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FLOATING TABLETS: A REALISTIC APPROACH IN GASTRORETENTIVE DRUG DELIVERY SYSTEM

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Abstract: The object of writing this review on floating tablets is to compile the recent literature with special focus on the principal mechanism of floating to achieve gastric retention. Floating tablet is new era for the successful development of controlled release formulation along with various features to provide a way of successful delivery of drug. Controlled- release system includes any drug delivery system that achieves a slow release of drug over an extended period of time and helps to improve therapy. The idea of gastric retention comes from the exigency to localize drugs at a specific region of gastrointestinal tract (GIT) such as stomach in the body. Gastro retentive dosage forms (GRDF) has received significant interest in the past few decades as they can improve the limitation of most conventional and oral controlled release drug delivery system related to fast gastric-emptying time. An optimum GRDF system can be defined as a system which retains in the stomach for a sufficient time interval against all the physiological barriers, releases active moiety in a controlled manner. Floating tablets is a type of GRDF that provides both immediate as well as sustained release of drug in a controlled manner with increased gastro residence time. These forms are expected to remain buoyant on gastric content without causing intrinsic rate of emptying. This concludes in prolonged gastric retention time of floating tablet which boost bioavailability of drug and also improve clinical situations. In this review, current & recent developments of stomach specific floating tablets are discussed.

Keywords: Gastric residence time, Gastro retention, Gastro intestinal tract, Narrow absorption window, Floating drug delivery systems.

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1.0 INTRODUCTION

In the present study, Floating drug delivery systems (FDDS) are aimed to retain the drug in the stomach and are beneficial for drugs that are poorly soluble or unbalanced in intestinal fluids. The underlying principle is very easy i.e., to make the dosage form lighter than the gastric fluids so that it can float on them.[1] The density of the system can be reduced by assimilate a number of low density fillers into the systems such as hydroxyl cellulose, lactates or microcrystalline cellulose. Oral delivery of drugs is the most preferred route of drug delivery due to the comfort of administration; short cost of therapy, patient compliance and flexibility in formulation etc. [2]

The scheme of floating tablets is mainly found on the matrix type drug delivery system such that the drug remains lodge in the matrix which after impending in contact with the gastric fluid swells up and the slow erosion of the drug lacking of disintegration of the tablet takes place.

Periodically for generating a floating system we even need to put some effervescent or gas generating agent which will also essentially reduce the density of the system and perform the goal of achieving a floating system. [3]

GASTRORETENTIVE DRUG DELIVERY SYSTEMS (GRDDS)

Dosage forms that can be kept in stomach are called gastroretentive drug delivery systems (GRDDS).

GRDDS are favourable drugs by improving their

- Bioavailability
- Therapeutics effective.
- Possible reduction of the dose. Reduces drug waste, and rise solubility for drugs that are less soluble in a high pH environment.

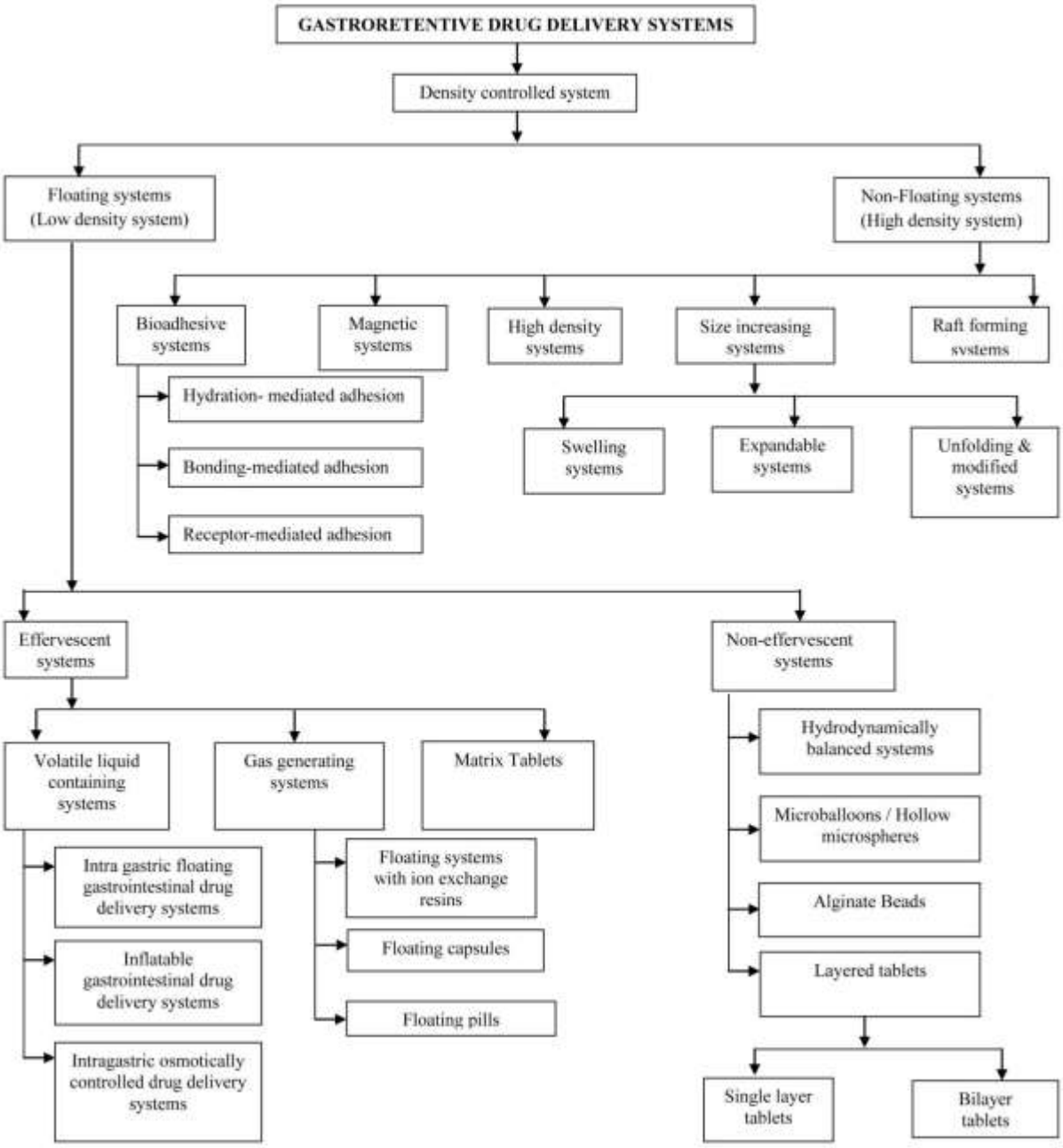

FIGURE 1. CLASSIFICATION OF GRDDS

FLOATING DRUG DELIVERY SYSTEM

Floating systems are low-density systems that have adequate buoyancy to float over the gastric contents and remain buoyant in the stomach without causing the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is delivering slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This concludes increase GRT and a better control of the

fluctuations in plasma drug concentration. Various buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films, beads and hollow microspheres. Over the last few decades, several gastroretentive drug delivery systems designed and spread, including: high density (sinking) systems that is retained at the bottom of the stomach [4], low density (floating) systems that affect buoyancy in gastric fluid [5-7], mucoadhesive systems that influence bioadhesion to stomach mucosa [8], superporous hydrogel systems [9], unfoldable, extendible or swellable systems which edge emptying of the dosage forms exceed the pyloric sphincter of stomach [10-11], magnetic systems [12] etc.

Floating systems can be classified into two systems: [13-14]

Effervscent System

Volatile liquid containing systems

Gas-generating Systems

Non- Effervescent System

Colloidal gel barrier structure

Micro porous Compartment System

Alginate beads

Hollow microsphere

These are systems which have a bulk density less than gastric fluids and because of this, these systems always buoyant (3-4 hours) for an extended period of time in the stomach without affecting the gastric emptying rate. The drug is liberating slowly at the desired rate from the system and after release of the drug; the remaining system is emptied from the stomach. As an outcome GRT is increased and changing in plasma drug concentration can be better controlled. [15]

Mechanism of Floating Systems

While the system is floating on the gastric content the drug is released slowly at the desired rate from the system. After release of drug, the remaining system is emptied from the stomach. However, apart from a minimal gastric content needed to allow the proper attainment of the buoyancy retention principle, a minimal level of floating force (F) is also need to keep the dosage form reliably buoyant on the surface of the meal. To evaluate the floating force kinetics, a novel era apparatus for determination of resultant weight has been reported in the literature. The apparatus generates by measuring unendingly the force equivalent to F (as a function of

time) that is required to keep the submerged object. The object floats superior if F is on the higher positive side. [16]

F = F buoyancy - F gravity = (D_f - D_s) gv

i.e., F= total vertical force, D_f = fluid density, D_s = object density, v = volume, g = acceleration.

FLOATING TABLETS

Floating tablet is a gastroretentive dosage form which increases the retention time of drug in g.i.t.

Types of Floating Tablets

Floating tablets are classified depending on the use of two formulation variables:

1.2.1.1 Effervescent Systems

1.2.1.2 Non-Effervescent Systems.

Effervescent Floating Tablets

These are matrix types systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, e.g. sodium bicarbonate, tartaric acid, and citric acid.

They are formulated in such a way that when in contact with the acidic gastric contents, CO_2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage.

A new 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 the two agents. These sub-layers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac.

When this system was immersed in the buffer at 37ºC, it settled down and the solution permeated into the effervescent layer through the outer swellable membrane. CO_2 was generated by the neutralization reaction between the two effervescent agents, producing swollen pills (like balloons) with a density less than 1.0 g/ml.

Non-Effervescent Floating Tablets

Non-effervescent floating tablets use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of < 1.

The buoyancy of the tablet is governed by both the swelling of the hydrocolloid particles on the tablet surface when it contacts the gastric fluids and the presence of internal voids in the centre of the tablet (porosity).

MATERIALS FOR PREPARATION OF FLOATING TABLETS

Drugs: Drugs with limited absorption window in GI tract, primarily absorbed from stomach and upper part of GIT, locally act in the stomach, reduce in the colon, and disturb normal colonic bacteria. e.g. amphicillin, amoxicillin trihydrate, atenolol, flurouracil, ranitidine HCL.

Polymers: Cellulose acetate, chitosan, eudragit, acrycoat, methocil, HPMC 4000 CPS,HPMC 10000 CPS, polyvinyl acetate, carbopol 934, sodium bicarbonate and polyethylene.[17-18-19]

Solvents: It should have good volatile properties, e.g. ethanol, isopropyl alcohol (IPA), hydrochloride.

Surfactants: They are stabilizers or emulsifiers, play the part of hardening the tablets. e.g. tween 80, span 80 and SLS.

METHOD OF PREPARATION

Preparation of Gastroretentive using Wet Granulation Method.

Floating tablets can be prepared by non-aqueous wet granulation (95% v/v ethanol as granulating agent) method using variable amounts of gas generating agent and water swellable polymer. The mixture is blended by geometric mixing as per the design, after enough cohesiveness was obtained. The granules are sieved (30 mesh) and dried in an oven at 45º C for 2 hours. The dried granules were subsequently lubricated with magnesium stearate (1% w/w) and purified talc (1% w/w) and compressed on a hydraulic press using flat punch.

Preparation of Gastroretentive using Direct Compression Method.

Briefly, preparation of tablets involved, passing all the ingredients except magnesium stearate and talc were passed through sieve 40 and mixing the blend in an octagonal blender for 10 min. Magnesium stearate and talc are then passed through sieve 60 and are used to lubricate the

blend. The lubrication is ready for 5 min. The lubricated blend is compressed into tablets by using flat faced punches.

FACTORS AFFECTING GASTRIC RESIDENCE TIME OF FLOATING TABLETS [20-30]

There are several reasons that can affect gastric emptying of an oral dosage form which include density, size and shape of dosage form, feeding state, biological elements such as age, gender, posture, body mass index, disease state etc. Most of these approaches are effect by a number of factors that affect their bioavailability and efficacy of the gastroretentive system.

Density of Tablets

Gastric retention time (GRT) is based upon the dosage form buoyancy which is further dependent on the density. Density of the dosage form are used for FDDS should be less than the gastric contents (1.004gm/ml).

Size and Shape

Dosage form unit with a diameter of higher than 7.5 mm are more acceptable candidate as compared to those which have a diameter of 9.9 mm since they have an inclined GRT. Similarly the dosage form having a tetrahedron shape and ring structure devises with a flexural Elasticity of 48 and 22.5 kilopond per square inch (KSI) are reported to have better GIT for 90 to 100% retention and thus more suitable for FDDS as compared with other shapes. [22-24]

Viscosity of Polymers

Viscosity of polymer and their interaction considerably affect the drug release and floating properties of FDDS. Low viscosity polymers (e.g., HPMC K100LV) were found to be more acceptable candidates for FDDS than high viscosity polymers (e.g., HPMC K4M) because they improve floating properties. Also, with an inclined in polymer viscosity a declined in the release rate was observed. [26]

Fed or Unfed

Under fasting conditions, GI motility is characterized by periods of strong motor activity or the migrating myoelectric complexes (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 can be expected to be very less. However, in the fed state, MMC is delayed and GRT is considerably longer. [27]

Nature of Meal

Motility arrangement of the stomach can change to fed state when indigestible polymers or fatty acid salts are fed and basically it is because of the gastric emptying rate is declined and drug release is prolonged. [25]

Frequency of Feed

When successive meals are given, the GRT can inclined by over 40 minutes compared with a single meal because of the low frequency of MMC. [21]

Gender

Mean GRT of a male in meals (3.4±0.4 hours) is less differentiate to the female of the same age and race (4.6±1.2 hours), despite of the height, weight, and surface area of the body two. [28]

Age

Elderly people have a significantly longer GRT, especially those who are over 70 years of age. [29]

EVALUATION OF FLOATING TABLETS

Floating tablets are protected by an upright position against postprandial emptying because at this site, the floating form remains above the gastric contents irrespective of its size [30] that can affect gastric emptying of an oral dosage form which include density, size and shape of dosage form, feeding state, biological elements such as age, gender, posture, body mass index, disease state etc. Most of these approaches are influenced by a number of factors that causes their bioavailability and efficacy of the gastro retentive system. [31-34]

Determination of Hardness of Tablets

Randomly sampled twenty tablets in every batch of formulations should be used for the determination of hardness with the help of Monsanto type hardness tester.

Determination of Weight Variation [35]

Twenty tablets selected at random are weighed accurately and the average weight of the tablet is calculated. Then the digression of individual weight from the average weight is calculated.

Determination of Thickness of the Tablets [37]

The individual crown – to – crown thickness of ten tablets is determined using slide callipers for each batch.

Measurement of Floating Capacity [36]

Three individual tablets are put in individual flask containing 400 ml of 0.1(N) HCl solutions. Then the time in minutes for each tablets to go from the bottom to the top of the flask (floating lag time) and the time for which tablets continuously float on the water surface (duration of floating) are measured.

Angle of Repose [37]

Angle of repose is determined by using with the help of funnel method; the accurately weighed granules are taken in funnel. The height of funnel is adjusted in such a way that the tip of funnel just touches the apex of heap of blends. The blends are then allowed to flow through funnel freely on to surface. The diameter of powder cone is measured; angle of repose is calculated by using following equation.

$\tan \theta = h/r$

Where h– height of pile, θ – angle of repose, r – radius of base pile <25-excellent flow, 25–30-good flow, 30–40- passable,> 40- very poor flow.

Measurement of the Density of the Formulation [38]

The apparent densities of the tablets are calculated from their volumes and masses in triplicate. The volume V of the cylindrical tablets are calculated from their height h and radius r (both determined with a micrometer gauge) using the mathematical equation for a cylinder ($V = A \times r^2 \times h$).

Determination of Drug Contents in Tablets

Three tablets from each batch are selected randomly and transferred to a 100 ml volumetric flask filled up with 0.1(N) HCl. Retain it for 48 hours then took 1 ml from each of volumetric flask and transferred to the test tubes. Samples are then purified, suitably diluted and analyzed spectrophotometrically at a suitable wavelength.

Determination of *In-Vitro* Dissolution Study [38]

Dissolution study is carried out in USP–II type dissolution apparatus (paddle type) Dissolution study was performed at 50 rpm in 900 ml 0.1(N) HCl. 5 ml of sample was withdrawn at a predetermined interval and the volume of dissolution medium is maintained by adding same volume of dissolution medium measured spectrophotometrically with suitable dilution and the corresponding concentration is determined from the respective calibration curve.

Friability [39]

The friability test is carried out in Roche Friabilator. Ten tablets were weighted (Wo) initially and put in a rotating drum. Then the tablets are subjected to 100 falls of 6 in height. After completion of rotation, the tablets are again weighted (W).

% Weight loss or friability (f) = $(1 - w/ w_0) \times 100$.

Disintegration Time

In-vitro disintegration time is determined by using with the help of disintegration test apparatus. For this, a tablet is laid in each of the six tubes of the apparatus and one disc is attached to each tube. The time taken for complete disintegration of the tablet with no noticeable mass remaining in the apparatus was measured.

Buoyancy Time

A tablet is introduces in to beaker containing 100 ml of 0.1N HCl. The time holded by the tablet to come up to the surface and floated was taken as the buoyancy time. An average of three determinations form of batch was taken for the floating forms.

***IN-VIVO* EVALUATION**

Radiology

X-ray is mostly used for examination of internal body systems. Barium Sulphate is mostly used Radio Opaque Marker. So, $BaSO_4$ is integrated inside floating tablet and X-ray images are getting holded at different intervals to view gastric retention time.

Gamma Scintigraphy

This process helps to locate dosage form in the gastrointestinal tract by which we can predict and correlate the gastric emptying time and the passage dosage form in the GIT. The inclusion of radio-opaque material into a solid dosage form allows it to be visualized by X-rays. Similarly, the inclusion of a γ-emitting radio nucleotide in a formulation allows secondary external observation using a γ -camera or scinti scanner. In case of γ -scintigraphy, the γ -rays emitted by the nucleotide are focused on a camera, which assists to monitor the location of the dosage form in the in the gastrointestinal tract. [40]

Gastroscopy

Gastroscopy is an examination of the inside of the gullet, stomach and duodenum. It is performed by using a thin, flexible fibre-optic tool that is passed through the mouth. Gastroscopy is per oral endoscopy used with the help of fibre optics or video systems. Gastroscopy is used to check visually the effect of prolongation in stomach.

APPLICATION OF FLOATING TABLETS

Enhanced Bioavailability

The bioavailability of riboflavin CR-GRDF is notably enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are various different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act related to effect the magnitude of drug absorption. [41]

Sustained Drug Delivery

Oral CR formulations are encountered with problems i.e. gastric residence time in the GIT. These problems can be overcome with the floating systems in the form of floating tablet which can remain in the stomach for extended periods and have a bulk density <1 as a result of which they can float on the gastric contents.

Site-Specific Drug Delivery Systems

These systems are extremely advantageous for drugs that are specifically absorbed from the stomach or the proximal wedge of the small intestine. The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic quantity and limits the systemic exposure to the drug. This reduces side effects that are caused by the drug in the blood circulation. In addition, the extend gastric availability from a site directed delivery system may also reduce the dosing frequency e.g. Furosemide and Riboflavin. [42]

Absorption Enhancement

Drugs which having poor bioavailability because of site specific absorption from the upper part of the GIT are probable candidates to be formulated as floating drug delivery systems, there by maximizing their absorption. [43]

Minimized Adverse Activity at the Colon

Retention of the drug in the floating tablets at the stomach minimizes the amount of drug that reaches the colon. Thus, unpleasant activities of the drug in colon may be prevented. This Pharmacodynamic aspect provides the rationale for GRDF formulation that are absorbed only from the small intestine. [44]

ADVANTAGES

• Decreasing the dosing amount and there's by improving the patient compliance.

• Better drug utilization will improve the bioavailability and reduce the intensity of adverse effects; despite first pass effect because fluctuations in plasma drug concentration is avoided.

• Enhanced absorption of drugs which solubilise only in stomach.

• Drug releases in controlled way for prolonged period.

• Site-specific drug delivery to stomach can be achieved with desirable plasma drug concentration.

• Avoidance of gastric irritation, because of sustained release effect.

• Better therapeutic effect of short half-life drugs can be achieved.

• Improving patient compliance by reducing dose. [45]

• Enhanced therapeutic efficacy.

DISADVANTAGES

• The revised release from the formulations.

• The release rate of the controlled release dosage form may vary from a choice of factors i.e. food and the rate of transit though gut.

• Differences in the release rate from one dose to another dose.

• Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the liberate characteristics of the dosage form may lead to potential toxicity.

• Dosage forms of this kind should not be crushed or chewed. [46]

TABLE 1: PATENTS FOR GASTRORETENTIVE DRUG DELIVERY SYSTEM [47-58]

US Patent / App. No	Patent Title	Issue/Publication Date	Patent Owner
2013/0078,290	Gastroretentive Dosage Forms of GABA Analogy	Mar 28, 2013	Rubicon Research Private Limited
2013/0022,654	Controlled Release Pharmaceutical	Jan 24, 2013	Lupin Limited

	Compositions of Tapentadol		
2013/0004,434	Gastroretentive, Extended Release Composition of Therapeutic Agent	Jan 3, 2013	Council of Scientific And Industrial Research
2012/0321,706	Novel Gastroretentive Dosage Forms of Poorly Soluble Drugs	Dec 20, 2012.	Intec Pharma Ltd
2012/0269,866	Gastroretentive Composition on the Basis of a Water- Soluble Reaction Product from a Vinyl Group-Containing Precursor	Oct 25, 2012	Basf Corporation
2012/0021,051	Zaleplon Gastroretentive Drug Delivery System	Jan 26, 2012	Intec Pharma Ltd.
2011/0268,666	Novel Gastroretentive Delivery System	Nov 3, 2011	Intec Pharma Ltd., Yissum
2011/0171,275	Gastroretentive Drug Delivery System, Preparation Method and Uses	Jul 14, 2011	Team Academy of Pharmaceutical Science
2007/0128,276	Controlled Release Compositions Comprising Nimesulide	Jun 7, 2007	Panacea Biotec Limited
2006/0121,106	Therapeutic System Comprising Amoxicillin and Clavulanic Acid	Jun 8, 2006	Lek Pharmaceuticals D.D.
2004/6,685,	Gastroretentive Controlled Release Pharmaceutical Dosage Forms	Feb 3, 2004	Yissum Research Development of the Hebrew University of Jerusalem

TABLE 2: REVIEW FROM PREVIOUS STUDIES OF GRDDS

DELIVERY SYSTEM	DRUG	POLYMER	METHOD
Floating Tablets [59]	Diltiazem Hydrochloride	Xanthan Gum, Karaya Gum, Guar Gum	Wet Granulation Method

Floating Tablets[60]	Metoprolol Tartarate	Hydroxypropyl Methylcellulose (HPMC K 4 M, HPMC K 100 M)	Direct Compression Method
Floating Tablets[61]	Ritonavir	HPMC E 15 LV, HPMC E 50 LV, HPMC K 100LV, HPMC	Direct Compression Method
Floating Tablets[62]	Ranitidine Hydrochloride	HPMC K 15 M, HPMC K 100 M, Polyethylene Oxide (Polyox WSR303)	Dry Granulation Method
Floating Matrix Tablet[63]	Stavudine	HPMC K 4 M, Ethyl Cellulose	Melt Granulation Method
Floating Tablet [64]	Quetiapine Fumarate	HPMC K 15 M, Sodium Carboxy-Methyl Cellulose, PVP K30	Wet Granulation Method
Floating Tablets [65]	Famotidine	Gelucire 43/01, HPMC K 4 M	Solvent Free Melt Granulation Method
Mucoadhesive Tablets [66]	Venlafaxine Hydrochloride	Carbopol 971P, Eudragit RS-PO	Direct Compression Method
Floating Matrix Tablets [67]	Ciprofloxacin Hydrochloride	HPMC K 15 M, Sodium Alginate	Direct Compression Method
Floating Tablets [68]	5-Fluorouracil	Carbopol 934P, HPMC K4M, HPMC K 15 M	Wet Granulation Method
Sustained Release Tablets[69]	Ofloxacin	Psyllium Husk, HPMC K 100 M	Wet Granulation Method

CONCLUSION

Floating Tablets have emerged as an efficient means of prolonged retaining ability in the stomach and thereby increase gastric residence time of drugs and also enhances bioavailability of drugs. In spite of number of difficulties to be worked out to reach prolonged gastric retention, a large number of companies are focussing towards commercializing this technique. Number of commercial products and patents issued in this field are evident of it.

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