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Research Paper

FLOATING DRUG DELIVERY OF RANITIDINE HYDROCHLORIDE

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The objective of the present investigation was to prepare and evaluate floating drug delivery system^{1,2,4} consisting of ranitidine hydrochloride (RH). Formulation of various concentration and grades were prepared with HPMC K4M, guar gum and xantham gum as sustained release polymers, and *in-vitro* floating profile was studied. As the result non- effervescent floating drug delivery system was achieved by in-vitro buoyancy with polymer HPMC K4 M8,9, but xantham gum, and guar gum did not exhibit sufficient swelling to provide *in vitro* buoyancy. So an effervescent approach was adopted, in which sodium bicarbonate was added as gas generating agent.

Keywords: Radiation emission, Dwelling zone, Ailments, Moody, Blood pressure

INTRODUCTION

Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation (Arora *et al.*, 2005; and Dave *et al.*, 2004). Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation (Korsemeyer *et al.*, 1983; and Martindale, 2002). Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs are required to achieve suitable therapeutic activity.

To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites the gastrointestinal tract (GIT). These drug delivery systems suffer from mainly two adversities: the short gastric retention time (GRT) and unpredictable short gastric emptying time (GET), which can result in incomplete drug release from

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the dosage form in the absorption zone (stomach or upper part of small intestine) leading to diminished efficacy of administered dose. To formulate a site-specific orally administered controlled release dosage form, it is desirable to achieve a prolonged gastric residence time by the drug delivery. Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drug solubility that are less soluble in a high pH environment (Danbrow and Samuelov, 1980; and Miyazaki *et al.*, 2000). Also prolonged gastric retention time (GRT) in the stomach could be advantageous for local action in the upper part of the small intestine e.g. treatment of peptic ulcer (Miyazaki *et al.*, 2003; and Nunamaker *et al.*, 2007) etc.

Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. Over the last few decades, several gastroretentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach, low density (floating) systems that causes buoyancy in gastric fluid, mucoadhesive systems that causes bioadhesion to stomach mucosa, unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach superporous hydrogel systems magnetic systems etc. The current review deals with various gastroretentive approaches that have

recently become leading methodologies in the field of site-specific orally administered controlled release drug delivery systems.

FACTORS CONTROLLING GASTRIC RETENTION OF DOSAGE FORMS

The stomach anatomy and physiology contain parameters to be considered in the development of gastroretentive dosage forms. To pass through the pyloric valve in to the small intestine the particle size should be in the range of 1 to 2 mm. The most important parameters controlling the gastric retention time (GRT) of oral dosage forms include : density, size and shape of the dosage form, food intake and its nature, caloric content and frequency of intake, posture, gender, age, sex, sleep, body mass index, physical activity and diseased states of the individual (e.g., chronic disease, diabetes, etc.) and administration of drugs with impact on gastrointestinal transit time for example drugs acting as anticholinergic agents (e.g., atropine, propantheline), Opiates (e.g., codeine) and prokinetic agents (e.g., metoclopramide, cisapride). The molecular weight and lipophilicity of the drug depending on its ionization state are also important parameters.

Density of Dosage Forms

The density of a dosage form also affects the gastric emptying rate and determines the location of the system in the stomach. Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to bottom of the stomach. Both positions may isolate the dosage system from the pylorus. Density of $<1.0 \text{ gm/cm}^3$ is required to exhibit floating property.

Shape and Size of the Dosage Form

Shape and size of the dosage forms are important in designing indigestible single unit solid dosage forms. The mean gastric residence times of nonfloating dosage forms are highly variable and greatly dependent on their size, which may be large, medium and small units. In most cases, the larger the dosage form the greater will be the gastric retention time (GRT) due to the larger size of the dosage form would not allow this to quickly pass through the pyloric antrum into the intestine. Dosage forms having a diameter of more than 7.5 mm show a better gastric residence time compared with one having 9.9 mm. Ring-shaped and tetrahedron-shaped devices have a better gastric residence time as compared with other shapes. Retention time (GRT) due to the larger size of the dosage form would not allow this to quickly pass through.

Food Intake and Its Nature

Food intake, viscosity and volume of food, caloric value and frequency of feeding have a profound effect on the gastric retention of dosage forms. The presence or absence of food in the gastrointestinal tract (GIT) influences the gastric retention time (GRT) of the dosage form. Usually the presence of food in the gastrointestinal tract (GIT) improves the gastric retention time (GRT) of the dosage form and thus, the drugs absorption increases by allowing its stay at the absorption site for a longer period. Again, increase in acidity and caloric value shows down gastric emptying time (GET), which can improve the gastric retention of dosage forms.

Effect of Gender, Posture and Age

Generally females have slower gastric emptying rates than male. The effect of posture does not

have any significant difference in the mean gastric retention time (GRT) for individuals in upright, ambulatory and supine state. In case of elderly persons, gastric emptying is slowed down (Higuchi, 1963; Indian pharmacopoeia, 1996; and Miyazaki *et al.*, 2000).

Floating Drug Delivery Systems

Floating drug delivery systems is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability. These delivery systems are desirable for drugs with an absorption window in the stomach or in the upper small intestine. This has a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period and the drug is released slowly as a desired rate from the system. After release of drug, the residual system is emptied from the stomach. This result in an increased gastric retention time (GRT) and a better control of the fluctuation in plasma drug concentration. The major requirements for floating drug delivery system are (Paulo and Jose, 2001; and Shabaraya and Narayanacharyulu, 2003):

- It should release contents slowly to serve as a reservoir.
- It must maintain specific gravity lower than gastric contents (1.004-1.01 gm/cm³).
- It must form a cohesive gel barrier.

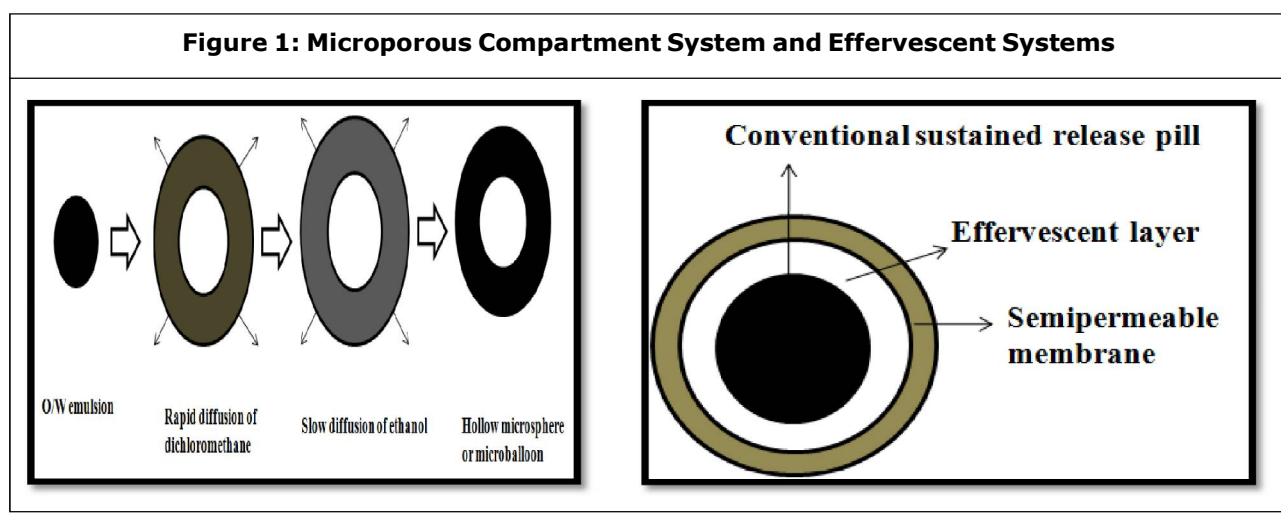
The inherent low density can be provided by the entrapment of air (e.g., hollow chambers) or by the incorporation of low density materials (e.g., fatty materials or oils, or foam powder). These following approaches have been used for the design of floating dosage forms of single and multiple-unit systems. Recently a single-unit floating system was proposed consisting of

polypropylene foam powder. Matrix forming polymers, drug and filler (Sahoo *et al.*, 2007; and Singh and Known, 2000). The good floating behavior of these systems could be successfully combined with accurate control of the resulting drug release patterns. Single-unit dosage forms are associated with problems such as sticking together or being obstructed in the gastrointestinal tract (GIT) which may produce irritation. On the other hand multiple-unit floating systems may be an attractive alternative since they have been shown to reduce the inter- and intra-subject availabilities in drug absorption as well as to lower the possibility of dose dumping. Various multiple-unit floating system like air compartment multiple-unit system, hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method, microparticles based on low density foam powder, beads prepared by emulsion gelatin method etc. can be distributed widely throughout the GIT, providing the possibility of achieving a longer lasting and more reliable release of drugs. Based on the mechanism of buoyancy two distinctly different technologies, i.e., non-effervescent and effervescent systems have been utilized in the development of floating drug delivery system.

Non-Effervescent Systems

Non-effervescent floating drug delivery systems are normally prepared from gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides or matrix forming polymers like polyacrylate, polycarbonate, polystyrene and polymethacrylate. In one approach, intimate mixing of drug with a gel forming hydrocolloid which results in contact with gastric fluid after oral administration and maintain a relative integrity of shape and a bulk density less than unity within the gastric environment. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxypropyl methylcellulose (HPMC) polyacrylates, polyvinyl acetate, carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonate. This system can be further divided into the sub-types.

1. Hydrodynamically balanced systems
2. Microballoons/Hollow microspheres
3. Alginate beads
4. Microporous compartment system (Figure 1)



5. Effervescent systems
6. Bioadhesive or Mucoadhesive drug delivery systems (Figure 2)
7. Expandable, unfoldable and swellable systems (Figure 3)
8. Super porous hydrogel systems and
9. Magnetic Systems

MATERIALS AND METHODS

(Arora *et al.*, 2005; Dave *et al.*, 2004; Santucci *et al.*, 1996; Shilpa *et al.*, 2003; and Whitehead *et al.*, 2004)

Materials

Ranitidine hydrochloride was received as a gift sample from Cadila Pharmaceuticals Ltd, Ahmedabad, India. Hydroxypropyl methylcellulose

Figure 2: Bioadhesive or Mucoadhesive Drug Delivery Systems

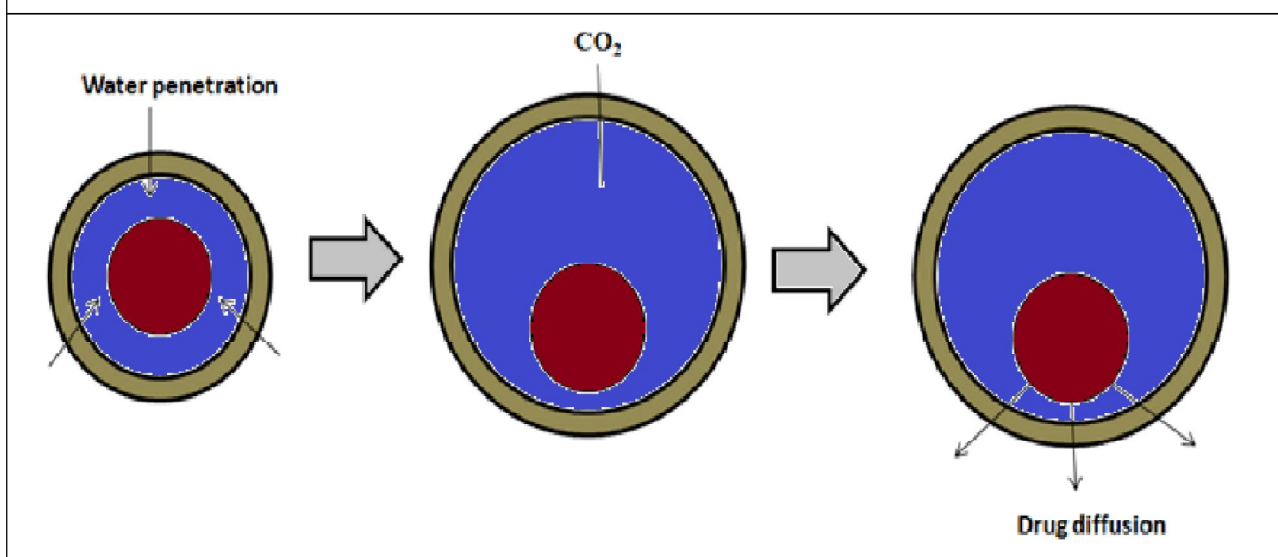
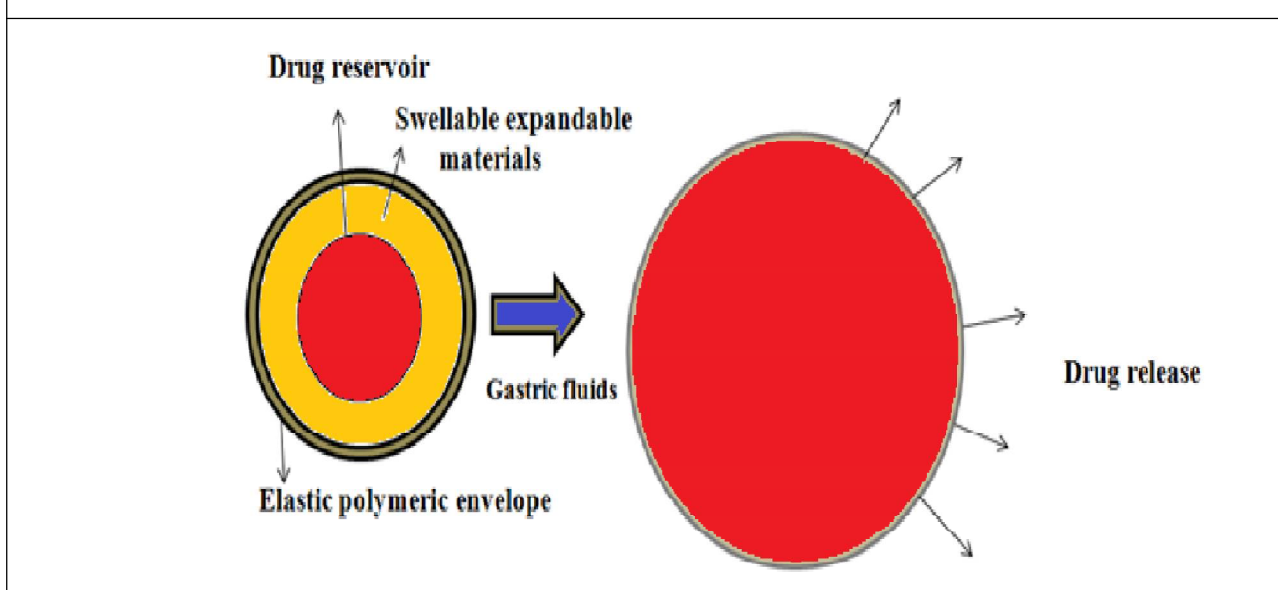


Figure 3: Drug Release From Swellable Systems



(HPMC K4 M), guar gum, and xanthan gum were received as gift samples from Zydus-Cadila Healthcare Ltd, Ahmedabad, India. Sodium bicarbonate, stearic acid, and citric acid anhydrous (hereafter referred to as citric acid) were purchased from SD. Fine-Chem. Ltd., Ahmedabad, India. All other ingredients were of laboratory grades.

Methods (Santucci *et al.*, 1996; Shilpa *et al.*, 2003; Whitehead *et al.*, 2004; and United States Pharmacopoeia, 1999)

Preparation of floating drug delivery system of ranitidine hydrochloride (United States Pharmacopoeia, 1999): Firstly RH was mixed with the required quantities of HPMC K4 M by geometric mixing. Then blended Then RH was dispersed in chloroformic solution of the required quantity of stearic acid. And the with stearic acid and magnesium stearate (1% wt/wt) and purified talc (1% wt/wt). Then a tablet is punched using multistation punching machine. The same procedure was repeated with Guar gum and Xanthum gum (Table 1).

Another set of formulation was prepared using sodium bicarbonate and citric acid for effervescence. For which RH was mixed with the required quantities of Xantham gum sodium bicarbonate, and citric acid dispersion was stirred and chloroform was evaporated to form an RH-citric. This mixture was then blended with other ingredients like lubricants, magnesium stearate

Table 1: Table Showing Various Formulations Prepared

Formulation	Ingredients
A1	RH and Guar gum
A2	Rh and Xantham gum
A3	RH and HPMC K ₄ M

(1% wt/wt) and guar gum (Table 2). This may improves the floating properties of the formulations.

Table 2: Second Set of Formulation

Formulation	Ingredients
F1	RH, guar gum, sodium bicarbonate, citric acid, magnesium stearate and talc.
F2	RH, Xantham gum, sodium bicarbonate, citric acid, magnesium stearate and talc

In-Vitro Studies

Floating Properties

The floating properties of the formulation were done in USP dissolution apparatus (paddle type), with 0.1 N Hcl. The floating time was calculated for each formulation separately.

Drug Release Profile

purified talc (1% wt/wt). The same procedure was repeated with The drug release profile was studied through the dissolution study in U.S.P. dissolution apparatus basket type and the rate of release of drug from the polymer matrix is mathematically calculated. And swelling was also monitored after every hour by measuring the diameter of the tablet.

RESULTS AND DISCUSSION

The RH tablets prepared using polymers such as HPMC K4 M, and then guar gum, and xanthan gum. The xanthan gum and guar gum did not exhibit sufficient swelling to provide *in vitro* buoyancy.

Floating Properties

A1 shows the excellent floating properties. The result was shown in Table 3.

Table 3: Floating Time

Formulation	Floating Time
A1	169 min
A2	35 min.
A3	26 min.
F1	143 min.
F2	138 min.

Drug Release Profile and Swelling Properties

The result of the dissolution studies shows the following result as shown in the Table 4. The drug content, entrapment efficiency and change in the size of the diameter given in the Table 4. In formulation A1 i.e., having HPMC only shows the prominent change in size, the entrapment efficiency and drug content is quite high as compared to other formulations of guar gum and xanthum gum. Adding sodium bicarbonate, citric acid and stearic acid changes the swelling properties only as not much changes is seen in case of drug content and entrapment efficiency.

Table 4: The Results of Dissolution Studies

Formulation	Drug Content (%)	Change in Diameter	Entrapment Efficiency (%)
A1	52.23	+0.8	64.98
A2	12.32	+0.2	35.55
A3	08.91	+0.5	23.90
F1	14.47	+0.7	37.30
F2	18.97	+0.65	22.76

Non-effervescent floating drug delivery was achieved by *in vitro* buoyancy. The RH tablets were prepared using polymers such as HPMC K4 M, and then guar gum, and xanthan gum. The xanthan gum and guar gum did not exhibit sufficient swelling to provide *in vitro* buoyancy. An effervescent approach was then adopted.

Another set of formulation was prepared using guar gum, and xanthan gum. Sodium bicarbonate was added as a gas generating agent. Sodium bicarbonate induced CO₂ generation in the presence of dissolution medium (0.1 N HCl). The gas generated was trapped and protected within the gel, formed by hydration of polymer, thus decreasing the density of the tablet. As the density of the tablet falls below 1, the tablet becomes buoyant. Whitehead *et al.* (2000) have demonstrated good correlation between *in vitro* buoyancy of floating dosage forms.

Three types of formulation were prepared i.e.,

A1, A2 and A3, A1 and A2 containing guar gum and xanthan gum, failed to form a gel with sufficient strength, while A3 with HPMC K4 M produced tablets with good gel strength, imparting stable and persistent buoyancy. To study the effect of sodium bicarbonate concentration on floating lag time, another formulation F1 and F2 was developed. Demonstrates sodium bicarbonate (50 mg per tablet) was essential to achieve optimum *in vitro* buoyancy.

CONCLUSION

The preparation of gastroretentive tablets of Ranitidine hydrochloride was studied and evaluated carefully. The study suggested that the effervescent based floating drug delivery was a promising approach to achieve *in vitro* buoyancy. The addition of gel-forming polymer HPMC K4 M and gas-generating agent sodium bicarbonate was essential to achieve *in vitro* buoyancy. Addition of citric acid, to achieve buoyancy under the elevated pH of the stomach, caused an enhancement in drug release that was retarded by incorporation of stearic acid in the formulation. Thus, by selecting a suitable composition of

release rate enhancer (citric acid) and release rate retardant (stearic acid), the desired dissolution profile can be achieved.

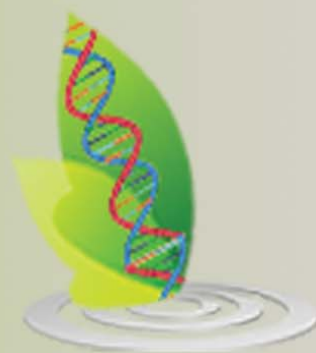
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