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(Review Article)

Various Approaches in Floating Drug Delivery

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ABSTRACT

Among all the drug delivery route, oral route is most preferred route mainly because of ease of administration. Bioavailability of many drugs is affected by short gastric residence of drugs, to overcome this limitation various approaches have been proposed to increase gastric residence of drug in upper GI tract includes floating drug delivery, swelling and expanding system, Mucoadhesive system, high density system, modified shape system, magnetic system. Current review focuses on technological developments in floating drug delivery and comprehensive evaluation of floating drug delivery system.

Key Words: Gastric residence time, Floating drug delivery, Hydrodynamically balanced system

INTRODUCTION

Oral controlled release dosage forms have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation. However, this approach is bedilled with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract due to variable gastric emptying and motility. Furthermore, the relatively brief gastric emptying time in humans which normally averages 2-3 h through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose¹. Therefore, control of placement of a drug delivery system in a specific region of the GI tract offers advantages for a variety of important drugs characterized by a narrow absorption window in the GIT or drugs with a stability problem

Basic Anatomy of Stomach and Its Physiology

The stomach is an organ for storage and mixing. 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, capable of displaying a large expansion to accommodate food without much increase in intragastric pressure. Whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions. The opening nearer to esophagus is called as cardiac end characterized by pyloric sphincter. Under fasting conditions the stomach is collapsed bag with residual volume of 50 ml and contains a small amount of gastric fluid and air. Basic structure of gastrointestinal tract and stomach are shown in figure-1 Mucosal lining is covered throughout the stomach under this layer specialized cells are present that secret gastric juice into stomach.



Figure-1: Anatomy of stomach

Gastric emptying occurs during fasting as well as fed states. The passage of drug from stomach to the small intestine is called gastric emptying. It is the rate limiting step for drug absorption because the major site for absorption in intestine. Generally rapid gastric emptying increase bioavailability of the drug. Faster onset requires for drugs that degrade in gastric environment. Delayed gastric emptying promotes



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dissolution of the drugs, which are poorly soluble drugs and for the drugs that is majorly absorbed from stomach or proximal part of the intestine. 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 are:

- Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
- Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
- Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
- Phase IV Period of transition from phase III and phase I last for 0 to 5 minutes.



Figure 2: Scematic representation of interdigestive motility

Advantages of Floating Drug Delivery System¹⁻⁵:

- Enhanced bioavailability.
- Reduced first pass metabolism.
- Sustained drug delivery with reduced frequency of dosing.
- Targeted therapy for local delivery of drugs in upper GI tract.
- Reduced fluctuations in plasma drug concentration.
- Improved receptor activation selectivity.
- Reduced counter activity of the body.
- Extended time over critical concentration.
- Reduced adverse activity at the colon.
- Site specific drug delivery.

Limitations of Floating Drug Delivery System ^{6,7}

- These systems require a high level of fluid in the stomach for delivery to float and work efficiently.
- Not suitable for drugs that have solubility or stability problem in GIT.
- Drugs such as nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable.
- Drugs which are irritant to gastric mucosa are not suitable.
- Drug substances that are unstable in the acidic environment of the stomach are not suitable.
- Dosage form should be administered with a full glass of water (200-250ml).

• Not suitable for those drugs which are absorbed throughout the GIT.

Table 1: Drug candidates for Floating drug delivery

Drugs exerting local therapeutic action in the stomach	Misoprostol, 5-Flurouracil, antacids and antireflux preparations, anti <i>Helicobacter</i> <i>pylori</i> agents and certain enzymes.
Drugs exhibiting site- specific absorption (absorption window) in the stomach or upper part of the small intestine:	Atenolol, furosemide, levodopa, <i>p</i> - Aminobenzoic acid, piretanide, sotalol, salbutamol, thiamide.
Drugs unstable in lower part of GI tract	Captopril
Drugs insoluble in intestinal fluids	Chlordiazepoxide, chlorpheniramine, cinnarizine, dizapam, diltiazem, metoprolol, prorenolol, Verapamil
Drugs with variable bioavailability	. Sotalol hydrochloride and levodopa

Drugs unsuitable for Gastroretenvie drug delivery system

1) Drugs that have very limited acid solubility e.g. phenytoin etc.

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

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

PHYSIOLOGICAL FACTORS CONTROLLING GASTRIC RETENTION OF DOSAGE FORMS

The gastric retention time (GRT) of dosage forms is controlled by several factors such as density and size of the dosage form, food intake, nature of the food, posture, age, sex, sleep and disease state of the individual (e.g., gastrointestinal diseases and diabetes) and administration of drugs such as prokinetic agents (cisapride and metoclopramide).

1. Density of Dosage Form

Dosage forms having a density lower or higher than that of gastric fluid experience floating or sinking behavior and hence gastric retention. A density of <1.0 gm/cm3 is required to exhibit floating property⁸. However, the floating tendency of the dosage form usually decreases as a function of time, as the dosage form gets immersed into the fluid, as a result of the development of hydrodynamic equilibrium.

2. Size of Dosage Form

The size of the dosage form is another factor that influences gastric retention. The mean gastric residence times of nonfloating dosage forms are highly variable and greatly dependent on their size, which may be small, medium, and large units. In fed conditions, the smaller units get emptied from the stomach during the digestive phase and the larger units during the housekeeping waves. In most cases, the larger the size of the dosage form, the greater will be the gastric retention time because the larger size would not allow the dosage form to quickly pass through the pyloric antrum into the intestine⁹. Dosage forms having a diameter of more than 7.5 mm show a better gastric residence time compared with one having 9.9 mm8. Ring-shaped and tetrahedron-shaped devices have a better gastric residence time as compared with other shapes ¹⁰. Thus the size of the dosage form appears to be an important factor affecting gastric retention.

3. Food Intake and Nature of Food

Food intake, the nature of the food, caloric content, and frequency of feeding have a profound effect on the gastric retention of dosage forms. The presence or absence of food in the stomach influences the GRT of the dosage form. Usually, the presence of food increases the GRT of the dosage form and increases drug absorption by allowing it to stay at the absorption site for a longer time. The above results are supported by the experiments of Whitehead et al which show an increase in the relative heights of the floating units after meal consumption. Again, increase in acidity and caloric value shows down gastric emptying time, which can improve the gastric retention of dosage forms¹¹

Food habits affect the GRT in the following ways:

Fed or unfed state - under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer. It was concluded that as meals were given at the time when the previous digestive phase had not completed, the floating form buoyant in the stomach could retain its position for another

digestive phase as it was carried by the peristaltic waves in the upper part of the stomach.

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 - GRT can be increased by four to 10 hours with a meal that is high in proteins and fats.

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.

4. Effect of Gender, Posture and Age

Generally females have slower gastric emptying rates than male. The effect of posture does not have any significant difference in the mean gastric retention time (GRT) for individuals in upright, ambulatory and supine state. In case of elderly persons, gastric emptying is slowed down¹². However, in supine position, the floating units are emptied faster than non-floating units of similar size.

FLOATING DRUG DELIVERY SYSTEMS



Figure 3: Intragastric floating system

Floating systems was first described by Davis in 1968. 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, 9}the drug is released slowly at the desired rate ^{10, 11}, While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in increased GRT and reduces fluctuation in plasma drug concentration⁷. Formulation of such system should exhibit following charecteristics,

- 1) Sufficient structure to form cohesive gel barrier,
- 2) Specific gravity less than gastric fluid (1.004-1.010)
- 3) Dissolve slowly enough to act as drug reservoir¹⁴

When floating on top of the gastric contects, floating doasge form are situated high in the stomach, closer to the fundus and relativerly distant from thr pyloric opening. Floating unit still require the fed state of the stomach to enhance the gastric emptying time significantly. Floatation of the dosage form is determined by resultant weight which is difference between the buoyancy force when entirely submerged and the weight of dosage form. The object will float if the resultant weight is positive.

Floating drug delivery can be broadly classified as,

- Effervescent system
- Non effervescent system

Effervescent System

Effervescent systems utilize gas (CO2) generating agents (e.g. sodium bicarbonate, citric acid or tartaric acid) to achieve floatability. After oral administration in the GIT, CO2 is liberated from these drug elivery systems, which reduces the density of the system and making it float on the gastric fluid²⁵. 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 acid¹⁸ or matrices containing chambers of liquid that gasify at body temperature¹⁹⁻²¹.

a. Volatile liquid containing systems

Gas can be introduced into the floating chamber by the volatilization of an organic solvent (e.g., ether or cyclopentane) or by the CO2 produced as a result of an effervescent reaction between organic acids and carbonatebicarbonate salts²³. The matrices are fabricated so that upon administration, 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. A decrease in specific gravity causes the dosage form to float on the chyme¹⁸

These type of systems consist of two chambers separated by an impermeable, pressure-responsive, movable bladder. The first chamber contains the drug and the second chamber contains the volatile liquid. The device inflates, and the drug is continuously released from the reservoir into the gastric fluid²².



Figure 4: Volatile liquid containing system

b) Gas generating system

Intragastric single-layered floating tablets are formulated by intimately mixing the CO2 generating components and drug candidates within tablet matrix²⁶. These have a bulk density lower than the gastric content and therefore achieve buoyancy in the stomach unflattering the gastric emptying rate for a prolonged period of time. The drug is released from the matrix tablet in a sustained manner at a desired rate. Even after completion of the drug release, the residual system is to be expelled from the stomach.



Figure 5: Gas generating system

Layered dosage form overcomes the constraint imposed by monolithic forms. Separate layer of dosage form are responsible for each function. Intra gastric bi-layered floating tablets may be compressed which contains the gas generating mechanism in one sustained release layer and immediate release layer²⁷.



Figure 6: Gas generating layered system

A multiple-unit type of floating pill, which generates CO2 gas, has been developed²⁸. The system consists of sustained release pills as seeds surrounded by double layers. The inner layer was an effervescent layer containing tartaric acid and sodium bicarbonate. The outer layer was a swellable membrane layer. Moreover, the effervescent layer was divided into two sub layers to avoid direct contact between these two gas generating agents. Sodium bicarbonate was contained in the inner sub layer, while tartaric acid was in outer layer. When the system was immersed in buffer

system at 37°C, it sank at once in the solution and form swollen pills, like balloons (density < 1 gm/ml), which float as they have lower density. The reaction was due to carbon dioxide generated by neutralization in the inner effervescent layers with the diffusion of water through the outer swellable membrane layers. The system was found to float completely within 10 min and approximately 80% remained floating over a period of 5 hr irrespective of pH and viscosity of the test medium. While the system was floating, a drug was released. A variant of this approach utilizing citric acid (anhydrous) and sodium bicarbonate as effervescing agents and HPC-H grade as a release controlling agent has also been reported²⁴. In vitro results indicated a linear decrease in the FT of the tablets with an increase in the amount of effervescing agents in the range of 10-20%. Attempts have also been made to develop SR floating tablets using a mixture of sodium bicarbonate, citric acid and chitosan.



Figure 8: Drug release from Multiple unit floating pill

A gastroretentive drug delivery system of ranitidine hydrochloride⁴³ was formulated using guar gum, xanthan gum, and hydroxy propyl methyl cellulose. Sodium bicarbonate was incorporated as a gas-generating agent. The effect of citric acid and stearic acid on drug release profile and floating properties was studied. The addition of stearic acid reduces the drug dissolution due to its hydrophobic nature. A 32 full factorial design was applied to systemically optimize the drug release profile and the results showed that a low amount of citric acid and a high amount of stearic acid favor sustained release of ranitidine hydrochloride from a gastroretentive formulation. Hence, it could be concluded that a proper balance between a release rate enhancer and a release rate retardant could produce a drug dissolution profile similar to a theoretical dissolution profile of ranitidine hydrochloride.

Floating capsules⁴⁵ was formulated containing plurality of granules that have different residence times in the stomach and consist of an inner foamable layer of gas generating

agents. This layer was further divided into 2 sublayers, the outer layer containing sodium bicarbonate and the inner layer containing tartaric acid. This layer was surrounded by an expansive polymeric film (composed of poly vinyl acetate [PVA] and shellac), which allowed gastric juice to pass through, and was found to swell by foam produced by the action between the gastric juices and the gas-generating agents.29 It was shown that the swellable membrane laver played an important role in maintaining the buoyancy of the pills for an extended period of time. Two parameters were evaluated: the time for the pills to be floating (TPF) and rate of pills floating at 5 hours (FP5h). It was observed that both the TPF and FP5h increased as the percentage of swellable membrane layer coated on pills having a effervescent layer increased. As the percentage of swellable layer was increased from 13% to 25% (wt/wt), the release rate was decreased and the lag time for dissolution also increased. The percentage of swellable layer was fixed at 13% wt/wt and the optimized system showed excellent floating ability in vitro (TPF ~10 minutes and FP5h ~80%)

independent of pH and viscosity of the medium.

Sustained release floating capsules of nicardipine HCl⁴⁸ were developed using hydrocolloids of high viscosity grades and to aid in buoyancy sodium bicarbonate was added to allow evolution of CO2. In vitro analysis of a commercially available 20-mg capsule of nicardipine HCl (MICARD) was performed for comparison. Results showed an increase in floating with increase in proportion of hydrocolloid. Inclusion of sodium bicarbonate increased buoyancy. The optimized sustained release floating capsule formulation was evaluated in vivo and compared with MICARD capsules using rabbits at a dose equivalent to a human dose of 40 mg. Drug duration after the administration of sustained release capsules significantly exceeded that of the MICARD capsules. In the latter case the drug was traced for 8 hours compared with 16 hours in former case.

Atyabi and coworkers³⁹ developed a floating system using ion exchange resin that was loaded with bicarbonate by mixing the beads with 1 M sodium bicarbonate solution. The loaded beads were then surrounded by a semipermeable membrane to avoid sudden loss of CO2. Upon coming

in contact with gastric contents an exchange of chloride and bicarbonate ions took place that resulted in CO2 generation thereby carrying beads toward the top of gastric contents and producing a floating layer of resin beads (Figure 4). The in vivo behavior of the coated and uncoated beads was monitored using a single channel analyzing study in 12 healthy human volunteers by gamma radio scintigraphy. Studies showed that the gastric residence time was prolonged considerably (24 hours) compared with uncoated beads (1 to 3 hours).



Figure 9: floating system using ion exchange resin

Multi-unit floating systems of a highly water-soluble drug, diltiazem HCl were prepared using hydrophobic lipid, Gelucire 43/01. Diltiazem HCl-Gelucire 43/01 granules were prepared by the melt granulation technique. The granules were evaluated for in vitro and in vivo floating ability, surface topography, and in vitro drug release. In vivo floating ability was studied by γ - scintigraphy in 6 healthy human volunteers and the results showed that the formulation remained in the stomach for 6 hours. Non effervescent system:

Non-effervescent Systems

Non-effervescent FDDS are normally prepared from gelforming or highly swellable cellulose type hydrocolloids, polysaccharides or matrix forming polymers. These systems can be further divided into following sub-types:

Hydrodynamically balanced systems (HBS):

HBSs have gained a lot of importance in recent days to improve absorption of drugs especially those are absorbed from stomach and small intestine or drugs such as weak bases, which dissolve better in the acid environment of the stomach²⁹. These systems contain drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. These are single-unit dosage forms, containing one or more gel-forming hydrophilic polymers. HPMC, hydroxethyl cellulose (HEC), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (NaCMC), polycarbophil, polyacrylate, polystyrene, agar, carrageenans or alginic acid are commonly used excipients to develop these systems³⁰. The polymer is mixed with drugs and usually administered in the HBS capsule. When the capsule containing drug-hydrocolloid mixture comes in contact with gastric fluid, the capsule shell dissolves and the mixture swells to form a gelatinous barrier. This imparts buoyancy in gastric juice for a long period due to its continuous erosion of the surface, which allows water penetration to the inner layers maintaining surface hydration and buoyancy to the dosage form ³⁰. Incorporation of fatty excipients gives low-density formulations reducing the erosion. Effective drug deliveries depend on the balance of drug loading and the effect of polymer on its release profile. Several strategies have been tried and investigated to improve efficiencies of the floating HBS.



Figure 10: Hydrodynamically balance system

The absorption of bromocriptine⁴² is limited to 30% from the gastrointestinal tract, however an HBS of the same can enhance the absorption. It was also studied that if metoclopramide is co delivered with bromocriptine, the side effects associated with high doses of bromocriptine can be prevented and the dosage from becomes therapeutically more potential.

Microballoons (Hollow microspheres):

Microballoons (hollow microspheres) loaded with drugs in their other polymer shelf were prepared by simple solvent evaporation or solvent diffusion/ evaporation method to create a hollow inner core³¹, which prolongs the GRT of the dosage form. Commonly used polymers to develop these systems are polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar and low methoxylated pectin etc. The polymer is dissolved or dispersed in the organic solvent and the drug is either dissolved or dispersed in the polymer solution. The solution containing the drug is emulsified into an aqueous phase containing polymers to form an oil-inwater emulsion and after formation of stable emulsion, the organic solvent is evaporated either by increasing the temperature under pressure or by continuous stirring. The

solvent removal leads to polymer precipitation at oil/water interface of the droplets with formation of cavity, and thus, hollow microspheres are formulated. Buoyancy and drug release from dosage form are dependent on quantity of polymers, the plasticizer polymer ratio and the solvent used for formulation. The microballoons floated continuously over the surface of an acidic dissolution media containing surfactant for >12 hours. At present hollow microspheres are considered to be one of the most promising buoyant systems because they combine the advantages of multiple-unit system and good floating.



Figure 11: Mechanism of microballon formation



Polycarbonate⁴³ microspheres by solvent evaporation technique. Polycarbonate in dichloromethane was found to give hollow microspheres that floated on water and simulated biofluids as evidenced by scanning electron microscopy (SEM). High drug loading was achieved and drug-loaded microspheres were able to float on gastric and intestinal fluids. It was found that increasing the drugtopolymer ratio increased both their mean particle size and release rate of drug.

Floating microballoons of riboflavin⁴¹, were prepared by an emulsion solvent technique. To assess the usefulness of the intragastric floating property of the developed microballoons of riboflavin, riboflavin powder, nonfloating microspheres of riboflavin, and floating microballoons of riboflavin were administered to 3 volunteers. Riboflavin pharmacokinetics was assessed by urinary excretion data. It could be concluded that although excretion of riboflavin following administration of floating microballoons was not sustained in fasted state, it was significantly sustained in comparison to riboflavin powder and nonfloating microspheres in the fed state. This

could be due to the reason that the nonfloating formulation passes through the proximal small intestine at once from where riboflavin is mostly absorbed, while the floating microballoons gradually sank in the stomach and then arrived in the proximal small intestine in a sustained manner. Total urinary excretion (%) of riboflavin from the floating microballoons was lower than that of riboflavin powder. This was attributed to incomplete release of riboflavin from microballoons at the site of absorption.

Alginate beads

These are a multiple-unit floating system based on crosslinked beads³². They were made by using Ca2+ and low methoxylated pectin (anionic polysaccharide), or Ca2+ low methoxylated pectin and sodium alginate. In this approach, generally sodium alginate solution is dropped into aqueous solution of calcium chloride and causes the precipitation of calcium alginate. In an another investigation, multiple-unit floating alginate beads have been developed by from freezedried calcium alginate using sodium alginate as the polymer and calcium chloride as a cross-linking agent45. These beads are separated and dried by air convection and freeze drying, leading to the formulation of a porous system, which can maintain a floating force for over 12 hrs. These beads improve GRT more than 5.5 hrs^{33,34}.

Pectin beads

Oil-entrapped calcium pectinate gel (CaPG) beads were perpered by emulsion gelation method as a carrier for intragastric floating drug delivery. The gel beads were prepared by gently mixing or homogenizing an oil phase and

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a water phase containing pectin, and then extruded into calcium chloride solution with gentle agitation at room temperature. The oil-entrapped calcium pectinate gel beads floated if a sufficient amount of oil was used. Scanning electron photomicrographs demonstrated very small pores, ranging between 5 and 40 μ m, dispersed all over the beads. The type and percentage of oil played an important role in controlling the floating of oil-entrapped CaPG beads. The oil-entrapped CaPG beads were a good choice as a carrier for intragastric floating drug delivery.

Wax-incorporated Calcium Pectinate Emulsion Gel Beads of metronidazole⁴⁶ were prepared for Intragastric Floating Drug Delivery. Calcium pectinate beads prepared by modified emulsion-gelation method. Various amounts of different waxes i.e. Polyethylene glycol, glyceryl monostearate, white wax, carnauba wax, spermaceti wax and stearyl alcohol were investigated. The waxes in pectinolive oil mixtures containing metronidazole, were hotmelted, homogenized and then extruded into calcium chloride solution The influence of various types and amounts of wax on floating and drug release behavior of emulsion gel beads of calcium pectinate was investigated. The drug-loaded gel beads were found to float on simulated gastric fluid if the sufficient amount of oil was used. Incorporation of wax into the emulsion gel beads affected the drug release. Water-soluble wax (i.e. polyethylene glycol) increased the drug release while other waterinsoluble waxes (i.e. glyceryl monostearate, stearyl alcohol, carnauba wax, spermaceti wax and white wax) significantly retarded the drug release. Different waxes had a slight effect on the

drug release. However, the increased amount of incorporated wax in the formulations significantly sustained the drug release while the beads remained floating.

NEWER TREND IN FLOATING DRUG DELIVERY

Floating Osmotic Drug Delivery

A floating osmotic drug delivery system employs the principal of osmotic pressure to float on the

gastric fluid. Basically these systems comprise of three parts; an osmotic core (containing drug

reservoir, osmotic agents, and other excipients), a shape retaining semipermeable membrane; and an outer compression coating consisting of gas generating and gel forming agents. For delivery of drug an orifice is bored through both the outer layers. After administration when this system comes in contact with gastric fluid, initially CO2 is generated due to the presence of a gas forming agent and this generated gas entraps within the bed of swelled gel, thus the system became buoyant due to diminished density. Delivery of drug then totally depends upon the osmotic pressure generated inside the osmotic core. First a saturated solution of drug is formed

due to the flow of fluid through the semipermeable membrane and second expulsion of drug through the orifice due to osmotic pressure develops within the osmotic core. A major advantage of floating osmotic drug delivery systems is that they deliver drug independent to physiological parameters like pH of gastric fluid^{37,38}.



Figure 13: Floating osmotic drug delivery system

In some cases the reduction in bioavailability is compensated by advantages offered by FDDS, for example a hydrodynamically balanced system of L-dopa provided better control over motor fluctuations in spite of reduced bioavailability of up to 50% to 60% in comparison with standard

L-dopa treatment. This could be attributed to reduced fluctuations in plasma drug levels in case of FDDS^{49,50}.

Floating Minitablets

Floating minitablets (MT) of levodopa prepared by melt granulation and subsequent compression. The investigation showed that MT composition and MT diameter had the greatest influence on drug release, which was sustained for more than 8 hrs. The best floating properties were obtained with 3mm MT prepared at low compression forces ranging between 50 and 100 N. It was found that dissolution profiles depend more on the prolonged release ability of Methocel® K15M than on the pH dependent solubility of levodopa⁵¹.

Scintigraphic and pharmacokinetic studies were conducted on sustained floating minitablets of levodopa on ten healthy fed volunteers. Two concepts of sustained-release floating minitablets – Levo- Form 1 (matrix) and 2 (coated) were evaluated and compared to the marketed product Prolopa®. HBS 125. It was shown that the three formulations offered almost the same mean gastric residence time, which was about 240 mins. Prolopa® HBS 125 and Levo-Form 2 presented intragastric disintegration, which can lead to a

more pronounced "peak and valley" effect on the plasma concentration-time profile of levodopa. In contrast, the plasma concentration- time profile of levodopa following the administration of Levo-Form 1 was more evenly distributed. Moreover, Levo-Form 1 provided the lowest variations between men and women in terms of AUC and Cmax values. Finally, when the same amount of inhibitors of extracerebral dopa decarboxylase - carbidopa and benserazide - had been administrated, the mean AUC, Cmax and Tmax values obtained for benserazide were lower than those obtained for carbidopa⁵³.

Novel sustained release dosage form consisting of immediate release mini-tablets (IRMT) and sustained release minitablets (SRMT) contained in a hydroxypropyl methyl cellulose (HPMC) capsule were developed. The IRMT contained pseudoephedrine (PSE), excipients and low substituted hydroxypropyl cellulose (a disintegrant), and the

tablets were coated with HPMC, water soluble polymer (Ishida et al., 2008). IRMT prepared with varying amounts of low substituted hydroxypropyl cellulose all dissolved completely within the first 60 mins, so low substituted hydroxypropyl cellulose content does not greatly influence PSE release. The SRMT contained only PSE and excipients, and were coated with a mixture of HPMC and the water insoluble polymer ethyl cellulose. The PSE release profile for the SRMT could be controlled by varying the thickness of the coat, and the lag time could be controlled by varying the amount of ethyl cellulose present in the polymer coat. PSE was released immediately from encapsulated mini tablet system and release was sustained over an extended period of time: the PSE in the IRMT dissolved within 60 mins, whereas the PSE in the SRMT was released over 8-10 hrs⁵².



Floating minitablets of furosemide⁵⁴ were developed based on gas formation technique. The system consists of core units (solid dispersion of furosemide: povidone and other excipients), coated with two successive layers, one of which is an effervescent (sodium bicarbonate) layer and other one an outer polymeric layer of polymethacrylates. Only the system using Eudragit RL30D and combination of them as polymeric layer could float within acceptable time. The time to float decreased as amount of the effervescent agent increased and, when the coating level of polymeric layer decreased. The drug release was controlled and linear with the square root of time. By increasing coating level of polymeric layer decreased the drug release. The rapid floating and the controlled release properties were achieved in this present study. The in vivo gastric residence time was examined by radiograms and it was observed that the units remained in the stomach for about 6 hrs.

EVALUATION OF FLOATING DRUG DELIVERY

Different studies reported in the literature indicate that pharmaceutical dosage forms exhibiting gastric residence in vitro floating behaviour exhibit prolonged gastric residence in vivo. However, it should be noted that good in vitro floating behaviour alone is not sufficient proof of

efficient gastric retention in vivo. The effects of the simultaneous presence of food and the complex motility of the stomach are difficult to assess. Obviously, only in vivo studies can provide definite proof that prolonged gastric residence is obtained.

Measurement of Buoyancy Capabilities of the FDDS

The floating behaviour was evaluated using resultant weight measurements. The system to check continuous floating

behavior contains a stainless steel basket connected to a metal string and suspended from asartorius electronic balance. The floating object is immersed at a fixed depth into a water bath, which is covered to prevent water evaporation. The upward floating force could be measured and the data transmitted to an online PC through RS@#@ interphase using a sarto wedge program. A lotus spreadsheet could automatically pick up the reading on the balance. The test medium used in floating kinetics measurement was 900ml simulated gastric fluid (PH 1.2) maintained at 37°C, data was collected at 30sec interval, baseline was recorded and subtracted from each measurement. Dissoulution basket had a holder at the bottom to measure the downward force58.



Figure 15: Floating monitoring system

The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain a submerged object. The object floats better if F is on the higher positive side (Fig. 1B). This apparatus helps in optimizing FDDS with respect to stability and sustainability of floating forces produced in order to prevent any unforeseeable variations in intragastric buoyancy [22].

F = Fbuoyancy – Fgravity = (Df – Ds) g v

Where, F = total vertical force, Df = fluid density, Ds = object density, v = volume and g = acceleration due to gravity.

The results showed that higher molecular weight polymers with a slower rate of hydration exhibit enhanced floating behaviour and this was observed more in a simulated meal medium

compared with deionised water.

Floating Time and Dissolution

The floating time measurement is usually performed in stimulated gastric fluid or 0.1M HCl maintained at 37°C. It is determined using USP dissolution apparatus containing 900 ml 0.1 mol/l HCl as the dissolution medium at 37°C. The time taken by the dosage form to float is termed as the floating lag-time and the time for which the dosage form floats is termed as the floating or floation time ⁵⁹.

Recently, Gohel *et al*⁶⁰ proposed a more relevant *in vitro* dissolution method to evaluate a floating drug delivery system (for tablet dosage forms). A 100-ml glass beaker was modified by adding a side arm at the bottom of the beaker so that the beaker could hold 70 ml 0.1 mol/l HCl dissolution medium and allow collection of samples. A burette was mounted above the beaker to deliver the dissolution medium at a flow rate of 2 ml/min to mimic the gastric acid secretion rate.

The performance of the modified dissolution apparatus was compared with that of USP dissolution Apparatus 2 (Paddle). A problem involving adherence of the tablets to the shaft of the paddle was observed with the USP dissolution apparatus. The tablets did not stick to the agitating device in the proposed dissolution method and the observed drug release followed zero-order

kinetics. A similarity in the dissolution curves was observed between the USP method and the proposed method at a 10% difference level (f2 = 57). The proposed test may exhibit a good *in vitro-in vivo* correlation since an attempt was made to mimic the *in vivo* conditions, such as the gastric volume, gastric emptying, and gastric acid secretion rate.



Figure 16: modified dissolution apparatus

Drug Release

Dissolution tests are performed using the dissolution apparatus. Samples are withdrawn periodically from the dissolution medium and replaced with an equal volume of fluid and then analyzed for their drug content after appropriate dilution.

Drug Loading, Drug Entrapment Efficiency, Particle Size Analysis, Surface Characterization (for floating microspheres and beads)

Drug loading is assessed by crushing an accurately weighed sample of beads or microspheres in a mortar and adding it to the appropriate dissolution medium which is then centrifuged, filtered and analyzed by a variety of analytical methods like spectrophotometry.

The percentage drug loading is calculated by dividing the amount of drug in the sample by the weight of total beads or microspheres. The particle size and the size distribution of the beads or microspheres are determined in the dry state by optical microscopy. The external and cross-sectional morphology (surface characterization) is carried out by scanning electron microscopy (SEM)⁶¹.

Powder X-ray Diffraction

X-ray powder diffraction is the predominant tool for the study of poly-crystalline materials and is eminently suited for the routine characterization of pharmaceutical solids.

Fourier Transform Infrared Analysis

Fourier transform infrared spectroscopy is a technique mostly used to identify organic, polymeric, and some inorganic materials as well as for functional group determination. Fourier Transform Infrared Analysis (FT-IR) measurements of pure drug, polymer and drugloaded polymer formulations were obtained on FTIR. The pellets were prepared on KBr-press under hydraulic pressure of 150kg/cm2; the spectra were scanned over the wave number range of 3600 to 400 cm-1 at the ambient temperature.

Differential Scanning Calorimetry (DSC)

DSC are used to characterize water of hydration of pharmaceuticals .Thermo grams of formulated preparations were obtained using DSC instrument equipped with an intercooler. Indium/Zinc standards were used to calibrate the DSC temperature and enthalpy scale. The sample preparations were hermitically sealed in an aluminum pan and heated at a constant rate of 10° C/min; over a temperature range of 25° C – 65° C. Inert atmosphere was maintained by purging nitrogen gas at the flow rate of 50ml/min.

X-ray/Gamma Scintigraphy

X-ray/gamma scintigraphy is currently a very popular method for evaluating parameters for floating dosage forms ⁶². It helps to locate the dosage form in the GIT and it can be used to predict and correlate the gastric emptying time and the passage of the dosage form in the GIT. Here, the inclusion of a radio-opaque material into a solid dosage form enables it to be visualized by X-rays. Similarly, the inclusion of a γ -emitting radio-nuclide in a formulation allows indirect external observation using a γ -camera or scintiscanner⁶³.

The main advantages of X- ray of over gamma scintigraphy are simplicity and cost, however use of X-ray is declined due to strict limitations regarding amount of exposure and often requirement in high quantity.

Gastroscopy

It comprises of peroral endoscopy, used with a fiberoptics and video system. It is suggested that gastroscopy may be used to inspect visually the effect of prolonged stay in stomach milieu on FDDS⁶⁷.

Magnetic Resonance Imaging

In last few years MRI has shown to be value tool in gastrointestinal research for the analysis of gastric emptying, motility and intragastric distribution of macronutrients and drug models. The advantage of MRI include high soft tissue contrast, high temporal and spatial reolution, and mainly the lack of ionizing radiation⁶⁸.

Pharmacokinetic Studies

Pharmacokinetic studies are an integral part of the in vivo investigations and several such studies have been published. Sawicki⁶⁴ studied the pharmacokinetics of verapamil, from floating pellets containing the drug, filled into a capsule, and compared with conventional verapamil tablets with a similar dose (40 mg). The tmax and AUC0-∞ values (3.75 h and 364.65 ng·h/ml respectively) for floating pellets were comparatively higher than those obtained for the conventional verapamil tablets (tmax value 1.21 h, and AUC value 224.22 ng·h/ml). Very little difference was found between the Cmax values of both formulations, suggesting the improved bioavailability of the floating pellets compared with the conventional tablets. An improvement in bioavailability has also been observed with piroxicam in hollow polycarbonate microspheres administered to rabbits ⁶⁵. The microspheres showed about a 1.4-fold higher more bioavailability, and the elimination half-life was increased by about 3-fold compared with the free drug. On the other hand, a reduction in bioavailability was observed with atenolol in floating multiple-unit capsules, compared with the immediate release tablets ⁶⁶. For the floating multiple-unit capsule, the first atenolol concentration detectable in plasma and the time to the peak tmax were delayed. The maximum plasma concentration was also reduced indicating delayed absorption. From these results, it is apparent that increasing the gastric retention time of the dosage form did not help in improving the bioavailability of atenolol.

CONCLUSION

Gastro-retentive floating drug delivery systems have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs. The increasing sophistication of delivery technology will optimize the delivery of molecules that exhibit absorption window, low bioavailability and extensive first pass metabolism. Floating drug delivery system promises to be a potential approach for gastric retention. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique. Formulating an efficient FDDS is of a great challenge and research will continue until an ideal approach is identified which can be applied on an industrial scale.

REFERENCES

 Shivkumar H.G., Vishakante G.D., Pramodkumar T.M., Formulation and evaluation of Mucoadhesive drug delivery system for some anti-asthmatic drugs Ind.J.Pharm.Edu., 2004,38 (4), 172-179.

- G. Chawala, P.Gupta, V.Koradia, A.K. Bansal, Gastroretention – A means to address regional variability in intestinal drug absorption, Pharm. Tech., 2003, 27(2),50-68.
- R.Garg, G.D. Gupta, Progress in Controlled Gastroretentive Delivery Systems Trop.J.Pharma. Res., 2008, 7(3), 1055-66.
- A. Hoffman, Pharmacodynamic aspects of sustained release preparations, Adv. Drug Deliv. Rev., 1998,33,185-99.
- 5) .Hoffman A, Strepensky D., Pharmacodynamic aspects of modes of drug administration for optimization of drug therapy, Crit.Rev. Ther. Drug Carrier Syst., 1999,16, 571-639
- S. Sangekar, Evaluation of effect of food and specific gravity of the tablets on gastric retention time Int. J. Pharm., 1987, 35(3), 34-53
- Mojaverian P, Vlasses PH, Kellner PE, Rocci Jr ML. Effects of gender, posture and age on gastric residence time of an indigestible solid: Pharmaceutical considerations. Pharm Res 1988; 10: 639-44.
- Arrora S, Ali J, Khar RK, Baboota S. Floatng drug delivery, systems: A review. AAPS Pharm Sci Tech 2005; 6(3): 372-90
- El-Kamel AH, Sokar MS, Al Gamal SS, Naggar VF. Preparation and evaluation of ketoprofen floating oral delivery system. Int J Parm 2001; 220: 13-21
- Garg S, Sharma S. Gastroretentive drug delivery systems. Business Briefing: Pharmatech 2003: 160-66.
- 11) Khosla R, Feely LC, Davis SS. Gastrointestinal transit of non-disintegrating tablets in fed subjects. Int J Pharm 1989; 53: 107-17.
- 12) Singh M, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention, J. Control Rel, 2000; 63: 235–259
- 13) Davis D.W., Method of Swallowing a Pill, US Patent No. 3,418,999, (31 Dec 1968).
- 14) Ichikawa 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. 80, 1991, 1062-1066.
- Mitra S.B., Sustained-Release Oral Medicinal Delivery Device, US Patent No. 4,451,260 (29 May 1984).
- 16) Kawashima Y., et al., Hollow Microspheres for Use as a Floating Controlled Drug Delivery System in the Stomach, J. Pharm. Sci. 81 (2), 1992, 135-140.
- Fell J.T., Whitehead L., and Collett J.H., Prolonged Gastric Retention Using Floating Dosage Forms, Pharm. Technol. 2000, 82-90.
- Rubinstein A., Friend D.R., Specific delivery to the gastrointestinal tract, in: A.J. Domb (Ed.), Polymeric Site-Specific Pharmacotherapy, Wiley, Chichester, 1994, 282-283.
- 19) Ritschel W.A., Targeting in the gastrointestinal tract: new approaches, Methods Find. Exp. Clin. Pharmacol. 13, 1991, 313-336.
- 20) Michaels A.S., Bashwa J.D., Zaffaroni A., Integrated device for administering beneficial drug at programmed rate, US Patent 3, 901, 232, August 26, 1975.

- 21) Michaels A. S., Drug delivery device with self actuated mechanism for retaining device in selected area, US Patent 3, 786, 813, (22 Jan 1974).
- Iannuccelli V. and et al., Air Compartment Multiple-Unit Systems for Prolonged Gastric Residence, Part I: Formulation Study, Int. J. Pharm. 174 (1), 1998, 47-54.
- 23) Sakr F.M., A Programmable Drug Delivery System for Oral Administration, Int. J. Pharm. 184 (1), 1999,131-139.
- 24) Watanabe K., Machida Y., Takayama K., Iwata M., Nagai T. et al., Preparation and evaluation of intragastric floating tablet having pH independent buoyancy and sustained release property, Arch. Pract. Pharm. Yakuzaigaku 53, 1993, 1-7.
- Sing S, Joshi V, Barpete PK. Gastroretentive drug delivery systems: Current approaches. J Pharm Res. 2009; 2(5): 881-886.
- 26) Hashim H, Li Wan Po A. Improving the release characteristics of water-soluble drugs from hydrophilic sustained release matrices by in situ gasgeneration. Int J Pharm. 1987; 35: 201-206.
- 27) Ichikawa M, Watanabe S, 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.
- 28) Ingani HM, Timmermans J, Moes AJ. Conception and *in vivo* investigation of peroral sustained release floating dosage forms with enhanced gastrointestinal transit. Int J Pharm. 1987; 35: 157-164.
- 29) Sahni JK, Ahmad FJ, Ahuja A, Khar RK. Formulation and evaluation of a hydrodynamically balanced system of paracetamol. The Indian Pharmacist. 2006; V(46): 64-66.
- Reddy LH, Murthy RS. Floating dosage system in drug delivery. Crit Rev Ther Drug Carrier Syst. 2002; 19(6): 553-585.
- 31) Kawashima Y, Niwa T, Takenchi H, Hino T, Itoh Y. Hollow microspheres for use as a floating controlled drug delivery system in the stomach. J Pharm Sci. 1992; 81: 135-140
- Talukdar R, Fassihi R. Gastroretentive delivery systems: hollow beads. Drug Dev Ind Pharm. 2004; 30: 405-412.
- 33) Garg R, Gupta GD. Progress in controlled gastroretentive delivery systems. Trop. J Pharm Res 2008; 7(3): 1055-66.
- Whiteland L, Fell JT, Collett JH. Development of gastroretentive dosage form. Eur J Pharm Sci 1996; 4(suppl.): S182.
- 35) Harrigan RM. Drug delivery device for preventing contact of undissolved drug with the stomach lining. US Patent 405 5178; October 25, 1977
- 36) Vyas SP, Khar RK. Gastroretentive systems. In: Controlled drug Delivery. Vallabh Prakashan, Delhi, India. 2006. 197-217.
- 37) Kumar, P., Singh, S., Mishra, B. 2008. Floating osmotic drug delivery system of ranitidine hydrochloride: development and evaluation-a technical note. AAPS PharmSciTech. 9, 480–485
- Pan, W., Guan, J., Zhou, L., Nie, S., Yan, T., Tang, X. 2010. A novel gastric resident osmotic pump

tablet: *In vitro* and *in vivo* evaluation. Int. J. Pharm. 383, 30-36

- 39) Atyabi F, Sharma HL, Mohammed HAH, Fell JT. In vivo evaluation of a novel gastro retentive formulation based on ion exchange resins. J Control Release. 1996;42:105-113
- 40) Thanoo BC, Sunny MC, Jayakrishnan A. Oral sustained release drug delivery systems using polycarbonate microspheres capable of floating on the gastric fluids. J Pharm Pharmacol. 1993;45:21Y24.
- 41) Sato Y, Kawashima Y. In vitro and in vivo evaluation of riboflavin containing microballoons for a floating controlled drug delivery system in healthy human volunteers. J Control Release. 2003;93: 39Y47.
- 42) Malcolm SL, Allen JG, Bird H, etal. . Single dose pharmacokinetics of Madopar HBS in volunteers. Eur Neurol. 1987;27:28S-35S.
- 43) Dave BS, Amin AF, Patel MM. Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and in vitro evaluation. AAPS PharmSciTech. 2004;5:E34
- 44) Sriamornsak P, Thirawong N, Puttipipatkhachorn S. Morphology and buoyancy of oil-entrapped calcium pectinate gel beads. The AAPS Journal. 2004;6:E24.
- 45) Ichikawa M, Watanabe S, Miyake Y. Granule remaining in stomach. US patent 4 844 905. July 4, 1989
- 46) Pornsak Sriamornsak et al. Wax-incorporated Emulsion Gel Beads of Calcium Pectinate for Intragastric Floating Drug Delivery. AAPS PharmSciTech, 2008 571-576
- 47) Moursy NM, Afifi NN, Ghorab DM, El-Saharty Y. Formulation and evaluation of sustained release floating capsules of Nicardipine hydrochloride. Pharmazie. 2003;58:38-43
- 48) Shimpi S, Chauhan B, Mahadik KR, Paradkar A. Preparation and evaluation of diltiazem hydrochloride-Gelucire 43/01 floating granules prepared by melt granulation. AAPS PharmSciTech. 2004;5: E43
- 49) Crevoisier C, Hoevels B, Zurcher G, Da Prada M. Bioavailability of L-dopa after Madopar HBS administration in healthy volunteers. Eur Neurol. 1987;27:36S-46S
- 50) Marion MH, Stochi F, Malcolm SL, Quinn NP, Jenner P, Marsden CD. Single dose studies of a slow release preparation of Levodopa and benserazide (Madopar HBS) in Parkinson's disease. Eur Neurol. 1987;27:54S-58S
- 51) Goole, J. et al. Development and evaluation of new multipleunit levodopa sustained release floating dosage forms. Int. J. Pharm. 2007. 334, 35–41
- 52) Ishida, M.,et al. A novel approach to sustained pseudoephedrine release: Differentially coated minitablets in HPMC capsules. Int. J. Pharm. 2008.359, 46–52.
- 53) Goole, J., et al. Pharmacoscintigraphic and pharmacokinetic evaluation on healthy human volunteers of sustained-release floating minitablets containing levodopa and carbidopa. Int. J. Pharm. 2008.364, 54–63.

Sushma Singh et al......Int.J.Pharm.Phytopharmacol.Res. 2013, 2(5): 360-371

- 54) Meka, L., et al.. Design and evaluation of polymeric coated minitablets as multiple unit gastroretentive floating drug delivery systems for furosemide. J. Pharm. Sci. 2009, 98(6), 2122-2132.
- 55) Timmermans J, Andre JM. Factors controlling the buoyancy and gastric retention capabilities of floating matrix capsules: new data for reconsidering the controversy. J Pharm Sci. 1994;83:18Y24.
- 56) Negi J et al., Effect of Psylium husk on floating behavior of atenolol bilayer tablets, Pharmacie Globale (IJCP) 2011, 4 (06): 1-4.
- 57) Dinesh Kumar et al, Formulation and characterization of Bilayer floating tablets of Ranitidine, P., Rasayan.J.Chem., Vol.3, No.2 (2010), 368-374.
- 58) Oth M et al., A bilayer floating capsule: A stomach directed drug delivery system for misoprostol, Pharm Res 9, 1992, 298-302.
- 59) Karande A. D., Yeole P. G., Comparative Assessment of Different Dissolution Apparatus for Floating Drug Delivery Systems. Dissolutiontech, 2006, 13: 20-23.
- 60) M. C. Gohel, et al, A More Relevant Dissolution Method for Evaluation of Floating Drug Delivery System Dissolutiontech. 2004, 11: 22-25.
- 61) S. A. Agnihotri, S. S. Jawalkar, T. M. Aminabhavi.Controlled release of cephalexin through gellan gum beads: Effect of formulation parameters on entrapment efficiency, size, and drug release, , Eur. J. Pharm. Biopharm. 2006, 63: 249-261.
- J. Fell, G. A. Digenis, Imaging and behaviour of solid oral, dosage forms *in vivo*. Int. J. Pharm., 1984, 22: 1-15.

- 63) D. Harries., H. L. Sharma, GI transit of potential bioadhesive formulations in man: A scintigraphic study. J. Control.Release, 1990, 12: 45-53.
- 64) W. Sawicki, Pharmacokinetics of verapamil and norverapamil from controlled release floating pellets in humans., Eur. J. Pharm. Biopharm., 2002, 53: 29-35.
- 65) N. J. Joseph, S. Lakshmi, A.Jayakrishnan, A floatingtype oral dosage form for piroxicam based on hollow polycarbonate microspheres: *in vitro* and *in vivo* evaluation in rabbits.. J. Control. Release, 2002: 79: 71-79.
- 66) N. Rouge, E. Allemann, M. Gex-Fabry, *et al.*, Comparative pharmacokinetics study of a floating multiple-unit capsule and a high-density multipleunit capsule and an immediate release tablet containing 25 mg atenolol. Pharm. Acta Helv, 1998; 73: 81-87.
- 67) Gastric retention dosage forms having multiple layers, Jao F et al., Int application WO0038650, July 6,2000.
- 68) Magnetic resonance imaging for the invivo evaluation of gastroretentive tablets, steingotterA et.al. Pharm.Res.20(2003) 2001-2007.

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