GRAPHICAL ABSTRACT

Gastroretentive Formulations for Improving Oral Bioavailability of Drugs- Focus on Microspheres and their Production

Woroud Alzaher, John Shaw and Raida Al-Kassas*

**School of Pharmacy, Faculty of Medical and Health Sciences, The University of Auckland, Private Bag 92019, Auck- land 1142, New Zealand*

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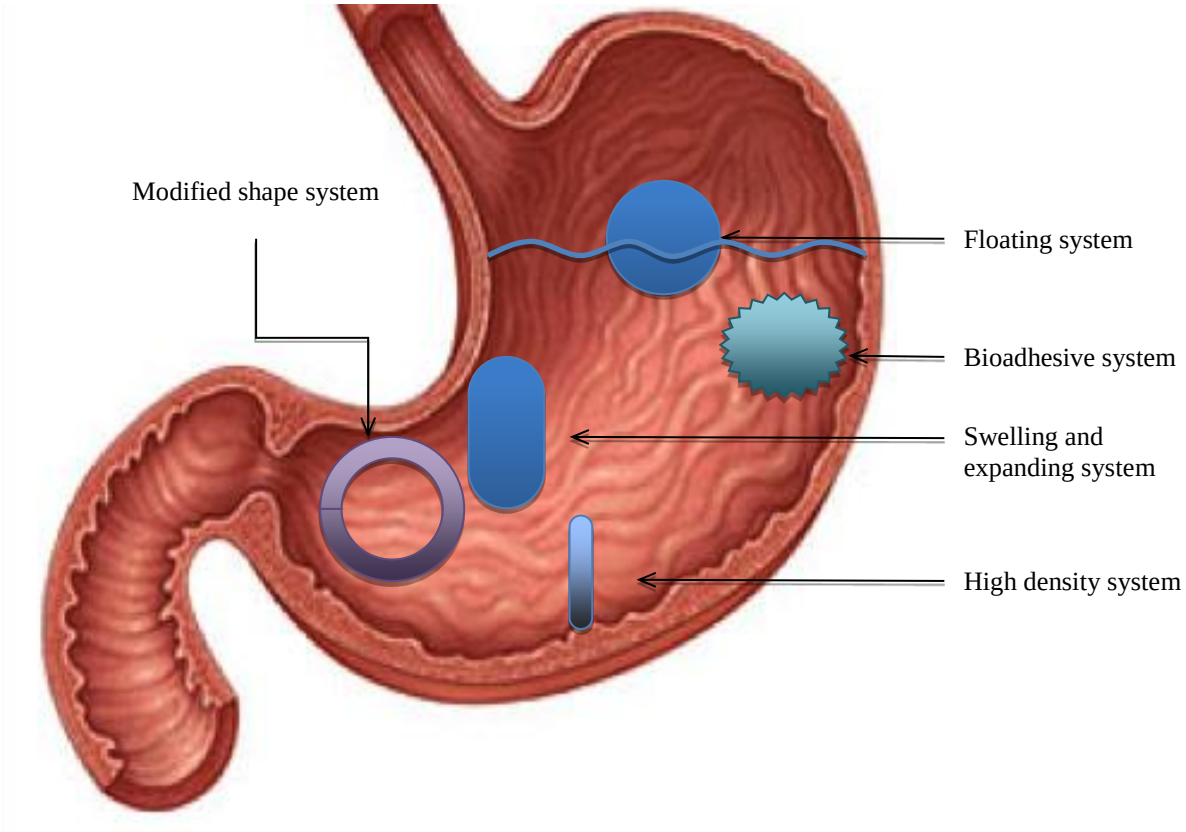

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Woroud Alzaher, John Shaw, Raida Al-Kassas

School of Pharmacy, Faculty of Medical and Health Sciences, The University of Auckland, Private Bag 92019, Auckland 1142, New Zealand

Abstract

Oral administration is the most commonly used drug delivery route for the majority of conditions. Given its advantages over other routes, such as convenience and cost, its use is increasing every year despite the major advances in drug delivery. Nevertheless, oral formulations are limited and challenged by physicochemical barriers and highly variable residence times. Gastric retention is a strategy that can overcome the highly variable gastric residence time by designing formulations that remain in the stomach longer than would otherwise be expected. This is especially beneficial for drugs that have an absorption window in the stomach and proximal intestine. Various techniques are discussed and include gas-generating tablets, floating microspheres, hydrodynamically balanced systems, bioadhesive particles, rafts and modified shape systems. Microspheres having the advantages of being multi-unit are further discussed with regard to their production methods and characterisation. Further, a summary of microsphere studies is presented that looks at methods used and key results.

Keywords: gastroretentive formulations; oral drug delivery; floating microspheres; microspheres production; microspheres characterisation.

*Corresponding Author:
Dr Raida Al-Kassas
School of Pharmacy
Faculty of Medical and Health Sciences
The University of Auckland
Private Bag 92019
Auckland
New Zealand
Email: r.al-kassas@auckland.ac.nz

1.0 Introduction

Despite the numerous innovations in drug delivery and promising alternative routes, orally administered forms comprise more than half the drug delivery market [1] Gabor et al., 2010). Oral drug administration remains the preferred route in most clinical applications for the treatment of acute and chronic conditions [2]. It is estimated that over 90% of all medicine usage is oral and the share is increasing at 10% per year [1]. Amongst the various oral delivery options such as liquids and semisolid formulations, tablets are the preferred choice given their advantages. Oral formulations are easy to self-administer. They are pain free, convenient, can accommodate a wide number of drugs, stable, easy to carry, inexpensive to manufacture and most importantly do not discourage patient compliance [1, 3. In addition, the healthcare system takes advantage of this easy and cost effective delivery especially as health care costs increase and the elderly population grows. It therefore seems like oral dosage forms are the ideal forms of therapy. However, the oral route is also one of the most challenging considering the biopharmaceutical issues such as physiochemical drug characteristics and gut physiological conditions [1].

The oral route of administration comes with important limitations. Gastric physiology presents many challenges with changing environments and barriers to absorption. Therefore, it is important to consider drug solubility, permeability, lipophilicity, crystalline form, size, charge and pKa in oral formulations because they may affect drug absorption, bioavailability and therapeutic effectiveness. Physiological considerations include regional pH, absorption area, enzyme degradation, residence time and presence of microorganisms [1]. In the stomach, the two most important parameters affecting the fate of the drug are the pH and residence time [4]. Longer gastric residence time allows greater and more reliable drug absorption, however, it is highly variable and despite excellent dosage form *in vitro* release profiles, drug absorption is highly variable and in many cases unsatisfactory [5]. In addition, this variability exists in the same individual at different times and between individuals leading to less predictable therapeutic outcomes. Various strategies have been researched to overcome these challenges, such as using sustained release formulations, pH responsive formulations, osmotic delivery devices, enzyme mediated release, prodrugs, antigen targeting to Meyer cells and use of absorption

and permeation enhancers [1]. However, all these strategies are still limited by gastric variability, which is an important determinant of bioavailability. Gastroretentive strategies are designed to control dosage form residence time therefore leading to enhanced, prolonged and predictable drug blood levels.

Gastroretentive formulations are very useful for drugs that are aimed at the stomach, drugs with poor solubility such as weakly basic drugs that do not dissolve well enough in basic environments, drugs that are unstable in the colon or drugs that have a narrow absorption window and drugs that are primarily absorbed from the stomach [5]. The concept of absorption window is relevant to compounds that have variable absorption in different regions in the gastrointestinal tract ([2]. For example, polar compounds are better absorbed from the upper gastrointestinal tract and large intestinal absorption is very poor. Therefore, their bioavailability is limited by absorption site. This is the case for many drugs, especially those in classes II to IV of the biopharmaceutical classification scheme. It is difficult and almost impossible to formulate modified release formulations for such substances and therefore absorption window targeting is a useful strategy. Other reasons that create an absorption window are differential drug solubility and stability due to pH or enzymatic degradation [2]. Figure 1 illustrates the concept.

Formulation residence time in the gastrointestinal tract determines how long the formulation will be in contact with its absorption window. In humans, gastric residence is very variable and mainly affected by the size of the objects inside and the feeding state in the stomach. This can range from 2 to 4 hours for a meal. On the other hand, transit in the intestine is more constant and around three hours. Transit through the colon is longer and can be 20 hours or more [2]. This therefore means that drugs that are mainly absorbed from the stomach or proximal small intestine will have a short contact time with the absorption window. Consequently, the bioavailability will be limited and will also be variable. A number of important drugs, such as those in Table 1, that are absorbed from the proximal intestine have low bioavailability after oral dosing due to this. Sustained or prolonged release formulations for such drugs have limited benefit because absorption is low in the colon. Gastroretentive strategies overcome the short and variable contact time in two ways: (1) retain drug formulation longer and (2) hold the drug formulation above the absorption window [2].

In effect, gastro-retentive strategies improve oral bioavailability and optimize drug plasma levels leading to enhanced and predictable therapeutic outcomes. Gastroretentive formulations also have fewer doses per day leading to dramatically improved patient compliance [6].

2.0 Gastric physiology

The stomach is a J shaped enlargement of the gastrointestinal tract and connects the oesophagus to the first part of the small intestine. Meals can be ingested faster than nutrients can be absorbed through the intestines and the stomach serves as a mixing chamber that liquefies food and holds churned food material for controlled feeding in to the intestine. Digestion of proteins and triglycerides begins, digestion of starch continues and some substances are absorbed. The stomach is divided in to four main regions: the cardia, fundus, body and pylorus. These are shown in figure 2. An empty stomach is about the size of a big sausage with a residual volume of 25 to 50ml, but it is the most distensible part of the gastrointestinal tract and can accommodate large amounts of food. Gastric volume is important for dosage form dissolution. At birth the stomach capacity is 30 ml, at puberty it is 1L and 1.5 to 2L in adults. The fasting stomach pH is between 1.2 to 2.0 and 3 to 6.5 when fed [3]. This is because food buffers, dilutes and neutralises gastric acid and causes its increase pH. Gastric pH affects the absorption of drugs, for example, basic drugs will be more likely to dissolve in the fed condition than the fasted condition. After a meal is finished, the stomach pH rapidly increases to 5 and then gradually reduces to the fasting condition levels over a few hours [3].

The gastric system is in constant motility, which is in two modes, the inter-digestive or migrating motor complex and the digestive motility pattern. Digestion begins a few minutes after food enters the stomach with peristaltic mixing waves. Few waves are seen in the fundus, which mostly has a storage function. These waves mix the food with gastric secretions and break it down to chyme. As digestion continues, more vigorous waves starting from the body and intensifying at the pylorus are produced. Most chyme is forced backward and the next wave pushes the chyme forward again and small amount may go past the pylorus. These movements are responsible for most mixing in the stomach. Stomach contents must be 1 -2 mm to pass through to the duodenum, the first part of the intestine. Food that has been held in the fundus and has not yet mixed with gastric content may be brought down, which may be held

in the fundus for an hour. The control of these movements and of gastric secretions is via neuronal and hormonal mechanisms. The events that occur in the stomach occur in three overlapping phases: the cephalic, gastric and intestinal phase [7]. Inter-digestive motility is dominant in the fasted state and its primary role is to clean up any residual content remaining in the stomach. The motility is cyclical and called the migrating motor complex (MMC) and leads to gastric emptying. MMC cycles, which last for 2 to 3 hours are separated by periods of inactivity. The cycle is divided into four phases summarised in table 2 and represented diagrammatically in figure 3. When a meal is eaten, the pattern of contractions changes to that of the fed state. The contractions in the fed state resemble phase II contractions in the MMC.

Gastric motility is highly variable and affected by various factors, such as age, posture, gender and type of meal consumed. These are summarised in Table 3. Time taken for a dosage form to traverse the stomach is the 'gastric emptying rate', which is highly variable and dependent on many factors, such as the dosage form itself and stomach fed or fasting condition. Usually, gastric residence is 5 minutes to 2 hours and large single unit dosage forms have been shown to remain for 12 hours or longer [3]. For a formulation to be gastroretentive, it must be able to resist the forces of the IMMC phase for a considerable period of time, especially the phase III forceful contractions. In addition, the IMMC phase which is occurring when the dosage form is taken affects its residence time [8].

In the fed state, drug residence time is affected by food residence time. This, in turn, is affected by the type and amount of food consumed. Solids and larger food particles spend longer in the stomach than liquids or small food particles [8]. The size of a gastroretentive dosage form is also important. The human pyloric sphincter is 12 ± 7 mm in diameter and is open in the fasting state. The first mouthful can therefore pass straight to the duodenum, after which the sphincter closes. Particles with a diameter less than 7mm are effectively evacuated, whereas a diameter of 15mm or greater is usually retained longer, especially during the fasting state. Indigestible solids larger than the pyloric sphincter are propelled back in to the stomach and go through several MMC activities. During the housekeeping waves the pyloric sphincter opens up and allows sweeping of these materials [9]. Whether a single unit is retained or lost in gastric emptying is determined by chance and therefore the high variability in gastric residence time is a drawback for gastroretentive single unit systems. Multiple unit systems can overcome this. They

may be evacuated as a linear profile or as a bolus at the end of the digestion [10], whereas the single unit systems would be evacuated at the end of digestion or during phase III of IMMC. In this way, multiple unit systems have more reliable gastric residence patterns because they do not suffer from the “all or none concept” [9].

The density of a gastroretentive system affects its location in the stomach. When a system has a density lower than that of the gastric content (1.004g/ml), they float at the top and denser systems sink to the bottom. Both situations may keep the formulation in the stomach and avoid the pylorus [10]. This is shown in figure 4. In a study by Timmermans and Andre,1994) [11] that examined the effect of floating properties on gastric residence time, it was found that floating units remained buoyant and were less likely to be expelled from the stomach compared to the non-floating units. These lay close to the antrum and the pylorus and were expelled into the intestine by the peristaltic waves. The dosage form parameters that affect its gastric residence are summarised in Table 4.

3.0 Gastroretentive strategies

Gastroretentive strategies are suitable for compounds that are:

- primarily absorbed from the stomach or upper gastrointestinal tract, for example, metronidazole
- drugs that act locally in the stomach, for example misoprostol, antacids and antibiotics
- drugs poorly soluble in alkaline pH, for example, diazepam, verapamil hydrochloride. Gastric retention prevents solubility being the rate limiting step
- drugs with a narrow absorption window in the stomach or upper intestine, for example, levodopa, furosemide and simvastatin [12].
- rapidly absorbed drugs, for example, amoxicillin
- drugs that degrade in the colon, for example, captopril [8].

Unsuitable candidates include drugs that are absorbed equally throughout the gastrointestinal tract, such as isosorbide dinitrate, drugs that are unstable in stomach pH, and drugs that irritate stomach mucosa [3]. Various strategies have been used to prolong gastric residence. These are summarised in the following sections. These strategies still depend on the presence of gastric fluid for the system to work

effectively. This translates into patient instructions to take the dosage form with food and water. In order for a dosage form to be successfully gastroretentive, it must be able to withstand the stomach waves and, equally important, it must be easily removed from the stomach once the drug release is complete [8].

3.1 Floating drug delivery systems

Floating gastroretentive systems, as the name implies, remain afloat over the gastric contents because of their buoyancy and low bulk density. This allows these systems to remain in the stomach for a prolonged period of time, while the drug is being released at a desired rate [5]. Eventually they are eliminated and emptied from the stomach. There are several methods used to create a floating delivery system and they can be broadly classified in to two categories: effervescent and non-effervescent formulations. Floating dosage forms may be designed as a single unit or a multiple unit.

3.1.1 Effervescent systems (gas generating)

Effervescent systems contain a floatation chamber, which is filled with an inert gas, air or vacuum [5, 13]. This chamber is created within the formulation when it is in contact with gastric fluid or warms up to body temperature, depending on the system used. Gas can be produced by an effervescent chemical reaction involving carbonates or bicarbonates with an acid. The acid can be from the surrounding gastric environment or can be included in the formulation as citric acid or tartaric acid [10]. This reaction generates carbon dioxide gas and fills the chamber with gas, keeping the delivery system afloat. Surrounding the gas chamber is a matrix of swellable hydrophilic polymer, which expands from the collapsed form to the expanded form as the chamber is filled with gas [5]. This matrix is insoluble and permeable to water but not carbon dioxide. Substances that have been used include chitosan and methocel. The effervescent substances may also be entrapped within the polymer matrix and the produced gas would trap bubbles in a swollen matrix [10]. Figure 5 illustrates this process.

In another technique, a volatile organic solvent such as ether or cyclopentane is included in the floatation chamber. This solvent evaporates at body temperature to fill the chamber and produce the same floating effect [5, 10]. *In vitro* the lag time until the unit floats is less than one minute and it remains afloat for 8 to 10 hours. *In vivo* studies in fasted dogs showed a mean gastric residence of up to 4 hours [10].

The effervescent systems can be formulated as a single unit system or a multiple unit system. A single unit system, such as a tablet or capsule, may be a one layer system that has the effervescent components in the hydrophilic polymer matrix and carbon dioxide bubbles are trapped in this swollen matrix. It may also be formulated as two or more layers, which are formulated separately, and further refinements involve coating with a semipermeable membrane [10]. Multiple unit systems avoid the 'all or nothing' emptying process.

In a study by Hu et al (2011) [14), sustained release floating tablets were prepared to deliver dextramethorphan via gas generation. The tablets were prepared by a wet granulation technique with HPMC, sodium bicarbonate as the gas generating agent, hexadecanol as a floatation assistant, lactose and ethylcellulose solutions the binding agent. The tablets took three minutes to float *in vitro* and floatation lasted over 24 hours. By 12 hours, over 85% of the drug was released. A pharmacokinetic study in humans comparing the floating tablets to a regular sustained release tablet showed increased area under the curve (AUC) in concentration time graph and a prolonged T_{max}. In a study by Goole et al. (2008) [15], sustained release floating mini tablets for levodopa that were made using sodium bicarbonate, calcium carbonate and tartaric acid as gas generators. Gastric residence time was evaluated in humans with gamma scintigraphy and compared to marketed Prolopa®. The results showed gastric retention of four hours and more constant drug pharmacokinetics.

In a study by Tadros (2009)[16], ciprofloxacin was prepared in an effervescent floating tablet using sodium or calcium carbonate to generate gas. The matrix was made of hyrdoxypropylmethylcellulose K15M. *In vitro* testing showed a 16 second lag time till floatation, which lasted longer than 12 hours suggesting that that generated gas was successfully entrapped and kept the system floating. *In vivo* studies in a human volunteer showed a lag time of 78 seconds, floatation for three hours in one location then further retention of another three hours in a lower location in the stomach. The mean gastric retention was 5.5 hours. This formulation showed promising results for the gastroretentive delivery of ciprofloxacxin.

3.1.2 Non effervescent (hydrodynamically balanced systems)

Hydrodynamically balanced systems are single unit dosage forms composed of a hydrophilic polymer matrix that contains the drugs. The polymer swells when it becomes hydrated and forms a lightweight gel. Usually they are administered as

gelatin capsules. In the gastric contents, the gelatin shell erodes away and dissolves in the gastric fluid. The polymer is now exposed to the gastric fluid and starts to swell at the surface, therefore forming a gel barrier surrounding the capsule dosage form. This hydrated outermost layer gives buoyancy and keeps the capsule afloat. It also keeps the capsule shape together to prevent it from disintegrating and controls the rate of drug release. Continuous erosion of the surface allows water to penetrate in to the inner layers thus maintaining surface hydration and buoyancy. Figure 6 illustrates the process.

Gel forming polymers that can be used for such formulations include hydroxypropylmethylcellulose (HPMC) [17], hydroxyethylcellulose (HEC), hydroxypropyl cellulose (HPC) sodium carboxymethylcellulose, agar and alginic acid. Ali et al (2007)[18] produced a hydrodynamically balanced system for metformin. HPMC and EC were used as polymers and the optimized formulation was tested in rabbits. *In vitro* buoyancy studies showed floatation up to 12 hours and gamma scintigraphy showed the formulation was buoyant for five hours in rabbits. The AUC was increased by 136% compared to the immediate release formulation and the release was prolonged with c_{max} being at 7 hours in the gastroretentive formulation and 3 hours in the immediate release formulation. The formulation was able to successfully remain in the stomach for a prolonged period of time and constantly deliver metformin to its site of absorption, the proximal small intestine.

3.1.3 Raft forming systems

Raft systems are gel forming solutions that swell and form a viscous cohesive gel which floats on the top of gastric fluid. The dosage form includes an alginate solution such as sodium alginate that contains carbonates or bicarbonates. When in contact with the gastric environment, the alginate solution forms the viscous gel with entrapped carbon dioxide bubbles. This enables the system to float. Figure 7 shows how these systems appear in the stomach. This floating delivery design is very useful for gastroesophageal reflux because the raft produced prevents gastric contents from seeping back to the oesophagus and cause irritation. A well-known and widely used product is Gaviscon (GlaxoSmithKline) [3]. Raft systems can also be used for antibiotics, for example, clarithromycin for *H.Pylori* eradication [19]. This formulation resulted in greater in vivo *H. Pylori* eradication as compared to the solution formulation.

3.1.4 Low Density Systems

Hollow microspheres are multiple unit dosage form with low density (<1g/cm^3) and immediate buoyancy. They are also called microcapsules or microballoons because of the low density core in their structure. Gastric contents have a density close to water, 1.004g/cm^3, and particles less dense than that float [10,20]. Other examples of low density systems are microparticles, hollow beads, emulgel beads and floating pellets [3]. Microspheres can be between 1 and 1000um in size, commercial microspheres are between 3 and 800 µm [21, 8] and ideally are smaller than 200 µm [10]. The core makes up 10 to 90% of the microparticle weight [8]. Polymers that can be used to formulate them include albumin, gelatin, starch, polymethyacrylate, polyacrylamine and polyalklcyanoacrylate. These microshperes are usually a free flowing powder with very good *in vitro* floatability and have a high loading capacity [5]. Currently, floating microspheres are considered to be the most promising buoyant systems because they combine the advantages of multiple unit systems and have good floating properties. Like all other floating systems, however, they still depend on the presence of enough liquid in the stomach, which requires frequent drinking [10].

In a study by Miyazaki et al (2007)[22], theophylline was incorporated into floating gastroretentive microspheres. The floating formulation showed *in vitro* floatation of 5 hours. An *in vivo* assessment was carried out in Beagle dogs and showed highest AUC for the floating formulations. The floating formulation improved gastric retention and oral bioavailability. Joseph et al (2002) [23], conducted a study for piroxicam loaded hollow polycarbonate microspheres via the solvent evaporation technique. The resultant floating microspheres had entrapment efficiencies over 95%, and over 90% of drug was released at 8 hours *in vitro*. *In vivo* evaluation in rabbits showed multiple peaking, suggesting enterohepatic recirculation and the bioavailability was 1.4 times the free drug control. The data showed that the formulation was successful in retaining the drug to provide sustained drug delivery and enhanced bioavailability.

3.2 Modified Shape Systems

Modified shape systems are composed of biodegradable polymers folded in a compressed form, which expand to form a three dimensional geometric shape in the stomach. This dosage form withstands gastric emptying because the expanded form is bigger than the pyloric sphincter and is small enough to swallow in the folded form. This folded form is incorporated in a capsule carrier, which dissolves in the stomach.

Expansion occurs via osmosis and the shape unfolds due to mechanical shape memory [5]. The device is eliminated when it reduces in volume and rigidity due to depletion of drug and expanding agent. The polymer also erodes and these prevent gastric obstruction or accumulation of repeated doses [10]. The different geometric forms are shown in figure 8.

Despite the interesting properties and mechanism of action of this dosage form, expandable systems have important drawbacks. The mechanical shape-memory is short lived and these systems are difficult to industrialise and may not be cost-effective. Storage of easily hydrolysable, biodegradable polymers is challenging. It is important for such systems to have reproducible 'collapse time' so that it does not cause obstruction or gastropathy [10].

3.3 Bioadhesive systems

Bioadhesive or mucoadhesive systems are designed with materials that adhere to the mucosal membranes. These systems resist emptying and therefore have prolonged gastric residence. For example, microspheres, microparticles [24]or liposomes can be coated with bioadhesive material. Bioadhesive polymers adhere to either the mucus lining or the biological membranes. Polymers include chitosan, carbopol, carboxymethyl chitin and carboxymethyl chitosan [3]. Several mechanisms have been proposed for mucoadhesion. The electrostatic theory proposes that adhesion is via attractive electrostatic forces between the glycoprotein mucin network and the polymer. The adsorption theory proposes that adhesion is due to Van der Waals and hydrogen bonding. The wetting theory is based on the polymers' ability to spread and the diffusion theory is based on the physical entanglement of mucin strands with the flexible polymer chains, or an interpenetration of the mucin strands in the porous polymer structure [10].

Formulation and clinical use issues of these systems include unpredictable adherence because the mucus layers are in a constant state of renewal. In addition, the gastric content is highly hydrated which reduces the binding property and it is difficult to target these dosage forms because they may adhere to membranes or mucus in other locations. This raises concerns about oesophageal binding, which also presents a challenge [5]. Figure 9 illustrates gastroretention of bio-adhesive microspheres. Liu et al (2004) [25] compared amoxicillin powder, amoxicillin entrapped in microspheres and bioadhesive amoxicillin loaded microspheres in

Helicobacter Pylori eradication. The results showed that mucoadhesion had prolonged gastric residence and greater amoxicillin levels leading to better therapy than the regular microspheres. Rajinikanth et al (2008) [19] formulated floating bioadehesive microspheres containing clarithromycin for H. Pylori eradication. The matrix polymer was ethylcellulose and carbopol P934. The resulting microspheres showed strong adhesion and buoyancy. *In vivo* studies in Mongolian gerbils showed that significantly less clarithromycin was needed for H. Pylori eradication using the designed formulation compared to the regular suspension. The formulation was also successful in stabilising clarithromycin, which is known for its acidic instability.

3.4 Swelling and Expanding Systems

Swelling and expanding systems are composed of super-porous hydrogels that swell to a large size, with a swelling ratio of approximately 100 times or more. Swelling occurs through rapid water uptake via capillary action through the pores, which are usually greater than 100 µm in size. In addition, they swell to equilibrium size in less than one minute. These properties set this system apart from conventional ones, which have pore sizes between 10nm and 10µm and have slow swelling that takes several hours to reach equilibrium [10]. Figure 10 illustrates swelling and expanding systems. The superporous hydrogels are also intended to have sufficient mechanical strength to withstand gastric contraction pressure. In a study by Gupta and Shivakumar (2010) [26], rosiglitazone was formulated in a swelling super-porous hydrogel. The drug is extensively absorbed from the stomach and therefore could benefit from gastroretention in anti-diabetic therapy. Chitosan and polyvinyl alcohol were used as a polymer network. The hydrogels were sensitive to pH and showed reversible swelling and de-swelling but still retaining its mechanical stability. Chitosan which acted as a cross linker, determined the swelling characteristics and polyvinyl alcohol gave the formulation the required mechanical strength. *In vitro* drug release was sustained for 6 hours and this formulation was found to be successful for rosiglitazone delivery in gastric pH. In another study by Chava and Patel (2011) [27], a super-porous hydrogel was made to deliver ranitidine hydrochloride. The system was made with hydroxypropylmethyl cellulose and had interconnected pores and channels. *In vitro*, the system remained afloat and continued to deliver ranitidine for 17 hours showing a Korsmeyer-Peppas release profile. The formulation proved to be a successful system for gastroretentive delivery of ranitidine. Others have used

gellan gum, sodium alginate, pectin and xanthan gum polymers to prepare size expanding gastroretentive systems [28].

3.5 Magnetic systems

Magnetic systems contain a small internal magnet and an external magnet placed externally on the abdomen and above the stomach to attract and hold the dosage form in place. This can be accomplished with the addition of ferrite [10]. Although these systems works very well in these trials and in theory, in practice the external magnet must be positioned with a degree of accuracy that may compromise patient compliance [10] or lead to sub-therapeutic treatment.

High density system

High density systems are made up of pellets with a density higher than gastric fluid density. When the patient is in the upright position, the system sinks to the bottom, withstands the peristaltic gastric waves and avoids the pylorus. It has been found that a density close to 2.5g/cm^3 is needed for sufficient residence time and excipients used include barium sulphate, zinc oxide, iron and titanium dioxide. Although these systems have shown successful gastric retention in animal models, they are not very effective in humans and there are no marketed systems utilising this strategy [10].

Gastroretentive formulations can be designed as single unit systems or multiple unit dosage forms. Single unit systems are inefficient in prolonging the gastric retention time of drugs due to their all-or-nothing emptying process which may lead to inter-subject variability in drug bioavailability. In addition, their use maybe associated with local irritation due to high concentration of the drug in particular site of the GIT. On the other hand, multiple unit dosage forms including microspheres distribute uniformly in the GIT, and therefore overcome the gastric emptying problems, provide consistent drug release in the GIT and avoid local irritation of the drug [29]. Processing techniques for formulation of multiple unit microspheres gastroretentive dosage forms have been extensively developed. They are shown below.

4.0 Microspheres production methods

Gastroretentive microspheres can be prepared by three main techniques: solvent evaporation, spray drying and coacervation. Other methods are modifications of these three basic methods [30]. A successful formulation of microspheres needs to (i)

have sufficient drug loading, (ii) be chemically and physically stable for a clinically acceptable shelf life, (iii) have controlled particle size, and (iv) have controlled drug release to achieve therapeutic effect and side effect minimisation ([31].

4.1 Solvent evaporation

Solvent evaporation for the preparation of low density systems has achieved tremendous popularity and floating microparticles were the primary dosage form of choice [5].This is an emulsion based method and does not involve highly elevated temperatures like spray draying and is therefore suitable for temperature sensitive compounds. It also does not involve phase separating agents. This means that the resulting microspheres do not have residual solvents, as is the case with phase separation and coacervation methods [6]. There are different ways to make microspheres via solvent evaporation and the choice of method depends on the drug's hydro- and lipophilicity [32, 33]. Lipophilic drugs are incorporated with oil-in-water (o/w), which is the simplest and most frequently used method [32]. Hydrophilic drugs formulated in this way would not be appropriate because the drug may not dissolve in the lipophilic solvent and also diffuse through to the hydrophilic continuous phase. These limitations for hydrophilic drugs can therefore be overcome with the addition of a co-solvent to increase drug solubility, drug addition as a dispersion of solid powder, using a system composed of a lipophilic solvent, such as mineral oil, and therefore form an oil in oil emulsion or the formation of a double emulsion with water-in-oil-in-water [32].

Solvent evaporation involves four steps to microsphere production. These are (i) dispersion or dissolution of the drug in an organic solvent that contains the matrix forming material, (ii) emulsification of organic phase in a lipophilic phase, (ii) solvent removal and finally, (iv) harvesting and microsphere drying [30, 31]. These steps are illustrated in figure 11. Polymers and solvents commonly used with this method are shown in Table 5. Emulsion formation in the second step is the primary determinant of final product particle size and particle size distribution. Microsphere size determines the rate of drug release, drug encapsulation efficiency and *in vivo* fate [6]. Factors that improve the encapsulation efficiency are (i) low polymer solubility in organic solvent, (ii) high solubility of organic solvent in water, (iii) high concentration of polymer, (iv) low dispersed phase to continuous phase ratio and (v) fast solvent removal rate [21]. Other factors that affect microsphere properties are summarised in table 6.

4.2 Spray drying

Spray drying is a process that involves transforming an emulsion, suspension, dispersion or liquid to a dry state by atomization followed by drying [34 35]. The spray process involves three steps: (1) atomization or droplet formation (2) solvent evaporation and (3) particle collection. However, these steps are continuous and are only described in different sections to make explanation easier. In brief, a stream of liquid is atomized to fine droplets, and then dried in a chamber to give solid particles. This is then collected with a suitable dry collector [36]. Spray drying is less dependent on the hydrophilicity or solubility of a compound or polymer and can be a good choice for hydrophilic drugs that leech out in solvent evaporation techniques. Parameters that affect the final product characteristics include inlet air temperature, liquid feeding rate, rate of atomized airflow and particle residence time. These variables affect the particle size, size distribution, particle morphology and bulk density [34]. Figure 12 illustrates how a spray dryer works.

4.2.1 Atomization:

In the atomization process, the liquid is reduced to fine droplets as it passes through the atomizer spray nozzle. This can be achieved with centrifugal, electronic or ultrasound pressure. Different types of atomizers are designed to produce different particle size ranges, for example, the ultrasonic neubilizer produces particles in the 1 to 10 µm range and hydraulic nozzle atomizer produces particles of 100 to 400µm size range. Other factors that influence droplet size are viscosity, density and surface tension in the liquid [36,34].

2.3 Solvent evaporation

The liquid droplets are carried by an inert gas through the drying chamber and they form solid particles. Usually drying chambers work with electric heaters. Homogenous particles result from laminar gas flow with uniform heating (Heng et al., 2011). Solvent evaporation is fast and by simultaneous heat and mass transfer. The drying rate is affected by the difference in temperature between the atomized droplets and the air in the spray drying chamber. In addition, the scale of the batch or rate of atomization can affect drying rate. This generally takes between a few seconds to a minute [34].

2.3.3 Particle collection

The most common method of solid particle collection and separation is the cyclone. This works with a rotating air stream, which generates a centrifugal force on the particles. This force pushes the particles against the walls of the collection chamber. Another method is via bag filtration, which uses fabric to separate the particles from the exhaust air. Electrostatic precipitators are also an option; however, they are not widely used due to their high cost. However, they have the potential to collect particles smaller than 2µm and down to 50nm [36].

4.3 Phase separation or coacervation

Phase separation, also called coacervation, is process where a system composed of colloidal particles dispersed in a medium separates in to two different phases, a colloid rich and colloid poor phase. This separation process can be brought upon with a coacervating agent to produce coacervate droplets, which can be solidified with a hardening agent to produce the microspheres [37].

In detail, coacervation involves several steps. Firstly, the polymer that will provide suitable coating or matrix characteristics is dissolved in a suitable solvent. In the case of a core that requires coating, it may be mixed at this stage with the polymer solution. The solvent should not dissolve this core. Coacervation is brought upon by various techniques, for example, the addition of a non-solvent for the polymer, salt addition or pH change. This causes the polymer to concentrate in a new separate phase, the ‘coacervate’, and polymer droplets form with stirring. Most of the solvent initially used to dissolve the polymer is now the polymer-poor phase. The solvent is removed, by evaporation for example, and the system is further desolvated to harden the formed polymer particles. This may be by solvent evaporation or other methods such as thermal desolvation or crosslinking. Finally the microparticles or microspheres are collected and may be rinsed to remove unwanted solvents or excipients [38, 39].

Another variation on this process is emulsion-coacervation. This process uses an oil-in-water emulsion of an organic phase that contains the drug in an aqueous phase that has the polymer and a stabilising agent. Mechanical stirring or ultrasound aids the emulsification. Coacervation is brought on with electrolytes, also called salting-out, or addition of a water miscible non-solvent or dehydrating agent [40]. This is the critical step of microsphere production and the polymer precipitates from the continuous phase to form a film on the emulsion droplets, which act as a template for

microsphere formation. Coacervation works through polymer desolvation. While the polymer is dissolved in water, the water molecules solvate and surround its functional groups through hydrogen bonding and van der Waals forces. When a coacervating agent is added, water solvation of the polymer decreases and the polymer concentrates in the coacervate phase. There is greater attraction among the polymer chains via secondary valent bonds and non-covalent weak crosslinks and the polymer forms a thin entangled network film as a shell around the emulsion droplets [41]. Finally, a crosslinking step produces rigid hollow core spheres. This can be done with addition of a crosslinking agent, or changing pH or temperature [40]. Solvent removal, by evaporation for example, leaves the microspheres with nothing to keep them suspended. It may therefore be necessary to provide another liquid such as liquid paraffin or water, which does not evaporate appreciably, to suspend the particles. The microspheres are collected and rinsed to remove solvent and excipients [38].

Microsphere Characterisation

Microparticles are characterised by their micromeritic properties such as particle size, tapped density, bulk density, compressibility and angle of repose. Scanning electron microscopy can be used to examine microsphere internal structure to confirm the hollow core nature [8, 42]. In addition, they are characterised on their specific gravity, content uniformity and drug release [9].

Particle size can be measured with laser diffraction particle size analysers and larger particles can also be examined under the light microscope. The mean particle size can be obtained from measurement of 200 to 300 particles using a calibrated micrometer [8]. Particle sizes and their distribution can also be obtained from sieving. This separates the microspheres into different size fractions using a mechanical shaker.

Drug release studies can be dissolution studies in USP dissolution apparatus ([;[43]. Samples are withdrawn at specified times and fresh medium is replaced. Floating dosage forms may not remain afloat for the dissolution test and therefore must be allowed to sink to the bottom first. The USP states “a small, loose piece of non-reactive material such as not more than a few turns of a wire helix may be attached to the dosage units that would otherwise float.” However, standard dissolution

methods are poor predictors of *in vitro* performance. In addition, *in vitro* results correlate poorly with *in vivo* results. Various ways to overcome these limitations have been suggested. Burnes et al (1995) [44] modified the standard method so that the paddle rotates at the surface. The results were reproducible and dissolution profiles were unaltered with rotation speed change, pH change and bile acid concentration increase. In this regard, this validated method is superior to the BP method. Pillay and Fasihi (1998) [45] proposed submerging the floating system under a mesh. The results showed increased drug release and consistent release profiles.

The specific gravity can be measured by the displacement method using benzene as a displacing medium [46]. Microspheres for gastroretentive purposes are designed to float. *In vitro* floatability studies can be done using a USP II dissolution apparatus. The medium is 900 ml of simulated gastric fluid and contains 0.1N hydrochloric acid, sodium chloride and 0.02% tween 80. This makes the medium pH 1.2 and gives it a surface tension resembling human gastric juice, which is between 35 to 50 mN/m^2 [8]. The temperature is maintained at $37^oC \pm 0.5^oC$ and stirred at 100rpm. The floatability is measured as percent buoyancy by noting the proportions of floating and settled microspheres [8]. The formula is given below:

Buoyancy percent = mass of floating spheres / (mass of floating spheres + mass of settled spheres) x100

A microsphere floats when the total force is positive and in the upward direction (9Arora et al., 2005). The forces acting on a sphere are the buoyancy (F_b) and the gravitational force (F_g). The sum of these forces gives the net force and this can be written as given by Timmermans and Andre:

$F = F_b - F_g$ (1)

Fluid density, solid object density, weight and volume of the test object also affect the net force and the relationship is given by equation 2, as described by Timmermans and Andre and further developed by Li et al, 2008 [38].

F = (fluid density – solid density) x g x solid volume (2)

These equations are useful in microsphere characterisation and in successful design of floating gastroretentive formulations. It can be seen for example, that the solid density and volume of the object are very important parameters for overall floating force. During buoyancy measurement, the spheres swell and increase in volume and the density increases due to water uptake. The solid density and solid volume

parameters therefore increase in equation 2, leading to a net upward force that keeps the formulation afloat [9]. Although the USP and BP methods give important information on floatability, the results do not correlate well with *in vivo* performance.

Floating studies may also be conducted *in vivo* in animals and humans. They are carried out under fed and fasted conditions using floating and non-floating forms to act as test and control. The T_{max}, C_{max} and AUC are obtained from graphical data of drug blood levels after administration of dosage form.

Visualisation of floating dosage forms is important for evaluating gastrointestinal retention because the pharmacokinetic data is an indirect assessment of gastric retention. This can be done by X-ray or gamma scintigraphy. Microparticles loaded with radio-opaque materials, such as barium sulphate, can be followed through by X-ray photographs. Gamma scintigraphy can also be used to monitor transit of labelled floating microspheres. This is done by including a gamma-emitting radionuclide in the formulation and visualisation is external with a gamma-camera or scintiscanner that capture emitted gamma waves to observe the location of the formulation in the gastrointestinal tract [3].

Application and case studies of floating microsphere

Floating drug delivery systems have important applications for drugs with poor bioavailability due to a narrow absorption window. They are particularly advantageous for drugs mostly absorbed from the stomach or upper intestine and for drugs that have poor solubility and limited absorption due to short gastric residence [9].

Site specific drug delivery is an advantage in floating drug delivery because most of the drug is released in the stomach and duodenum. Conditions such as stomach ulcers infected with *Helicobacter Pylori* are more successfully eradicated with targeted delivery than regular therapy. *H. Pylori* infections have been associated with short and long term morbidity including reduced gastric motility, reduced acid secretion, increased stomach membrane permeability, dyspepsia, gastritis, gastric cancer and mucosa-associated lymphoid tissue (MALT) lymphomas [10]. Standard and best practice therapy for H. Pylori eradication is 1g amoxicillin twice daily for one week along with 500 mg clarithromycin and 20 mg omeprazole, also taken twice daily (NZGG, 2004). This triple treatment requires good patient compliance for

success and missed doses lead to treatment failure. Many studies have been conducted to assess the success of gastro-retentive strategies in improving *H. Pylori* eradication. Liu et la (2004) [25] formulated bioadhesive microspheres as a floating gastroretentive dosage form for the delivery of amoxicillin. *In vitro* studies showed that amoxicillin release was faster in acidic pH than in slightly basic pH. Amoxicillin is known to be unstable in acidic pH and given that the dosage form increase gastric residence time, this factor had significant importance. It was found that microspheres entrapment was useful to keep it stable.

In vitro and *in vivo* mucoadhesive tests showed that the mucoadhesive microspheres have certainly adhered more strongly to gastric mucosa and were retained for longer periods in the stomach. Rats infected with *H. Pylori* and treated with plain amoxicillin powder, amoxicillin microspheres and mucoadhesive amoxicillin microspheres showed interesting results. Amoxicillin concentrations were directly measured from gastric juice and mucoadhesive formulations showed greater concentrations (Concentration ratios of 1.38, 1.74 and 1.15 at 1, 2 and 3 hours respectively). This significantly greater antibiotic concentration at the target delivery site strongly suggests that such formulations can have enhanced efficacy. The results also showed that the increase in amoxicillin dose, which increases *H. Pylori* eradication, was more pronounced in the mucoadhesive formulation. The authors concluded that this preliminary study has significant finding and similar studies need to be conducted in larger animals to confirm the results.

Floating drug delivery systems have controlled release applications. They remain in the stomach for a prolonged period of time and the drug release rate can be controlled. Regular controlled release formulations suffer from variable and short gastric residence and cannot deliver drugs with narrow absorption windows successfully. In a study by Dong et al (2010) [47] sustained release microspheres were formulated for rosiglitazone, a drug which is used to increase sensitivity to insulin in patients with type 2 diabetes and important in its treatment. Currently, it is used as adjuvant therapy in patient that cannot get sufficient insulin sensitivity from first line treatment [48]. Rosiglitazone has a narrow absorption window in the stomach and duodenum benefits from gastroretentive sustained delivery. Ethylcellulose and octadecyl alcohol were used as carriers and over 90% of the microspheres floated *in vitro* for 12 hours. The pharmacokinetic studies conducted on human volunteers showed that the formulation had a superior profile to

commercial tablets because peak plasma concentration was decreased and rosiglitazone concentration remained in the plasma for a longer time ($T_{1/2}$ increased from 4 to 7 hours). At the same time, the area under the curve was comparable in the commercial and developed formulations, indicating that the bioavailability was not reduced. The study concluded that the developed once daily rosiglitazone sustained release microspheres formulation is good alternative to conventional tablets.

Marketed systems

The last thirty years of intensive gastroretentive formulation research has led to the marketing of a large number of products. In 1999, literature cites the marketing of five products, in 2007 eight products are cited (Kumar and Philip, 2007)[3] and in 2011, 24 gastroretentive products are in the market [5]. The popularity of gastroretentive strategies is rapidly growing day by aday and some formulations are described below.

Madopar LP® is a marketed formulation using a hydrodynamically balanced system to deliver 100mg of levodopa and 25mg benserazide. It was marketed by Roche in the 1980s [10] and is commercially available in Europe but not the US [46]. This is a controlled release formulation that is made up of a gelatin capsule that floats on gastric fluid. This capsule shell dissolves and the mucus body is formed. The drug diffuses through the hydrated outer layers of the matrix as it slowly dissipates [46].

Valrelease® is another marketed gastroretentive formulation that contains 15mg diazepam. The system is a hydrodynamically balanced system made of a floating capsule and is marketed by Hoffmann-La Roche [3]. Diazepam is a good drug candidate for gastroretentive strategies because its pKa of 3.4 makes its absorption favourable in the stomach and not the small intestine. The HBS allows maximal dissolution of diazepam in an environment where it has maximal solubility and absorption. The pharmacokinetic data illustrates the benefit of this gastroretentive formulation, with once daily dosing of Valrelease being equivalent to 3 times daily dosing of regular 5mg Valium® tablets [46].

Topalkan® and Almagate Flot-Coat® are two other gastroretentive formulations that deliver antacids locally to the stomach by forming a floating raft on the stomach contents [3]. Toplakan® is a third generation aluminium-magnesium antacid that has greater availability of alginic acid in the formula. This property, in addition to its

antacid property, sets it apart from other formulations. Almagate Flot-Coat® is also a novel formulation because it has a higher antacid potency than regular formulations and provides relief over a prolonged period of time owing to its gastroretentive properties. Unlike regular antacid formulations that are rapidly neutralised in the stomach or sediment to the fundus and are eliminated, these formulations provide greater antipeptic and stomach membrane protective benefits.

Conviron® is a ferrous sulphate formulation based on a gel forming floating drug delivery system marketed by Ranbaxy [3]. Iron suffers from poor oral bioavailability and need for prolonged treatment to increase iron stores to clinically acceptable levels. In addition, this has necessitated the use of high doses, which lead to side effects such as constipation, gastric upset and diarrhoea. A summary of the marketed gastroretentive formulations is presented in table 7.

Conclusion

The oral route is a very important and widely used in drug delivery. Gastroretentive strategies inherently have several advantages in overcoming the variable gastric residence and targeting to absorptive windows. In effect, gastroretentive strategies improve oral bioavailability and optimise drug plasma levels leading to enhanced and predictable therapeutic outcomes. Microspheres are widely used for gastroretention and have the advantage of being multi-unit. They may be successfully manufactured via solvent evaporation, spray drying or coacervation. Floating drug delivery has important applications such as sustained release and drug targeting. The success of gastroretentive strategies can be seen in the increasing numbers of marketed products.

Declaration of interest

The authors report no conflicts of interest.

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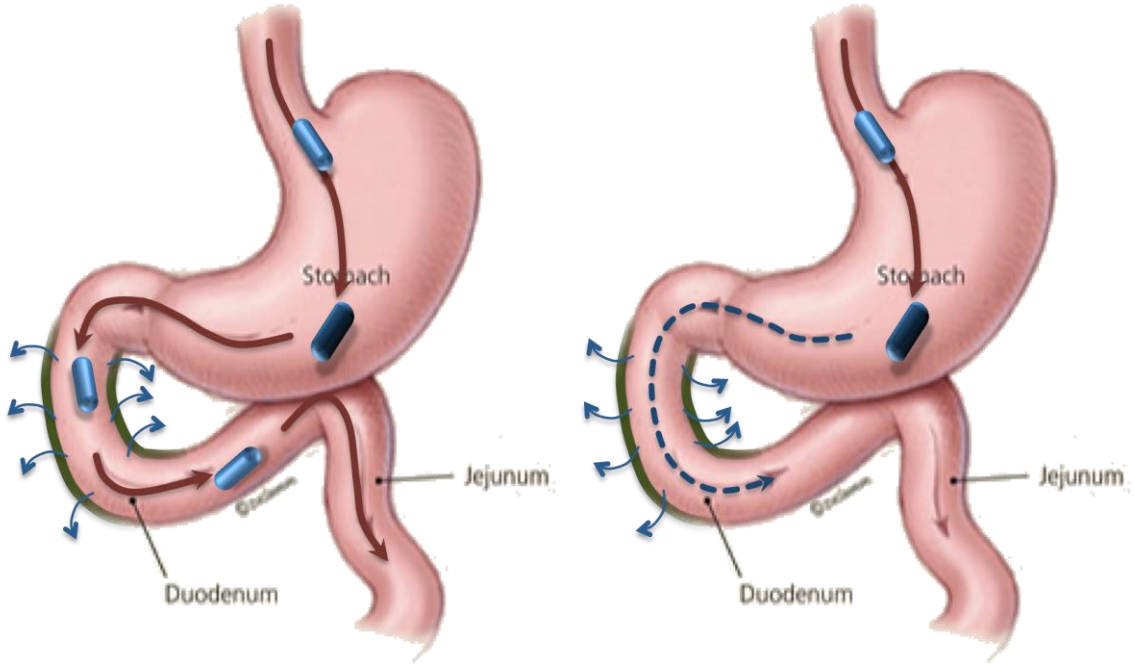


a. b.

Figure 1: Drug absorption through the absorption window. In (a) a regular dosage form. There is little absoprtion beyoynd the absorption window (b) a gastroretentive formulation, where there is continued release above the absoprtion window and constant absorption thorugh it.

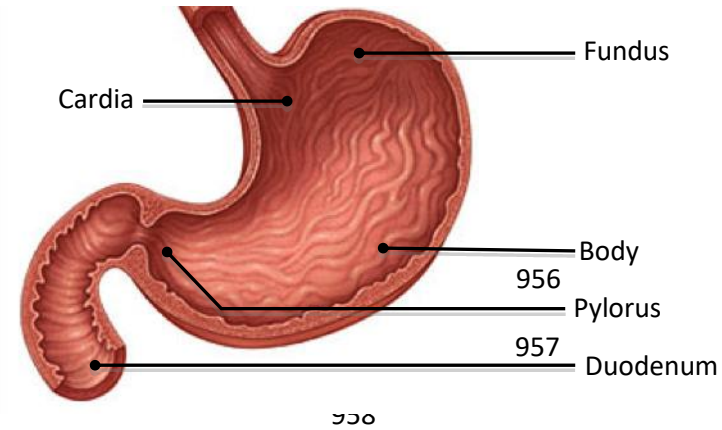


Figure 2: Stomach anatomy

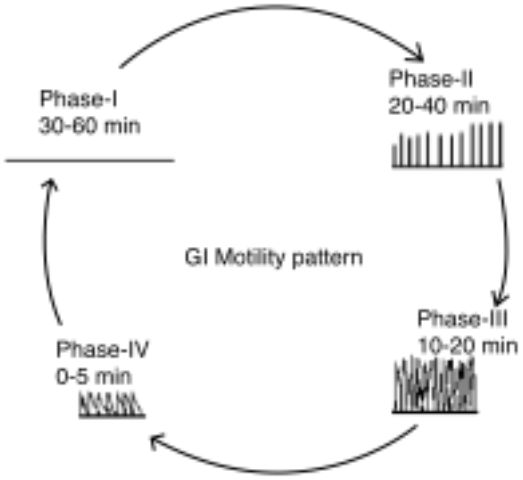


Figure 3: Simple representation of intergastric motility pattern, showing frequency, intensity and pattern of contractions. (Talukder and Fassihi, 2004).

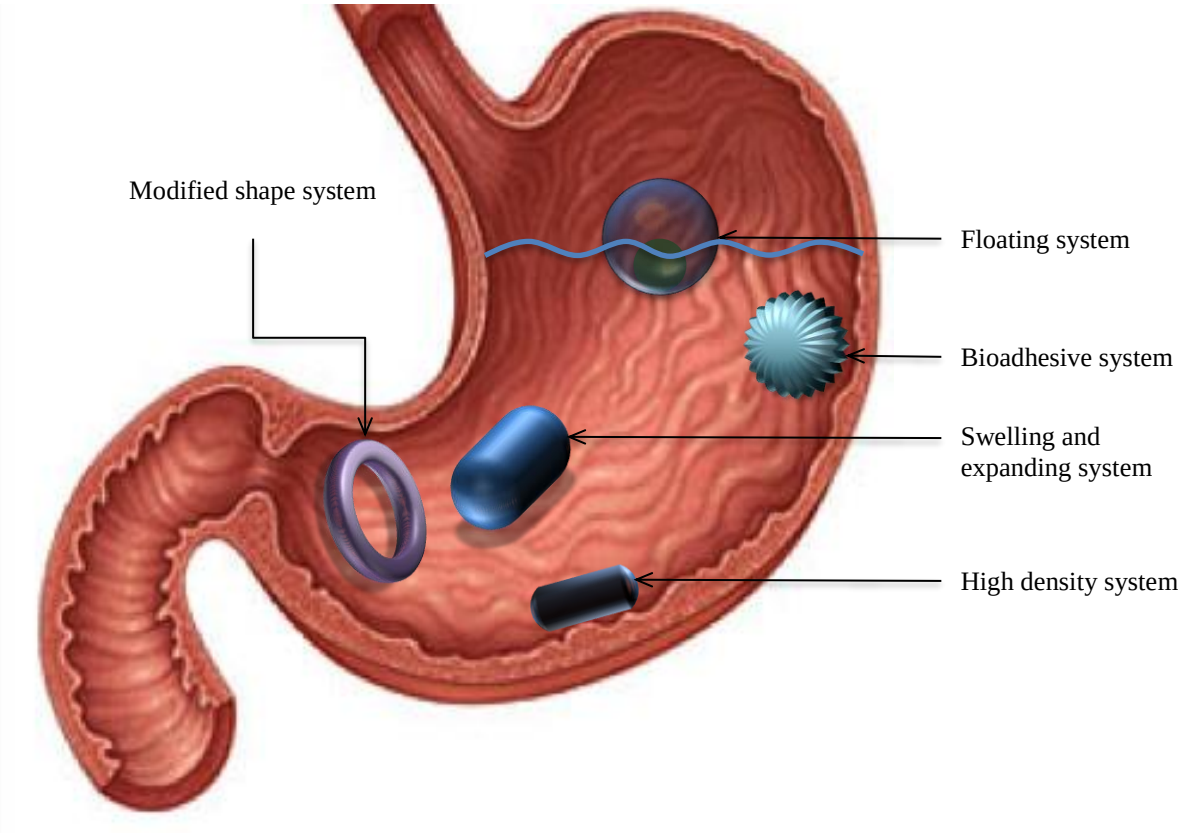


Figure 4: Positions of various gastroretentive drug delivery systems

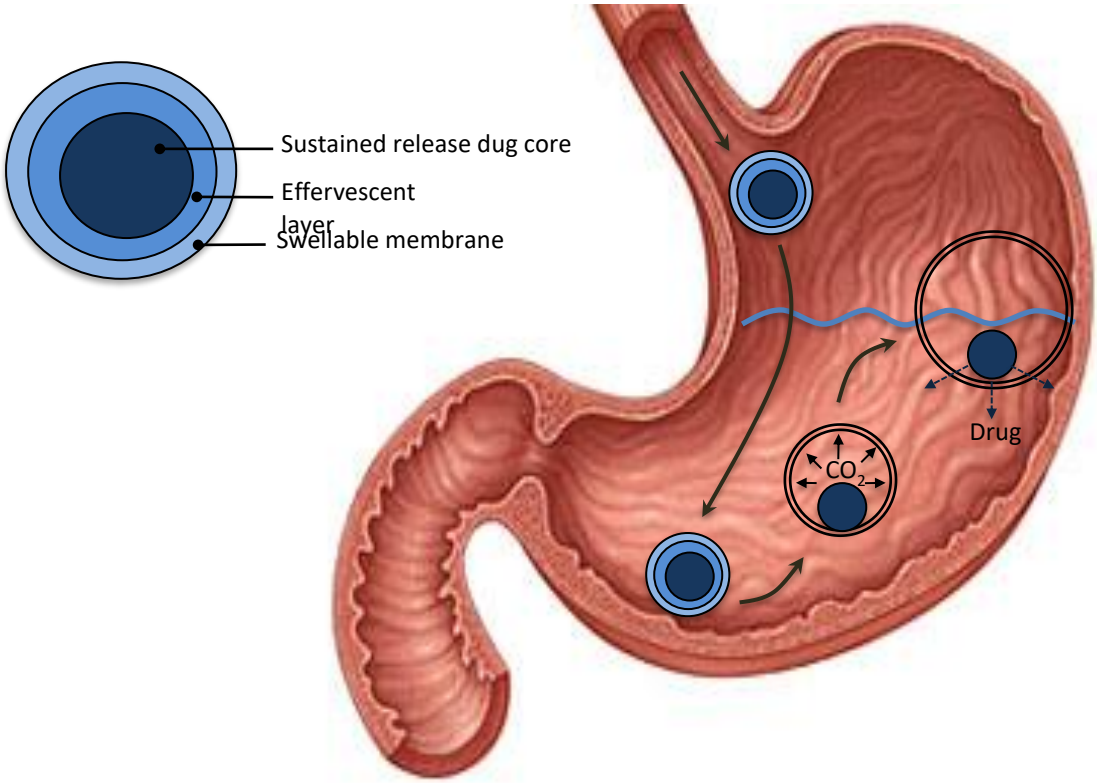


Figure 5: Effervescent floating formulation in the stomach

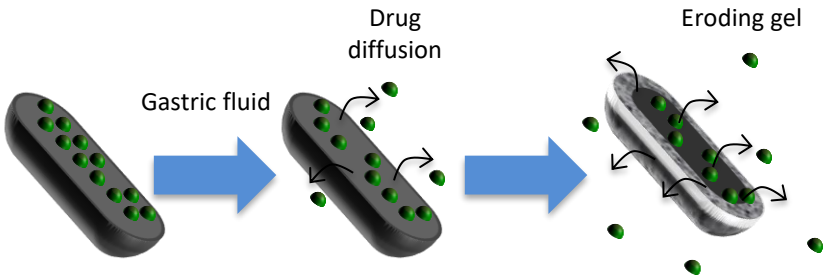


Figure6: hydrodynamically balanced systems

Figure 7: Raft forming systems (adapted from Bardonnet et al., 2005)

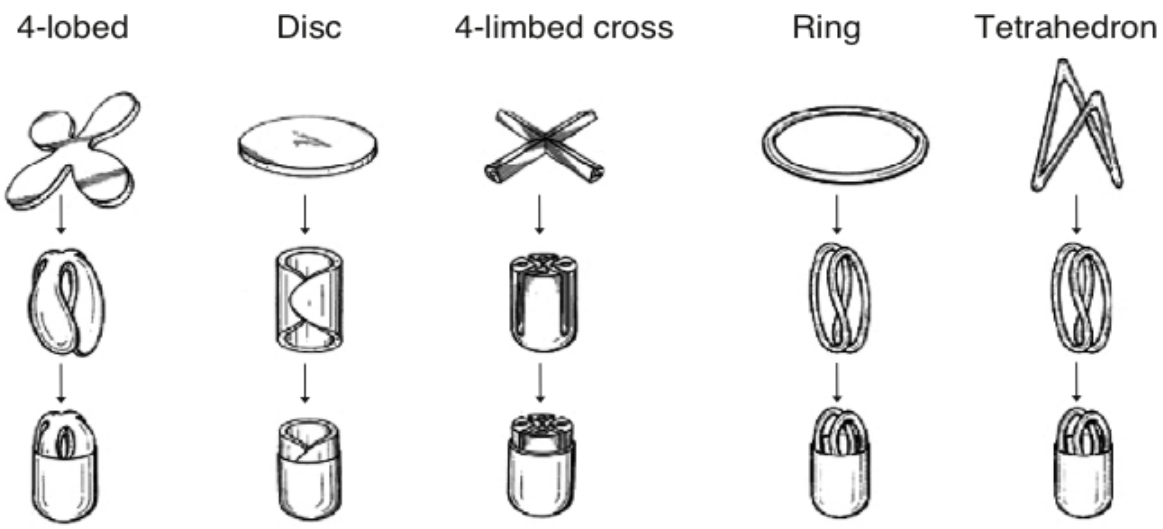


Figure 8: various examples of modified shape systems (Bardonnet et al., 2005; Klausner et al., 2003)

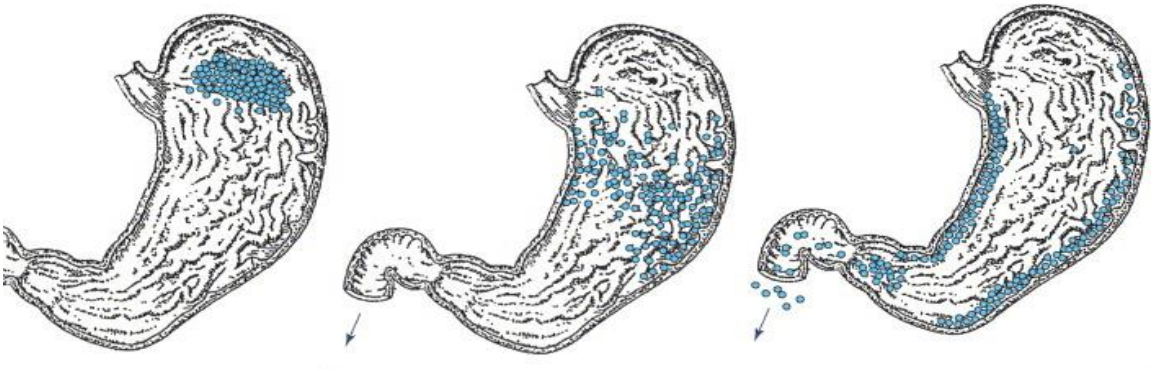


Figure 9: Bioadhesive microspheres in the stomach have gastroretentive properties (Adebisi and Conway 2011)

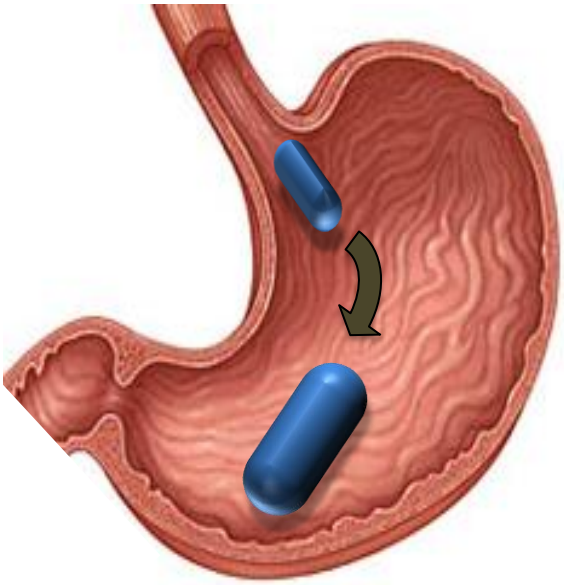


Figure 10: Swelling and expanding systems

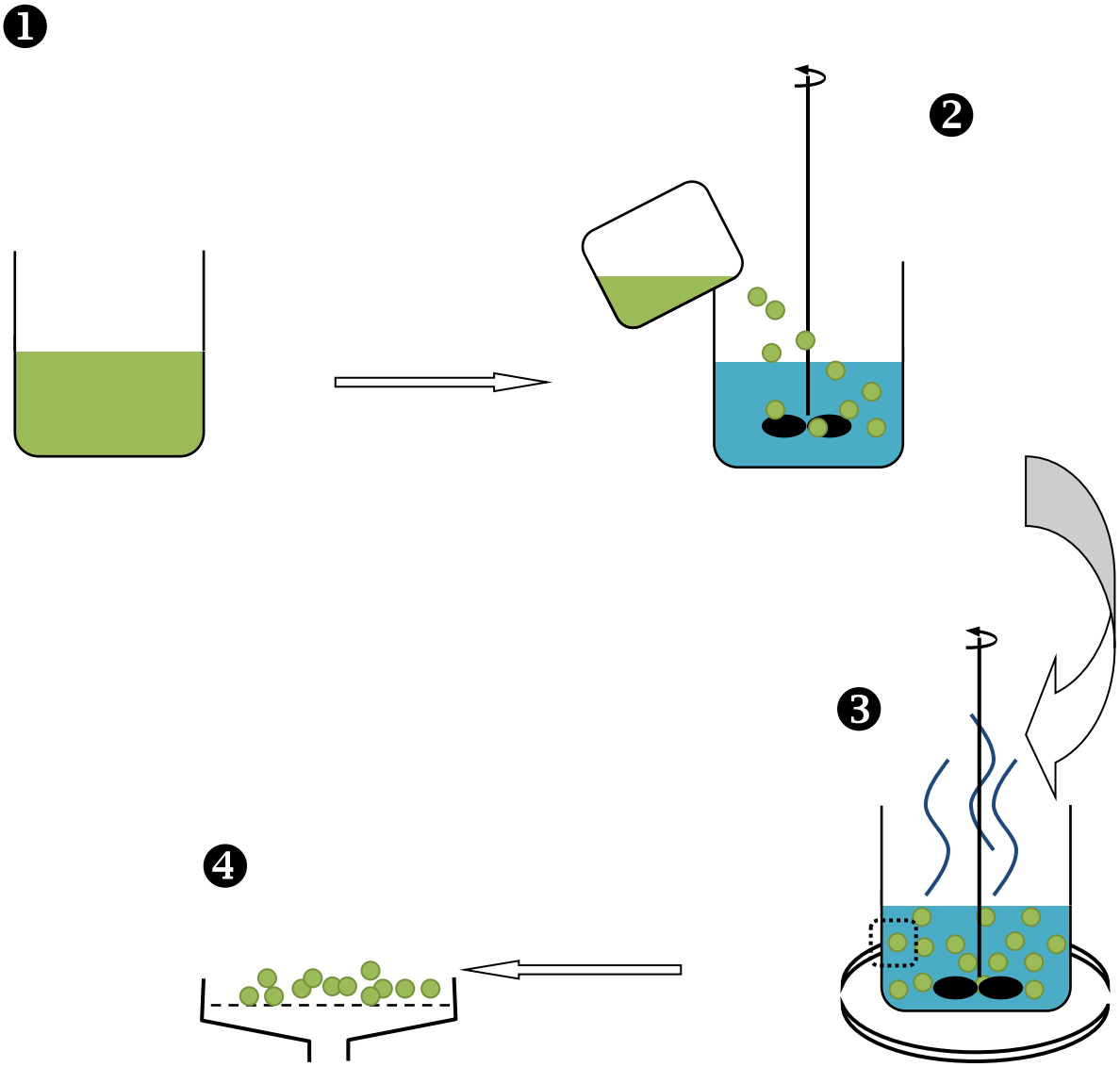
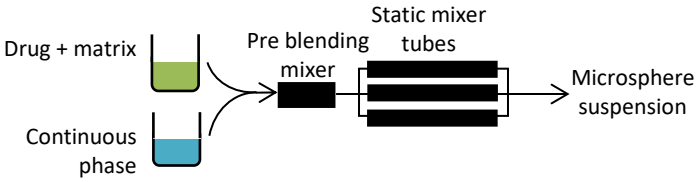
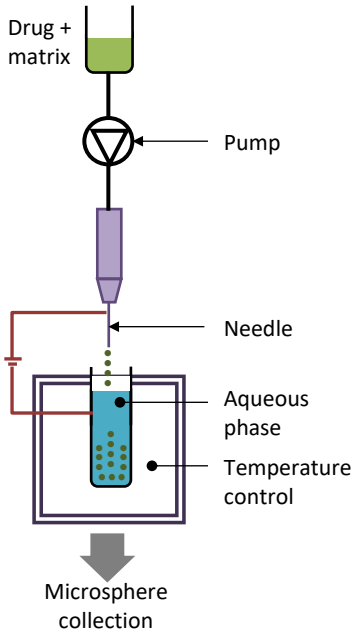
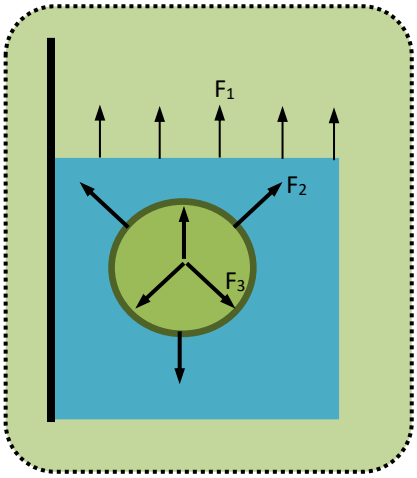


Figure 11a: steps of solvent evaporation technique.







There are three processes occurring during solvent evaporation, (i) solvent evaporation at the air liquid interface (F_1), (ii) solvent diffusion in to the continuous phase (F_2) and (iii) solvent diffusion inside the drop (F_3).

Figure 11b: solvent evaporation technique.

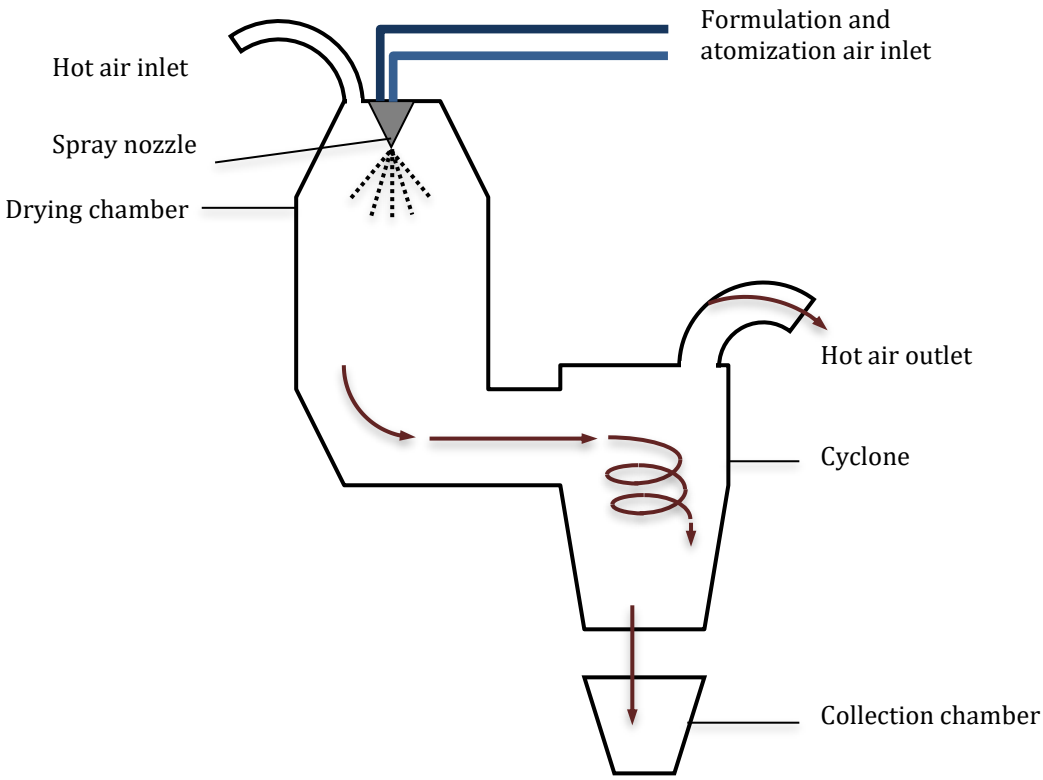


Figure 12: Spray dryer.

Table 1: Examples of drugs with narrow absorption window

Acyclovir
Captopril
Furosemide
Metformin
Gabapentin
Levodopa
Baclofen
Ciprofloxacin

Table 2: Phases in migrating motor complex (fasting state) (Arora et al., 2005, Kumar and Philip 2007)

Phase	Description
I: basal phase	Lasts 40-60 minutes Rare contractions
II: preburst phase	Lasts 40-60 minutes Intermittent contractions that increase in intensity and frequency gradually
III: burst phase	Lasts 4-6 minutes Regular and intense contractions All undigested material is swept out of the stomach Also called the housekeeping wave
IV: transition phase	Lasts 0 to 5 minutes Separates phase III from phase I of the next cycle

Table 3: Factors affecting gastric motility (Kumar and Philip 2007, Arora et al, 2005, Pawar et al., 2011)

Factor	**Effect**
Age	Elderly, over 70 years, have significantly slower gastric motility
Gender	Males have shorter gastric residence (3.4 ± 0.6h) than females (4.6 ± 1.2h) regardless of weight, height and body surface area
Posture	Upright position allows floating dosage forms to float Floating dosage forms have no advantage in the supine position
Fed state	Increased gastric residence time due to presence of food Frequent meal intake constantly delays MMC and increases gastric residence by over 6 hours
Meal type	Higher caloric content remains increases gastric residnce by 4-10 hours Solids remain longer than liquids Starch, cellulose and other fatty acid salts delay the MMC and decrease gatric emptying rate
Disease state	Stress conditions increase gastric motility and depression slow it down
Concomitant drug administration	Anticholinergics, opiates, clonidine, lithium, metoclopramide and other drugs may slow down gastric motility. Erythromycin on the other hand increases gatric motility

Table 4: Factors affecting drug gastric residence time (Arora et al., 2005, Pawar et al., 2011)

Factor	**Effect**
Density	Gastric residence is a function of buoyancy
Shape	Tetrahedron and ring shaped unfolding expandable systems have better retention compared to stick, planar disc or planar multilobe or string.
Size	Solids larger than 1-2mm are retained during postprandial period Solids larger than 13mm remain in the stomach in the postpradial period and not expelled until phase III of the MMC
Single or multiple unit	Multiple unit systems have more predictable residence
Gastric motility phase	Drug administration during the fasting state encounters strong MMC phase III waves that lead to its fast expulsion. Administration during the fed state has longer gastric residence.

Table 5: Polymers, solvents and stabilisers commonly used in solvent evaporation for microsphere formation (Obeidat, 2009, Li et al., 2008, Tran et al., 2011, Freitas et al., 2005)

Abbreviation	Name	Notes
Polymers		
PLG, PLGA	Poly(lactide-co-glycolide), Poly(lactic-co-glycolic acid)	Good biodegradability Good biocompatability
PLA	Poly(lactic acid) or polylactide	Good biodegradability Good biocompatability
PEG	Poly(ethylene glycol)	Used as co-polymer
EC	Ethyl cellulose	Biodegradable Biocompatible Low cost
PHB, PHB-HV	Poly-3-hydroxybutyrate Poly-3-hydroxybutyrate with hydroxyvalerate	Bacterial storage polyester Slower degradation than polylactic polymers
PMMA	Polymethyl methacrylate	Non-biodegradable Biocompatible
ploysaccharides	E.g. chitosan, alginate	Used at a lower frequency
protiens	E.g. albumin, collagen, gelatine	
Lipids	E.g. glyceryltripalmitate	
Solvents		
	Chloroform	High toxicity Low water solubility
	Dichloromethane	High toxicity (lower than chloroform) Almost immiscible in water
	Ethyl acetate	Low toxicity Partially water soluble
	Ethyl formate	Low toxicity Partially water soluble
Stabilisers		
PVA	Polyvinyl alcohol	Non ionic Most widely used Gives smallest microspheres
MC	Methyl cellulose	Non ionic
	Tween	Non ionic
	Span	Non ionic
SDS	Sodium dodecyl sulphate	Anionic
CTAB	Cetyltrimethyl ammonium bromide	Cationic

Table 6: Summary of factors affecting microspheres properties prepared via solvent evaporation (Li et al., 2008)

Factor	**Microsphere properties**		
	Size	**Surface morphology**	**Encapsulation efficiency**
Higher dispersed phase viscosity	Larger	smoother	Increased efficiency
Higher dispersed phase to continuous phase volume ratio	Smaller		Increased
Larger amount of drug		More porous, irregular shape	Decreased at high drug concentrations
Increased surfactant concentration	Smaller		No effect
Increased agitation rate	Smaller	Smoother	
Increased temperature	Smaller	Coarser surface	Decreased
Reduced pressure	Smaller	Smoother	Increased

1288 Table 7: A summary of the marketed gastroretentive formulations (Pawar et al.,
1289 2011, Kumar and Philip, 2007, Brahma and Kwon 1999)

Brand name	**Drug**	**Formulation**	**Company**
Zanocin OD	Ofloxacin	Effervescent floating system	Ranbaxy
Riomet OD	Metformin	Effervescent floating system	Ranbaxy
Cifran OD	Ciprofloxacin	Effervescent floating system	Ranbaxy
Inon Ace Tablets	Simethicone	Foam based floating system	Sato Pharma
Gabapentin GR	Gabapentin	Acuform technology: uses polymer based swelling	Depomed
ProQuin XR	Ciprofloxacin	Acuform technology: uses polymer based swelling	Depomed
Glumetza	Metformin	Acuform technology: uses polymer based swelling	Depomed
Metformin GR	Metformin	Acuform technology: uses polymer based swelling	Depomed
Kadiam	Morphine sulphate		Sumitomo Pharma
Prazopress XL	Prazosin	Effervescent and swelling based system	Sun Pharma
Metformin Hcl LP	Metformin	Minextab floating®	Galenix
Cefaclor LP	Cefaclor	Minextab floating®	Galenix
Tramadol LP	Tramadol	Minextab floating®	Galenix
Cipro XR	Ciprofloxacin + betaine	Erodible matrix system	Bayer
Accordion Pill TM		Expandable film filled in capsule (modified shape system)	Intec Pharma
Baclofen GRS	Baclofen	Multilayer floating and swelling system	Sun Pharma
Coreg CR	Carvedilol	Osmotic system	Glaxosmithkline
Madopar	Levodopa, benserzide	Hydrodynamically balanced system, floating capsule	Roche
Gaviscon liquid	Alginic acid, sodium bicarbonate	Floating raft system	Reckitt Benckiser Healthcare
Valrelease	Diazepam	Hydrodynamically balanced system, floating capsule	Roche
Topalkan	Aluminium magnesium antacid	Floating raft system	Pierre Fabre Medicament
Conviron	Ferrous sulphate	Colloidal gel forming GDDS	Ranbaxy
Almagate Flat Coat	Antacid	Flaoting raft	
Oflin	Ofloxacin	Gas generating floating tablet	Ranbaxy
Cytotex	Misoprostol	Bilayer floating tablet	Pharmacia Limited

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