



AN OVERVIEW ON VARIOUS APPROACHES TO ORAL CONTROLLED DRUG DELIVERY SYSTEM VIA GASTRORETENTIVE DRUG DELIVERY SYSTEM

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ABSTRACT

In recent years scientific and technological advancements have been made in the research and development of oral drug delivery system. Oral sustained drug delivery system is complicated by limited gastric residence times (GRTs). In order to understand various physiological difficulties to achieve gastric retention, we have summarized important factors controlling gastric retention. To overcome these limitations, various approaches have been proposed to increase gastric residence of drug delivery systems in the upper part of the gastrointestinal tract includes floating drug dosage systems (FDDS), swelling or expanding systems, mucoadhesive systems, magnetic systems, modified-shape systems, high density system and other delayed gastric emptying devices.

Keywords: Gastroretentive systems; Floating systems; buoyant delivery Systems; Swelling System

INTRODUCTION

The oral route is the one, most frequently used for drug administration. Oral dosage forms are usually indicated for systemic effects resulting from drug absorption through various epithelia and mucosa of the gastro intestinal tract. Compared with other routes, the oral route is the simplest, most convenient and safest means of drug administration.¹ The treatment of illness has been accomplished by administering drug to the human body via various pharmaceutical dosage forms like tablet, capsule, and microspheres. To achieve and maintain the therapeutics range extensive effort have recently been focused on targeting a drug or drug delivery system in a particular region of the body for extended period of time, not only for local targeting of drug but for better control of systemic drug delivery. To achieve and maintain the drug concentration in the body within the therapeutics range required for medication, it is necessary to take this type of drug delivery system several times a day this yield undesirable 'seesaw' drug level in body. A number of advancement has been made recently in the development of new technique for drug delivery, the technique capable of regulating the rate of drug delivery system²

To gain an appreciation for the value of controlled drug therapy it is useful to review some fundamental aspects of conventional drug delivery. Depending on the route of administration, a conventional dosage form of the drug, e.g. a solution, suspension, capsule, tablet etc. can produce a drug blood level versus time profile which does not maintain drug blood level within the therapeutic range for extended periods of time. An alternative approach is to administer the drug repetitively using a constant dosing interval, as in multiple dose therapy. There are several potential problems inherent in multiple dose therapy:

The dosing interval is not appropriate for biological half life of the drug, large peaks and valleys in the drug blood level may result.

The drug blood level may not be within the therapeutic range at sufficiently early times, an important consideration for certain disease states.

Patient non compliance with the multiple dosing regimens can result in failure of this approach. However, these problems are significant enough to make drug therapy with

conventional dosage forms less desirable than controlled release drug therapy.²

Controlled release dosage form covers a wide range of prolonged action formulations which provides continuous release of their active ingredients at a predetermined rate and for a predetermined time. The majority of these formulations are designed for oral administration. The most important objective for the development of these systems is to furnish an extended duration of action and thus assure greater patient compliance.³

Rationale of controlled drug delivery system

The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery systems or by modifying the molecular structure and/or physiological parameters inherent in a selected route of administration. Thus, optimal design of controlled release systems necessitates a thorough understanding of the pharmacokinetics and pharmacodynamics of drug.⁴ However, when doses are not administered on schedule, the resulting peaks and valleys reflect less than optimum drug therapy.

Extended release tablets and capsules are commonly taken only once or twice daily compared with counterpart conventional forms that may need to be taken three to four times daily to achieve the same therapeutic effect. Typically, extended release products provide an immediate release of drug which then is followed by the gradual and continual release of additional amounts of drug to maintain this effect over a predetermined period of time (Fig 1).²

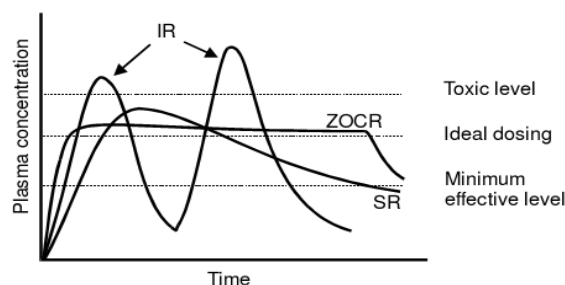


Fig.1 Characteristic representation of plasma concentrations of a conventional immediate release dosage form (IR), a sustained release dosage form (SR) and an idealized zero-order controlled release (ZO) dosage form (in combination with a start-up dose).

ADVANTAGES AND DISADVANTAGES OF CONTROLLED RELEASE DOSAGE FORM

The design of controlled release dosage forms holds many advantages over conventional dosage forms like:^{5, 6, 7}

- Reduction in frequency of drug administration.
- Improved patient compliance.
- Reduction in drug level fluctuation in blood.
- Reduction in total drug usage when compared with conventional therapy.
- Reduction in drug accumulation with chronic therapy.
- Reduction in drug toxicity (local/systemic).
- Stabilization of medical condition (because of more uniform drug levels).
- Improvement in bioavailability of some drugs because of spatial control.
- Economical to the health care providers and the patient.

Disadvantages of Controlled drug delivery system:

- Decreased systemic availability in comparison to immediate release conventional dosage forms; this may be due to incomplete release, increased first pass metabolism, increased instability, pH dependent solubility, etc.^{8, 9}
- Poor in vitro-in vivo correlation.
- Possibility of dose dumping due to food, physiologic or formulation variables or chewing or grinding of oral formulation by the patients and thus, increased risk of toxicity.
- Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reaction.^{8, 9}
- Higher cost of formulation.

WHY IS CONTROLLED DRUG DELIVERY NEEDED ?

1. To localize certain drugs at a specific site in the body.^{2, 4, 12}
2. The extend of drug absorption is limited by the residence time of the drug at the absorption site, localizing oral drug delivery system in the stomach or in the duodenum would significantly improve the extend of drug absorption .
3. They provide intimate contact between a dosage form and the absorbing tissue which may result in high concentration at a local area and hence drug flux through the absorbing tissue.
4. Maintenance of drug concentration within an optimal therapeutics range for prolongs duration of treatment.

CLASSIFICATION OF ORAL CONTROLLED DRUG DELIVERY SYSTEMS

Continuous Release Systems

1. Dissolution controlled release systems
2. Diffusion controlled release systems
3. Dissolution and diffusion controlled release systems
4. Ion-exchange resin-drug complexes
5. Slow dissolving salts and complexes
6. Osmotic pressure controlled systems
7. pH-dependent formulations
8. Hydrodynamic pressure controlled systems

Delayed Transit and Continuous Release Systems

1. Altered density systems
2. Mucoadhesive systems
3. Size-based systems

Delayed Release Systems

1. Intestinal release systems
2. Colonic release systems

GASTRO-RETENTIVE DRUG DELIVERY SYSTEMS

The limitations conferred by CRDDS have led to the development of gastro-retentive drug delivery systems (GR-

DDS). Poor absorption or stability issue of many drugs in the lower gastrointestinal (GI) tract necessitates controlled release dosage forms to be maintained in the upper GI tract, particularly the stomach and small intestine. GR-DDS are designed on the basis of delayed gastric emptying and controlled release principles. As rapid GI transit can prevent complete drug release in absorption zone and reduce efficacy of the administered dose, these systems are intended to restrain and localize the dosage form in the stomach or within the upper parts of the small intestine, for a prolonged and predictable period of time, until the system is devoid of the drug^{8, 10, 11, 12}.

GIT Anatomy

The GI tract is essentially a tube about nine meters long that runs through the middle of the body from the mouth to anus and include throat(pharynx), oesophagus ,stomach, small intestine (consisting of duodenum, jejunum and ileum),and large intestine(consisting of the cecum, appendix, colon and rectum). The wall of GI tract has the same general structure throughout most of its length from oesophagus to anus, with some local variation for each region⁸.

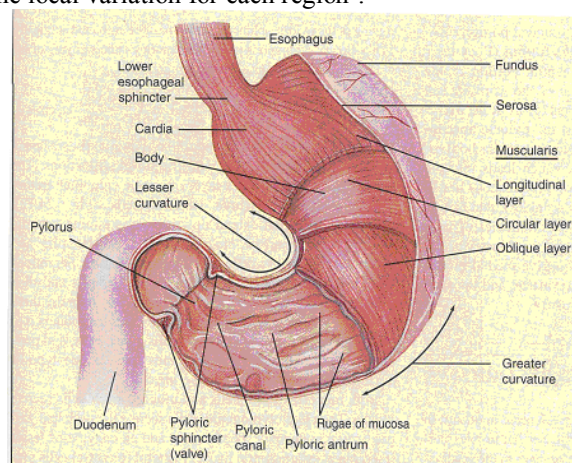


Fig. 2 Human Stomach

The stomach is an organ with a capacity of storage and mixing. The stomach is situated in the left upper part of the abdominal cavity immediately under the diaphragm^{9, 33}. Its size varies according to the amount of distention: up to 1500ml following a meal; after food is emptied a collapsed state is obtained with a resting volume of only 25-50ml^{20, 33, 34}. Anatomically the stomach is divided in to three region fundus, body and antrum (pylorus).The proximal part made of fundus and body acts as a reservoir for undigested materials, where as the antrum is the main site for mixing motions and acts as a pump for gastric emptying by propelling actions. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours^{12, 36}. This is called the interdigestive myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington^{13, 35}.

Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.

Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to

this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

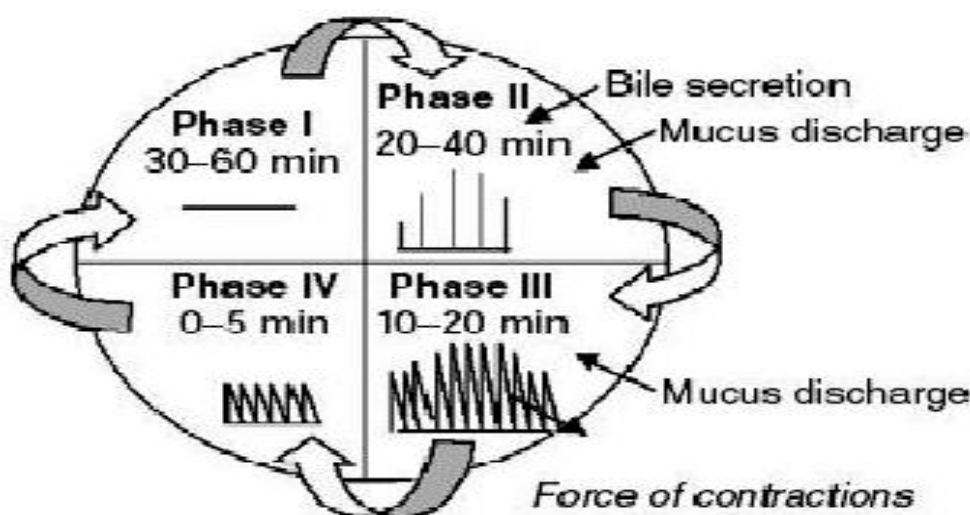


Fig. 3 Gastrointestinal Motility Pattern

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate¹⁴.

ADVANTAGES OF GASTRO-RETENTIVE DRUG DELIVERY SYSTEMS

The advantages associated with increased gastric residence time of drug can be listed as^{8, 12, 14}:

- Retention of dosage form in the stomach for an extended period of time.
- Prolonged dosing interval.
- Controlled and continuous release of the drug.
- Site-specific drug delivery.
- Enhanced bioavailability of drugs.
- Reduced drug plasma level fluctuations.
- Improved pharmacotherapy of stomach through local drug release.
- Improved solubility for drugs that are less soluble in a high pH environment.
- Delivery of drugs with narrow absorption windows in the small intestinal region.
- Better in vivo-in vitro correlation have been observed in some cases.

LIMITATIONS OF GASTRO-RETENTIVE DRUG DELIVERY SYSTEM

- GR-DDS like floating drug delivery system requires a sufficiently high level of fluids in the stomach for the delivery system to float and work efficiently.^{8,13}
- GR-DDS are not feasible for drugs that have solubility or stability problems in the gastric fluid.
- Drugs which have nonspecific, wide absorption sites in the GIT, drugs that are well absorbed along the entire GIT are not suitable candidates for GR-DDS; e.g. nifedipine.^{8,13}

- Similarly drugs that are irritant to the gastric mucosa and drugs that undergo significant first-pass metabolism are not preferred for GR-DDS.^{8,13}

FACTOR AFFECTING GASTRIC RESIDENCE TIME OF DRUG

1. Density – gastric retention time (GRT) is a function of dosage form buoyancy that is dependent on the density.¹
2. Size – dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm.
3. Shape of dosage form – tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes.⁴
4. Single or multiple unit formulation – multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.
5. Fed or unfed state – under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.
6. Nature of meal – feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.
7. Caloric content – GRT can be increased by four to 10 hours with a meal that is high in proteins and fats.¹²

8. Frequency of feed – the GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.
9. Gender – mean ambulatory GRT in males (3.4 ± 0.6 hours) is less compared with their age and race matched female counterparts (4.6 ± 1.2 hours), regardless of the weight, height and body surface).
10. Age – elderly people, especially those over 70, have a significantly longer GRT.¹⁴

APPROACHES TO GASTRO-RETENTIVE DRUG DELIVERY SYSTEMS

Taking into consideration rapid transit of dosage form from stomach, various approaches such as mucoadhesive, expandable/swelling, high density, superporous hydrogel and floating drug delivery systems have been developed to increase gastric residence time of dosage forms.^{14, 15}

1. Mucoadhesive systems

The mucoadhesive systems are intended to extend the GRT by adhering them to the gastric mucosa membrane. Bioadhesion on soft tissues of certain natural or synthetic polymers has been exploited to control as well as to prolong the gastric retention of the delivery system. The adhesion of the polymers with mucous membrane may be mediated by hydration, bonding, or receptor mediated. In hydration mediated adhesion, the hydrophilic polymers become sticky and mucoadhesive upon hydration. Bonding mediated adhesion may involve mechanical or chemical bonding. Receptor mediated adhesion takes place between certain polymers and specific receptors expressed on gastric cells. The polymers could be anionic or cationic or neutral. Materials commonly used for mucoadhesion/ bioadhesion are poly (acrylic acid), carbopol, polycarbophil, chitosan, cholestyramine, HPMC, polylactic acid etc. Smart and Kellaway reported prolonged gastric retention of dosage forms coated with carbomer in mice¹⁶. In vivo data of granules containing microcrystalline chitosan and furosemide showed higher AUC than that of the conventional dosage form. Also, the granules exhibited slow release characteristics with a marked lag time. It appeared that due to its mucoadhesive properties, chitosan retained the drug in the gastric mucosa for longer period of time¹⁷.

2. Swelling / expandable systems

The presence of polymers in the systems promotes their swelling to a size that prevents their passage through pyloric sphincter resulting in prolonged GRT. However, a balance between the rate and extent of swelling and the rate of erosion of the polymer is crucial to achieve optimum benefits and to avoid unwanted side effects. Agyiliraha¹⁸ developed a polymeric coating system that formed an outer membrane on the conventional tablets. In the dissolution media the membrane detached from the core and swelled to form a balloon that kept the unit floating.¹⁸

3. High- density systems

High density systems are intended to lodge in the rugae of the stomach withstanding the peristaltic movements. Systems with a density of 1.3 g/ ml or higher are expected to be retained in the lower part of the stomach¹⁹. The formulation of heavy pellets is based on the assumption that the pellets might be positioned in the lower part of the antrum because of their higher density. Devreux et al²⁰ reported that the pellets with density of at least 1.5 g/ ml have significantly higher residence time both in fasted and fed state.

4. Floating systems

The floating system is intended to float in and over the gastric contents resulting in prolonged GRT. They have bulk density lower than the gastric content. Various patents have been granted on different floating systems including hydrodynamically balanced system (HBS) and gas generating systems.²¹

I. Hydro dynamically balanced systems

These are single-unit dosage forms, containing one or more gel-forming hydrophilic polymers. Hydroxypropylmethylcellulose (HPMC) is the most commonly used excipient; although hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), sodium carboxymethylcellulose (NaCMC), agar, carrageen or alginic acid are also used. The polymer is mixed with drug and usually administered in a gelatin capsule. The capsule rapidly dissolves in the gastric fluid, and hydration and swelling of the surface polymers produces a floating mass.

Drug release is controlled by the formation of a hydrated boundary at the surface. Continuous erosion of the surface allows water penetration to the inner layers, maintaining surface hydration and buoyancy²². Incorporation of fatty excipients gives low-density formulations and reduced penetration of water, reducing the erosion. Effective drug delivery depends on the balance of drug loading and the effect of polymer on its release profile²³.

II. Gas-generating systems

Floatability can also be achieved by generation of gas bubbles. Carbon dioxide (CO_2) can be generated in situ by incorporation of carbonates or bicarbonates, which react with acid, either the natural gastric acid or co-formulated as citric or tartaric acid.

Gastric floating drug delivery system (GFDDS) offers numerous advantages over other gastric retention systems. These 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 desired rate from the stomach.

Other approaches to extend gastric residence time are magnetic systems, geometric systems (modified-shaped systems), co-administration of fatty acid salts, opiates and anticholinergics like propantheline, atropine, and polycarbophil or enzyme-digestible hydrogels.^{13, 24}

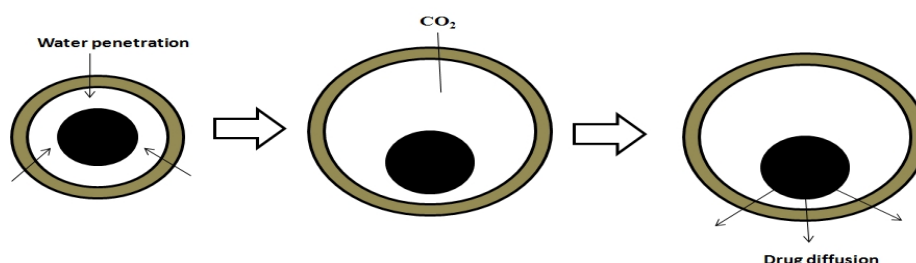
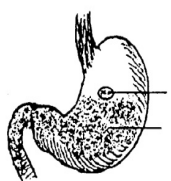
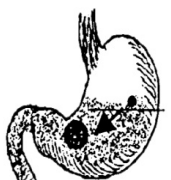
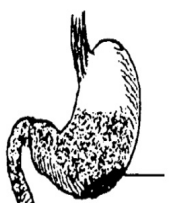
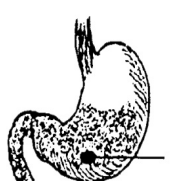


Fig. 4 Drug release from gas generating system

Table 1: Schematic representation for approaches to gastro retentive drug delivery systems^{25,26,27}

Approach	Diagram	Mechanism of action
Floating systems		Remains buoyant over gastric fluid for prolonged time as their density is less than that of the gastric contents, i.e. less than 1.0 g/ml.
Expandable systems		Swells or unfolds and increases in size, remains lodged at sphincter. Hence exit from stomach is prevented.
Mucoadhesive systems		Adheres to epithelial surface of GIT
High-density/ Sedimentation systems		Retains in rugae or antrum of stomach.

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. 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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