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FLOATING DRUG DELIVERY OF ANTIDIABETIC DRUGS: AN OVERVIEW

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ABSTRACT

Despite the tremendous advancement in drug delivery, oral route remains the preferred route for the administration due to higher levels of patient compliance. But conventional forms offer no control over drug delivery, leading to fluctuations in plasma drug level. These have a disadvantage of a release all or nothing emptying process while the multiple unit particulate system pass through the gastrointestinal tract to avoid the vagaries of gastric emptying and thus release the drug more uniformly. Floating drug delivery systems (FDDS) are one of the important categories with gastric retentive behavior. Incorporation of the drug in a controlled release gastroretentive dosage forms, can remain in the gastric region for several hours which significantly prolong the gastric residence time, improve bioavailability, reduce drug waste and enhance the solubility of drugs. Several approaches are currently utilized including FDDS, swelling and expanding systems, polymeric bioadhesive systems, high-density and low-density systems, modified-shape systems and other delayed gastric emptying devices. Various low density polymers as cellulose acetate, chitosan, eudragit, acrycoat, methocil, polyacrylates, polyvinyl acetate, carbopol, agar, polyethylene oxide, polycarbonates, acrylic resins and polyethylene oxide cellulose are utilized for formulation of floating drug delivery. These systems are useful to several problems encountered during the development of a pharmaceutical dosage form. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique. The present literature review summarizes some FDDS of antidiabetic drugs.

KEYWORDS: Floating system, bioavailability, antidiabetic drugs and gastric emptying.

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INTRODUCTION

Oral controlled release (CR) dosage forms have been developed for the past 3 decades due to their considerable therapeutic advantages and still remains the route of choice for the majority of clinical applications[1]. However, this approach has not been suitable for a variety of important drugs, characterized by a narrow absorption window in the upper part of the gastrointestinal tract i.e. stomach and small intestine. This is relatively due to the short transit time of the dosage form in these anatomical segments. Thus, after only a short period of less than 6 hrs, the controlled release dosage forms left the upper gastrointestinal tract and drug is released in non absorbing distal segments. As a result the short absorption phase and is often accompanied by lesser bioavailability. The Biopharmaceutical Classification System, introduced by the Food and Drug Administration (FDA) in 1995, has categorized drugs in terms of their solubility and intestinal permeability. Class I compounds are defined as those with high solubility and high permeability, and are predicted to be well absorbed when given orally. All other compounds (classes II–IV) suffer from low solubility, low permeability or both, and will present challenges to the development of products with acceptable oral bioavailability[2].

Oral bioavailability of polar compounds and those that rely on some form of facilitated transport process can be affected by the limited absorptive site, as generally display good absorption from the upper gastrointestine tract, but are poorly absorbed in the large intestine (or colon). In addition, the development of a modified release products, such as those designed to provide once daily dosing will be difficult, if not impossible. Hence, the concept of 'absorption window' has become popular[3].

The medications that are included in the category of narrow absorption window drugs are mostly associated to improved the absorption at the jejunum and ileum due to their enhanced absorption properties (e.g. large surface area in comparison to the colon) or because of the enhanced solubility of the drug in the stomach[4].

Drug biodisponibility is a crucial fact in therapeutic effectiveness. One of the essential factor is the residence time of the drug at the absorption site. Over the last two decades, numerous gastroretentive dosage forms have been designed to prolong gastric residence time[5, 6, 7].

Absorption window

Absorption windows in the proximal gut can limit the bioavailability of orally administered compounds and can be a major obstacle to the development of controlled release formulations for important drugs. A good understanding of gastrointestinal transit in humans and the effect of factors such as food can be helpful in the design of rational systems that will have clinical benefit.

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[8]. Active transport mechanisms for drugs involving carriers and pump systems have been described well[9].. Today, it is possible to assess regional differences in intestinal drug absorption by conducting non-invasive human drug absorption (HDA) study using a remote controlled delivery capsule[2]. Gamma scintigraphy is used for real-time visualization of capsule location, and a radio frequency signal is used to activate the capsule at the target site.

Basic Gastrointestinal Tract Physiology

Anatomically the stomach is divided into 3 regions: fundus, body and antrum (pylorus).

The proximal part made of fundus and body acts as a reservoir for undigested material, where as the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions[10]. Normal gastric residence time usually range between 5 min. to 2 hrs. (Figure 1)

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however, distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2-3 hrs[11]. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases[12].

1. Phase I (Basal phase) lasts from 40-60 minutes with rare contractions.
2. Phase II (Preburst phase) lasts for 30-45 minutes with intermittent action potential and contractions and involves bile secretion[13]; as the phase progresses the intensity and frequency also increases gradually.
3. Phase III (Burst phase) is also termed 'housekeeper wave' and extends for 5-15 minutes. It is initiated in the stomach in most cases (71%), or in the duodenum[14]. It includes intense and regular contractions for short time period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine.
4. Phase IV lasts for 0-5 minutes and connects between the maximal amplitude contractions to the basal phase[15].

After the 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 (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate[16].

Gastroretention

In theory, an elegant and simple way to improve drug absorption is to hold a drug delivery system above the absorption window and allowed to be released at an appropriate rate. Because most absorption windows are thought to be located in the proximal small intestine, the obvious strategy will be to hold the formulation in stomach (i.e. gastroretention). The Holy Grail remains the retention of a delivery system in the fasting human stomach using a system that will be safe and effective[17]. The intimate contact of the drug delivery system with the absorbing membrane and also the potential to maximize drug absorption may influence the rate of drug absorption. These considerations have led to the development of oral controlled release (CR) dosage forms possessing gastric retention capabilities. Drug may not be absorbed uniformly over the length of the gastrointestinal tract, because dosage form may be rapidly transported from more absorptive upper regions of the intestine to lower regions where the drug is less absorbed and drug absorption from colon is usually erratic and inefficient. Moreover, certain drugs are absorbed only from the stomach or the upper part of small intestine[18].

Based on this knowledge, various approaches have been devised for gastroretention. These fall into two main classes: (i) small particles that have bioadhesive properties (and also a propensity to float on the stomach contents); and (ii) large swelling objects that will be retained in the stomach because of their size. These swelling systems might also have floating characteristics, usually provided by the generation of carbon dioxide[19, 20].

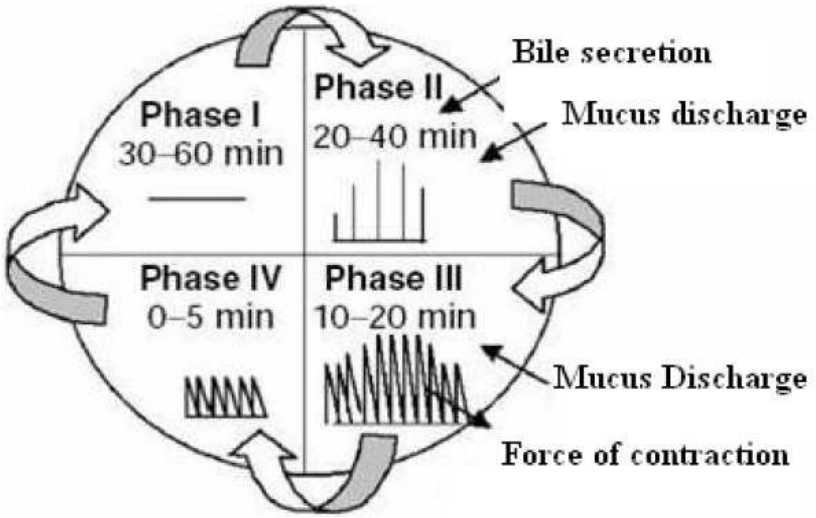

Figure 1
Schematic representation of interdigestive motility

A. Approaches to Gastric Retention:

A number of approaches have been used to increase the gastric retention time (GRT) of a dosage form in stomach by employing a variety of concepts.

1. Floating Drug Delivery System (FDDS)

The concept of FDDS was described in the literature as early as 1968[21], when Davis disclosed a method for overcoming the difficulty experienced by some persons of gagging or choking while swallowing medicinal pills. The author suggested that such difficulty could overcome by providing pills having a density of less than 1.0 g/ml so that pill will float on water surface. Since then several approaches have been used to develop an ideal floating delivery system. The various buoyant preparations include hollow microspheres (micro balloons), granules, powders, capsules, tablets (pills) and laminated films. Most of the floating systems reported in literature are single-unit systems, such as the HBS and floating tablets. These systems are unreliable and irreproducible in prolonging residence time in the stomach when orally administered, owing to their fortuitous ('all-or-nothing') emptying process[22]. On the other hand, multiple-unit dosage forms appear to be better suited since they are claimed to reduce the inter subject variability in absorption and lower the probability of dose-dumping[23].

Based on the mechanism of buoyancy, two distinctly different technologies i.e. noneffervescent and effervescent systems have been utilized in the development of FDDS. The various approaches used with their mechanisms of buoyancy are discussed in the following subsections.

1.1 Noneffervescent FDDS

Non effervescent floating drug delivery system after swallowing, unrestrained via imbibitions of gastomach. Non effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides and matrix-forming polymers. Polymers used most commonly in these systems include hydroxypropyl methyl cellulose (HPMC), polyacrylate polymers, polyvinyl acetate, carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates. 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 lesser than 1

g/cm^3. The air trapped by the swollen polymer confers buoyancy to these dosage forms. In addition, the gel structure acts as a reservoir for sustained drug release since the drug is slowly released by a controlled diffusion through the gelatinous barrier[24, 25].

One of the floating formulations is a gel forming hydrocolloid in a capsule, which swells in contact with gastric fluid after oral administration and remain buyout for extended period of time[26]. Sheth and Tossounian[27] postulated that when such dosage forms come in contact with an aqueous medium, the hydrocolloid starts to hydrate by first forming a gel at the surface of the dosage form. The resultant gel structure then controls the rate of diffusion of solvent-in and drug-out of the dosage form. As the exterior surface of the dosage form goes into solution, the gel layer is maintained by the immediate adjacent hydrocolloid layer becoming hydrated. As a result, the drug dissolves in and diffuses out with the diffusing solvent, creating a 'receding boundary' within the gel structure.

1.2 Effervescent FDDS

The effervescent floating drug delivery system utilize matrices prepared with swellable polymers such as methocel, polysaccharides (e.g. chitosan), effervescent components (e.g. sodium bicarbonate, citric acid or tartaric acid)[28] or matrices containing chambers of liquid that gasify at body temperature[29,30,31]. The system is so prepared that upon arrival in the stomach; carbon dioxide is released, causing the formulation to float in the stomach. This produces an upward motion of the dosage form and maintains its buoyancy[32]. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76: 1[33]. An alternative is to incorporate a matrix with entrapment of liquid, which forms a gas at body temperature[34,35].

Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate[32], multiple unit floating pills that generate carbon dioxide when ingested, floating minicapsules with a core of sodium bicarbonate, lactose and polyvinylpyrrolidone coated with hydroxypropyl methylcellulose (HPMC) and floating systems based on ion exchange resin technology, etc.

In FDDS, the carbondioxide generating components may be intimately mixed within the tablet matrix to produce a single layered[36] tablet or a bilayered tablet may be compressed which contains the gas generating mechanism in one hydrocolloid containing layer and the drug in the other layer formulated for a sustained release effect[37].

2. Expandable systems

Expandable gastroretentive dosage forms (GRDFs) have been designed over the past 3 decades. A dosage form in the stomach will withstand gastric transit if it is bigger than the pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, three configurations are required: a small configuration for oral intake, an expanded gastroretentive form and a final small form enabling evacuation following drug release[38]. Unfold able and swellable systems have been investigated. Unfold able systems are made of biodegradable polymers. The concept is to make a carrier, such as a capsule, incorporating a compressed system which extends in the stomach. Caldwell et al. proposed different geometric forms (tetrahedron, ring or planar membrane [4-lobed, disc or 4-limbed cross form]) of biodegradable polymer compressed within a capsule[39, 40].

3. Bio/Muco-adhesive systems

The study of mucoadhesive polymers was initiated by Park and Robinson in 1984[41]. Shortly afterwards, Smart et al.reported in vitro tests of adhesiveness of various materials to mucus[42]. 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[43]. Different theories are invoked to explain these mechanisms. Firstly, the electronic theory proposes attractive electrostatic forces between the glycoprotein mucin network and the bioadhesive material. Secondly, the adsorption theory suggests that bioadhesion is due to secondary forces such as vander waals forces and hydrogen bonding. The wetting theory is based on the ability of bioadhesive polymers to spread and develop intimate contact with the mucus layers and lastly the diffusion theory proposes physical entanglement of mucin strands and the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate. 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. Furthermore, the stomach content is highly hydrated, decreasing the bioadhesiveness of polymers. Materials commonly used for bioadhesion are polyacrylic acid (carbopol, polycarbophil), chitosan, gantrez (Polymethyl vinyl ether/ maleic anhydride copolymers), cholestyramine, tragacanth, sodium alginate, HPMC, sephadex, sucralfate, polyethylene glycol, dextran, poly (alkylcyanoacrylate) and polylactic acid[44, 45].

4. High-density systems

Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rugae 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/cm^3) trapped in rugae also tend to withstand the peristaltic movements of the stomach wall. With pellets, the gastrointestinal transit time can be extended from an average of 5.8-25 hrs, depending more on density than on the diameter of the pellets[46]. Commonly used excipients are barium sulphate, zinc oxide, titanium dioxide and iron powder etc. These materials increase density up to 1.5-2.4g/cm^3. Although encouraging results were reported in ruminants[47,48], effectiveness in human beings was not observed[49] and no system has been marketed[50].

5. Magnetic system

Magnetic system is based on a simple idea: the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Ito and coworkers used this technique in rabbits with bioadhesives granules containing ultrafine ferrite. They guided them to the esophagus with an external magnet (1700 G) for the initial 2 mins and almost all the granules were retained in the region after 2 hrs[51]. Although these systems seem to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance[52].

B. *Gastroretentive system of different categories of antidiabetic drugs*:

Floating drug delivery system prepared using different polymers are being extensively investigated for various classes of antidiabetic drugs. The findings of these research studies are summarized in the following sections.

1. Microspheres

1.1 Rosiglitazone

Kamila et al. (2009) prepared rosiglitazone maleate loaded eudragit RS100 microspheres by nonaqueous emulsification/solvent evaporation method. Results of the study suggested that floating microspheres could be successfully prepared with good % yield (69-75%), high entrapment (78-97%), narrow size distribution and desired target release with promising approach for control of blood glucose level in hyperglycemic condition for prolonged period. Buoyancy percentage of the microspheres were in the range of 65.32-96.34% at the end of 12 hrs[53]. In another study, Chaurasia et al. (2007) developed floating microspheres using different ratios of acrylic polymers and drug in a mixture of

dichloromethane and ethanol by solvent evaporation technique. The percent yield of microspheres was found to be 86.69 ± 3.70 with good drug loading efficiency and floating ability (>12 hrs) [54].

Hu Ld. et al. (2010) investigated the pharmacokinetic profile of rosiglitazone maleate containing ethyl cellulose microspheres prepared by emulsion-solvent diffusion method. The percentage of microspheres floating after 12 hrs was (91.45 ± 1.62%), the drug loading and entrapment efficiency was found to be (9.31 ± 0.31%) and (89.55 ± 1.65%) respectively. The results show that floating microspheres are a feasible approach for the sustained-release preparation of drugs which have limited absorption sites in the upper small intestine[55].

Rao et al. (2009) prepared floating microspheres of rosiglitazone maleate, using ethyl cellulose and hydroxypropylmethylcellulose (HPMC) polymers by solvent diffusion-evaporation method. In addition to the central composite experimental design, full factorial design procedures were used to evaluate the parameters required for optimized formulation. Preliminary studies revealed that the polymer: drug ratio, concentration of polymer, and stirring speed significantly affected the characteristics of microspheres. The optimum batch exhibited a prolonged drug release, remained buoyant for more than 12 hrs, high entrapment efficiency and particle size in the order of 350 micron[56].

1.2 Pioglitazone

The floating microspheres of pioglitazone hydrochloride were prepared and optimized using the 3^2 factorial designs by shirolkar et al. (2010). Ethyl cellulose and HPMC K100M polymers were used in different ratios for preparation of microspheres using emulsion solvent diffusion-evaporation method. Formulation was studied for morphology, drug content, particle size distribution, differential scanning calorimeter, powder X-ray diffraction properties, drug release profiles, % drug entrapment efficiency and stability studies. The concentration of ethyl cellulose (EC) had significant impact on drug entrapment efficiency and particle size. HPMC K100M was selected in combination with ethylcellulose to increase the drug release from microspheres but at the same time drug entrapment efficiency and yield of microsphere decreases with increase in concentration of HPMC K100M. Evaluation of five formulations, chosen as optimal from grid searches, indicated that the formulation composing (EC: HPMC, 12:1% and stirring speed: 900rpm) fulfilled maximum requisites for better drug entrapment efficiency, sustained release of the drug with optimum particle size[57].

1.3 Repaglinide

Jain et al. (2005) formulated a new controlled release system to increase residence time of repaglinide in the stomach without contact with the mucosa, through floating microspheres by the emulsion solvent diffusion technique consisting of calcium silicate as porous carrier and eudragit S as polymer. Differences in *invitro* drug release from calcium silicate based microspheres and without calcium silicate microspheres were statistically analyzed by one way analysis of variance (ANOVA) with post test (DunnettTs multiple comparison tests). The effect of various formulation and process variables on the internal and external particle morphology,

micromeritic properties, *invitro* floating behavior, physical state of the incorporated drug, drug loading and *invitro* drug release were studied. All the calcium silicate based formulations showed good floating ability (84±6.0%) and percent drug entrapment (75±3.0%). More than 80% of the particles kept floating for at least 10 hrs. The high entrapment efficiency of repaglinide is believed due to its poor aqueous solubility. Result of *invitro* release show that formulation without carrier released the drug more rapidly as compared to formulations containing porous carrier. The release pattern also provides an idea about the effect of porous carrier content

on drug release, i.e., more the content, lesser was the drug release[58].

Jain et al. (2006) further investigated the gastroretentive performance and pharmacokinetic parameters of optimized floating microspheres and compared with non-floating microspheres of repaglinide prepared from the identical polymer. The organ distribution study was performed in adult male sprague dawley rats in order to measure labeling efficiency of the formulation with 99mTc. The gamma scintigraphy of the formulations was carried out in albino rabbits to monitor the transit of formulations in the gastrointestinal tract. Prolonged gastric residence time (GRT) of over 6 hrs was achieved in all animals for calcium silicate based floating microspheres of repaglinide. Pharmacokinetic parameters of floating microspheres were compared with that of marketed tablet formulation using albino rabbits. The relative bioavailability of drug loaded floatingmicrospheres were found to be increased about 3.17 times as compared to the marketed tablet. The enhanced bioavailability and elimination half-lives of repaglinide formulation observed in the present study are attributed to the floating nature of the designed formulations which was further confirmed by gamma scintigraphy studies. The comparison of pharmacokinetic data clearly indicates that the Cmax was not much varied but AUC was increased almost three times in case of floating microspheres[59].

1.4 Nateglinide

Samal et al. (2011) have designed and characterized floating microspheres with nateglinide as model drug for prolongation of gastric residence time. Microspheres were prepared by w/o/w emulsification solvent diffusion technique using rate controlling polymers ethyl cellulose and hydroxy propyl methyl cellulose. Effects of polymer concentration, solvent composition, particle size, drug entrapment efficiency and drug release were also observed. The mean particle size of the microspheres significantly increased and the drug release rate decreased with increasing polymer concentration. Particle size was in the range of 220.4 ± 3.7 to 261.9 ± 3.5 µm. The encapsulation efficiency of the prepared microspheres was in the range 72.8±3.7 to 94.2±1.4. The release rate data were investigated by using zero-order, first-order, hixson-crowel and Higuchi kinetics. *Invitro* studies demonstrated diffusion controlled drug release from the microspheres[60].

1.5 Glipizide

Tripathi et al. (2011) formulated and evaluated the gastro-retentive floating microballoons of glipizide using hydrophilic polymers HPMC and eudragit RS100 by emulsion solvent evaporation technique. The densities of floating microspheres (0.475-0.975 g/cm^3) were found to be less than the density of gastric fluid (1.004 g/cm^3) and thus shows an extended floating time of more than 12 hrs over the gastric fluid. The entrapment efficiency of prepared floating microspheres was satisfactory (41.32-76.19%). The scanning electron microscopy confirmed the hollow nature of microspheres with pores on the surface which imparts floating properties. Formulation compose of drug:HPMC:RS, 100:: 1:4:3 was found to be the best as it exhibited highest drug release (99.12%) in 12 hrs followed by diffusion mechanism and was stable for three months at ambient conditions[61].

Sarode et al. (2011) examined the gastric residence time of glipizide loaded microspheres prepared by emulsion solvent diffusion technique or solvent evaporation technique. The polymers used in the study were acrycoat, eudragit and ethyl cellulose. The result of the study shows that as the ratio of the drug: polymer increased average particle size of the microspheres increased. Particle size of the microspheres using different polymer and drug releasing rate are in following order: acrycoatS 100 < eudragit RS 100 < ethyl cellulose. Buoyancy of microspheres were found to be more than 40% and because of their low density and internal

voids the floating time was found to be more than 12 hrs[62].

1.6 Metformin

Patel et al. (2006) studied the preparation and evaluation of metformin hydrochloride floating microspheres. Floating microspheres were prepared by non-aqueous emulsification solvent evaporation technique using ethylcellulose as the rate controlling polymer. Effect of mixing ratio of components in the organic phase was extensively studied. Among all the formulation studied best results were obtained at the ratio of drug: polymer: solvent (250:750:12 and 250:146.45:9 [mg: mg: ml]). The data obtained were size distribution (250-1000 µm), drug content (61-134% of theoretical load), yield (58-87%) and drug release (47-87% after 8 hrs), floating time (> 8 hrs)[63].

In another study sustained release floating microcapsules of metformin hydrochloride was prepared by oil-in-oil emulsion solvent evaporation method by Nath et al. (2009). Two polymers of different permeability characteristics were used separately and in combination (1:1) i.e. cellulose acetate butyrate (MW of 16,000) and eudragit RL100 (MW of 150,000). An increase in the concentration of polymer resulted in an increase in yield as well as in encapsulation efficiency. No significant difference in drug loading in microcapsules made from different polymer was noted, however, it increases as the concentration of polymer is increased relative to drug concentration. All the prepared microcapsules showed higher amount of drug release in phosphate buffer (pH 6.8) as compared to the release in 0.1M HCl (pH 1.2). The two polymers were selected in such a way that eudragit RL100 will give initial burst release, while CAB will control the drug release by maintaining the buoyancy. Evaluation of the release data reveals that microcapsules prepared from RL100, cellulose acetate butyrate and combination of both the polymers exhibit higuchi spherical matrix release, followed by first order and zero-order release kinetics. Stability data of the formulation shows no significant change in the percentage amount of drug content[64].

Ghodake et al. (2010) prolongs gastric residence time by microencapsulating metformin hydrochloride with hydroxypropylmethylcellulose K4M and eudragit RS100 as polymer. The drug entrapment efficiency of different formulations were in range of 41.1-74.1% which slightly decreases with increase HPMC content and decreased eudragit ratio in microballoons. The mean particle size increased and the drug release rate decreased at higher polymer concentration. No significant effect of the stirring rate during preparation on drug release was observed. The results reveal that the floating ability of microsphere also decreases by increasing the HPMC K4M ratio; this is due to less solubility of eudragit RS100 in acidic pH. *Invitro* drug release studies were performed and drug release kinetics wasevaluated using the linear regression method. The release of drug in 0.1 N HCl was generally low as compared to phosphate buffer pH 6.8[65].

Salukar et al. (2010) examined the prolonged gastric residence time and increased drug bioavailability with decreased gastrointestinal side effects of metformin hydrochloride by formulating floating beads (prepared by ionotropic gelation method). Beads were prepared by dispersing drug with calcium carbonate and sodium bicarbonate separately into a mixture of anionic sodium alginate, as primary polymer with oppositely charged counter ion polymer namely HPMCK4M, EC and mixture of both the polymer into a solution of calcium chloride containing acetic acid. The prepared micro carriers were in range of 447.1-801.8 µm. Percentage yield was found in the range of 48.36-98.59 %. It was observed that on increasing the polymer and gas forming agent in formulation there is significant low production yield, due to production of high viscous polymer dispersion which may lost during manufacturing process. The formulations were optimized for different weight ratios of gas-forming agent and combination of

polymer. The results of the study indicate that calcium carbonate is superior to sodium bicarbonate as a gas forming agent in polymer combination microcarriers[66].

2. TABLETS

2.1 Rosiglitazone

In order to exhibit a unique combination of floatation and bioadhesion to prolong residence in the stomach, new bilayer and floating-bioadhesive drug delivery system of rosiglitazone maleate was developed Sonar et al. (2007). During formulation the sustained layer was compressed and granules of the floating layer were added to it and then both layers were compressed together. Floating layer composed of HPMC K100M, starch and sodium bicarbonate. The prepared formulations were subjected to physical evaluation, buoyancy lag-time study, i*nvitro* dissolution study, stability study and finally i*nvivo* scintigraphic study of the optimized formulation was performed. The *invitro* drug release from the tablet was controlled by the amount of HPMC in the sustained release layer and it was observed that the release was found to be decreased with increasing concentration of HPMC K100M. The drug release from the tablets followed the matrix first-order release model. The gamma scintigraphy studies shows that the tablets maintained their matrix integrity, indicating that the gastric conditions had no effect on the gelling properties of the tablets. The result of stability studies indicates that, irrespective of the concentration of polymer, the formulations remained stable for three months[67].

Irene et al. (2011) studied the preparation and optimization of rosiglitazone maleate bilayered floating bioadhesive tablets. The first layer was a fast releasing layer consisting of a loading dose of the drug prepared by wet granulation method while the second layer was a sustaining layer containing maintenance dose of the drug. Different grades of HPMC K4M, HPMC K10M and Sodium carboxymethyl cellulose were used as swellable polymers. The granules and tablets were subjected to evaluation of various pre compression and post compression parameters. The results of various parameters studied such as preformulation, physical evaluation and drug release were found to be within the acceptable limits. The release data were investigated by using first order kinetics and higuchi model, which indicates the process of drug release, is through diffusion pathway[68].

In another study, floating tablets of rosiglitazone maleate were developed by Kavitha et al. (2010) using gas forming agents, like sodium bicarbonate, tartaric acid and polymers like HPMC K15M, xanthan gum. The prepared formulation was evaluated for precompression parameters, physical characteristics, *invitro* release, buoyancy and buoyancy lag time. The result of *invitro* release study of optimized formulation shows sustain drug release (98%) for 12hrs. The mechanism of drug release was predominantly diffusion with a minor contribution from polymeric relaxation. Stability data reveals that optimized formulation shows no significant change in physical appearance, drug content, and buoyancy lag time or *invitro* dissolution study after storage at 45°C/75% RH for three months[69].

2.2 Pioglitazone

Nagalaxmi et al. (2009) developed a hydrodynamically balanced system of pioglitazone hydrochloride, by non-effervescent and effervescent techniques. The tablets were prepared by wet granulation technique. During the study various grades of polymers (e.g. HPMC K-100M, HPMC K-4M, HPMC K-30, HPMC K-15, SCMC and MC) were used alone and in combination. Sodium bicarbonate was used as a gas generating agent in effervescent technique. Various trial studies were carried out to fix the concentration of polymers and sodium bicarbonate. It was observed from the result that formulation containing 60% of polymer and 20mg of sodium bicarbonate shows good floating behavior and the possible shortest lag time[70].

2.3 Glipizide

A new monolithic matrix system to completely deliver glipizide, in a zero order manner over an extended time period was developed by Shahla et al. (2006). Two approaches were examined using drug in formulations that contain swellable hydroxypropylmethylcellulose (HPMC) or erodible polyethylene oxide (PEO). The matrices were prepared by dry blending selected ratios of polymers and ingredients using direct compression technique. During the study glucotrol XL push-pull osmotic pump (PPOP) was used as the reference. The interrelationship between matrix hydration, erosion and textural properties were determined and analyzed under the dissolution test conditions. Linear and reproducible release similar to that of glucotrol XL was achieved for optimized formulation independent of hydrodynamic conditions. HPMC matrices showed a significantly greater degree of hydration and swelling and stronger texture property relative to PEO matrices. The kinetics of drug release was shown to be in accordance with kinetics of hydration/swelling in HPMC-based formulation, while in PEO system erosion kinetics dominated the release operation. The results indicate that in the case of low dose / low soluble drug, total drug release in a zero order manner heavily depends on the synchronization of erosion and swelling fronts during the entire dissolution study[71].

Sudharshini et al. (2010) designed hydrodynamically balanced drug delivery systems for glipizide using HPMC K4M and HPMC K15M polymers with solvent casting sintering technique. The various batches of matrix tablets were prepared with varying concentrations of the polymers under direct compression method. The study reveals that the formulations exhibited a floating lag time of less than 5 minutes and floating time of more than 22 hrs. The formulations were subjected to various physicochemical properties, buoyancy study, swelling study, *invitro* dissolution, curve fitting analysis and stability study. The result of i*nvitro* drug release studies reveals that matrix tablets containing HPMC K15M, which was exposed to acetone vapors for a period of 4.5 hrs, showed 69.17% drug release in 12 hrs and showed better release in comparison with the marketed preparation. The *invitro* release data was treated with mathematical equations, and was concluded that drug released from the tablet followed peppas model with non-fickian diffusion. The results indicate that gas powered hydrodynamically balanced tablets of glipizide containing HPMC K15M provides a better option for controlled release action and improved bioavailability[72].

In another study glipizide tablets were prepared by direct compression method using various polymers like HPMC, methylcellulose and ethylcellulose by Sivabalan et al. (2011). The tablets were evaluated for physical characterization, drug content, *invitro* release profile and buoyancy. The variation in weight was within the range of ±3% complying with pharmacopoeial specifications. The drug content varied between 9.127±0.1317mg and 9.923±0.0183mg in different formulations indicating content uniformity. The buoyancy of the tablets was ranged between 10.917-16.237 hrs. The *invitro* drug release was in the range of 59.25-79.50%[73].

Patel et al. (2010) studied formulation and *invitro* evaluation of floating bioadhesive tablet of glipizide. Effervescent tablets were prepared using chitosan, hydroxypropyl methylcellulose,carbopolP934, polymethacrylic acid, citric acid, and sodium bicarbonate. Results shows that type of polymer had no significant effect on the floating lag time. Increasing carbopolP934 caused higher bioadhesion than chitosan ($p < 0.05$). All formulations showed a higuchi, non-fickian release mechanism. Optimization and evaluation data shows that tablets with 10% effervescent base, 80% chitosan/ 20% HPMC, or 80% carbopol/ 20% polymethacrylic acid are desirable[74].

The formulation and *invitro* release profile of floating tablets of glipizide prepared by effervescent technique was investigated by

Mallikarjun V (2009). The release of the drug from two different grades of HPMCK4 and HPMC K15 polymers were compared with marketed formulation. Sodium bicarbonate was incorporated as a gas-generating agent. The floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, *invitro* buoyancy and dissolution studies. The result of cumulative drug release of formulations shows good release (85-95%). The release of promising formulations exhibits a fairly comparable release pattern with marketed formulations. The tablet swelled radially and axially during *invitro* buoyancy studies and remained buoyant for 12-20 hrs. The tablets with HPMCK15M were found to float for longer duration as compared to formulations containing HPMCK4 M[75].

2.4 Metformin

Floating effervecent tablets of metformin were prepared by wet granulation method and *invitro* drug release data was studied using zero order, first order, higuchi release model, hixson and crowell powder dissolution method and korsmeyer and peppas model. Different ratios of HPMC K15M, HPMC K100LV and carbopol polymers were used for the formulation. The formulation was optimized on the basis of buoyancy and *invitro* release in simulated gastric fluid pH 1.2. Tablets prepared with HPMC K15M and carbopol gave the best *invitro* drug release and were taken as the optimized formulation. By fitting the data into zero order, first order, korsmeyer and peppas, and higuchi model it was concluded that the release followed korsmeyer and peppas release, as the correlation coefficient (R^2 value) was higher for korsmeyer and peppas release[76].

In another study, Raju et al. (2010) gastroretentive floating tablets of metformin hydrochloride were prepared by wet granulation method and evaluated for hardness, friability, weight variation, drug content, floating properties and in vitro release pattern. During the study HPMC K4M and carbopol 934P as polymers and sodium bicarbonate as gas generating agent to reduce floating lag time were used. Results of drug release shows that formulation containing carbopol 934P 150 mg, sodium bicarbonate 50 mg demonstrated good sustained release and its data was compared with the release of marketed formulation (gluformin XL-500 mg)[77].

Ali et al. (2007) developed a hydrodynamically balanced system of metformin as a single unit floating capsule using low-density polymers such as HPMC K4M and three different grades of polyethylene oxide (PEO 60 K, PEO WSR 301 and PEO WSR 303). Effect of various release modifiers such as ethylcellulose, liquid paraffin and cellulose acetate phthalate was also studied to ensure the delivery of drug from the HBS capsules over a prolonged period. The formulation was optimized on the basis of *invitro* buoyancy and *invitro* release. *Invivo* studies were carried out in rabbits to assess the buoyancy, as well as the pharmacokinetic parameters of the formulation using gamma scintigraphy. Capsules prepared with HPMC K4M and ethyl cellulose gave the best in vitro percentage release and were taken as the optimized formulation. By fitting the data into zero order, first order and higuchi model it was concluded that the release followed zero order release. The comparative pharmacokinetic study was also performed by administration of the optimized formulation and immediate release capsule, both with radiolabeled metformin, using gamma counter. The result shows that there was an increase in AUC in optimized capsules of metformin as compared to immediate release formulation[78].

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