Review Article

Gastro-Retentive Floating Drug Delivery System Containing Anti-Diabetic Drug - An Overview

Vadaliya SK[1*], Desai HT[1], Patel JK[2] and Vadaliya KR[3]

[1]School of Pharmacy, RK University, Rajkot, India. NirLife Health care, Ahmedabad, India.
[2]Nootan Pharmacy College, Visnagar, Gujarat, India.
[3] Shree H. N. Shukla Institute of Pharmaceutical Education and Research, Rajkot, Gujarat, India.

ABSTRACT

The purpose of writing this review on Gastro-retentive floating drug delivery systems (GRDDS) was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. Diabetes mellitus is one of the world's major diseases. It currently affects an estimated143 million people worldwide and the number is growing rapidly. Research is directed towards overcoming physiological adversities such as short gastric residence time (GRT) & unpredictable gastric emptying time (GET). These systems will be very much useful to deliver 'narrow absorption window' drugs. Four technologies have involved a substantial number of human clinical trials: floating, mucoadhesion, density modification, and expansion. The floating drug delivery system can remain in the gastric region for several hours via float on the gastric contents and hence significantly prolong the gastric residence time of drugs.

Keywords: Gastro-retentive drug delivery systems, floating drug delivery system, narrow absorption.

INTRODUCTION

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa[1]. Thus small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Basic human physiology with the details of gastric emptying, motility patterns, and physiological and formulation variables affecting the cosmic emptying are summarized. Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion[2,3] flotation[4] sedimentation,[5,6] expansion,[7,8] modified shape Systems,[9,10] or by the simultaneous administration of pharmacological agents [11,12] that delay gastric emptying. Based on these approaches, classification of floating drug delivery systems (FDDS) has been described in detail. In vivo/in vitro evaluation of FDDS has been discussed by scientists to assess the efficiency and application of such systems. Several recent examples have been reported showing the efficiency of such systems for drugs with bioavailability problems.

Basic Git physiology

Anatomically the stomach is divided in to three regions Fundus, Body and Antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested materials, where as the antrum is the main site for mixing motions and acts as a pump for gastric emptying by propelling actions. Gastric emptying occurs in both the fasting and fed states. During the fasting state an interdigestive series of electrical events take place which cycle both through stomach and intestine every 2-3 hrs, which is called as interdigestive myloelectric cycle or migrating myloelectric cycle (MMC) which is further divided in to four phases after the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state which is also termed as digestive motility pattern (Fig 1)[14, 15].

1. Phase 1-(Basic phase) - last from 30-60 minutes with rare contractions.
2. Phase 2-(Preburst phase) - last for 20-40 minutes with intermittent action potential and contractions.
3. Phase 3-(Burst phase) - last for 10-20 minutes which includes intense and regular contractions for short period.
4. Phase 4-last for 0-5 minutes and occurs between phase 2 and 1 of 2 consecutive cycles (Fig 1). [16]

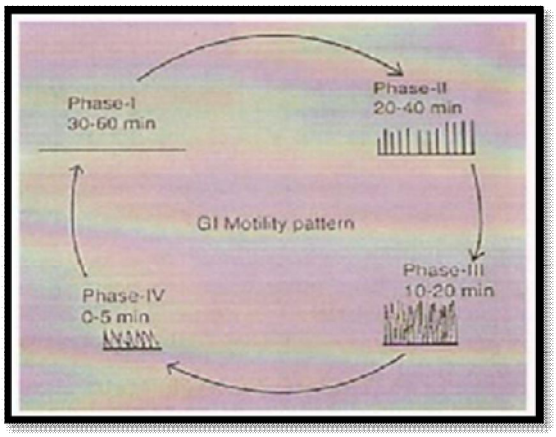

Fig. 1: Gastrointestinal motility pattern

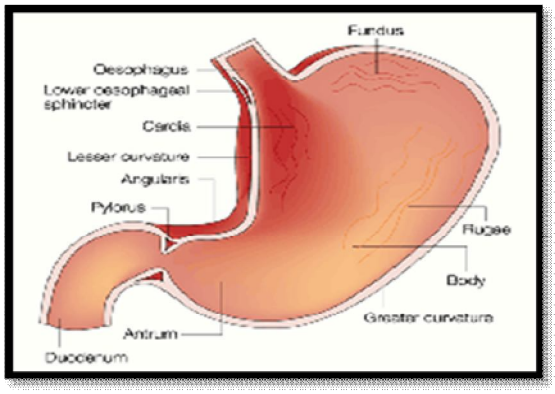

Fig. 2: Structure of stomach

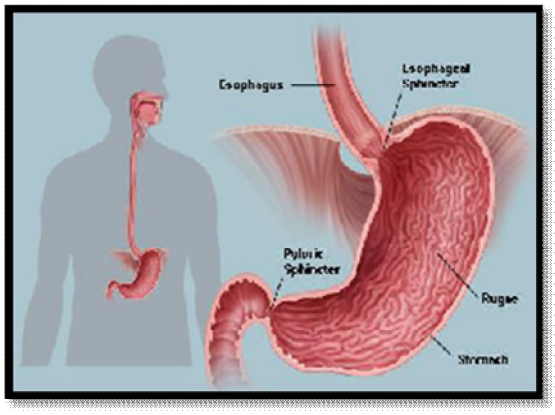

Fig. 3: Gastro intestinal tract

Need for gastroretention

1. Some drugs display region-specific absorption that can be related to differential drug solubility and stability in different regions of the intestine as a result of changes in environmental pH, degradation by enzymes present in the lumen of the intestine or interaction with endogenous components such as bile[17].
2. Many drugs show poor bioavailability (BA) in the presence of intestinal metabolic enzymes like cytochrome P450 (CYP3A), abundantly present in the intestinal epithelium. Their activity decreases longitudinally along the small intestine, with levels rising slightly from the duodenum to the jejunum and declining in the ileum and colon[18].
3. An absorption window exists because of physiological, physicochemical or biochemical factors. Drugs having site-specific absorption are difficult to design as

oral CRDDS because only the drug released in the region preceding and in close vicinity to the absorption window is available for absorption[19].

4. After crossing the absorption window, the released drug goes waste with negligible or no absorption. This phenomenon considerably decreases the time available for drug absorption after its release and expose the success of the delivery system
5. The GRDDS can improve the controlled delivery of the drugs which exhibit an absorption window by continuously releasing the drug for a prolonged period before it reaches its absorption site, thus ensuring its optimal bioavailability.

Approaches to increase gastric residence time[20,21]

A number of systems have been used to increase the gastric retention time (GRT) of dosage forms by employing a variety of concepts. These systems have been Floating Drug Delivery Systems .

Floating Drug Delivery Systems

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids (<1 g/cm3) and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. 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 an increased GRT and a better control of the fluctuations in plasma drug concentration.

Classification of Floating Drug Delivery [22]

Based on the mechanism of buoyancy

FDDS broadly classified into two main classes: effervescent and noneffervescent floating systems.

(a) Effervescent Floating system

These are matrix types of systems prepared with the help of swelleble polymers like HPMC, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO2 is liberate and gas entrapped in swollen hydrocolloids which provides buoyancy to dosage forms.

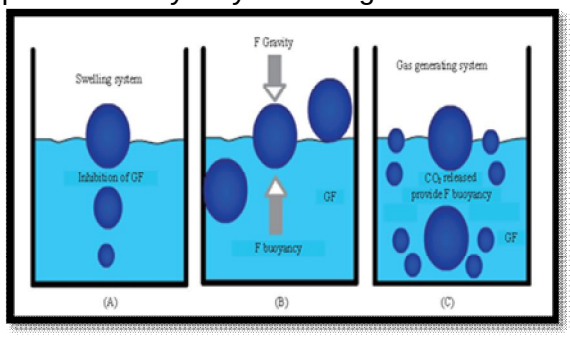

Fig. 4: Mechanism of floating systems

(b) Non-Effervescent Systems

This type of system, after swallowing, swells unrestrained via imbibitions of gastric fluid to an extent that it prevents their exit from the stomach. One of the formulation methods of such dosage forms involves the mixing of the drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier[23].

The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxy propyl methyl cellulose (HPMC), olyacrylate polymers, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates.

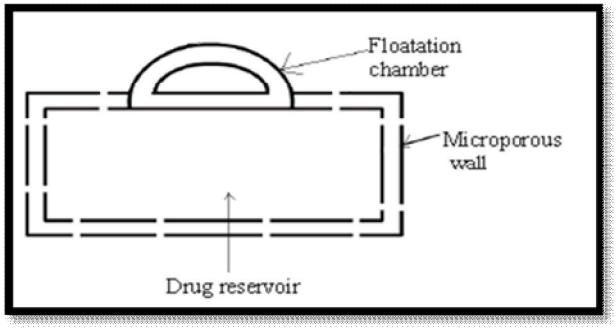

Fig. 5: Gas filled floatation Chamber

This system can be further divided into four sub-types:

(i) Colloidal Gel Barrier System

Sheth and Tossounian first designated this 'Hydrodynamically balanced system.'[24] Such a system contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug that reaches its absorption sites in the solution form for ready absorption. This system incorporates a high level of one or more gel-forming highly soluble cellulose type hydrocolloid, e.g., Hydroxy Propyl Cellulose, Hydroxy Ethyl Cellulose, Hydroxy Propyl Methyl Cellulose (HPMC), polysaccharides and matrix-forming polymer such as polycarbophil, polyacrylate and polystyrene. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloid gel barrier around its surface.

Swellable Matrices as Systems for Oral Delivery

Monolithic devices or matrices represent a substantial part of the drug delivery systems. Matrices containing swellable polymers are referred to as hydrogel matrices, polymeric matrices involving moving boundaries, swellable controlled release systems or hydrophilic matrix tablets. Swellable matrices for oral administration are commonly manufactured as tablets by the compression of hydrophilic micro particulate powders. Therefore, the most appropriate classification for these systems is swellable matrix tablets. They are constituted of a blend of drug and one or more hydrophilic polymer. In general drug release from swellable matrix tablets is based on glassy-rubbery transition of polymer as a result of water penetration into the matrix. Whereas the primary factors which can influence drug release rate to greater or lesser degree are interactions between water, polymer and drug and various formulations variables, such as

- Polymer grade,
- Drug/polymer ratio,
- Drug solubility, and
- Drug and polymer particle size

However the central element of the mechanism of drug release is the gel layer (rubbery polymer) which is formed around the matrix. The gel layer is capable of preventing matrix disintegration and further rapid water penetration. Phenomena determining gel layer thickness are water penetration, polymer swelling, and drug dissolution, diffusion and matrix erosion.

Finally, drug release is controlled by drug diffusion through the gel layer and/or by erosion of the gel layer. In order to follow gel layer dynamics during drug release in swellable matrices, the boundaries of such a layer have to be defined. It is well known that gel layer is physically separated by two sharp fronts. The boundaries separating swollen matrix from solvent and glassy from rubbery polymer.

However the possibility of the presence of a third front inside the gel layer has also been described. This additional front was termed undissolved drug front or diffusion front and turned out to be a function of drug solubility and loading. Its presence can create conditions such that the release will be more controlled by drug dissolution than by polymer swelling. Thus in swellable matrix tablet three fronts could be expected:

1) The swelling front - The boundary between the still glassy polymer and its rubbery state.

2) The diffusion front - The boundary in the gel layer between the solid, has yet undissolved drug and the dissolved drug.

3) The erosion front - The boundary between the matrix and the dissolution medium.

(ii) Microporous Compartment System

This technology is based on the encapsulation of a drug reservoir inside a Microporous compartment with pores along its top and bottom walls. [25] The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric surface with the undissolved drug. In the stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the

aperture, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.

(iii) Alginate Beads

Multi-unit floating dosage forms have been developed from freeze-dried calcium alginate.[26] Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40ºC for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12 hours. These floating beads gave a prolonged residence time of more than 5.5 hours.

(iv) Hollow Microspheres / Microballoon

Hollow microspheres loaded with drug in their outer polymer shelf were prepared by a novel emulsion solvent diffusion method[39]. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40ºC. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed and internal cavity in the microsphere of the polymer with drug. The microballoon floated continuously over the surface of an acidic dissolution media containing surfactant for more than 12 h.

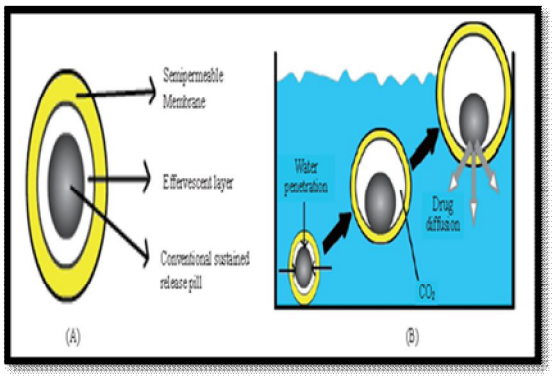

Fig. 6: (A) Different layers i) Semi-permeable membrane, ii) Effervescent layer iii) Core pill layer. (B) Mechanism of floatation via CO2 generation.

Expandable Systems

Expandable gastroretentive dosage forms (GRDFs) have been designed over the past 3 decades. They were originally created for possible veterinary use but later the design was modified for enhanced drug therapy in humans. These GRDFs are easily swallowed and reach a significantly larger size in the stomach due to swelling or unfolding processes that prolong their GRT. After drug release, their dimensions are minimized with subsequent evacuation from the stomach[27]. Gastroretentivity is enhanced by the combination of substantial dimensions with high rigidity of the dosage form to withstand the peristalsis and mechanical contractility of the stomach. Positive results were obtained in preclinical and clinical studies evaluating the GRT of expandable GRDFs. Narrow absorption window drugs compounded in such systems have improved in vivo absorption properties.

Bio / Muco-Adhesive Systems

Bioadhesive drug delivery systems (BDDS) are used as a delivery device within the lumen to enhance drug absorption in a site- specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. [28] Gastric mucoadhesion does not tend to be strong enough to impart to dosage forms the ability to resist the strong propulsion forces of the stomach wall. The continuous production of mucous by the gastric mucosa to replace the mucous that is lost through peristaltic contractions and the dilution of the stomach content also seem to limit the potential of mucoadhesion as a gastroretentive force. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan and gliadin, etc.

High-Density Systems

Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rogue or folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an

upright posture. Dense pellets (approximately 3g/cm3) trapped in rogue also tend to withstand the peristaltic movements of the stomach wall. With pellets, the GI transit time can be extended from an average of 5.8–25 hours, depending more on density than on the diameter of the pellets. [29] Commonly used excipients are barium sulphate, zinc oxide, titanium dioxide and iron powder, etc. These materials increase density by up to 1.5–2.4g/cm3.

Mechanism of floating systems

When floating drug delivery system (FDDS) are administered orally, they retained in the stomach for a prolonged period of time by virtue of their floating properties, which can be acquired by several means. One of the basic mechanisms beside the floatation can be explained by the concept of density. Mathematically density may be defined as; [30]

Density (ρ) = mass (m) / volume (v) (1)

In case of effervescent floating dosage form which is composed of gas generating agents and swellable polymers when come in contacts with acidic content of the stomach, CO2 is librated and is trapped in gellified hydrocolloid, which creates upward motion of dosage form and thus reducing the density of system and making it float on gastric content.

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. 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 an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of gastric contents. The floating force (F) can be mathematically expressed as; [31]

F = F buoyancy - F gravity (2)

Equation 2 can be rewritten as,

F = (Df – Ds) g v (3)

Where,

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

Factors affecting FDDS

Density: GRT is a function of dosage form buoyancy which is dependent on density.

Size

Dosage form units with a diameter more than 7.5 mm are reported to increase GRT compared with those with a diameter of 9.9mm.

Shape

Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to exhibit a better GRT and 90%–100% retention at 24 h compared with other shapes[32,33].

Single or multiple unit formulations: Multiple unit formulations exhibit a more predictable release profiles and insignificant impairment of performance due to unit failures, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety with regard to dosage form failure compared with single unit dosage forms.

Fed or fasted state

Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myloelectric complex (MMC) that occurs every 1.5 to 2 h. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MC, 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.[32, 34].

Nature of the meal

Consumption of indigestible polypolymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus

reducing the gastric emptying rate and prolonging drug release[33].

Caloric content
GRT can be increased by 4 to 10 h with a meal that is high in proteins and fats[33].

Frequency of feeding
The GRT can increase by over 400 min when successive meals are given compared with a single meal due to the low frequency of MMC[19]
Gender: Mean ambulatory GRT in males (3.4 ± 0.6 h) is less compared with age and race matched females (4.6 ± 1.2 h), regardless of the weight, height and body surface area.

Age
Elderly people, especially those over 70, have a significantly longer GRT.

Posture
GRT can vary between supine and upright ambulatory patient states.

Concomitant drug administration
Anticholinergics, like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride, affect the FDDS.

Biological factors
Diabetes and Crohn's disease, also affect the FDDS.

Drug candidates criteria for gastro-retentive floating drug delivery system [35,36]

1. Desirable Half-Life (2 -8 h)
2. High Therapeutic Index of the drug
3. Small Dose of the drug
4. Aqueous Solubility of the drug
5. GI Absorption of the drug
6. Drug Stability to Wide pH Range, GI Enzymes and Flora
7. First Pass Clearance of the drug

ADVANTAGES OF FLOATING DRUG DELIVERY SYSTEMS[37,38]

1. Enhanced Bioavailability
2. Enhanced First-Pass Biotransformation
3. Sustained Drug Delivery/Reduced
4. Frequency of Dosing
5. Targeted Therapy for Local Ailments in the Upper GIT
6. Reduced Fluctuations of Drug Concentration
7. Improved Selectivity in Receptor Activation
8. Reduced Counter-Activity of the Body
9. Extended Time over Critical (Effective) Concentration
10. Minimized Adverse Activity at the Colon
11. Site Specific Drug Delivery.

Limitations of FDDS
The main disadvantage of floating systems is that they require sufficiently high levels of fluid in the stomach for the DDS to float therein and work efficiently. However, this can be overcome by administrating the dosage form with a glass full of water (200-250 ml) with frequent meals or by coating the dosage form with bioadhesive polymers, thereby enabling them to adhere to the mucous lining of the stomach wall. Floating system is not feasible for those drugs that have solubility or stability problem in gastric fluids.

Review of literature
Alagusundaram.M et al review that Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200 µm. Approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion microspheres as carriers for drugs. Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumor[40].
Nirmal H.B et al review the formation of gels depends on factors like temperature modulation, pH change, presence of ions and ultra violet irradiation, from which the drug gets released in a sustained and controlled manner by using biodegradable polymers such as gellan gum, alginic acid, xyloglucan, pectin, chitosan, poly (DLlactic acid), poly (DL-lactide-co-glycolide) and poly-caprolactone for the formulation of in

situ gels. The production of In-Situ gel is less complex and thus lowers the investment and manufacturing cost[41].

Sanjay P Boldhane et al developed Gastro retentive Drug Delivery of Metformin Hydrochloride using sodium alginate, and sodium carboxymethylcellulose was used as a gelling agent, and release modifiers, respectively. Eudragit NE 30 D was used as sustained release polymer to control the initial burst release. The optimization study using a 32 full factorial design revealed that the amount of sodium alginate and sodium carboxymethylcellulose had a significant effect on t50, t90, Flag and f2[42].

Puneeth, K P et al developed Gastro retentive Drug Delivery System RZM by wet granulation method using sodium bicarbonate and tartaric acid, HPMC K15 M and Xanthan gum. Prepared tablets were evaluated in terms of pre-compression and post-compression parameters. All the prepared batches showed satisfactory floating lag time and total floating time found to be more than 12hr. Formulation F1 and F3 follows first order release kinetics remaining all formulation F2, F4, F5, F6, F7, F8, F9 follows zero order, non fickian diffusion mechanism, it indicates release mechanism is both by diffusion and erosion. Higuchi confirms diffusion. Formulation F9 showed desired drug release selected as a best formulation[43].

Priyanka D. Solanki et al develop Bilayered floating tablet containing Repaglinide and Glipizide by the floating bioadhesive sustained release layer is compressed and immediate release layer is added over it, then both layers are compressed. Evaluated for in vitro drug release, buoyancy lag time (BLT), swelling ability, floating behavior, adhesion retention period, mucoadhesion study[44].

Pratim K. Choudhury et al formulated metformin hydrochloride using cellulose acetate as the polymer and evaluated in vitro for physicochemical characteristics and drug release in phosphate buffered saline (pH 7.4), and evaluated in vivo in healthy male albino mice. Microspheres exhibited prolonged drug release (more than 10 hours) and remained buoyant for over 10 hours. Spherical and smooth-surfaced microspheres with encapsulation efficiency ranging from 73% to 98% were obtained. The release rate decreased and the mean particle size increased at higher polymer concentrations. Stirring speed affected the morphology of the microsphere[45].

P Phutane et al developed Glipizide microspheres by the emulsion solvent diffusion-evaporation technique by using the modified ethanol,-dichloromethane co-solvent system. The polymer mixture of ethyl cellulose and Eudragit® S100 was used in different ratios (1:0, 1:1, 2:3, 1:4 and 0:1) to formulate batches F1 to F5. Microspheres were evaluated for particle size, densities, flow properties, morphology, recovery yield, drug content, and *in vitro* drug release behavior. Among all batch F3 had shown the optimum percent drug encapsulation of microspheres and the sustained release of the Glipizide for about 12 h[46].

Ram Chand Dhakar et al formulated mucoadhesive microspheres of Rosiglitazone Maleate by emulsification solvent evaporation techniques. Formulation F1 containing sodium carboxy methyl cellulose and F2 containing Carbopol 934 showed the reproducible results. The formulation F1 and F2 showed consistent drug release for up to 12 h time period[47].

T. M. Kalyankar et al developed Pioglitazone HCL mucoadhesive microsphere which prepared from Orifice Ionic Gelation Method using various polymers viz, Sodium Alginate, Carbopol 934 P, Carbopol 971 P NF, Carbopol 974 P NF, HPMC K 100 M and Polycarbophil in different proportion. The best batch exhibited a high drug entrapment efficiency of 65% and a swelling index of 1.21 percentage mucoadhesion after 1 hour was 78%. The drug release was also sustained for more than 12 hours[48].

S.K. Dash et al prepare sustained release microspheres of Glibenclamide by using Eudragit RS 100 by nonaqueous emulsion solvent evaporation method. Magnesium stearate was used as hydrophobic dispersant and droplets stabilizer. The yield varies from 90-97% and encapsulation efficacy is up to 94%. The desired sizes of microspheres were

obtained when the stirring was carried out at 600 rpm. The in-vitro dissolution profile of optimized formulation batch i.e., F5 is resulted up 11.5 hours[49].

Patel JK et al Glipizide microspheres containing chitosan were prepared by simple emulsification phase separation technique using glutaraldehyde as a cross-linking agent. A 3(2) full factorial design was employed to study the effect of independent variables, polymer-to-drug ratio (X(1)), and stirring speed (X(2)) on dependent variables percentage mucoadhesion, t(80), drug entrapment efficiency, and swelling index. The best batch exhibited a high drug entrapment efficiency of 75% and a swelling index of 1.42; percentage mucoadhesion after 1 hour was 78%. The drug release was also sustained for more than 12 hours[50].

Ghodake J.D et al formulated Metformin Hydrochloride microspheres by the emulsification solvent diffusion technique using polymers Hydroxypropylmethyl cellulose K4M and Eudragit RS100. Effects of the stirring rate during preparation, polymer concentration, solvent composition and dissolution medium on the size of microspheres and drug release were also observed. The prepared microspheres exhibited prolonged drug release (8 h)[51].

Jitendra R. Amrutkar et al formulated Bilayer tablet of Metformin Hydrochloride and Gliclazide using Hydrogenated castor oil and HPMC K100 M polymers. Drug to polymer ratio (125:1:4) with lactose monohydrate as a diluent to showed better performance among all and shows Higuchi model as the best suited. Sodium starch glycolate at the concentration range of 16 % gives fastest disintegration i.e. in 17 s[52].

Brahmeshwar Mishra et al developed floating in situ gel system of acetohydroxamic acid (FIGA) for eradication of Helicobacter pylori (H. pylori) and by gellan and calcium carbonate. In vitro results revealed that in situ gelling formulation floated for longer period time of time in SGF pH 1.2. FIGA showed a significant anti-H. Pylori effect in the in vivo gerbil model[53].

Ramesh C. Nagarwal et al development Metformin in situ gel using 33 full factorial design. The effect of three independent factors—concentrations of sodium alginate (X1), gellan gum (X2), and metformin (X3). Five dependent variables—release exponent (Y1), dissolution efficiency (Y2), drug release at 30 min (Y3), 210 min (Y4), and 480 min (Y5) were considered as optimization factors. The data were statistically analyzed using ANOVA and a $p<0.05$ was considered statistically significant. Of the prepared 27 formulations, the responses exhibited by batch F17 containing medium level sodium alginate (X1), low level gellan (X2), and medium level metformin (X3) were similar to the predicted responses. [54]

Rama Sarrof et al developed Metformin in-situ gelling by using sodium alginate, calcium carbonate and sodium citrate. The formulation (1.25% sodium alginate, 3.75% Metformin, 1.5% calcium carbonate, 2.5% sodium citrate) showed optimum drug release and the release was 90 % in 8 hours. The gels were evaluated with respect to in-vitro gelation time, floating lag time, duration of floating and in-vitro dissolution[55].

Dipen R. Bhimani et al developed Clarithromycin floating in situ gelling systems (CFIG) were prepared by gellan gum (0.25% to 1.0 %) and calcium carbonate (0.5% to 2.0%). From F1 toF11 batches F8 batch show good floting duration (17.3 hr) and gel strength characteristic. Compatibility study done by DSC. The gels were evaluated with respect to in-vitro gelation time, floating lag time, duration of floating and in-vitro dissolution (SGF PH 1.2)[56].

Patel R.P et al formulated In situ gel of Clarithromycin and Metronidazole Benzoate. Sodium alginate used as a polymer and CaCO3 was used as a cross-linking agent. The results of a 32 full factorial design revealed that the concentration of sodium alginate and concentration of CaCO3 significantly affected the dependent variables Q1, Q12 and T80[57].

Subhashis Debnath et al developed situ gel of Metoclopramide Hydrochloride by Sodium alginate used as a polymer and CaCO3 was used as a cross-linking agent. The formulation containing 2.5% of

sodium alginate control the release of drug for longer duration. The in-situ gel exhibited the expected, viscosity, drug content, pH, in vitro gelling capacity, in vitro floating ability, water uptake ability and sustained drug release[58].

Chellus N. et al developed simultaneous determination of Sitagliptin phosphate monohydrate and Metformin hydrochloride by ultra performance liquid chromatographic (UPLC) method. The chromatographic separation was achieved on Aquity UPLC BEH C8 100 x 2.1 mm, 1.7 µm, column using a buffer consisting of 10 mM potassium dihydrogen phosphate and 2 mM hexane-1-sulfonic acid sodium salt (pH adjusted to 5.50 with diluted phosphoric acid) and acetonitrile as organic solvent in a gradient program. The flow rate was 0.2 mL min−1and the detection wavelength was 210 nm. The limit of detection (LOD) was 0.2 and 0.06 µg mL−1, respectively. The limit of quantification (LOQ) was 0.7 and 0.2 µg mL−1, respectively. This method was validated with respect to linearity, accuracy, precision, specificity and robustness[59].

Bala sekaran C et al developed method is based on condensation of the primary amino group of Sitagliptin phosphate with acetyl acetone and formaldehyde producing a yellow colored product, which is measured spectrophotometrically at 430 nm. The color was stable for about 1 hour. Beer's law is obeyed over a concentration range of 5-25 µg/ml. The apparent molar absorptivity and Sandell sensitivity values are 1.067 x 104 Lmol-1cm-1 and 0.0471 µ gcm-2 respectively[60].

Sudha Talasila et al formulate the Gelatin Microspheres Loaded with Lisinopril Dihydrate by using Co-acervation phase separation technique. Blend of gelatin-carbopol 934P NF and Gelatin-Sodium alginate as release retardant used. Microspheres were formulated by using different drug; gelatin-carbopol and gelatin-sodium alginate in 6 batches was F1, F2, F3, F4, F5 & F6. (F6) was able to sustain the drug release for 24 hours[61].

Kanakapura Basavaiah et al developed spectrophotometric method for the determination of Lisinopril. The calibration curve is linear over the range of 5.0-50.0 µg/mL and is described by the regression equation A = (-) 0.0175 + 0.0079 C with a regression coefficient (r) of 0.9979 (n = 6). The calculated molar absorptivity and Sandell sensitivity values are 2.02 × 103 L/mol/cm and 0.219µg/cm^2, respectively. The limits of detection (LOD) and quantification (LOQ) calculated as per ICH guidelines are 0.68 and 2.07 µg/mL, respectively. The within-day accuracy expressed as relative error was better than 2.5% with precision (RSD) ranging from 1.02 to 1.93%. The between-day accuracy ranged from 1.5-3.0% with a precision less than 4%[62].

Patents on GRDDS

Table 1: List of some patent gastro retentive drug delivery systems

US Patent Number	Patent Title
6,207,197	Gastro retentive controlled-release microspheres for improved drug delivery
5,972,389	Gastric retention , oral drug dosage forms for the controlled release of sparingly soluble drugs and insoluble matter
5,443,843	Gastro-retentive systems for controlled-release
5,232,704	Sustained-release , bilayer buoyant dosage form
5,169,638	Buoyant controlled-release powder formulation
6,814,179	Floating sustained-release therapeutic composition
4,767,627	Drug delivery device that can be retained in the stomach for a controlled period of time.
4,167,558	Novel sustained-release formulations
4,126,672	Sustained-release pharmaceutical capsules
20030232895	Hydro gels having enhanced elasticity and mechanical strength properties
6,776,999	Expandable gastro retentive therapeutic system with prolonged stomach retention

	time
6,685,962	Gastro retentive controlled release pharmaceutical dosage forms
5,076,107	Apparatus and method for resultant-weight measuring system
4,844,905	Granule remaining in stomach
20020119192	Controlled release formulations for oral administration
20030021846	Active ingredient-containing floating forms comprising polyvinyl acetate and polyvinylpyrrolidone , their use and production
20030138486	Methods and dosage forms for improving the bioavailability of therapeutic agents

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