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An Approach of Developing Floating Tablet of Lisinopril

Nidhi Jain and Rahul Gupta

ABSTRACT

Lisinopril is an antihypertensive agent with 12 hr half life, pH-dependent solubility, and narrow absorption window. So, the present study aimed to prolong its gastric residence time that entailed a development of an optimized gastro retentive floating tablets (GRFTs). The tablets were fabricated by direct compression using hydroxypropyl methylcellulose and carbopol 934 as release retarding polymers. The quality attributes of the tablets were evaluated. The buoyancy lag time, total floating time, swelling ability and in vitro release studies were also carried out in 0.1 N HCl (pH 1.2) at 37 ± 0.5 °C. Statistical data analysis revealed that the optimized formulation containing 21.91% HPMC and 15% carbopol 934 had acceptable hardness, optimum floating behavior and 24h controlled-release pattern. The design succeeded to develop CVD-GRFTs with floating ability and controlled release behavior that could improve its solubility, and improve its availability at the best absorptive site.

Keywords: Floating tablet, Dissolution studies, HPMC, floating lag time.

1. INTRODUCTION

Lisinopril is a potent, competitive inhibitor of angiotensin-converting enzyme (ACE), the enzyme responsible for the conversion of angiotensin I (ATI) to angiotensin II (ATII). ATII regulates blood pressure and is a key component of the renin-angiotensin-aldosterone system (RAAS)[1]. Lisinopril may be used to treat hypertension and symptomatic congestive heart failure, to improve survival in certain individuals following myocardial infarction, and to prevent progression of renal disease in hypertensive patients with diabetes mellitus and micro albuminuria or overt nephropathy[2]. Lisinopril exhibit half life of 10 to 12hrs. Lisinopril is uniformly absorbed from the gastro intestinal tract but has very less solubility in the intestinal fluid therefore, the present study involves preparation and evaluation of floating tablet with lisinopril as model drug for prolongation of gastric residence time so that drug would not reach to intestinal fluid. The sustain release gastro retentive dosage form offer many advantages to Lisinopril drug. Gastro retentive dosage form improves the bioavailability and reduces the side effect of Lisinopril. The oral route is the most common and preferable route for the delivery of drugs. This may be due to ease of administration, patient compliance, and flexibility in formulation[3,4]. The concept of floating tablet can also be utilized to minimize the irritant effect of weakly acidic drugs in the stomach by avoiding direct contact with stomach mucosa and providing a means of getting a low dosage for a prolonged period[5]. The purpose of the present study was to develop an optimized gastric floating drug delivery system (GFDDS) to prolong the gastric residence time after oral administration, at a particular time and controlling the release of drug especially useful for achieving controlled plasma level as

well as improving bioavailability[6,7]. Floating dosage form containing Lisinopril as drug was designed for the treatment of hypertension. The dosage form was formulated by using polymers of different viscosity as gelling agents, sodium bicarbonate as gas generating agent and other excipients. Incorporation of gas generating agent together with polymer improved drug release. Effect on varying the concentration of ingredients was seen on hardness, in vitro buoyancy, in vitro drug release.

2. MATERIALS AND METHODS

Lisinopril was obtained as a gift sample by Sun Pharmaceutical Pvt. Ltd. India, HPMC K15, K4M, Carbopol 934P, PVP, Sodium bicarbonate, Microcrystalline cellulose were obtained from Central Drug House (P) Ltd, India; Mg. stearate were supplied by Effective enterprises, Bhopal. All other reagents used were of analytical and pharmaceutical grade.

2.1 Preparation of floating tablet

Lisinopril floating tablet were prepared by direct compression technique using varying concentrations of different grades of polymers with sodium bicarbonate and citric acid. All the ingredients were accurately weighted and pass through different mesh sieves. Then except magnesium stearate all other ingredients were blended uniformly in glass mortar after sufficient mixing of drug as well as other components, magnesium stearate was added, as post lubricant, and further mixed for additional 2-3 minutes. The tablets were compressed using rotary tablet machine. The weights of tablets were kept constant for all formulation[8]

2.2 Evaluation parameters[9-12]

2.2.1 Angle of Repose

Fixed funnel method was used. A funnel was fixed with its tip at a given height (h), above a flat horizontal surface on which a white paper is placed. Powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of funnel. These studies were carried out before and after incorporating lubricant/glidant. The angle of repose (θ) was then calculated.

$\tan \theta = h/r$

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

Where, θ = Angle of repose,

Table 1. Tablet Composition

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
DRUG	10	10	10	10	10	10	10	10	10	10
HPMC K15M	100	-	75	50	50	75	50	75	100	100
HPMC K4M	-	-	25	50	-	25	25	-	-	50
CARBOPOL-934 P	-	100	-	-	50	25	25	25	50	-
MCC	100	100	100	100	100	75	100	100	50	50
SODIUM BICARBONATE	30	30	30	30	30	60	60	60	60	60
CITRIC ACID	15	15	15	15	15	30	30	30	30	30
PVP	5	5	5	5	5	10	10	10	10	10
MAGNESIUM STEARATE	10	10	10	10	10	10	10	10	10	10
Total	260	260	260	260	260	310	310	310	310	310

All the weights are in milligrams.

h = Height of the cone base

r = Radius of the cone base

2.2.2 *Bulk Density*

Bulk density was determined using bulk density apparatus by placing a stack of powder into a measuring cylinder.

Bulkiness= 1/ Db

Where, Db = Bulk density.

Db=M/Vb

Where, Db =Bulk density M = Weight of sample (gm), Vb = Bulk volume (untapped volume)

2.2.3 *Tapped Density*

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 tapped volume of powder/granules.

Tapped density is expressed in g/ml and is given by formula:

Dt = M / Vt

Where, M = Mass of powder

Vt =Tapped volume of the powder

2.2.4 Carr's index (or) % compressibility

It is also known as compressibility index as it is used to determine compressibility of a powder. If powder particles are more compressible that means they have less flowing property. Carr's index also expressed as percentage and can be given as:

I = Dt-Db /Dt x 100

Where,

Dt = Tapped density of the powder

Db = Bulk density of the powder.

2.2.5 Hausner's ratio

Hausner's has given an index to explain flow property of powder. This ration is known as Hausner's ratio and can be given as;

Hausner's ratio = Dt/ Db

Where, Dt = Tapped density. Db = Bulk density.

Hausner's ratio <1.25 – Good flow which means 20% compressibility index

Hausner's ratio >1.25 – Poor flow which means 33% compressibility index

2.2.6 Weight variation

20 Tablets were selected randomly from the batch and weighted individually to check for weight variation. Weight variation specifications were as per I.P.

Table 2. Weight Variation Specification as per IP

Average Weight of Tablet	**% Deviation**
80 mg or less	±10
More than 80 mg but less than 250 mg	±7.5
250 mg or more	±5

2.2.7 Friability

Pre weighted tablets were placed in the friability test apparatus. Friability test apparatus consist of a plastic chamber that revolves at 25rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets were rotated in the friability test apparatus for at least 4 minutes. At the end of test tablets were dusted and reweighed; the loss in the weight of tablet was measured of friability and is expressed in percentage as:

% Friability = [(W0—Wf) / W0] ×100

W0 = Initial weight of tablets

Wf= Final weight of tablets

Limit- less than 1%

2.2.8 Hardness (Crushing strength)

A tablet was kept b/w jaws of Monsanto hardness tester and load required to crush the tablet was measured. The hardness of floating tablets is generally kept lower than conventional tablets as increased hardness delays the disintegration of the tablet. The force is measured in kg and the hardness of about 3-5 kg/cm2 is considered to be satisfactory for uncoated tablets.

2.2.9 Drug content uniformity

Twenty tablets were powdered, and 100 mg equivalent weight of lisinopril was weighed and transferred into a 100 ml volumetric flask. Initially, 10 ml of 0.1 NHCL (pH 1.2) was added and shaken for 10 min. Then, the volume was made up to 100 ml with same buffer. The solution in the volumetric flask was filtered, diluted suitably and analyzed by UV visible spectrophotometer at 246nm.

2.2.10 In vitro buoyancy studies

In vitro buoyancy studies were performed for all formulations. The randomly selected tablets from each formulation were kept in a 100ml beaker containing simulated gastric fluid, pH 1.2 as per IP. The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT). The duration of time the dosage form constantly remained on the surface of the medium was determined as the total floating time (TFT).

2.2.11 In vitro Dissolution study

The in vitro dissolution study (n=3) were carried out using USP dissolution test apparatus (type-2). The release

studies were performed at 50rpm in 900ml, 1.2 pH 0.1N HCl at 37±0.5□C. Aliquots of 5ml were withdrawn at 1 hr interval for 12 hrs. Dissolution study and the volume of dissolution medium were maintained by adding the 5ml of fresh dissolution medium. The test sample was filtered through Whatman filter paper and the concentration of Lisinopril was measured by UV-Visible Spectrophotometer at 246 nm and the percentage of drug release was plotted against time to determine the release profile.

3. RESULT AND DISCUSSION

3.1 Flow properties

The prepared granules were determined for following flow properties as presented in table and their characteristics were also made on the basis of standard.

3.2 Weight Variation

The weight of the tablet varied between 260mg to 310mg for different formulations with indicating uniformity of weight. The variation in weight was within the range of ±5% complying with pharmacopoeial specifications (Indian Pharmacopoeia 1996). Tablets prepared by direct compression were under the limits.

Table 3. Determining flow properties of the granules

Parameters	F7	F8	F9	Characteristics
Angle of repose	36	26	25	Good flow properties
Bulk Density	0.42	0.47	0.57	Lighter in density
Tapped density	0.58	0.57	0.59	Lighter in density
Carr's index	12.1	13.20	14.03	Good flow properties
Hausner's ratio	1.380	1.212	1.035	Good flow properties

Table 4. Evaluation of the tablets

Batch no.	Weight variation	Hardness (kg/cm^2)	Friability (%)
F7	Passed	2.5	0.3
F8	Passed	3.8	0.36
F9	Passed	2.8	0.5

3.3 Friability

The friability of tablets comes under the limit of less than 1 as presented in table 4.

3.4 Hardness

The hardness of tablet was presented in table 4 and the values showed the good crushing strength that can bear wear and tear losses.

3.5 Drug content uniformity

The drug content uniformity was found to be around 92%, 90% and 88.9% respectively of batch F7, F8,F9.

3.6 *In vitro* buoyancy study

The tablet floating lag time (FLT) was found to be less than 30s and total floating time more than 12 h. the floating lag time may be explained as a result of the time required for dissolution medium to penetrate the tablet matrix and develop the swollen layer for entrapment of CO_2 generated in situ. The tablet mass decreased progressively due to liberation of CO2 and release of drug from the matrix. On the other hand as solvent front penetrated the glassy polymer layer, the swelling of carbopol 934P and HPMC K15M caused an increase in volume of the tablet. The combined effect is a net reduction in density of the tablets, which prolongs the duration of floatation beyond 12 h. Both the swelling polymers (cabopol 934P and HPMC K15M) appeared to prolong the lag time while sodium bicarbonate appeared to reduce the lag time as expected. This is in perfect agreement with release rate and mechanism observed, since the polymers did not swell initially, but helped in keeping the tablet a float during the late hours of dissolution.

3.7 *In vitro* drug release study

The In vitro drug release study was performed for best optimized formulation F8. The release was determined using 0.1N HCl buffer solution (pH 1.2).

Table 7. % drug release formulation code F8

S. No.	Time(hrs.)	% drug release
1.	1	17.09
2.	2	29.87
3.	3	34.27
4.	4	48.52
5.	5	54.82
6.	6	61.72
7.	7	67.82
8.	8	73.45
9.	9	78.21
10.	10	82.52
11.	11	86.01
12.	12	89.87

% CD= Cumulative drug release

Table 8. *In vitro* Drug Release Studies of Formulation F8.

Time (hrs)	Log Time	Square root of Time	% CD Release	% CD Retained	Log % CD Release	Log % CD Retained
1	0	1	17.09	82.91	1.23	1.91
2	0.30	1.41	29.87	70.13	1.47	1.84
3	0.47	1.73	34.27	65.73	1.53	1.81
4	0.60	2	48.52	51.48	1.68	1.71
5	0.69	2.23	54.82	45.18	1.73	1.65
6	0.77	2.44	61.72	38.28	1.79	1.58
7	0.84	2.64	67.82	33.18	1.83	1.52
8	0.90	2.82	73.45	26.55	1.86	1.42
9	0.95	3	78.21	21.79	1.89	1.33
10	1	3.16	82.52	17.48	1.91	1.24
11	1.01	3.31	86.01	13.99	1.93	1.14
12	1.07	3.46	89.87	10.13	1.95	1.00

Table 9. Regression coefficient values of different release order kinetic model for formulation F8.

S. no.	Release order kinetic model	Regression coefficient (R^2)
1.	Zero order kinetics model	0.966
2.	First order kinetics model	0.986
3.	Korsemeyer Peppas model	0.991
4.	Higuchi kinetic model	0.994

As per data of regression coefficient, it was inferred that release kinetics of drug from formulation F8 was according to Higuchi kinetic model.

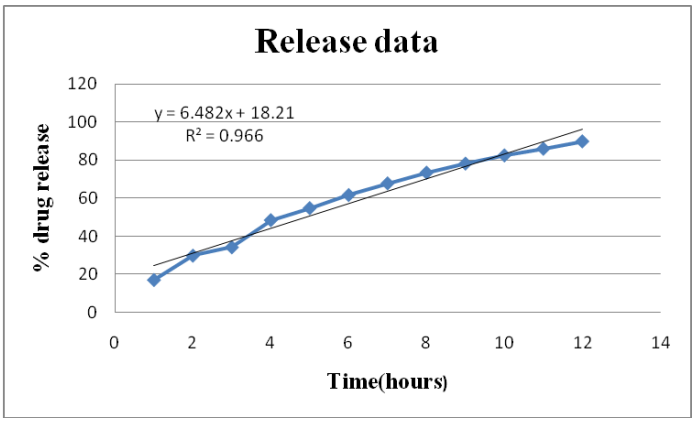

Figure 1. % Drug release of formulation F8(89.87 of drug release for 12 hours.)

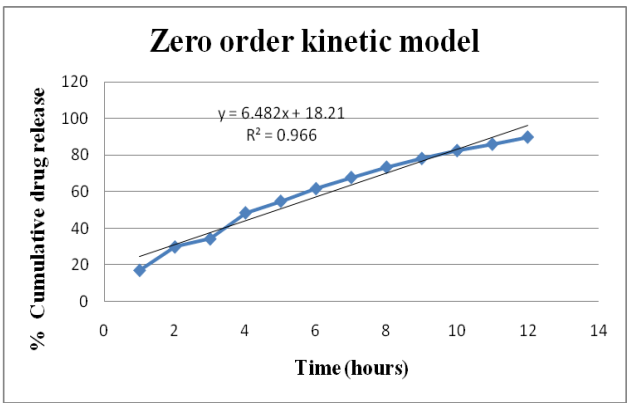

Figure 2. Zero order kinetics model of drug release from formulation F8.

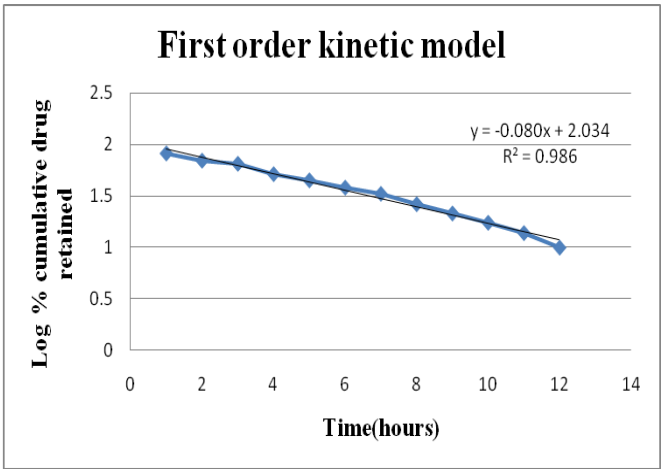

Figure 3. First order kinetics model of drug release from formulation F8.

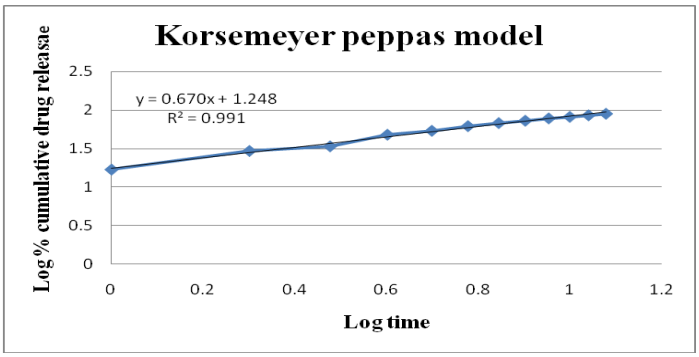

Figure 4. Korsemeyer Peppas model of drug release from formulation F8.

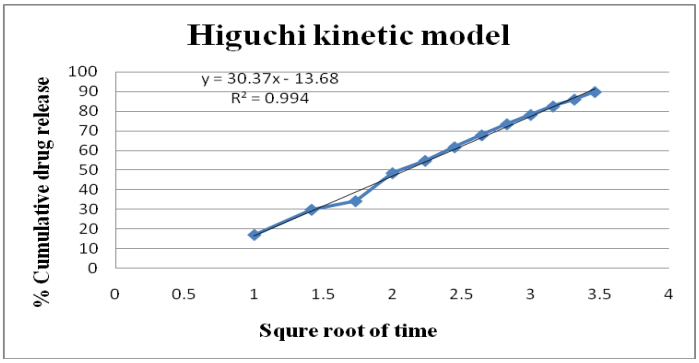

Figure 5. Higuchi kinetics model of drug release from formulation F8.

4. CONCLUSION

Thus, from the above study it was concluded that floating tablet used as Anti-hypertension drug Lisinopril could be formulated as an approach to increase gastric residence time and there by improve its bioavailability. Formulated tablets gave satisfactory result for various physicochemical evaluations for tablet like, hardness, weight variation, floating time, Lag time, and in vitro drug release formulation F8 gave better controlled drug release in comparison to other prepared formulation. Thus the objective of formulating floating drug delivery dosage form of Lisinopril has been achieved. The various concentrations of HPMC K15M and Carbopol 934P was used in formulation, sustained the release of lisinopril for 12 hrs. The reason behind choosing the HPMC K15M and Carbopol 934P polymer was its low density hydrocolloid system. HPMC K15M and Carbopol 934P provide several advantages i.e. sustained release, good stability in varying pH values and moisture levels.

REFERENCES

1. Kurra N, Baru CR, Dhara V, Kumar VP. Formulation and evaluation of fast dissolving sublingual lisinopril tablets. IAJPS. 2014; 1: 378-391.
2. Lancaster SG, Todd PA. Lisinopril: A preliminary review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in hypertension and congestive heart failure. Drugs. 1988; 35: 646-669.
3. Gupta R, Mishra AK, Pathak AK. A critical review on different pharmaceutical aspects of solid dispersion technique for solubility enhancement. Int J Pharm Biol Sci. 2015; 5: 119–128.
4. Kumari K, Sharma P, Gupta R. Polysorbate-Phospholipid Complex Micelles as P-glycoprotein Inhibitor Drug Delivery System. J B Pharmaco Toxi. 2017; 1: 2-7.
5. Menon A, Ritschel WA, Sakr A. Development and Evaluation of monlolithic floating dosage form for furosemide. J Pharma Sci. 1994; 83: 239-245.
6. Kamble S, Ghorpade P. Gastro-Retentive Floating Drug Delivery System Containing Antihypertensive Drug-An Overview. W J Pharma Res. 2014; 3: 1076-1092.
7. Hamman JH, Demana PH, Olivier EI. Targeting Receptors, Transporters and Site of Absorption to Improve Oral Drug Delivery. Drug Tar Ins. 2007; 2: 71–81.

8. Garg R, Gupta GD. Progress in Controlled Gastroretentive Delivery Systems. T J Pharm Res. 2008; 7: 1055-1066.
9. Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating Drug Delivery Systems: A Review. AAPS Pharm Sci Tech. 2005; 6: 372-390.
10. Jose GR, Khalid US. Gastric Retention of Solid Dosage Forms: A Review of the Current Climate. AAPS Pharm Sci Tech. 2004; 10: 22-23.
11. Sharma R, Gupta R, Jhat RK. Development and evaluation of sustained release bilayer matrix tablet of glipizide and metformin hydro chloride. Int J Drug Res Technol. 2013; 3: 60–66.
12. Jain A, Jain P, Jain SK, Agrawal RK, Agrawal GP. Calcium-silicate-based floating granular delivery system of ranitidine hydrochloride for effective management of peptic ulcer. Med Chem Res. 2008; 17: 305–317.