyancy studies:

The in vitro buoyancy was determined as per the method described by Rosa et al.

a. **Floating Lag Time (FLT):** A tablet was placed in a 100 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as the Floating Lag Time (FLT).
b. **Total Floating Time (TFT):** A tablet was placed in a 100 ml beaker containing 0.1N HCl. The duration of time up to which the tablet constantly floats on the dissolution medium was noted as the Total Floating Time (TFT).
c. **Matrix integrity:** During the period of TFT the swelled matrix tablets were observed for integrity. For 12 hrs

8. In vitro Dissolution Study:

900 ml of 0.1N HCl was placed in the vessel and the USP-II apparatus (Paddle method) was assembled. The medium was allowed to equilibrate to temperature of $37^0C \pm 0.5^0C$. A tablet was placed in the vessel and was covered; the apparatus was operated up to 12 hrs at 50 rpm. At definite time intervals, 5 ml of dissolution medium was withdrawn; filtered and again replaced with 5 ml of fresh medium to maintain sink conditions. Suitable dilutions were done with dissolution medium and were analyzed spectrophotometrically at λ_{max} =238 nm using a UV-spectrophotometer (Lab India).

Table 5: Dissolution parameters

Parameter	Details
Dissolution apparatus	USP -Type II (paddle)
Medium	0.1N HCl.
Volume	900 ml
Speed	50 rpm
Temperature	37± 0.5 ºC
Sample volume withdrawn	5ml
Time points	0.5,1,2,3,4,6,8,10,12,
Analytical method	Ultraviolet Visible Spectroscopy
λ_{max}	248 nm

C) In vitro Release Kinetics Studies:

The analysis of drug release mechanism from a pharmaceutical dosage form is important but complicated process and is practically evident in the case of matrix systems. The order of drug release from FDDS was described by using zero order kinetics or first order kinetics. The mechanism of drug release from FDDS was studied by using Higuchi equation and the Peppa's-Korsemeyer equation.

1. Zero Order Release Kinetics: It defines a linear relationship between the fractions of drug released versus time.

$$\mathbf{Q=k_0t.}$$

Where, Q is the fraction of drug released at time t and $k_o$is the zero order release rate constant. A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

2. First Order Release Kinetics:

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that the drug release from most of the slow release tablets could be described adequately by the first-order kinetics. The equation that describes first order kinetics is

$$\mathbf{Log\ C= Log\ C_o\text{-}kt/2.303}$$

Where C is the amount of drug dissolved at time t,

C_o is the amount of drug dissolved at t=0 and

k is the first order rate constant.

A graph of log cumulative of log % drug remaining vs time yields a straight line. Will be linear if the release obeys the first order release kinetics.

3. Higuchi equation:

It defines a linear dependence of the active fraction released per unit of surface (Q) and the square root of time.

$$Q=K_2t^{1/2}$$

Where K_2 is release rate constant. A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependent[20].

4. Peppa's-Korsemeyer equation (Power Law): In order to define a model, which would represent a better fit for the formulation, dissolution data was further analysed by Peppa's-Korsemeyer equation (Power Law).

$$Mt/\mathbf{M}_\infty = K.t^n$$

Where, Mt is the amount of drug released at time t

M_α is the amount released at time α,

M_t/M_α is the fraction of drug released at time t,

K is the kinetic constant and n is the diffusion exponent.

To characterize the mechanism for both solvent penetration and drug release n can be used as abstracted. A plot between log drug release upto 60% against log of time will be linear if the release obeys Peppa's-Korsemeyer equation and the slope of this plot represents "n" value[21].the kinetic data of the formulations were included. Nature of release of the drug from the designed tablets was inferred based on the correlation coefficients obtained from the plots of the kinetic models. The data were processed for regression analysis using MS EXCEL

Table 6: Drug release kinetics mechanism

Diffusion exponent(n)	Mechanism
0.45	Fickian diffusion
0.45 < n <0.89	Anomalous(Non- Fickian) diffusion
0.89	Case II transport
n > 0.89	Super Case II transport

Construction of Standard calibration curve of Model drug in 0.1N HCl:

The absorbance of the solution was measured at 248nm, using UV spectrometer with 0.1N HCl as blank. The values are shown in table no 20. A graph of absorbance Vs Concentration was plotted which indicated in compliance to Beer's law.

Table 7: Standard Calibration graph values of Model drug in 0.1N Hcl at λ_{Max} = 248 nm

Conc.(µg / ml)	Absorbance at λ_{Max} = 238 nm
0	0
5	0.086
10	0.157
15	0.231
20	0.297
25	0.389

Evaluation of Tablets:
A) Pre Compression studies

Table 8: Pre compression studies of Model drug Floating tablets *n=3

Formulation Code	Bulk density (Kg/cm^3)	Tapped density (Kg/cm^3)	Cars index	Hausners ratio	Angle of repose (˚)
F1	**0.38 ± 0.3**	0.44 ± 0.5	12.38 ± 0.4	1.14 ± 0.4	25.33 ± 1.52
F2	**0.35 ± 0.4**	0.41 ± 0.6	15.45 ± 0.5	1.18± 0.5	22.33 ± 0.57
F3	0.33 ± 0.3	0.40 ± 0.3	14.67 ± 0.3	1.17± 0.3	22 ± 1.52
F4	0.36 ± 0.5	0.42 ± 0.4	13.03 ±0.45	1.14 ± 0.45	22.66 ± 0.57
F5	0.45 ± 0.2	0.52 ± 0.7	13.4 ± 0.4	1.15 ± 0.4	22.66 ± 1
F6	0.38 ± 0.2	0.45 ± 0.5	15.5 ± 0.35	1.18 ± 0.35	21 ± 1.15

Post compression studies:

Table 9: Post compression studies of Model drug floating tablets

Formulation Code	Avg wt ± SD n=20 (mg)	Thickness± SD n=3 (mm)	% *friability	%Drug Content± SD n=3	Hardness (Kg/cm^2) Avg wt hardness ±SD n=3
F1	pass	5.03±0.115	0.112	100.2 ±1.1	4.1 ±0.1
F2	pass	5.06±0.057	0.116	100.1 ±1.4	4.0 ±0.1
F3	pass	4.83±0.057	0.131	100.4 ±1.1	3.53 ±0.115
F4	pass	5.1±0.01	0.146	100.3± 1.5	3.5 ±0.1
F5	pass	5.16±0.057	0.133	100.3± 1.1	4.5 ±0.1
F6	pass	4.96±0.057	0.131	100.1 ±1.3	4.46 ±0.115

***In- vitro* Buoyancy Studies of Model drug floating tablets:**

Table 10: In vitro Buoyancy Studies of Model drug floating tablets

Formulation Code	Floating lag time n = 3	Total floating time n = 3	Matrix Integrity upto 12 hr. n = 3
F1	22	4hrs	eroding
F2	55	6hrs	eroding
F3	16	1hrs	eroding
F4	25	2hrs	eroding
F5	10	12hrs	Non eroding
F6	14	12hrs	Non eroding

***In-vitro* dissolution studies of model drug floating tablets**:

Parameter	Details
Dissolution apparatus	USP -Type II (paddle)
Medium	0.1N HCl.
Volume	900 ml
Speed	50 rpm
Temperature	37± 0.5 ºC
Sample volume withdrawn	5ml
Time points	0.5,1,2,3,4,6,8,10,12hr
Analytical method	Ultraviolet Visible Spectroscopy
λ_{max}	248 nm

Table 11: *In vitro Dissolution Data*

Time(hr)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
0.5	20	18	36	31	15	12
1	35	31	44	39	23	18
2	49	45	59	52	31	25
3	62	57	71	65	48	39
4	73	74	88	79	62	51
6	83	85	99	86	79	66
8	96	94	100	95	94	78
10	100	100	100	100	100	84
12	100	100	100	100	100	93

Table 12: R^2 value and n Result Table

Formulation code	R square value				n value
	Zero order	First order	Higuchi plot	Pepas plot	
F6	0.975	0.95	0.99	0.97	0.676

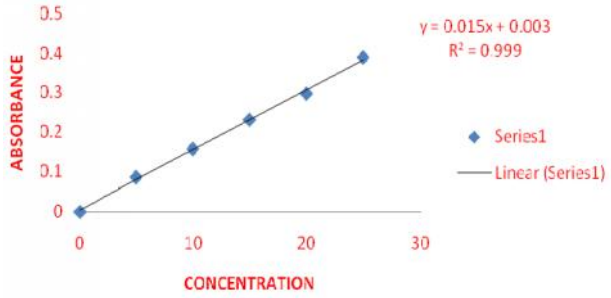

Figure 1: Standard calibration curve of Model drugin 0.1N Hcl at λ_{Max} = 248nm

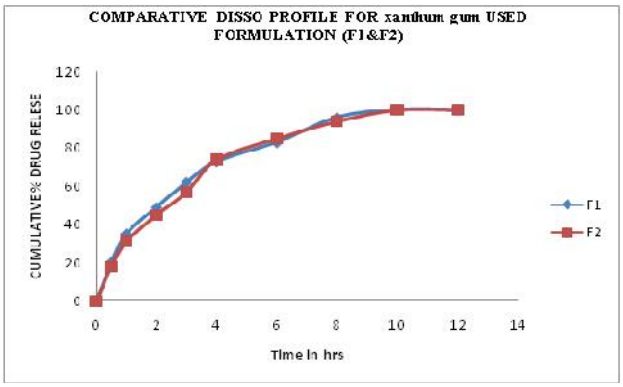

Figure 2: Comparative dissolution profile of F1 & F2

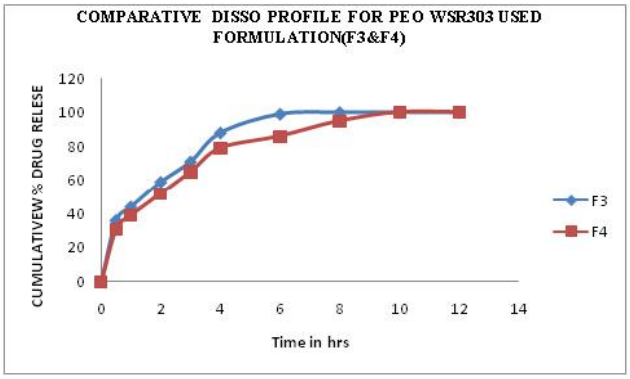

Figure 3: Comparative Dissolution Profile of F3 & F4

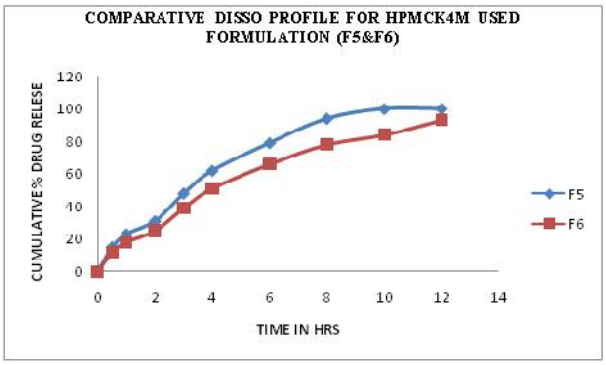

Figure 4: Comparative dissolution profile of F5 & F6

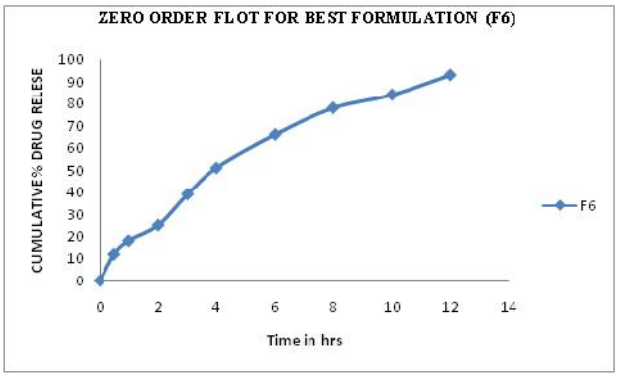

Figure 5: Zero Order Plot for Best Formulation **(F6)**

4. Conclusion

Floating Tablets of drug model drug are formulated to increase gastric residence time and thereby improve its therapeutic efficacy. The formulations with poly ethylene oxide AND XANTHUM GUM as CR polymer not even able to maintain the matrix integrity upto 12 hrs. Among different grades of polymers (HPMC K4M, PEO WSR 303, XANTHUM GUM) used , Physical parameters & floating characterstics were not good with the PEO AND XANTHUM GUM as CR polymers. Higher the viscosity grades of the HPMC, greater the retarding rate of model drug and the order of Controlled release is: HPMC K4M >XANTHUM GUM > PEO WSR 303. HPMC K4M at Drug : Polymer ratio :: 1:1.5 respectively showed better Sustained drug release of model drug. Formulated tablets showed satisfactory results for various Post compression evaluation parameters like: tablet thickness, hardness, weight variation, floating lag time, total floating time, content uniformity and *in vitro* drug release. Formulation F6 gave better-controlled drug release and floating properties in comparison to the other formulations. The release pattern of the F6 formulations was best fitted to Korsmeyer-Peppas model, Higuchi and ZERO-order model. The most probable mechanism for the drug release pattern from the formulation was non-Fickian diffusion or anomalous diffusion. When the Concentration of Polymer Increases the Drug Release Rate Decreases Because The Diffusion Path Length of Polymer Increases.

5. References

1. Yeole PG. Floating Drug Delivery System: Need and Development, Ind. J.Pharm Sci. 2005;67: 265-272.
2. ShwetaArora. Floating Drug Delivery: A Review, AAPS Pharm Sci Tech, 2005; 47: 268-272.
3. Libo Yang. A New Intragastric Delivery System for the Treatment of H.Pylori associated with gastric ulcers, J. Cont. Rel., 1999; 34: 215-222.
4. Singh BN and Kim H. Floating drug delivery system an approach to control delivery via gastric retention, J. Cont. Rel.,2000; 63:235-259.
5. Choi BY and Park HJ. Preparation of alginate beads for floating drug delivery system: effect of CO2 gas forming agent. J ContRel., 2000; 25:488-491.
6. Timmermans J and Moes AJ. The cut off size for gastric emptying of dosage forms, J Pharm Sci. 1993; 82 : 854.
7. Ichikawa M, Watanabe S and Miyake Y. A new multiple-unit oral floating dosage system: Preparation and in-vitro evaluation of floating and sustained-release characteristics. J Pharm Sci. 1991, 80: 1062-1066.
8. Menon A, Wolfgang AR and Saks A. Development and evaluation of monolithic floating dosage form for Furosemide, J.Pharm. Sci.1994; 83: 239-245.

9. Ozdemir N, Ordu S and Ozkan Y. Studies of floating dosage forms of Furosemide: in-vitro and in vivo evaluations of bilayer tablet formulations, Drug DevInd Pharm., 2000;26: 857-866.
10. Streubel A, Siepmann J and Bodmeier R. Floating matrix tablets based on low density foam powder: effects of formulation and processing parameters on drug release. Eur J Pharm Sci. 2003;18: 37-45.
11. Nur OA and Zhang JS. Captopril floating and/or bioadhesive tablets: design and release kinetics. Drug DevInd Pharm., 2000; 26:965-969.
12. Shah S, Quaqish R, Patel V, Amiji M. Evaluation of the factors influencing stomach specific delivery of antibacterial agents for H.pyloriinfections. J Pharm Pharmacol. 1999, 51: 667-672.
13. Hilton AK and Deasy BP, In vitro and in vivo evaluation of an oral sustained-release floating dosage form of Amoxycillintrihydrate. IntJ Pharm. 1992, 86: 79-88.
14. Basak SC. Development and in vitro evaluation of oral matrix floating tablets formulation of Ciprofloxacin. Ind J Pharm Sci. 2004;66: 313-316.
15. Himasankar K. Design and Biopharmaceutical evaluation of gastric floating drug delivery system of Metformin HCl. Ind J Pharm Edu Res.2006;40:369-382.
16. Dave BS, Amin AF and Patel MM.Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and in-vitro evaluation. AAPS Pharm Sci Tech. 2004;5: 1-6.
17. Cooper J, Gunn C, Powder flow and compaction, In: Carter SJ, eds. Tutorial Pharmacy. New Delhi, India: CBS Publishers and Distributors; 1986; 211-233.
18. Lakade SH, Bhalekar MR, Formulation and Evaluation of Sustained release Matrix Tablet of Anti-Anginal Drug, Influence of Combination of Hydrophobic and Hydrophilic Matrix Former,Research J. Pharm. and Tech.2008;1: 410-413.
19. Aulton ME, Wells TI, Pharmaceutics:The Science of Dosage Form Design, London, England: Churchill Livingstone; 1988.
20. Higuchi T. Mechanism of Sustained-action medication. Theoretical Analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci. 1963;51: 1145-1149.
21. Peppas NA. Analysis of Fickian and Non-Fickian drug release from polymers. Pharma Aceta.Helv, 1985, 60: 110-111.
22. Swati C. Jagdale,Formulation and Evaluation of Gastroretentive Drug Delivery System of Propranolol Hydrochloride.American Association of Pharmaceutical Scientists. Vol. 10, No. 3, September 2009,1071-1079.
23. Vobalaboina Venkateshwarlu, Dumpeti Janardhan, Meka Lingam, Chinnala Krishna Mohan: Formulation and In Vitro Evaluation of Gastroretentive Drug Delivery System for Ranitidine Hydrochloride. International Journal of Pharmaceutical Sciences and Nanotechnology, 2008; Vol 1.Iss.3:227-232.
24. Javed Ali,Formulation and Development of Floating Capsules of Celecoxib: In Vitro and In Vivo Evaluation AAPS PharmSciTech 2007; 8 (4) Article 119. Javed Ali, Formulation and development of hydrodynamically balanced system for metformin. In vitro and in vivo evaluation. European Journal of Pharmaceutics and Bio pharmaceutics 67 (2007) 196–201.
25. Kyriakos Kachrimanis,Solid dispersions in the development of a nimodipine floating tablet formulation and optimization by artificial neural networks and genetic Programming. European Journal of Pharmaceutics and Biopharmaceutics 77 (2011) 122–131.
26. Mahesh D. Chavanpatil, Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin. International Journal of Pharmaceutics 316 (2006) 86–92.
27. Leopoldo Villafuerte-Robles, Sustained delivery of captopril from floating matrix tablets. International Journal of Pharmaceutics 362 (2008) 37–43.
28. Anilkumar j. Shinde,formulation and in vitro evaluation of sustained release floating tablet of cephalexin using hydrophilic polymers. International journal of pharmacy and pharmaceutical sciences. Issn- 0975-1491 vol 2, suppl 2, 2010, 58-65.
29. Madhusudan Rao Y Development of gastroretentive systems for famotidine: in vitro characterization. Acta Pharmaceutica Sciencia 52: 495-504 (2010).
30. Vishal g. karkhile: Formulation and evaluation of floating tablets of furosemide, ijprd/2010/pub/arti/vov-1/issue-12/feb/009,1-10 pages.
31. Sanjay P.Boldhane, Bhanuda S.Kuchekar, "development and optimization of Metoprolol succinate gastro retentive drug delivery system, Acta pharmaceutica, Dec 2010, Vol.60 (4), P. 415-425.
32. A.I.Siddiqui, B.V.Bakde, K.K.Tappar: Flooating Strategy For Low Absorption window Diltiazem Hydrochloride. International Journal of Pharmacy and Technology,2011;Vol 3.Iss.1:1893-1903.
33. P Subhash Chandra Bose, P Srikanth Reddy, Valluru Ravi, D Sarita, T M Pramod Kumar; formulatin and evaluation of sustained release floating tablets of diltiazemHcl using xanthan gum, RJPBCS, 2011, 2(2), 319-328.

34. Ajay Bagherwal, Dinesh Kumar Patidar, Pradeep Sharma; studies on formulation and evaluation of floating tablets of ciprofloxacin Hcl,IJCP, 2010, 5(2),1-4.
35. Raja Benhar Dickson, Thakkar Hardik Rajeshbai, Paramasivam Sureshkumar, JamsheerAssinkk, Adimoolam Senthi; formulation and evaluation of gastro retentive floating tablets of glipizide, IJRAP, 2011, 2(3), 911-917.
36. A. Kotwal, A.K. Pathak, formulation and evaluation of intra gastric buoyant tablets of amoxicillin trihydrate; IJPLS, 2011, 2(2), 546-550.
37. Patel VM, Prajapati BG, Patel AK. Controlled release gastroretentive dosage form of verapamil hydrochloride. Int J Pharm Tech Res 2009; 1(2):215-21.
38. Jaimini M, Rana AC, Tanwar YS. Formulation and evaluation of famotidine floating tablets. Curr Drug Deliv 2007; 4(1):51-5.
39. Prabhu P, Harish NM, Guljar AM, Yadav B, Narayana CR, Satyanarayana D, Subrahmanayam EVS. Formulation and In Vitro Evaluation of Gastric Oral Floating Tablets of Glipizide. Indian J Pharm Educ Res 2008; 42(2):174-83.
40. Deshmukh VN, Jadhav JK, Sakarkar DM. Formulation and in vitro evaluation of theophylline anhydrous bioadhesive tablets. Asian J Pharm Sci 2009:54-8.
41. Rahman Z, Ali M, Khar R. Design and evaluation of bilayer floating tablets of captopril. Acta Pharm 2006; 56(1):49-57.
42. Gambhire MN, Ambade KW, Kurmi SD, Kadam VJ, Jadhav KR. Development and in vitro evaluation of an oral Floating matrix table formulation of diltiazem hydrochloride. AAPS Pharm Sci Tech. 2007; 8: E1-E9.
43. Arza RAK, Gonugunta CSR, Veerareddy PR. Formulation and evaluation of swellable and floating gastroretentiveciprvenlafaxinehcl hydrochloride tablets. AAPS PharmSciTech 2009; 10(1):220-6.
44. Prajapati ST, Patel LD, Patel DM. Gastric floating matrix tablets: Design and optimizationusing combination of polymers. Acta Pharm 2008; 58: 221-9.
45. Sungthongjeen S, Sriamornsak P, Puttipipatkhachorn S. Design and evaluation of floating multi-layer coated tablets based on gas formation. Eur J Pharm Biopharm 2008; 69(1):255-63.
46. Singh S, Singh J, Muthu MS, Balasubramaniam J, Mishra B. Gastroretentive drug delivery system of metoclopramide hydrochloride: Formulation and in vitro evaluation. Curr Drug Deliv 2007; 4(4):269-75.
47. ICH Q1A (R2) stability testing guidelines: stability testing of new drug substances and products.
48. Lachman Leon, Lieberman Herbert A. Pharmaceutical Dosage Forms: Tablets. In: The Theory and Practice of Industrial Pharmacy. Lea and Febiger, U.S.A, 1991; 3rd edition: 293-345.
49. A.A. Deshpande., N.H. Shah. C.T. Rhodes., W. Malick., 1997. **'**Development of novel drug controlled-release system for gastric retention'., Pharm. Res., 14., 815–819.
50. Ahuja, A., Khar, R.K., Ali, J., 1997. 'Mucoadhesive drug delivery system'**,** Drug Dev. Ind. Pharm**.,** 23**,** 489-492.