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REVIEW ARTICLE

A Review Article of Gastroretentive Drug Delivery System

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Abstract

The purpose of writing this review was to investigate, compile and present the recent as well as past literatures in more concise way with special focus on approaches which are currently utilized in the prolongation of gastric residence time. Drug absorption in GIT varies and increased gastric retention time of the dosage form extends the time of drug absorption. Thereby implementing site specific drug release in the stomach for local and systemic effect. It is very useful for the drugs which having narrow absorption Rate. These includes floating system, swelling and expanding system, bio / mucoadhesive system, high density system and other delayed gastric emptying devices.

Keywords: *Gastric retention, Oral controlled release, Floating dosage form, Drug delivery system.*

Introduction

Advancement in drug delivery, oral route is the most common route to the systemic circulation due to easiest way of administration, low cost of drug, patient compliance and flexibility in formulation. About 90% of all drugs used are administered by oral route.

Though the drugs are administered orally, solid oral dosage forms is the most common class of products. Tablets are the most common type of solid dosage form in use which is classified based on the drug release pattern, i.e. immediate release and modified release. The immediate release tablets have many drawbacks including non-site specific drug release. However, many drugs are absorbed from specific sites and they require release at that site only for better absorption [1].

Drug absorption in the GIT is a highly variable process and it is depending on the factors like gastric emptying process, gastrointestinal transit time of dosage forms, drug release from the dosage form, and site of absorption of drugs. Drugs that are absorbed easily from the GIT and have short half-lives are eliminated quickly from the systemic circulation. Frequent dose is required to achieve suitable therapeutic activity[2]. Gastro retentive drug delivery is one of those approaches to prolong gastric residence time, thereby targeting site specific drug release in the stomach for local or systemic effects. These dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time of the drugs. It will release the drug in stomach in a controlled manner, so that the drug could be supplied continuously to absorption site in GIT i.e. stomach [3].

Advantages [4, 5]

- Increased bioavailability: The bioavailability of the drugs having absorption in the upper part of the GIT like riboflavin, levodopa has tremendously been increased than that of the normal dosage forms.
- Sustained drug release and reduced frequency of dosing. This improves patient compliance.
- Targeted delivery of the drug at the upper part of the GIT making it suitable for the

local treatment of the disease of the region e.g.; antacids, anti-ulcer drugs, antibacterial for H. pylori infection.

- Suitable for the drugs which degrade in the intestine or column e.g., Ranitidine hydrochloride.
- Drug level fluctuation is not observed and maintains the optimal therapeutic plasma and tissue concentrations over prolonged time period. This avoids sub-therapeutics as well as toxic concentration and minimizes the risk of failure of the medical treatment and undesirable side effects.

Disadvantages [6]

It is not suitable for the drugs which are not stable in acidic environment.

- It is not suitable for the drugs which are absorbed better in the lower part of GIT.
- Difficulty to attain the desired outcome and problem of the dose dumping.
- Gastric retention is influenced by many factors like gastric motility, pH and presence of food. Hence, the dosage form must be able to withstand the grinding and churning force of peristaltic wave of stomach.
- Poor in vitro and in vivo correlation.
- Higher cost of formulation.

Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reaction

Floating Drug Delivery System

Floating drug delivery systems is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability. This delivery systems is desirable for drugs with an absorption window in the stomach or in the upper small intestine.

This have a bulk density less then gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period and the drug is released slowly as a desired rate from the system [7]. After release of drug, the residual system is emptied from the stomach. This result in an increased gastric retention time (GRT) and a better control of the fluctuation in plasma drug concentration [8].

The major requirements for floating drug delivery system are.

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

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

The good floating behavior of these systems could be successfully combined with accurate control of the resulting drug release patterns [9]. Single-unit dosage forms are associated with problems such as sticking together or being obstructed in the gastrointestinal tract (GIT) which may produce irritation.

On the other hand multiple-unit floating systems may be an attractive alternative since they have been shown to reduce the inter- and intra- subject availabilities in drug absorption as well as to lower the possibility of dose dumping, Various multiple-unit floating system like air compartment multiple-unit system, hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method, microparticles based on low density foam powder, beads prepared by emulsion gelatin method etc. can be distributed widely throughout the GIT, providing the possibility of achieving a longer lasting and more reliable release of drugs. Based on the mechanism of buoyancy two distinctly different technologies, i.e. non-effervescent and effervescent systems have been utilized in the development of floating drug delivery system [10-12].

Non-effervescent Systems

Non-effervescent floating drug delivery systems are normally prepared from gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides or matrix forming polymers like polyacrylate, polycarbonate, polystyrene and

polymethacrylate [13]. In one approach, intimate mixing of drug with a gel forming hydrocolloid which results in contact with gastric fluid after oral administration and maintain a relative integrity of shape and a bulk density less than unity within the gastric environment [14]. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxypropyl methylcellulose (HPMC) polyacrylates, polyvinyl acetate, carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates [15].

Hydrodynamically Balanced Systems [16, 17]

Sheth and Tossounian first designated these '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 LP®, 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.

Microballoons / Hollow Microspheres [18]

Microballoons / hollow microspheres loaded with drugs in their other polymer shelf were prepared by simple solvent evaporation or solvent diffusion / evaporation methods (Figure 1) 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.

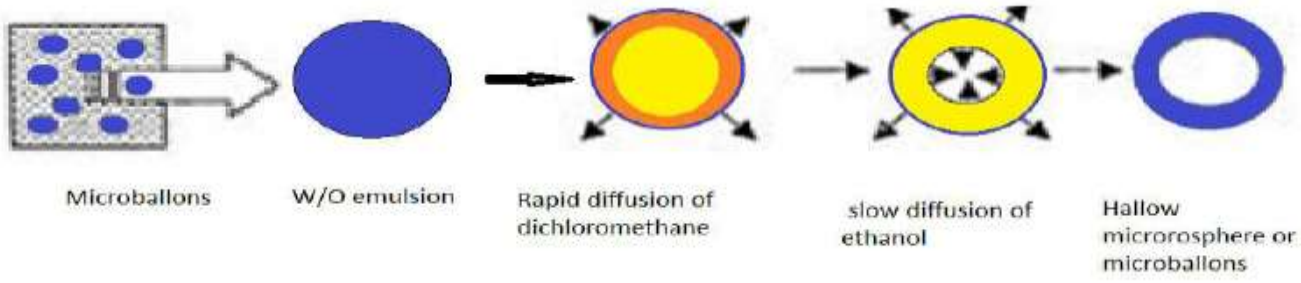

Figure 1: Formulation of floating hollow microsphere or microballoon

Alginate Beads [19]

Talukdar and Fassihi recently developed a multiple-unit floating system based on cross-linked beads. They were made by using Ca2+ and low methoxylated pectin (anionic polysaccharide) or Ca2+ low methoxylated pectin and sodium alginate. In this approach, generally sodium alginate solution is dropped into aqueous solution of calcium chloride and causes the precipitation of calcium alginate. These beads are then separated and dried by air convection and freeze drying, leading to the formulation of a porous system, which

can maintain a floating force for over 12 hrs. These beads improve gastric retention time (GRT) more than 5.5 hrs.

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 present any direct contact of the gastric surface with the undissolved drug [20]. 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 [21].

Effervescent (Gas Generating) Systems

Floatability can be achieved by generation of gas bubbles. These buoyant systems utilize matrices prepared with swellable polymers such as polysaccharides (e.g. chitosan), effervescent components (e.g. sodium bicarbonate, citric acid or tartaric acid). The optimal stoicheometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76: 1 . In this system carbon dioxide is released and causes the formulation to float in the stomach (Figure 2 and Figure 3). Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate, multiple unit floating dosage forms that generate gas (carbon dioxide) when ingested, floating mini capsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone (PVP) coated with hydroxypropyl methylcellulose (HPMC), and floating system based on ion exchange resin technology etc.

Bilayer or multilayer system has also been designed. Drugs and excipients can be formulated independently and the gas generating material can be incorporated in to any of the layers. Further modifications involve coating of the matrix with a polymer which is permeable to water, but not to carbon dioxide. The main difficulty of these formulations is finding a good compromise between elasticity, plasticity and permeability of the polymers [22-24].

Bioadhesive or Mucoadhesive Drug Delivery Systems

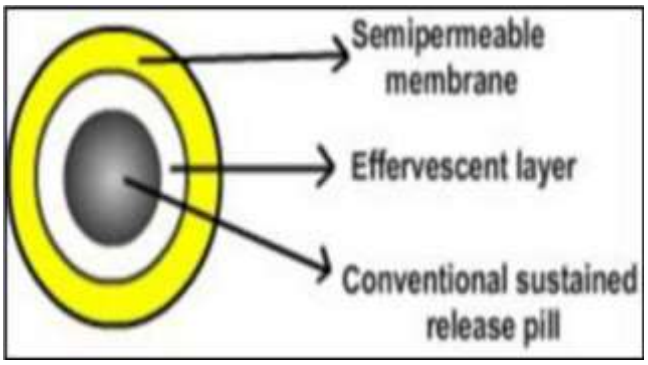

Figure 2: Effervescent (gas generating) systems

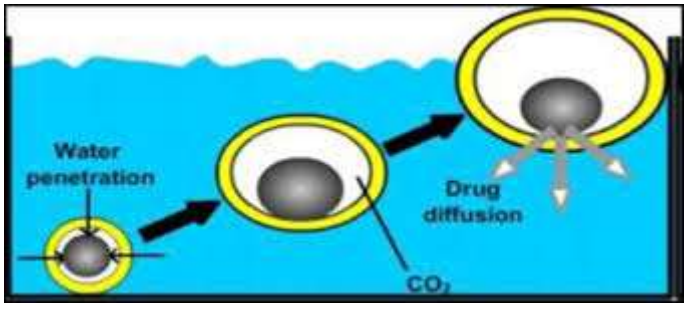

Figure 3: Drug release from effervescent (gas generating) systems

Bioadhesive drug delivery systems are used as a delivery device within the human to enhance drug absorption in a site-specific manner. In this approach, bio adhesive polymers are used and they can adhere to the epithelial surface in the stomach. Thus, they improve the prolongation of gastric retention. The basis of adhesion in that a dosage form can stick to the mucosal surface by different mechanism. These mechanisms are:

- The wetting theory, which is based on the ability of bioadhesive polymers to spread and develop intimate contact with the mucous layers.
- The diffusion theory, which proposes physical entanglement of mucin strands the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate.
- The absorption theory, suggests that bioadhesion is due to secondary forces such as Vander Waal forces and hydrogen bonding.
- The electron theory, which proposes attractive electrostatic forces between the glycoprotein mucin net work and the bio adhesive material.

Materials commonly used for bioadhesion are poly acrylic acid, chitosan, cholestyramine, sodium alginate, hydroxypropyl methylcellulose (HPMC), sucralfate, tragacanth, dextrin, polyethylene glycol(PEG) and polylactic acids etc. Even though some of these polymers are effective at producing bioadhesive, it is very difficult to maintain it effectively because of the rapid turnover of mucus in the gastrointestinal tract (GIT) [25,26].

Expandable, Unfoldable and Swellable Systems

A dosage form in the stomach will withstand gastric transit if it bigger than pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation.
Thus, their configurations are required to develop an expandable system to prolong gastric retention time (GRT):

- A small configuration for oral intake,
- An expanded gastroretentive form, and
- A final small form enabling evacuation following drug release from the device.

Thus, gastroretentivity is improved by the combination of substantial dimension with high rigidity of dosage form to withstand peristalsis and mechanical contractility of the stomach. Unfoldable and swellable systems have been investigated and recently tried to develop an effective gastroretentive drug delivery [27].

Unfoldable systems are made of biodegradable polymers. They are available in different geometric forms like tetrahedron, ring or planner membrane (4 - label disc or 4 -limbed cross form) of bioerodible polymer compressed within a capsule which extends in the stomach. Swellable systems are also retained in the gastro intestinal tract (GIT) due to their mechanical properties. The swelling is usually results from osmotic absorption of water and the dosage form is small enough to be swallowed by the gastric fluid (Figure 4).

Expandable systems have some drawbacks like problematical storage of much easily hydrolysable, biodegradable polymers relatively short-lived mechanical shape memory for the unfolding system most difficult to industrialize and not cost effective.50 Again, permanent retention of rigid, large single-unit expandable drug delivery dosage forms may cause brief obstruction, intestinal adhesion and gastropathy [28].

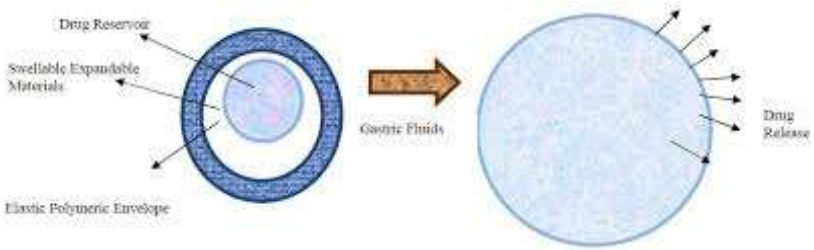

Figure 4: Drug release from swellable systems

Super Porous Hydrogel Systems

These swellable systems differ sufficiently from the conventional types to warrant separate classification. In this approach to improve gastric retention time (GRT) super porous hydrogels of average pore size >100 micro miter, swell to equilibrium size within a minute due to rapid water uptake by capillary wetting through numerous interconnected open pores . They swell to a large size (swelling ratio: 100 or more) and

are intended to have sufficient mechanical strength to withstand pressure by gastric contraction. This is advised by co-formulation of hydrophilic particulate material [29,30].

Magnetic Systems

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 wok the external magnet must be positioned with a degree of precision that might compromise patient compliance [31].

Floating Tablets Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Captopril, Cinnerzine, Chlorpheniramine maleate, Ciprofloxacin, Diltiazem, Fluorouracil, Isosorbide dinitrate, Isosorbid mononitrate, pAminobenzoic acid(PABA), Prednisolone, Nimodipine, Sotalol, Theophylline, Verapamil [32].

Floating Capsules Chlordiazepoxide HCl, Diazepam, Furosemide, L-DOPA and Benserazide, Nicardipine, Misoprostol, Propranolol, Pepstatin[33].

Floating Microspheres Aspirin, Griseofulvin, p-nitro aniline, Ibuprofen, Terfenadine, Tranilast [34,35].

Floating Granules Diclofenac sodium, Indomethacin, Prednisolone [36]

Powders Several basic drugs

Films Cinnerzine

Conclusion

Based on the literature surveyed, it may be concluded that gastroretentive drug delivery offers various potential advantages for drug with poor bioavailability due their absorption is restricted to the upper gastrointestinal tract (GIT) and they can be delivered efficiently thereby maximizing their absorption and enhancing absolute bioavailability. Due to complexity of pharmacokinetics and pharmacodynamics parameters, in vivo studies are required to establish the optional dosage form for a specific drug. Another promising area of research for gastroretentive drug delivery system is eradication of Helicobacter pylori, which is now believed to be causative bacterium of chronic gastritis and peptic ulcers.

Although, this microorganism is highly sensitive to many antibiotics, its complete eradication requires high concentration of antibiotics be maintained within gastric mucosa for prolonged time period. An important feature to take into account is the stomach physiology. The time when the drug is taken (during or apart from the meal) is an important parameter.

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 gastroretentive 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 pharmacotherapies.

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