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Research Article

Gastroretentive Microspheres: An Innovative Approach for Prolonging Gastric Residence

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ABSTRACT

Gastro-retentive drug delivery systems (GRDDS) like gastro-retentive microspheres have gained immense popularity in the field of oral drug delivery. It is a widely employed approach to retain the dosage form in the stomach for an extended period of time and release the drug slowly that can address many challenges associated with conventional oral delivery, including poor bioavailability. Different innovative approaches like magnetic field assisted gastro-retention, swelling systems, mucoadhesion techniques, floating systems with or without effervescence are being applied to fabricate gastro-retentive microspheres. Apart from *in-vitro* characterization, successful gastro-retentive microspheres development demands well designed *in-vivo* study to establish enhanced gastro-retention and prolonged drug release. Gama scintigraphy and MRI are popular techniques to evaluate *in-vivo* gastric residence time. However, checking of their overall *in-vivo* efficacy still remains a major challenge for this kind of dosage form, especially in small animals like mice or rat. Reported *in-vivo* studies with beagle dogs, rabbits, and human subjects are only a handful in spite of a large number of encouraging *in-vitro* results. In spite of the many advantages, high subject variations in gastrointestinal physiological condition, effect of food, and variable rate of gastric emptying time are the challenges that limit the availability of gastro-retentive microspheres in the market.

Keywords: Gastro- retentive, Floating systems, Mucoadhesion, Effervesence, Microspheres.

INTRODUCTION

Oral administration is the most convenient and preferred means of any drug delivery to the systemic circulation. 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. 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 is required to achieve suitable therapeutic activity[1]. 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 in 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 the dosage form in the absorption zone (stomach or upper part of small intestine) leading to diminished efficacy of administered dose[2]. Sustained-controlled release formulations can be of two types i.e. single unit type like tablets or multi unit type like microspheres or microcapsules.

Advantages of Microspheres or Microcapsules over Single Unit Dosage Forms[3-9]

Microspheres spread out more uniformly in the GIT, thus avoiding exposure of the mucosa locally to high concentration of drug.

Microspheres ensure more reproducible drug absorption.

The risk of dose dumping also seems to be considerably lower than single unit dosage form.

Microspheres allow the administration of much smaller doses than are normally required. This reduces local irritation when compared to single unit dosage forms.

Drug discharge in the stomach may be hindered and local unwanted effects may be reduced or eliminated.

Microspheres posses many other advantages such as high bioavailability, rapid kinetic of absorption and improvement of patient compliance.

Microspheres received much attention not only for prolonged release, but also for targeting of drugs.

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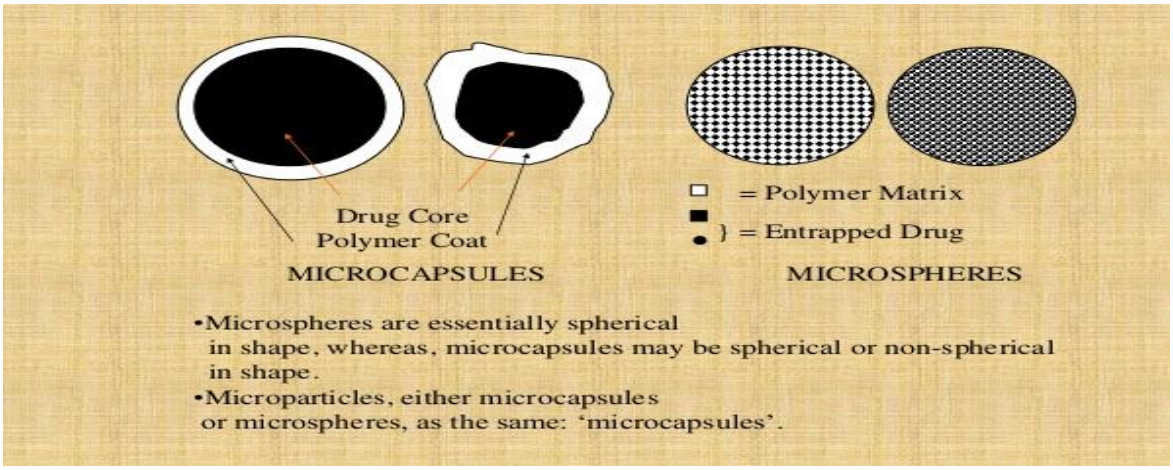

Figure 1: Representation of microcapsules and microspheres.

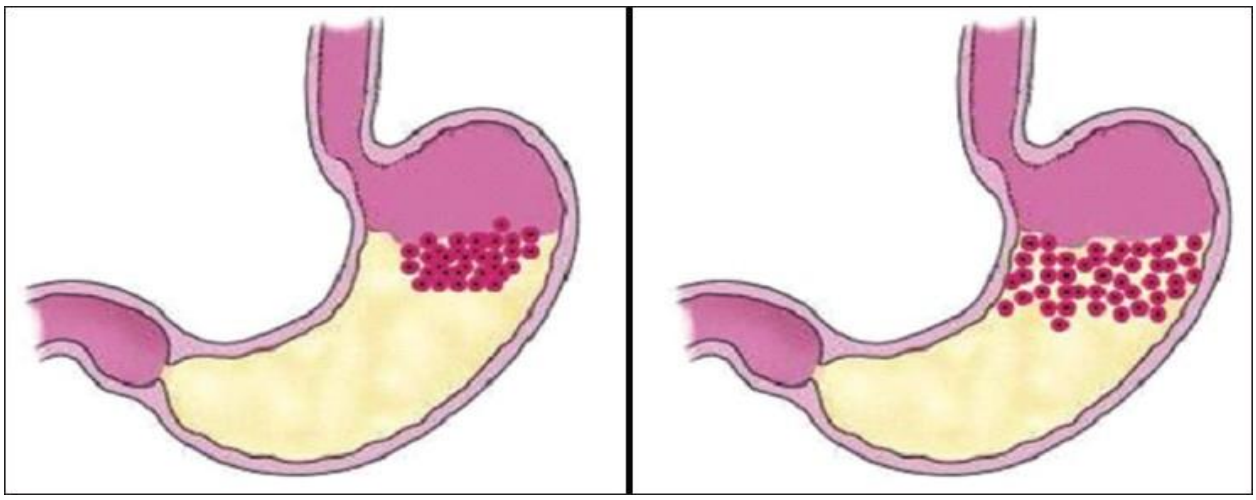

Figure 2: Diagrammatic representation of gastro-retentive floating microspheres.

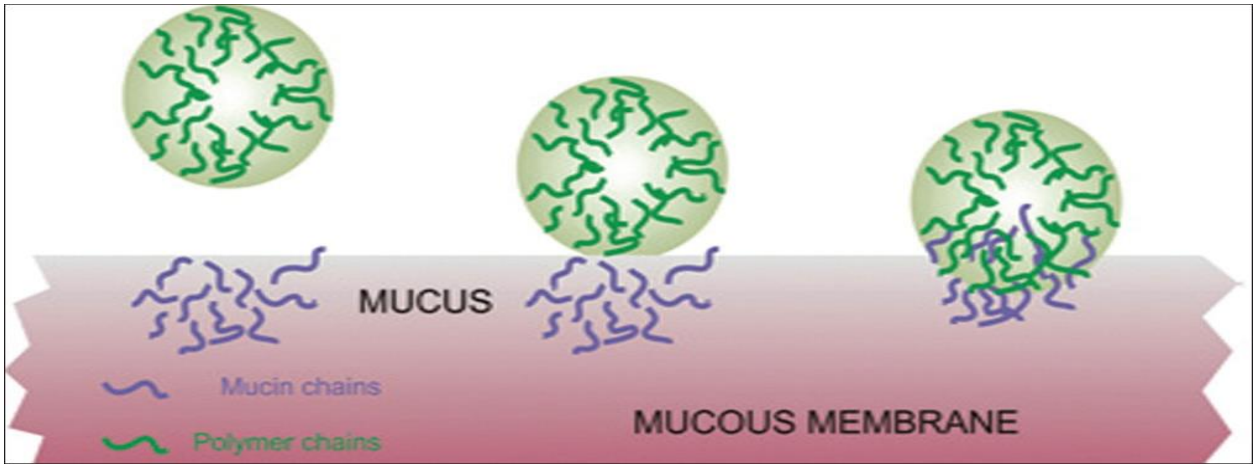

Figure 3: Schematic representation of microspheres attaching to the mucous membrane and releasing the drug.

Gastric Retention through Microencapsulation[4, 10]

Sucessesful gastric retention is possible when the microspheres must obey following requirements.

They must be able to withstand the forces caused by peristaltic waves in the stomach and the constant contractions and grinding and churning mechanisms.

To function as a gastric retention device, they must resist premature gastric emptying.

If their purpose has been served, the microspheres should be removed from the stomach with ease.

Advantages of gastro retentive microspheres[11-14]

Reduced frequency of dosing with improved patient compliance for drugs with relatively short half life.

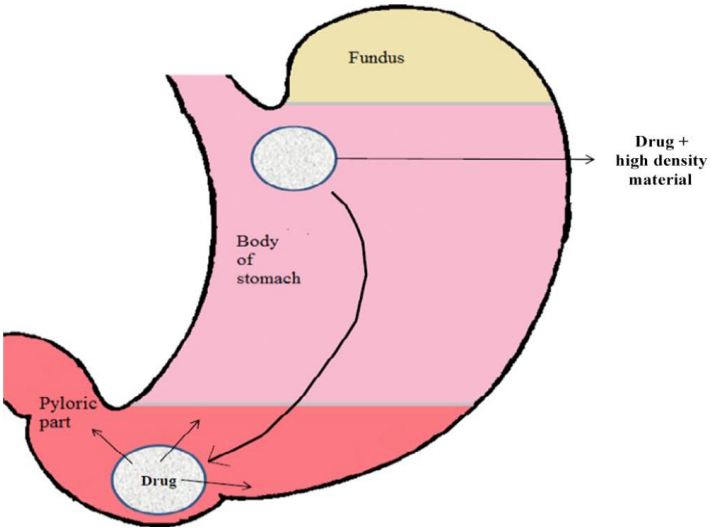

Figure 4: Gastro-retentive drug delivery system based on high density.

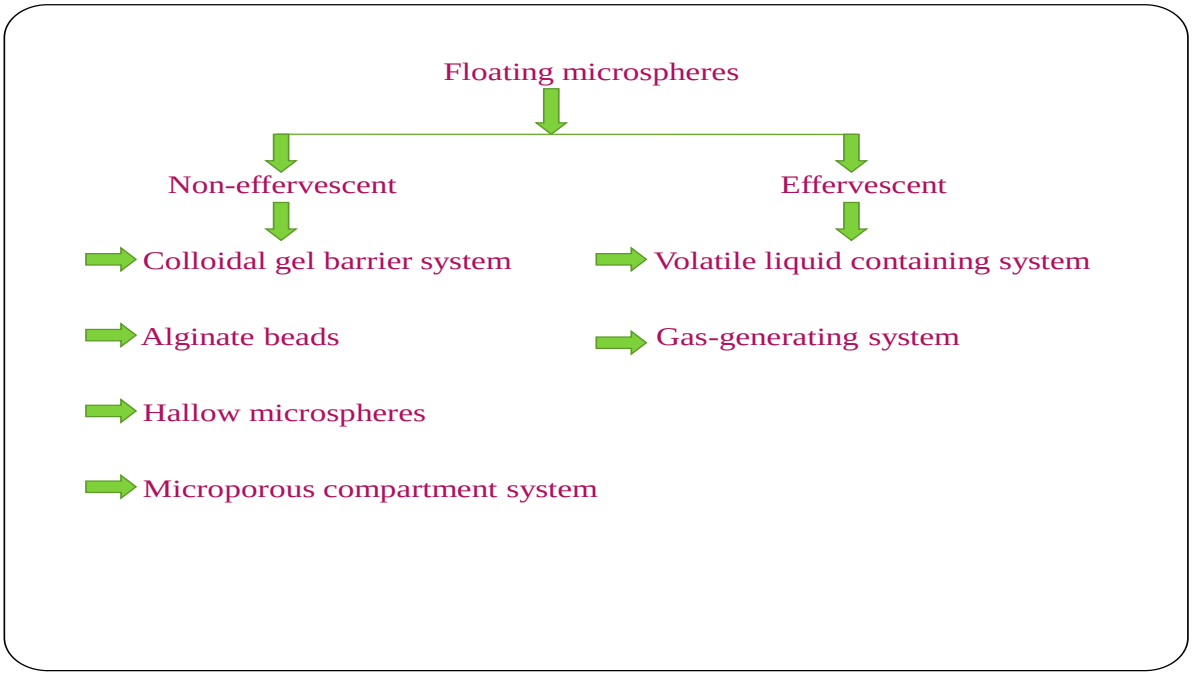

Figure 5: Types of floating microspheres.

Buoyancy increases gastric residence time. Better therapeutic effect of short half life drugs. There is increase in bioavailability of drugs. They also have an advantage over the conventional system as they can be used to overcome the adversities of the gastric retention time as well as the gastric emptying time. Gastric irritation can be avoided by designing sustained release. Gastro-retentive microspheres minimize the fluctuation of drug concentrations and effects. By using this drug delivery we can prolong and sustain release of drugs from dosage. This site-specific drug delivery reduces undesirable effects of side effects. No risk of dose dumping by making single unit floating unit such as microspheres releases drug uniformly.

Microencapsulation[15-17]

It is the process by which individual particles or droplets of solid or liquid material (the core) are surrounded or coated with a continuous film of polymeric material (the shell) to produce capsules in the micrometer to millimeter range, known as microcapsules. Microencapsulation results in microspheres and microcapsules.

Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 µm to 1000 µm). These are characteristically free flowing powders can be manufactured from various natural and synthetic materials which are biodegradable in nature. Microspheres received much attention not only for prolonged release, but also for targeting of drugs. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective in vivo delivery and supplements as miniature versions of diseased organ and tissues in the body.

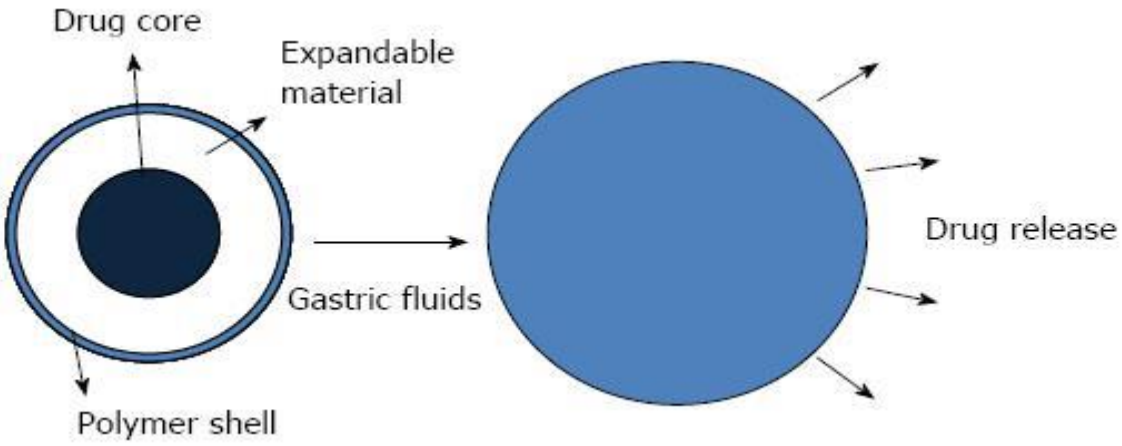

Figure 6: Representation of drug release from microspheres.

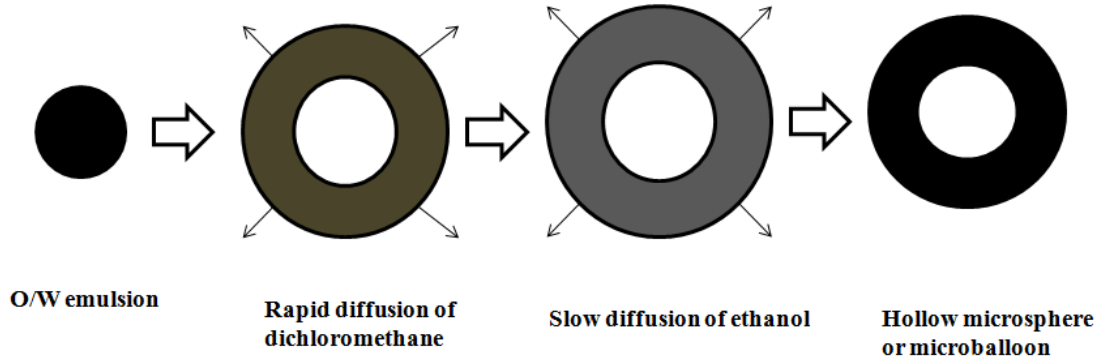

Figure 7: Formulation of floating hollow microsphere or microballoon.

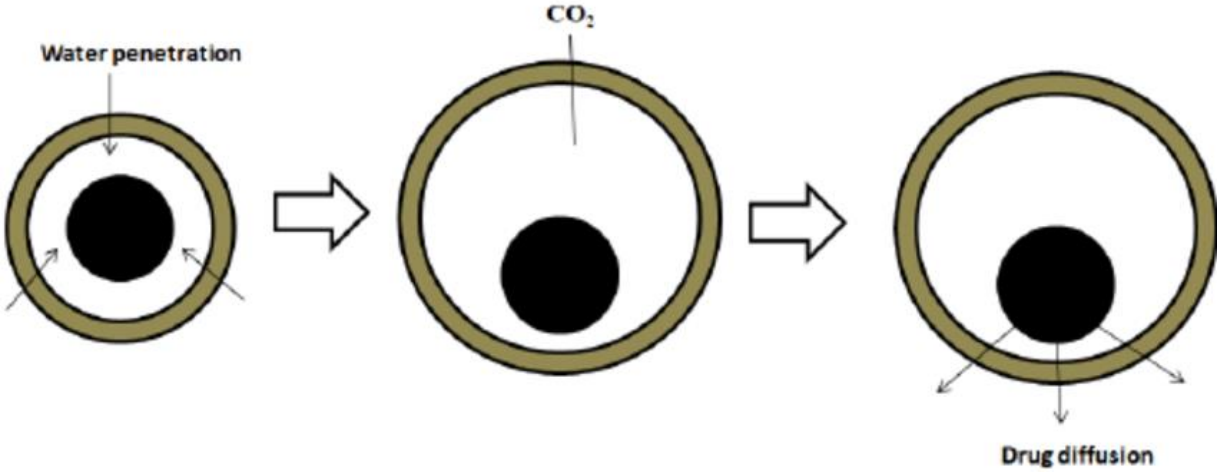

Figure 8: Drug release from effervescent (gas generating) systems.

Various types of gastro-retentive microspheres can be achieved through the process of microencapsulation.
Some of them are as follows:

Floating microsphere[18, 19]

Floating microspheres are gastro-retentive drug delivery system based on non-effervescent approach and characteristically free flowing powders consisting of proteins or synthetic polymers with diameters 1 µm to 1000 µm. Hydro dynamically controlled drug delivery systems (Floating microspheres) are low density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the dosage form floats on the gastric contents, the drug is released continuously at the desired rate from the system. This results in an increased gastric retention time and a better control of the fluctuations in plasma drug concentration.

Mucoadhesive microspheres[20, 21]

Mucoadhesive microspheres include microparticles and microcapsules of 1 to 1000 µm in diameter consisting either entirely of mucoadhesive polymer or having an outer coating with adhesive property. Microspheres have the potential to be used for controlled as well as spatial drug

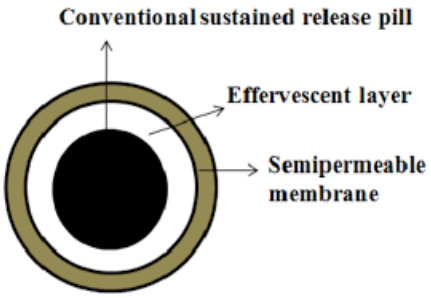

Figure 9: Effervescent (gas generating) systems.

delivery. Incorporating mucoadhesiveness to microspheres leads to efficient absorption and enhanced bioavailability of drug. Specific targeting of drug to the absorption site is achieved by using homing devices (ligand) like plant lactin, bacterial adhesion etc. on the surface of the microspheres. Mucoadhesive microspheres can be tailored to adhere to mucosal linings of GIT, thus offering the possibilities of localized as well as systemic absorption of drug in controlled manner.

Altered density microspheres[22, 23]

Low density microspheres

Empty globular shells, which have a visible density lower than that of gastric juice, can be used as carriers of drugs for sustained or controlled release purposes. Conventional polystyrol, gelatin capsules, and poprice are candidates as carriers. The surface of the empty shell is undercoated with polymers, such as acrylic and methacrylic copolymer, cellulose acetate phthalate or sugar. This undercoated shell is further coated with a drug-polymer mixture and polymeric material that shows dissolution controlled dug release (ethyl cellulose, cornstarch). This type of carrier floats on the gastric juice for an extended period with slow release the drug.

High density microspheres[18, 23]

An increase in density from 1.0 to 1.6 extended the average transit time from 7 to 25 hours. The microspheres are dispersed throughout the small intestine at a rate that depends principally on their density. Titanium dioxide, zinc oxide, barium sulphate, and iron powder are the substances used to increase microsphere density. Density of the microspheres must exceed the normal stomach contents and should therefore be an at least 1.4. Furthermore, a diameter of 1.5mm is considered maximal for a true multiple unit formulation. The drug can be coated on a heavy core or mixed with heavy inert materials, and then the weighted microsphere can be covered with a diffusion controlling membrane.

Magnetic microspheres[2, 24]

This approach to enhance the gastric retention time (GRT) is based on the simple principle that the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Although magnetic system seems to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance.

Novel Approaches Adopted for Floating Microspheres[25, 26]

Floating microspheres have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting 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[16]. Floating microspheres can be divided into:

Non-effervescent microspheres[27-29]

Floating dosage forms involves intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density less than unity within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass.

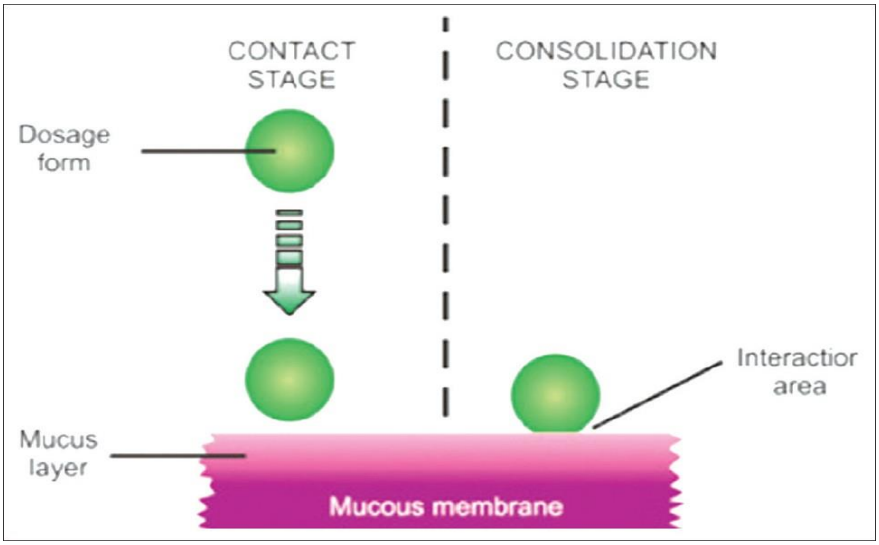

Figure 11: Mechanism of Mucoadhesion.

Table 1: Some of the recently developed mucoadhesive microspheres containing the following drugs and polymers[53-55].

S. No.	Drug	Category	Polymer
1	Metformin Hcl	Antidiabetic	Sodium alginate
2	Amoxicillin trihydrate	Antibiotic	Ethyl Cellulose
3	Ibuprofen	Analgesic	Sodium alginate
4	Pioglitazone Hcl	Antidiabetic	Carbopol 934
5	Trimetazidine Hcl	Antianginal	Chitosan
6	Furosemide	Diuretic	Sodium alginate, Carbopol
7	Insulin	Antidiabetic	Sodium alginate, Chitosan
8	Furazolidine	Antiulcer	Eudragit RS100, Carbopol 974P, HPMC
9	Aceclofenac	Analgesic	Sodium alginate HPMC, Chitosan, Carbopol.
10	Acyclovir	Antiviral	Sodium alginate
11	Atenolol, Propranolol	β Blockers	Polyacrylic acid, Polyvinyl pyrrolidine
12	Rantidine Hcl	Antacid	Sodium alginate
13	Glipizide	Oral Hypoglycemic	Chitosan
14	Captopril	ACE Inhibitor	Sodium alginate, HPMC, Chitosan, Carbopol 934P, Cellulose acetate phthalate
15	Ketoprofen	Analgesic	Sodium alginate, Chitosan, Pectin, Xanthum gum
16	Salbutamol sulphate	Bronchodilator	Carbopol, HPMC
17	Torsemide	Diuretic	Sodium alginate , HPMC
18	Ketorolac	Antiinflammatory and Analgesic	Eudragit RS100, Eudragit RL100
19	Acetazolamide	Diuretic	Eudragit RS, Eudragit RL
20	Metronidazole	Antiamoebic	Guargum, Sodium alginate
21	Famotidine	Antiulcer	Sodium CMC, Sodium alginate
22	Monteleukast sodium	Antiallergic	HPMC, Eudragit, Carbopol
23	Salbutamol sulphate	Bronchodilator	HPMC, Carbopol

For example: Gupta R. *et al.*, (2014) have formulated novel stomach specific floating microspheres of famotidine (stomach ulcer) by modified solvent evaporation method by using rate controlling polymer eudragit S-100. The prepared microspheres showed good flow properties. The maximum yield of microspheres was around 95.11%. Prepared microspheres were capable to float up to 20 hours in simulated gastric fluid[18].

Colloidal gel barrier systems[26, 30]

Hydrodynamically balance system (HBSTM) was first design by Sheth and Tossounian in 1975. Such systems contains drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. This prolongs GRT and maximizes the amount of drug that reaches its absorption sites in the solution form for ready absorption. This system incorporates a high level of one or more gel forming highly swellable cellulose type hydrocolloids. e.g. HEC, HPMC, NaCMC, Polysacchacarides and matrix forming polymer such as polycarbopil, polyacrylates and polystyrene, incorporated either in tablets or in capsule. 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 these dosage forms.

Microporous compartment system[19, 31]

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

Alginate beads[20, 32]

To develop multi-unit dosage forms the freeze dried calcium alginate has been used. Spherical beads of approximately 2.5 mm in diameter can be prepared by the precipitation of calcium alginate via dropping sodium alginate solution into aqueous solution of calcium chloride. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40 ^{0}C for 24 hours, it leads to the formation of a porous system which can maintain a floating force for over 12 hours. These floating beads prolong residence time for more than 5.5 hours.

Hollow microspheres / Microballons[33, 34]

A novel emulsion solvent diffusion method was used to prepare hollow microspheres loaded with drug in their outer polymer shelf. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into agitated solution of poly vinyl alcohol (PVA) that was thermally controlled at 40 ^{0}C. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed in the internal cavity of microsphere of the polymer and drug. The microballoon floated continuously over the surface of an acidic dissolution media containing surfactant for more than 12 hours.

Effervescent microspheres [35, 36]

These buoyant systems utilize matrices prepared with not only synthetic polymers but also natural polymers are used for this system. These are matrix type of systems prepared

with the help of swellable polymers such as Methylcellulose and chitosan and various effervescent compounds, e.g. sodium bicarbonate, tartaric acid and citric acid. They are formulated in such a way that when in contact with the gastric contents, CO_2 is liberated and gets entrapped in swollen hydrocolloids, produces an upward motion of the dosage form and maintains its buoyancy. A decrease in specific gravity causes the dosage form to float on the chime.

Steps involved in floating of dosage form
Penetration of water
Generation of CO_2 and floating
Dissolution of drug

This system can also be further described as:

Volatile liquid containing systems[23, 37]

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.

Gas-generating systems[38-40]

The effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2 occurred in these delivery systems, which gets entrapped in the gelled hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chime. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. The common approach used for the preparation of 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 reported 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 mini-capsules 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.

Mucoadhesion[41-43]

Bioadhesion is defined as a phenomenon in which materials are held for a longer period of time to the mucus membrane by means of interfacial forces. In biological systems, bioadhesion can be classified into 3 types.

Type 1, adhesion between two biological phases, for example, platelet aggregation and wound healing.

Type 2, adhesion of a biological phase to an artificial substrate, for example tissue, cell adhesion to culture dishes and biofilm formation on prosthetic devices and inserts.

Type 3, adhesion of an artificial substance to a biological substrate, for example, adhesion of synthetic hydrogels to soft tissue.

Mechanism of mucoadhesion[44-45]

Mechanism of bioadhesion can be described in two successive steps of formulation:

Wetting and Contact stage- Wetting and swelling of polymer to permit intimate contact with biological tissue.

Consolidation stage- Interpenetration of bioadhesive polymer chains and entanglement of polymer and mucin chains.

Advantages of mucoadhesive microspheres[46-52]

Increased prolonged time of drug at the absorption site results in enhanced bioavailability of the drug due to adhesion and intimate contact.

Use of specific bioadhesive polymers results in targeting of sites or tissues.

It offers an excellent route for systemic delivery of drugs with high first-pass metabolism thereby offering greater bioavailability.

Maintenance of therapeutic plasma drug concentration.

CONCLUSION

It was concluded that gastro-retentive microspheres offer numerous potential advantages for drug with poor bioavailability due to their restricted residence time in the upper gastrointestinal tract (GIT) and they can be delivered efficiently, thereby maximizing their absorption and enhancing absolute bioavailability. The drug delivery system must remain for a sufficient time in the stomach, which is not compatible with its normal physiology. All these gastro-retentive microspheres (high density, floating, expandable or unfoldable or swelling, superporous, bioadhesive, magnetic systems etc.) are interesting and present their own advantages and disadvantages. It is widely acknowledged that extent of drug absorption is related to contact time of drug with gastro intestinal mucosa. Therefore, gastro-retentive microspheres are found to be efficient in enhancing the contact time, thus improving drug bioavailability.

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