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Review Article

A review on Advanced approaches and polymers used in gastroretentive drug delivery systems

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Abstract

Insufficient pharmacokinetic characteristics may be associated with the widespread use of oral dosage forms in the treatment of disease. In some cases, the drug is barely soluble; in others, the formulation's rapid transit through the gastrointestinal tract (GIT) makes it difficult to achieve therapeutic levels in body; in addition, some drugs must act locally due to a gastric pathology, but they remain in the stomach for only a short time. Numerous studies have focused on the development of formulations that are capable of enhancing all of these characteristics and extending the stomach residence duration. The prolonged stomach retention duration afforded by gastroretentive controlled drug delivery devices increases the therapeutic efficacy of many orally administered drugs. In the present investigation, we reviewed the advanced methods and polymers used to develop effective gastroretentive drug delivery systems. These methods include swelling and expansion, mucoadhesive, high density, low density, ion exchange, raft forming, magnetic, and floating drug delivery systems. The development of gastroretentive devices involves a broad array of polymeric materials. This work intends to expedite the development of innovative methods by offering a comprehensive understanding of unique gastroretentive approaches along with the polymeric materials utilised in the fabrication of gastroretentive drug delivery systems for oral drug delivery.

Keywords: Gastroretentive; mucoadhesive; floating; raft forming system; mucoadhesive; swellable.

INTRODUCTION

Although various drug delivery strategies are employed to optimise the therapeutic index and reduce the side effects of drugs, the oral route remains the most preferred, dependable, and effective route for administering therapeutic agents. Even though therapeutic costs are low, administration simplicity, technique adaptability, and administration contribute to improved patient compliance. Approximately 50 percent of drug delivery systems on the market are oral drug administration systems. [1] Even though significant progress has been achieved over the past two decades in the de novo design of an oral controlled drug delivery system, it has had mixed results with drugs with poor absorption across the gastrointestinal tract (GIT). Due to the unpredictability of stomach refilling and motility, this approach is plagued by a number of physiological issues, such as the inability to confine and localise the controlled drug delivery system within the targeted GIT. In addition, a relatively short stomach refilling time in humans, which typically extends 2–3 h through the primary absorption zone, i.e., the abdomen and upper portion of the intestine, might result in inadequate drug release from the drug delivery system and a decreased dose efficacy.[2]

To eradicate Helicobacter pylori, a gastroretentive drug delivery system (GRDDS) is necessary for drugs with minimal gastrointestinal tract absorption, a short half-life, poor solubility at alkaline pH, and the ability to interact locally in the upper intestinal tract. [3-5] Common GRDDS controlled release systems, such as bio/mucoadhesive, superporous hydrogel, raft-forming, magnetic, ion exchange, expandable, and low- and high-density systems, have been established using a variety of action mechanisms. [6-9] In addition, the physicochemistry of excipients plays a crucial role in several GRDDS. In effervescent floating systems, for instance, the excipient density and structure of the effervescent agent are crucial concerns. In the case of superporous hydrogel procedures, the creation of a superporous hydrogel requires excipients with a high swelling capacity in addition to crospovidone and sodium carboxymethyl cellulose. [3-4]

Gastroretentive formulation remains in the stomach for an extended duration and permit both spatial and temporal control of drug release. Essentially, gastroretentive systems swell after consumption and are held in the stomach for a period of hours while continually releasing the integrated drug at a controlled rate to selected absorption sites in the upper gastrointestinal tract. In the case of drugs that are mostly absorbed in the upper GIT or that are unstable in the middle or distal intestinal areas, their application can be helpful. They can also be utilised for the treatment of the stomach locally. Prolonged stomach retention of the drugs may offer a number of benefits, including increased bioavailability, therapeutic efficacy, and the potential for dose reduction. For drugs with an absorption window in the upper small intestine, however, traditional controlled-release dose forms offer very limited benefits. [5]

ADVANCED APPROACHES TO GASTRIC RETENTION

To enhance the GRT of a certain pharmaceutical type in the stomach, a variety of principles employed a plurality of ways.[6] These are related to:

LOW-DENSITY SYSTEMS

Low-density/floating systems are the most technical and carefully researched gastroretentive dose characteristics.[7] A selective gastric retention can be performed to optimise the bioavailability of the drug. The floating drug delivery method is a novel approach to this issue.[8] Required are medications with an absorption window in the stomach or small intestines. Long-term, this surgery has no influence on the level of stomach emptying. A multitude of strategies was used by a wide range of principles to improve the GRT of a drug type in the stomach.[9]

Types of floating drug delivery systems (FDDSs)

Two different processes were used in the implementation of FDDS based on the flotation mechanism: [9]

1. Effervescent system
2. Non-effervescent system.

Effervescent system

Effervescent methods including the use of gas-generating agents, carbonates, as well as other organic acid in the formulation are to produce carbon dioxide (CO2) gas, thus reducing the density cycle and enable to float the gastric fluid. The alternative is to incorporate a sequence involving part of the fluid that produces gas that evaporates at body temp. These are further categorized into two types.[10]

1. Gas-generating systems

These buoyant delivery methods use effervescent actions between carbonate/bicarbonate salts and citric/tartaric acid to release CO_2, which is then captured in the hydrocolloid layer of the system, reducing its specific gravity and allowing it to float above stomach content.

2. Volatile liquid/vacuum containing systems.

The GRT of a drug delivery system can be maintained by including an inflatable chamber containing a liquid, such as ether or cyclopentane, which, when exposed to body temperature, causes the chamber to inflate in the stomach. The system may also include a bio erodible plug consisting of Polyvinyl alcohol, Polyethylene, etc. that dissolves over time to allow the spontaneous expulsion of the inflatable systems from the stomach. [10]

Non-Effervescent Systems [11]

Through tablets or capsules, non-effervescent systems integrate a significant amount of gel-forming, expanding, cellulosic hydrocolloids and sodium carboxymethyl cellulose, polysaccharides, or matrix-formed polymers. When these gel formers, polysaccharides, and polymers come into contact with stomach fluid, they hydrate and form a colloidal gel barrier that regulates the stimulation level of fluid within the device and the consequent release of medications. As both dosage forms dissolve the outer surface, the hydration of the surrounding hydrocolloid coating maintains the gel layer.[12] The air captured by the expanded polymer decreases the volume and imparts elasticity to the shape of the dosage. The foregoing methods have been utilised in the creation of intragastric floating systems.

HIGH-DENSITY SYSTEMS

Dense structures transcend the density of gastric fluid. These systems frequently employ barium sulphate, zinc oxide, iron powder, and titanium dioxide as excipients. [12] In 1930, Hoelzel initially characterised the effects of dosage type size on both GRTs for numerous animal groups. The studied dose forms had densities ranging from 0.90 to 10.50 g/cm3. The designer indicated that high-density materials had slower GRTs than low-density materials. The effect of dose type density on GRT was then investigated. Due to their persistence in the antrum rugae or folds, tiny high-density pellets were able to endure the peristaltic movements of the stomach, increasing the GIT duration from 5.8 to 25 hours. In addition, only a few clinical investigations on high-density pellet formulations have been documented in the literature; hence, the predictive usefulness of these structures remains dubious. In addition, in order to evaluate the scientific validity of such dosage forms, future efforts must be based on animal testing.

Microballoons or Hollow Microspheres

Using a simple solvent evaporation or solvent diffusion procedure, microballoons/hollow microspheres with pharmaceuticals in their other polymer shelves are created in order to extend the duration of the GRT dose type. Polymers are used extensively in the building of these structures. Low-density materials, typically free-flowing powders with particle sizes less than 200 µm, that exhibit rapid buoyancy by entrapping oil or air. The volume of polymers, the ratio of polymer-plasticizer, and the formulation solvent influence the dose form's elasticity and drug discharge. These microballoons floated continuously for >12 hours over the majority of a surfactant-containing acid dissolving medium's surface. Since they combine the advantages of a multi-unit system with significant buoyancy, hollow microspheres are considered to be among the most effective buoyant processes [13]. By employing Eudragit S as a polymer in an emulsion solvent diffusion process, repaglinide-based microspheres with a porous calcium silicate core were created. In vitro, the formulation exhibited favourable floating and releasing properties. The integration of calcium silicate into the microspheres proved to be an efficient means of attaining the necessary release behaviour and buoyancy.

Microporous Compartment System

This design focuses on encapsulation within a microporous chamber of a drug storage tank whose upper and bottom walls contain pores. To prevent any contact between the undissolved drug and the gastrointestinal surface, the peripheral walls of the substance reservoir chamber are adequately sealed. There is compressed air in the floatation compartment of the abdomen, allowing the distribution network to flow over the majority of the stomach material. Gastric fluid reaches the aperture, disintegrates the drug, and transports the dissolved drug to the intestine for absorption. [14]

HBSS or Colloidal Gel Barrier System

These are single-unit dosage forms containing one or more hydrophilic polymers; hydroxypropyl methylcellulose is the most commonly used excipient, although HEC, HPC, NaCMC, agar, and alginic acid are also utilised. The polymer is typically combined with both drugs and administered in gelatin capsules. These capsules dissolve rapidly in the gastric fluid, and a floating mass is generated by the polymer's swelling and hydration. Development of the surface hydrated boundary regulates the production of drugs. [15]

Alginate Beads

Freezing-dried calcium alginate has created different forms of floating doses. Calcium alginate can precipitate from an aqueous solution of calcium chloride and sodium alginate to produce curved beads with an anticipated diameter of 2.5 mm. Then The beads are removed, flash-frozen in liquid nitrogen, and frozen at 40°C for 24 hours, resulting in the formation of a porous structure capable of supporting a floating force for more than 12 hours. These floating beads gave a longer stay than 5,5 hours. [15] Although Ca alginate beads can be manufactured using simple and gentle techniques, they suffer from a number of significant drawbacks, including low drug entrapment, limited floating duration, long floating lag time, and burst drug release due to drug leaching via the beads' pores. Several of these factors can be enhanced through various methods. For instance, the issue of drug leaching has been resolved by ionically crosslinking alginate and combining it with other polymers such as neutral gums, pectin, chitosan, HPMC, and Eudragit.

Raft-Forming Systems

Floating rafts operate as blockades between the oesophagus and stomach, hence raft systems are primarily concerned with confined effects. The created raft can remain intact for several hours in the stomach, supporting the continuous release of the drug. Consequently, they can be utilized to effectively treat gastric esophageal reflux illness as well as gastrointestinal infection and diseases. Raft-forming processes are another type of GRDDS and are constructed using effervescent excipients and polymer-forming gel for the short-term delivery of drugs. Raft system incorporates alginate gels containing carbonate that, when reacted with gastric acid, generate bubbles in the gel and permit floating. A great deal of attention has been given to raft formation mechanisms for the administration of drugs for GI diseases and disorders. The process involves the production of a highly cohesive gel in interaction with stomach fluids, with each component of the fluid swelling to form a continuous layer known as a raft. [16]

Expandable Systems

Expandable drug delivery systems are designed with a higher GRT to increase their density or size. They were first utilised solely for animal health purposes until their applications were expanded to include people. For the process to operate normally, three specific installations must be considered: a smaller size for rapid oral administration, an improved stomach shape to prevent passage through the pyloric sphincter, and a system with a smaller footprint since the drug's launch to facilitate rescue operations. This procedure is also referred to as a "plug-type system" since it might block the pyloric sphincter. The expansion of a process occurs by means of two tactics, swelling and taking form, both of which provide volume and form adjustments. Diffusion is the fundamental mechanism for swelling and drug release from a process [16].

Bioadhesive/Mucoadhesive Systems

It was engineered to stick to the surface of the gastric epithelial cell and prolong GRT. In this manner, drugs are incorporated into a mucoadhesive agent, which may consist of natural or synthetic polymers. Utilized are bioadhesive polymers that stick to the GIT epithelial surface. There are three main forms of polymer binding to the epithelial surface: bonding-mediated adhesion, hydration-mediated adhesion, bonding-mediated adhesion, and receptor-mediated adhesion. Both types of systems connect to the biological membrane of the stomach (mucosa) and create long-term tight contact with the membrane while sustaining their release in the stomach. [14]

Swelling Systems

After consumption, these substances swell to a size that prevents them from passing through the pylorus. As a result, the drug kind is kept in the stomach for an extended period of time. These devices are sometimes referred to as plug-type systems because they typically remain lodged at the pyloric sphincter. These polymeric matrices have continued to work in the gastrointestinal cavity for the previous few hours, occasionally during the feeding state. By selecting a polymer with the proper molecular weight and swelling characteristics, controlled and continuous medication release can be achieved. The polymer absorbs water and expands when in contact with stomach fluid. Due to the presence of physical-chemical crosslinks in the hydrophilic polymer system, these polymers are inflammatory. This connection prevents the polymer from dissolving, preserving the dosage form's physical integrity. The quantity of cross-linking between the two polymer chains strikes a balance between the swelling's amplitude and duration. [15] A high level of cross-linking delays the expansion of the scheme and preserves its physical integrity for an extended length of time.

Magnetic System:

This approach is based on the basic concept that the dose form contains a small magnet and a magnet is placed on the abdomen above the stomach's position. Utilizing an extracorporeal magnet, the stomach residence time of a dose form can be lengthened. [16]

POLYMERIC MATERIALS IN GASTRORETENTIVE FORMULATIONS

Hydroxypropylmethyl Cellulose (HPMC)

Hydroxypropyl methylcellulose (HPMC) is the most important hydrophilic carrier material used for the manufacture of oral controlled drug delivery systems [17]. Also known as hypromellose, HPMC belongs to the group of cellulose ethers in which one or more of the three hydroxyl groups from the cellulose glucopyranose units have been substituted producing ether linkages. It is, thus, a semisynthetic polymer made from highly purified natural pulp that is etherified with the combination of methyl chloride and propylene oxide to form a water-soluble, non-ionic cellulose ether [18]. The most frequently used marketed HPMC belongs to the trade names Methocel® and Pharmacoat®.

Hydroxypropyl cellulose (HPC) and hydroxyethyl cellulose (HEC)

Due to its low Tg, HPC has been utilised as the primary matrix-forming polymer in formulations prepared using hot-melt extrusion and 3D printing technologies, indicating that the formulations might be processed at a relatively low temperature. HPC has proven its ability to produce bioadhesive films [19]. The effect of different additives on the bioadhesive characteristics of HPC-based films was examined, and it was determined that the insertion of Carbomer 971P and a polycarbophil into HPC films considerably boosted bioadhesion compared to the film containing HPC and PEG 3350.

Hydroxyethyl cellulose (HEC) is utilised in the fabrication of biostructures for the administration of hydrophobic drugs as a gelling and thickening agent. Mucoadhesive films of enalapril, for instance, were produced with combinations of HEC and sodium carboxymethylcellulose and exhibited promising swelling characteristics and regulated drug release [20]. Similar to HPC, hydroxyethyl cellulose (HEC) has been included into multicomponent polymeric matrices in order to provide the required gastro-retentive qualities. Using sodium bicarbonate

as a gas-forming agent and a mixture of HEC and sodium alginate as a polymeric matrix, for instance, effervescent floating tablets of pentoxifylline were successfully produced.

Carboxymethyl cellulose (CMC)

Carboxymethyl cellulose (CMC) is a semisynthetic, non-toxic, water-soluble cellulose derivative containing carboxymethyl groups (-CH2-COOH) attached by an ether bond to some of the hydroxyl groups of the glucopyranose repeating units of the cellulose backbone. Due to the anionic nature of the carboxylate groups found in NaCMC, the interaction with non-ionic hydrocolloids, such as HPMC and HEC, might increase their gel-viscosity qualities [20].

Natural Gums

In addition to synthetic cellulose ethers, naturally occurring polymers have been used as hydrocolloids to successfully control drug release from swellable systems [21]. Natural polymers have advantageous features, such as biocompatibility and safety, and hence have valuable pharmaceutical and biological uses. Natural gums—gellan gum, guar gum, carrageenans and xanthan gum—other polysaccharides, such as alginates and chitosan [22], and natural polymers, such as pectin and gelatin [18], are natural hydrocolloids or gel-forming agents with the ability to swell in contact with gastric fluid, maintain a relative shape integrity, and have a bulk density less than the gastric content.

Guar gum

Guar gum is a polysaccharide extracted from the seeds of Cymopsis tetragonolobus (family Leguminosae). It swells fast in the presence of water with a translucent suspension due to the dual composition of guar gum: an approximately 85 percent water-soluble fraction termed Guaran and an insoluble component. Due to the mannose units in hydrated guar gum, the addition of borate ions creates cohesive structural gels [18]. Guar gum increases viscosity and acts as a disintegrant and binder in pharmaceutical industries when used in solid dosage forms [22].

Carrageenans

Carrageenans are anionic polysaccharides with a high molecular weight derived from red seaweeds of the Rhodophyceae class. They showed beneficial as tablet excipient agents due to their great durability, good compatibility, and persistent viscoelasticity of the tablet throughout granulation and compression. Carrageenans are therefore appropriate excipients for sustained-release formulations. Notably, the real density measurements of the carrageenans were found to be significantly greater than those of the cellulose ethers (MC, HPMC, NaCMC and HPC) [22].

Gellan Gum

Gellan gum can be utilised for in-situ gel production when Ca2+ ions are present as a crosslinking agent. Gellan gum can be used to generate in-situ gels in conjunction with Ca2+ ions as a crosslinking agent.

Xanthan Gum

Xanthan gum is utilised in food stuffs, cosmetics, and topical and oral pharmaceutical formulations since it is non-toxic and non-irritant. Its presence is responsible for influencing the zero-order kinetics of drug release from formulations [23].

Crosslinked polyacrylates: Carbomers, Carbopol® and Polycarbophyl (PCP)

Carbomers are synthetic polyacrylic acids with a high molecular weight that are cross-linked with allyl ethers of polyalcohols, such as pentaerythritol polyallylether and polyallyl sucrose. Carbopol® polymer grades vary in their physical structure and chemical composition, crosslink density, polymerization solvent, crosslinking type, network electrical charge, and physical appearance, and hence in their performance qualities. When carbomers are utilised as controlled release polymers in matrix tablets, polymer ratios of 3 to 30 percent are necessary. Hydrogels derived from Carbopol and polycarbophil are generally extremely permeable to a variety of pharmacological compounds and can be designed to "swell," thereby releasing entrapped molecules via their network-like structures [24-25]. By adjusting the polymer concentration, the drug release can be fine-tuned.

Poly(ethylene oxide) (PEO)

Because the rate of swelling and erosion of the polymer permits the prolonged release of APIs, high molecular weight PEO has been successfully utilised in controlled release dosage forms. In its swelled condition, high molecular weight PEO is viscoelastic because it may form dense polymeric networks in aqueous settings [26]. PEO is therefore of relevance as an addition for enhancing the mechanical properties of highly swellable and mechanically strong matrix tablets.

Kollidon® SR

Kollidon® SR is a combination of poly(vinyl acetate) (PVAc) and povidone (poly(N-vinyl pyrrolidone) (PVP) that is primarily employed as a matrix retarding agent. It is particularly suited for the direct compression or hot melt extrusion of pH-independent sustained-release matrix tablets. PVAc is a polymeric substance that creates a cohesive matrix even when subjected to low compression stresses. When the tablets are administered to gastric or intestinal fluid, the water-soluble PVP is leached out to generate pores through which the active ingredient slowly diffuses. Kollidon® SR is inert to drug compounds and its sustained-release features are unaffected by ions or salts because it has no ionic groups [29-30].

CONCLUSIONS

To date, extensive research has been conducted on GRDDS to overcome the drawbacks of conventional dosage forms, with gastroretentive formulations being the most promising methods. However, there is no answer to the problems associated with each and every dosage form of the many APIs in the therapeutic arsenal. Each drug has specific needs that must be met by formulations competent to provide therapeutic bioavailability. Consequently, it is essential to examine gastroretentive dose forms separately. Important quality parameters of gastroretentive formulations include, among others, buoyancy, floating force, gel strength, drug release in vitro, swelling capacity, and hydrogel porosity. Understanding polymer behaviour and its role in formulations is crucial for the formulation-based logical design of gastroretentive dosage forms. For the advancement of the creation of gastroretentive formulations, the choice of polymeric components in each formulation, either singly or in combination, is a significant variable. In addition, the deficiencies of floating systems can be reduced by dual-working systems, which are typically less affected by physiological variables. Numerous techniques are currently applied to improve gastric retention. The objective of this review was to aid in the design of such systems through the knowledge of suitable polymers or the development of innovative materials with tailor-made characteristics that provide ideal physicochemical attributes and in-vitro and in-vivo performance.

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