ISSN 2229-3566
Review Article

IJRAP
www.ijrap.net

REVIEW ON FLOATING DRUG DELIVERY SYSTEMS: AN APPROACH TO ORAL CONTROLLED DRUG DELIVERY VIA GASTRIC RETENTION

Kadam Shashikant M*, Kadam.S.R, Patil.U.S, Ratan.G.N, Jamkandi.V.G.
Department of Pharmaceutics, KLE'S College of pharmacy, Hubli, India

Received on: 14/09/11 Revised on: 22/10/11 Accepted on: 06/11/11

***Corresponding author**
Shashikant Kadam, Student. Email**:** shashikadam96@gmail.com

ABSTRACT
Controlled release (CR) dosage forms have been extensively used to improve therapy with many important drugs. Several approaches are currently utilized in prolongation of gastric residence time, including floating drug delivery system, swelling and expanding system, polymeric bioadhesive system, modified shape system, high density system and other delayed gastric emptying devices. However, the development processes are faced with several physiological difficulties such as the inability to restrain and localize the system within the desired region of the gastrointestinal tract and the highly variable nature of the gastric emptying process. On the other hand, incorporation of the drug in a controlled release gastroretentive dosage forms (CR-GRDF) which can remain in the gastric region for several hours would significantly prolong the gastric residence time of drugs and improve bioavailability, reduce drug waste, and enhance the solubility of drugs that are less soluble in high pH environment. Gastroretention would also facilitate local drug delivery to the stomach and proximal small intestine. Thus, gastroretention could help to provide greater availability of new products and consequently improved therapeutic activity and substantial benefits to patients. The purpose of this paper is to review the recent literature and current technology used in the development of gastroretentive dosage forms.

KEYWORDS: Gastroretention, Oral controlled release, Swelling, Narrow absorption window, Floating dosage form.

INTRODUCTION

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa.[1] Thus; small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Basic human physiology with the details of gastric emptying, motility patterns, and physiological and formulation variables affecting the cosmic emptying are summarized. GRFDDS has also applications for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients[2].

Basic Gastrointestinal Tract Physiology

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions[3]. Gastric emptying occurs during fasting as well as fed states. 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. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington[4]. (Figure 1)

Phase I (basal phase) lasts from 30 to 60 minutes with rare contractions.

Phase II (preburst phase) lasts for 20 to 40 minutes with intermittent action potential and contractions. In this phase bile secretion takes place. As the phase progresses the intensity and frequency also increases gradually.

Phase III (burst phase) lasts for 10 to 20 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material and mucus 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.

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.

Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically 2 complications, that of short gastric residence time and unpredictable gastric emptying rate.[5]

Factors Affecting Gastric Retention: Gastric residence time of an oral dosage form is affected by several factors. To pass through the pyloric valve into the small intestine the particle size should be in the range of 1 to 2 mm[6]. The rate of gastric emptying and gastric retention of GRFDDS depends mainly on-

A) Meals: The rate of gastric emptying depends mainly on nature of meal and caloric content of meals.

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.

Caloric content of meal: GRT can be increased by four to 10 hours with a meal that is high in proteins and fats

B) Volume of GI fluid: The resting volume of the stomach is 25 to 50 mL. When volume is large, the emptying is faster. Fluids taken at body temperature leave the stomach faster than colder or warmer fluids.

C) Dosage form related factors

- **Density:** A buoyant dosage form having a density of less than that of the gastric fluids floats. Since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period.
- **Size:** Dosage form units with a diameter of more than 7.5mm are reported to have an increase GRT compared with those with a diameter of 9.9mm. Small-size tablets leave the stomach during

the digestive phase while the large-size tablets are emptied during the housekeeping waves.

- **Shape of dosage form:** Tetrahedron and ringshaped devices with a flexural modulus of 48 and 22.5 kilopounds per square inch (KSI) are reported to have better GRT ≈90% to 100% retention at 24 hours compared with other shapes.
- **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.

D) Fed Conditions

- **Fed or unfed state:** Under fasting conditions, the GI motility is characterised by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. However, in the fed state, MMC is delayed and GRT is considerably longer.
- **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.

E) Patient related factors

- **Gender:** Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and racematched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.
- **Age:** Elderly people, especially those over 70, have a significantly longer GRT.
- **Posture:** GRT can vary between supine and upright ambulatory states of the patient.
- **Concomitant drug administration:** Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride.

F) Biological factors: Diabetes and Crohn's disease, etc[7].

Current Approaches To Gastroretentive Drug Delivery System

A) Floating drug delivery systems (FDDS): Floating FDDS is an effective technology to prolong the gastric residence time in order to improve the bioavailability of the drug. FDDS are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period[8]. Floating systems can be classified as effervescent and noneffervescent system.

I) Effervescent systems

These buoyant delivery systems utilize matrices prepared with swellable polymers such as Methocel or polysaccharides, e.g., chitosan, and effervescent components, e.g., sodium bicarbonate and citric or tartaric acid or matrices containing chambers of liquid that gasify at body temperature.

Gas can be introduced into the floating chamber by the volatilization of an organic solvent (e.g., ether or cyclopentane) or by the carbon dioxide produced as a result of an effervescent reaction between organic acids and carbonate–bicarbonate salts (Figure 2). The matrices are fabricated so that upon arrival in the stomach, carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in the gellified hydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy. Recently a multiple-unit type of floating pill, which generates carbon dioxide gas, has been developed[8].

II) Noneffervescent systems

Noneffervescent systems incorporate a high level (20–75% w/w) of one or more gel-forming, highly swellable, cellulosic hydrocolloids (e.g., hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose[HPMC], and sodium carboxymethylcellulose), polysaccharides, or matrix-forming polymers (e.g., polycarbophil, polyacrylates, and polystyrene) into tablets or capsules[9]. Upon coming into contact with gastric fluid, these gel formers, polysaccharides, and polymers hydrate and form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release[10-11]. The air trapped by the swollen polymer lowers the density of and confers buoyancy to the dosage form.

B) Bio Mucoadhesive systems

Bio mucoadhesive systems bind to the gastric epithelial cell surface, or mucin, and increase the GRT by increasing the intimacy and duration of contact between the dosage form and the biological membrane. The adherence of the delivery system to the gastric wall increases residence time at a particular site, thereby improving bioavailability[12]. A bio mucoadhesive substance is a natural or synthetic polymer capable of adhering to a biological membrane or the mucus lining of the GIT (mucoadhesive polymer). On the basis of binding of polymers to the mucin-epithelial surface can be subdivided into two broad categories[13].

a. Hydration-mediated adhesion

Certain hydrophilic polymers tend to imbibe large amount of water and become sticky, thereby acquiring bioadhesive properties[14].

b. Bonding-mediated adhesion

The adhesion of polymers to a mucus or epithelial cell surface involves various bonding mechanisms, including physical-mechanical bonding and chemical bonding. Chemical bonds may be either covalent (primary) or ionic (secondary) in nature. Secondary chemical bonds consist of dispersive interactions (i.e., Vander Waals interactions) and stronger specific interactions such as hydrogen bonds. The hydrophilic functional groups responsible for forming hydrogen bonds are the hydroxyl and carboxylic groups[14].

C) Receptor-mediated adhesion

Certain polymers can bind to specific receptor sites on the surface of cells, thereby enhancing the gastric retention of dosage forms. Certain plant lectins such as tomato lectins interact specifically with the sugar groups present in mucus or on the glycocalyx[14].

D) Expandable, unfoldable and swellable Systems

Gastroretentivity of a pharmaceutical dosage form can be enhanced by increasing its size above the diameter of the pylorus (Figure 3). If the dosage form can attain the larger size than pylorus, the gastroretentivity of that dosage form will be possible for long time. This large size should be achieved fairly quickly; otherwise dosage form will be emptied through the pylorus. Thus, configurations required to develop an expandable system to prolong GRT are:

I. a small configuration for oral intake,

ii. An expanded gastroretentive form, and

iii. A final small form enabling evacuation following drug release from the device.

In addition they should be able enough to withstand peristalsis and mechanical contractility of the stomach[14].

However, owing to significant individual variation, the cut-off size cannot be determined exactly. Unfoldable systems are available in various shapes as shown in figure-4.The concept is to make a carrier, such as a capsule, which extends in the stomach. *Caldwell et al,* proposed different geometric forms like tetrahedron[15], ring or planar membrane (4-lobed, disc or 4-limbed cross form) of bioerodible polymer compressed within a capsule[16].

E) High-density systems

Gastric contents have a density close to water (¯1.004 g/cm3). When high density pellets is given to the patient, it will sink to the bottom of the stomach and are entrapped in the folds of the antrum and withstand the peristaltic waves of the stomach wall[17]. Sedimentation has been employed as a retention mechanism for high density systems. A density ~3g/cm3 seems necessary for significant prolongation of gastric residence time. Barium sulphate, zinc oxide,

iron powder, titanium dioxide may be used to formulate such high density systems due to their high density. The only major drawbacks with this systems is that it is technically difficult to manufacture them with a large amount of drug (>50%) and to achieve the required density of 2.4–2.8 g/cm^3.

F) Magnetic systems

This approach to enhance the GRT is based on the simple principle that the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. *Ito et al,* used the technological approaches in rabbits with bioadhesive granules containing ultra-fine ferrite (ã-Fe2O3). They guided them to oesophagus with an external magnet (~1700G) for the initial 2 minutes and almost all the granules were retained in the region after 2 hours[18].

G) Raft systems

Raft systems incorporate alginate gels these have a carbonate component and, upon reaction with gastric acid, bubbles form in the gel, enabling floating[19].

H) Super porous hydrogel systems

Recent developments include use of super porous hydrogels that expand dramatically (hundreds of times their dehydrated form within a matter of seconds) when immersed in water. With pore size ranging, 10 nm to 10 µm, absorption window by conventional hydrogel is a very slow process and several hours may be needed to reach an equilibrium state during which, parameter evacuation of the dosage form may occur[20]. Super porous hydrogels, average pore size less than 100 µm, swell to equilibrium size within a minute, due to rapid water uptake by capillary wetting through numerous interconnected open pores[21].

Drugs reported to be used in the formulation of FDDS

Local treatment of the GI wall or targeting the intestine mucosa is aimed. GRDF is the formulation of choice when the drug is mainly absorbed in the upper GI tract and a reduction of plasma level fluctuations is required to minimize concentration-dependant adverse drug reactions[22]. A good example for such drug is given in table No 3.

Polymers and Ingredients to be used in the formulation of FDDS

Following types of ingredients can be incorporated into HBS (hydrodynamically balanced system) dosage form in addition to the drugs:

- Hydrocolloids (20%-75%): They can be synthetics, anionic or non-ionic like hydrophilic gums, modified cellulose derivatives. E.g. Acacia, pectin, Chitosan, Agar, Casein, Bentonite, veegum, HPMC (K4M, K100M and K15M), Gellan gum (Gelrite), Sodium CMC, MC, HPC.
- Inert fatty materials(5%-75%): Edible, inert fatty materials having a specific gravity of less than one can be used to decrease the hydrophilic property of formulation and hence increase buoyancy. Eg. Beeswax, fatty acids, long chain fatty alcohols, Gelucires 39/01 and 43/01.
- Effervescent agents: Sodium bicarbonate, citric acid, tartaric acid, Di-SGC (Di-Sodium Glycine Carbonate, CG (Citroglycine). Release rate accelerants (5%-60%): e.g. lactose, mannitol. Release rate retardants (5%-60%): e.g. Dicalcium phosphate, talc, magnesium stearate. Buoyancy increasing agents (upto80%): e.g. Ethyl cellulose. Low density material: Polypropylene foam powder[23].

Advantages of Gastro retentive Drug delivery system

Enhanced bioavailability

The bioavailability of therapeutic agents can be significantly enhanced especially for those which get metabolized in the upper GIT by gastroretentive drug delivery approaches in comparison to the administration of non-gastroretentive drug delivery[24].

Sustained drug delivery

HBS or bioadhesive or expandable systems type dosage forms can remain in the stomach for several hours and therefore, significantly prolong the GRT of numerous drugs.

Site specific drug delivery

This site-specific drug delivery reduces undesirable effects. Hence they are useful in the treatment of disorders related to stomach and small intestine (e.g. eradication of *Helicobacter pylori*).

Reduced fluctuation of drug concentrations

Continuous input of the drug following controlled release gastroretentive delivery produces systemic drug concentrations within a narrower range compared to the immediate release oral dosage forms.

Improved selectivity in receptor activation

The controlled release mode of drug administration of gastroretentive systems have the important feature that have an impact on the magnitude of the pharmacologic response, which minimizes fluctuation in blood drug concentrations (i.e. between peak and trough).

Limitations Gastro Retentive Drug Delivery System

- The residence time in the stomach depends upon the digestive state. Hence, FDDS should be administered after the meal[25].
- The ability to float relies on the hydration state of the dosage form. In order to keep these tablets floating *in vivo*, intermittent administration of water (a tumbler full, every 2 hours) is beneficial[25].
- The ability of drug to remain in the stomach depends upon the subject being positioned upright[26].
- FDDS are not suitable for the drugs that have solubility or stability problems in the gastric fluid[27].
- Drugs like nifedipine, which is well absorbed along the entire GIT and which undergoes significant first pass metabolism, may not be desirable candidates for FDDS since the slow gastric emptying may lead to the reduced systemic bio-availability[27].

Marketed Preparations And Some Patents On Gastroretentive Drug Delivery System

Some marketed preparations and patents on gastroretentive drug delivery system are listed in table 2 and table 3.

DISCUSSION

Controlled release gastroretentive dosage forms (CR-GRDF) enable prolonged and continuous input of the drug to the upper parts of the gastrointestinal tract and improve the bioavailability of medications that are characterized by a narrow absorption window. CR-GRDF provides a means to utilize all the pharmacokinetic and pharmacodynamic advantages of controlled release dosage forms for such drugs. Due to the complexity of pharmacokinetic and pharmacodynamic parameters, *in vivo* studies are required to establish the optimal dosage form for a specific drug. For a certain drug, interplay of its pharmacokinetic and pharmacodynamic parameters will determine the effectiveness and benefits of the CR-GRDF compared to the other dosage forms.

REFERENCES

1. Hirtz J. The GIT absorption of drugs in man: a review of current concepts and methods of investigation. Br J Clin Pharmacol, 1985;19:77-83.

2. Amnon Hoffman, David Stepensky, Eran Lavy, Sara Eyal, Eytan Klausner, Michael Friedman. Pharmacokinetic and pharmacodynamic aspects of gastroretentive dosage forms. Int J Pharm 2004; 277:141-153.

3. Desai S. A Novel Floating Controlled Release Drug Delivery System based on a Dried Gel Matrix Network [master's thesis].1984 Jamaica, NY, St John's University.

4. Vantrappen GR, Peeters TL, Janssens J. The secretory component of interdigestive migratory motor complex in man. Scand J Gastroenterol.1979;14:663-667.

5. Wilson CG, Washington N. The stomach: its role in oral drug delivery. In: Rubinstein MH, ed. Physiological Pharmacetical: Biological Barriers to Drug Absorption. Chichester, UK: Ellis Horwood; 1989:47-70.

6. Desai S, Bolton S. A floating controlled release drug delivery system: in vitro- in vivo evaluation. Pharm Res. 1993; 10:1321-1325.
7. R Garg, GD Gupta. Progress in Controlled Gastroretentive Delivery Systems. Trop J of Pharm Res 2008; 7 (3): 1055-1066.
8. Chikawa M., Watanabe S., and Miyake Y. A New Multiple-Unit Oral Floating Dosage Systems, I: Preparation and In Vitro Evaluation of Floating and Sustained-Release Characteristics, .J. Pharm. Sci. 1991; 80: 1062-1066.
9. Hilton A.K. and Deasy P.B., In Vitro and In Vivo Evaluation of an Oral Sustained-Release Floating Dosage Form of Amoxicillin Trihydrate, Int. J. Pharm. 1992;86 (1):79-88.
10. Sheth P.R. and Tossounian J.L., Novel Sustained- Release Tablet Formulations," US Patent os, 755: 1979.
11. Sheth P.R. and Tossounian J.L. The Hydrodynamically Balanced System: A Novel Drug Delivery System for Oral Use. Drug Dev. Ind.Pharm. 1984; 10(2):313-339.
12. Wilding I.R, Davis S.S, O'Hagan D.T. Targeting of Drugs and Vaccines to the Gut, in Pharmaco. Ther. C.J.Hawkey, Eds 1994: 98-124.
13. Park K, Robinson J.R. Bioadhesive Polymers as Platforms for Oral-Controlled Drug Delivery: Method to Study Bioadhesion, Int. J. Pharm. 1984; 19 (1):107-127.
14. Amit Kumar Nayak, Jadupati Malakar, Kalyan Kumar Sen. Gastroretentive drug delivery technologies: Current approaches and future potential. J Pharm Educ Res 2010; 1 (2): 1-12.
15. Caldwell LJ, Gardner CR, Cargill RC. Drug delivery device which can be retained in the stomach for controlled period of time. US Patent 473 5804. April 5, 1988.
16. Clarke GM, Newton JM, Short MD. Gastrointestinal transit of pellets of differing size and density. Int J Pharm. 1993; 100(13): 81-92.
17. Shweta Arora, Javed Ali, Alka Ahuja, Roop K. Khar, Sanjula Baboota. Floating Drug Delivery Systems: A Review. AAPS PharmSciTech 2005; 6 (3): 372-390.
18. Abubakr O. Nur, Jun S. Zhang. Recent progress in sustained: controlled oral delivery of
captopril: an overview. Int J Pharm. 2000; 139-146.
19. Patel Geeta M, Patel Hitesh R, Dr. Madhabhai Patel, Floating Drug Delivery System: An Innovative Approach to Prolong Gastric Retention, Pharmainfo.net. 2007; 5(6):11-18.
20. Bardonnet PL, Faivre V, Pugh WJ, Piffaretti JC, Falson F.Gastroretentive dosage forms: overview and special case of *Helicibacter pylori.* J Control Release. 2006; 111: 1-18.
21. Chen J, Blevins WE, Park H, Park K. Gastric retention properties of super porous hydrogel composites. J Control Release. 2000; 65: 73-82.
22. Encyclopedia of pharmaceutical technology Third Edition volume 1.
23. Shah S.H, Patel J.K, Patel N.V. Stomach specific floating drug delivery system: a review, Int J Pharm Tech Res 2009; 1 (3):623-633.
24. Sigal Saphiera, Amir Rosnerb, Rachel Brandeisc, Yishai Kartona. Gastro intestinal tracking and gastric emptying of solid dosage forms in rats using X-ray imagining. Int J Pharm 2010; 388: 190-195.
25. N. Rouge, P. Buri, E. Doelker, Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery, Int. J. Pharm. 1996;136:117–139.
26. Gerogiannis VS, Rekkas DM. Floating and swelling characteristics of various excipients used in controlled release technology. Drug Dev Ind Pharm. 1993; 19: 1061-1081.
27. Talwar N, Himandri S, Ftaniforth KN. Orally administered controlled drug delivery system providing temporal and spatial controlled. 2001; US Patent (6, 261, 601).

Table 1: Examples of drugs used in floating formulation[22]

Floating microspheres	Diclofenac sodium and prednisolone.
Floating granules	Indomethacin and prednisolone.
Floating tablets and pills	Acetaminophen, acetylsalicylic acid, ampicillin, amoxicillin Trihydrate, atenolol, diltiazem.
Floating capsules	Chlordiazepoxide hydrogen chloride, diazepam, furosemide, misoprostol, L-Dopa, benserazide, ursodeoxycholic acid, pepstatin.
Films	Albendazole, Cinnarizine.

Table 2: Marketed preparations of gastroretentive drug delivery system

Sr.No.	Product	Active ingredient	Remark	Reference
1	Cifran OD	Ciprofloxacine	Gas generating Floating Tablet	Chawla *et al,*2004
2	Cytotec	Misoprostol	Bilayer Floating Capsule	Chawla *et al,*2004
3	Glumetza GRTM	Metformin HCL	Metformin HCL extended release tablet	Bioavail oin north America; LG life sciences Korea

Table 3: Some patents on gastroretentive drug delivery system

US PATENT NUMBER	YEAR	PATENT TITLE
6,207,197	2001	Gastroretentive controlled release microsphere for improved drug delivery
20060013876	2006	Novel floating dosage form
200702817	2007	Gastroretentive sustain release dosage form
2008020060	2008	Gastroretentive formulation and manufacturing process
20090324694	2009	GRDDS comprising an extruded hydratable polymer
20100286660	2010	Gastroretentive duodenal pill

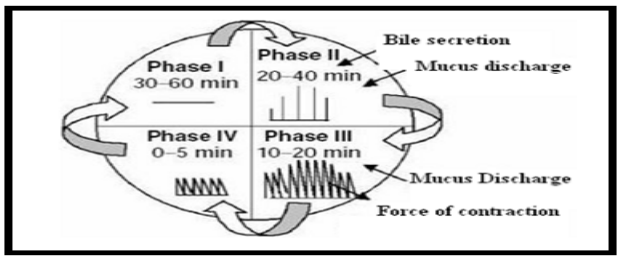

Figure 1: Interdigestive Motility

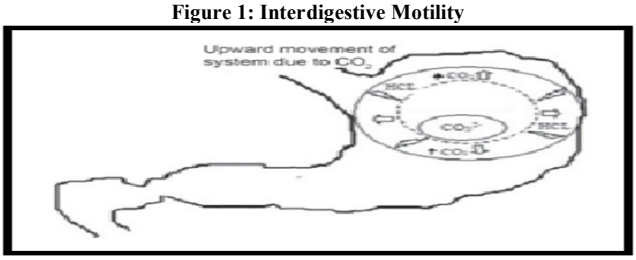

Figure 2: Effervescent systems

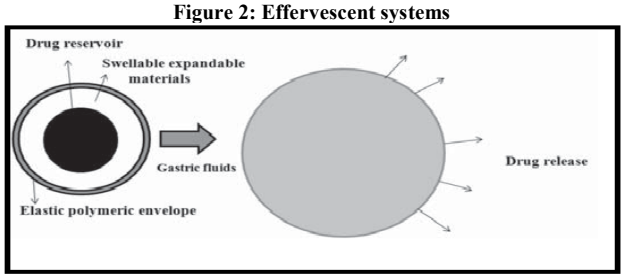

Figure 3: Drug release from swellable systems

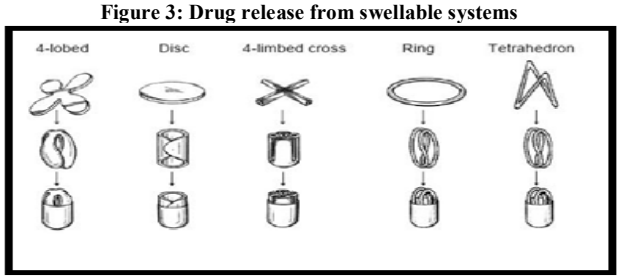

Figure 4: Shapes of unfoldable systems