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NOVEL APPROACH: FLOATING MICROBEADS SYSTEM FOR GASTRIC RETENTION

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ABSTRACT

Floating drug delivery systems are designed for the poorly soluble, unstable and locally acting drugs. Floating drugs are having low density property than the gastric content which enables them to float in the stomach fluid for a prolonged period. This novel approach inspires to design a floating microbeads is one of the approach in delivering a dosage form to the target site in sustained controlled release fashion, to achieve good peak plasma concentration by increasing bioavailability of drug or dosage form Comparing to the conventional dosage form floating microbeads have improved G.I.T absorption, controlled release , site specificity and have potential to improve local action with maximum gastric retention time and predictable gastric emptying time. Microbeads release of the drug at specific site with specific rate. These systems have several advantages over conventional multi dose therapy. One such approach is using microbeads as carriers for drugs. Microbeads efficiently utilized in controlled delivery of many drugs but wastage of drug due to low drug entrapment efficiency is the major drawback of such micro-particulate system. This review provides a brief information about types of microbeads, method of preparations, evaluation and application of microbeads for controlled drug delivery.

INTRODUCTION

To develop oral drug delivery systems, it is necessary to optimize both the residence time of the system within the gastrointestinal tract and the release rate of the drug from the system. Various attempts have been made to prolong the residence time of the dosage forms within the stomach. The prolongation of the gastric residence time (GRT) of delivery devices could be achieved by adhesion to the mucous membranes, by preventing their passage through the pylorus or by maintaining them in buoyant fashion in gastric juice.The extended GRDFs are also required if either drug action is required at stomach or if the drug is not absorbed through the small intestine. In such cases the dosage form that can spend much time in stomach such as microbeads, floating tablets etc., are well employed. Floating systems have the property of retaining the dosage units in the stomach for prolonged period of time and are useful for drugs acting locally in the gastro intestinal tract (GIT), drugs which are poorly soluble and unstable in intestinal fluids. Floating drug delivery systems (FDDS) remain buoyant due to lower density than gastric and intestinal fluids.[1,3,4]

Oral delivery of drugs is the most preferable route of drug administration due to ease of patient compliance and flexibility in formulation . Several difficulties are found while designing controlled release systems, especially to obtain better absorption and enhanced bioavailability. Floating drug delivery system (FDDS) or Hydro dynamically balanced system (HBS) are among the several approaches of controlled drug delivery systems that have been developed in order to increase the gastric retention time of dosage.[3,9] Gastro retentive floating drug delivery system (GRFDDS) has bulk density lower than gastric fluids and thus remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. Both single and multiple unit system have been developed. Both have several advantages over immediate release dosage form including the minimization of fluctuations in drug concentration in plasma and at the site of action over prolonged periods of time . But among them the multiple unit dosage forms may be better suited because they are claimed to reduce the inter subject variability in absorption and lower the probability of dose dumping . Such a dosage form can be distributed widely throughout the gastrointestinal tract, affording the possibility of a longer lasting and more reliable release of the drug from the dosage form. An investigation was performed on pectin based amoxicillin oil entrapped microgel bed prepared by ion gelation technique using castor oil and mineral oil. The developed microbeads were regular and spherical in shape.[1]A major

constraint in oral controlled drug delivery is that, not all drug candidates are absorbed uniformly throughout the Gastrointestinal Tract (GIT) . Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract . The extent of GIT drug absorption is related to contact time with the small intestinal mucosa.[10]

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. 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. The system is based on the expansion of the core (non effervescent FDDS or low density approach), which lead to floating due to low density. Also the air entrapped by the swollen polymer confers buoyancy to this dosage forms. Floating multiparticulate oral sustained release drug delivery system includes; hollow microspheres (microballoons), low density floating micropellets and Floating microbeads.[2] Microbeads are small, solid and free flowing particulate carriers containing dispersed drug particles either in solution or crystalline form that allow a sustained release or multiple release profiles of treatment with various active agents without major side effects. The beads also maintain functionality under physiological conditions and can incorporate drug to deliver locally at high concentration ensuring that therapeutic levels are reached at the target site while reducing the side effects by keeping systemic concentration low.[3,9]

The advantages of microbeads include:[2,7]

1. Improves patient compliance by decreasing dosing frequency.

2. Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration is avoided, a desirable plasma drug concentration is maintained by continuous drug release.
3. Better therapeutic effect of short half-life drugs can be achieved.
4. Gastric retention time is increased because of buoyancy.
5. Drug releases in controlled manner for prolonged period.
6. Site-specific drug delivery to stomach can be achieved.
7. Enhanced absorption of drugs which solubilise only in stomach.

Gastroretentive technologies (GRT):[2,4]

A number of systems have been used to increase the GRT of dosage forms by employing a variety of concepts. These systems have been classified according to the basic principles of gastric retention.

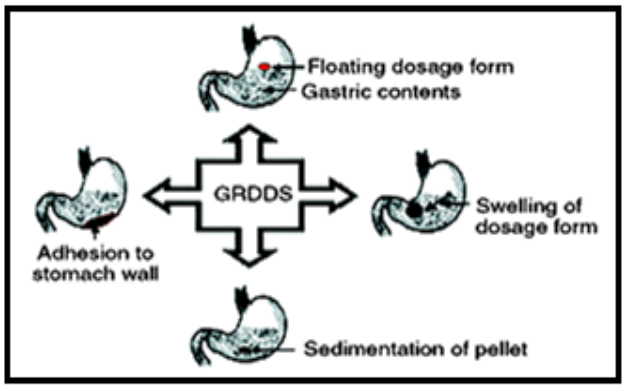

Fig. no. 1. Classification of gastroretentive drug delivery system [2]

1. Floating DDS (FDDS), with low density providing sufficient buoyancy to float over the gastric contents.

A) Non-Effervescent system

1.Colloidal gel barrier system

2.Micro porous compartment system

3.Alginate beads

4.Hollow microspheres

B) Effervescent system

1. Volatile liquid containing system
2. Gas generating system-floating multiparticulate drug delivery system

2. Bioadhesive systems, the localized retention of the system in the stomach.
3. Swelling and expanding systems, preventing transit from the gastric sphincter.

Factors affecting gastric retention [4,8]

Density: Density of the dosage form should be less than the gastric contents (1.004gm/ml).

Size: Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT competed to with those with a diameter of 9.9 mm.

Shape: The dosage form with a shape tetrahedron and ring shape devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT, 90 to 100% retention at 24 hours compared with other shapes.

Fed or Unfed State: Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complexes (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

Gender: Generally females have slower gastric emptying rates than males. Stress increases gastric emptying rates while depression slows it down [9].

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

Posture: GRT can vary between supine and upright ambulatory states of the patients.

Diseased state of the individual: biological factors also affect the gastric retention e.g. Crohn's disease , gastrointestinal diseases and diabetes.

APPROACHES TO GASTRIC RETENTION [2,4,9]

Various approaches have been followed to encourage gastric retention of an oral dosage form. Floating systems have low bulk density so that they can float on the gastric juice in the stomach. The problem arises when the stomach is completely emptied of gastric fluid. In such a situation, there is nothing to float on. Floating systems can be based on the following

• Hydrodynamically balanced systems (HBS) – incorporated buoyant materials enable device to float.

• Effervescent systems – gas-generating materials such as carbonates are incorporated. These materials react with gastric acid and produce carbon dioxide, which allows them to float.

• Low-density systems have a density lower than that of the gastric fluid so they are buoyant.

• Raft systems incorporate alginate gels – these have a carbonate component and, upon reaction with gastric acid, bubbles form in the gel, enabling floating.

• 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.

METHOD OF PREPARATION OF MULTIPARTICULATE SYSTEM [2,5,6,7,8]

A) 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. 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.

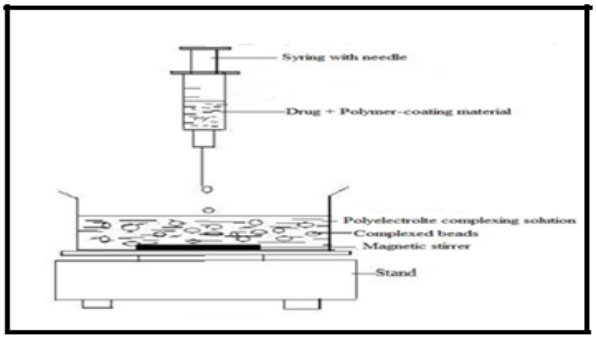

Fig.no.2. Ionotropic gelation method [6]

SOME EXAMPLES OF PREPARATION OF FLOATING MICROBEADS

I) Chitosan floating beads by ionotropic gelation method:-

Mechanism of chitosan beads formation is based on electrostatic interaction between amine group of chitosan and negatively charge group of polyanion such as tripolyphosphate. This technique offers a simple and mild preparation method in the aqueous environment. First, chitosan can be dissolved in acetic acid which can be added in the tripolyphosphate solution

containing gas forming agent like sodium bicarbonate, calcium carbonate. Chitosan beads formed with development of carbon dioxide from the reaction of carbonate salts with acid. The evolving gas permeated through the chitosan matrix, leaving gas bubbles or pores, which provided the beads buoyancy.

II) Calcium alginate floating beads by ionotropic gelation method:-

Calcium alginate beads prepared by electrostatic interaction between sodium alginate and calcium chloride. Sodium alginate dissolved in aqueous medium then added gas forming agent like sodium bicarbonate, calcium carbonate this solution added in to calcium chloride solution of acetic acid. Calcium alginate beads were formed, as alginate undergoes ionotropic gelation by calcium ions and carbon dioxide develops from the reaction of carbonate salts with acid. The evolving gas permeated through the alginate matrix, leaving gas bubbles or pores, which provided the beads buoyancy.

Characterization of floating microbeads [2,5,6]

- **Micromeritic Studies of Floating Microbeads**
  Floating microbeads are characterized by their micromeritic properties such as particle size,bulk and tapped density, compressibility index, true density and flow properties.
- **Particle size determination**
  Size of microbeads 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 microbeads was done by optical microscopy using motic microscope. A small quantity of microbeads 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.
- **Bulk and Tapped density**
  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
- **Carr's Compressibility Index**
  Compressibility index (C.I.) or Carr's index value of microbeads was computed according to the following equation: C.I.= ρt – ρo / ρt × 100 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**

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

Hausner ratio = ρt /ρo _____eq.3

Where, ρt = tapped density, ρo = bulk density

- **The Angle of repose (θ)**

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). 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,

$$\tan \theta = h / r$$

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

- **Determination of drug content and encapsulation efficiency**.

Accurately weighed grounded powder of beads was soaked in 50 ml of methanol and allowed to disintegrates completely for 24 hrs. The resultant dispersion was sonicated using a probe sonicator for 20 minute then filtered through a 0.45 µm filter. The filtrate was diluted by methanol to maintain proper concentration and drug content was measured by spectrophotometricaly. Encapsulation efficiency was calculated by the following equation.

Encapsulation efficiency= (Actual drug content) / (Total mass of microbead) X100

- **Scanning electron microscopy (SEM):**

Morphological examination of the surface and internal structure of the floating microbeads was performed by using a scanning electron microscope (SEM). For examination of the internal structure of the microbeadss, they were cut in half with a steel blade.

- **X-ray diffraction technique (XRD) and differential scanning colorimetry (DSC):**

The determination of physical state of the drug in the multiple unit systems is important. There may be chances of change in crystallinity of the drug during the process, and such

changes may influence the drug release properties. The crystallinity of drug can be studied by X-ray powder diffraction technique (XRD) and differential scanning colorimetry (DSC)

- **Floating Behavior**

  Fifty milligrams of the floating microbeads 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 at100 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 microbeads were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles.

Buoyancy (%) = Wf / Wf + Ws

Where, Wf and Ws are the weights of the floating and settled microparticles

CONCLUSION

Formulate floating alginate microbeads using gas forming agent as sodium bicarbonate and curing agents as a gastro retentive drug delivery system adopting ionic-gelation method can alternatively be used to avoid multiple dosing, thereby reducing the chance of dose dumping and minimizing resistance. 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 beads with different compositions or release patterns.

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