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Research Article

FORMULATION AND EVALUATION OF RANITIDINE FLOATING TABLETS

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ABSTRACT

Formulation of floating drug delivery system is to increase the safety of the drug and to extend its duration of action. This novel drug delivery system is essential for the drugs that are degraded in the intestine. This floating drug delivery system is aimed at providing increased bioavailability. Floating drug delivery system can be retained in the stomach for long time by formulating Ranitidine with low density polymers like hydroxyl propyl methyl cellulose and gas generating agents are added to the system to reduce the density of the system. Intimate contact of the drug with the absorbing membrane has the potential to maximize the drug absorption. The controlled release of drug is according to the physiological state of the subject and design of the pharmaceutical formulation. Formulation was optimized on the basis of floating time and in-vitro drug release. The tablet was subjected to evaluation for physical characteristics like weight variation, hardness, friability, drug content uniformity, floating lag time, total floating time and in-vitro drug release. Four different formulations of ranitidine were formulated by variation in the ratio of hydroxyl propyl methyl cellulose. From the investigation it's found that Ranitidine incorporated with concentration of 33% of HPMC was found to be better formulation by considering all the evaluated parameters like floating lag time, total floating time, hardness, friability and weight variation and percentage drug release.

INTRODUCTION[1]

Floating drug delivery systems is retained in stomach and is useful for drugs that are poorly soluble or insoluble in gastric fluids. In this system, the dosage form is less dense than gastric fluids so that it can float. The density of the system can be reduced by incorporating a number of low density fillers or polymers into the system such as hydroxyl cellulose, lactates or microcrystalline cellulose. The basic idea behind the development of such a system is to maintain a constant level of drug in the blood plasma inspite of the fact that the drug does not undergo disintegration. The drug usually keeps floating in the gastric fluid and slowly dissolves at a predetermined rate to release the drug from the dosage form and maintain constant drug levels in the blood levels.

Concept of floating

It is mainly based on the matrix type drug delivery system such that the drug remains embedded in which after coming in contact with gastric fluid swells up and the slow erosion of the drug without disintegration of take place. In addition, we need to add some effervescent or gas generating agent which will also ultimately reduce the density of the system.

Gastro-retentive system[2]

Sustain release through gastric retention

The sustain release of dosage form of drug which have aimed at the prolongation of gastric emptying time. Controlled release drug delivery system that can be retained in the stomach for a longer time are necessary for drugs that can be degraded in intestine for drugs like antacid or certain enzymes that should act locally in the stomach . If the drugs are poorly soluble in intestine due to alkaline PH gastric retention may increase solubility before they are emptied or resulting in improved gastrointestinal absorption of drugs with narrow absorption

window as well as for controlling release of drugs having site specific absorption limitation. Gastric retention will provide advantage such as the delivery of drugs with narrow absorption window in the small intestine region. Also longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine. For examples treatment of peptic ulcer disease further more improved bio-availability is expected for drugs that are absorbed readily upon release in the GI-tract. These drugs can be delivered ideally by slow release from the stomach.

Application of floating drug delivery system

Floating drug delivery offers several application for drugs having poor bio-availability because the narrow absorption window in the upper part of the GIT. It retains the dosage format narrow absorption and thus enhances the bio-availability.

Sustained drug delivery system[3]

HBS (hydrodynamic balanced system) systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. These systems have a bulk density of less than 1as a result of which they can float on gastric contents.

Site specific drug delivery

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine. E.g. Ranitidine, Furosemide.

MATERIALS AND METHODS

MATERIALS

Ranitidine and HPMC were received as gift samples from Lincoln pharmaceuticals Ltd, Ahmedabad, India. MCC, PVP, Sodium bicarbonate, Aerosil and Megnesium stereate supllied from the Sd fine chem limited, mumbai

Method[4]

The drug and all other excipients were sifted through #40 sieves and mixed thoroughly. The above blend was pre lubricated with aerosil and lubricated with magnesium stearate. The above lubricated blend was compressed using standard flat faced punch on a sixteen station rotary tablet punching machine. Each tablet contained 300 mg of ranitidine hydrochloride and other pharmaceutical ingredients as listed in tables in each section.

Table 1: Formulation data for Ranitidine floating tablet with various ratios of polymer (HPMC)

DRUG & EXPIENTS	F1 (mg)	F2(mg)	F3(mg)	F4(mg)
RANITIDINE	300	300	300	300
MCC	225.6	175.6	125.6	75.6
HPMC K 15	50	100	150	200
PVP K 30	7	7	7	7
SODIUM BI CARBONATE	15	15	15	15
AEROSIL	1.2	1.2	1.2	1.2
MAGNESIUM STEARATE	1.2	1.2	1.2	1.2
TOTAL	600	600	600	600

EVALUATION STUDIES

PREFORMULATION PARAMETERS

Angle of Repose[5,6]

The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation. tan □ = h/r Where, h and r are the height and radius of the powder cone.

Bulk Density and Tapped Density[7]

Both loose bulk density (LBD) and tapped bulk density (TBD) was determined. A quantity 2gm of powder blend from each formula, previously shaken to break any agglomerates formed, was introduced in to 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued until no further change in volume was noted. LBD and TDB were calculated using the following equations. LBD= Weight of the powder blend/Untapped Volume of the packing TBD=Weight of the powder blend/Tapped Volume of the packing

Compressibility Index[5]
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

Carr's Index (%)=[(TBD-LBD) x100]/TBD

Hausner's Ratio[8]
It is the ratio of bulk volume to tapped volume or tapped density to bulk density. Hausner's ratio is an important character to determine the flow property of powder and granules. This can be calculation by the following formula.

Hausner's ratio = Tapped density / Bulk Density

EVALUATION OF TABLETS[9,10]
Weight Variation Test
To study weight variation twenty tablets of the formulation were weighed using a Sartorius electronic balance and the test was performed according to the official method.

Drug Content
Five tablets were weighed individually, and the drug was extracted in 0.1 N HCl, and the solution was filter through 0.45 membrane. The absorbance was measured at 315 nm after suitable dilution using a Shimadzu UV-1601 UV/Vis double beam spectrophotometer5

Hardness
The hardness of five tablets was determined using the fizer hardness tester and the average values were calculated.[10]

Friability
Friability is the measure of tablet strength. Roche friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined.

Floating Lag Time[11]
The lag time was carried out in beaker containing 100 ml of 0.1 N HCl as a testing medium maintained at 37 °C. The time required for the tablet to rise to the surface and float was determined as floating lag time.

Floating Time
Floating time was the time, during which the tablet floats in 0.1 N HCL dissolution medium (including floating lag time)

In vitro Drug Release Study[12,13,14]
The release rate of Ranitidine HCl from floating tablets was determined using USP Dissolution Testing Apparatus II (Paddle type). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37 ± 0.5°C and 50 rpm. Aliquot volume was withdrawn from the dissolution apparatus hourly for 8 hr, and the samples were replaced with fresh dissolution medium. After filtration and suitable dilution the amount of drug release was determined from the calibration curve.

Details of Dissolution Test
1. Apparatus : USP Type II
2. Volume of medium : 900 ml
3. Temperature : 37 °C
4. Paddle Speed : 50 rpm
5. Dissolution medium used : 0.1 N HCl
6. Aliquot taken at each time interval: 5 ml

RESULTS
CALIBRATION CURVE FOR RANITIDINE
The development was started with standard calibration curve using UV Spectrophotometric method. The UV Spectrophotometric method was developed in 0.1N HCl at 322nm. The method shows linearity in concentration range 2 - 10µg/ml with regression coefficient of 0.999.

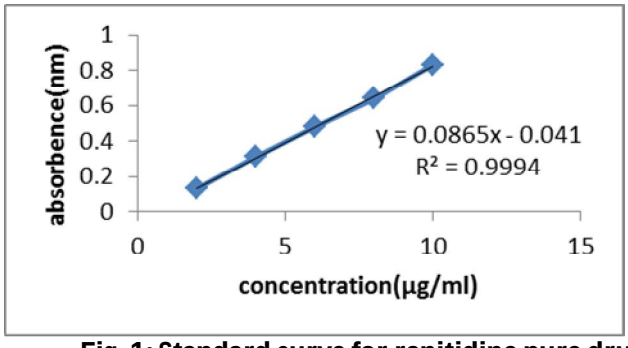


Fig. 1: Standard curve for ranitidine pure drug

Table 2: Preformulation studies

formulations	Bulk density	Tapped density	Angle of repose	% compressibility	Hausners ratio
F1	0.49	0.57	27.40	14.04	1.16
F2	0.46	0.53	26.38	13.20	1.15
F3	0.41	0.47	31.94	12.76	1.14
F4	0.48	0.55	29.06	12.72	1.14

Table 3: Post formulation studies

Formulation	Weight variation	hardness	friability	Content uniformity	Floating lag time	Total floating time
F1	Pass	6.0	0.24	99.24	14 min	24 hrs
F2	Pass	5.9	0.16	99.62	12 min	24 hrs
F3	Pass	6.0	0.53	99.19	11 min	24 hrs
F4	Pass	6.0	0.28	99.49	10 min	24 hrs

Table 4: Invitro dissolution studies

Formulation code/Parameter	F1(%)	F2(%)	F3(%)	F4(%)
1 hr	38	34	28	24
2 hr	54	57	39	32
4 hr	67	62	44	42
6 hr	71	75	52	49
8 hr	86	81	63	59
10 hr	98	89	69	69
12 hr		97	78	75
14 hr			86	79
16 hr			94	82
18 hr			98	87
20 hr				92
22 hr				96
24 hr				98

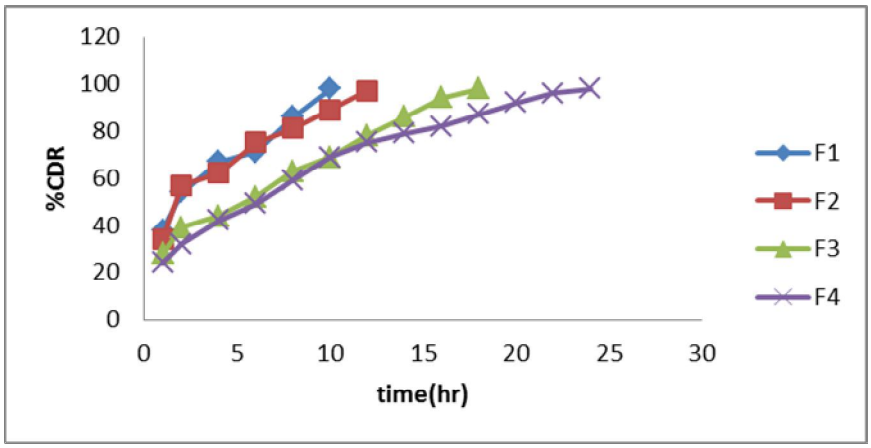


Fig. 2: Drug release profile of formulated ranitidine floating tablets

DISCUSSION

Formulation development was carried out using different concentrations of HPMC K15 polymer, PVP and excipients added, all together 4 formulations are carried out. The powder of blend of 4 formulations was evaluated for pre formulation studies like angle of repose, Bulk density, Tapped density, % compressibility, Hausner ratio, and all the parameters are within the range they can compressed as tablets by using direct compression method.

Formulation development was carried using HPMC K15 polymer of various ratios. Initial formulation developed with HPMC K15 8.33% concentration. The formulation showed FLT 14 sec, TFT 10 hrs and 98% drug released within 10hrs. Kinetic graphs zero order and first order were plotted regression values of 0.956, 0.926 respectively.

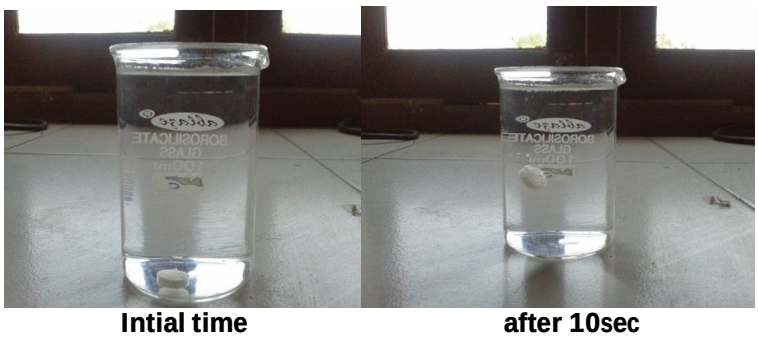
In order to improve the LFT, TFT the polymer concentration was increased. The formulation development was carried using HPMC K15 in 16.66% concentration. The parameters like LFT, TFT was observed 13sec and 12hrs respectively and 97%drug released within 12 hrs. Kinetic graphs zero order and first order were plotted regression values of 0.924, 0.906 respectively. The formulation also studied for Higuchi, Peppas and Erosion mechanism having regression values of 0.964, 0.727 and 0.965 respectively.

Further formulation development was carried out increasing the concentration of polymer 25% concentration of HPMC K15 was used. The LFT, TFT was observed12 sec and 18hrs respectively, 98% drug release was observed in 18 hrs. Kinetics were studied for zero order, first order, higuchi, peppas and erosion mechanism having regression values of 0.956, 0.926, 0.995, 0.603 and 0.954 respectively.

Finally the formulation development was carried using 33.33% concentration of HPMC K15 polymer. The formula showed better LFT and TFT as 10sec and 24hrs respectively. 98% drug release was observed in 24hrs. Kinetics were studied for zero order, first order, higuchi, peppas and erosion mechanism having regression values of 0.956, 0.926,0.995,0.676 and 0.988 respectively. Based on the LFT, TFT, %CDR and regression values of Kinetics the F4 formula having perfect linearity in log% cumulative drug release vs. time thus following zero order kinetics and based on peppas and Hixon crowel erosion mechanism data, the formula obeys erosion kinetics and follows non-fickian diffusion.

Table 5: Comparison of FLT and TFT of F1, F2, F3 and F4 for ranitidine floating tablets by various concentrations of polymer (HPMC K15)

Formulation	FLT	TFT
F1	14 sec	10 hr
F2	12sec	12 hr
F3	11sec	16 hr
F4	10sec	24 hr



Intial time **after 10sec**

Fig. 3: Formulation 4 floating lag time

CONCLUSION

The different formulations of Ranitidine were prepared by using different concentration of HPMC. Formulation-4 exhibit combined excellent buoyant ability and sustained drug release pattern could possibly be advantages in terms of enhanced pharmacokinetic profile and increased bioavailability, when compare with other formulations.So formulation-4 is the best formulation for Ranitidine floating drug delivery system.

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