



Gastro retentive drug delivery systems: An overview

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Abstract

The current review deals with various gastro-retentive approaches that have recently become leading methodologies in the field of site-specific orally administered controlled release drug delivery systems. Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Various drugs have their greatest therapeutic effect when released in the stomach, particularly when the release is prolonged in a continuous, controlled manner. Drugs delivered in this manner have a lower level of side effects and provide their therapeutic effects without the need for repeated dosages or with a low dosage frequency. The success and degree of gastric retention is influenced by various polymer based properties and the techniques which are followed for such system. Various *In vitro* and *In vivo* tests are carried out for the evaluation of gastro-retentive drug delivery systems.

1. **Introduction:** 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. 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). Over the few decades, several gastroretentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach , low density (floating) systems that causes buoyancy in gastric fluid, mucoadhesive systems that causes bio adhesion to stomach mucosa , unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach , superporous hydrogel systems, magnetic systems etc. The current review deals with various gastroretentive approaches that have recently become leading methodologies in the field of site-specific orally administered controlled release drug delivery systems.

1.1 NEED FOR GASTRORETENTIVE SYSTEM

Various drugs have their greatest therapeutic effect when released in the stomach, particularly when the release is prolonged in a continuous, controlled manner. Drugs delivered in this manner have a lower level of side effects and provide their therapeutic effects without the need for repeated dosages or with a low dosage frequency. Sustained release in the stomach is also useful for therapeutic agents that the stomach does not readily absorb, since sustained release prolongs the contact time of the agent in the stomach or in the upper part of the small intestine, which is where absorption occurs and contact time is limited.

The following properties of drug are essential for gastro-retentive drug delivery system.

- Drugs acting locally in the stomach
e.g. Antacids and drugs for H. Pylori .
- Drugs that are primarily absorbed in the stomach
e.g. Amoxicillin
- Drugs that is poorly soluble at alkaline pH
e.g. Furosemide, Diazepam, Verapamil, etc.
- Drugs with a narrow window of absorption
e.g. Cyclosporine, Methotrexate, Levodopa, etc.
- Drugs which are absorbed rapidly from the GI tract.
e.g. Metonidazole, tetracycline.
- Drugs that degrade in the colon.
e.g. Metoprolol.
- Drugs that disturb normal colonic microbes
e.g. antibiotics against *Helicobacter pylori*.

The following categories of drugs are unsuitable for gastro-retentive drug delivery systems.

- Drugs that have very limited acid solubility.
e.g. phenytoin etc.
- Drugs that suffer instability in the gastric environment.
e.g. erythromycin etc.
- Drugs intended for selective release in the colon.
e.g. 5- amino salicylic acid and corticosteroids etc.

1.2. Approaches for Gastric Retention.

The strategies for delaying drug transit time through the GIT fall into one of three categories:-

Pharmacological approach

It involves co-administration or incorporation of a drug into the dosage form that delays either gastric emptying e.g. antimuscurinic agent such as propanthalin or a drug that retards gastric motility e.g. Loperamide.

Physiological approach

It involves the use of natural materials or fat derivatives such as Triethanolamine myristate which stimulate the duodenal receptors to slow gastric emptying. Use of large amount of volume filling polymer such as Polycarbophil can also slow gastric emptying.

Pharmaceutical approach

The first two approaches are not used because of toxicity problems. The various pharmaceutical approaches that are used for gastroretention can be classified as:-

1.3. FLOATING – A LOW DENSITY APPROACH

Floating drug delivery systems (FDDS) or hydro-dynamically balanced systems have a bulk density lower than gastric fluids and thus 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 a desired rate from the stomach. After the release of the drug, the residual system is emptied from the stomach.

This results in an increase in the gastric retention time and a better control of fluctuations in the plasma drug concentration in some cases.

1.4. Effervescent systems

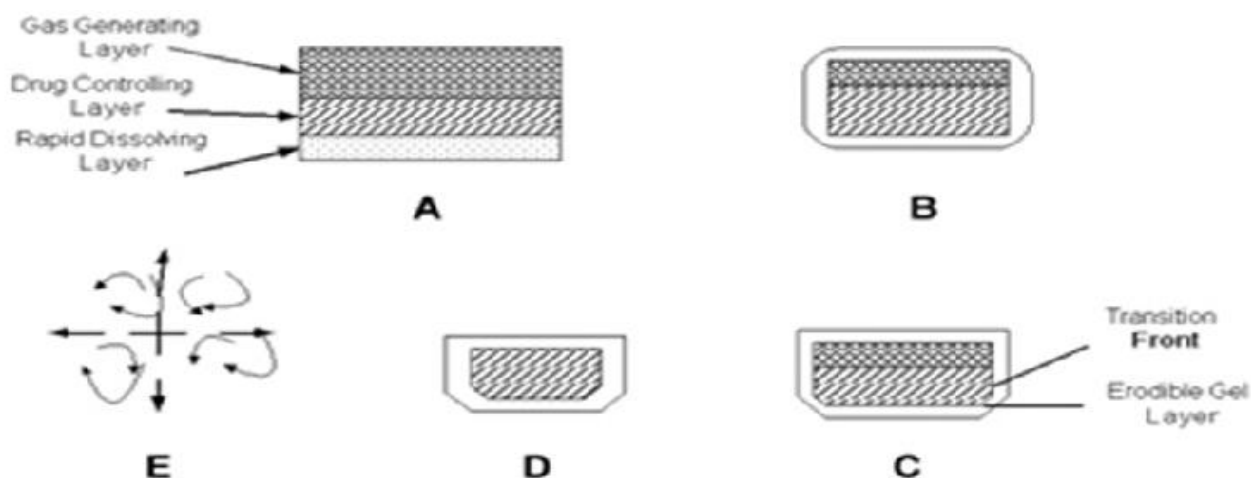
These are matrix type of systems prepared with the help of swellable polymers such as Methylcellulose and chitosan and various effervescent compounds, e.g. sodium bicarbonate, tartaric acid and citric acid. They are formulated in such a way that when in contact with the gastric contents, CO₂ is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms.

These buoyant systems utilised 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.



Matrix Tablets

Single layer matrix tablet is prepared by incorporating bicarbonates in matrix forming hydrocolloid gelling agent like HPMC, chitosan, alginate or other polymers and drug. Bilayer tablet can also be prepared by gas generating matrix in one layer and second layer with drug for its SR effect. Floating capsules also prepared by incorporating such mixtures. Triple layer tablet also prepared having first swellable floating layer, second sustained release layer of 2 drugs (Metronidazole and Tetracycline) and third rapid dissolving layer of bismuth salt. This tablet is prepared as single dosage form for Triple Therapy of H.Pylori.



Triple layer matrix tablet

Noneffervescent system

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of < 1 . The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass.

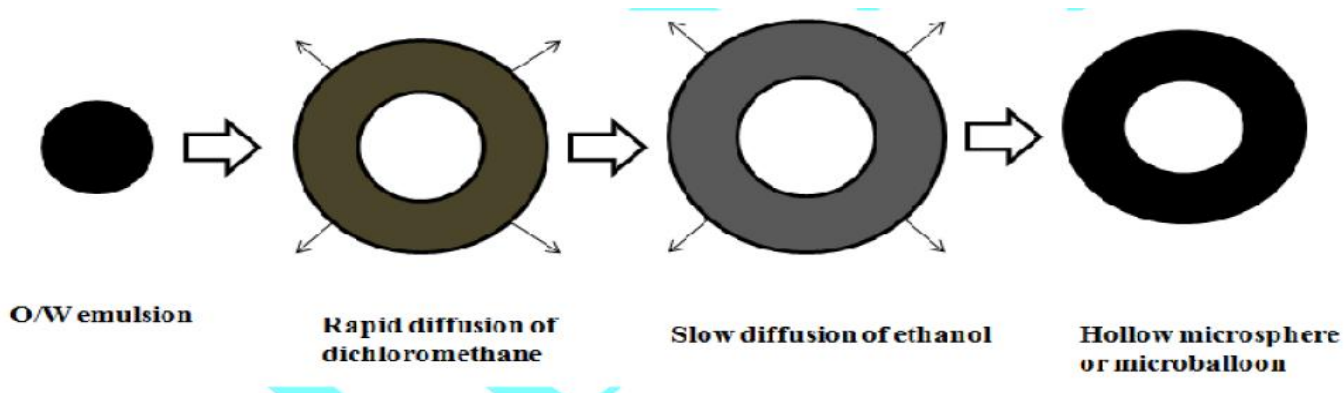
1. Hydrodynamically balanced systems.

These systems contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. These are single-unit dosage form, containing one or more gel-forming hydrophilic polymers. Hydroxypropyl methylcellulose (HPMC), hydroxethyl cellulose (HEC), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (NaCMC), polycarbophil, polyacrylate, polystyrene, agar, carrageenans or alginic acid are commonly used excipients to develop these systems. The polymer is mixed with drugs and usually administered in hydrodynamically balanced system capsule. The capsule shell dissolves in contact with water and mixture swells to form a gelatinous barrier, which imparts buoyancy to dosage form in gastric juice for a long period. Because, continuous erosion of the surface allows water penetration to the inner layers maintaining surface hydration and buoyancy to dosage form. Incorporation of fatty excipients gives low density formulations reducing the erosion. Madopar LPR, based on

the system was marketed during the 1980's. Effective drug deliveries depend on the balance of drug loading and the effect of polymer on its release profile several strategies have been tried and investigated to improve efficiencies of the floating hydrodynamically balanced systems.

2. Microballoons / Hollow microspheres:

Microballoons / hollow microspheres loaded with drugs in their other polymer shell were prepared by simple solvent evaporation or solvent diffusion evaporation methods to prolong the gastric retention time (GRT) of the dosage form. Commonly used polymers to develop these systems are polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar and low methoxylated pectin etc. Buoyancy and drug release from dosage form are dependent on quantity of polymers, the plasticizer polymer ratio and the solvent used for formulation. The microballoons floated continuously over the surface of an acidic dissolution media containing surfactant for >12 hours. At present hollow microspheres are considered to be one of the most promising buoyant systems because they combine the advantages of multiple-unit system and good floating.



3. Microporous compartment system:

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

Advantages of Floating Drug Delivery

Enhanced bioavailability

The bioavailability of some drugs (e.g. riboflavin and levodopa) CR-GRDF is significantly enhanced in comparison to administration of non- GRDF CR polymeric formulations.

Enhanced first-pass biotransformation

When the drug is presented to the metabolic enzymes (cytochrome P-450, in particular CYP-3A4) in a sustained manner, the presystemic metabolism of the tested compound may be considerably increased rather than by a bolus input .

Sustained drug delivery/reduced frequency of dosing

The drugs having short biological half life, a sustained and slow input from FDDS may result in a flip-flop pharmacokinetics and it reduces the dose frequency. This feature is associated with improved patient compliance and thus improves the therapy.

Targeted therapy for local ailments in the upper GIT

The prolonged and sustained administration of the drug from FDDS to the stomach may be useful for local therapy in the stomach.

Minimized adverse activity at the colon

Retention of the drug in GRDF at stomach minimizes the amount of drugs that reaches the colon and hence prevents the degradation of drug that degraded in the colon.

Site specific drug delivery

A floating dosage form is a widely accepted approach especially for drugs which have limited absorption sites in upper small intestine.

BIOADHESIVE SYSTEMS

Bio/mucoadhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the Gastro retention of drug delivery system (DDS) in the stomach by increasing the intimacy and duration of contact of drug with the biological membrane. A bio/muco-adhesive substance is a natural or synthetic polymer capable of producing an adhesive interaction based on hydration-mediated,

bonding-mediated or receptor mediated adhesion with a biological membrane or mucus lining of GI mucosa.

The binding of polymers to the mucin-epithelial surface can be subdivided into three broad categories-

1. Hydration-mediated adhesion
2. Bonding-mediated adhesion
3. Receptor-mediated adhesion

1. Hydration-mediated adhesion

Certain hydrophilic polymers tend to imbibe large amount of water and become sticky, thereby acquiring bioadhesive properties.

2. Bonding-mediated adhesion

The adhesion of polymers to a mucus or epithelial cell surface involves various bonding mechanisms, including physical-mechanical bonding and chemical bonding. Physical-mechanical bonds can result from the insertion of the adhesive material into the crevices or folds of the mucosa. Chemical bonds may be either covalent (primary) or ionic (secondary) in nature. Secondary chemical bonds consist of dispersive interactions (i.e., vander Waals interactions) and stronger specific interactions such as hydrogen bonds. The hydrophilic functional groups responsible for forming hydrogen bonds are the hydroxyl and carboxylic groups.

3. Receptor-mediated adhesion

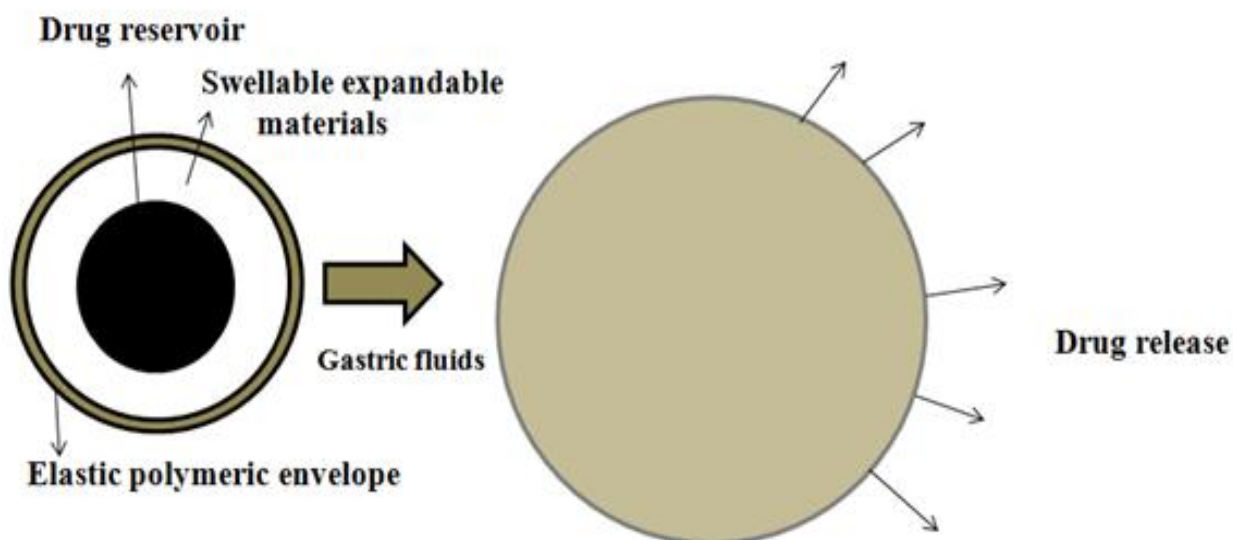
Certain polymers can bind to specific receptor sites on the surface of cells, thereby enhancing the gastric retention of dosage forms. Certain plant lectins such as tomato lectins interact specifically with the sugar groups present in mucus or on the glycocalyx.

SWELLING OR EXPANDING SYSTEM

After being swallowed, these dosage forms swell to a size that prevents their passage through the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems are sometimes referred to as plugtype systems because they tend to remain lodged at the pyloric sphincter. These polymeric matrices remain in the gastric cavity for several hours even in the fed state. Sustained and controlled drug

release may be achieved by selecting a polymer with the proper molecular weight and swelling properties. As dosage form coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive swelling of these polymers is a result of the presence of physical-chemical crosslinks in the hydrophilic polymer network.

i)



(i)Swelling system

HIGH DENSITY SYSTEMS

These systems with a density of about 3 g/cm³ are retained in the antrum part of the stomach and are capable of withstanding its peristaltic movements. The only major drawbacks with such systems is that it is technically difficult to manufacture such formulations with high amount of drug (>50%) and to achieve a density of about 2.8 g/cm³. It is necessary to use diluents like barium sulfate, zinc oxide, titanium dioxide, iron powder etc. to manufacture such high density formulations.

RAFT FORMING SYSTEMS

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids,

wherein each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of low bulk density created by the formation of CO₂.

Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO₂ to make the system less dense and float on the gastric fluids. The system contains a gel forming agent (e.g. alginic acid), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft) when in contact with gastric fluids. The raft thus formed floats on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the esophagus by acting as a barrier between the stomach and esophagus.

MAGNETIC SYSTEMS

This system is based on a simple idea that the dosage form contains a small internal magnet and a magnet placed on the abdomen over the position of the stomach. Ito et al. used this technique in rabbits with bioadhesives granules containing ultrafine ferrite (g-Fe₂O₃). They guided them to the esophagus with an external magnet (1700 G) for the initial 2 min and almost all the granules were retained in the region after 2 h10. Although these systems seem to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance.

CONCLUSION

To develop an efficient gastroretentive dosage form is a real challenge to pharmaceutical technology. Indeed, the drug delivery system must remain for a sufficient time in the stomach, which is not compatible with its normal physiology. All these gastroretentive drug delivery systems (high density, floating, expandable or unfoldable or swelling, superporous, bioadhesive, magnetic systems etc.) are interesting and present their own advantages and disadvantages. Now, a lot of work is running to develop different types of gastro retentive delivery systems of various drugs. In the future, it is expected that they will become of increasing importance, ultimately leading to improved efficiencies of various types of pharmacotherapy.

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