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EFFECT OF RANITIDINE HYDROCHLORIDE AS FLOATING DRUG DELIVERY SYSTEM

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Abstract

The objective of this study was to evaluate the effect of formulation variables on the release properties, floating lag time, and hardness, weight variability, compressibility index, hausners ratio, angle of repose and invitro dissolution studies by developing floating tablets of Ranitidine hydrochloride by increasing its bioavailability. Ranitidine is a H2 receptor antagonist having short biological half life (2-3.5 h), absorption in the initial part of the small intestine and 50% absolute bioavailability of drug favour development of sustained release floating formulation. Floating matrix tablets of Ranitidine were developed using different effervescent salts and polymer combinations. The tablets were prepared by direct compression technique, using polymers such as carboxy methyl cellulose (CMC), Carbopol in combination. Sodium bicarbonate, citric acid, stearic acid was incorporated as a gas-generating agent. The effects of citric acid and stearic acid on drug release profile and floating properties were investigated. The addition of stearic acid reduced the drug dissolution due to its hydrophobic nature. The formulation was optimized on the basis of acceptable tablet properties, floating lag time, total duration of floating and *in-vitro* drug release.

Keywords: Ranitidine hydrochloride, Carboxy methylcellulose, Carbopol, Gastric retention, Bioavailability.

Introduction

Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost-effective manufacturing process.[1] Drugs that are easily absorbed from the G.I.T and having a short half-life are eliminated quickly from the blood circulation. To avoid this problem, the oral controlled release formulations has been developed, as these will release the drug slowly into the GIT and maintain a constant level of drug in the blood plasma in spite 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. More than 50% of drug delivery systems available in the market are oral drug delivery systems. These systems have the obvious advantages of case of administration and patient acceptance. The goal of a drug delivery system is to provide a therapeutic amount of drug to the proper site of the body, to achieve promptly and then maintain the desired therapeutic drug concentration that elicits the pharmacological

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action and to minimize the incidence and the severity of unwanted adverse effects. To achieve this goal, it would be advantageous and more convenient to maintain a dosing frequency to once, or at most, a twice-daily regimen. An appropriately designed extended release dosage form can be a major advance in this direction.As most absorption windows are located in the proximal small intestine (duodenum), the most effective strategy to improve drug absorption will be to retain the formulation in the stomach[2].Ranitidine hydrochloride is a histamine H2-receptor antagonist. It is widely prescribed in active duodenal ulcers, gastric ulcers, Zollinger-Ellison syndrome, gastroesophageal reflux disease and erosive esophagitis[3]. The recommended adult oral dosage of ranitidine is 150 mg twice daily or 300 mg once daily. The effective treatment of erosive esophagitis requires administration of 150 mg of ranitidine 4 times a day. A conventional dose of 150 mg can inhibit gastric acid secretion up to 5 hours but not up to 10 hours. An alternative dose of 300mg leads to plasma fluctuations; thus a controlled release dosage form of RHCl is desirable. The short biological half-life of drug (~2.5-3 hours) also favors development of a controlled release formulation. The present investigation concerns the development of the floating matrix tablets, which after oral administration are designed to prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. To provide good floating behavior in the stomach, the density of the device should be less than that of the gastric contents (~1.004 g/cm3).

The objective of the research work is to formulate and evaluate the floating drug delivery system containing ranitidine as a model drug by using polymers (CMC and Carbopol 974P), gas generating agent (sodium bicarbonate), diluent (calcium carbonate), and micro crystalline cellulose. This can be done to achieve better therapeutic success compared to conventional dosage form of the same drug. It has some advantages like

1. Reduced dosing frequency.
2. Better patient compliance and convenience.
3. Less fluctuating plasma drug level.

Materials and methods

Preparation of ranitidine hydrochloride floating tablets

Table No. 01: Tablet Formulations for Preliminary Trials

Ingredients (mg)	F1	F2	F3	F4	F5
Ranitidine Hydrochloride	150	150	150	150	150
CMC	10	20	30	40	50
Carbopol 974P	10	20	30	40	50
Sodium bicarbonate	10	20	30	40	50
Calcium carbonate	10	10	10	10	10
Microcrystalline cellulose	295	260	225	190	155
Citric acid anhydrous	5	10	15	20	25
Talc	5	5	5	5	5
Magnesium stearate	5	5	5	5	5

The five formulations were prepared by direct compression method and evaluated.

Method of preparation

Floating tablets containing Ranitidine hydrochloride 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 weighed and passed through different mesh sieves accordingly prior to the preparation of the dosage form. Then, except Magnesium stearate all other ingredients were blended uniformly in glass mortar

as geometric ratio. After sufficient mixing of drug as well as other components, Magnesium stearate was added, as post lubricant, and further mixed for additional 2-3 min. The tablets were compressed using single punch tablet machine. The weights of the tablets were kept constant for all formulations.

Experimental results

Tablets of Ranitidine (gastro retentive drug delivery systems) were prepared and evaluated to increase its local action and bioavailability. In the present study, five formulations with variable concentration of polymer were prepared and evaluated for physiochemical parameters, *in-vitro* buoyancy studies, *in-vitro* release studies and stability studies.

Preformulation Studies

Preformulation activities range from supporting discovery's identification of new active agents to characterizing physical properties necessary for the design of dosage form. Critical information provided during preformulation can enhance the rapid and successful introduction of new therapeutics entities for humans. Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage form.

Melting Point Determination

Melting point of Ranitidine Hydrochloride was found to be in the range 69-70^{0}c, which complied with BP standards, indicating purity of the drug sample.

Drug-excipient compatibility studies

The proper design and formulation of a dosage form requires consideration of the physical, chemical and biological characteristics of all drug substances and excipients to be used in the fabricating the product. The drug and excipients must be compatible with one another to produce a product that is stable, efficacious, attractive, and easy to administer and safe.

Physical stability of the admixture

The drugs along with the excipients were kept under conditions specified and the results are given in table.

Table No. 02: Drug – Excipient stability profile

S.No	Contents	1 month / control	1 month / 60ºC
1.	RH	No Change	No Change
2.	RH + CMC	No Change	No Change
3.	RH + CARBOPOL 974P	No Change	No Change
4.	RH + CALCIUM CARBONATE	No Change	No Change
5.	RH+SODIUMBICARBONATE	No Change	No Change
6.	RH + MICROCRYSTALLINE CELLULOSE	No Change	No Change
7.	RH + CITRIC ACID	No Change	No Change
8.	RH + Talc	No Change	No Change
9.	RH + Magnesium Stearate	No Change	No Change

RH= Ranitidine Hydrochloride

There was no physical change observed in the admixture after one month at 60 ºC

Pre compression parameters[6]

a) Angle of repose

Table No. 03: Angle of repose, Compressibility Index & Hausner's ratio of powdered Blend

Formulation	Angle of repose(θ)	Hausner's ratio(HR)	Carr's Index(Ic)
F1	29.49±0.22	1.129	0.112
F2	25.32±0.13	1.161	0.139
F3	25.28±009	1.130	0.109
F4	27.82±0.20	1.156	0.125
F5	23.23±0.12	1.181	0.161

b) Bulk density and Tapped density[4]

Table 04: Bulk density and Tapped density of powdered Blend

Formulation	Loose Bulk density (g/cm^3)	TappedBulk density (g/cm^3)
F1	0.560±0.01	0.630±0.02
F2	0.567±0.05	0.658±0.01
F3	0.575±0.05	0.671±0.05
F4	0.581±0.04	0.675±0.06
F5	0.574±0.03	0.679±0.04

Post-compression Parameters

a) Weight Variation Test& drug content uniformity[7,8,9] results

The percentage weight variations for all formulations were tabulated. All the formulated (F1 to F5) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values. The weight of the tablet varied between 496 to 502mg.

Table No. 05: weight variation & drug content uniformity results

Formulation	Weight of the tablet(mg)	Drug content (mg)
F1	498±3.95	149.45±3.99
F2	496±6.89	151.10±7.23
F3	502±1.23	149.93±6.12
F4	497±4.72	149.96±3.17
F5	498±3.23	150.83±1.23

b) Hardness test& Friability Test

The measured hardness of tablets of each batch ranged between 5.99 to 7.90kg/cm2.This ensures good handling characteristics of all batches. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Table No. 06: Hardness test and friability results

Formulation	Hardness (Kg/cm^3)	Friability(%)
F1	5.99±0.12	0.21±0.01
F2	6.63±0.73	0.17±0.02
F3	7.90±0.58	0.26±0.03
F4	5.92 ±0.23	0.91±0.04
F5	6.78±0.24	0.32±0.02

***c) In-vitro* Buoyancy Study**

On immersion in 0.1N HCl solution pH (1.2) at 37^{0}C, the tablets floated, and remained buoyant without disintegration. Table shows the results of Buoyancy study

Table No. 07: Results for Floating lag time and Total floating time

Formulation	Floating lag time (sec)	Total floating time(h)
F1	65.22±2.33	6.63±0.02
F2	61.51±2.15	7.32±0.21
F3	54.62±4.52	8.22±0.02
F4	51.20±2.25	8.93±0.03
F5	46.95±3.52	9.42±0.05

***In-vitro* dissolution studies**[5]

Table No. 08: Comparitive invitro drug release profile of formulations F1 to F5:

S.No	Time (Hours)	Percentage of drug release				
		F1	F2	F3	F4	F5
1	1	7.24	6.91	7.31	7.66	7.91
2	2	16.39	15.66	13.23	12.33	13.13
3	3	24.29	23.71	24.89	26.03	24.76
4	4	31.38	33.42	39.23	40.39	39.12
5	5	39.42	36.66	41.39	46.13	44.29
6	6	48.63	46.98	48.33	50.22	49.77
7	7	55.21	53.21	54.99	56.31	55.32
8	8	63-98	61.77	60.93	62.32	61.33
9	9	72.23	70.29	68.43	70.46	70.01
10	10	79.91	75.12	73.67	76.99	72.99
11	11	86.61	85.23	86.77	89.71	81.38
12	12	93.23	92.19	93.88	96.97	90.63

The drug release rates from formulated floated tablets (F1 to F5) was shown in fig.

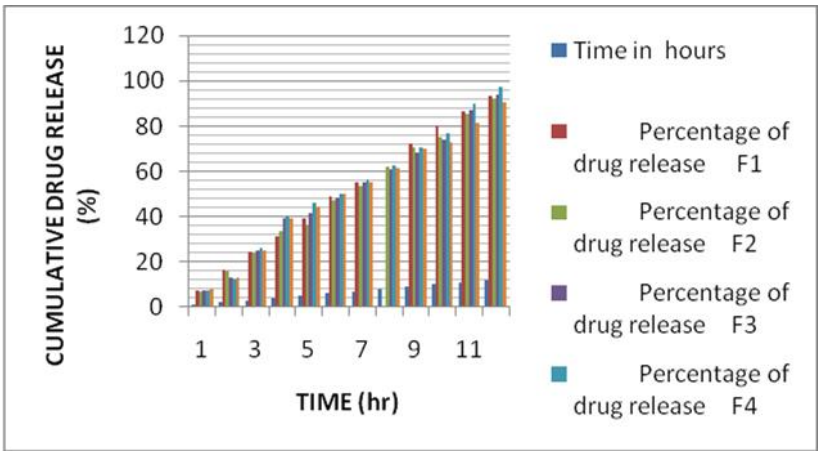

Fig. No. 01: *In-vitro* dissolution profiles of formulated tablets

The drug release from formulated floated tablets (F1 to F5) was found to be 90.63 to 96.97%

Results and discussion

The floating tablets of Ranitidine Hydrochloride were prepared by effervescent technique using Carboxy MethylCellulose, carbopol, sodium bicarbonate, citric acid and calcium carbonate. The magnesium stearate and talc were used as lubricant and glidant respectively.

Preformulation Studies

In the pre-formulation study it was found that the estimation of Ranitidine is carried out by ELICO SL-210 UV-Visible Spectrophotometer at λmax 322nm in 0.1 N HCl had a good reproducibility and this method was used in the study. The results of the drug-excipients compatibility studies revealed that there was no chemical interaction between the pure drug and excipients. The results of the FT-IR Spectrophotometer study show that IR spectrum of pure Ranitidine and optimized are matching with each other. Hence there was no chemical interaction occur in optimized formula.

Evaluation Parameters

Pre compression Parameters

In pre-compression parameter the angle of repose of optimized formula was found to be 23.23 to 29.49^0. Hence it indicates good flow property. The densities of Optimized formula were evaluated and it is Optimum for the formulated tablets.

Post Compression Parameters

The formulated floating tablets showed uniformity in weights. The variation in weight was within the range of ±5% complying with pharmacopeial specifications. The hardness of formulated tablets was more than 5kg/cm^2 indicates satisfactory mechanical strength. The formulated tablets showed uniformity in drug content. All the tablets were prepared by effervescent approach. The combination of sodium bicarbonate and citric acid provided desired floating ability but, additionally calcium carbonate was included to increase the effervescent and it act as antacid. So, this combination was selected for the formulation of the floating tablets. It was observed that the gas generated is trapped and protected within the gel, formed by hydration of polymer (CarboxylMethyl Cellulose and Carbopol 974P), thus decreasing the density of the tablet below one and the tablet becomes buoyant. The tablet swelled radially and axially during *In-vitro* buoyancy studies. All the batches of tablets were found to exhibit short floating lag times due to presence of sodium bicarbonate and citric acid. Decrease in the citric acid level increased the floating lag time and tablets were found to float for longer duration. The pH of the stomach is elevated under fed conditions, therefore citric acid was incorporated in the formulation to provide an acidic medium for sodiumbicarbonate; more over citric acid has an stabilizing effect on Ranitidine Hydrochloride formulation. It is evident from the I*n-vitro* dissolution data that increase in citric acid concentration increased the release rate but reduced the floating time, probably due to of excess carbondioxide, disturbing the monolithic tablet. The prepared formulations sustained the drug release for a period of 8-10 hours. Comparing the two different grades of Carboxymethyl cellulose , it was found that low-viscosity grade Carboxyl Methyl Cellulose provide better-controlled release characteristics with excellent *In-vitro* buoyancy. It was observed that the release of Ranitidine from such formulations increased on decreasing the proportion of Carboxy methyl cellulose in formulation but duration of floating decreased. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release.[10]

Summary

An attempt was made to formulate and evaluate the floating drug delivery system containing Ranitidine Hydrochloride as a model drug. Direct compression method of Ranitidine Hydrochloride tablet containing CMC, carbopol 974P, lactose, MCC and gas generating agent (sodium bicarbonate). Direct compression method was employed to formulate the tablets, because of its cost effectiveness and due to reduce number of manufacturing steps. In the pre-formulation study it was found that the estimation of Ranitidine Hydrochloride is carried out by ELICO SL-210 UV-Visible Spectro - photometer at λmax 322nm in 0.1 N HCl had a good reproducibility and this method was used in the study. In pre-compression parameter the angle of repose of optimized formula was found to be 23.05 to 28.21^0. Hence it indicates good flow property. In post compression parameter, the thickness of tablet indicates that, die fill was uniform. The thickness depends on the size of the punches (12 mm) and the weight of one tablet (504.0 mg). The thickness of trial formula from F1 to F5 was found to be 3 ± 0.5 mm and hardness was found to be 5.62 to 7.81 Kg / cm2. It has good mechanical strength. These formulations are floating with a lag time 1 sec to 5 minutes. The results of the drug-excipients compatibility studies revealed that there was no chemical interaction between the pure drug and excipients. The present investigation the Sodium bicarbonate and calcium carbonate acts as an antacid because sodium bicarbonate interacts with citric acid and produces effervescence and calcium carbonate interacts with gastric fluids it produces effervescence therefore it reduces acid secretion. Finally it acts as dual antacid property.

Conclusion

The effervescent based floating drug delivery system was a promising approach to achieve *In-vitro* buoyancy. The addition of gel-forming polymer Carboxymethyl cellulose and gas-generating agent, Sodium bicarbonate along with citric acid was essential to achieve in vitro buoyancy. Incorporation of Calcium carbonate results in increase in effervescent efficacy additionally it has antacid property. The drug release from the tablets was sufficiently controlled. As a part of an ongoing project on the formulation and evaluation of floating drug delivery system containing Ranitidine Hydrochloride system as a

model drug, different excipients were tested for their compatibility with Ranitidine Hydrochloride such as FT-IR studies which revealed that there is no chemical interaction occurs with other excipients. In the present investigation there are two polymers i.e., hydrophilic polymer CMC and hydrophobic polymer Carbopol 974P. The hydrophilic polymer acts as an enhancing drug release but hydrophobic polymer and microcrystalline cellulose acts as drug release retardant property there by its prolong the duration of action in the stomach as a controlled release formulation.

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