



STOMACH TARGETED DRUG DELIVERY SYSTEMS: ADVENTS AND FUTURE PERSPECTIVES

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ABSTRACT

Stomach targeted or gastro retentive dosage forms are one of the most widely known and accepted forms of oral controlled release drug delivery systems. These systems are designed with an objective to overcome the shortcomings of conventional dosage forms, particularly of short gastric residence time and erratic gastric emptying time. For years, several approaches are devised to surpass above problems, yet there is a lot of scope and research potential in these delivery systems which is to be discovered. This article deals with the major advancements of this field and highlights the future perspectives of such systems.

Keywords: Stomach targeted, gastro retentive, controlled release drug delivery systems, advents and future perspectives.

INTRODUCTION

During past 4 decades, the idea of gastro retention is known to researchers and is popularly cultured. Davis, in 1968, 1st described the concept of floating drug delivery systems¹. To understand the approaches for gastro retention, it is necessary to overview gastric physiology and gastric motility. Human stomach has a resting volume of 25-50ml, which can distend up to 1500ml following a meal^{2,3,4}. It is divided into 3 anatomical parts; Fig.1.

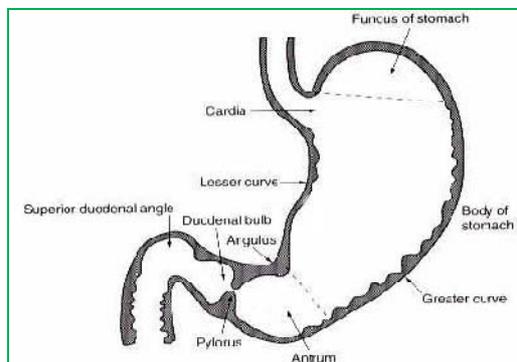


Figure 1: Anatomy of Stomach⁵

- Fundus: also called proximal stomach, which acts as food reservoir.
- Body
- Pylorus or antrum: also called distal stomach, which acts as a site of mixing motions to propel gastric contents for emptying⁵. Pyloric sphincter has a diameter of 12.8±7mm in humans and serves as a sieve and stricture to passage of large particles^{4,6,7}.

Gastric motility is also a key factor in stomach specific drug delivery. Thorough knowledge of motility is prerequisite for developing a retentive form of drug. Gastric motility differs in fasting and fed states. In fasting states, an Interdigestive myoelectric motor complex

(IMMC), a 2 hr. cycle of peristalsis is generated which progresses to ileocecal junction⁵. It consists of 4 phases:

- Phase I: also called quiescent period with rare low amplitude contractions, lasting for 30-60 min.
- Phase II: it comprises of intermediate amplitude contractions with bile secretion, lasting for 20-40 min.
- Phase III: also called Housekeeper waves, it forms of very high amplitude contractions offering maximum pyloric opening and efficient evacuation of stomach contents. It lasts for 10-20 min. with a frequency of 4-5/min.
- Phase IV: transitional phase between phase III and I of two consecutive cycles. It lasts for less than 5 min^{1,8,9}.

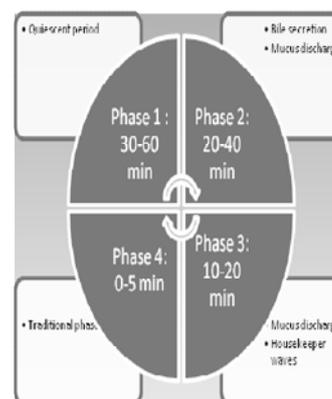


Figure 2: Schematic presentation of IMMC

In fed states, motility is induced 5-10 min after ingestion and persists as long as food remains in stomach, typically 3-4 hr. Activity is same as phase2 of IMMC¹.

Gastro retentivity of drug was required to increase the bioavailability of drug and to reduce the undesirable

effects caused by exposure of drug to other regions of GIT. It is mainly devised for^{5, 12}

a) Drugs having low bioavailability or narrow absorption window eg. L-DOPA, Para Amino benzoic acid, furosemide, riboflavin etc.

b) Drugs those are locally active in the stomach eg. Misoprostol, antacids etc.

c) Drugs those are unstable in the intestinal or colonic environment e.g. captopril, metronidazole.

d) Drugs that disturb normal colonic microbes e.g. antibiotics against *Helicobacter pylori*.

e) Drugs that exhibit low solubility at high pH values e.g. diazepam, chlordiazepoxide, Verapamil HCl.

f) Drugs that absorb specifically in stomach eg. Ferrous salts.

g) Drugs that absorb efficiently from gastric barriers rather than intestinal or colonic barriers.

However, this approach is not suitable for drugs having following characteristics^{5, 12}:

a) Drugs that have very limited acid solubility eg. Phenytoin etc.

b) Drugs that suffer instability in the gastric environment e.g. erythromycin etc.

c) Drugs intended for selective release in the colon e.g. 5-amino salicylic acid and corticosteroids etc.

d) Drugs that irritate gastric mucosa or cause lesions on slow release eg. Aspirin, NSAIDS etc.

APPROACHES TO GASTRIC RETENTION

Various techniques have been developed towards such delivery forms, of which some are proven efficacious while some are inefficient. These are designed to prolong the gastric resiliency of dosage form, thereby targeting site specific drug release in upper GIT for local or systemic effects¹³.

One approach is to make a high density dosage form with density (>2.5gm/cm³) higher than density of normal gastric contents (1.004 gm/cm³), which sinks and retained for longer. It was prepared by coating drug on heavy core or heavy inert material eg. BaSO₄, ZnO, Fe powder etc. However, it wasn't found effective and not marketed^{12, 14, 15}. On the other side, floating dosage forms are designed having low density (< 1.00 gm/cm³), with or without effervescent agents eg. Sodium bicarbonate, calcium carbonate etc., which helps system to float over gastric fluid and enhance GRT¹⁶. These are found successful and formulated as films¹⁷, floating tablets (eff. or non eff., single/bilayer/multilayer tablet)^{18, 19} hydro dynamically balanced systems²⁰, micro compartment porous systems²¹, micro spheres /micro balloons²², floating beads (sodium alginate/pectin + Calcium chloride)^{23, 24}, floating granules and powders¹³.

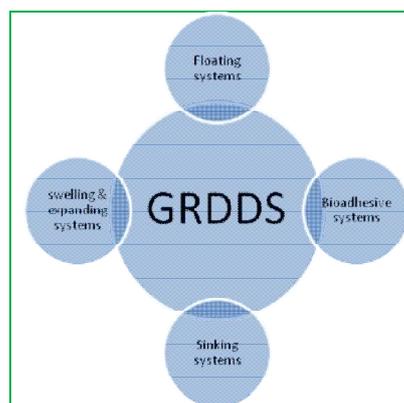


Figure 3: Approaches for Gastro retention

Another approach is to formulate a bioadhesive/mucoadhesive system that adheres to gastric mucosa / epithelium using bioadhesive polymers eg. Poly acrylic acid, HPMC, poly lactic acid, dextrin, tragacanth, sucralfate, chitosan, cholestyramine etc. Mechanism of adhesion is proposed by various theories such as wetting, diffusion, absorption, electron theory^{12, 25}.

Again, swellable (plug type) or expandable (unfoldable) systems are designed having a small form for oral intake which swells or expands to a retentive form on exposure to gastric fluids. After complete drug release, it again collapses or reduces to small form and successfully evacuated by housekeeper waves of peristaltic cycle⁴. Swellable forms are composed drug surrounded by a swelling agent and polymer layer for controlled release while expanded forms have drug formulated with shape memory polymers which expands or unfolds favouring gastric retention^{12, 26}.

Magnetic systems were also developed that contains a small magnetic core inside the dosage form and an external magnet placed on abdomen that retains the dosage form in gastric region. However, these are not used widely because of patient non-compliance^{12, 25}.

RECENT ADVENTS

Release module assemblages: An innovative drug delivery platform based on a modular technology has been developed at the University of Parma. Release modules are disc shaped devices made of a swellable hydrophilic polymeric matrix prepared by direct compression²⁷. These modules have one concave and one convex base, named Dome Matrix, which are to be assembled accordingly. Two assemblies can be obtained through interlocking of modules:

- Piled (stacked) configurations:** It is obtained by staking two or more modules convex face into concave base.
- Void configuration:** It is obtained by soldering concave base with the concave base of another module base forming a void inside which makes the device feasible to float and promote sustained drug release into the stomach. This assembly enhanced

the GRT up to 4 hr. This cavity could also be utilized as a reservoir to delivery drugs in the colon²⁸.

Moreover, Dome Matrix technology makes possible to administer two or more drug with different kinetics and delivery sites in one assembly for a once a day administration²⁵.

Colombo et al have done extensive studies on module assemblages. The correlation between swelling and drug release pattern of convex and concave bases was investigated against flat base cylindrical matrix having same weight and composition. The convex base (higher surface area/volume ratio) was found to release drug at faster rate than concave base, whereas flat base was intermediate between the two. Also, drug release from individual bases showed significant dependence on swelling process²⁹. Again, the drug release rate in void configuration was found slightly higher than that of piled configuration³⁰.

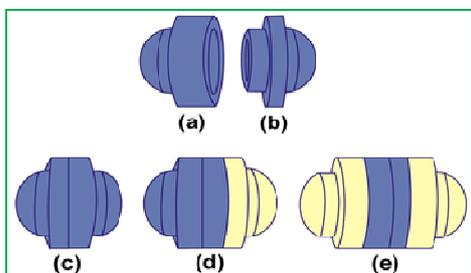


Figure 4: Schematic of (a) release module, (b) male module, (c) void configuration assembly, made by sticking male and female modules concave base to concave base, Assembled systems with additional barrier module to one (d) or both (e) convex bases of void configuration³⁰.

Minitablets for biphasic release: Biphasic multiple unit delivery system of 6mm size comprising of a fast release (loading dose) and a prolonged release (maintenance dose) component has also been developed³¹. Loading dose helps to attain a desirable therapeutic concentration and maintenance dose helps in avoiding frequent administration.

These dosage forms have an advantage of uniform size, regular shape, smooth surface, low porosity and high strength over usual pellets or granular form of drug.

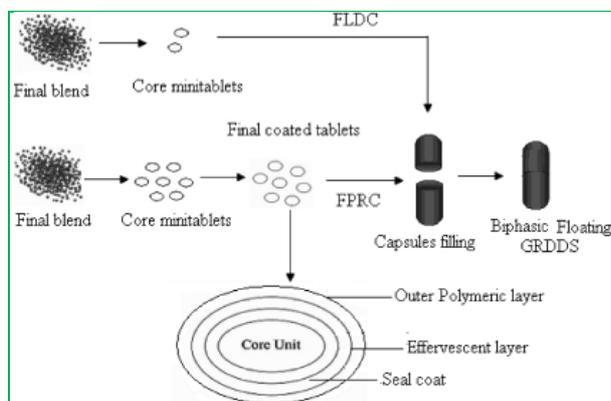


Figure 5: Schematic preparation steps for biphasic release systems³²

FLDC (Floating loading dose component) is prepared by direct compression of a blend containing drug, super disintegrant and effervescent agent. **FPRC** (floating prolonged release component) comprises of minitables containing drug and matricing agent. This is coated with a seal coat having a suitable polymer (HPMC) and a plasticizer (PEG). Then, a layer of effervescent agent is applied and finally, surrounded by outer polymeric layer (eg. Polymethacrylate dispersions) offering controlled release. Both FLDC and FPRC units are filled in capsule shell and sealed. On administration, capsule shell dissolves and releases FLDC immediately while FPRC swells and offers sustained drug release³².

Tablets with hollow cylinders: A novel approach which comprises of two drug loaded HPMC matrix tablets, placed within an open impermeable, hollow polypropylene cylinder. Each tablet closes one end of the cylinder and the air space between them provides the required buoyancy to the systems. Buoyancy is retained until at least one tablet is dissolved^{10,19}.

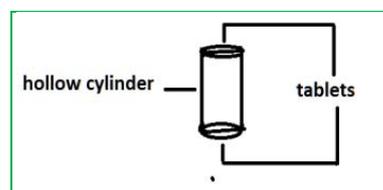


Figure 6: Tablet with hollow cylinder

Programmable drug delivery: A controlled release form is developed as a non-digestible capsule utilizing an automatically operated geometric obstruction that retains the device in stomach. Capsule consists of a slowly eroding drug matrix offering a sustained drug release. These matrices have an in-built ballooning systems housed by capsule core matrix. After complete erosion of core matrix, ballooning system is flattened off, rendering the device its normal size and evacuates from GIT^{33,34}.

Different viscosity grades of HPMC have been studied and used as model eroding matrices. The duration for which device maintains its geometric obstruction was found to be dependent on the erosion rates of used polymers.

FIGC: Rajnikanth and Mishra³⁵ have developed a floating *in situ* gelling system for clarithromycin (FIGC) using gellan as the gelling polymer and calcium carbonate as the effervescent agent for the treatment of Helicobacter pylori induced peptic ulcer. Gellan-based FIGC was prepared by dissolving different concentrations of gellan in deionized water into which different concentrations of drug and sucralfate had been uniformly dispersed. FIGC was found to have a significant anti-*H. pylori* effect as compared with that of conventional clarithromycin suspension. The addition of sucralfate was done to suppress the degradation of clarithromycin by gastric acid and it showed better action against *H. pylori* than formulations without sucralfate. In addition, the required amount of clarithromycin for eradication of *H. pylori* was found to be less with FIGC than for the corresponding

clarithromycin suspension. It was concluded that the prolonged gastric residence time and enhanced clarithromycin stability resulting from the floating *in situ* clarithromycin gel contributed to the more complete clearance of *H. pylori*³⁶.

FDDS in chronotherapy: Sher *et al*³⁷ used floating and pulsatile principles for chronotherapy of arthritis using low density microporous polypropylene, Accurel MP 1000®, as a multiparticulate carrier with ibuprofen as a model drug. The amount of carrier and solvent volume were kept constant in developing this system by adsorbing the drug via melting or solvent evaporation using different carrier: drug ratios. For solvent evaporation, methanol and dichloromethane were used. The drug-loaded multiparticulate system was characterized and evaluated for the effect of adsorption. This delivery system contained no additives/excipients influencing drug release and exhibited different behaviour from other approaches of chronotherapy like low drug release in acidic medium, overcoming the limitations of process variables, reducing consumption time due to a single step process and the property of controlled release.

Badve *et al*³⁸ also developed calcium pectinate beads of diclofenac sodium based on floating pulsating principle for chronotherapy. This system exhibited enhanced gastric resiliency having a lag phase followed by a burst release of the drug.

Casein-gelatin beads: Bulgarelli *et al*³⁹ have prepared casein-gelatin floating and non-floating beads for controlled drug delivery in stomach. Casein is simple and economical chemical having emulsifying properties and thus causes air bubbles incorporation acting as air reservoirs in floating systems. Floating beads were prepared by adding 30% solution of casein and gelatin in deionised water at 60°C and stirred to form an emulsion. Following this, temperature was lowered to 5°C by rapid cooling and then, previously cooled acetone was added to get solid beads. These are sieved and dried under vacuum. Non-floatable beads are prepared in the same manner using pretreated casein-gelatin solution under reduced pressure to remove air bubbles¹.

Super porous hydrogels (SPH): These systems have pore size ranging from 10 nm to 10 µm having very high swelling index i.e. 100 or more. They swell to a larger size & withstand pressure by gastric contractions facilitating their resiliency¹². SPH are polymeric materials which are glassy in dry state but on contact with water transforms to rubbery gel form. Water uptake in SPH is induced by capillary/osmotic/hydration forces. These are prepared by two techniques. One, copolymerization of monomers induced by irradiation or chemical stimulation using crosslinking agents. Second, gas blowing method using inorganic carbonates as foaming agents⁴⁰. However, poor mechanical strength is one of the shortcomings. To

overcome this limitation, super porous hydrogel composites (SPHC) were developed using composite agents such as chitosan, Ac-Di-Sol, carbopol etc. Mechanical strength and stability was found proportional to concentration of composite agents on account of increased physical entanglement⁴¹. In addition, these systems were advantageous having low density and good swelling properties⁴².

Intragastric osmotically controlled drug delivery systems:

An osmotically controlled floating system comprising of a hollow deformable unit which is convertible from collapsed to expanded form and then returns to collapsed state after a specific period of time. Housing was attached to a deformable unit which is internally divided into two chambers by an impermeable, pressure responsive movable bladder. One chamber contains the active drug while other chamber contains a volatile liquid eg. Cyclopentane or ether, which vaporizes at physiological temperature and imparts the required buoyancy to the system. When the drug is completely leached out, bioerodible plug degrades and allows the vapour to escape enabling its evacuation^{43, 44}.

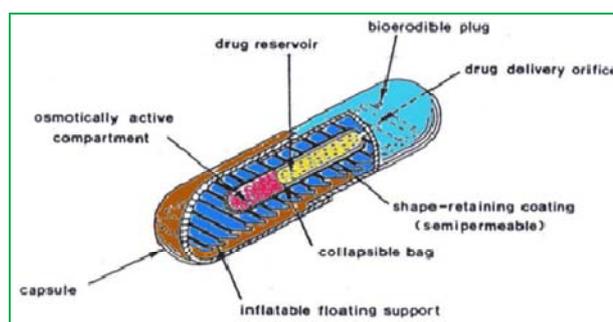


Figure 7: Intragastric Osmotic device⁵

Approaches to anti *H. pylori* action: *H. Pylori*, a gram negative microbe, is the main etiologic factor in development of gastritis, gastric ulcer, carcinoma and GERD etc⁴⁵. Torre and Torrado⁴⁶ developed freeze dried polyionic hydrogels of antibiotics for treatment of infections caused by *H. pylori*. An attempt was made to formulate controlled release hydrogel of Amoxicillin by using poly (acrylic acid) and chitosan interpolymeric complexes. This study revealed that these hydrogels show delayed gastric emptying with proton pump inhibitors or Al-Mg antacid pretreatment. A possible strategy to improve the pursuit of *H. pylori* eradication would be a combination of polyionic complex with antibiotic regime eg. Clarithromycin.

NOVEL BIOPOLYMERS FOR GASTRORETENTION

Apart from being biodegradable, economical and non-toxic, natural polymers provide the distinct advantage of gel formation and chemical modification; they have been extensively studied for their potential use site specific delivery to gastric region. (Table 1).

Table 1: Natural polymers for floating devices⁴⁷

Natural polymer	Basic chain	Solubility	Source
Chitosan	Deacetylated P-1, 4-N-acetyl-1-D-glucosamine	Insoluble in neutral and alkaline pH	Shell of marine invertebrates
Pectin	α -(1,4)-linked D-galacturonic acid	Soluble in water, insoluble in ethanol (95%) & organic solvents	Citrus peel, apple pomace, sugar beet pulp etc.
Xanthum gum	α -(1,4)-linked D-glucose	Soluble in hot/cold water and acid/alkane conditions	Fermentation of glucose by <i>Xanthomonas campestris</i>
Guar gum	α -D-mannopyranose	Swells in water, insoluble in organic solvents	Endosperm of the seeds of <i>Cyamopsis tetragonolobus</i>
Gellan gum	D-glucose, D-glucuronic acid and rhamnose in β -1, 4 linkage	Soluble in hot water	<i>Pseudomonas elodea</i>
Karaya gum	Mixture of d-galactose & L-rhamnose and D-galacturonic acid	Insoluble but swells in water (most of all gums)	Plant (<i>Sterculia urens</i>)
Psyllium husk	β -(1-4)-linked D-xylopyranosyl	Swells in water	Seed coats of <i>Plantago ovata</i>
Starch	α -(1,4)-linked D-glucose and β -(1,6)-linked D-glucose	Amylose is soluble in boiling water but amylopectin is insoluble	Storage polysaccharide in plants
Alginates	1-4' β -D-mannuronic acid and α -L-glucuronic acid	Insoluble in ethanol (95%), ether, chloroform and slowly soluble in water, forming viscous colloidal solution	<i>Laminaria hyperborea</i> , <i>Ascophyllum nodosum</i> , <i>Macrocystis pyrifera</i> etc

CONCLUSION AND FUTURE POTENTIAL

Over the past decades, researchers have worked on ways to control the drug release profile and had succeeded to a great extent. Yet, this area of drug delivery has a lot of possibility. For next decades, Scientists need to focus on controlling gastrointestinal transit profile to develop a rational gastroretentive form. Some of the unresolved, critical issues include the quantitative efficiency of floating delivery systems in fasted and fed states, the role of buoyancy in enhancing the GRT of FDDS, the correlation between the prolonged GRT and the pharmacokinetic characteristics of drug⁴⁷.

Further studies that can be done are^{1, 4, 34, 48, 49}:

- To identify minimum size of dosage form for prolonged retention in stomach.
 - Effect of various geometric shapes of expandable dosage forms with high rigidity on GRT. Effect of shape can also be investigated on floating (buoyant) systems.
 - Design of novel shape memory polymers to ensure effective unfolding and subsequent evacuation.
 - Evaluation of efficacy of gastric motility retarding agents on GRT with biocompatible polymeric materials.
 - Bioadhesive polymer coated liposome for stomach targeting.
 - Lack of availability of biocompatible chemical cross linking agent which is a major stumbling block in development of covalently cross linked hydrogels.
- Formulations using herbal extracts eg. Black myrobalan, ginger, turmeric, thyme, liquorice, berberine etc. for eradication of *H. pylori* from gastric environment. Various chinese herbs eg. *Rheum palmatum*, *Panax ginseng*, *Evodia rutaecarpa* etc. have also shown considerable anti *H. pylori* action.
 - Parkinson disease treatment with levodopa and carbidopa combination. Controlled co administration of bromocriptine and metoclopramide can offer great therapeutic potential for Parkinsonism.
 - The chronic administration of anti-inflammatory or anti-asthma drugs and careful dose adjustment of oral anticancer drugs are therapies that can be optimized by appropriate delivery schedules.
 - Discovery of new natural polymers having myriad spectrum of desired polymer characteristics and ability to withstand pharmaceutical sophistication is also a key area of research.

In nutshell, though gastro retentive forms are widely developed and recognised, there are still great possibilities undiscovered. Researchers and investigators need to design and formulate a system that is economic, offers maximum gastric residence time with minimum side effects and will improve the efficiency of various pharmacotherapies.



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