A Review on Formulation and Evaluation of Floating Beads of Rebamipide: Gastroprotective

SAURAV SHARMA[1], ANJANA DEVI[1]*

School of Pharmacy
Career Point University Hamirpur, H.P-India
Corresponding author: Sharma Saurav

***Abstract*- Oral administration is the most popular and convenient way to distribute the medicine. Many oral routes of administration have been developed in order to enhance drug absorption; one example is a gastric retentive drug administration. A gastrointestinal drug delivery system is one in which a medicine can remain in the gastric cavity for several hours to improve its gastric residence period. Rebamipide is a derivative of amino acids that is used to treat gastritis and to prevent the formation of stomach ulcers. Rebamipide is now commercially available in solid dose forms (tablets and capsules). Rebamipide will significantly metabolise into its inactive metabolite inside the liver. There are several techniques to gastro retention, including high density, low density, swelling, bio adhesive, expandable, magnetic, and ion exchange resin systems, each with advantages and disadvantages. A combination strategy is now favoured to achieve optimal gastro retention of the system.**

Key words: Rebamipide, Gastro-retentive, Alginate beads, gastritis

INTRODUCTION

According to the World Health Organisation, 23% of gastroduodenal gastric ulcers lead to cancer, and cancer is the leading cause of sickness and early death worldwide. Around 10 million individuals die each year as a result of GI illnesses, notably chronic gastritis. The advancements in oral controlled delivery of medication formulations have sparked increased interest because these pharmaceutical systems offer several advantages over conventional release, including affordable prices, minimised dosing rate, convenience, increased safety, simple therapeutic regime, and greater absorption in the intestines due to the large surface area. Rebamipide, also known as a muco-protective agent, is an antiulcer medication that protects the stomach mucosa from acute damage produced by numerous noxious agents and speeds up gastric ulcer healing without interfering with gastric acid output. It also inhibits ulcer relapse and delays the healing of stomach ulcers caused by a Helicobacter pylori infection.

Anti-secretory medications that include PROTON PUMP INHIBITOR and H2 -receptor antagonists have less side effects than gastrointestinal protective agents such as rebamipide. They also outperform prostaglandin derivatives. Rebamipide is a BCS class IV medication. Because rebamipide has a very low oral bioavailability of around 10%, it is used as an example drug to plan various techniques for improving bioavailability.

Gastroprotective floating beads

Micro beads are small, solid, flowing freely particle carriers that have a pharmaceutical coating or core. Beads can give controlled features, increasing medication bioavailability. Gastro retentive beads are used not only to maintain medication release, but also to improve stomach residence of dosage forms till the entire drug is released at the desired time. When compared to single unit preparations, multi-particulate dosage forms have numerous advantages, including:

- Increased adaptability
- Avoid dose dumping and insufficient drug release
- Reduce inter- and intra-subject variability in medication absorption
- Increase absorption
- Improve flow property

Limitation of floating beads

- The regulated release dosage form's release rate may vary depending on a number of factors such as food and the rate of transit through the stomach.
- Because controlled-release formulations have a larger drug load, any lack of robustness in the release characteristics of the form of administration may result in possible toxicity.
- These dosage forms should not be mashed or chewed.

Mechanism of floating drug delivery system

Floating drugs delivery systems are low density systems that have enough buoyancy to float above the contents of the gastric cavity and stay in the stomach for a longer period of time. When the system is floating over the gastric contents, the drug releases itself at the desired rate, resulting in increased gastro-retention time and minimised fluctuation.

A minimum quantity of floating force (F) is also essential to maintain the dosage form buoyant on the surface, in addition to a minimal stomach content required to achieve the buoyancy retention principle.

The equipment operates by continually measuring the force equal to F as a function of time required to keep the submerged objects submerged. The object floats better if F is on the higher positive side as shown in figure 1.
This apparatus assists in optimising FDDS in terms of the stability and endurance of the floating forces produced, hence avoiding the disadvantages of unforeseen intragastric buoyancy capability fluctuations.
F = F buoyancy – F gravity
F = (DF – Ds) gv--- (1)
Where,
F= total vertical force,
DF = fluid density,
Ds= object density,
g = acceleration due to gravity
v = volume

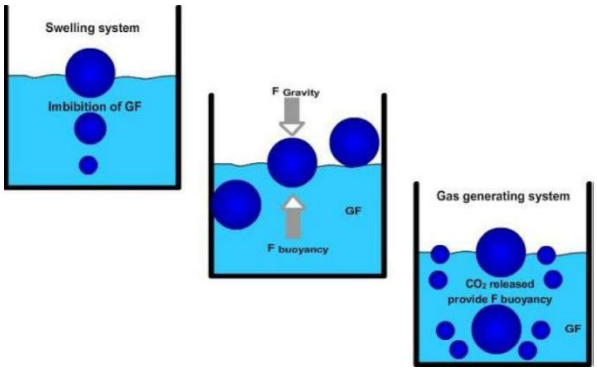

Fig. 1 Mechanism of Floating System, GF= Gastric Fluid

Polymers used in preparation of gastro retentive floating beads

- **Sodium alginate**

Sodium alginate is an organic polysaccharide and an anionic linear polymer having -1, 4-linked L-glucuronic acid and -1, 4-linked D-mannuronic acid residues randomly distributed with the chains. It is a stable gel that contains divalent cations, such as Ca2+, which are employed for medication release over time. Alginate has high biocompatibility, mucoadhesive properties, biodegradability, and mild gelation conditions. It is also utilised for floating medication administration because alginate beads are stable in acidic environments, limiting drug degradation in the acidic environment of the stomach.

- **Pectin**

Pectin is a soluble poly-galacturonic acid with methyl groups that are esterified on some of the carboxylic chains. Pectin's main component is D-galacturonic acid. It is an extremely low methoxy polysaccharides polymer with a 50% esterification. In the presence of ions of calcium or other multivalent cations, it can form gels. Pectin is used to prepare emulsions by reducing the tension that exists between the oil and water phases. According to the USP 28, pectin is a pure carbohydrate product derived from a diluted acid extraction of the inner section of the rind of the citrus fruit or apple pomace.

- **Chitosan**

Chitosan is an effective excipient for creating extended-release formulations and enhancing the bioavailability of drugs that are poorly water soluble. Chitosan is a safe, and biodegradable polymer that is generated via alkaline deacetylation of chitin. In both the pharmaceutical and medical industries, chitosan-based gelatin polymeric beads were investigated as Nano or micro-particulate transporters. The presence of calcium ions in the solution containing chitosan had a significant effect on the capacity of a gel bead to bind chitosan during the incubation. The rate and extent of the chitosan binding process will increase as the amount of calcium chloride increases.

- **Guar gum**

Guar gum is a galactomannan derived from the Cyamopsis Tetragonolobus plant. It is a polysaccharide composed of galactose and mannose repeating units. The backbone is a straight chain of 1, 4-linked the mannose residues to which galactose residues are 1, 6-linked at every other mannose, resulting in small side branches. Guar gum is temperature and acidic pH (range 5-7) stable. Strong acids (pH 3 or less) and temperatures above 500°C cause hydrolysis and viscosity loss in guar gum. Guar gum is easier to dissolve than locust bean gum and a superior emulsifier since it has more galactose branch points.

Floating Beads Preparation

- **Emulsion Gelation Method**

The polymer is mixed in distilled water and agitated with a magnetic stirrer in this process. After the polymer has been completely homogenised, the required amount of oil is added, followed by the drug. The resulting homogeneous mixture of medication, oil, and polymer is delivered into 5% calcium chloride solution using a 21G needle and allowed to sit at room temperature. After filtering the solution for a set amount of time, the resulting beads were washed twice with water that was distilled and dry at room temperature for 12 hours.

- **Ionotropic gelation method**

Ionotropic gelation is based on polyelectrolytes' ability to cross link in the presence of counter ions to produce hydrogel beads known as gel spheres. Gel spheres are spherical crosslinked hydrophilic polymeric entities capable of substantial gelation and

swelling in simulated biologic fluids and drug release via polymer relaxation. Dropping a drug-loaded polymeric mixture into an aqueous solution which includes polyvalent cations yields the hydrogel beads. The cations infiltrate into the drug-loaded polymeric droplets, generating an ionically crosslinked moiety lattice in three dimensions. Under mild conditions, biological molecules can also be filled into these gel spheres to preserve their three-dimensional structure.

The hydrogel beads are made by inserting a drug-loaded polymeric solution through a 21G needle into a water-based solution of polyvalent cations. The cations permeate into the drug-loaded polymer droplets, forming a lattice with three dimensions of ionically crosslinked moieties. These beads are then immersed in a 1% glutaraldehyde aqueous solution for roughly 1 hour. Under mild conditions, biomolecules can also be filled into these gel spheres to maintain their three-dimensional structure. To analyse the changes in beads, beads are dried in an air convection type oven at 40°C for 6 hours and then in a freeze drier.

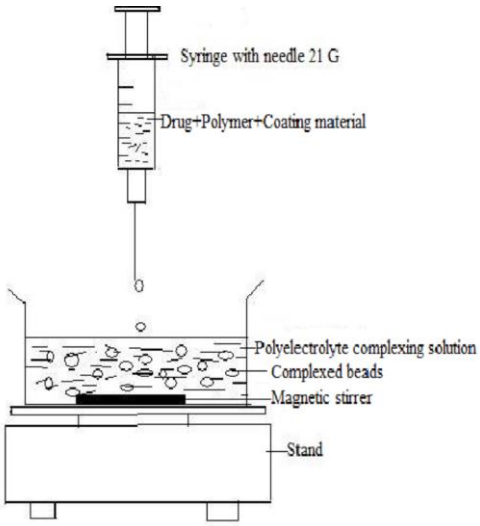

Fig. 2 Ionotropic gelation method

- **Solvent evaporation method**

To construct the hollow inner core of the floating multi particulate dosage form, solvent diffusion and evaporation procedures were used. The polymer solution is dissolved in an organic solvent, and the medication is either dissolved or distributed in it. The medication solution is then emulsified in an aqueous phase containing polyvinyl alcohol to generate an oil in water emulsion. The organic solvent is evaporated after the development of a stable emulsion, either by increasing the temperature under pressure or by continuous stirring. The elimination of the solvent cause's polymer precipitation at the o/w interface of the droplets, producing cavities and hollowing them out to give them floating capabilities. Cellulose acetate, Chitosan, Eudragit, Acrycoat, Methocil, Polyacrylates, and Polyvinyl alcohol, Polyvinyl acetate, Carbopol, Agar, Polyethylene oxide and Polycarbonates have all been investigated for use in the creation of such systems. Furthermore, in and, a novel multi-particulate gastro-retentive drug delivery system based on lowdensity foam powder was proposed and demonstrated. An oil-in-water solvent extraction/evaporation process was used to create floating micro particles using Polypropylene foam powder, Verapamil HCl (as the model medication), and Eudragit RS, Ethylcellulose, or Poly (methyl methacrylate) (PMMA).

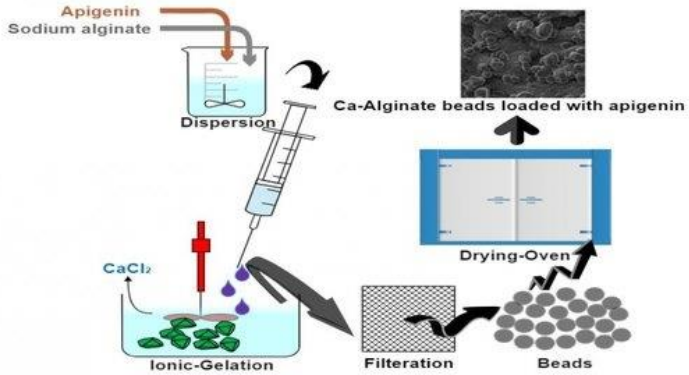

Fig 3 Solvent evaporation method

<u>Application of floating beads</u>

- **Enhanced bioavailability**

In comparison to the use of non-GRDF CR polymeric formulations, the bioavailability of folic acid CR-GRDF is significantly increased. There are numerous processes associated to drug absorption and transit in the gastrointestinal system that influence the degree of drug absorption.

- **Sustained drug delivery**

Oral Controlled release preparations have challenges, such as gastric residence duration in the GIT. Floating beads enable sustained drug release behaviour and allow the drug to be released over time. As a floating control drug delivery system, floating systems are built**.**

- **Site-specific drug delivery systems**

These methods are very beneficial for medications that are absorbed specifically from the gastrointestinal tract or the proximal wedge of the small intestinal tract. Controlled, delayed delivery of medication to the stomach allows for sufficient local therapeutic amount while limiting systemic exposure to the medication. This lowers the adverse effects of the medication in the bloodstream. Furthermore, the increased gastric availability provided by a site-directed delivery system may reduce dosing frequency. For example, furosemide and riboflavin.

- **Absorption enhancement**

Drugs that have poor bioavailability due to site specific absorption from the upper part of the Stomach are likely candidates for preparation as floating beads, maximising bioavailability**.**

- **Eradicating helicobacter pylori**

Floating beads may significantly enhance stomach pharmacotherapy by causing high levels of drugs at the gastric mucosa, eliminating helicobacter pylori from the stomach's submucosal tissue and allowing the treatment of stomach and ulcers of the duodenum, gastritis, and esophagitis.

Evaluation parameters of floating beads:

- **Percentage yield**

Floating beads that had been prepared were collected and weighed. The following formula can be used to compute yield.
Formula –

% yield= Weight of the prepared beads /Total weight of the drug and excipients

- **Particle size determination**

Optical microscopy with a calibrated ocular lens was used to assess the distribution of particle sizes of the rebamipide-loaded alginate beads. The experiment was carried out after fifty beads were acknowledged.

- **Scanning electron microscopy (SEM)**

A scanning electron microscope (SEM) can be used to perform morphological evaluation of both the outside and inside structure of the prepared air-dry beads.

- **Stability studies**

The developed beads were placed in vials and stored at 400°C/75% RH for 90 days. After 90 days of exposure, the beads were examined for drug content and invitro release.

- **In-vitro release studies for floating beads:**

The in-vitro dissolution studies were performed at specified rpm using the USP Dissolution Apparatus type II.
The dissolution medium is composed of 0.1 N HCl (900 ml) kept at 370.50C. To keep the sink condition, 5ml samples were taken at regular intervals and replaced with new medium. The drug content was measured using spectrophotometry. The method used computes the percentage CDR.

CONCLUSION

According to the review, it is possible to conclude that the floating beads have gastro-retentive sustained release characteristics. Floating beads with minimal density and sufficient buoyant to float over the contents of the gastric cavity and remain in the stomach for a prolonged period of time. As a result, the medication is slowly removed from the system at the desired rate, resulting in increased stomach retention with low changes in plasma drug concentration. Floating beads may have a better position in the future by using several different tactics, specifically in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted, and potent in vivo delivery diseased tissue and organs in the body. When compared to commercial conventional drugs, the floating beads have a higher bioavailability.

REFERENCES:

1. Fayaz W, Chasta P, Hassan Sheikh T, Ahmad M, Hussain Kumar A, Mustafa A. Gastroretentive Drug Delivery System Journal of Drug Discovery and Development, 2018; 2(1):11-17.
2. Kumar R, Chandra A, Saloni S, Gautam PK. Advanced multiple unit-controlled release floating beads: A review. World J Pharm Res. 2017; 6: 238- 59.
3. Ghareeb MM, Issa AA, Hussein AA. Preparation and characterization of cinnarizine floating oil entrapped calcium alginate beads. International Journal of Pharmaceutical Sciences and Research. 2012 Feb 1; 3(2):501.
4. Pahwa R, Bhagwan S, Kumar V, Kohli K. Role of Natural Polymers in The Development of Floating Drug Delivery Systems, Journal of Pharmacy Research 2010; 3(6):1312-1318.
5. Ganesh N, Bharathi G, Joshi H, Jayanthi C, Singh DP. Buoyant Multiparticulate Drug Delivery – A Focus on Hydrogel Beads, World J Pharm Res 2013; 2(2):450- 64.
6. Archana DK, Chandewar A.V. Formulation and Evaluation of Oral Floating Beads of Tramadol Hydrochloride, Journal of Drug Delivery &Therapeutics, 2016; 6(4):7-16.
7. Raj BS, Punitha ISR, Janki B. Formulation and Evaluation of Chitosan Prazosin Beads By Ionotropic Gelation Method, International Journal of Research in Pharmacy and Chemistry, 2012;2(4):974-83.
8. Deepthi A, Venugopal K, Vali S, Sunitha, Kannan SV, Sivakameswari S. Design and Evaluation of Muco Adhesive Sustained Release Tablets of Etodolac by Using Natural Polymers, World Journal of Pharmaceutical Research, 2016; 5(2):433-465.;.
9. Pawan P, Mayur P, Ashwin S. Role of Natural Polymers in Sustained Release Drug Delivery System-Applications and Recent Approaches, International Research Journal of Pharmacy,2011; 2(9):6-11.

10. Patil JS, Kamalapur MV, Marapur SV, Kadam DV. Ionotropic Gelation and Polyelectrolyte Complexation. The Novel Techniques to Design Hydrogel Particulate Sustained, Modulated Drug Delivery System- A Review, Digest Journal of Nanomaterials and Biostructures, 2010;5(1):241-48.
11. Shravya, Shabaraya AR, Narasimharaj A. Floating Drug Delivery System – An Approach for Gastroretentive Drug Delivery, International Journal of Pharma and Chemical Research, 2018; 4(3):179- 87.
12. Setia M, Kumar K, Teotia D. Gastro-Retentive Floating Beads a New Trend of Drug Delivery System, Journal of Drug Delivery & Therapeutics, 2018; 8(3): 169-180
13. Aparna, C.M. Shalini, D.V.R.N.Bhikshapathi Formulation Development and Evaluation of Rebamipide Floating Microspheres Am. J. PharmTech Res. 2018; 8(2)
14. Pooja Kashid, Rajendra Doijad, Amol Shete, Sachin Sajane, Abhimanyu Bhagat Studies on Rebamipide Loaded Gastroretentive Alginate Based Mucoadhesive Beads: Formulation & In-vitro, In-vivo Evaluation Pharm Methods, 2016; 7(2): 132-138.
15. Fathimath Thanziya, Shabaraya AR and Vinayak K. A review on gastroretentive floating beads International Journal of Pharmaceutical Chemistry 2019; 09(02): e5128.
16. Agrawal Swapnil,Jain Sanjay; Floating Beads International Journal of Pharmaceutical Research and Applications Volume 8, Issue 1 Jan-Feb 2023, pp: 2406-2412