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MICROBALLOONS: A REVIEW OF MICROBALLOONS AS A NOVEL ROUTE FOR GASTRORETENTIVE DRUG DELIVERY SYSTEMS

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ABSTRACT
Oral administration of drugs is a popular route and formulation for both existing and new drugs. Gastro retentive drug delivery is a method of extending gastric residence time, allowing for site-specific drug release in the upper gastrointestinal tract (GIT) for either local or systemic effects. Floating Drug Delivery Systems (FDDS) have a lower bulk density than gastric fluids and thus remain buoyant in the stomach for an extended period of time. Microballoons are based on a non-effervescent system containing empty spherical particles with no core that are ideally less than 200 micrometers in size. Microballoons have been shown to be more effective at controlling the release rate of drugs with site specific absorption. The floating microballoons illustrated gastroretentive controlled release delivery with efficient bioavailability enhancement and promise to be a promising approach for gastric retention. The advantages, limitations, methods of preparation of hollow microballoons, applications, polymers used in hollow microballoons, characterizations of microballoons, and formulation aspects with various evaluation techniques and marketed products are all covered in detail. Basic anatomy and physiology of the stomach are also studied.

KEYWORDS: Microballoons, Gastro retentive drug delivery system, Sustained release drug delivery, Polymers.

INTRODUCTION

Conventional oral dose forms, such as tablets and capsules, deliver a precise medication concentration in systemic circulation, but do not release the drug at a steady pace throughout time. Controlled release drug delivery system (CRDDS) enables drug release at a pre-controlled, predictable rate, either systemically or locally, for the specified period of time and improves a medications therapeutic efficacy by managing its release into the body with lower and less frequent dosage.[1] The oral route has various physiological issues, such as an unpredictable gastric emptying rate that varies from person to person, a short gastrointestinal transit time (80-12h), and the presence of an absorption window in the upper small intestine for several medications.[2]

These challenges have encouraged researchers to develop a medicine delivery method that can remain in the stomach for an extended and predictable period of time. Efforts are being made to develop a therapeutic drug delivery system that can provide drug concentration in plasma for a longer period of time, reducing dosing frequency and reducing fluctuation in plasma drug concentration at steady - state condition by delivering the medication in a controlled and reproducible manner.[3]

GASTRORETENTIVE DRUG DELIVERY SYSTEMS (GRDDS)

Gastroretentive drug delivery systems (GRDDS) are dosage forms that can be held in the stomach for extended periods of time. GRDDS are appropriate and effective for such medications because they improve absolute bioavailability, therapeutic efficiency, increase gastric residence time (GRT), allow for a possible dose decrease, minimise waste, and enhance solubility for pharmaceuticals that are less soluble in a high pH environment.[4]

The most difficult issues for oral drug delivery systems are delivering a medication at a therapeutically effective rate to a target place, modulating GI transit time, and minimising first pass elimination. The controlled release dosage form provides optimal and effective drug levels for an extended period of time with reduced dosing frequency and adverse effects.[5]

The modified release oral drug delivery systems classified as are:

- Controlled release
- Sustained release
- Extended release
- Prolonged release
- Delayed release

SUSTAINED RELEASE DRUG DELIVERY SYSTEM

Any drug delivery system achieves drug release over a prolonged period of time which is not depending on timing. Sustained dose forms are commonly made with a hydrophilic polymer matrix. The role of an ideal drug delivery system is to deliver the appropriate amount of drug at regular time intervals and at the appropriate site of action in order to maintain the therapeutic level of drug in blood plasma.[6]

PRINCIPLE OF SUSTAINED RELEASE DRUG DELIVERY

The active chemicals in conventional dose forms are rapidly released into an absorption pool. This is illustrated in Figure 1 by a simple kinetic scheme. The absorption pool represents a drug solution at the site of absorption, with Kr, Ka, and Ke representing first-order rate constants for drug release, absorption, and total elimination, respectively. The fact that a standard dose form provides immediate drug release suggests that Kr > Ka. Kr Ka, i.e., the release of medication from the dosage form, is the rate-limiting phase for non-immediate release dosage forms. The drug should be released from the dosage form using zero-order kinetics, as illustrated by the equation below:

Kr° = Rate In = Rate Out = Ke Cd Vd

Where, Kr°: Zero-order rate constant for drug release-Amount/ time, Ke: First-order rate constant for overall drug elimination-time, Cd: Desired drug level in the body – amount/volume, and Vd: Volume space in which the drug is distributed in lite.[7]

Figure 1: Schematic representation of the kinetics of sustained-release DDS.

ADVANTAGES OF SUSTAINED RELEASE DRUG DELIVERY DOSAGE FORMS OVER THE CONVENTIONAL DOSAGE FORM[8]

a. Since the frequency of drug administration is decreased, patient compliance can be enhanced, and drug administration can be made more convenient.
b. Blood level variation is reduced as a result of multiple dosing of standard dose forms.
c. Moreover, prolonged release dosage forms provide for effective management of medication absorption by lowering blood level peaks that may occur following administration of a dose of a high availability drug.
d. The safety margin of high-potency medications can be raised, and the incidence of both local and systemic adverse side effects can be minimised in sensitive patients.
e. Overall, the use of continuous release forms increases the dependability of therapy.

DISADVANTAGES OF SUSTAINED RELEASE DRUG DELIVERY DOSAGE FORMS[9]

a. Production costs are more when compared to standard dose forms.
b. The relationship between in vivo and in vitro studies is low.
c. The potential of first pass metabolism has enhanced.

BASIC PHYSIOLOGY OF THE GIT

The stomach is anatomically separated into three sections: the fundus, the body, and the antrum (or pylorus). The fundus and body sections of the proximal stomach serve as a reservoir for ingested materials, whereas the distal part (antrum) is the primary site of mixing motions, working as a pump to effectuate gastric emptying. Gastric emptying happens both when fasting and when fed.[9] Figure 2 represents the anatomy of the stomach.

During a fasting, an interdigestive series of electrical events occur that cycle through the stomach and intestine every 2-3 hours. This is known as the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), and it is further divided into four segments.

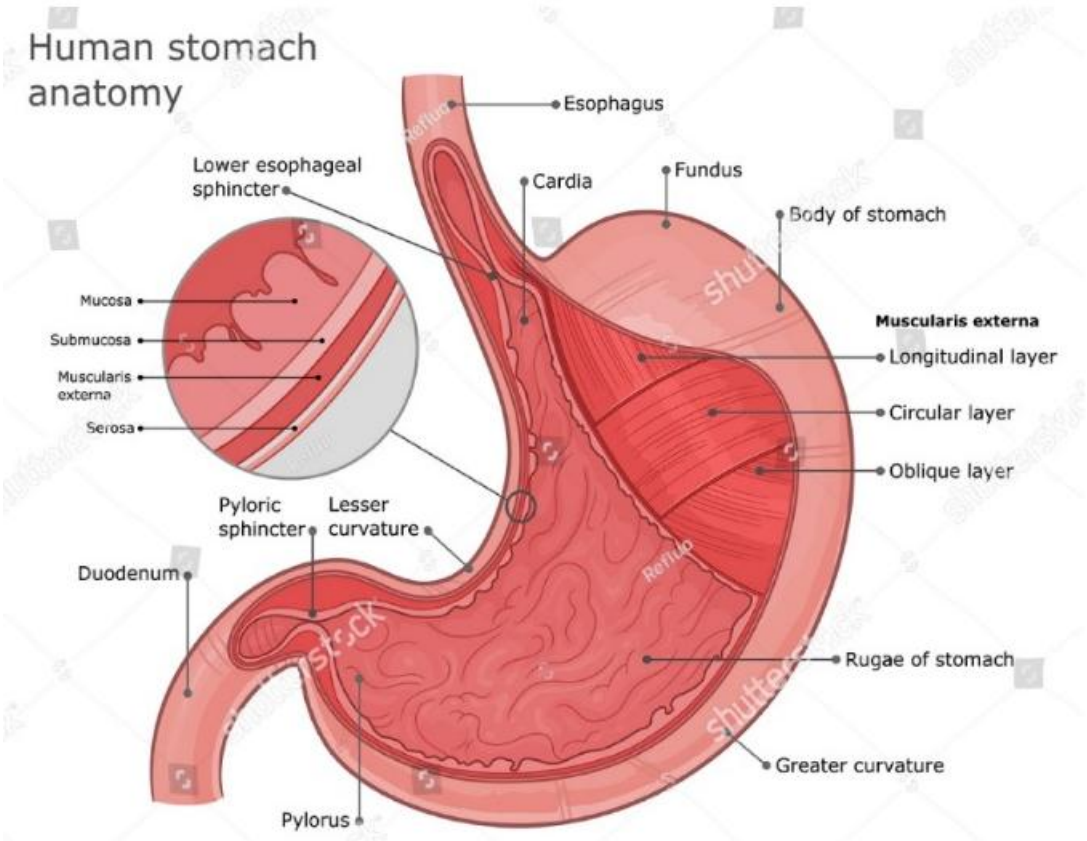

Figure 1: Anatomy of stomach.

After consuming a mixed meal, the pattern of contractions changes from fasted to fed, which is also known as the digestive motility pattern, as seen in Figure 3.

- **Phase 1**-(Basic phase)-lasts 30-60 minutes with rare contractions.
- **Phase 2**-(Preburst phase): 20-40 minutes of intermittent action potential and contractions.
- **Phase 3**-(Burst phase) - last for 10-20 minutes which includes intense and regular contractions for short period.
- **Phase 4**-last for 0-5 minutes and occurs between phase 2 and 1 of 2 consecutive cycles.[10]

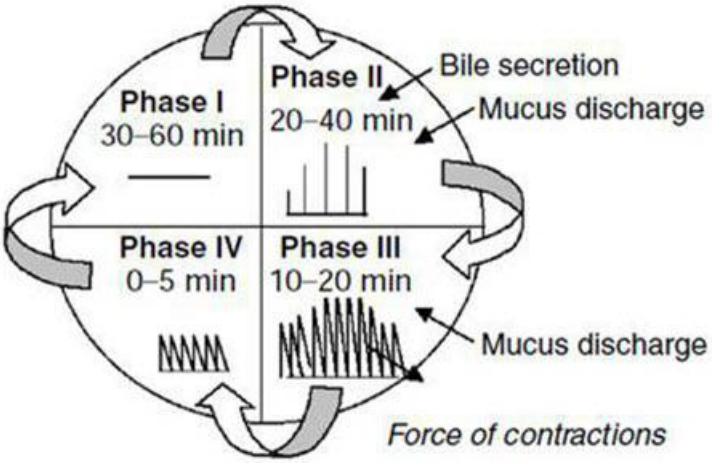

Figure 2: Gastrointestinal motility pattern.

FLOATING DRUG DELIVERY SYSTEM

Floating systems, also known as hydrodynamically controlled systems, are low-density systems with enough buoyancy to float above the gastric contents and remain buoyant in the stomach for an extended period of time without impacting the gastric emptying rate. The

medication is slowly released from the system while the system is floating on the gastric contents. The residual system is discharged from the stomach once the medication is released. As a result, GRT is raised and fluctuations in plasma drug concentration are better controlled. However, in addition to the minimum gastric content required to meet the buoyancy retention principle, a minimum level of floating force (F) is also required to keep the dose form dependably buoyant on the meal's surface (Fig 4). Many buoyant systems have been created, including granules, powders, capsules, tablets, laminated films, and hollow microballoons.[11]

MECHANISM OF FLOATING SYSTEMS[12]

While the system is floating on the stomach contents at the desired rate, the medicine is gently released from the system. Following medication administration, the stomach's residual system is evacuated. In addition to the minimal stomach content required to achieve the buoyancy retention principle, a minimal level of floating force is also required to keep the dose form consistently buoyant on the meal's surface. A novel apparatus for determining resultant weight was reported in the literature to measure the floating force kinetics. The apparatus works by continuously measuring the force equivalent to F as a function of time that is required to keep the submerged objects submerged. The apparatus aids in optimising FDDS in terms of stability to stability and durability of floating forces produced in order to avoid the disadvantages of unexpected intragastric buoyancy capability variations.

F = F buoyancy - F gravity

= (D f - D s) g v

Where, F = Total vertical force, Df = fluid density, Ds = object density, v = volume

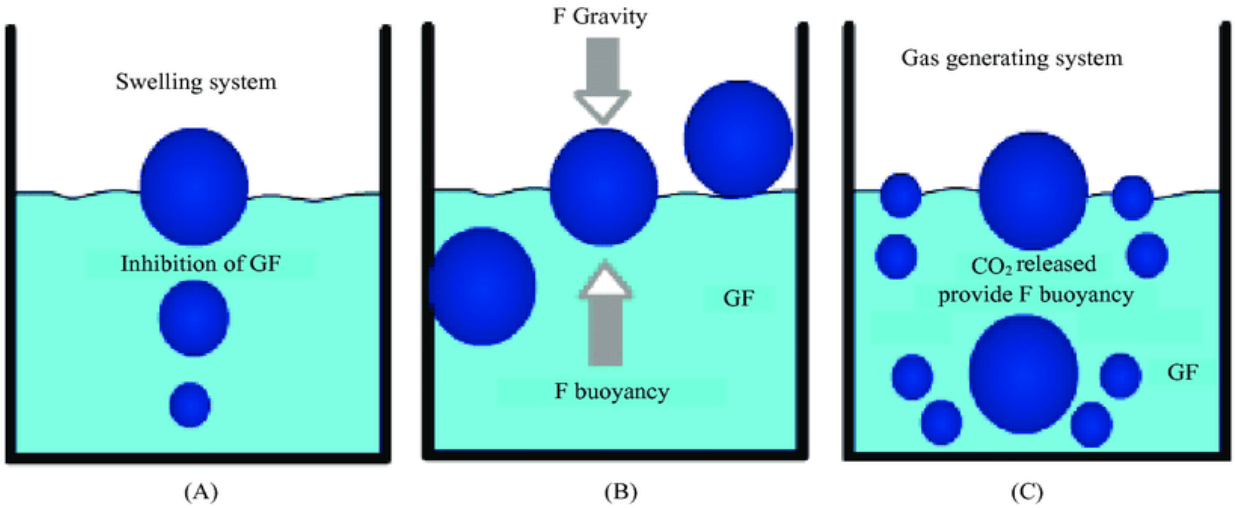

Figure 3: Mechanism of Floating system.

Classification of floating drug delivery systems[13]

According to the principle of buoyancy and Figure 5, which displays the many forms of floating drug delivery systems, two separate technologies have been used in the creation of FDDS.

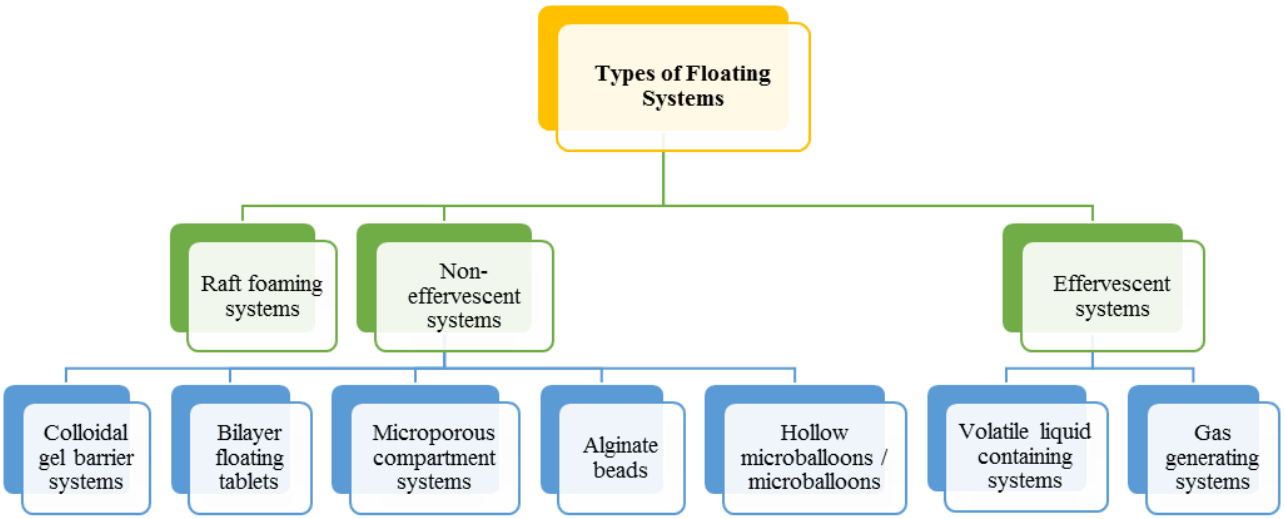

Figure 4: Types of Floating systems.

1. EFFERVESCENT FDDS

This system employs a floating chamber filled with water, vacuum, air, or inert gas. CO_2 can be introduced into the floating chamber as a result of an effervescent reaction between organic acid (citric acid) and carbonate / bicarbonate salts. A matrix constructed with swellable polymers such as chitosan-like polysaccharides, effervescent materials such as citric acid, sodium bicarbonate, and tartaric acid, or chambers containing a liquid that gasifies at body temperature are used in such a system.[14]

2. THE NON-EFFERVESCENT FDDS

It is based on the mechanism of polymer swelling or bioadhesion to the mucosal layer in the GI tract. The most often used excipients in non-effervescent FDDS include gel forming or highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides, and matrix forming materials such as polycarbonate, polyacrylate, polymethacrylate, polystyrene, and bioadhesive polymers such as Chitosan.[15]

TYPES OF NON-EFFERVESCENT FDDS

a. COLLOIDAL GEL BARRIER SYSTEMS (HYDRODYNAMIC BALANCED SYSTEMS)

By extending gastric retention time, this system increases the amount of drug that reaches the absorption site in solution form. It basically combines the drug with gel-forming hydrocolloids to make it float on the stomach content. In such a system, one or more gel-forming cellulose type hydrocolloids are used. HPMC, polysaccharides, and matrix forming polymers such as polycarbophil, polystyrene, and polyacrylate are examples. When the hydrocolloid in the system comes into contact with GI fluid, it hydrates and forms a colloid gel barrier to its surroundings.[16]

b. MICROPOROUS COMPARTMENT SYSTEMS

This system contained a drug reservoir within a microporous compartment with pores on both the top and bottom surfaces. To keep the undissolved drug out, the reservoir compartment's peripheral walls were completely sealed. A novel gastro retentive dosage form based on unfolding polymeric membranes that combines extended dimensions with high rigidity is used. This system can produce large gelatin capsules. In vitro studies showed that the unfolded form was reached within 15 minutes of administration, which was confirmed in vivo with beagle dogs. For at least two hours, the unfolded form was kept. It was determined that the use of this system could improve the therapy of various drugs with a narrow absorption window.[17]

c. ALGINATE BEADS

Calcium alginate was freeze dried and used to create multi-unit floating dosage forms. Dropping sodium alginate solution into aqueous solution of calcium chloride causes precipitation of calcium alginate, resulting in the formation of a porous system that can maintain a floating force for more than 12 hours. When compared to solid beads, which had a short residence time of 1 hour, these floating beads had a longer residence time of more than 5.5 hours.[18]

d. HOLLOW MICROBALLOONSL

Microballoons are non-effervescent gastro-retentive drug delivery systems. Microballoons are spherical empty particles in the strictest sense. These microballoons are typically free-flowing powders made of proteins or synthetic polymers, with a size of less than 200 micrometres. Gastro-retentive Microballoons are low-density systems with enough buoyancy to float over gastric contents and remain in the stomach for an extended period of time. Microballoons can improve patient compliance by reducing dosing frequency, resulting in a better therapeutic effect of short half-life drugs.[19]

PROCESS OF FORMATION OF MICROBALLOONS[20]

The figure 6 will depicts the formation of Microballoons.

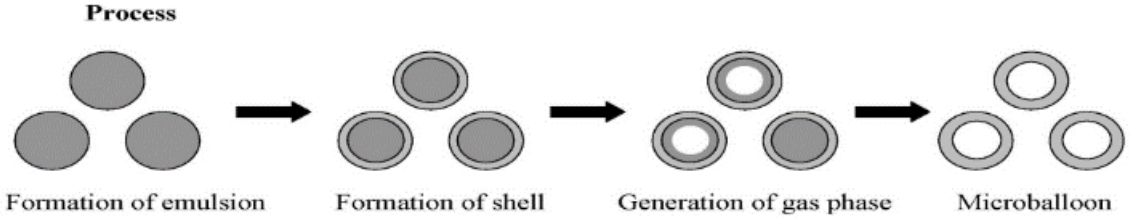

Figure 6: Process of formation of Microballoons.

METHOD OF PREPARATION OF MICROBALLOONS

a. SOLVENT EVAPORATION METHOD

A polymer is dissolved in an organic solvent in this technique, and the drug is either dissolved or dispersed in the polymer solution. The drug solution is then emulsified in an aqueous phase with appropriate additives (surfactants/polymer) to form an oil in water emulsion. The organic solvent is evaporated after the formation of a stable emulsion, either by increasing the temperature under pressure or by continuous stirring. Polymer precipitation occurs at the oil/water interface of droplets as a result of solvent removal, forming cavities and hollowing them out to give them floating properties. Polymers used in the development of such systems include Eudragit, HPMC K4M, and ethyl cellulose,

among others. To create a homogeneous polymer solution, polymers are combined with drugs and dissolved in ethanol, acetone, or dichloromethane solutions, either alone or in combination. Following that, the solution is poured into 100 mL of liquid paraffin and rotated at 1500 rpm. The emulsion is formed and heated for three hours at 35 degrees Celsius. After forming a stable emulsion, the acetone or dichloromethane is completely evaporated, and the solidified microballoons are filtered through Whatman filter paper. The hollow microballoons provide the floating and sustained properties.[21] Figure 7 depicts the solvent evaporation method.

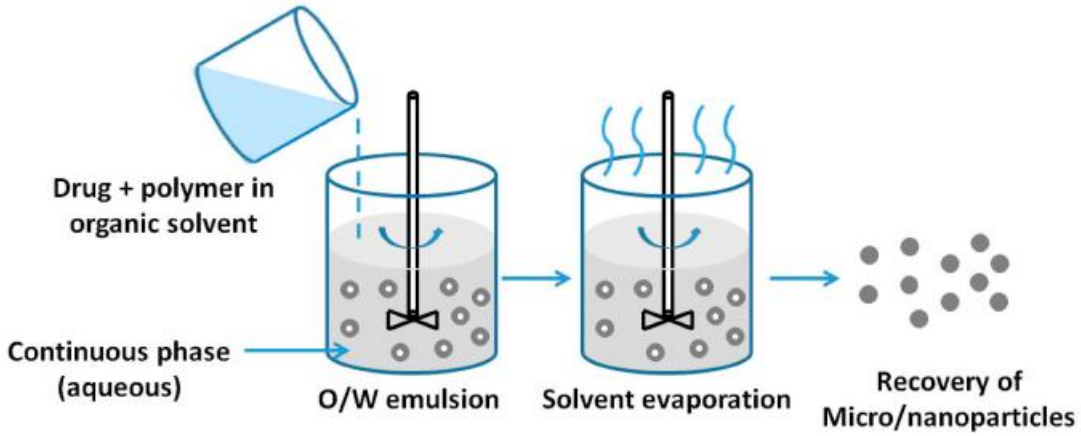

Figure 7: Solvent evaporation method.

b. EMULSION SOLVENT DIFFUSION METHOD

The affinity between the drug and the organic solvent is greater in the emulsion solvent diffusion method than between the organic solvent and the aqueous solvent. Despite the fact that the organic solvent is miscible, the drug is dissolved in it and the solution is dispersed in the aqueous solvent to form emulsion droplets. The organic solvent gradually diffuses out of the emulsion droplets into the surrounding aqueous phase, while the aqueous phase diffuses into the droplets where the drug crystallises.[22] Figure no 8 show the emulsion solvent diffusion method.

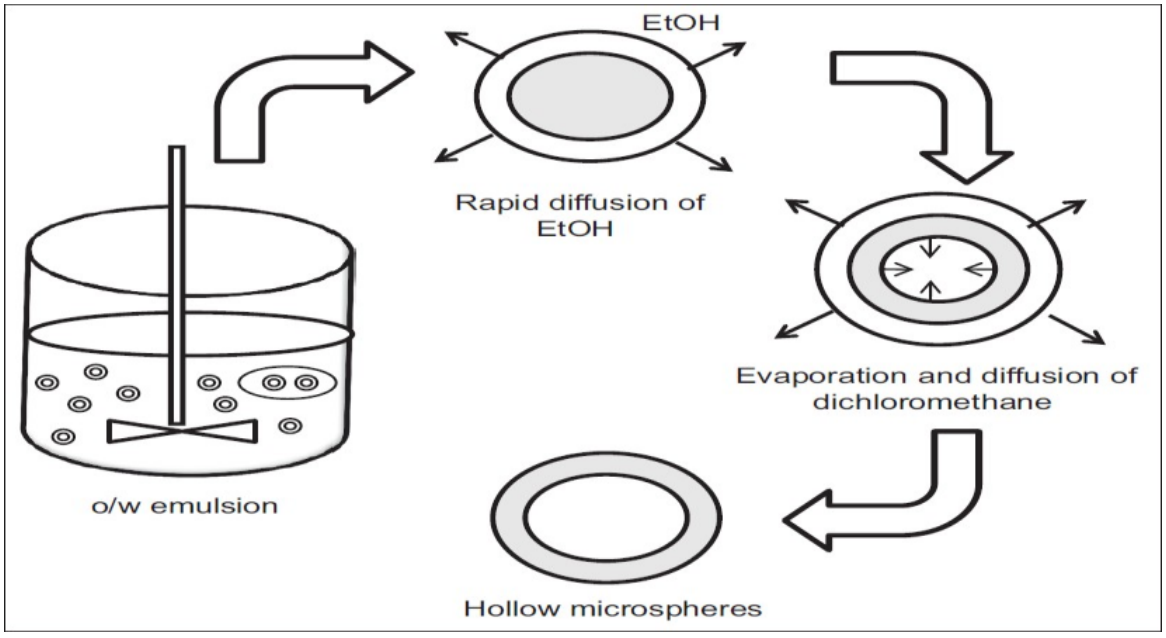

Figure 8: Emulsion Solvent Diffusion method.

IONOTROPIC GELATION METHOD

An ionotropic gelation technique has been widely used since the use of Alginates, Gellan gum, Chitosan, and Carboxymethyl cellulose for the encapsulation of drugs and even cells. Natural polyelectrolytes contain certain anions in their chemical structure, despite their ability to coat the drug core and act as release rate retardants. By combining with polyvalent cations, these anions form meshwork structures and induce gelation by binding primarily to anion blocks. Dropping a drug-loaded polymeric solution into an aqueous solution of polyvalent cations produces the hydrogel beads. Under

mild conditions, biomolecules can also be loaded into these beads and retain their three-dimensional structure.[23] and the figure 9 which shows the Ionotropic gelation method

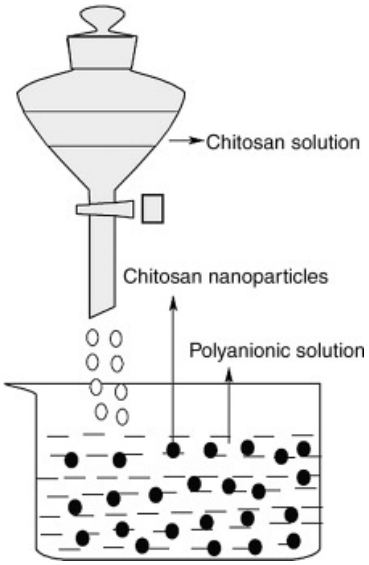

Figure 9: Ionotropic gelation method.

d. SPRAYED DRYING METHOD

Spray drying is by far the most popular particulate formation and drying method. It is an ideal process because it can achieve the desired particle size, bulk density, and particle shape distribution in a single step. To begin, a polymer slurry is formed inside an appropriate organic volatile solvent such as dichloromethane, acetone, and so on. Following spraying the mixture into the drying chamber, a gradient of solute concentration forms within the small droplet, with the highest concentration at the droplet surface. This is due to the fact that the time required for the solute to diffuse is longer than the time required for the solvent in the drops to evaporate, even during the drying process. The formation of microballoons is then followed by the development of a solid shell. The solid products are usually separated from the gases using a cyclone separator, while the trace amounts of solvent are removed by evaporation and the product lines are stored for later use.[24] and the figure 10 which shows the sprayed drying method

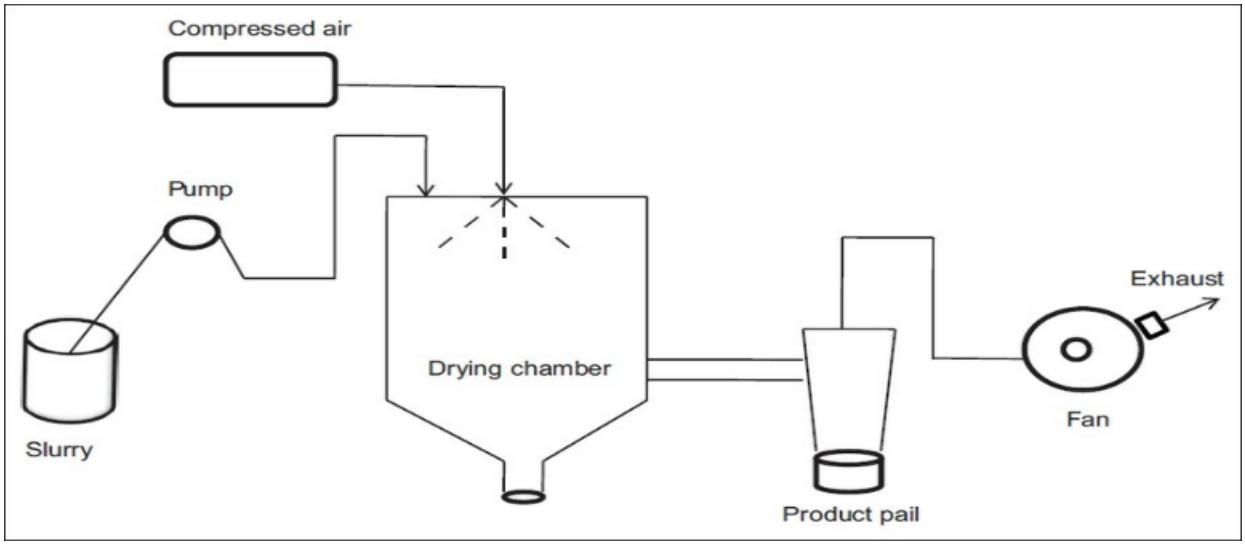

Figure 10: Sprayed Drying Method.

CHARACTERIZATION AND EVALUATION PARAMETERS FOR HOLLOW MICROBALLOONS

1. PARTICLE SIZE[25]

An optical microscope is used to measure particle size, and mean particle size is calculated by measuring 200-300 particles with a calibrated ocular micrometre. The different sizes of microballoons and their distribution in each batch are determined by sieving in a mechanical shaker with a nest of standard sieves (ASTM) and a 15-minute shaking period. Using the following formula, the

particle size distribution is determined and the mean particle size of microballoons is calculated.

Mean particle size = ∑(mean particle size of the fraction× weight fraction) / ∑(weight fraction)

2. ANGLE OF REPOSE[26]

Angle of repose (θ) of all the formulations was determined by using a fixed funnel method, which measures the resistance to particle flow and calculated as follows.

ETan θ = 2H/D

Where **H** is height and **D** is the diameter microballoons heap of the pile, which is formed on a graph paper after making the microballoons flow from the glass funnel.

3. *IN VITRO* DRUG RELEASE STUDY[27]

The rate of drug release from microballoons was measured using the USP dissolution testing apparatus I. (Basket type). At 37 0.5°C and 100 rpm, 900 mL of 0.1 N HCl was used for the dissolution test. For the test, microballoons containing drug were used. For 12 hours, aliquots (5 mL) were withdrawn at hourly intervals. The equivalent volume of dissolution medium was used to replace the samples. The samples were filtered through Whatman filter paper, and the solutions were analysed with a UV spectrophotometer at 228 nm. PCP Disso v2.08 Software was used to calculate the cumulative percentage drug release.

4. *IN VITRO* EVALUATION OF FLOATING ABILITY[28]

The floating behaviour of hollow microballoons was investigated using a USP dissolution test apparatus II and 900 ml of 0.1 N HCl containing 0.02% Tween 80 as a surfactant. The medium was agitated with a paddle that rotated at 100 rpm and was kept at 37°C. After 10 hours, the floating and settled portions of microballoons were separated. The microballoons were weighed after drying. Using the following equation, the percentage of floating microballoons was calculated.

$$\% \text{ Floating Microballoons} = \frac{\text{Weight of Floating Microballoons}}{\text{Total weight of Microballoons}} \times 100$$

5. SCANNING ELECTRON MICROSCOPY[29]

The SEM analysis sample was created by sprinkling microballoons onto one side of the double adhesive stub. The stubs were then coated with gold using a polaran SC 500 sputter coater to neutralise the electrons and achieve a clear morphology of the spheres. The optical micrographs were also taken with a Leica storeoscan 440. SEM was used on microballoons after and before dispersing them in 0.1N HCl.

6. BUOYANCY TEST[29]

At 37°C-0.5°C, microballoons were dispersed in 900 mL of either enzyme-free simulated gastric fluid (HCl/NaCl solution containing 0.02% Tween-80; pH 1.2) or enzyme-free simulated intestinal fluid ($KH_2 PO_4$ / NaOH solution containing 0.02% Tween-80; pH 7.4). The dispersing medium was stirred at 100 g using the Chinese Pharmacopoeia appendix Xc. No 2.31 standard paddle method. The number of microballoons that remained buoyant on the test medium was used to assess buoyancy capacity.

7. STABILITY STUDIES[30]

If studies are performed at normal temperatures during storage, they will take longer, so it would be more convenient to conduct accelerated stability studies where the product is stored under extreme temperature conditions. Optimized formulation sealed in aluminium packaging coated inside with polyethylene, and various samples kept in humidity chamber maintained at 40°C and 75% RH for 2 months. At the end of the studies, samples were examined for physical appearance, drug content, and drug release.

ADVANTAGES OF HOLLOW MICROBALLOONS[31]

- Enhanced bioavailability
- Enhanced first-pass biotransformation
- Sustained drug delivery/reduced frequency of dosing
- Targeted therapy for local ailments in the upper GIT
- Reduced fluctuations of drug concentration
- Improved selectivity in receptor activation
- Reduced counter-activity of the body
- Extended time over critical (effective) concentration
- Minimized adverse activity at the colon
- Site specific drug delivery

LIMITATION OF HOLLOW MICROBALLOONS[32]

- The controlled release dosage form's release rate may vary depending on a number of factors such as food and the rate of transit through the gut.
- Variations in the rate of release from one dose to another.
- Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity.
- These dosage forms should not be crushed or chewed.

APPLICATIONS OF FLOATING MICROBALLOONS[33]

Floating microballoons have a variety of applications for drugs with low bioavailability due to a narrow absorption window in the upper gastrointestinal tract. It remains at the site of absorption, increasing bioavailability. These are summarised below.

1. **Sustained drug delivery:** Hollow microballoons of nonsteroidal anti-inflammatory drugs are very effective for controlled release while also reducing the major side effect of gastric irritation; for example, floating microballoons of Indomethacin are very beneficial for rheumatoid arthritis patients.

2. **Site-Specific Drug Delivery:** Floating microballoons can greatly improve stomach pharmacotherapy by allowing for local drug release, resulting in high drug concentrations at the gastric mucosa, eradicating Helicobacter pylori from the stomach's submucosal tissue and allowing for the treatment of stomach and duodenal ulcers, gastritis, and oesophagitis.
3. **Absorption enhancement:** Drugs with low bioavailability due to site-specific absorption from the upper gastrointestinal tract are potential candidates for formulation as floating drug delivery systems, which would maximise absorption.
4. **Enhanced Solubility:** Floating microballoons are particularly effective in the delivery of sparingly soluble and insoluble drugs. It is well known that as a drug's solubility decreases, the time available for drug dissolution decreases, and thus transit time becomes a significant factor affecting drug absorption. By restricting such drugs to the stomach, hollow microballoons may avoid the possibility of solubility becoming the rate-limiting step in release for weakly basic drugs that are poorly soluble at an alkaline pH.
5. **As carriers:** Floating microballoons can be used as carriers for drugs with so-called absorption windows, which are substances such as antiviral, antifungal, and antibiotic agents (Sulphonamides, Quinolones, Penicillins, Cephalosporins, Aminoglycosides, and Tetracyclines) that are only taken up from very specific sites of the GI mucosa.

FUTURE POTENTIAL OF FLOATING HOLLOW MICROBALLOONS

It is expected that various new products utilising gastro retentive drug delivery technologies will amplify this possibility. Further research may focus on the microballoon concepts:

- Development of a variety of gastro-retentive drug delivery systems, each with a narrow GRT for use based on clinical need, such as dosage and disease stage.
- Establishment of a minimal cut-off size above which dosage forms are retained in the GIT for an extended period of time.
- Design and development of gastro-retentive drug delivery systems as a useful strategy for treating gastric and duodenal cancers, as well as Parkinson's disease.
- Creation of various anti-reflux formulations based on gastro-retentive technologies.
- Investigating the use of antibiotics to eradicate Helicobacter pylori.

CONCLUSION

According to a recent review, the floating hollow microballoons demonstrated gastro retentive controlled release delivery system, which promises to be a potential approach for gastric retention.

Microballoons have a low density and enough buoyancy to float over gastric contents and remain in the stomach for an extended period of time. When the drug floats over gastric contents, it is released slowly at the desired rate, resulting in less fluctuation in plasma drug concentration. It is an effective method of increasing bioavailability.

Optimized microballoons will play an important role in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene and genetic materials, and safe, targeted, and effective *in vivo* delivery.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCE

1. Ayalasomayajula LU, Navya K, Earle RR, Pravallika AA. Review on non effervescent gastro retentive drug delivery systems-microballoons. Asian Journal of Pharmaceutical Research. 2020; 10(4): 312-8.
2. Rouge N, Buri P, Doelker E. Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery. International journal of pharmaceutics. 1996 Jun 14; 136(1-2): 117-39.
3. Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery system. Expert Opin Drug Deliv., 2006; 3(2): 217-233.
4. Kawade AV, Ashwini V. A review of microballoons: An advance technique for Gastroretentive drug delivery system. International Journal of Research in Pharmacy and Pharmaceutical Sceinces. 2019; 4(4): 3-4.
5. Jain S, Gahlyan M. Oral controlled release drug delivery system-a review. PharmaTutor. 2014; 2(8): 170-8.
6. Ratnaparkhi MP, Gupta Jyoti P. Sustained release oral drug delivery system-an overview. Terminology. 2013; 3(4): 10-22270.
7. Nautyal U, Gupta D. Oral Sustained Release Tablets: An Overview with a Special Emphasis on Matrix Tablet. Intl Journal H & Bio Sci., 2020; 3(1): 06-13.
8. Shukla AK, Kumar M, Bishnoi RS, Kachawa VS, Jain CP. Dosage from design of sustained release drug delivery systems: An overview. Asian Journal of Biomaterial Research. 2017; 4(3): 1-7.
9. Parmar PD, Pande S, Shah SH, Sonara N, Patel GH. Floating drug delivery system: A novel approach to prolong gastric retention. World J Pharmacy Pharm Sci., 2014; 3(4): 418-44.
10. Bhardwaj V, Nirmala HS. Floating drug delivery system: A review. Pharmacophore. 2013; 4(1): 26-38.

11. Mayavanshi AV, Gajjar SS. Floating drug delivery systems to increase gastric retention of drugs: A Review. Research Journal of Pharmacy and Technology. 2008; 1(4): 345-8.
12. Khan R, Ojha A, Arora R, Upadhyay K, Chopra H. RECENT TRENDS IN GASTRORETENTIVE FLOATING DRUG DELIVERY SYSTEM-A REVIEW. system. 2017; 16: 3-4.
13. Bhosale AR, Shinde JV, Chavan RS. A comprehensive review on floating drug delivery system (FDDS). Journal of Drug Delivery and Therapeutics. 2020; 10(6): 174-82.
14. Lodh H, Sheeba FR, Chourasia PK, Pardhe HA, Pallavi N. Floating drug delivery system: A brief review. Asian Journal of Pharmacy and Technology. 2020; 10(4): 255-64.
15. Jassal M, Nautiyal U, Kundlas J, Singh D. A review: Gastroretentive drug delivery system (grdds). Indian journal of pharmaceutical and biological research. 2015; 3(1): 82.
16. Niharika MG, Krishnamoorthy K, Akkala M. Overview on floating drug delivery system. Int J App Pharm., 2018; 10(6): 65-71.
17. Kumari B. Recent Development inFloating Drug Delivery System: A Review. Asian Journal of Pharmacy and Pharmacology. 2018; 4(2): 131-9.
18. Jamil F, Kumar S, Sharma S, Vishvakarma PS, Singh L. Review on stomach specific drug delivery systems: development and evaluation. Int J Res Pharm Biomed Sci., 2011; 2(4): 14271433.
19. Patel S, Aundhia C, Seth A, Shah N, Pandya K, Shah C, Ramani V, Javia A. Microballoons: a novel approach in gastro-retention floating drug delivery system (FDDS). An International Journal of Pharmaceutical Science. 2016; 7(2): 332-45.
20. Hafeez A, Maurya A, Singh J, Mittal A, Rana L. An overview on floating microballoons: Gastro Retention Floating drug delivery system (FDDS). The Journal of Phytopharmacology. 2013; 2(3): 1-2.
21. Hajare PP, Rachh PR. Gastroretentive microballoons: a novel approach for drug delivery. International Journal of Pharmaceutical Sciences and Research. 2020; 11(3): 1075-83.
22. Negi R, Goswami L, Kothiyal P. Microballoons: A better approach for gastro retention. Indian Journal of Pharmaceutical and Biological Research. 2014 Apr 1; 2(2): 100.
23. Dhole AR, Gaikwad PD, Bankar VH, Pawar SP. A review on floating multiparticulate drug delivery system-A novel approach to gastric retention. Int J Pharm Sci Rev Res., 2011; 2: 205-11.
24. Kothawade S, Pande V, Bole S, Autade K, Sumbe R, Albhar S, Raut K. A Floating System for Drug Delivery using Microballoons. 2022; 7: 1-9.
25. Mukund JY, Kantilal BR, Sudhakar RN. Floating microspheres: a review. Brazilian Journal of Pharmaceutical Sciences. 2012; 48: 17-30.
26. Gangadharappa HV, Biswas S, Getyala A, Gupta VN, Pramod Kumar TM. Development, in vitro and in vivo evaluation of novel floating hollow microspheres of rosiglitazone maleate. Der Pharmacia Lettre., 2011; 3(4): 299-316.
27. Rao MR, Borate SG, Thanki KC, Ranpise AA, Parikh GN. Development and in vitro evaluation of floating rosiglitazone maleate microspheres. Drug development and Industrial pharmacy. 2009; 35(7): 834-42.
28. Shirolkar SV, Tawar MG, Gandhi NS, Deore NB. Development and evaluation of floating microballoonss of Pioglitazone hydrochloride using ethyl cellulose. Der Pharmacia Lettre., 2010; 2(5): 261-77.
29. Ramachandran S, Shaheedha SM, Thirumurugan G, Dhanaraju MD. Floating controlled drug delivery system of famotidine loaded hollow microspheres (microballoons) in the stomach. Current Drug Delivery. 2010; 7(1): 93-7.
30. Gandhi NS, Shirolkar SV, Tawar MG. Development and evaluation of microballoons of pioglitazone hydrochloride using eudragit S-100. International Journal of Pharmaceutical Sciences and Research. 2012; 3(1): 201.
31. Garg RG, Gupta GD. Progress in controlled gastroretentive delivery systems. Tropical journal of pharmaceutical research. 2008; 7(3): 1055-66.
32. Raju T, Sarkar T, Patil BS, Raskar AA. Microballoons-Novel Carriers in Gastro Retentive Drug Delivery. Research Journal of Pharmaceutical Dosage Forms and Technology. 2015; 7(4): 266-73.
33. Faizi SM, Rathi PN, Tajane SV, Burghate RM, Wasankar SR. Drug delivery to absorption window through floating microspheres: A Review. Research Journal of Pharmaceutical Dosage Forms and Technology. 2012; 4(3): 135-42.