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FORMULATION AND INVITRO EVALUATION OF RANITIDINE HYDROCHLORIDE 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 hydrochloride 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 invitro drug release. The tablet was subjected to evaluation for physical characteristics like weight variation, hardness, friability, drug content uniformity, floating lag time and floating time and invitro drug release. Three different formulations of ranitidine hydrochloride were formulated by variation in the ratio of hydroxy propyl methyl cellulose. From the investigation it's found that Ranitidine hydrochloride incorporated with 120mg of HPMC was found to be better formulation by considering all the evaluated parameters like lag time, hardness, friability and weight variation and percentage drug release.

Keywords:- Ranitidine hydrochloride, Hydroxyl propyl methyl cellulose, Floating drug delivery system.

INTRODUCTION

Floating drug delivery systems (Bamba M *et al.*, 1979) 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.

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Concept of floating

It is mainly based on the matrix type drug delivery system such that the drug remains embedded in matrix 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

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 (Basit A *et al.*, 2001).

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

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 (Chawla G *et al*., 2003).

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 METHOD

MATERIALS

Ranitidine Hydrochloride and HPMC were received as gift samples from Lincoln pharmaceuticals Ltd, Ahmedabad, India. Sodium bicarbonate was a Gift sample from Molychem, Mumbai. Stearic acid and Citric acid was a Gift sample from Loba chemistry, Mumbai. All other chemicals and ingredients were used for study are of Analytical grade. Chloroform, Talc, Magnesium stearate was obtained from Enar Chemicals Pvt Ltd, India.

METHOD

PREPARATION OF RANITIDINE HYDROCHLORIDE FLOATING TABLETS

Ranitidine hydrochloride (RHCL) was mixed with required quantities of hydroxy propyl methyl cellulose (HPMC), sodium bicarbonate, and citric acid by geometric mixing (Grant S 1989). RHCL was dispersed in chloroform solution with required quantity of stearic acid, the dispersion was stirred and chloroform was evaporated to form a RHCL- Stearic acid mixture. This mixture was then mixed with other ingredients. The powder blend was then lubricated with magnesium stearate (1%wt/wt) and purified talc (1%wt/wt) and compressed using tablet punching machine (Gibaldi M *et al*., 1967).

EVALUATION PARAMETERS OF FORMULATED FLOATING TABLETS (Drug Facts and Comparisons, 1996)

The following parameters of the formulated ranitidine hydrochloride floating tablets were studied.

Hardness and friability

Tablet requires a certain amount of strength as hardness and resistance to friability to withstand mechanical shock of handling in manufacturing, packaging and shipping. There exists a direct relationship between hardness and dissolution studies.

Hardness

Hardness is defined as the force required breaking a tablet in diametric compression test. Hardness is hence termed as tablet crushing strength. Devices which are used to test hardness are Monsanto tester, strong cob tester, Pfizer tester etc.

Friability

The laboratory friability tester is known as Roche friabilator. This consists of a device which subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm, dropping the tablet a distance of six inches with each revolution. Normally, a pre weighed tablet sample is placed in the friabilator which is then operated for 100 revolution conventional compressed tablet that loss less than 0.5 to 1.0% of the weight are generally acceptable. Most of the effervescent tablet undergo high friability weigh loses which accounts for the special stack packaging that may be required for these types of tablets.

Weight variation (Hixson AW *et al*., 1931)

With a tablet designed to contain a specific amount of drug in a specific amount of formula, the weight of the tablet being made is routinely measured to help ensure that a tablet contain the proper amount of drug. In practice samples of tablets (usually 10) are taken and weighed throughout the compression process. The composite weight divided by 10, however provides an average weight but contain a problem of average value. To help alleviate this problem, the USP provides limit for the permissible variation test by weighing tablets individually, calculating the average weight and comparing the tablet weight to the average, the tablet meet the USP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

***In vitro* buoyancy Studies**

The in *vitro* buoyancy was determined by floating lag time; the tablets were placed in 100ml beaker containing 0.1N HCL. The time required for the tablet to rise to the surface and float was determined as floating lag time.

***In vitro* dissolution Studies**

The release rate of Ranitidine hydrochloride floating tablet was determined using INDIAN PHARMACOPEIA (IP) 96; Dissolution test apparatus (paddle method). The dissolution test was performed using 900mL of 0.1N HCL, at 37± 0.5ºC and 75 rpm. 10ml of the solution was withdrawn from the dissolution apparatus hourly for 10 hours and the sample were replaced with fresh dissolution medium. The sample were filtered through membrane filter and diluted with suitable concentration with 0.1N HCL. Absorbance of this solution was measured at 315 nm using a Shimadzu UV-1601 UV/Vis spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from standard curve. The time for 50% and 80% drug release were calculated (Korsemeyer R *et al*., 1983).

Table 1. FORMULATION OF FDDS USING DIFFERENT RATIOS OF HPMC (Higuchi T *et al*., 1963)

S.NO	INGREDIENTS	FORMULATION		
		1	**2**	**3**
1	Ranitidine Hydrochloride	15gms	15gms	15gms
2	Hydroxy Propyl Methyl Cellulose	6gms	9gms	12gms
3	Sodium bi-carbonate	5gms	5gms	5gms
4	Citric acid	1gms	1gms	1gms
5	Stearic acid	2gms	2gms	2gms

RESULTS

Table 2. EVALUATION OF TABLETS

PARAMETERS	60mg HPMC	90mg HPMC	120mg HPMC
Lag time	10 mins	6-7mins	2mins
Wt. Variation	6.3%	6.2%	6.4%
Hardness	4kg/cm2	4kg/cm2	4kg/cm2
Friability	0.2%	o.1%	0.2%

***IN VITRO* BUOYANCY STUDIES**

Fig 1. In Vitro Buoyancy Study of Ranitidine Floating Tablet Using 60mg HPMC

After 10 Minutes

Fig 2. In Vitro Buoyancy Study of Ranitidine Floating Tablet Using 90mg HPMC

After 6 Minutes

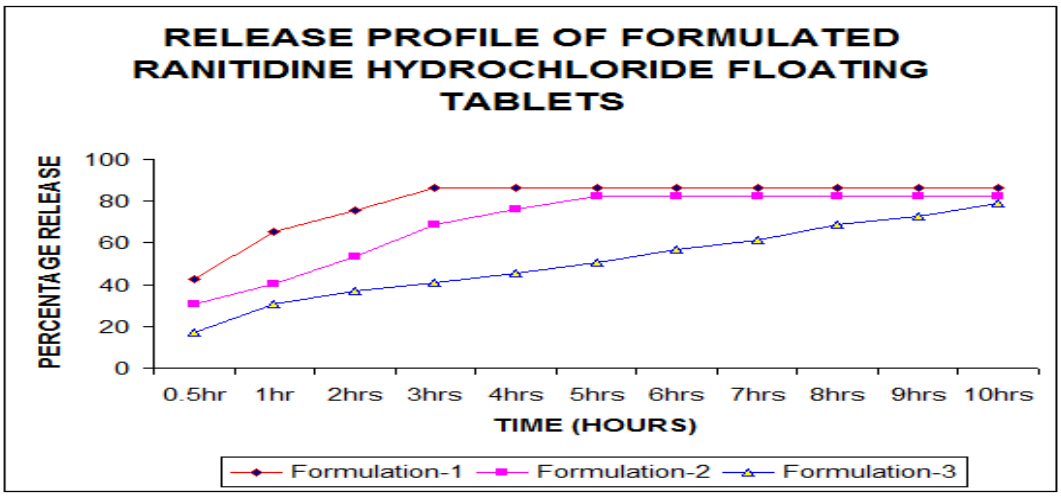
Fig 3. In Vitro Buoyancy Study of Ranitidine Floating Tablet Using 120mg HPMC

After 97 Seconds

Table 3. RELEASE PROFILE OF FORMULATED RANITIDINE HYDROCHLORIDE FLOATING TABLETS

Time in hours	% of Drug release		
	Formulation-1 (60mg HPMC)%	**Formulation-2 (90mg HPMC)%**	**Formulation-3 (120mg HPMC)%**
0.5hr	42.5	30.8	17.2
1hr	65.3	40.3	30.6
2hrs	75.5	53.4	36.9
3hrs	86.5	68.5	40.8
4hrs	86.5	75.9	45.6
5hrs	86.5	82.6	50.4
6hrs	86.5	82.6	57.1
7hrs	86.5	82.6	61.2
8hrs	86.5	82.6	68.8
9hrs	86.5	82.6	72.6
10hrs	86.5	82.6	79.1

Fig 4. RELEASE PROFILE OF FORMULATED RANITIDINE HYDROCHLORIDE FLOATING TABLETS



DISCUSSION

In this gastro-retentive drug delivery system of ranitidine hydrochloride, hydroxy propyl methyl cellulose was used as a polymer, sodium bi-carbonate was incorporated as a gas generating agent. The addition of stearic acid reduces the drug dissolution due to its hydrophobic nature. The amount of citric acid anhydrous and stearic acid were selected as independent variables. The results of the design indicated that a low amount of citric acid and a high amount of stearic acid favours sustained release of ranitidine hydrochloride from a gastroretentive formulation (Lauritsen K *et al*., 1990).

Floating tablets of different formulations showed good in vitro buoyancy. Formulation with HPMC-60 showed a lag time of approximately 10 minutes, formulation with HPMC-90 showed a lag time of approximately 6 to 7 minutes, whereas formulation with HPMC-120 showed a lag time of approximately 2 minutes (table-2). The results of in vitro buoyancy clearly indicates, increase in polymer concentration decrease in lag time. Floating tablets with HPMC-120 showed a better floating time of 2 minutes. The tablet swelled rapidly and axially. The tablet also remained buoyant for 10 hours and floated throughout the entire study (Moore J *et al*., 1996).

The dissolution study for all the three formulations was evaluated. Floating tablets incorporated with HPMC-60 showed a maximum percentage of drug release at (4 hrs) of 86.5%, floating tablets incorporated with HPMC-90 showed a percentage release of 82.6% at (5 hrs) whereas, floating tablets incorporated with HPMC-120 showed a percentage release of 79.1% at 10 hours which is shown in table -3.

In this study, Ranitidine hydrochloride incorporated with 120mg of HPMC was found to be better formulation by considering all the evaluated parameters like lag time, hardness, friability, weight variation and percentage drug release (Peppas NA *et al*., 1985).

CONCLUSION

Floating tablets have plenty of advantages than other conventional tablets. These floating tablet dosage form are stable and provide a sustain release dosage system

(Rosa M *et al*., 1994). The most important application of FDDS is that they provide a new possibility of stomach infected with Helicobacter pylori. The most important criteria which has to be looked into for the production of a floating drug delivery system is that the density of the dosage form must be less than that of the gastric fluid and the dosage form also serves the best in the treatment of diseases related to GIT and for extracting a prolonged action from a drug with a short half life (Singh B *et al*., 2000).

When it is formulated with gel containing hydrocolloids such as HPMC, it swells in fluid with a bulk density less than GIT and then remains buoyant and floats in gastric fluid, affording a prolonged gastric residence time. This floating system is HBS (hydro dynamically balanced system) (Somade S *et al*., 2002) Floating drug delivery system has a controlled release drug profile which has been a major aim of pharmaceutical research and development in the past two decades. The control of GIT transit profiles could be the focus of next two decades and might result in the availability of new product with new therapeutic possibilities and substantial benefits for patients. Soon, (Wagner JG *et al*., 1969) the so-called "once-a-day" formulations may be replaced by novel gastroretentive product with release and absorption phases of approximately 24 hours.

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