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DESIGN AND EVALUATION OF LISINOPRIL FLOATING TABLET

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ABSTRACT

Lisinopril is an antihypertensive drug with 12 hr half life narrow absorption window and PH dependant solubility so the present study aimed to prolong it's gastric residence time that entailed development of an optimised gastro retentive floating tablets(GRFTs). Tablets were fabricated by direct compression using hydroxy propyl methyl cellulose and carbopol 934 as release retained in polymers. The total floating time, swelling ability, buoyancy lag time and in vitro release studies were also carried out in 0.1N HCl(pH 1.2) at 37+/-0.5. Statistical data analysis revealed that the optimised formulation containing 21.91% HPMC and 50%carbachol934 had acceptable hardness. Optimum floating behaviour and 24 hr controlled releasepattern. The design succeeded to develop CVD-GRFTs with floating ability and controlled releasebehaviour that could increase solubility and improved it's availability at the absorption site.

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

INTRODUCTION

Floating Tablet

Floating systems or dynamically controlled systems are low density systems that have sufficiently buoyancy to float over the gastric contents and remain float 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.

Approaches for Prolonging The Gastric Residence Time HDS

Mucoadhesive

Swelling and expanding systems

Floating systems

High-density systems

Bioadhesive systems

Importance of FDDS

Suitable dosage forms for the drugs those are primarily absorbed in the stomach. Beneficial in the treatment of gastric diseases. Less side effects and Lower dosing. In humans the gastric emptying time normally 2-3 hours through the major absorption zone (upper part of intestine and stomach) can result in incomplete drug release from the drug delivery system leading to reduced efficacy of administered dose.

Mechanism of floating systems

FDDS has a bulk density less than gastric fluids so it remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.

F = F buoyancy - F gravity = (Df - Ds) gv Where, F= total vertical force, Df = fluid density, Ds = object density, v = volume and g = acceleration due to gravity.

AIM

The aim of the present study was to develop floating tablets of lisinopril to achieve prolong residence time, leading to an increase in drug bioavailability and patient compliance.

OBJECTIVE

The objective of present work was,

1. To design and formulate floating tablet lisinopril an antihypertensive agent and polymer HPMC K15M and carbopol 934. To evaluate the physical characteristics of lisinopril.
2. To find out the best formulation by evaluating the floating time an in-vitro drug release.

Scope Of Study

The goal of present study is to attain an optimum and perfect formulation of a floating tablet for lisinopril that would have the following behaviors,

- Excellent floating behavior.
- Good physical and chemical stability

PLANOF WORK

The present investigation was planned to carry out in a systematicway as follows,

- To review the literature for the drug delivery system and itsevaluation.
- To prepare various formulations of floating tablet of Lisinopril
- To evaluate their in-vitro dissolution and floatingcharacteristics.
- To findanoptimized formulation of lisinopril with required characteristics
- To carryout in vitro dissolution and buoyancy studies for theoptimized formulations.

MATERIALS AND METHODS

Material used

Table no: 01.

SL NO	MATERIALS
1	Lisinopril
2	HPMC K15
3	HPMC K4M
4	Carbopol 934P
5	PVP
6	Sodium bicarbonate
7	Microcrystalline cellulose
8	Mg stearate
9	Citric acid

Instrument used

Table no: 2.

Sl no	Equipments Usedz	Model/Company
1	Electronic weighing balance	Shimadzu typeAY220
2	Uv visible spectrophotometer	Shimadzu
3	Dissolution Apparatus	USP dissolutionapparatus
4	Hot Air Oven	Kemi S.no 6760

METHODS

- **Formulation of Lisinopril Floating Tabletgranules**
  - Wet gum method

- **Evaluation of Lisinopril Floating Tabletgranules**
  - Bulk density
  - Tapped density
  - Carr's index
  - Hausner's ratio

- Angle of repose

- **Formulationof Lisinopril Floating Tablet**
- Punching method

- **Evaluationof Lisinopril Floating Tablet**
- Friability
- Hardness
- Drug content uniformity
- In vitro Buoyancy studies
- Weight variation
- Dissolution study

Formulation of Lisinopril Floating Tablet Granules

Floating granules of lisinopril were prepared by wet granulation method using water soluble polymer HPMC K15, HPMC K4M and Carbopol 934P as hydrophilic matrix in formulation. The composition of formulation is given in Table 2. The composition with respect to polymer was selected based on trial preparation of granules that did not float more than 4 hours.

The ingredients were thoroughly mixed in a polybag and passed through sieve no: 60. Granulation was done with a solution of calculated quantity of PVPK 30 in sufficient isopropyl alcohol. The wet mass passed through sieve no:12 and dried at 45-55^{o}C for 30 minutes. The dried granules were sized by sieve no:18. The obtained granules were stored in desiccators.

All the weights are in milligrams.

Table no 03: Formulation of lisinopril floating tablet granules.

INGREDIENT	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
DRUG	10	10	10	10	10	10	10	10	10	10
HPMC K15M	100	-	50	75	50	75	50	75	100	100
HPMC K4M	-	-	50	25	-	25	25	-	-	50
CARBOPOL934P	-	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

Evaluation of Lisinopril Floating Tablet Granules

1) Bulk density (Db)

Is the ratio of total mass of powder to the bulk volume of powder. It is measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and the initial volume is noted. This initial volume is called the bulk volume. From this, the bulk density is calculated according to the formula mentioned below. It expressed in g/cc and is given by:

$$Db = M/V_0$$

Where, M is the mass of powder, V0 is the bulk volume of the powder.

Tapped density (Dt)

Is the ratio of total mass of powder to the tapped volume of powder. The volume was measured by tapping the powder for 500 times. Then the tapping was done for 750 times and the tapped volume was noted. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. It is expressed in g/cc and is given by:

$$Dt = M/V_t$$

Where, M is the mass of powder, Vt is the tapped volume of the powder.

Carr's index (%)

The bulk density is the measurement of weight to the volume of the sample. The percentage compressibility (Carr's index) was calculated as 100 times the ratio of the difference between tapped density and bulk density to the tapped density.

$$\text{Carr's index} = \frac{\text{Tapped density Bulk - density Tapped}}{\text{Tapped density}}$$

Hausner's ratio

Hausner's ratio is the ratio of tapped density to bulk density. Lower the value of Hausner's ratio better is the flow property. The powder with Hausner's ratio less than 1.18, 1.19-1.25, 1.3-1.5 and greater than 1.5 indicates excellent, good, passable and very poor flow properties, respectively.

$$\text{Hausner's Ratio} = \text{Tapped density/Density Tapped}$$

Angle of repose (θ)

It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane.

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

Where, θ is the angle of repose

h is the height

r is the radius

Procedure: The powder mixture was allowed to flow through the funnel with its tip fixed to stand at a definite height (h) from a graph paper placed on a horizontal surface. The angle of repose was then calculated by measuring the height and radius of the heap of powder formed.

Formulation of Lisinopril Floating Tablet

Lisinopril floating tablet were prepared by direct compression technique using varying concentrations of different grades of polymer with sodium bicarbonate and citric acid. All the ingredients were accurately weighed 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 postlubricant, 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.

Evaluation of Lisinopril Floating Tablet

Friability Test

The friability of tablets was determined using Roche friabilator. It is expressed inpercentage (%). Twenty tablets were initially weighed (w_0 initial) and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again(w). The % friability was then calculated by

$$\text{Percentage of Friability} = 100\ (1\text{-}(w/w0))$$

Hardness

Hardness indicates the ability of a tablet to with stand 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

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.

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).

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.

In vitro Dissolution Studies

The release rate of AI floating tablets was determined using USP dissolution Testing Apparatus Type II (paddle method). The dissolution test was performed using 900 ml of 0.1N HCl, at37±0.5° and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus time intervals 0,0.5,1,2,3,4,6,8,10,12 hours and the samples were replaced with fresh dissolution medium. Absorbance of these solutions was measured at 244nm using a double-beamspectrophotometer.

RESULTS AND DISCUSSION

1) Evaluation of Lisinopril Floating Tablet Granules

(A) Physical Characteristics of Granules

Table no:04-Physical characteristics of granules.

Sl.no	Physical properties	Formulation code			
		A1	A2	A3	A4
1	Bulk Density	0.43g/mL	0.46 g/mL	0.58 g/mL	0.50g/mL
2	Tapped Density	0.58 g/mL	0.56 g/mL	0.59 g/mL	0.57g/mL
3	Carr's index	12.1	13.30	14.15	13.98
4	Hausner's ratio	1.38	1.21	1.13	1.25
5	Angle of repose	28°	26°	30°	34°

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.

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.

Friability

The friability of tablets comes under the limit of less than 1% as presented in table 3.

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.

Drug content uniformity

The drug content uniformity was found to be around 92%, 90%, 91.5% and 92.5% respectively of batch B1, B2, B3 and B4 respectively.

2) Evaluationof Lisinopril Floating Tablet

(A) Physical Characteristics of Tablet

Table no: 05-Physical characteristics of tablet.

SL.NO	Physical Parameter	Tablet Code			
		B1	B2	B3	B4
1	Friability(%)	0.35	0.32	0.42	0.38
2	Hardness(kg/cm$^{2)}$	2.8	3.4	4.1	3.8
3	Weight variation	Passed	Passed	Passed	Passed
4	content Uniformity(%)	92	90	91.5	92.5

Invitro Drug Release-Dissolution Studies

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 no: 06-In vitro drug release-Dissolution studies.

SL.NO	Time(hr)	Cumulative percentage of drug release(%)			
		B1	B2	B3	B4
0	0	0	0	0	0
1	1	25.26	3.10	35.15	41.75
2	2	36.05	44.26	47.87	50.61
3	3	54.23	54.32	60.54	63.34
4	4	57.37	60.74	71.55	74.56
5	5	63.17	68.85	74.32	78.67
6	6	68.42	73.64	81.56	81.12

7	7	70.21	75.12	85.34	84.34
8	8	73.75	80.34	87.77	86.86
9	9	74.52	83.56	90.12	88.65
10	10	74.62	83.60	90.32	90.64

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 CO2 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 the net reduction in density of the tablets, which prolongs the duration of floatation beyond 12 hrs. 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.

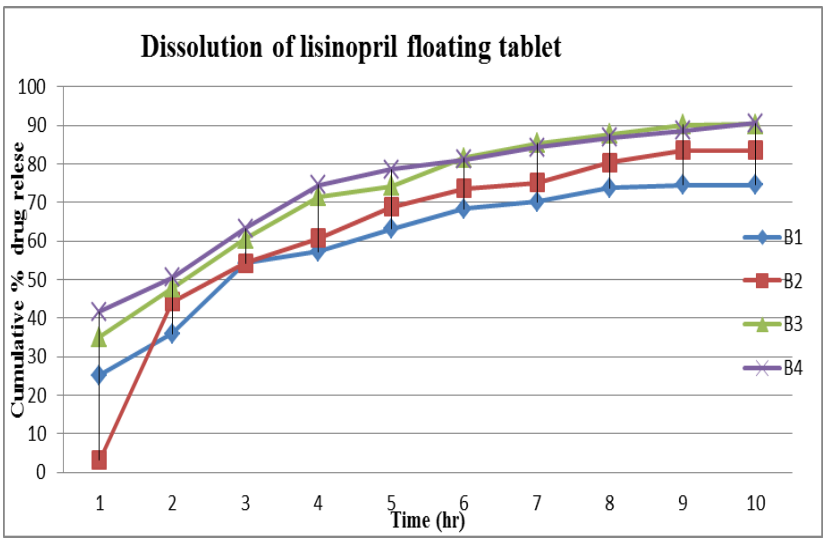

Fig 7: Dissolutuion of lisinopril floating tablet.

SUMMARY

Review of literature reveals that floating drug delivery systems are easiest approach for technical and logical point of view among gastroretentive drug delivery system, so for present study, floating drug delivery system was chosen to increase the gastric residence time of dosage form which led to increased bioavailability of various drug substances. Lisinopril is

an antihypertensive drug, So in present investigation, an attempt was made to deliver lisinopril via floating drug delivery system to the vicinity of absorption site by prolonging the gastric residence time of the dosage form.

Tablets were subjected to various evaluation parameters such as hardness, friability, thickness, tablet density, weight variation, in vitro drug release study. It was revealed that tablets of all batches had acceptable physical parameters.

The effervescent-based Gastroretentive drug delivery is a promising approach to achievein vitro buoyancy by using gel-forming polymer HPMC K4M, carbopol and gas generatingagent sodium bicarbonate.

The drug content of all the formulations was found to be in the range of 90% to 92.5%, which indicates the uniform drug content. In vitro drug release studies were performed for all the prepared formulations. All the prepared floating tablets exhibited good drug release.

CONCLUSION

From the following studies it was concluded that lisinopril an antihypertensive drug is used as a floating tablet which is an approach to increase gastric residence time such that its bioavailability is improved. Various physicochemical evaluation for the tablet have been done like hardness, lag time, weight variation etc, which gave satisfactory result. The objective of evaluation of lisinopril has been achieved.

FUTURE PROSPECTS

Due to limitation of time, various studies have not been completed which may be left for future study.

- Stability study in accelerated conditions and long term stability studies.
- In-vivo study in animals and IVIVC
- Pharmacokinetics studies by assessment of bioavailability by rapid analytical methods like HPLC, LC-MS etc.

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