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A REVIEW ON FLOATING MULTIPARTICULATE SYSTEM FOR GASTRIC RETENTION

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ABSTRACT

Oral drug administration is by far the most preferable route for taking medications. However, their short circulating half-life and restricted absorption via a defined segment of intestine limits the therapeutic potential of many drugs. Such a pharmacokinetic limitation leads in many cases to frequent dosing of the medication to achieve therapeutic effect. This results in pill burden and consequently, patient complains. In extreme cases drugs that are insufficiently absorbed due to narrow absorption window cannot be delivered entirely and are either given by the parenteral route or the development of such medication, which is otherwise safe. A rational approach to enhance bioavailability and improve pharmacokinetic and pharmacodynamic profile is to retain the drug reserve above its absorption region in GIT. Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery system (FDDS), also known as hydro dynamically balanced systems (HBS), swelling and expanding systems, modified shape systems and high density system. In this review, the current status of floating multiparticulate drug delivery systems including hollow microspheres (micro balloons), low density floating micro pellets and floating micro beads (acrylic resin based), microcapsules etc.

1. INTRODUCTION

The increased interest in developing oral controlled release dosage forms can be attributed to their ability to maintain an effective drug concentration in the systemic circulation for a long time and offering improved therapeutic advantages such as ease of dosing administration, patient compliance, flexibility in formulation. However, the short gastric retention time and unpredictable rapid gastric rate can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine) leading to decreased therapeutic efficacy of administered dose[1]

However 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) [2] 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 gastroretentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach [3], low density (floating) systems that causes buoyancy in gastric fluid [4,5,6] etc. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluid and therefore remain floating in the stomach without affecting gastric emptying rate for prolonged period. The drug is slowly released at the desired rate from the floating system. After release of drug, the residual system is expelled from the stomach. These floating dosage forms may have a number of advantages in oral drug delivery because they prolong retention in the gastrointestinal tract, particularly in the stomach. It facilitate sustained drug release and maintain high concentrations of drug within the gastric mucosa. This property may also be performed for treatment of *Helicobacter pylori* infection.[7,8]

2. POTENTIAL DRUG CANDIDATES FOR GASTRORETENTIVE DRUG DELIVERY SYSTEMS

1. Drugs those are locally active in the stomach e.g.misroprostol, antacids etc.
2. Drugs that have narrow absorption window in gastrointestinal tract (GIT) e.g. L-DOPA, para aminobenzoic acid, furosemide, riboflavin etc.
3. Drugs those are unstable in the intestinal or colonic environment e.g. captopril, ranitidine HCl, metronidazole.
4. Drugs that disturb normal colonic microbes e.g. antibiotics against Helicobacter pylori.
5. Drugs that exhibit low solubility at high pH values e.g. diazepam, chlordiazepoxide, verapamil HCl.

3. MULTIPARTICULATE SYSTEM

Multiparticulate drug delivery system applies specially to multiple particles such as pellets,beads, microspheres, microcapsules. In recent years, multiparticulate dosage forms or microparticles have gained in popularity for a variety of reasons. Considerable research efforts have been spent on oral sustained or controlled release multiparticulate drug delivery system due to its advantages over monolithic dosage forms[9]. Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles with diameter of 0.05-2.00mm. Thus multiparticulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet and encapsulated or compressed into a tablet[10]

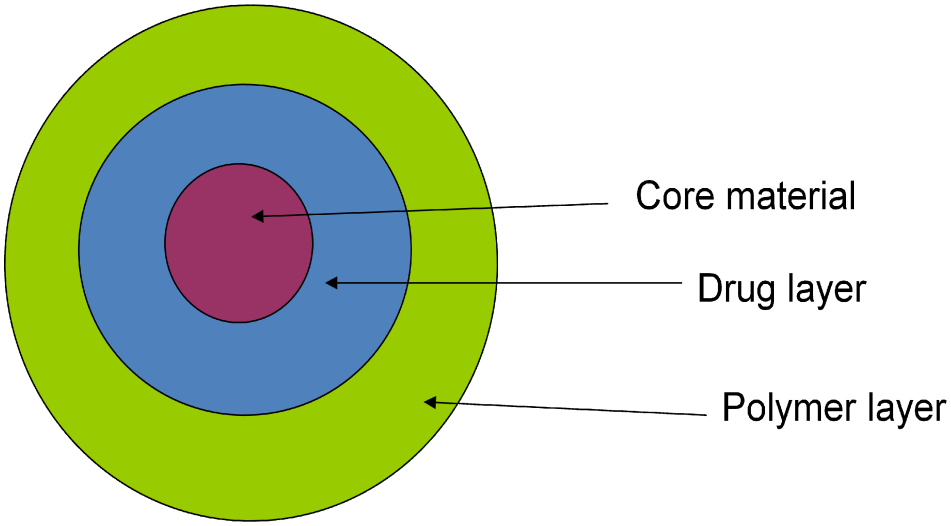

Figure 1: Multiparticulate Drug Delivery Systems

Rationale behind designing the multiparticulate drug delivery systems

There are many reasons for designing and delivering drug as a multiparticulate system :

1. To facilitate disintegration in the stomach. Shows better reproducible pharmacokinetic behaviour then conventional (monolithic) formulations.
2. After disintegration, the individual subunit particles pass rapidly through the g.i.t. If these subunits have diameter of less than 2 mm, they are able to leave the stomach continuously, even if the pylorus is closed. These results in lower intra and inter individual variability in plasma levels and bioavailability.
3. Drug safety may also increased by using multiparticulate dosage forms

4. METHOD OF PREPARATION OF MULTIPARTICULATE SYSTEM

4.1. Solvent Evaporation Method

Floating multiparticulate dosage form was prepared by solvent diffusion and evaporation methods to create the hollow inner core. The polymer is dissolved in an organic solvent and the drug is either dissolved or dispersed in the polymer solution. The solution containing the drug is then emulsified into an aqueous phase containing Polyvinyl alcohol to form oil in water emulsion. After the formation of a stable emulsion, the organic solvent is evaporated either by increasing the temperature under pressure or by continuous stirring[11,12]. The solvent removal leads to polymer precipitation at the o/w interface of droplets, forming cavity and thus making them hollow to impart the floating

properties[13,14.] The polymers studied for the development of such systems include Cellulose acetate, Chitosan, Eudragit, Acrycoat, Methocil, Polyacrylates, Polyvinyl acetate, Carbopol, Agar,Polyethylene oxide and Polycarbonates.

4.2. Ionotropic gelation Method

Ionotropic gelation is based on the ability of polyelectrolytes to cross link in the presence of counter ions to form beads. Since, the use of Alginates, Gellan gum, Chitosan and Carboxymethyl cellulose for the encapsulation of drug and even cells, ionotropic gelation technique has been widely used for this purpose[15]. The natural polyelectrolytes inspite, having property of coating on the drug core and acts as release rate retardants contains certain anions on their chemical structure. These anions forms meshwork structure by combining with the polyvalent cations and induce gelation by binding mainly to the anion blocks. The hydrogel beads are produced by dropping a drug-loaded polymeric solution into the aqueous solution of polyvalent cations. Biomolecules can also be loaded into these beads under mild conditions to retain their three dimensional structure[16].

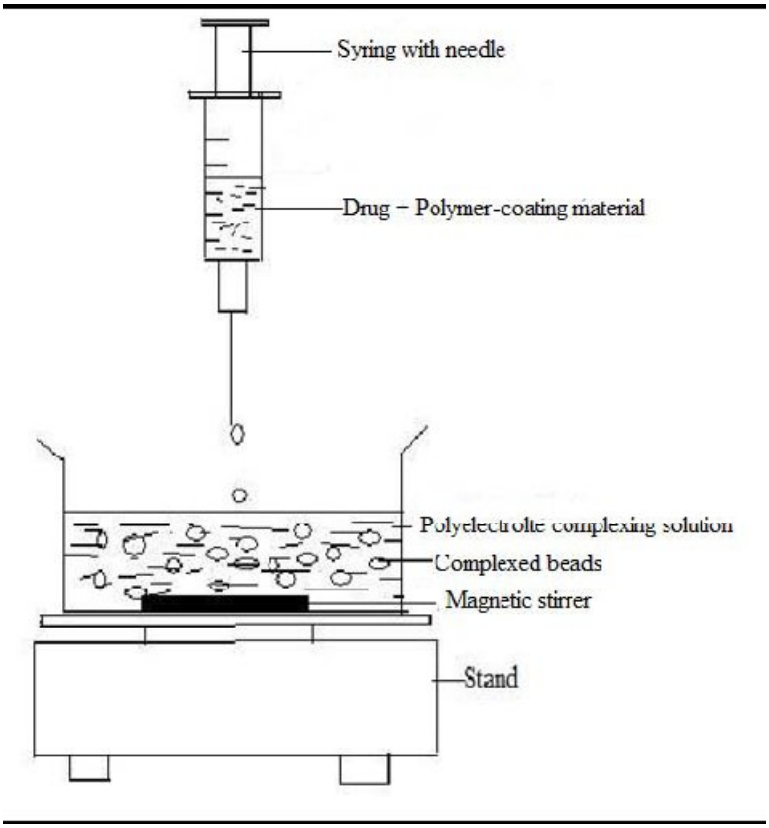

Figure 2: Ionotropic gelation method

5. CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEM

a) **Non – Effervescent system**

b) **Effervescent system**

Non Effervescent system

Non-effervescent floating drug delivery systems are normally prepared from gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides or matrix forming polymers like polyacrylate, polycarbonate, polystyrene and polymethacrylate. In one approach, intimate mixing of drug with a gel forming hydrocolloid which results in contact with gastric fluid after oral administration and maintain a relative integrity of shape and a bulk density less than unity within the gastric environment [17]. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxypropyl methylcellulose (HPMC) polyacrylates, polyvinyl acetate, carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates. This system can be further divided into the sub-types:

Microballoons / Hollow microspheres:

Microballoons / hollow microspheres loaded with drugs in their other polymer shelf were prepared by simple solvent evaporation or solvent diffusion / evaporation methods [18] to prolong the gastric retention time (GRT) of the dosage form. Commonly used polymers to develop these systems are polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar and low methoxylated pectin etc. Buoyancy and drug release from dosage form are dependent on quantity of polymers, the plasticizer polymer ratio and the solvent used for formulation. The microballoons floated continuously over the surface of an acidic dissolution media containing surfactant for >12 hours. At present hollow microspheres are considered to be one of the most promising buoyant systems because they combine the advantages of multiple-unit system and good floating.

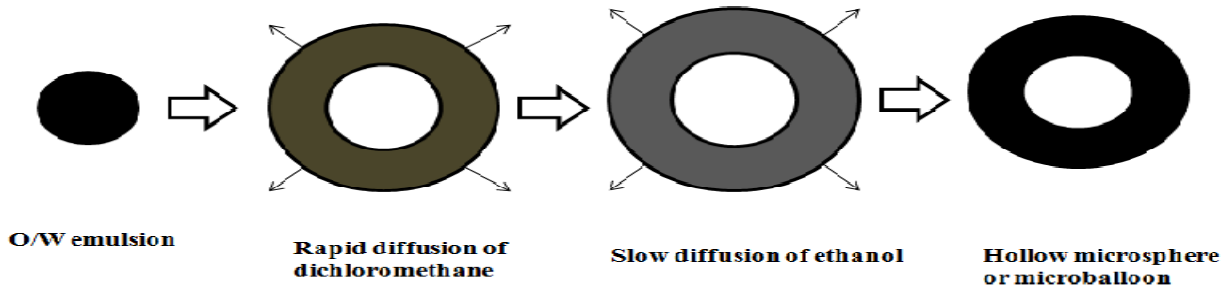

Figure 3 : Microballoons / Hollow microspheres

Microporous compartment system:

This approach is based on the principle of the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls [19]. The peripheral walls of the device were completely sealed to present any direct contact of the gastric surface with the undissolved drug. In the stomach the floatation chamber containing entrapped air causes the delivery system to float in the gastric fluid [20]. Gastric fluid enters through the aperture, dissolves the drug and causes the dissolved drug for continuous transport across the intestine for drug absorption.

Effervescent System

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme[21,22].

These buoyant systems utilize matrices prepared with swellable polymers like methocel, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. The common approach for preparing these systems involves resin beads loaded withbicarbonate and coated with ethylcellulose. The coating, which is insoluble but permeable, allows permeation of water. Thus, carbon dioxide is released, causing the beads to float in the stomach .Other approaches and materials that have been reported are highly swellable hydrocolloids and light mineral oils, a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide

when ingested, floating minicapsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with hydroxypropyl methylcellulose (HPMC), and floating systems based on ion exchange resin technology, etc.[23]

(A)Multiple-unit oral floating drug delivery system
(B) Working principle of effervescent floating drug delivery system

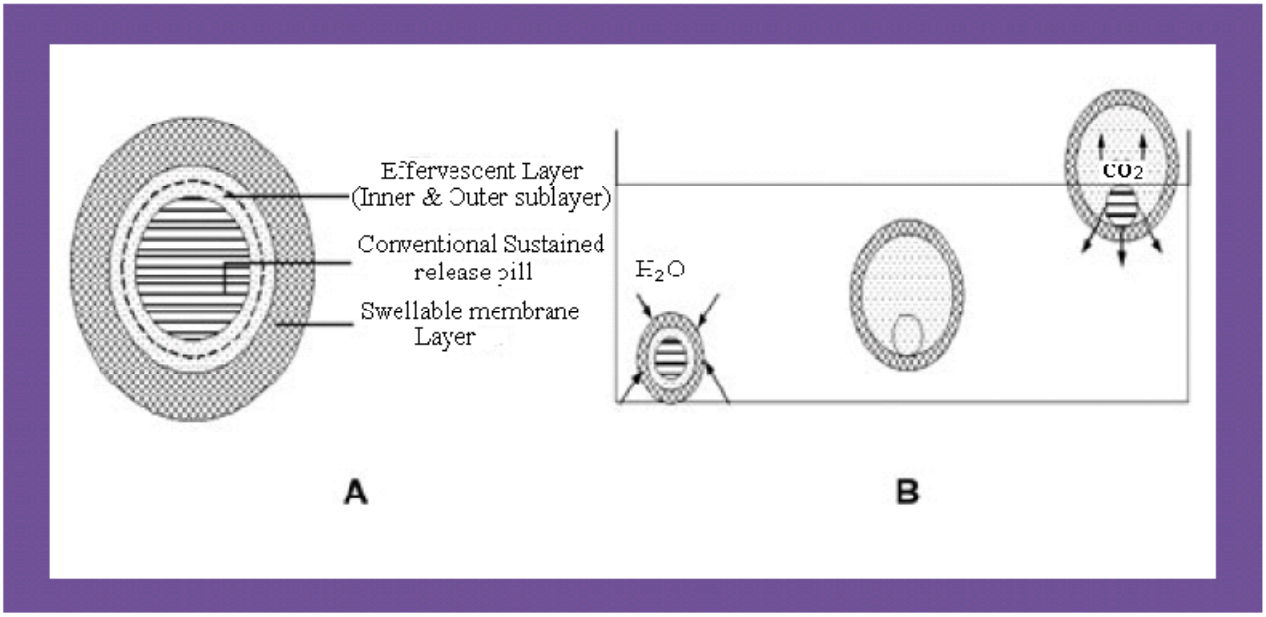

Figure 4 : Effervescent System

6. Evaluation of Multiparticulate system

Micromeritic Studies of Floating Multiparticulates

Floating multiparticulates are characterized by their micromeritic properties such as particle size, bulk and tapped density, compressibility index, true density and flow properties[24].

Particle size determination

Size of multiparticulates affects the release rate of the drug. Increase in size, decreases the effective surface area which ultimately decreases the release rate. Size distribution analysis of microspheres was done by optical microscopy using motic microscope. A small quantity of microspheres was dispersed on the slide with the help of capillary tube. The diameters were sized using a suitable objective (10X and 40X). An average of 50 particles was calculated for each variable studied [25].

Bulk and Tapped density[26]

Bulk and tapped densities were measured by using 10 ml of graduated cylinder. The sample poured in cylinder was tapped mechanically for 100 times, then tapped volume was noted down and bulk density and tapped density were calculated.

Tapped density = Mass of Formulation / Volume ____ eq.1

Carr's Compressibility Index[26]

Compressibility index (C.I.) or Carr's index value of microparticles was computed according to the following equation:

$$C.I. = \rho_t - \rho_o / \rho_t \times 100 \_\_\_\_\_ \text{eq.2}$$

Where, ρt = tapped density, ρo = bulk density

The value given below 15% indicates a powder with usually give rise to good flow characteristics, whereas above 25% indicate poor flow ability.

Hausner ratio[26]

Hausner's ratio of microparticles was determined by comparing the tapped density to the bulk density using the equation:

$$\text{Hausner ratio} = \rho_t / \rho_o \_\_\_\_\_ \text{eq.3}$$

Where, ρt = tapped density, ρo = bulk density

Angle of repose

Angle of repose has been defined as the maximum angle possible between the surface of pile of powder and horizontal plane. Angle of repose of different formulations was measured according to fixed funnel standing method (n= 3)[27]. The granules mass was allowed to flow out of the funnel orifice on a plane paper kept on the horizontal surface. This forms a pile of granules on the paper. The angle of repose was calculated by substituting the values of base radius 'r' and pile height 'h' in the following equation,

$$\tan \theta = h / r \_\_\_\_\_ \text{eq.4}$$

Where, θ is the angle of repose, h is the height and r is the radius

Scanning electron microscopy (SEM):

Morphological examination of the surface and internal structure of the floating multiparticulate was performed by using a scanning electron microscope (SEM). For

examination of the internal structure of the multiparticulates, they were cut in half with a steel blade[28].

Floating Behavior

Fifty milligrams of the floating multiparticulates were placed in 100 ml of the simulated gastric fluid (SGF, pH 2.0) containing 0.02% w/v Tween 20. The mixture was stirred at 100 rpm with a magnetic stirrer. After 8 hours, the layer of buoyant multiparticulate was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in a desiccator until constant weight was achieved. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles[29].

$$\text{Buoyancy (\%)} = W_f / W_f + W_s \quad \text{eq.5}$$

Where, W_f and W_s are the weights of the floating and settled microparticles

7. CONCLUSION

Multiparticulate dosage forms are gaining much favor over single-unit dosage forms. The potential benefits include increased bioavailability; predictable, reproducible and generally short gastric residence time, no risk of dose dumping; reduced risk of local irritation, and the flexibility to blend pellets with different compositions or release patterns. Continuous input of the drug following Controlled Release Gastro Retentive Dosage Form administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.

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