Review Article

Floating Microspheres: Recent Trends in the Development of Gastroretentive Floating Drug Delivery System

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ABSTRACT: Oral controlled release systems are designed to release the drug in-vivo with prediction so as to increase efficacy, minimize adverse effects and increase bioavailability of drugs. Floating drug delivery systems (FDDSs) are expected to remain buoyant in a lasting way upon the gastric contents. The various buoyant preparations include hollow microspheres, granules, powders, tablets, capsules, pills and laminated films. Floating microspheres are especially gaining attention due to their wide applicability in the targeting of drugs to the stomach. These floating microspheres have the advantage that they remain buoyant and distributed uniformly over the gastric fluid to avoid the vagaries of gastric emptying and release the drug for prolonged periods of time. Multiparticulate low-density particles can successfully prolong the gastric retention time of drugs. This article provides an overview of two important approaches utilized to prepare and improve the performance of floating microspheres.

Introduction

Among the different routes of drug administration, the oral route has achieved the most attention and is quite successful. This can be partly due to the ease of administration as well as the fact gastrointestinal (GI) physiology offers more flexibility in dosage form than most other routes. Oral administration of a medication by means of a controlled drug delivery system should ideally produce the required plasma levels and maintain it at steady levels for a prolonged period of time. The development of oral drug delivery systems for a specific drug involves the optimization of the dosage form and characteristics of GI physiology (Soppimath et al., 2001).

But for oral solid drug delivery systems, drug absorption can be unsatisfactory and highly variable between the individuals despite excellent in-vitro release patterns. The major problem may be the physiological variability such as GI transit in addition to the gastric retention time (GRT), as the latter plays a dominating role in the overall transit of the dosage form. Another problem associated with the performance of the oral controlled release systems is that even though slowed release can be achieved, the drug released after passing the absorption site can’t be fully utilized because the GRT of the delivery system is less than 12 hrs. Therefore it can’t be possible to deliver the drug for more than 12 hrs through the oral route (Soppimath et al., 2001).

This has promoted researchers to retain the drug delivery system in the stomach for prolonged and predictable time. Such a prolonged gastric retention not only controls the time but also the space in the stomach by maintaining the delivery system positioned at a steady site and thereby properly delivering the drug. 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 intestine. Gastric retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

Approaches to gastric retention

Several approaches have been attempted in the preparation of gastroretentive drug delivery systems (Bhowmik et al., 2009). These includes floating systems, swellable and expandable systems, high density systems, bioadhesive systems, altered shape systems, gel forming solution or suspension systems and sachet systems.

Various approaches have been followed to encourage gastric retention of an oral dosage form. Floating systems have low bulk density so that they can float on the gastric juice in the stomach. The floating systems can be based on the following,
Hydrodynamically balanced systems (HBS): It incorporated buoyant materials to enable the device to float.

Effervescent systems: In this system gas generating agents like sodium bicarbonate or other carbonate salts can be used.

Low density systems: These have a density lower than the gastric fluid hence they are buoyant.

Bioadhesive or mucoadhesive systems: These system permits a given drug delivery system (DDS) to be incorporated with bio/mucoadhesive agents, enabling the device to adhere to the stomach walls, thus resisting gastric emptying.

High density systems: Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rugae or folds of the stomach body near the pyloric region. Dense pellets (3 gm/cm³) trapped in rugae also tend to withstand the peristaltic movements of the stomach wall and GI transit time can be extended over 5.8 - 25 hrs, depending on the density and diameter of the pellets. Excipients commonly used in these formulations are barium sulphate, zinc oxide, titanium dioxide and iron powder. These materials increase the density upto 1.5-2.4 gm/cm³.

Large single unit dosage forms: These dosage forms are larger than the pyloric opening and so retained in the stomach. The drawback with these systems is the permanent retention of large single unit systems causes bowel obstruction, intestinal adhesion and gastroplasty.

Co-administration of gastric emptying delaying drugs: The concept of simultaneous administration of a drug to delay gastric emptying along with a therapeutic drug has not yet been encountered because of the questionable factor of benefit to risk ratio associated with these formulations.

Raft systems incorporate alginate gels: These systems have a carbonate component and upon reaction with gastric acid, bubbles form in the gel, enabling floating or raft on gastric fluid.

Floating Drug Delivery Systems

Floating systems have the property of retaining the dosage units in the stomach for prolonged period of time and are useful for enhancing the bioavailability. Recent efforts made to design the floating system are floating drug delivery system (FDDS), swelling and expanding system, bioadhesive systems, modified shape systems, high density systems etc. These systems can be advantageous in improving the GIT absorption of drugs with controlled release due to specific site absorption limitations. These systems are developed with the objective to increase the safety of a product and decrease the side effects of drugs (Yadav et al., 2009). These systems have more flexibility than the conventional dosage forms. There are certain drugs that can benefit from using gastroretentive devices are:

(a) Acting locally in the stomach.
(b) Primarily absorbed in the stomach.
(c) Poorly soluble at an alkaline pH.
(d) Narrow window of absorption.
(e) Degrade in the colon.

These buoyant preparations include microspheres, granules, powders, capsules, tablets, pills and laminated films. Most of the floating systems are generally single unit systems which are unreliable and non-reproducible in prolonging residence time in the stomach when administered orally owing to their fortuitous emptying process. In contrast to that the multiple unit dosage forms (e.g. microspheres) have the advantages that they pass uniformly through the GI tract to avoid the vagaries of gastric emptying and provide adjustable release thereby avoiding the variability in absorption and risk of local irritation. Thus floating microspheres offers more advantages as compared to other conventional and controlled release delivery systems (Jain et al., 2008).

Types of Floating Drug Delivery Systems

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS (Sing et al., 2009), which are:

A. Effervescent system.
B. Non-effervescent system.

A. Effervescent system: Effervescent systems include use of gas generating agents carbonates (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO₂) gas, thus reducing the density of the system and making it float on the gastric fluid. An alternative method can be the incorporation of matrix containing portions of liquid, which produces gas that evaporate at the body temperature.
These effervescent systems can be further classified into two types:

I. Gas generating systems.

II. Volatile liquid/vacuum containing systems.

I. Gas generating systems:

1. Intra gastric single layer floating tablets or hydrodynamically balanced system (HBS): These are formulated by intimately mixing the CO$_2$ generating agents and drug within the matrix tablet. These have a bulk density lower than the gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged time period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to a better gastric residence time (GRT) and better control over fluctuations in plasma drug concentration (Fig. 1).

Ciprofloxacin hydrochloride was developed into a gastroretentive controlled-release drug delivery system with swelling, floating, and adhesive properties. Formulations were prepared using hydroxypropyl methylcellulose (HPMC K15M) and/or sodium alginate (Na alginate) as release-retarding polymer(s) and sodium bicarbonate (NaHCO$_3$) or calcium carbonate (CaCO$_3$) as a gas former. Tablets showed excellent floating properties, extended adhesion periods and sustained drug release characteristics. Abdominal X-ray imaging of formulation loaded with barium sulfate, in six healthy volunteers revealed a mean gastric retention period of $5.50 \pm 0.77$ hrs. (Tadros et al., 2010)

![Fig. 1 Intragastric sigle layer floating tablets](image1)

2. Intragastric bilayer floating tablets: These are also compressed tablets containing two layer as shown in Fig. 2.
   a. Immediate release layer
   b. Sustained release layer.
   
   Bilayer floating tablets of theophylline were formulated using Methocel K100M and Methocel K15M. Sodium bicarbonate and citric acid were incorporated as gas generating agents. Polymer content and amount of floating agent significantly altered the drug release and gastroretention respectively (Khan et al., 2009).

![Fig. 2 Intragastric bilayer floating tablets](image2)

3. Multiple unit type floating pills: These system consists of sustained release pills as ‘seeds’ surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temperature, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. These lower density can be due to the generation and entrapment of CO$_2$ within the system.

A multiple unit floating pill which generates CO$_2$ gas has been developed. The system consists of SR pills surrounded by double layers. The inner layer was an effervescent layer containing both sodium bicarbonate and tartaric acid. The outer layer was a swellable membrane layer. Moreover the effervescent layer was divided into two sublayers to avoid the direct contact between sodium bicarbonate and tartaric acid. Sodium bicarbonate was contained in the inner sublayer and tartaric acid in the outer layer. When the system is immersed in the buffer solution at 37°C, it sank at once in the solution and get swollen like a balloon with gastric retention for more than 12 hrs (Ingani et al., 1987).
FIG. 3 (a) A multi unit oral floating dosage system. (b) Stages of floating mechanism: (A) penetration of water; (B) generation of CO\textsubscript{2} and floating; (C) dissolution of drug.

Key: (a) conventional SR pills; (b) effervescent layer; (c) swellable layer; (d) expanded swellable membrane layer; (e) surface of water in the beaker (37°C).

II. Volatile liquid / vacuum containing system:

1. Intragastric floating gastrointestinal drug delivery system: These system can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microporous compartment as shown Fig. 4.

The intragastric floating drug delivery device comprised of a drug reservoir encapsulated in microporous compartment having pores along its top and bottom surfaces. Peripheral wall of drug reservoir compartment were completely sealed to prevent any physical contact of undissolved drug with the stomach walls. Floatation chamber caused the system to float in the gastric fluid (Harrigan et al., 1977).

2. Inflatable gastrointestinal delivery system: In these systems, an inflatable chamber can be incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be an impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug was continuously released from the reservoir into the gastric fluid. This system is shown in Fig. 5.

A removable inflatable beneficial agent delivery device is adapted to reside in the stomach for a prolonged time period. The device comprises: (1) an inflatable member which in its deflated state can be inserted into the stomach via a naso-gastric tube and which in its inflated state resides comfortably in the stomach but cannot pass through the pyloric sphincter, (2) an inflation tube connected to the inflatable member by which the inflatable member can be inflated from outside the body and which is dropped into the stomach after inflation, and (3) one or more agent-containing cartridges that are carried exteriorly on the inflatable member or the inflation tube and are capable of delivering agent to the gastrointestinal tract over a prolonged time period (Patil et al., 2006).

FIG. 4 Intragastric floating gastrointestinal drug delivery device

3. Intragastric osmotically controlled drug delivery system: It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule disintegrates quickly to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at the body temperature to inflate the bag. The osmotic pressure controlled drug...
delivery device consists of two compartments; the drug reservoir compartment and an osmotically active compartment.

The drug reservoir compartment is enclosed by a pressure responsive collapsible bag which can be impermeable to vapour and liquid has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semipermeable housing.

In the stomach, the water in the GI fluid is continuously absorbed through the semipermeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate the drug release through the delivery orifice.

The floating support can be also made to contain bioerodable plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach. It is shown in Fig. 6.

An osmotically controlled floating system comprised of a hollow deformable unit that was convertible from a collapsed to an expanded position and returnable to a collapsed position after an extended period of time. A housing was attached to the deformable unit and it was internally divided into first and second chamber with the chambers separated by an impermeable, pressure responsive movable bladder. The first chamber contained an active drug, while the second chamber contains volatile liquid such as cyclopentane or ether that vaporizes at physiological temperature to produce a gas, enabling the drug reservoir to float. To enable the unit to exit from stomach the device contained a bioerodable plug that allowed the vapour to exit (Michaels et al., 1975 and Michaels et al., 1974).

B. Non effervescent system: The non effervescent FDDS based on the mechanism of swelling of polymer or bioadhesion to mucosal layer in the GI tract. The most commonly used excipients in non effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming materials such as polycarbonate, polymethacrylate, polyacrylates as well as bioadhesive polymer such as chitosan and carbopol. The various types of these system are:

1. Single layer floating tablets: They are formulated by intimate mixing of drugs with a gel forming hydrocolloid, which swells in contact with gastric fluid and maintain the bulk density of less than a unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

The most commonly used excipients in noneffervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers like polycarbonate, polyacrylate, polymethacrylate and polystyrene. The air entrapped by the swollen polymer confers buoyancy to these dosage forms. When such a dosage form comes in contact with an aqueous medium, the hydrocolloid starts to hydrate by forming a gel, which controls the rate of diffusion of solvent in and drug out of the dosage form. As the exterior surface of the dosage form goes into the solution, the immediately adjacent hydrocolloid layer which is becoming hydrated maintains the gel layer. As a result the drug dissolves in and diffuses out with the diffusing solvent creating a receding within the gel structure (Krogel et al., 1999 and Sheth et al., 1984).

2. Bilayer floating tablets: A bilayer tablet contains two layers, one immediate release layer which releases the initial dose of the drug from the system while the another sustained release layer absorbs gastric fluid forming an impermeable colloidal gel barrier on its surface and maintains a bulk density of less than unity and hence remains buoyant in the stomach.

Bilayer buoyant dosage form consisting of bilayer formulation in which one layer was a drug release layer containing misoprostol and the other a buoyant or floating layer. Each layer included a
hydrocolloid gelling agent such as HPMC, gums, gelatin, polysaccharides which upon contact with gastric fluid form a gelatinous mass sufficient for cohesive binding of the drug release layer and the floating layer. Dosage form remains buoyant in the gastric fluid for a period of about 13 hrs whereby a substantial amount of drug is released in the stomach (Franz et al., 1993).

3. Alginate beads: Multiple unit floating dosage forms are developed from freeze dried calcium alginate. Spherical beads of diameter 2.5 mm (approx) can be prepared by dropping a sodium alginate solution into an aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to the formation of a porous system, which can remain buoyant over 12 hrs. These have a prolonged residence time of more than 5.5 hrs.

The multiple-unit floating dosage form from freeze dried calcium alginate shows spherical beads (approx diameter \(\approx 2.5 \text{ mm}\)) which were prepared by dropping a sodium alginate solution into aqueous calcium chloride. After internal gelation was complete, beads were separated from the solution and snap frozen in liquid nitrogen before being freeze dried at – 40\(^\circ\)C for 24 hrs. The dosage form remains floating over 12 hrs (Whitehead et al., 1996).

4. Hollow microspheres: Hollow microspheres (microballoons), loaded with drug in their outer polymer shells were prepared by the emulsion solvent diffusion technique. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of polyvinylalcohol that was thermally controlled at 40\(^\circ\)C. The gas phase generated in dispersed polymer droplets by evaporation of dichloromethane formed an internal cavity in microsphere of polymer with drug. The microballoons floated continuously over the surface of the acidic dissolution media for more than 12 hrs.

Hollow microspheres with a drug loaded in their outer shells can be prepared by an emulsion solvent diffusion method. The ethanol/ dichloromethane solution of a drug and an enteric acrylic polymer was poured into an aqueous solution of polyvinyl alcohol that was maintained at 40\(^\circ\)C. The latter solution was constantly stirred while adding the former solution to form emulsion droplets. The gas phase generated in the dispersed polymer droplets by the evaporation of dichloromethane formed an internal cavity in the microsphere of the polymer with the drug (Kawashima et al., 1991 and Kawashima et al., 1992). Table 1 and 2 provides a list of drug products prepared with FDDS.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>List of drugs along with flotable drug delivery systems (Singh et al., 2000)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SR. NO.</strong></td>
<td><strong>DOSAGE FORM</strong></td>
</tr>
<tr>
<td>1</td>
<td>Microspheres</td>
</tr>
<tr>
<td>2</td>
<td>Granules</td>
</tr>
<tr>
<td>3</td>
<td>Films</td>
</tr>
<tr>
<td>4</td>
<td>Powders</td>
</tr>
<tr>
<td>5</td>
<td>Capsules</td>
</tr>
<tr>
<td>6</td>
<td>Tablets/pills</td>
</tr>
</tbody>
</table>
Table 2 Marketed products of FDDS (Bhowmik et al., 2009).

<table>
<thead>
<tr>
<th>SR. NO.</th>
<th>BRAND NAME</th>
<th>DRUG (DOSE)</th>
<th>COMPANY COUNTRY</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Modapar®</td>
<td>Levodopa (100 mg), Benserazide (25 mg)</td>
<td>Roche Products, USA</td>
<td>Floating CR capsule</td>
</tr>
<tr>
<td>2.</td>
<td>Valrelease®</td>
<td>Diazepam (15 mg)</td>
<td>Hoffmann-LaRoche, USA</td>
<td>Floating capsule</td>
</tr>
<tr>
<td>3.</td>
<td>Liquid Gavison®</td>
<td>Al hydroxide (95 mg), Mg carbonate (358 mg)</td>
<td>Glaxo Smith Kline, India</td>
<td>Effervescent floating liquid alginate preparation</td>
</tr>
<tr>
<td>4.</td>
<td>Topalkan®</td>
<td>Al-Mg antacid</td>
<td>Pierre Fabre Drug, France</td>
<td>Floating liquid Alginate preparation</td>
</tr>
<tr>
<td>5.</td>
<td>Convirion®</td>
<td>Ferrous sulphate</td>
<td>Ranbaxy, India</td>
<td>Colloidal gel forming FDDS</td>
</tr>
<tr>
<td>6.</td>
<td>Cifran OD®</td>
<td>Ciprofloxacin (1 gm)</td>
<td>Ranbaxy, India</td>
<td>Gas-generating floating tablet</td>
</tr>
<tr>
<td>7.</td>
<td>Cytotec®</td>
<td>Misoprostal (100 mcg/200 mcg)</td>
<td>Pharmacia, USA</td>
<td>Bilayer floating capsule</td>
</tr>
<tr>
<td>8.</td>
<td>Oflin OD®</td>
<td>Ofloxacin (400mg)</td>
<td>Ranbaxy, India</td>
<td>Gas generating floating tablet</td>
</tr>
</tbody>
</table>

Floating microspheres

Gastric emptying is a complex, highly variable and makes the in-vivo performance of the drug delivery system uncertain (Tanwar et al., 2006).

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 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. In order to avoid this variability, efforts have been made to increase the retention time. (Chien et al., 1990 and Cremer., 1997)

Floating system was first described by Davis (1968). These are the 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 gastroretention time and reduces fluctuations in plasma drug concentration (Chawla et al., 2003 and Chickering et al., 1995).

Floation of drug delivery system in the stomach can be achieved by effervescent systems, incorporating a floating chamber filled with vacuum, air or carbon dioxide produced as a result of effervescent reaction between the organic acids and carbonates incorporated. These buoyant systems utilize matrices prepared with swellable polymers (e.g. methocel), polysaccharides (e.g. chitosan), effervescent components containing sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature. Non-effervescent systems incorporate a high level (20-75% w/w) of one or more gel forming, cellulosic hydrocolloids (e.g. hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylecellulose, and sodium carboxymethyl cellulose), polysaccharides, or matrix-forming polymers (e.g., polyacrynot, polyacrylates, polystyrene) into hollow microspheres, tablets or capsules (Garg et al., 2003 and Ichikawa et al., 1991).

Advantages of floating microspheres

Floating microspheres offer several advantages such as (Tanwar et al., 2006):

- Improves patient compliance by decreasing dosing frequency.
- 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.
- Better therapeutic effect of short half-life drugs can be achieved.
- Gastric retention time is increased because of buoyancy.
- Drug releases in a controlled manner for a prolonged period.
- Site-specific drug delivery to the stomach can be achieved.
- Enhanced absorption of drugs which solubilise only in the stomach.
- Superior to single unit floating dosage forms such as microspheres, releases drug uniformly and there is no risk of dose dumping.
Avoidance of gastric irritation, because of sustained release effect, floatability and uniform release of drug through multiparticulate system.

**Development of floating microspheres**

Gastro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in the stomach for a prolonged period (Tanwar et al., 2006). As the system floats over gastric contents, the drug is released slowly at the desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration. 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 is needed to allow proper achievement of buoyancy (Garg et al., 2003 and Ichikawa et al., 1991).

**Hollow Microspheres or Microballoons**

These microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 micrometer. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs (Vyas et al., 2002).

Hollow microspheres of acrylic resins, Eudragit, PMAA, polyethylene oxide, and cellulose acetate; Polystyrene floatable shells; polycarbonate floating balloons and gelucire floating granules are the recent developments. Hollow microspheres are prepared by solvent diffusion and evaporation methods to create the hollow inner core. The polymer is dissolved in an organic solvent 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 (Streubel et al., 2002). The solvent removal leads to polymer precipitation at the o/w interface of droplets, forming a cavity and thus making them hollow to impart the floating properties. The polymers studied for the development of such systems include cellulose acetate, chitosan, eudragit, acrycoat, methocel, polycarbophil, polyvinyl acetate, carbopol, agar, polyethylene oxide and polycarbonates.

**Use of Low-Density Porous Carrier:** (Jain et al., 2008).

Low-density porous carriers have been used for formulation of FDDS. Porous carriers are low-density solids with open or closed pore structure and provide large exposed surface areas for drug loading. Their hydrophobicity varies from completely hydrophilic carriers, which immediately disperse or dissolve in water, to completely hydrophilic ones, which float on water for hours. Due to the wide range of useful properties, porous carriers have been used in pharmaceuticals for many purposes; some of these include development of novel drug delivery systems like floating drug delivery systems, sustained drug delivery systems; improvement of solubility of poorly soluble drugs; enzyme immobilization etc. Examples of pharmaceutically exploited porous carriers include porous silicon dioxide (Sylysia®), polypropylene foam powder (Accurel®), porous calcium silicate (Florite®), magnesium aluminometasilicate (Neusilin®), porous ceramic.

Polypropylene foam powder was used as a porous carrier for the development of verapamil HCl loaded floating microparticles. A highly porous, hydrophobic polypropylene foam powder with open-cell structure and low inherent density was chosen as the carrier material. Microparticles of Eudragit RS, ethyl cellulose or polymethylmethacrylate (PMMA) were prepared using o/w solvent evaporation method. The drug and release-rate-controlling polymer were dissolved in dichloromethane. Polypropylene foam powder was then dispersed within this organic phase. The resulting suspension was subsequently emulsified into an external aqueous poly (vinyl alcohol) solution and agitated with a stirrer to allow microparticle formation. The microparticles were irregular in shape and highly porous. Importantly, the drug encapsulation efficiency was high and good in-vitro floating behavior was observed (Streubel et al., 2003).

Floating microspheres of repaglinide and orlistat were developed using low density calcium silicate (CS) as a porous carrier. Calcium silicate, [2CaO·0.3SiO₂·nSiO₂·nH₂O] which has a characteristically porous structure with many pores and a large pore volume, has been used as an industrial liquid absorber or a
compressive adjuvant of powder. It also has a sustained release property. CS has floating ability due to the air trapped within its pores when they are covered with a polymer. The schematic presentation of CS based floating microspheres is shown in Fig. (8). The porous carrier (CS) was thrown into 10 ml ethanolic solution of repaglinide. This solution was ultrasonicated to imbibe the drug solution inside the pores of porous carrier, while removing the air. The excess ethanolic solution was removed by filtration and dried in vacuum, which produced the drug absorbed porous carrier. The ultrasonication produced drug absorbed CS in a fine state of subdivision. Good in-vitro floating behavior was observed for all of the microsphere formulations. More than 80% of the particles kept floating for at least 10 hrs. This may be attributed to the low trapped density of the microspheres resulted due to entrapment of low density CS within the system. Incorporation of CS in the microspheres proved to be an effective method to achieve the desired release behavior and buoyancy. It was found that a saturated solution of polymer produced smooth and high yield of microspheres. The undissolved polymer produced irregular and rod shaped particles. The ratio of dichloromethane with ethanol also affected the morphology of the microspheres and the best result with a spherical shape was obtained when the ratio of ethanol to dichloromethane was 2:1. It is obvious that the rotation speed of the propeller affected the yield and size distribution of microspheres. As the rotation speed of the propeller increased from 250 to 1000 rpm, the average particle size decreased, while maintaining its morphology. The optimum rotation speed for experimental system was 500 rpm (Jain et al., 2002).

In-vivo investigations of CS based floating microspheres of repaglinide were done. The gamma scintigraphy of the formulations was carried out in rabbits (NewZealands) to monitor the transit in the GI tract. The gastro-retentive behavior of the optimized formulation was compared with non-floating microspheres prepared from the identical polymer. Prolonged GRT of over 6 hr was achieved in all animals for CS based floating microspheres of repaglinide. The drug loaded optimized formulation was orally administered to rabbits and blood samples were used to determine pharmacokinetic parameters of repaglinide from floating microspheres, which were compared with pharmacokinetic parameters of the marketed tablet formulation (Rapilin). The relative bioavailability of repaglinide loaded floating microspheres was found to be increased about 3.17 times in comparison to that of the marketed tablet (Jain et al., 2002).

<table>
<thead>
<tr>
<th>Sl.No</th>
<th>Approach utilized</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Hollow microspheres</td>
<td>Tranilast, Aspirin, Salicylic acid, Ethoxybenzamide, Indomethacin and Riboflavin, Cimetidine, Riboflavin, Piroxicam, Ketoprofen, Cholestyramine, Aspirin, Griseofulvin and p-Nitroaniline, Nifedipine, Nicardapine HCl, Verapamil HCl and Dipyridamole, Ketoprofen, Cinnamic acid and Terfenadine, Theophylline, Ibuprofen, Ketoprofen, Tenoxicam, Piroxicam and Acetohydroxamic acid, Lansoprazole</td>
</tr>
<tr>
<td>2.</td>
<td>Use of porous carrier</td>
<td>Verapamil HCl, Chlorpheniramine maleate, diltiazem HCl, theophylline and verapamil HCl, Repaglinide, Orlistat.</td>
</tr>
</tbody>
</table>

**Characterization of Floating Microspheres**

Floating microspheres can be characterized by their micromeritic properties such as particle size, tapped density, compressibility index, true density and flow properties including angle of repose. The particle size can be determined by optical microscopy; true density can be determined by liquid displacement method; tapped density and compressibility index are calculated by measuring the change in volume using a bulk density apparatus; angle of repose can be determined by fixed funnel method. The hollow nature of microspheres can be confirmed by scanning electron microscopy (Streubel et al., 2003).
Floating behavior of hollow microspheres can be studied in a dissolution test apparatus by spreading the microspheres on a simulated gastric fluid (pH 1.2) containing tween 80 as a surfactant; the media is stirred and a temperature of 37°C is maintained throughout the study. After specific intervals of time, both the fractions of the microspheres floating and settled can be collected; the buoyancy of the floating microspheres can be calculated using the data. (Tanwar et al., 2006)

Applications of Floating Microspheres

Floating microspheres are especially effective in delivery of sparingly soluble and insoluble drugs (Tanwar et al., 2006). It is known that as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption. For weakly basic drugs that are poorly soluble at an alkaline pH, hollow microspheres may avoid the chance for solubility to become the rate-limiting step in release by restricting such drugs to the stomach. The positioned gastric release is useful for drugs efficiently absorbed through stomach such as verapamil hydrochloride. The gastro-retentive floating microspheres will alter beneficially the absorption profile of the active agent, thus enhancing its bioavailability. Drugs that have poor bioavailability because of their limited absorption to the upper gastrointestinal tract can also be delivered efficiently thereby maximizing their absorption and improving the bioavailability.

Floating 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 submucosal tissue of the stomach and making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis. The development of such systems allows administration of non-systemic, controlled release antacid formulations containing calcium carbonate and also locally acting anti-ulcer drugs in the stomach; e.g. lansoprazole. Buoyant microspheres are considered as a beneficial strategy for the treatment of gastric and duodenal cancers. The floating microspheres can be used as carriers for drugs with narrow 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. In addition, by continually supplying the drug to its most efficient site of absorption, the dosage forms may allow for more effective oral use of peptide and protein drugs such as calcitonin, erythropoietin, vasopressin, insulin, low-molecular-weight heparin, and LHRH.

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 Indomethacin are quiet beneficial for rheumatic patients. The drugs recently reported to be entrapped in hollow microspheres include aspirin, griseofulvin, ibuprofen, terfenadine, diclofenac sodium, indomethacin, prednisolone, lansoprazole, celecoxib, piroxicam, theophylline, diltiazem hydrochloride, verapamil hydrochloride and riboflavin.

Conclusion

Gastro retentive floating microspheres have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs. The increasing sophistication of delivery technology will ensure the development of increasing number of gastro-retentive drug delivery systems to optimize the delivery of molecules that exhibit absorption window, low bioavailability, and extensive first pass metabolism. The control of gastrointestinal transit could be the focus of the next decade and may result in new therapeutic possibilities with substantial benefits for patients.

References


