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BRIEF REVIEW OF POLYMERS USE IN RAFT FORMING SYSTEM

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Abstract: In recent era various technologies have been made in research and development of controlled release oral drug delivery system to overcome various physiological difficulties such as variation in gastric retention and emptying time. To overcome this drawback and to maximize the oral absorption of various drugs, novel drug delivery systems have been developed. Gastroretentive drug delivery system is facing many challenges which can be overcome by upcoming newly emerging approach i.e. raft forming system. The purpose of writing this review is to focus on recent used polymers in raft forming system to circumvent the difficulties associated with formulation design. Various gastroretentive approaches that have been developed till now are also discussed. The present study provides valuable information & highlights advances in this raft forming system. Different types of smart polymers used for their formulation have also been summarized. The review focuses on the mechanism, formulation and development of the raft forming system.

Keywords: Polymers, Raft Forming, GIT

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INTRODUCTION

Oral drug delivery is the most desirable and preferred method of administering therapeutics agent for their systemic effect. The high level of patient compliance in taking oral dosage forms is due to the ease of administration patient compliance, flexibility in formulation and handling of these forms. This system has been of limited success. Oral dosage forms have proved to be successful in achieving a plethora of controlled release objectives ranging from immediate release to site specific delivery[1-2]. An although tremendous advances have been seen in oral controlled drug delivery system during last two decades. Oral formulations are being developed into different types, such as controlled release, delayed release, fast dissolving and taste masking formulations (Appaji, 2001) and other delivery technologies are being tried to deliver already existing and new drug molecules, oral formulations still control more than 60% of the market inability to restrain and localize the DDS within the desired regions of the GIT (Rouge et al., 1996; Hajeri and Amiji,2002).This approach has several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract (GIT) due to variable gastric emptying and motility[3].

Gastro-Retentive Drug Delivery Systems

Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. 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 intestines. Slowed motility of the gastrointestinal tract by concomitant administration of drugs or pharmaceutical excipients also increase gastric retention of drug [4]

Approaches to Gastro-Retentive Drug Delivery Systems [5]

1. High Density Drug Delivery System
2. Floating Drug Delivery System
3. Hydro dynamically Balanced Drug Delivery System
4. Gas Generating Drug Delivery System
5. Raft-Forming Drug Delivery System
6. Low Density Drug Delivery System
7. Expandable Drug Delivery System
8. Supper porous Hydro Gel
9. Mucoadhesive Drug Delivery System
10. Magnetic Drug Delivery System

FLOATING DRUG DELIVERY SYSTEM

DEFINITION

Floating Oral Drug Delivery System (FDDS) are retained in the stomach and are useful for drugs that are poorly soluble or unstable in intestinal fluids. Floating drug delivery system (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time (Yie W. Chein et al, 1992). 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 fluctuations in plasma drug concentration [6]

Basic GIT Physiology

Anatomically the stomach is divided in to three regions Fundus, Body and Antrum (pylorus). The design and evaluation of FDDS is based on anatomy and physiology of GIT. The stomach is J shaped dilated portion of the alimentary tract situated in the epigastria, umbilical and left hypochondriac regions of abdominal cavity [7] .The Gastrointestinal tract is essentially a tube about nine metres long that runs through the middle of the body from the mouth to the anus and includes the throat (pharynx), oesophagus, stomach, small intestine (consisting of the duodenum, jejunum and ileum) and large intestine (consisting of the cecum, appendix, colon and rectum) (Bannister, 1995). The wall of the gastrointestinal tract has the same general structure throughout most of its length from the oesophagus to the anus, with some local variations for each region (Figure 1). The stomach is an organ with a capacity for storage and mixing [8]. The average length of the stomach is about 0.2 meter and the apparent absorbing surface area is about 0.1 sq. meters. The proximal part made of fundus and body acts as a reservoir for undigested materials, where as the site for mixing motions and acts as a pump for gastric emptying by propelling actions [9]

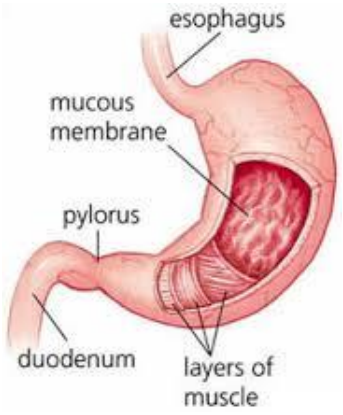


Figure 1 (human stomach)

Process of Gastric Emptying

Gastric emptying occurs in both the fasting and fed states. During the fasting state an interdigestive series of electrical events take place which cycle both through stomach and intestine every 2-3 hrs, which is called as interdigestive myloelectric cycle or migrating myloelectric cycle (MMC) which is further divided in to four phases. After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state which is also termed as digestive motility pattern (Figure2).

1. Phase 1-(Basic phase)-last from 30-60 minutes with rare contractions.

2. Phase 2-(Preburst phase)-last for 20-40 minutes with intermittent action potential and contractions.

3. Phase 3-(Burst phase) - last for 10-20 minutes which includes intense and regular contractions for short period.

4. Phase 4-last for 0-5 minutes and occurs between phase 2 and 1 of 2 consecutive cycles.

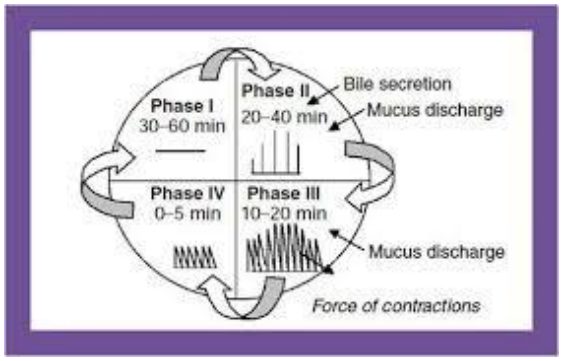


Figure 2 (phase of stomach)

MERITS OF GRDDS

- Delivery of drugs with narrow absorption window in the small intestine region.
- Longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease.
- Improved bio-availability is expected for drugs that are absorbed readily upon release in the GI tract such as cyclosporine, ciprofloxacin, ranitidine, amoxicillin, captopril, etc.
- Patient compliance by making a once a day therapy.
- Improved therapeutic efficacy [10]

DRUGS WHICH REQUIRE GASTRIC RETENTION

1) Drugs acting locally in the stomach E.g. Antacids and drugs for H. Pylori viz., Misoprostol

2) Drugs that are primarily absorbed in the stomach E.g. Amoxicillin

3) Drugs those are poorly soluble at alkaline pH E.g. Furosemide, Diazepam, Verapamil, etc.

4) Drugs with a narrow window of absorption E.g. Cyclosporine, Methotrexate, Levodopa, etc.

5) Drugs which are absorbed rapidly from the GI tract. E.g. Metonidazole, tetracycline.

LIMITATIONS OF THE TECHNIQUES OF GASTRORETENTION

More predictable and reproducible floating properties should be achieved in all the extreme gastric conditions.

1. The floating systems in patients with achlorhydria can be questionable in case of swellable systems, faster swelling properties are required and complete swelling of the system should be achieved well before the gastric emptying time.

2. Bio adhesion in the acidic environment and high turnover of mucus may rise. Questions about the effectiveness of this technique. Similarly retention of high density systems in the antrum part under the migrating waves of the stomach is questionable.

3. Not suitable for drugs that may cause gastric lesions e.g. Non- steroidal anti-inflammatory drugs. Drugs that are unstable in the strong acidic environment, these systems do not offer significant advantages over the conventional dosage forms for drugs that are absorbed throughout the gastrointestinal tract.

4. The mucus on the walls of the stomach is in a state of constant renewal, resulting in unpredictable adherence.

5. In all the above systems the physical integrity of the system is very important and primary requirement for the success of these systems [11,12]

Table 1: comparison of conventional drug delivery system and GRDDS [13]

CONVENTIONAL DRUG DELIVERY SYSTEM	GASTRORETENTIVE DRUG DELIVERY SYSTEM
High risk of toxicity	Very low risk of toxicity
Less patient compliance	Improves patient compliance
Not suitable for delivery of drugs with narrow absorption window in small intestine region	Suitable for delivery of drugs with narrow absorption window in small intestine region
Not much advantageous for	Very much advantageous for
-Drugs having rapid absorption through GIT	-Drugs acting locally in the stomach
-Drugs which degrade in the colon	-Drugs which degrade in the colon
-Drugs acting locally in the stomach	-Drugs having rapid absorption through GIT
No risk of dose dumping	Possibility of dose dumping

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, where in 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 an antacid Raft forming floating system. The system contains gel forming agent (e.g. alginic bicarbonate, calcium carbonate, mannitol and a sweetener. These ingredients were granulated, and citric acid was added to the granules. The formulation produces effervescence and aerates the raft formed, making it float 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 (figure 3). A patent assigned to Reckitt and Colman Products Ltd., describes a raft forming formulation for the treatment of helicobacter pylori (H. Pylori) infections in the GIT [14].

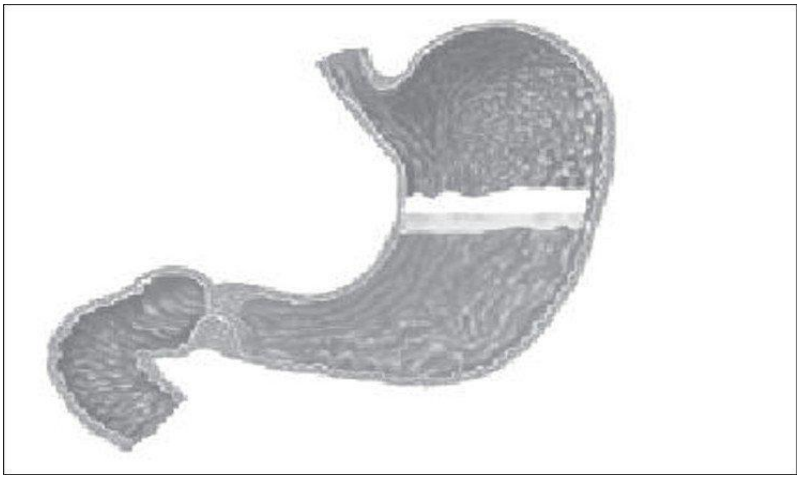
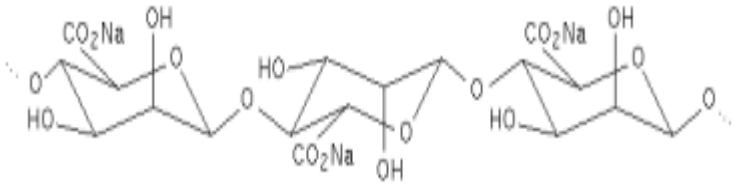


Figure (3) Raft forming system

DIFFERENT TYPES OF POLYMERS USE IN RAFT FORMING SYSTEM

Sodium alginate

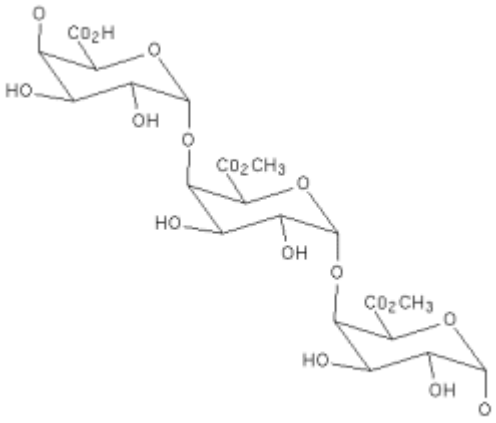
Sodium alginate is a widely used polymer of natural origin. Chemically, it is alginic acid salt, consisting of –L-glucuronic acid and -D-mannuronic acid residues connected by 1,4-glycosidic linkages. Solution of alginates in water form firm gels in presence of di-or trivalent ions (e.g. calcium and magnesium ions). Alginates salts, specifically, sodium alginate is mostly used for preparation of gel forming solution, for delivery of the drugs and proteins. Alginate salts are considered most favourable because of biodegradable and non toxic nature, with additional bio- adhesive property .Sodium alginate is a salt of Alginic acid - a linear block copolymer polysaccharide consisting of β- D-mannuronic acid and α-L-glucuronic acid residues joined by 1,4-glycosidic linkages. Aqueous solutions of alginates form firm gels on addition of di- and trivalent metal ions. The results indicated that the alginates form compact structures when the ionic radical of the cation are lower. Sodium alginate has been employed in the preparation of gels for the delivery of bio molecules such as drugs, peptides and proteins [15, 16, 17, 18].



Pectin

These are plant origin anionic characteristics can be divided into two polysaccharides isolated from the cell wall of most plants and basically consist of -(1-4) -D-galacturonic acid residues. Pectin undergoes gel formation in presence of medium, a stiff gel is produced. The gelling capacity divalent ions (e.g. Ca) which causes cross linking of the is determined on the 2+ basis

of stiffness and time galacturonic acid units (ionic cross linking) and also in the period for which gel remains, as such .presence of the H+ ions (pH dependent gelling). Pectin is a complex polysaccharide comprising mainly esterified D-galacturonic acid residues in an a-(1–4) chain. The acid groups along the chain are largely esterified with methoxy groups in the natural product. The hydroxyl groups may also be acetylated. Pectin gelatine types: high-methoxy and low-methoxy gelation. Gelation of highmethoxypectin usually occurs at pH < 3.5. Low-methoxy pectin is gelled with calcium ions and is not dependent on the presence of acid or high solids content [15].



Gellan gum

Gellan gum (FDA approved) secreted by the *Sphingomonas elodea (Pseudomonaselodea)* and chemically is anionic deacetylated polysaccharide with repeating tetrasaccharide units composed of -D-glucuronic acid (1 unit), -L-rhamnose (1 unit) and -D-glucuronic acid (2 units) residues. Gellan gum undergoes gel formation due to change in temperature or due to presence of cations (e.g. Na+K+, Ca2+). Gellan gum is an anionic deacetylatedexocellular polysaccharide secreted by Pseudomonas elodea with a tetrasaccharide repeating unit of one α-L- rhamnose, one β-D-glucuronic acid and two β-D-glucuronic acid residues. It is a water soluble polysaccharide. It forms a gelvia formation of double helices, followed by their ionic cross-linking [16, 17, 18] .

Xyloglucan

It is a plant based polysaccharide obtained from seeds of tamarind. Chemically, this polysaccharide composed of a chain of (1-4)- -D-glucan having (1-6)-D xylose units as branches which have partial (1-2)- -D-galactoxylose substitution. Xyloglucan, itself, does no undergo gel formation but dilute solutions partly degraded by galactosidase exhibit gelling properties on heating (temperature dependent gelformation). Besides the use in oral drug delivery, it is also being used for ocular and rectal drug delivery. Xyloglucan has shown a very low gelation time of

up to few minutes. Xyloglucan is a polysaccharide derived from tamarind seeds and is composed of a (1-4)-β-D- glucan backbone chain, which has (1-6)-α- D xylose branches that are partially substituted by (1-2)-β-D-galactoxylose. Xyloglucan is composed of heptasaccharide, octasaccharide and nonasaccharide oligamers, which differ in the number of galactose side chains. Although xyloglucan itself does not gel, dilute solutions of xyloglucan which has been partially degraded by galactosidase exhibit a thermally reversible sol–gel transition on heating [15].

Xanthan gum

Xanthan gum is a high molecular weight extra cellular polysaccharide seeds and is composed of a (1-4)-β-D- glucan backbone chain, which has (1-6)-α- D xylose branches that are partially substituted by (1-2)-β-D-galactoxylose. Xyloglucan is composed of heptasaccharide, octasaccharide and nonasaccharideoligamers, which differ in the number of galactose side chains. Although xyloglucan itself does not gel, dilute solutions of xyloglucan which has been partially degraded by galactosidase exhibit a thermally reversible sol–gel transition on heating [18].

Pluronic F-127

Poloxamers or pluronic (marketed by BASF Corporation) are the series of commercially available difunctional triblock copolymers of non-ionic nature. They comprise of a central block of relatively hydrophobic polypropylene oxide surrounded on both sides by the blocks of relatively hydrophilic poly ethylene oxide. Due to the PEO/PPO ration of 2:1, when these molecules are immersed into the aqueous solvents, they form micellar structures above critical micellar concentration. They are regarded as PEOPPO- PEO copolymers. Chemically they are Oxirane, methyl-, polymer with oxirane or α-Hydro-ω- hydroxypoly (oxyethylene) a poly (oxypropylene) b poly (oxyethylene) a block copolymer. The pluronic triblock copolymers are available in various grades differing in molecular weights and physical forms. Depending upon the physical designation for the grades are assigned, as F for flakes, P for paste, L for liquid. Pluronics or Poloxamers also undergo in situ gelation by temperature change [19] .

Chitosan

Chitosan is a biodegradable, thermo sensitive, polycationic polymer obtained by alkalinedeacetylation of chitin, a natural component of shrimp and crab shell. Chitosan is a biocompatible pH dependent cationic polymer, which remains dissolved in aqueous solutions up to a pH of 6.2 Neutralization of chitosan aqueous solution to a pH exceeding 6.2 leads to the formation of a hydrated gel like precipitate. The pH gelling cationic polysaccharides solution are transformed into thermally sensitive pH dependent gel forming aqueous solutions, without any chemical modification or cross linking by addition of polyol salts bearing a single

anionic head such as glycerol, sorbitol, fructose or glucose phosphate salts to chitosanaqueous solution [20].

Carbopol

Carbopol is a well known pH dependent polymer, which stays in solution form at acidic pH but forms a low viscosity gel at alkaline pH. HPMC is used in combination with carbapol to impart the viscosity to carbopol solution, while reducing the acidity of the solution. Various water triblock copolymers consisting of poly (oxyethylene) and poly (oxypropylene) units that undergo changes in solubility with change in environment temperature. Pluronic ™ F 127. A 25-40% aqueous solution of this material will gel at about body temperature, and drug release from such a gel occurs over a period of up to one week [21, 22].

CONCLUSION:

Controlled release gastroretentive dosage forms (CR- GRDF) enable prolonged and continuous input of the drug to the upper parts of the gastrointestinal (GI) tract and improve the bioavailability of medications that are characterized by a narrow absorption window. 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. Usually, the raft system contains a gel forming polymers 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 different polymers (e.g. alginic acid), sodium bicarbonate and acid neutralizer, which forms a foaming raft gel 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 although a large number of companies are focusing toward commercializing this technique. It can be concluded that these polymers serve the best in the treatment of diseases related to the GIT.

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