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Buoyant Drug Delivery Systems: A Comprehensive Review

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ABSTRACT

Novel drug delivery systems are need of recent developments. Controlled drug delivery systems for oral route are widely acceptable and easy to formulate. Oral controlled release systems developed to overcome short comings of conventional controlled released formulations such as short gastric residence time, unpredictable gastric emptying time, unstable at higher pH, site specific absorption, etc. Various approaches have been developed to retain dosage form in stomach for longer period of time. Bioadhesive systems, high density systems, expanding or swelling systems, effervescent buoyant systems has been discovered till date. Drugs those having narrow absorption window in stomach, stable at acidic pH and unstable in the intestinal or colonic pH, having low solubility at higher pH are suitable to develop as buoyant drug delivery systems. Present review focuses on various aspects of buoyant drug delivery systems.

Keywords: Buoyant drug delivery, Effervescent, Non-effervescent and Microballoon.

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INTRODUCTION

Oral route is the most convenient and being used for the delivery of various drugs due to the low cost and high level of compliance. Different novel strategies have been undertaken for the development of oral drug delivery[1] systems to act as drug reservoirs from which active substance can be released over a predefined time at a predetermined controlled rate. A problem frequently encountered with conventional sustained release[2, 3] dosage forms is the inability to increase their residence time in stomach and no control over drug delivery, leading to fluctuations in plasma drug level. One of the major challenges in the development of oral controlled drug delivery systems[4, 5] is to modify the GI transit time. Hydrodynamically controlled systems are low density systems that have sufficient buoyancy for prolong period of time to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate. Gastro retentive systems[6] can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drug. For the drugs with low solubility in high pH environment, prolonged gastric retention improves bioavailability, solubility and reduces drug waste.

Mechanism of buoyancy

Several techniques are reported in the literature to increase the gastric retention time of drugs. These techniques include mucoadhesive systems, modified-shape systems, high-density systems, gastric–emptying delaying devices and floating systems (swelling and expanding systems).Floating dosage forms have been the most commonly used among the other systems. Floating systems have a bulk density less than gastric fluids and hence remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time .While floating on the gastric content, the drug is released slowly at the desired rate. This results in an increased gastric retention time and a better control over the fluctuations in plasma drug concentration.[7]

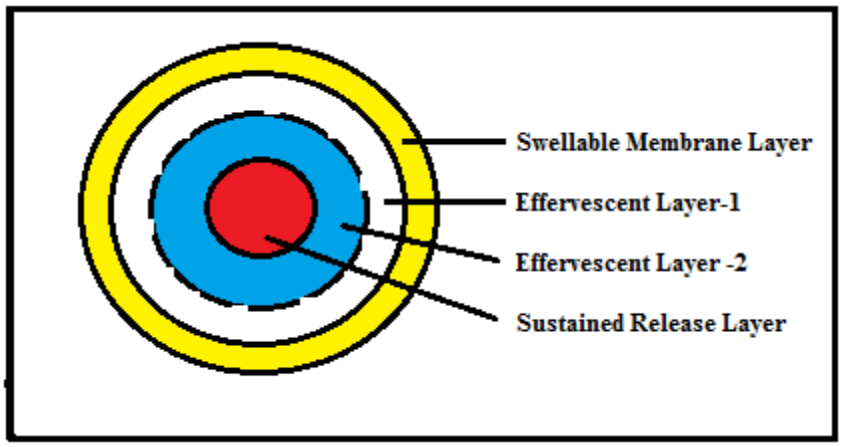

Figure 1: Multiple unit oral drug delivery system

The effervescent drug delivery system functions on the formation of CO_2 gas. It utilizes effervescent components such as sodium bicarbonate and additionally citric or tartaric acid. Upon contact with the acidic environment, a gas is liberated, which 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 chyme. The CO_2 generating components may be mixed with the tablet matrix components, producing a single layered matrix tablet.

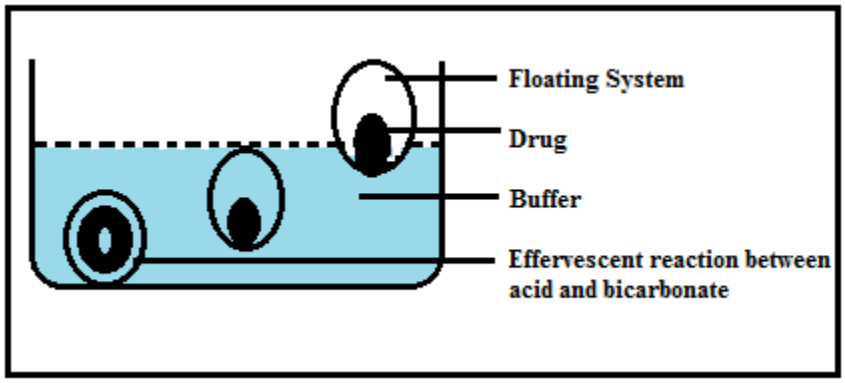

Figure 2: Working principle of effervescent drug delivery system

Anatomy and Physiology of Gastrointestinal Track (GIT) [8]

The main function of the stomach is to process and transport the food. It serves as a short term storage reservoir for ingested food. Enzymatic digestion of proteins is initiated in stomach. Anatomically the stomach is divided into three regions: Fundus, Body and Antrum (pylorus), Illustrated in Figure 3. The proximal part is fundus and body serves as reservoir for undigested food whereas the distal region is the major site for mixing motions and acting as a pump for gastric emptying by propelling actions. The release, dissolution and absorption of orally administered dosage forms are significantly influenced by the complex anatomy and physiology of the GIT.

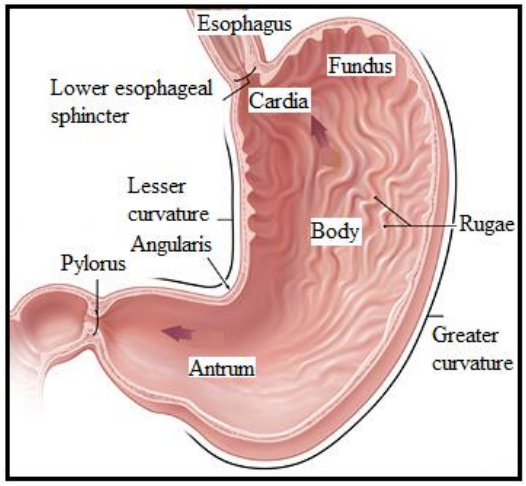

Figure 3: Anatomy of Stomach

Gastric Motility Pattern [9, 10]

During fasting and fed state gastric empting is continuously occurring. But motility differs distinctly in both states. During fasting state series of electrical events in cyclic manner at every 2-3 hours are occurring in the stomach and intestine. This is called inter-digestive myoelectric cycle or migrating myoelectric cycle (MMC), which comprises of following four phases as shown in figure 4.

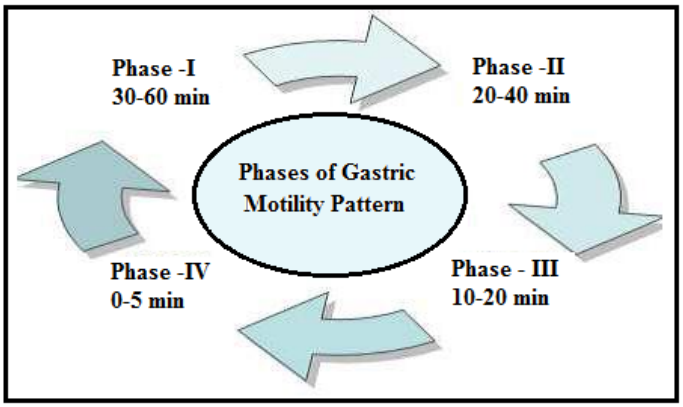

Figure 4: Phases of gastric motility pattern

Phase I is a quiescent period with virtually no contractions. It lasts from 30 to 60 min and is characterized by a lack of secretary, electrical, and contractile activity.

Phase II consists of intermittent, irregular low-amplitude contractions. It lasts for 20–40 min and it increase in frequency and size. Bile enters the duodenum during this phase, whereas gastric mucus discharge occurs during the latter part of Phase II and throughout Phase III.

Phase III consists of short burst of regular high-amplitude contractions. It also termed as housekeeper waves. These waves sweep off undigested food. Phase III contractions periodically occurs every 90-120 minutes and lasts for 10–20 min.

Phase IV is the transition period between Phases III and I. This lasts for 0-5min. This series of electrical events originates in the foregut and continues to the terminal ileum. It repeats at every 2–3 hrs during fasted state. Feeding sets off a continuous pattern of spike potentials and contractions called postprandial motility.

The particular phase during which a dosage form is administered influences the performance of peroral CDDS and GRDDS. When CDDS are administered in the fasted state, the MMC may be in any of its phases, which can significantly influence the total gastric residence time (GRT) and transit time in the GIT. This assumes even more significance for drugs that have an absorption window in stomach because it will affect the amount of time the dosage form spends in the region preceding and around the window. The less time spent in that region, the lower the degree of

absorption. Therefore, the design of GRDDS should take into consideration the resistance of the dosage form to gastric emptying during Phase III of the MMC in the fasted state and also to continuous gastric emptying through the pyloric sphincter in the fed state. This means that GRDDS must be functional system quickly after administration and able to resist the onslaught of physiological events for the required period of time. After ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (≤ 1 mm), which are propelled towards the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate.

Gastric Emptying and Limitations[11]

Stomach always acts as reservoir for orally administered sustained release dosage form. The proximal stomach serves as a reservoir for ingested materials, while the distal region is the major site for the mixing motion, acting as a pump to accomplish gastric emptying. The process of the gastric emptying occurs during fasting and fed stages. Scintigraphy study involving measurement of gastric emptying rates in healthy human subject have revealed that an orally administered controlled release dosage form is mainly subjected to two physiological adversities[12]

1. The short gastric residence time
2. Variable (unpredictable) gastric emptying time

Yet another major adversity encountered through the oral route is the first pass effect, which leads to reduce systematic availability of a large number of a drug. These problems can be exacerbated by alteration in the gastric emptying that occur due to factors such as age, race, sex and disease states, as they may seriously affect the release of a drug from DDS. It is therefore desirable to have a controlled release product that exhibits an extended, GI residence and a drug release profile[13] independent of patient's related variables.

Factors affecting gastric resistance time

The gastric retention time (GRT) of dosage form is controlled by several factors that affect their efficacy as a gastro retentive system. These factors are enlisted in table 1.

Table 1: Factors Affecting Gastric Residence Time

Factors	Details
Density	More is the density of formulation more will be the GRT.
Size	Formulations with ≥ 9.5 mm diameter have increased GRT.
Shape of dosage form	Tetrahedron and ring-shaped devices are reported to have 90% better gastric retention compared with other shapes.

Single or multiple unit formulation	Multiple unit dosage forms are having desired release profile. If there is failure in desired release then it can be administered with different release profiles. Thus there is a larger margin of safety as compared to single unit dosage forms.
Fed or fasting state	Motor activity or the migrating myoelectric complex (MMC) is strong during fasting than fed state. If the timing of dosage administration and strong MMC coincides, then there will be very short GRT. However, in the fed state, MMC is delayed and GRT is considerably longer.
Nature of meal	High fat content or indigestible diet decrease the gastric emptying rate by changing the motility pattern, thus prolonging drug release.
Caloric content	Diet with high caloric value can increase GRT.
Frequency of feed	There is low frequency of MMC with single meal and it increases with frequency of feeding and thus increase in GRT
Gender	Irrespective of the weight, height and body surface, GRT is less in male compared with female counterparts.
Age	Elderly people, especially those over 70, have a significantly longer GRT.
Concomitant drug administration	Anticholinergics drugs like Atropine and Propantheline, Opiates like Codeine and Prokinetic agents like Metoclopramide and Cisapride also changes GRT.
Biological factors	There is change in GRT in Diabetes and Crohn's disease.

Characteristics of suitable drug candidates for gastro retentive buoyant drug delivery systems

1. Drugs with narrow absorption window e.g., Riboflavin and levodopa
2. Drugs having absorption window in stomach and upper GI track e.g., Cinnarazine
3. Drugs having site of action only in stomach e.g., Antacids
4. Drugs which degrades in colonic pH e.g., Ranitidine
5. Drugs that disturbs normal colonic bacterial flora e.g., Amoxicilline trihydrate.

Table 2: Examples of various drugs formulated as different forms of FDDS.

Dosage form	List of Drugs
Tablets	Chlorpheniramine maleate, Theophylline, Furosemide, Ciprofloxacin, Pentoxyfillin, Captopril, Acetylsalicylic acid, Nimodipine, Amoxycillin trihydrate, Verapamil HCl, Isosorbide di nitrate, Sotalol, Atenolol, Isosorbide mono nitrate, Acetaminophen, Ampicillin, Cinnarazine, Diltiazem, Fluorouracil, Piretanide, Prednisolone, Riboflavin- 5′ Phosphate.
Capsules	Nicardipine, L- Dopa and Benserazide, Chlordiazepoxide HCl, Furosemide, Misoprostol, Diazepam, Propranolol, Ursodeoxycholic Acid.
Microspheres	Verapamil, Aspirin, Griseofulvin and p-nitroaniline, Ketoprofen, Tranilast, Ibuprofen, Terfenadine.
Granules	Indomethacin, Diclofenac sodium, Prednisolone.
Films	Cinnarazine.

There are several commercial products available based on the research activity of floating drug delivery enlisted in Table 3.

Table 3: Marketed Preparations of Floating Drug Delivery Systems[14]

Drug Name	Brand Name	Manufacturer	Dosage Form
Benserazide HCl and Levodopa	Madopar®	Roche, USA	Floating Capsule
Diazepam	Valrelease®	Roche, USA	Floating Capsule
Alginic Acid and Sodium Bicarbonate	Gaviscon®	Glaxo Smith Kline, USA	Floating Liquid
Alginic Acid, Aluminum Hydroxide, Hydrated Silica, Magnesium Carbonate	Topalkan®	Pierre Fabre Drug, France	Floating Suspension
Misoprostol	Cytotec®	Pfizer, USA	Floating Tablet
Ciprofloxacin	Cifran OD®	Ranbaxy, India	Floating Tablet
Ofloxacin	ZinocinOD®		
Metformin	Riomet OD®		
Magnesium Aluminosilicates, Magnesium Hydroxide, Simethicone	Inon Ace Tablet®	Sato Pharma Japan	Foam based Floating system
Prazocin HCl	Prazopress XL®	Sun Pharma Japan	Floating system
Ciprofloxacin HCl and betaine	Cipro XR®	Bayer, USA	Erodible matrix

Classification of buoyant drug delivery system

Buoyant drug delivery systems are classified depending upon the use of formulation variables: effervescent and non-effervescent systems.

Effervescent Systems

These are the matrix types of systems prepared with swellable polymers like methylcellulose and polysaccharides like chitosan and various effervescent compounds like citric acid, tartaric acid and sodium bicarbonate. The system is formulated by loading of resin bead with bicarbonate and then coated with ethyl cellulose. The coating is permeable, when comes in contact with gastric contents, CO_2 is released, which provides buoyancy to the dosage forms. Various attempts have been done to formulate these systems as follows

Baumgartener et al [15] developed floating matrix tablets with high dose of freely soluble drugs. Compressed tablet contains HPMC, drug and different additives. Tablet composition and mechanical strength have greater influence on the floating properties and drug release. With the incorporation of gas generating agent, besides optimum floating lag time of 30 sec and duration of floating > 8 hr, the drug release was also increased.

Choi et al [16] prepared floating alginate beads using calcium carbonate and sodium bicarbonate and studied for the effect of CO_2 generation on the physical properties, morphology and release rates. The study discovered that the amount type of gas generating agent had an effect on the size, pore structure, floating capacity, mechanical strength and the release rate of the floating beads. It is found that calcium carbonate formed smaller but stronger beads than sodium bicarbonate. Calcium

carbonate was found to be a less effective gas forming agent but it produced superior floating beads with improved control of drug release rates. The beads with gas generating agents in ratio of 5:1 to 1:1 established excellent floating during in-vitro floating studies.

Fassihi and Yang [17] revealed in their US Patent a multilayer floating tablet with zero-order controlled release. Multilayer tablet consist of two barrier layers, one with high percentage of polymers and another drug layer with similar polymers. One of two barrier layer consist of gas generating agent, upon contact with aqueous medium CO_2 generates and tablet float for prolong period of time. High percentage of polymer releases drug at zero order in controlled manner.

Ichikawa et al [18] developed a multiple type of floating dosage system composed of effervescent layers and swellable membrane layers coated on sustained release pills. The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into two sub layers to avoid direct contact between two agents. Polyvinyl acetate and purified shellac sub layers were used for swellable membrane. In the buffer these systems settled down and the solution crosses swellable membrane and then permeated into the effervescent layer. Due to reaction between sodium bicarbonate and tartaric acid CO_2 generate and it swollen pills having density less than 1.0 g/mL. It was found that the system had pH independent floating ability and viscosity.[19]

Li et al [20, 21] used continuous floating monitoring device and statistical experimental design to evaluated effects of formulation variables on the floating properties. HPMC was used as a low-density polymer and citric acid as gas generating agent. Analysis of variance (ANOVA) test demonstrated that high-viscosity polymers had good effect on floating properties. Different grades of HPMC (K4 M~ E4 M~K100 LV9 E5 LV) were evaluated for floating force values. It revealed that different polymers with same viscosity, i.e., HPMC K4M, HPMC E4M did not show any significant effect on floating property.

Moursy et al [22] developed sustained release floating capsules of Nicardipine HCl. High viscosity grades of hydrocolloids were used for floating. Sodium bicarbonate was added to allow evolution of CO_2 to aid in buoyancy. In vitro analysis of developed formulation was compared with commercially available Nicardipine Tablets 20 mg (MICARD). Results showed an increase in buoyancy with increase in proportion of hydrocolloid whereas the inclusion of sodium bicarbonate increased floating lag time. In-vivo comparison of optimized formulation with MICARD capsules using rabbits at a dose equivalent to human dose of 40 mg. Drug duration after the administration of sustained release capsules significantly exceeded than that of MICARD Capsules.

Ozdemir et al [23] developed floating bilayer tablets for furosemide. One layer contained the polymers HPMC 4000, HPMC 100, CMC for the control release of the drug and mixture of

sodium bicarbonate and citric acid was used in second layer for floating. In vivo studies on 6 healthy male volunteers showed that tablets were remained floated in stomach for 6 hours. Also tablets showed 1.8 times more bioavailability and prolong diuretic effect than the conventional tablets.

Penners et al [24] developed an expandable matrix tablet using mixture of polyvinyl lactams and polyacrylate. When it comes in contact with aqueous media it swells rapidly and gas generating agents release CO_2 makes tablets float in stomach for over an extended period of time.

Talwar et al [25] revealed in their US patent a once-daily formulation for oral administration of ciprofloxacin. The formulation was composed of drug base, sodium alginate, xanthum gum, cross-linked poly vinyl pyrrolidone and sodium bicarbonate. Sodium alginate, xanthum gum and cross-linked poly vinyl pyrrolidone were used as the viscolysing agent and the gel-forming agent. Sodium bicarbonate used as gas generating agent. When tablet comes in contact with aqueous medium it forms a hydrated gel matrix that entrapsthe gas, causing the tablet to float. The hydrated gel matrix created a convoluted diffusion path for the drug, resulting in sustained release of the drug.

Yang et al [26] developed a swellable asymmetric triple-layer tablet. Triple drug regimen was developed for Helicobacter pylori–associated peptic ulcers using hydroxy propyl methyl cellulose (HPMC) and poly (ethylene oxide) (PEO) as the rate-controlling excipients. Core layer of Tetracycline and metronidazole is made up of polymer matrix for controlled delivery. Gas-generating layer consist of sodium bicarbonate: calcium carbonate (1:2 ratios) along with the polymers. The in vitro results showed sustained and prolong localized delivery of tetracycline and metronidazole over 6 to 8 hours.

Non- effervescent Systems

This type of systems are made up of gel forming or swellable cellulose type of hydrocolloids, polysaccharides and matrix forming polymers like polycarbonate, polyacrylate, polymethacrylate and polystyrene. After oral administration, this dosage form swells in contact with gastric fluids and attains bulk density less than one within the outer gelatinous barrier. The air entrapment within the swollen matrix imparts buoyancy to the dosage form which allows sustained release of the drug through the gelatinous mass. Till date various attempts have been done to formulate this system as available in the literature.

Shimpi S et al [27] prepared floating granules using Gelucire 43/01. Diltiazem HCl is a highly water soluble drug. Hot melt granulation technique was used to prepare granules with Gelucire. In vivo

studies using γ-scintigraphy showed that granules were remained floated in stomach at least for 6 hrs and approximately 65% to 80% drug was released over 6 hrs.

H R Chueth, et al [28] formulated extended release tablet formulation which posses a unique combination of floatation and bioadhesion for prolong residence in the stomach. Formulation containing 240 mg Sotalol HCl is designed with different ratio of sodium CMC: HPMC and Ethyl cellulose: Crospovidone.

Nakamichi K et al [29] prepared a formulation for nicardipine hydrochloride (NH) using hot melt extrusion technology. Hydroxypropyl methylcellulose acetate succinate is used as floating polymer and calcium phosphate dihydrate as pore forming agent. It was found that the porosity and pore diameter could be controlled by the varying amount of calcium phosphate dihydrate.

Thanoo et al [30] developed floating microspheres by solvent evaporation technique. Polycarbonate is used as floating polymer, which forms hollow microspheres when volatile solvent get evaporated. These microspheres were floated in aqueous medium. Release rate of drug can be altered by change in polymer ratio.

Nur and Zhang [31] developed floating tablets using HPMC-K4M and HPMC-K15M and Carbopol 934P.Floating tablets of captopril with different hardness range were formulated. Tablets within 2-4 kg/cm hardness range after immersion into the floating media remained floating for 24 hours. A prolonged release from these floating tablets was observed as compared with the conventional tablets and a 24-hour controlled release from the dosage form of captopril was achieved.

Bulgarelli et al [32] used casein gelatine to form floating beads. Due to its emulsification properties air bubbles are incorporate and forms large hole in beads. This porous nature of beads helps formulation to float on gastric medium. The drug loading efficiency is higher in low porous matrices than high porous matrices.

Whitehead et al [33] prepared floating alginate beads by addition of sodium alginate into calcium chloride solution. Uniform size bead were produced at slow and drop wise addition of sodium alginate. Beads removed from solution by filtration and freeze dried. Dried bead are having buoyancy up to 20 hours and good drug loading capacity.

Streubel et al [34, 35] Floating microparticles were prepared using solvent extraction/evaporation method (Figure 5a). Polypropylene foam powder is used as floating agent due to its low density. Polypropylene foam powder is mixed with organic solution of drug and polymer. This mixture is added into aqueous phase under stirring to form microparticles. Solution with microparticles filtered, washed and dried. Highly porous and irregular shape microparticles were formed. In case of solvent evaporation method (Figure 5b) mixture of polypropylene powder and drug polymer

solution allowed to dry in teflon dish, after complete evaporation of solvent uniform microparticles were formed.

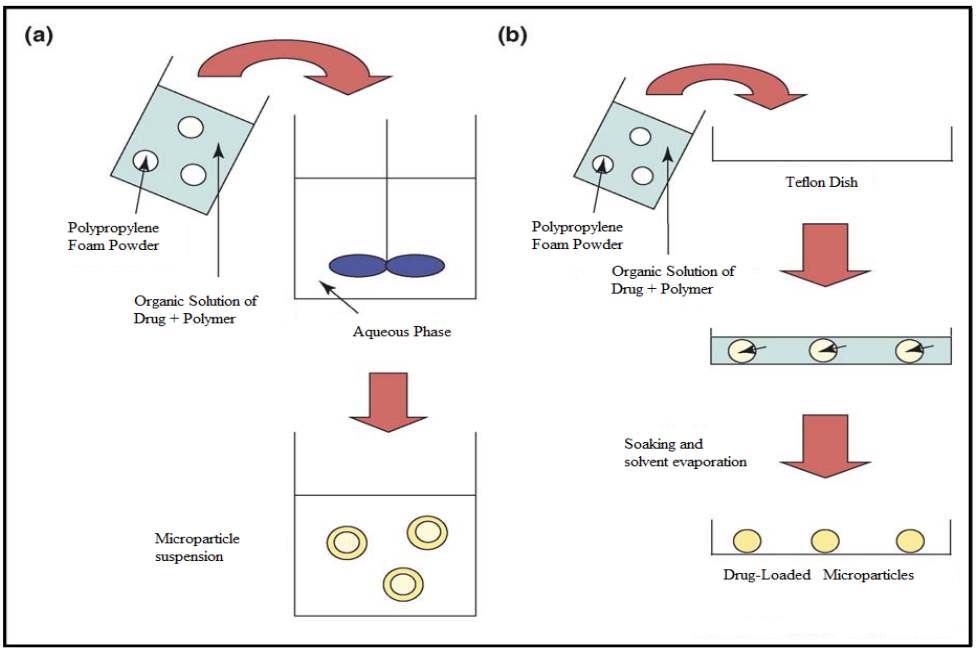

Figure 5: Preparation of floating microparticles based on low-density foam powder, using (a) the solvent evaporation method or (b) the soaking method.

El-Kamel et al [36] used emulsion solvent method to prepared floating microparticles. Different grade of Eudragit were used to formulate floating microparticles.

Illum and Ping [37] used spray drying technique to formulate microspheres. Drug was encapsulated into bioadhesive membrane prepared by water insoluble polymers. Bioadhesive membrane acts as controlled release membrane. O/W or W/O emulsions containing drug and polymer solutions were spray dried to form uniform microsphere.

Sheth and Tossounian [38] formulated uniform dry mix of drug with hydrocolloids and filled in capsule shells. When these filled capsules ingested orally comes in contact with gastric fluid and form gel mass having low bulk density. These hydrodynamically balance system remains floated for longer period of time and release drug in stomach.

Ushomaru et al [39] used starch and cellulose derivatives as gelling agents and higher fatty acid and alcohols used as floating agents. Solid mixture of these ingredients mixed and filled in capsules, then heated above melting point of fatty acid, cooled and allowed to solidify.

Dennis et al [40] used mixture of pH dependent and pH independent polymers. It released a drug of a basic character at a controlled rate at the entire pH environment of GI track. Alginic acid used as pH-dependent polymer and HPMC as pH-independent polymer and gelling agent.

Franz and Oth [41] prepared bilayer formulation of misoprostol. One layer is of drug with rate controlling polymers and other layer is of polymers having tendency to float when come in contact with aqueous media. This bilayer formulation was filled in capsules and remained floated for 13 hours.

Wu et al [42] used HPMC and PEG 6000 as rate controlling and floating agent. Nimodipine used as drug candidate and its solubility was improved by solid dispersion technique. Nimodipine solid dispersion, HPMC and PEG 6000 blended and compressed to form floating tablets.

Wong et al[43] developed a gastro retentive swellable formulation. It consists of insoluble material band that prevent swelling of the covered portion. When formulation comes in contact with gastric media, covered portion maintains its rigidity and delayed the expulsion of formulation from the stomach.

Kawashima et al [44] used solvent diffusion method to prepare floating microballoons as shown in figure 6. Acrylic polymer was used as floating polymers and polyvinyl alcohol was used as rate controlling polymer. Drug and acrylic polymers forms O/W emulsion when added into aqueous solution of polyvinyl alcohol. Microballoons remained floated for 12 hours in aqueous medium.

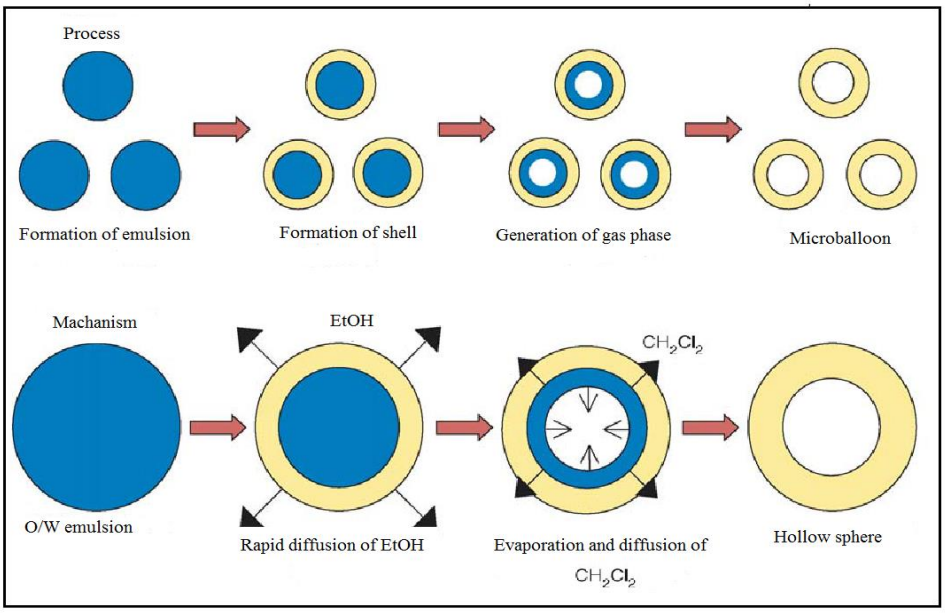

Figure 6: Mechanism for preparation of microballoon using emulsion-solvent diffusion method.

Mitra[45] developed a sustained release multilayered sheet like medicament device. It was buoyant on the gastric contents and consisted of at least 1 dry, self-supporting carrier film of water-insoluble polymer. The drug was dispersed or dissolved in this layer and a barrier film overlaid the carrier film. The barrier film was composed of 1 water-insoluble layer and another water-soluble

and drug-permeable polymer or copolymer layer. The 2 layers were sealed together in such a way that pluralities of small air pockets were entrapped that gave buoyancy to the formulation.

Joseph et al[46] formulated polycarbonate microspheres of piroxicam using solvent evaporation method and achieved approximate 95 % encapsulation. In vivo studies showed 1.4 times more bioavailability from microspheres compared to free drug and 4.8 times more bioavailability from a dosage form consisting of microspheres plus the loading dose.

Applications of Buoyant Drug Delivery Systems

Floating drug delivery offers several applications for drugs having poor bioavailability, narrow absorption window in the upper gastrointestinal tract and site specific absorption. The applications are discussed in detail as follows.

I. Sustained Release of Drug

These drug delivery systems can remain in the stomach for longer period of time and hence can release the drug over a prolonged period of time. *In vitro* study of hydrodynamically balance system of Madopar[47, 48] showed controlled drug release up to 8 hours and Madopar standard formulation showed complete release in 30 minutes.

J .A. Raval et al [49] formulated floating matrix tablet using poly (styrene-divinyl benzene) copolymer for floating aid and different viscosity grades of HPMC were used for controlled release matrix formation. Matrix tablet float in the gastric medium and release drug in sustained manner for longer period of time.

II. Absorption Enhancement:

Buoyant drug delivery systems releases drug in controlled manner for longer period of time, which maintains constant drug concentration in upper part of gastrointestinal tract. Thus availability of drug for absorption is more as compared to conventional dosage forms. Furosemide is primarily absorbed from the stomach followed by the duodenum. Floating formulation of furosemide showed higher bioavailability than commercially available LASIX (Furosemide) Tablets.[57]

III. Site specific drug delivery:

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine.

For the treatment of chronic gastritis and peptic ulcer buoyant drug delivery systems are an excellent drug delivery system. To eradicate Helicobacter pylori infection, high drug concentration is required to be maintained in gastric mucosa. Floating drug formulations remain buoyant in gastric mucosa for longer period and releases drug in controlled manner for extended period.[50]

A bilayer-floating capsule of misoprostol[51] slowly releases drug to the stomach for prolong period of time and thus therapeutic level could be achieved. As misoprostol is a synthetic analog of prostaglandin E1, it is used as a protectant of gastric ulcers caused by administration of NSAIDs.

Polymers and ingredients used in buoyant drug delivery system [52, 53]

Different types of ingredients can be incorporated into buoyant dosage form in addition to the drugs; few of them are enlisted below in table 4.

Table 4: Different types of ingredients and their percentage use in gastro retentive buoyant drug delivery systems.

Type of Ingredients	Percentage used	Examples
Hydrocolloids	20-75 %	Acacia, pectin, Chitosan, agar, casein, bentonite, veegum, HPMC(K4M, K100M and K15M),Gellan gum (Gelrite®), Sodium CMC,MC, HPC
Inert fatty materials	5-75%	Beeswax, fatty acids, long chain fatty alcohols, Gelucires® 39/01 and 43/01.
Effervescent agents	15-50%	Sodium bicarbonate, citric acid, tartaric acid, Di-SGC (Di-Sodium Glycine Carbonate, CG (Citroglycine).
Release rate accelerants	5-60%	Lactose, mannitol.
Release rate retardants	5-60%	Di-calcium phosphate, Talc, magnesium stearate
Buoyancy increasing agents	20-80%	Ethyl cellulose
Low density material	5-55%	Polypropylene foam Powder (Accurel MP 1000®).

Evaluation parameters of buoyant drug delivery system

Various *in vitro* and *in vivo* methods are reported in the literature to indicate gastric residence of buoyant formulation. Though these formulations are showing enough *in vitro* floating behavior to prolonged *in vivo* gastric residence, the effect of fed status and gastric motility affects the *in vivo* buoyancy and thus extended release profile. Obviously, only *in vivo* studies can provide definite proof that prolonged gastric residence is obtained.

***In vitro* Evaluation**[54,55,56]

Floating Time:

Test for buoyancy is usually performed in Simulated Gastric Fluid maintained at 37ºC. The time for which the dosage form continuously floats on the dissolution media is termed as floating time.

Buoyancy Lag Time:

It is time required by formulation to float on surface of medium, after it is placed into the medium. These parameters can be measured as a part of the dissolution test.

Specific Gravity/Density:

Density can be determined by the displacement method using Benzene as displacement medium.

Water Uptake:

It is an indirect measurement of swelling property of swellable matrix. Here dosage form is immersed in purified water and removed at regular intervals and weight changes are determined with respect to time.

$$\text{Water uptake} = \frac{(Wt - Wo)}{Wo} \text{ X } 100$$

Where,

Wt = weight of dosage form at time t

Wo = initial weight of dosage form

Swelling Index:

After immersion of dosage form into simulated gastric fluid at 37ºC, dosage form is removed out at regular interval and dimensional changes are measured in terms of increase in tablet thickness / diameter with time.

Drug Release:

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

Physical Evaluation:

Different physical evaluating tests were performed to ensure uniformity and physical strength of dosage form e.g. Angle of repose, Bulk Density, Tapped Density, Compressibility Index, Flowdex Index, Hausner Ratio, Particle Size Distribution, Weight variation, Content Uniformity, Hardness, Friability (Tablets) etc.

Other Tests:

Drug loading and entrapment efficiency, particle size analysis, surface characterization (for floating microspheres and beads) etc.

***IN VIVO* EVALUATION**[57,58]

X-Ray Scintigraphy[57]*:*

It is a very efficient & economic evaluation parameter for floating dosage form. One can estimate gastric retention time by locating dosage form in GIT. Radioactive materials were added to

formulation and X-ray images were produce after specific interval of time to locate exact position of floating dosage form.

Gamma Scintigraphy[58]*:*

Gamma emitting radioisotopes were mixed with other material of floating dosage form and compounded into control release dosage forms. For example a stable isotope[58] (e.g. Sm) is used to formulate buoyant dosage form. The γ-rays emitted by the radionuclide are focused on a camera, which helps to monitor the location of the dosage form. They are expensive preparations, having limited topographic information and are associated with radiation to the patients.

Radiography[58]*:*

Radiography plays an important role in the preclinical evaluation of stomach specific drug delivery systems. It is simple and economic than γ-Scintigraphy. Barium Sulphate is commonly used for radiography. However, use of X-ray is declined due to strict limitations, regarding the amount of exposure and it's often requirement in high quantity

Gastroscopy[59]*:*

The endoscopy is performed using fiber optic and small video camera. It is used for visual study of prolong floating behavior for buoyant dosage form or may be used to remove dosage form out of stomach for further detailed studies.

Ultrsonoghraphy[60]:

It is mainly used to identify intragastric position of hydrogels, penetration solvent into gel and in-vivo gastric wall and dosage interaction during peristalsis. Ultrasonic waves reflected substantially different acoustic impedances across interface enable the imaging.

Magnetic Resonance Imaging (MRI) [61]:

It is mainly helpful in gastrointestinal research for the analysis of gastric emptying, motility and intra gastric distribution of drug models. MRI is a superior technique than other mentioned above because it include soft tissue contrast, high temporal and special resolution, as well as lack of ionizing irradiation. It is paramagnetic and supramagnetic contrast agent can help to improve and suppress the interfering tissue and fluid signals.

CONCLUSION

After ingestion of drug, it passes through highly variable procedure in the gastrointestinal tract. There are several factors affecting absorption of drug in GI tract. It is critical task to develop oral rate controlled drug delivery systems, considering gastric residence time and absorption window in the upper small intestine. Adequate control of the gastric residence time combined with time-

controlled drug release patterns can significantly increase the bioavailability of the drug. Hence, this can be achieved efficiently by formulating drug into bioadhesive, size-increasing and floating drug delivery systems. Recent advances in the field of buoyant drug delivery systems revealed various dosage forms and devices. After ingestion they float on gastric mucosa, increase in size or adhere to gastric mucosa, thus assuring prolonged gastric residence and release of drug in predetermined way. In conclusion, promising *in vitro* and *in vivo* results have been reported with several different types of buoyant drug delivery systems. In the future, it is expected that they will become of escalating importance and ultimately leading to improved efficiencies of various types of pharmacotherapies. The improvement in sophistication of drug delivery technology will guarantee the development of amplify number of buoyant drug delivery systems to overcome disadvantages of conventional drug delivery systems.

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