

AN OVERVIEW OF GASTRORETENTIVE DRUG DELIVERY SYSTEM RESEARCH

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ABSTRACT

The reason of writing this research article on gastro retentive drug delivery systems was to gather the recent literature with special focus on various gastro retentive approaches that have recently become leading methodologies in the field of site-specific orally administered controlled release drug delivery. In order to identify with various physiological difficulties to achieve gastric retention, we have summarized important factors controlling gastric retention. Afterwards, we have reviewed various gastro retentive approaches designed and developed until now, i.e. microspheres, microcapsules, floating gel beads, floating matrix tablets and in-situ gel, with advantages and limitations of gastro retentive drug delivery systems in detail.

Keywords: gastro retentive drug delivery, microspheres, microcapsules, floating gel beads, floating matrix tablets and in-situ gel

INTRODUCTION

Oral administration is the most convenient and preferred means of any drug delivery to the systemic circulation. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT)¹.

Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long

periods and hence significantly prolong the gastric retention time (GRT) of drugs.

Over the last few decades, several gastro retentive drug delivery approaches being designed and developed, including

- High-density systems.
- Floating systems.
 1. Hydrodynamically balanced systems: HBS
 2. Raft-forming systems.
 3. Low-density systems.
 4. Gas-generating systems.
- Expandable systems.
- Super porous hydro gel.
- Mucoadhesive or bioadhesive systems.

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/cm³) trapped in rugae 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 diameter of the pellets, although

many conflicting reports stating otherwise also abound in literature. Commonly used Excipients are barium sulphate, zinc oxide, titanium dioxide and iron powder, etc. These materials increase density by up to 1.5–2.4 g/cm³. However, no successful high density system has made it to the market.

1. **Large Single-unit Dosage Forms** – these dosage forms are larger than the pyloric opening and so are retained in the stomach. There are some drawbacks associated with this approach. Permanent retention of rigid large-sized single-unit forms can cause bowel obstruction, intestinal adhesion and gastroplasty
2. Floating systems can be based on the following:
 1. **Hydrodynamically balanced systems (HBS)** – incorporated buoyant materials enable the device to float;
 2. **Effervescent systems** – gas-generating materials such as sodium bicarbonates or other carbonate salts are incorporated. These materials react with gastric acid and produce carbon dioxide, which entraps in the colloidal matrix and allows them to float;
 3. **Low-density systems** – have a density lower than that of the gastric fluid so they are buoyant;
 4. **Bioadhesive or Mucoadhesive systems** – these systems permit a given drug delivery system (DDS) to be incorporated with bio/Mucoadhesive agents, enabling the device to adhere to the stomach (or other GI) walls, thus resisting gastric emptying. However, the mucus on the walls of the stomach is in a state of constant renewal, resulting in unpredictable adherence.²

Advantages Of Gastroretentive Drug Delivery System

Gastro retentive drug delivery systems have numerous advantages listed below³:

1. The principle of HBS can be used for any particular medicament or class of medicament.
2. The HBS formulations are not restricted to medicaments, which are principally absorbed from the stomach. Since it has been found that these are equally efficacious with medicaments which are absorbed from the intestine e.g. Chlorpheniramine maleate.
3. The HBS are advantageous for drugs absorbed through the stomach e.g. ferrous salts and for drugs meant for local action in the stomach and treatment of peptic ulcer disease e.g. antacids.
4. The efficacy of the medicaments administered utilizing the sustained release principle of HBS has been found to be independent of the site of absorption of the particular medicaments.
5. Administration of a prolonged release floating dosage form tablet or capsule will result in dissolution of the drug in gastric fluid. After emptying of the stomach contents, the dissolve drug

available for absorption in the small intestine. It is therefore expected that a drug will be fully absorbed from the floating dosage form if it remains in solution form even at alkaline pH of the intestine.

- When there is vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.
- Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region.
- Many drugs categorized as once-a-day delivery have been demonstrated to have suboptimal absorption due to dependence on the transit time of the dosage form, making traditional extended release development challenging. Therefore, a system designed for longer gastric retention will extend the time within which drug absorption can occur in the small intestine.
- Certain types of drugs can benefit from using gastro retentive devices. These include:
 - Drugs acting locally in the stomach;
 - Drugs those are primarily absorbed in the stomach;
 - Drugs those are poorly soluble at an alkaline pH;
 - Drugs with a narrow window of absorption;
 - Drugs absorbed rapidly from the GI tract; and
 - Drugs those degrade in the colon.³

Disadvantages of gastro retentive drug delivery systems

- There are certain situations where gastric retention is not desirable. Aspirin and nonsteroidal anti-inflammatory drugs are known to cause gastric lesions, and slow release of such drugs in the stomach is unwanted.
- Thus, drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastro retentive systems.
- Furthermore, other drugs, such as isosorbide dinitrate, that are absorbed equally well throughout the GI tract will not benefit from incorporation into a gastric retention system.⁴

Applications of GRDDS

Gastroretentive drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows^{5,6}.

Sustained Drug Delivery

HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of GI as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited.

Site-Specific Drug Delivery

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g., riboflavin and Furosemide.

Absorption Enhancement

Drugs that have poor bioavailability because of site specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption. GRDDS also serves as an excellent drug delivery system for the eradication of *Helicobacter pylori*, which causes chronic gastritis and peptic ulcers. The treatment requires high drug concentrations to be maintained at the site of infection that is within the gastric mucosa. By virtue of its

floating ability these dosage forms can be retained in the gastric region for a prolonged period so that the drug can be targeted.

An Overview of Gastroretentive Drug Delivery System Research Microspheres

Shrivastava A et al prepared cimetidine loaded microspheres by solvent evaporation method using polymers HPMC & EC and reported that the prepared microspheres exhibit prolonged drug release (~8 hrs) & remained buoyant for 9-10 hrs. The mean particle size decreased at higher polymer concentration. In vitro studies demonstrated diffusion controlled release from microspheres⁷. Hollow microspheres or microballoons (MB) of riboflavin were prepared by Sato Y et al using emulsion solvent diffusion method by dissolving enteric acrylic polymers in a mixture of dichloromethane and ethanol. The pharmacokinetics of MB riboflavin was investigated by analysis of urinary examination. Strong correlations were observed between the excretion half life, buoyancy, riboflavin release from the MB and the total urinary excretion⁸.

Streubel A et al used polypropylene foam powder as porous carrier for development of verapamil HCL loaded microparticles by o/w solvent evaporation method. The encapsulation efficiency was high and almost independent of the microparticles loading. Good in vitro floating behavior was observed that release rate was increased with increasing drug loading and decreasing polymer amounts⁹. Jain sk et al have developed and reported in vitro characterization of calcium silicate (CS) based floating microspheres of repaglinide by emulsion solvent diffusion technique comprising of calcium silicate (CS), repaglinide and Eudragit S. The formulation demonstrated favorable in vitro floating and release characteristics and high encapsulation efficiency¹⁰. Kawashima et al described Hollow microspheres (microballoons) consisting of Eudragit S an enteric polymer, loaded with drug in the outer shells, the ethanol rapidly partitioned into an external aqueous phase and the polymer precipitated around methylene chloride droplets. The subsequent evaporation of the entrapped methylene chloride led to the formation of internal cavities within the microparticles¹¹. Ali J et al prepared microspheres for celecoxib to enhance its bioavailability by increasing gastric residence time using four different polymers polyethylene oxide, Eudragit S, cellulose acetate, and Eudragit RL by an emulsion-solvents (dichloromethane and ethanol) that differed in the rate of diffusion led to formation of a hollow core in the microspheres, which was partially responsible for the floatation ability¹². Methylcellulose and chitosan micro pellets loaded with lansoprazole have prepared by Muthusamy et al micro pellets had a lower density than gastric contents and exhibited better encapsulation efficiency¹³. Heng P.W.S et al prepared the formative process of alginate microspheres using emulsification technique. The alginate microspheres were produced by cross linking alginate globules dispersed in a continuous organic phase using various calcium salts: calcium chloride, calcium acetate, and calcium lactate and calcium gluconate. The size, shape, drug content and Ca²⁺ content of the microspheres were evaluated. The tack, viscosity and pH of the calcium salt solution and percentage of Ca²⁺ partitioned into the organic phase were determined. Microscopic examination of the test emulsion at various stages of the emulsification process was also carried out¹⁴. Synthesis and characterization of cross linked chitosan microspheres containing a hydrophilic drug, hydroquinone were carried out. By Dini E. et al microspheres were prepared by the suspension cross linking method using glutaraldehyde as the cross linking agent of the polymer matrix. The effect of degree of cross linking, chitosan molecular weight concentration and the amount of encapsulated drug on the hydroquinone release kinetics was extensively investigated¹⁵. Rokhade A.P. patel and et al prepared hollow microspheres of cellulose acetate butyrate (CAB) and poly(ethylene oxide) (PEO) by emulsion solvent evaporation

method. Repaglinide was successfully encapsulated into the floating microspheres¹⁰. Hyuk sang yoo prepared biodegradable polymeric hollow microspheres by double oil and water emulsion using the lipophilic surfactant, labrafil® M 1994 CS. Olive oil was emulsified in biodegradable polymer-dissolved dichloromethane mixed with labrafil by vigorous sonication. This oil in oil emulsion was directly re-emulsified in 0.1% polyvinyl alcohol (PVA) solution, subsequently solidified by evaporating dichloromethane. Olive oil and labrafil were extracted from the microspheres by using hexane¹⁷. Yang YC *et al* prepared and evaluated sustained release EC microspheres containing aspirin by emulsification solvent evaporation technique. The release rate follows 1st order kinetics during first 12hr, suggesting a monolithic system with aspirin uniformly distributed in the microcapsules, recovered weight and loading affiance but decreasing the release rate¹⁸. Saravan M, *et al* prepared EC microspheres loaded with ibuprofen with or without polystyrene, which was used to retard drug release from the microspheres by solvent evaporation technique. The microspheres show 80-92% entrapment depending upon drug polymer ratio. High concentration was obtained in Higuchi and Korsmeyer-Peppas models. Drug release was found to be diffusion controlled¹⁹. Cheu JS *et al* prepared a controlled release micro particulate dosage form for acyclovir with EC by oil in water solvent evaporation technique. A 2³ full factorial design was applied to study effect of viscosity of polymer, drug polymer ratio and polymer concentration on the drug encapsulation and dissolution characteristics. A faster release of drug was observed when a high viscosity polymer was used²⁰. Fernandez-Urrutuno R, *et al* prepared controlled release formulation of alachlor in EC by solvent evaporation technique. Results showed that microspheres retard the release of alachlor in different degrees. The pesticide alachlor-polymer ratio and particle size were important factors for determining that alachlor release. EC microspheres may prove useful for prolonged release of alachlor²¹. Mohan Kamila M, *et al* have developed a multiunit floating drug delivery system of rosiglitazone maleate by encapsulating the drug into Eudragit RS100 through non aqueous emulsification/solvent evaporation method. The results showed that floating microspheres could be successfully prepared with good yields (69-75%), high entrapment (78-97%), narrow size distribution, and desired target release with the help of statistical design of experiments from very small number of formulations. In vivo evaluation in albino rats suggested that floating microspheres of rosiglitazone could be a promising approach for better glycemic control²². Sato Y *et al* developed a dosage form capable of floating in the stomach. Hollow microspheres prepared by the emulsion solvent diffusion method using enteric acrylic polymers with riboflavin dichloromethane and ethanol. The optimum loading amount of riboflavin micro balloon was found to impart ideal floatable properties to the microballoons²³. Kalmel AH *et al* prepared floating microparticles by emulsion-solvent diffusion technique. Four different ratios of Eudragit S 100 (ES) with Eudragit RL (ERL) were used to form the floating microparticles. The drug retained in the floating microparticles decreased with the increase in ERL content. All floating microparticles showed good flow properties and packability²⁴. Sharma S *et al* developed multiparticulate floating-pulsatile drug delivery system using porous calcium silicate (fluorite RE) and sodium alginate, for time and size specific drug release of meloxicam developed formulation was evaluated²⁵. Liu Z *et al* prepared amoxicillin Mucoadhesive microspheres (amo-ad-ms) using ethyl cellulose (ES), as matrix and carbopol 934P as Mucoadhesive polymer for the potential use of gastric and duodenal ulcers. *In vitro* and *in vivo* Mucoadhesive test showed that amo-ad-ms adhered more strongly to the gastric than nonadhesive amoxicillin microspheres amo-ec-ms did. The result showed that

amo-ad-ms had a better clearance effect than amoxicillin powder did in the rats²⁶.

Microcapsule

Moldenhaver *et al* relate the solubility properties of EC microcapsule, different microcapsule systems was prepared using various solvent and non solvents. Results indicated that microcapsules prepared using solvent mixtures added a solubility parameter²⁷. Jones DS *et al* observed the effects of some process variables on the microcapsule of propranolol HCl by solvent evaporation method with EC using a factorial design. Minimum percent w/w entrapments of propranolol when external aqueous phase contains 1.5% w/v gelatin at PH 6.00 and maximum entrapment of the drug occurred when the external phase was composed of 0.5% w/v gelatin at the PH 9.00. Gelatin concentration and pH significantly affects the entrapment²⁸. Ertan Gand *et al* formulated dual Nitrofurantoin and amoxicillin microcapsules with oxolamine citrate, EC and gelatin. Nitrofurantoin release from microcapsules was lower. The dissolution rate results of amoxicillin: gelatin with carboxy methyl cellulose and dual EC microcapsules showed a good sustained action²⁹. Ali J *et al* prepared hydrodynamically balanced system (HBS) for metformin as a single floating capsule with HMPC K4M and EC. The formulation remained buoyant during 5 hr study in rabbits. The comparative pharmacokinetic studies were performed by administration of the optimized HBS and immediate release capsules both with radiolabelled metformin, using gamma counter. There was an increase in AUC in optimized HBS capsules of metformin when compared with immediate release metformin³⁰. Dennis A *et al* proposed a loose powder filled capsule that is Buoyant so that it will float on a gastric juices and thereby improved drug availability³¹. Gibaly Fist prepared floating microcapsules containing melatonin by ionic interaction and a negatively charged surfactant, sodium dioctyl sulfosuccinate (DOS). The characteristics of the Floating microcapsules generated compared with conventional non floating microspheres manufactured from chitosan and sodium tripolyphosphate (TPP) were also investigated. The dissolution profiles of most microcapsules showed near zero order kinetics in simulated gastric fluid (S.G.F: pH 1.2) moreover, release of the drug from these microspheres was greatly retarded with release lasting for several hr. (t_{50%} (S.G.F): 1.75-6.7 hr, depending on the processing factor), compared with the Non Floating microspheres where drug release was almost instant. Most of the hollow spheres developed tended to float over simulated fluids for more than 12 hr³².

Floating gel beads

Tang Y *et al* synthesized a multi-unit floating gel bead with calcium alginate, sunflower oil and a drug of interest through an emulsification/ gelatin process. The alginate beads with oil addition were able to continuously float over the medium for 24 hr. Under the constant agitation while the non-oily beads could not. Three kind of drug with different hydrophilicities ibuprofen, niacinamide and metaclopramide HCl were tested in the study³³. Badve S *et al* developed hollow /porous calcium pectinate beads for floating-pulsatile release of diclofenac sodium intended for chronopharmacotherapy. The floating beads obtained were porous (34% porosity), hollow with bulk density ≤1 and had FT50% of the 14-24 hr. In vivo studies by γ -scintigraphy determined on the rabbits showed the gastro retention of beads up to 5 hr³⁴. Sriamornsak P, *et al* developed emulsion gel beads of calcium pectinate capable of floating in the gastric condition using an emulsion gelation method and their release properties were investigated. The metronidazole-loaded emulsion gel was found to float on the simulated gastric fluid. The additives (PEG 10000, glyceryl monostearate and Eudragit L) had a slight in significant effect on the drug release. The result suggest that emulsion gel beads are suitable as a carrier for intra gastric floating drug delivery system

and that their release behavior could be modified by hardening with glutaraldehyde or by coating with Eudragit L³⁵. Mutara Y *et al* prepared two types of alginate beads capable of floating in the gastric cavity. The first alginate gel bead containing vegetable oil (ALGO), releases model drug metronidazole which is inversely proportional to the percentage of oil. The second alginate gel bead containing chitosan (ALCS) is a dried gel. The drug release profile was not affected by the kind of chitosan in the matrix when ALCS containing metronidazole was administered orally to guinea pig, it float on the gastric juice and release the drug in the stomach³⁶. Ishak R *et al* prepared a metronidazole loaded chitosan-treated alginate beads by ionotropic gelation method. A 3² factorial designed experiment was used in which the three viscosity imparting polymers namely methyl cellulose, carbopol 934P and κ-carrageenan and the clearance rate was studied³⁷. Alaa Eldeen B. Yassin, Ibrahim A design a new extended release gastro retentive multi particulate delivery system for verapamil by incorporation into hydro gel beads made of chitosan. The beads were formed by dropping solutions of VP and chitosan in a solution of tripolyphosphate using a syringe pump with adjustable constant rate. The formed beads were then further cross linked using glutaraldehyde and the excess glutaraldehyde was then washed³⁸. Fell JT *et al* prepared floating alginate beads incorporating amoxicillin. The beads were produced by drop wise addition of alginate into calcium chloride solution, followed by removal of gel beads and freeze-drying. The beads containing the dissolved drug remained buoyant for 20 hours and high drug-loading levels were achieved³⁹.

Floating matrix tablets

Strubing S *et al* have prepared floating kolidon SR matrix tablets containing propanolol HCL. The tablet floats immediately and continued for 24 hr. They found that the floating strength was related to kolidon SR level. Floating characteristics for sample improved with a high polymer/drug ratio. Swelling characteristics of the tablets were also related to the polymer content but it was marginal⁴⁰. Ozdemir *et al* developed floating bilayer tablets with controlled release for furosemide. They have design bilayer dosage form in which one layer contained HPMC 4000, HPMC 100 and carboxy methyl cellulose and the second layer contained the effervescent mixture of sodium bicarbonate and citric acid. The radiographic studies showed that floating tablets were retained in the stomach for 6 hr and blood analysis showed that bioavailability of these tablets was 1.8 times more than that of the conventional tablets⁴¹. A floating multi-layer coated tablets was prepared by Scrisagul Sunghongjeen *et al* which consist of drug containing core tablets coated with a protective layer and a polymeric membrane. And found that polymeric film with the high flexibility (Eudragit RL30D) had the high capability to entrap the generated gas CO₂ and subsequent good floating properties. The floating properties and the drug release from the floating tablets were dependent on the core preparation method, the amount of gas forming agent and the level of gas entrapped membrane⁴². Streubel *et al*'s single unit floating controlled drug delivery systems consisting of polypropylene foam powder, matrix foaming polymer, drug and filler. They studied the different types of matrix foaming polymers like HPMC, polyacrylates, sodium alginate, corn starch, carrageenan, guar gum and gum Arabic. It was found that release rate could effectively be modified by varying the matrix foaming polymer and the foam polymer ratio, initial drug loading, tablet geometry, the types of matrix foaming polymer, the use of polymer blends and the addition of water soluble or water insoluble fillers (such as lactose or microcrystalline cellulose)⁴³. Duce B *et al* had prepared a gastro retentive drug delivery system of ranitidine HCL. They evaluated guar gum, xanthan gum, and HPMC for gel-forming properties and sodium bicarbonate as a gas generating agent. Also found that the addition of stearic acid reduces the drug dissolution due to its

hydrophobic nature. Hence concluded that the proper balance between a release rate enhancer and the release rate retardant can produce a drug dissolution profile similar to a theoretical dissolution profile⁴⁴. Sun woo jang *et al* has developed an effective floating matrix system of a new synthetic falconoid derivative i.e. (DA-6034) for the treatment of gastritis. The therapeutic limitation of DA-6034 caused by its solubility in low acidic conditions was overcome by using the effervescent floating matrix system, which was designed to cause tablet to float in the gastric fluid. They concluded that the release of DA-6034 from the tablet in the acidic medium was significantly improved by this technique, which is attributed to the effect of solubilizers and the alkalizing agent such as sodium bicarbonate used as gas generating agent⁴⁵. Ziyaur rehman *et al* prepared a bilayer floating tablet for captopril using direct compression technology with one layer as floating and other as a release layer. The floating layer contained HPMC K grade and effervescent mixture of sodium bicarbonate and citric acid. While the release layer contained captopril and various polymers such as HPMC K15 M, PVP K30 and carbopol 934P. Excellent release was observed⁴⁶. Shrivastava *et al* have developed floating matrix tablets of atenolol. Tablet were prepared using polymer such as HPMC K15M, HPMC K4M, guar gum and sodium carboxy methyl cellulose alone or in combination. They found that the tablet containing guar gum and sodium carboxy methyl cellulose shows the greater swelling indices and the tablet exhibit controlled and prolonged drug release and floats effectively in the dissolution medium⁴⁷. Xiaoqiang Xu *et al* have worked on Floating matrix dosage form for phenoprolamine HCL based on the gas forming agent. HPMC K4M and carbopol 971 NF were used in the formulation. They float over 6 hrs and the dissolution profile shows the non fickian diffusion. Also found that the carbopol 971 NF was capable of sustained release and increase in the bioavailability⁴⁸. Sigmund W *et al* have described a gamma scintigraphy evaluation of the fate of micro crystalline chitosan granules in the fasted human stomach⁴⁹. Talwar *et al* developed once a daily formulation for ciprofloxacin. The formulation was composed of ciprofloxacin, sodium alginate, xanthan gum, sodium bicarbonate and croscopolvidone. The viscolysing agent and the gel forming polymer formed a hydrated mixture that entrapped the gas, causing the tablet to float and be retained in the stomach or upper part of small intestine. The hydrated gel matrix created a tortuous diffusion path for the drug, resulting in sustained release of the drug⁵⁰. Penners *et al* developed an expandable tablet containing mixtures of polyvinyl lactones and polyacrylates that swell rapidly in the aqueous environment and thus reside in the stomach over an extended period of time in addition to this, gas forming agents were also incorporate. The gas formed decrease the system and thus the system tend to float on the gastric content⁵¹. Yang *et al* developed new strategy for the triple drug treatment (tetracycline, metronidazole and bismuth salt) of *Helicobacter pylori* associated with gastric ulcer. They have designed sellable asymmetric triple layer tablet with floating ability which prolongs the gastric residence time of the drug regimen of *Helicobacter pylori*. Hydroxy propyl methyl cellulose and poly (ethylene oxide) were use as major rate controlling polymeric Excipients. Tetracycline and metronidazole were incorporated in the core layer of the triple-layer matrix for controlled delivery, while the bismuth salt included in one of the outer layers for the instant release. The resultant drug delivery system has the potential to increase the efficacy of the therapy and the patient compliance⁵². A multi-unit levodopa sustained release floating dosage forms was developed by Goole *et al*. This minitabets (MT) were prepared by melt granulation and subsequent compression. From the dissolution profile of levodopa at different pH values it was found that dissolution profiles depend more on the prolonged release ability of Methacel K15M than on the pH dependent solubility of levodopa⁵³. Talukedar *et al* have evaluated

xanthan gum as the potential Excipients for the oral controlled-release matrix tablet. Investigate the controlled release properties of xanthan gum. Indomethacin and the sodium salt of Indomethacin were selected as a model drug. The performance of XG was compared with marketed controlled release products of Indomethacin. It was found that the drug released from the test products reached the minimum effective concentration earlier and remained longer within the therapeutic range⁵⁴. Viral patel *et al* have developed an intra gastric drug delivery system for cefixime axetil and evaluated contribution of HPMC K4M/K100LV ratio (polymer blend) and sodium lauryl sulfate (SLS) on drug release. It was found that polymer blend and SLS significantly affected the time required for 50% of drug release and percent release drug release at 12 hr⁵⁵. Maria Elena *et al* had studied the influence of the HPMC viscosity grade and release profile of metronidazole matrix tablet. The effluence was evaluated at viscosity grades of 15, 860, 5000, 20000 and 30000 CP and particle sizes of 163, 335 and 505 μ m. The results showed a linear relationship between the inverse of release rate and the viscosity grade of HPMC. An increasing burst effect occurred with increase viscosity grades and increasing particle sizes of HPMC⁵⁶. Dasharath patel *et al* have prepared carbamazepine floating tablets by melt granulation technique using beeswax, HPMC, EC were used as matrix foaming agent while gas generating and floating enhancer. The results of multiple regression analysis indicated that low levels of HPMC and EC and a high level of sodium bicarbonate should be used to manufacture the tablet formulation with desired in vitro floating time and dissolution⁵⁷. Sasa Baumgartner *et al* developed the floating matrix tablets, which after oral administration are designed to prolong the gastric residence time, increasing the drug bioavailability and diminish the side effects of irritating drugs. Tablets containing HPMC, drug and different additives were compressed. The investigation showed that tablet composition and tablet strength have greater influence on the floating properties and the drug release. ⁵⁸Quan liu *et al* had developed Zero-order delivery of a highly soluble, low dose drug alfazosin HCL gastro-retentive system. Two system containing polyethylene oxide (PEO), HPMC, sodium bicarbonate, citric acid and polyvinyl pyrrolidone were dry blended and compressed into triple layer and bi-layer composite matrices. Both system proved to be effective in providing prolonged floatation, zero -order release. They suggested that the kinetics of drug release, swelling, erosion and dynamics of textural changes during dissolution for developing gastro-retentive drug delivery system that has potential to enhance bioavailability and site-specific delivery of the proximal small intestine⁵⁹. Muralidher nama *et al* have developed the Hydrodynamically balanced delivery system of clarithromycin which has the ability to prolong the gastric residence time with desired in vitro release profile for the localized action in the stomach. The tablet was prepared by wet granulation technique. In vivo radiographic studies were also performed with the barium sulphate loaded formulation. It was found that the formulation containing 66.2% Clarithromycin 12%, HPMC K4M, polymer, 8% sodium bicarbonate had floating lag time of 12 hr and the in vitro release profile very near to the desired release⁶⁰. Korgel I, and bodmeier R developed a floating and a pulsatile drug delivery system based on the resevoir system consisting of drug containing effervescent core and a polymeric coating. Eudragit RL: acetyl tributyl citrate was selected as to initiate the effervescent reaction and floating process. Ethyl cellulose: dibutyl sebacate was used for formulation of weak semi permeable film they found that, the polymeric coating did not retard the drug release but a polymer (cellulose acetate or hydroxy propyl methyl cellulose) added to the core controlled the drug release. A quick releasing core was formulated in order to obtain a rapid drug release after the rupture of polymer coating⁶¹. A floating matrix tablet was developed by Baumgartner *et al* which incorporate a high dose of freely soluble

drug. The formulation containing 54.7% of drug, HPMC K4M, Avicel pH 101, and a gas generating agent gave the best results. It took 30 second to become buoyant. *In vivo* experiment with the fasted state beagle dog revealed prolonged gastric residence time. The results showed that the mean gastric residence time of the tablet was 240 $\pm$ 60 minutes in dogs⁶². Mousni *et al* prepared an oral drug delivery of the anti-psychotic agent carbamazepine facilitated by non-disintegrating floating dosage form. The polymer used was HPMC, guar gum, carbopol and NaHCO₃ as a gas generating agent. It was observed that the carbamazepine release form floating dosage form was uniform followed a zero-order release. The devices containing higher portion of HPMC (high viscosity) show the slower release and maintain the integrity of device as guar gum and NaHCO₃ causes the tablet to float for required time⁶³. Chaudhari pravin *et al* have developed a bilayer floating tablet of tizanidine HCL using direct compression technique. HPMC K-grade, NaHCO₃ and starch 1500 form the floating layer. The release layer contains the drug and various polymers such as HPMC K15 M, gelucire 43/07 and xanthan gum in combination with HPMC K15 M⁶⁴. Nagalakshmi, Abdul Hasan Sathali developed a hydrodynamically balanced system of Pioglitazone hydrochloride (HCL), by non-effervescent and effervescent techniques. 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 (NaHCO₃) was used as a gas generating agent in effervescent technique. From the studies, it was found that 60 per cent of polymer concentration and 20mg of NaHCO₃ provided good tablet floating behavior and also the possible shortest lag time was achieved⁶⁵. Katayama.H. *et al* developed a sustained release (SR) liquid preparation of Ampicillin containing sodium alginate, which spreads out and aids in adhering to the gastric mucosal surface. Thus, the drug is continuously released in the gastric region⁶⁶.

In situ gel

Attwood D. *et al* evaluated theophylline gel formed in situ following oral administration of 1% (w/v) aqueous solution of gellan to rats and rabbits as sustained release vehicles. Formulation complex contain calcium ions which leads to gelation in acidic environment and sustain the release. Bioavailability was increased 4-5 folds in rats and 3 folds in rabbits as compare to commercial oral formulation⁶⁷. Attwood D. *et al* evaluated theophylline gel formed in situ following oral administration of 1-2% (w/v) aqueous solution of sodium alginate to rats as sustained release vehicles. Formulation complex contain calcium ions which leads to gelation in acidic environment and sustain the release. Bioavailability was increased 1.3-2 folds in rats compared with that from a proprietary oral sustained release formulation containing an identical drug formulation⁶⁸. Attwood D. *et al* evaluated potential for oral sustained delivery of paracetamol of 2 formulations with in situ gelling properties. Oral administration of Formulation complex of gellan gum 1% (w/v) or sodium alginate 1.5% w/v contain calcium ions which leads to gelation in acidic environment and sustain the release. Bioavailability of paracetamol from the gel formed in situ in stomach of rabbits following oral administration of the liquid formulation was similar to that of commercial available sustention containing dose of paracetamol⁶⁹. Attwood D. *et al* examine the influence of variation of gastric pH over the range 1-3 on the gelation of liquid formulations of pectin and on in vitro in vivo release of paracetamol and ambroxol from resultant gels of pectin using gastric acidity controlled rabbits. The bioavailability of these drug were not significantly different when released from gel formed at the 2 different when released from gels formed at the 2 different limits suggesting that normal variation of gastric acidity in the fasting state will have no effects on the bioavailability of these drugs when delivered using this vehicle⁷⁰. Allhaque F. *et al* studied the ability of gellan to form gel in the presence of calcium ions

enable to form gel in presence of calcium ions unable to prepare capsule by gelation of this polysaccharide around a core containing starch, calcium chloride and a model drug. Released was studied in vivo from dried capsule from different environmental condition (distill water, pH 2 and 8) the effect of presence of increasing amount of drug in the formulation where investigated. The behavior of gellan capsules was compared with that of beads prepared with the same polysaccharide containing different additives. Result obtained indicated that gellan is suitable for formulating suitable capsules and that solvent uptake the dried capsule is more likely the main factor capable of affecting the rate of delivery the tested preparations⁷¹. Floating in situ gel system of clarithromycin was prepared by B. Mishra and Rajnikanth P.S. using varying concentration of gellan as gelling polymer in de-ionized water to which varying concretion of drug and surfactant was dispersed and carbohydrate as floating agent⁷². Intra gastric floating in situ gel system of amoxicillin for the treatment of peptic ulcer caused by H. pylori containing varying concentration of gellan as gelling polymer in de-ionized water to which varying concretion of drug and sodium citrate was dispersed and calcium carbohydrate as gas forming agent was prepared by B. Mishra *et al.* the in vivo H. pylori clearance efficacy of prepared amoxicillin floating in situ gel in reference to amoxicillin suspension followed by repeated oral administration of H. pylori infected Mongolian gerbils was examined by polymerase chain reaction technique and by a microbial culture method⁷³. Dettmar P. W. *et al.* tested the in vitro effectiveness of range of liquid product in raft that where cohesive, buoyant, voluminous, resistance to reflux durable under conditions of movement (resilient). The product tested has wide range of acid neutralizing capacity⁷⁴. Dojjad R. C. *et al.* described the formulation and evaluation of an ophthalmic delivery system of gatifloxacin, based on concept of ion activation system. Sodium alginate was used as a gelling agent in combination with HPMC which acted as viscosity enhancing agent, formulation provided sustain release of drug over an 8 hour period⁷⁵. Juning Tang *et al.* investigated the influence of divalent (Ca^{2+} and Mg^{2+}) and monovalent (Na^{+} and K^{+}) cations on the failure stress and strain in the gel formed with gellan polymer⁷⁶. Katayama *et al.* reported a liquid sustained release formulation containing sodium alginate intended for the eradication of H pylori in which in situ gelling was achieved by the separating oral administration of a solution of calcium salt immediately following that of sodium alginate solution⁷⁷. Miyazaki S. *et al.* assessed 3 liquid formulations with in situ gelling properties for oral delivery of cimetidine. The formulations were dilute solutions of: (a) enzyme degraded xyloglucan, which forms thermally reversible gel on warming to body temperature; (b) gellan gum and; (c) sodium alginate containing complexed ions that forms gel when these ions are released in acidic environment of the stomach. Plasma level of cimetidine after oral administration to rabbits of each of the formulation where compared with those of the formulations where compared with those resulting from administration of a commercial cimetidine/alginate with an identical drug loading⁷⁸. A patent assigned to Reckitt and Colman products described a raft forming formulation using triclosan. The drug was mixed with alginic acid, sodium bicarbonate, calcium carbonate and mannitol. The mixture was granulated and citric acid was added to the granules and then packed in sachets or compressed to formed tablets. Bicarbonate and carbonate salts produce effervescence, which aerated the raft structure formed by alginates, causing it to float⁷⁹. Shah D.P. and Jain G.K. modified gellan gum using microwave technology and sowed it to be used as Excipients in tablet formulation. Result of this study show that modified gellan gum can be used as a disintegrant in tablet formulation. Only physical modification was carried out in the microwave oven. Modified gellan gum showed excellence swelling capacity, flow property and compressibility⁸⁰. Yuguchi Y. *et al.*

studied the effect of potassium ions on the structural characteristics of gellan gum gel. The cross linking domain structure in various concentrations of K^{+} salts was observed by small angle X-ray scattering. The result was analyzed by means of molecular models of associated double helices. It found that the gelation yielded the mono-layer flat particles concentrated by side by side aggregation of double helices at lower salt concentration and then they grew up to the multilayer aggregate by further addition of salt⁸¹. Zatz and Woodfords developed a suspension formulation of theophylline which contained sodium alginate and which formed a gel when in contacted with stimulated gastric fluid⁸².

CONCLUSION

The literature searched during the review of the topic revealed that gastro retentive approach is best alternative for the formulation of drug with Narrow therapeutic window to increase the bioavailability. In the ongoing research work in the field of gastro retentive drug delivery various novel approaches and techniques have been successfully tried by various researchers. At present many formulations based on these approaches have find their way to the market and used by the physicians for treatment of patients.

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