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Microballoons: A Novel Gastro-Retentive Drug Delivery System

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Abstract

In recent years scientific and technological advancements have been made in the research and development of controlled release oral drug delivery systems by overcoming physiological adversities like short gastric residence times and unpredictable gastric emptying times. Floating system are the systems which are retained in the stomach for a longer period of time and thereby improve the bioavailability of drugs. For that the novel approach is microballoons which are gastro-retentive drug delivery systems based on non-effervescent approach. These are characteristically free flowing powders consisting of proteins or synthetic polymers. Microballoons are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. Microballoons to improve patient compliance by decreasing dosing frequency, better therapeutic effect of short half-life drugs can be achieved. Gastroretention would also facilitate local drug delivery to the stomach and proximal small intestine. The purpose of this paper is to review the recent literature and current technology used in the development of gastroretentive dosage forms.

Keywords: Gastroretention, swelling system, microballoons, effervescent system, floating dosage form.

Introduction

The oral route is considered as the most promising route of drug delivery. Effective oral drug delivery may depend upon the factors such as gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drugs. Most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit, because of variable gastric emptying leading to non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach. This leads to incomplete absorption of drugs having absorption window especially in the upper part of the small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed. The gastric emptying of dosage forms in humans is affected by several factors because of which wide inter- and intra-subject variations are observed. Since many drugs are well absorbed in the upper part of the gastrointestinal tract, such high variability may lead to non-uniform absorption and makes the bioavailability

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unpredictable. Hence a beneficial delivery system would be one which possesses the ability to control and prolong the gastric emptying time and can deliver drugs in higher concentrations to the absorption site i.e. upper part of the small intestine (Rouge et al. 1996).

Gastric emptying of dosage form is extremely variable process and ability to prolong and control the emptying time is valuable asset for dosage forms, which reside in the stomach for a long period of time than conventional dosage forms. Several difficulties are faced in designing controlled released systems for better absorption and enhanced the bioavailability. Conventional oral dosage forms such as tablets, capsules provide specific drug concentration in systemic circulation without offering any control over drug delivery and also cause great fluctuations in plasma drug levels. Although single unit floating dosage forms have been extensively studied, these single unit dosage forms have the disadvantage of a release all or nothing emptying process while the multiple unit particulate system pass through the GIT to avoid the vagaries of gastric emptying and thus release the drug more uniformly. The uniform distribution of these multiple unit dosage forms along the GIT could result in more reproducible drug absorption and reduced risk of local irritation; this gave birth to oral controlled drug delivery and led to development of Gastro-retentive floating microspheres (Chien 1990, Jain 2002).

Over the last three decades, various attempts have been done to retain the dosage form in the stomach as a way of increasing retention time. *High-density systems* having density of ~3 g/cm^3 are retained in the rogue of the stomach. The only major drawbacks with such systems is that it is technically difficult to manufacture them with a large amount of drug (>50%) and to achieve the required density of 2.4–2.8 g/cm^3. *Swelling systems* are capable of swelling to a size that prevents their passage through the pylorus; as a result, the dosage form is retained in the stomach for a longer period of time. Upon coming in contact with gastric fluid, the polymer imbibes water and swell. *Bio/mucoadhesive systems* bind to the gastric epithelial cell surface, or mucin, and extend the GRT by increasing the intimacy and duration of contact between the dosage form and the biological membrane. The epithelial adhesive properties of mucin have been applied in the development of Gastro retentive drug delivery systems. *Floating systems* first described by Davis (1968), are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation in plasma drug concentration.

The identification of new diseases and the resistance shown towards the existing drugs called for the introduction of new therapeutic molecules. In response, a large number of chemical entities have been introduced, of which some have absorption all over the gastrointestinal tract (GIT), some have absorption windows (i.e. absorption sites, especially the upper part of the small intestine) and some drugs have poor solubility in intestinal media. The drugs belonging to the second and third categories, and the drugs which are required for local action in the stomach, require a specialized delivery system. All the above requirements can be met and effective delivery of the drugs to the absorption window, for local action and for the treatment of gastric disorders such as gastro-esophageal reflux, can be achieved by floating drug delivery systems (FDDS). Various approaches have been worked out to improve the retention of oral dosage form in the stomach, e.g. floating systems, swelling and expanding systems, bioadhesive systems, and high density systems (Arora et al. 2005).

One such approach is Floating Microspheres (Hollow Microspheres). Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Hollow microspheres are in strict sense, spherical empty particles without core. These microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 micrometer. Gastro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. The drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration. Floating microspheres to improve patient compliance by decreasing dosing frequency, better therapeutic effect of short half-life drugs can be achieved. Enhanced absorption of drugs which solubilise only in stomach, Gastric retention time is increased because of buoyancy (Vyas and Khar 2002). Floating microspheres are prepared by emulsion solvent diffusion and evaporation methods to create the hollow inner core. Floating microspheres are characterized by their micromeritic properties such as particle size, tapped density, compressibility index, true density and flow properties including angle of repose, scanning electron microscopy, in vitro floatability studies, in vivo floatability studies in dogs, in vitro drug release studies and stability studies etc.

The current review deals with the novel gastro-retentive approaches that have recently become leading methodologies in the field of controlled and site specific drug delivery system.

Suitable Drug Candidates for FDDS

For the floating system the drug candidates should have the appropriate properties like poor absorption in colonic region but are characterized by better absorption in the upper part of GI tract.

So, the ideal drug candidates should have the following criteria:

- Primarily absorbed from stomach and upper part of GI tract, e.g., calcium supplement, cinnarazine.
- Narrow absorption window in GI tract, e.g., riboflavin and levodopa.
- Drugs that degrade in the colon, e.g., ranitdine HCL, metronidazole.
- Drugs that act locally in the stomach, e.g., antacids and misoprostol.
- Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate.
- Drugs are locally active in the stomach, e.g., drugs used in the eradication of *helicobacter pylori,* which is now believed to be the causative bacterium for chronic gastritis and peptic ulcer (tetracycline).
- Drugs have low solubility at high pH values, e.g., Verapamil.

Factors Controlling Gastro-Retention of Dosage Forms

The gastric retention time (GRT) of dosage forms is controlled by several factors such as density and size of dosage form, food intake, nature of the food, posture ,age, sex , GI diseases states (Diabetes), concomitant administration of food and drugs such as prokinetic agents (cisapride and metoclopropamide), anti-cholinergic agent (Atropine) and opiates (Codeine).

i. Density of Dosage form

Dosage forms having a density lower than that of gastric fluid experience floating behavior and hence gastric retention. A density of <1.0 gm/cm^3 is required to exhibit floating property. However, the floating tendency of the dosage form usually decreases as a function of time, as the dosage form gets immersed into the fluid, as a result of the development of hydrodynamic equilibrium.

ii. Size of Dosage form

The size of the dosage form is another factor that influences gastric retention. The mean gastric residence times of non-floating dosage forms are highly variable and greatly dependent on their size, which may be small, medium, and large units. In fed conditions, the smaller units get emptied from the stomach during the digestive phase and the larger units during the housekeeping waves. In most cases, the larger the size of the dosage form, the greater will be the gastric retention time because the larger size would not allow the dosage form to quickly pass through the pyloric antrum into the intestine. Thus the size of the dosage form appears to be an important factor affecting gastric retention (El-Kamel et al. 2001).

iii. Food intake and nature of food

Food intakes, the nature of the food, caloric content, and frequency of feeding have a profound effect on the gastric retention of dosage forms. The presence or absence of food in the stomach influences the GRT of the dosage form. Usually, the presence of food increases the GRT of the dosage form and increases drug absorption by allowing it to stay at the absorption site for a longer time. In a gamma scintigraphic study of a bilayer floating capsule of misoprostol, the mean gastric residence time was 199 ± 69 minutes; after a light breakfast, a remarkable enhancement of average GRT to 618 ± 208 minutes was observed. The above results are supported by the experiments of Whitehead et al which show an increase in the relative heights of the floating units after meal consumption (Whitehead et al. 1998).

iv. Effect of gender, posture and age

A study by Mojaverian et al. (1988) found that females showed comparatively shorter mean ambulatory GRT than males, and the gastric emptying in women was slower than in men. The authors also studied the effect of posture on GRT, and found no significant difference in the mean GRT for individuals in upright, ambulatory and supine state. On the other hand, in a comparative study in humans by Gansbeke (Gansbeke et al. 1991) the floating and non-floating systems behaved differently. In the upright position, the floating systems floated to the top of the gastric contents and remained for a longer time, showing prolonged GRT. But the non-floating units settled to the lower part of the stomach and underwent faster emptying as a result of peristaltic contractions, and the floating units remained away from the pylorus. However, in supine position, the floating units are emptied faster than non-floating units of similar size (Timmermans et al. 1994).

Approaches to Gastro-Retention

Over the last three decades, various approaches have been pursued to increase the retention of an oral dosage form in the stomach as a way of increasing retention time. Following are the some approaches to gastro-retention:

a) Floating Systems

Floating systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation in plasma drug concentration (Chawla et al. 2001).

b) Bio/Mucoadhesive Systems:

The term bioadhesion describe materials that bind to the biological substrates, such as mucosal membranes. Adhesion of bioadhesive drug delivery devices to the mucosal tissue offers the possibility of creating an intimate and prolonged contact at the site of administration. This prolonged residence time can result in the enhanced absorption and in combination with a controlled release of drug also improved patient compliance by reducing the frequency of administration. The epithelial adhesive properties of mucin have been applied in the development of gastro retentive drug delivery systems (Vasir et al. 2003).

c) Swelling Systems

These are capable of swelling to a size that prevents their passage through the pylorus; as a result, the dosage form is retained in the stomach for a longer period of time. Upon coming in contact with gastric fluid, the polymer imbibes water and swells (Singh et al. 2000).

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time while the system is floating on the gastric contents. The drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal.

To measure the floating force kinetics, a novel apparatus for determination of resultant weight (RW). The RW apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if RW is on the higher positive side. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations (Timmermans et al. 1990).

$$RW \text{ or } F = F_{buoyancy} - F_{gravity} = (D_f - D_s)\, gV,$$

Where, RW is total vertical force, D_f is fluid density, D_s is object density, V is volume, g is acceleration due to gravity.

Types of Floating Drug Delivery System

FDDS can be divided into two systems:

A. Effervescent systems

B. Non-effervescent systems

A. *Effervescent Systems*

i. "Volatile liquid containing systems"

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflatation of the chamber in the stomach. The device may also consist of a bioerodible plug made up of PVA, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach (Yyas and Khar 2002).

ii. *"Gas-generating Systems"*

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme (Chawla et al. 2003).

These buoyant systems utilize matrices prepared with swellable polymers like methocel, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethyl cellulose. The coating, which is insoluble but permeable, allows permeation of water. Thus, carbon dioxide is released, causing the beads to float in the stomach .Other approaches and materials that have been reported are highly swellable hydrocolloids and light mineral oils, a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating minicapsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with hydroxypropyl methylcellulose (HPMC), and floating systems based on ion exchange resin technology, etc.

B. Non-Effervescent Systems

This type of system, after swallowing, swells unrestrained via imbibition of gastric fluid to an extent that it prevents their exit from the stomach. These systems may be referred to as the 'plug-type systems' since they have a tendency to remain lodged near the pyloric sphincter. One of the formulation methods of such dosage forms involves the mixing of drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms (Hilton et al. 1992).

i. *"Colloidal gel barrier systems"*

Hydrodynamically balance system (HBS) was first design by (Sheth and Tossounian 1975). Such systems contains drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. This system incorporate a high level of one or more gel forming highly swellable cellulose type hydrocolloids e.g. HEC, HPMC, NaCMC, Polysacchacarides and matrix forming polymers such as polycarbophil , polyacrylates and polystyrene, incorporated either in tablets or in capsules. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around the gel surface. The air trapped by

the swollen polymer maintains a density less than unity and confers buoyancy to this dosage forms (Jain 2004).

ii. "Microporous Compartment System"

This technology is based on the encapsulation of drug reservoir inside a microporous compartment with aperture along its top and bottom wall (Harrigan 1977). The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the undissolved drug. In stomach the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the apertures, dissolves the drug, and carries the dissolve drug for continuous transport across the intestine for absorption.

iii. "Hollow microspheres"

Hollow microspheres (microballons), loaded with Diclofenac sodium in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer was poured in to an agitated aqueous solution of PVA that was thermally controlled at 40°.The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed in internal cavity in microspheres of the polymer with drug. The microballons floated continuously over the surface of acidic dissolution media containing surfactant for greater than 12 h *in vitro* (Kawashima et al. 1992).

iv. "Alginate beads"

Multiple unit floating dosage forms have been developed from freeze-dried calcium alginate (Whitehead et al. 1996). Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping a sodium alginate solution in to aqueous solutions of calcium chloride, causing precipitation of calcium alginate. The beads are then separated snap and frozen in liquid nitrogen, and freeze dried at -40° for 24 h, leading to the formation of porous system, which can maintain a floating force over 12 hours.

Advantages of Floating Microspheres

1. Improves patient compliance by decreasing dosing frequency.
2. Site-specific drug delivery to stomach can be achieved.
3. Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration is avoided, a desirable plasma drug concentration is maintained by continuous drug release.
4. Gastric retention time is increased because of buoyancy.
5. Enhanced absorption of drugs which solubilise only in stomach
6. Drug releases in controlled manner for prolonged period.
7. Superior to single unit floating dosage forms as such microspheres releases drug uniformly and there is no risk of dose dumping.
8. Avoidance of gastric irritation, because of sustained release effect.
9. Better therapeutic effect of short half-life drugs can be achieved.

Mechanism of Floating Microspheres

When microspheres come in contact with gastric fluid the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the microspheres. However a minimal gastric content needed to allow proper achievement of buoyancy. Hollow microspheres of acrylic resins, eudragit, polyethylene oxide, and cellulose acetate; polystyrene floatable shells; polycarbonate floating balloons and gelucire floating granules are the recent developments.

Some Polymers and Drugs Recently Used In Formulation of Microballoons

In general, there are several polymers used for the preparations of the floating microspheres to achieve controlled release of drugs in the GI tract.

Following are the some polymers and drugs used for developing floating microspheres:

Table 1. List of polymers and drugs

Sr.No	Polymers	Sr.No	Drugs
1	Ethyl cellulose	1	Tranilast
2	HPMC Grades	2	Pentoxyphylline
3	Methocel	3	Aceclofenac
4	Polyacrylates	4	Famotidine
5	Cellulose acetate	5	Clarithromycin
6	Chitosan	6	Piroxicam
7	Polyvinyl acetate	7	Repaglinide
8	Carbopol	8	Verapamil HCL
9	Alginates	9	Lansoprazole
10	Polycarbonates	10	Acylovir
11	Gelatin	11	Ranitidine HCL
12	Acryclic resins	12	Riboflavin

Methods of Preparation of Floating Microspheres

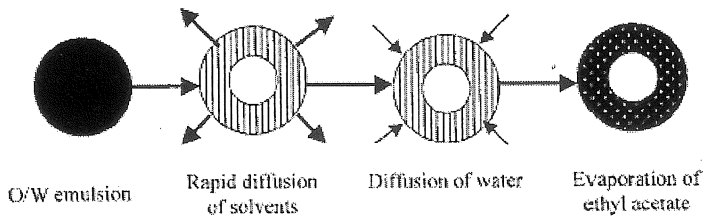

Figure 1. Mechanism of formation of microballoons

Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Hollow microspheres are in strict sense, spherical empty particles without core. These microspheres are characteristically free flowing powders consisting of proteins or

synthetic polymers, ideally having a size less than 200 micrometer. Gastro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. Hollow microspheres are prepared by solvent diffusion and evaporation methods to create the hollow inner core. Polymer is dissolved in an organic solvent like dichloromethane, ethanol or acetone etc., and the drug is either dissolved or dispersed in the polymer solution. The solution containing the drug is then emulsified into an aqueous phase containing polyvinyl alcohol to form oil in water emulsion. After the formation of a stable emulsion, the organic solvent is evaporated either by increasing the temperature under pressure or by continuous stirring using mechanical stirrer with variable speed. Finely developed microspheres were then filtered, washed with water or petroleum ether and dried overnight at 40^0c to produce microspheres. The solvent removal leads to polymer precipitation at the o/w interface of droplets, forming cavity and thus making them hollow to impart the floating properties (Streubel 2006, Kawashima 1992).

Works on Floating Microspheres

Following are the some works on the Floating Microspheres as a Gastro-retentive system:

Kawashima et al. (1991) prepared Hollow Microspheres of tranilast as a floating controlled drug delivery in the stomach by emulsion-solvent diffusion method using Eudragit as an enteric acrylic polymer. The ethanol: dichloromethane solution of drug (tranilast) and an enteric acrylic polymer were poured into an agitated aqueous solution of polyvinyl alcohol that was thermally controlled at 40 ^{0}C. The flowability and packability of the resultant microballoons were much improved compared with the raw crystals of drug. The microballoons floated continuously over the surface of acidic dissolution media containing surfactant for >12 h in vitro. Therefore, it was found that Hollow microspheres were very useful for sustained release pharmacological action.

Lee et al. (1999) developed the floating microspheres of ketoprofen for oral drug delivery by solvent diffusion and evaporation method using acrylic polymer. The different solvents like ethanol, Isopropanol and dichloromethane is used. The effects of various processing parameters for the preparation of acrylic resin microspheres were investigated on the size distribution, yield (recovery rate), loading efficiency, drug release profile and the morphology of the microspheres. Effects of solubility of various drugs on the loading efficiency and dissolution characteristics of the prepared microspheres were also investigated.

Aminabhavi et al. (2001) developed Hollow Microspheres of cardiovascular drugs like nifedipine, nicardapine hydrochloride, Verapamil hydrochloride, and dipyridamole as a floating controlled release system by novel solvent-diffusion method using Cellulose acetate as a polymer. The O/W emulsion prepared in an aqueous solution of poly (vinyl alcohol) medium with ethyl acetate was used as the dispersing solvent. The yield of the microspheres was up to 80%. The microspheres had smooth surfaces, with free-flowing and good packing properties. Scanning electron microscopy (SEM) confirmed their hollow structures, with sizes in the range 489–350 μm. The drug loaded in hollow microspheres was in an amorphous state, as confirmed by differential scanning microscopy (DSC). The release of the drugs was controlled for more than 8 h. The release kinetics followed different transport mechanisms depending on the nature of the drug molecules. Then it shows that the hollow microspheres developed floated for more than 12 h, so we can deliver drugs like nifedipine and nicardapine hydrochloride for a longer time (≥15 h) for effective management of hypertension.

Lee et al. (2001) studied effect of adding non-volatile oil as a core material for floating microspheres prepared by emulsion solvent diffusion method using an acrylic polymer to prolong the gastric residence time. For this study, the effects are investigated of adding non-volatile oil as a core material on the characteristics of acrylic microspheres, such as floating time, morphology, drug loading efficiency, and release profile of the drugs. It was expected that non-volatile oil may improve the floating behavior of the microspheres. Also, it may enhance the absorption rate of cyclosporine A when appropriate vegetable oil is entrapped together. The results were compared with the conventional o/w solvent diffusion and evaporation method used in a previous study. Three kinds of low-density, non-volatile oils, mineral oil (MO), isopropyl myristate (IPM), and Labrafil®1944, were tested.

El-Kamel et al. (2001) prepared floating microparticles of ketoprofen by emulsion solvent diffusion technique. Four different ratios of Eudragit S 100 (ES) with Eudragit RL (ERL) were used. The drug retained in the floating microparticles decreased with increase in ERL content. The formulation containing 1:1 ratio of the above-mentioned polymers exhibited high percentage of floating particles in all the examined media.

Umamaheswari et al. (2002) formulated floating bioadhesive microspheres containing acetohydroxamic acid for the clearance of *helicobacter pylori* infection in GI tract. Floating microspheres containing the antiurease drug acetohydroxamic acid (AHA) were prepared by a novel quasi-emulsion solvent diffusion method. The microballons were coated with 2% w/v solution of polycarbophil by the air suspension coating method. The bioadhesive property of the microspheres was investigated by the detachment force measurement method. *In vitro* growth inhibition studies were performed in isolated *H. pylori* culture. The results suggest that AHA-loaded floating microspheres are superior as potent urease inhibitors whereas urease plays an important role in the colonization of *H. pylori.* Then it indicates that an oral dosage containing floating bioadhesive microspheres may form a useful drug delivery system for the treatment of *H. pylori.*

Sato et al. (2003) prepared microballons (MB) of aspirin, riboflavin, indomethcin by emulsion solvent diffusion method utilizing enteric acrylic polymers co-dissolved with drug in a mixture of dichloromethane and ethanol. The release properties of different drugs exhibiting distinct water solubilities entrapped within microballoons were investigated. Buoyancy of the microballoons decreased with increasing drug release rate.

Zhenqiu et al. (2004) prepared Microspheres with Microballoons Inside for Floating Drug-Delivery Systems. He developed a novel, multiple-unit, floating drug-delivery system of microspheres with microballoons inside from xanthan gum (XG) and gelatin (GA) by a W/O method with theophylline as the model drug, four formulations with different ratios of the two polymers were prepared. The ratio of the two polymers influenced the size distribution, encapsulation efficiency, and drug release appreciably. With increasing amounts of GA, the percentage yield of the floating microspheres and the drug-encapsulation efficiency decreased from 100 and 84.5% to 31 and 56.2%, respectively. The drug-release rate also decreased with increasing GA content, which was attributed to an increase in the crosslinking extent. An initial burst was observed, and after that, the drug was released slowly by a near-zero-order pattern, which was attributed to the low solubility of theophylline and the possible complexes formed by XG and GA in the simulated gastric fluid (pH 1.2). The system had good floating properties and high drug encapsulation efficiency and sustained drug release over several hours after an initial burst. This system could be useful for the delivery of drugs with narrow absorption windows and/or for gastric- site specific delivery.

Sato et al (2004) developed microballons (MB) of Riboflavin as a gastro-retentive drug delivery system by emulsion solvent diffusion method using acrylic polymer and studied Pharmacokinetics of drug in healthy human volunteers using urinary excretion data. The *in vivo* evaluation of the MB was conducted, the buoyancy of the MB correlated closely with the excretion half-life ($t1/2$). In addition, a strong correlation was observed between riboflavin release from the MB and total urinary excretion. So, the buoyancy of MB is an essential factor in terms of the sustained urinary excretion. Factors influencing the buoyancy of MB were the particle size and polymer in the formulation of MB. So, it was found that microballons were very useful for improving drug bioavailability, resulting in more sustained release pharmacological action.

Srivastava et al. (2005) prepared floating microspheres of cimetidine with HPMC and ethyl cellulose using solvent evaporation method. The shape and surface morphology of the microspheres were characterized by optical and scanning electron microscopy. *In vitro* drug release studies were performed and drug release kinetics was evaluated using the linear regression method. Effects of the stirring rate during preparation, polymer concentration, solvent composition and dissolution medium on the size of microspheres and drug release were also observed. The microspheres exhibit prolonged drug release (8 h) and remained buoyant for more than 10 h. *In vitro* studies demonstrated diffusion-controlled drug release from the microspheres.

Jain et al. (2005) designed a controlled release system to increase GRT without contact with gastric mucosa. It was achieved through the preparation of floating microspheres by emulsion solvent diffusion technique consisting of calcium silicate (FLR) as a porous carrier, repaglinide and a Eudragit polymer. The effect of various formulation and process variables were studied. Incorporation of FLR in the microspheres proved to be an effective method to achieve the desired release behavior and buoyancy. The designed system, combining excellent buoyant ability and suitable drug release pattern, could possibly be advantageous in terms of increased bioavailability of repaglinide.

Tayade et al. (2007) prepared multiple units floating drug delivery system of piroxicam using eudragit as a polymer by emulsion solvent diffusion method. Evaluation parameters like DSC and X- ray diffraction studies showed that drug incorporated in the outer shell of the polymer was completely amorphous. The microspheres remained buoyant continuously over the surface of gastric media foe a period of 8-12 h *in vitro.*

Zhao et al. (2008) studied in vitro and in vivo evaluation of Ranitidine HCL containing Hollow microspheres for floating drug delivery system in healthy rabbits. Hollow microspheres containing ranitidine hydrochloride were prepared by using ethyl cellulose (EC) as a polymer dissolved in a mixture of ethanol and ether. The *in vitro* release profiles showed that the drug release rate decreased with increasing viscosity of EC and the diameter of hollow microspheres, while increased with the increase of RH/EC weight ratio. Hollow microspheres could prolong drug release time (approximately 24 h) and float over the simulate gastric fluid for more than 24 h. Pharmacokinetic analysis showed that the bioavailability from RH-hollow microspheres alone was about 3.0-times that of common RH gelatin capsules, and it was about 2.8-times that of the solid microspheres. These results demonstrated that RH hollow microspheres were capable of sustained delivery of the drug for longer period with increased bioavailability.

Barhate et al. (2009) developed multiparticulate gastro retentive drug delivery system of Ketorolac Trometamol. The gastro retentive drug delivery system can be prepared to improve

the absorption and bioavailability of ketorolac Trometamol by retaining the system in to the stomach for prolonged period of time. The floating drug delivery system of kT was prepared by emulsion solvent diffusion method by using ethyl cellulose, HPMC K4M, Eudragit R 100, Eudragit S 100 polymers in varying concentration. Formulations were evaluated for percent yield, particle size, entrapment efficiency, *in vitro* buoyancy and *in vitro* release studies. The optimized formulations show good buoyancy and *in vitro* controlled release of ketorolac Trometamol.

Characterization of Hollow Microspheres

Following are the some characterization parameters for hollow microspheres:

i. Micromeritic properties

Floating microspheres are characterized by their micromeritic properties such as particle size, tapped density, compressibility index, true density and flow properties (Martin 1993) Particle size is measured using an optical microscopy. True density is determined by liquid displacement method; tapped density and compressibility index are calculated by measuring the change in volume using a bulk density apparatus.

$$Tapped\ density = \frac{Mass\ of microspheres}{Volume\ of microspheres\ after\ tapping}$$

The *compressibility index* was calculated using following formula:

$$I = V_b - V_t / V_b \times 100$$

Where, V_b is the bulk volume and V_t is the tapped volume. The value given below 15% indicates a powder with usually give rise to good flow characteristics, whereas above 25% indicate poor flow ability.

The *angle of repose (θ)* of the microsphere, which measures the resistance to particle flow, was determined by the fixed funnel method using following formula:

$$\text{Tan}\ \theta = 2H / D$$

Where, 2H/D is the surface area of the free- standing height of the heap that formed after making the microspheres flow from the glass funnel. The value given below 20^0 indicates excellent flow characteristics, whereas above 40^0 indicates very flow properties.

Particle or microspheres size was determined by placing random sample of dried microspheres on a glass slide with a drop of liquid paraffin, and the size was measured using an optical microscope and mean diameter (MD) was calculated by measuring 200-30 particles with the help of a calibrated ocular micrometer (Martin 1991).

ii. Recovery

Recovery or percentage yield of hollow microspheres containing a drug was determined by the weight ratio of the dried hollow microspheres to the loading amount of drug, polymers and other non- volatile components (Sato et al. 2004).

iii. Surface morphology

The hollow nature and surface morphology of the microspheres was confirmed by scanning electron microscopy (SEM). Also to investigate the internal morphology, hollow microspheres were dissected with a knife (Yu-meng et al. 2008).

iv. Floating Behavior

Fifty milligrams of the floating microspheres were placed in 100 ml of the simulated gastric fluid (SGF- pH 2.0) containing 0.02% w/v Tween 20. The mixture was stirred at 100 rpm with a magnetic stirrer. After 8 h, the layer of buoyant microspheres was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in a desiccator until constant weight was achieved. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles (Jain et al. 2006).

Buoyancy (%) = (weight of floating microspheres / initial wt. of floating microspheres) ×100

v. Incorporation efficiency

For incorporation efficiency, accurately weighed about 50mg dried hollow microspheres and get mechanically busted. These powders were dissolved in suitable solvents by ultrasonication at room temperature and filtered through filter paper. The dissolved drug amount was measured spectrophotometrically with a UV detector. The amount of drug incorporation in the microspheres was calculated by using the following formula-

$$IE = (\text{Calculated drug concentration} / \text{Theoretical drug concentration}) \times 100$$

vi. Identification of crystalline form of the drug in hollow microspheres

The crystalline form of the drug dispersed in the crust of microballooons and in the physical mixture of drug and polymer was analyzed by X-ray powder diffractometry (Sato et al. 2004).

vii. In-Vitro Release Studies

The release rate of floating microspheres was determined in a United States Pharmacopoeia (USP) XXIII basket type dissolution apparatus. A weighed amount of floating microspheres equivalent to 50 mg drug was filled into a hard gelatin capsule (No. 0) and placed in the basket of dissolution rate apparatus. Five hundred milliliters of the SGF containing 0.02% w/v of Tween 20 was used as the dissolution medium. The dissolution fluid was maintained at 37 ± 1° at a rotation speed of 100 rpm. Perfect sink conditions prevailed during the drug release study. 5ml samples were withdrawn at each 30 min interval, passed through a 0.25 μm membrane filter (Millipore), and analyzed using LC/MS/MS or UV method to determine the concentration present in the dissolution medium. The initial volume of the dissolution fluid was maintained by adding 5 ml of fresh dissolution fluid after each withdrawal. All experiments were run in triplicate (Jain et al. 2006).

viii. In-Vivo Studies

The in-vivo floating behavior can be investigated by X-ray photography of hollow microspheres loaded with barium sulphate in the stomach of beagle dogs. The in-vitro drug release studies are performed in a dissolution test apparatus using 0.1N hydrochloric acid as dissolution media. The in-vivo plasma profile can be obtained by performing the study in suitable animal models (e.g. beagle dogs).

ix. Stability study of Hollow microsphere capsule

The acceleration test and long-term test were carried out according to the Technical Standard of Drug Stability Test (Ch. P appendix XIX C). When packaged with market capsule, the microsphere capsules were stored at 40 ± 2^0 C, RH 75% ± 5% for 6 months in case of the accelerate stability examination, and sampled at months 1, 2, 3, and 6. In the long-term test,

the microsphere capsules were preserved at 25 ± 2^0 C, RH 60% ± 10% for 12 months, and sampled at months 0, 3, 6, 9, and 12. The physical properties, floating ratio after 24 h and drug loading amount of all the samples in both experiments were determined according to the methods described above (Jain et al. 2002).

Applications

Following are the some applications of the floating microspheres-

1. The floating microspheres can be used as carriers for drugs with so-called absorption windows, these substances, for example antiviral, antifungal and antibiotic agents (Sulphonamides, Quinolones, Penicillins, Cephalosporins, Aminoglycosides and Tetracyclines) are taken up only from very specific sites of the GI mucosa.
2. Hollow microspheres of non-steroidal anti inflammatory drugs are very effective for controlled release as well as it reduces the major side effect of gastric irritation; for example floating microspheres of Indomethcin are quiet beneficial for rheumatic patients.
3. Floating microspheres are especially effective in delivery of sparingly soluble and insoluble drugs such as Verapamil hydrochloride. The gastro-retentive floating microspheres will alter beneficially the absorption profile of the active agent, thus enhancing its bioavailability.
4. Hollow microspheres can greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentrations at the gastric mucosa, thus eradicating *Helicobacter pylori* from the sub-mucosal tissue of the stomach and making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis (Umamaheswari et al. 2002).

Conclusion

In recent years, scientific and technological advancements have been made in the research and development of rate controlled oral drug delivery systems by overcoming physiological barriers such as short gastric residence time (GRT) and unpredictable gastric emptying time (GET). Currently used approaches utilized in the prolongation of the GRT, including floating drug delivery system (FDDS) also known as hydro dynamically balance systems (HBS), swelling and expanding systems, polymeric bio-adhesive systems, modified shape systems, high density systems, low density systems and other delayed gastric emptying devices. Finally, while the control of drug release profiles has been a major aim of pharmaceutical research and development in the past three decades, the control of GI transit profiles could be the focus of the next two decades and might result in the availability of new products with new therapeutic possibilities and substantial benefits for patients. Soon, the so-called 'once-a-day' formulations may be replaced by novel gastro retentive products with release and absorption phases of approximately 24 hours.

One of such approach is of a new type of multiple-unit, floating drug-delivery system based on microspheres with microballoons for the controlled release of drug in the upper part of GI tract for better absorption and enhanced bioavailability of some drug, prolongation of retention time of the dosage form in the stomach is essential. This problem can be solved by preparation of gastro-retentive drug delivery systems. The system had good floating properties

and high drug-encapsulation efficiency and sustained drug release over several hours after an initial burst. This system could be useful for the delivery of drugs with narrow absorption windows and/or for gastric-specific site delivery.

Therefore, our data concluded that Floating microsphere may be an effective strategy for the development of easy, reproducible and cost effective method to prove its potential for safe and effective oral drug delivery therapy.

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