*The Pharmaceutical and Chemical Journal*, 2024, 11(6):24-29

*Available online www.tpcj.org*

**Review Article**

**ISSN: 2349-7092**
**CODEN(USA): PCJHBA**

# A Review on Floating Microsphere as Gastroretensive Drug Delivery

**Imran Khan[*1], Dr. Gaurav Bhaduka[2], Dr. Dilip Agrawal[3]**

[*1]Research Scholar, Mahatma Gandhi College of Pharmaceutical Sciences, Jaipur, Rajasthan
Mail id: imrankhantahir@gmail.com

**Abstract** The floating microsphere's purpose is to improve gastric retention time. Floating drug delivery systems are lower in bulk thickness than gastric juice and remain floating on gastric juice for a long period of time without impacting the gastric-emptying rate and increasing bioavailability. arious gastroretentive dosage forms are available, including tablets, capsules, pills, laminated films, granules and powders. Floating microspheres to improve patient compliance by decreasing dosing frequency, better the rapeutic effect of short half-life drugs can be achieved. Enhanced absorption of drugs which solubilize only in stomach, Gastric retention time is increased because of buoyancy. Floating microspheres are prepared by solvent diffusion and evaporation methods to create the hollow inner core. Floating microspheres is one among the several approaches to gastroretention, like mucoadhesion, flotation, sedimentation, expansion, modified shape systems etc. Floating microspheres have been gaining attention due to the uniform distribution of these multiple-unit dosage forms in the stomach, which results in more reproducible drug absorption and reduced risk of local irritation.

**Keywords:** Floating Microspheres, Gastroretensive, Patient Compliance, Diffusion

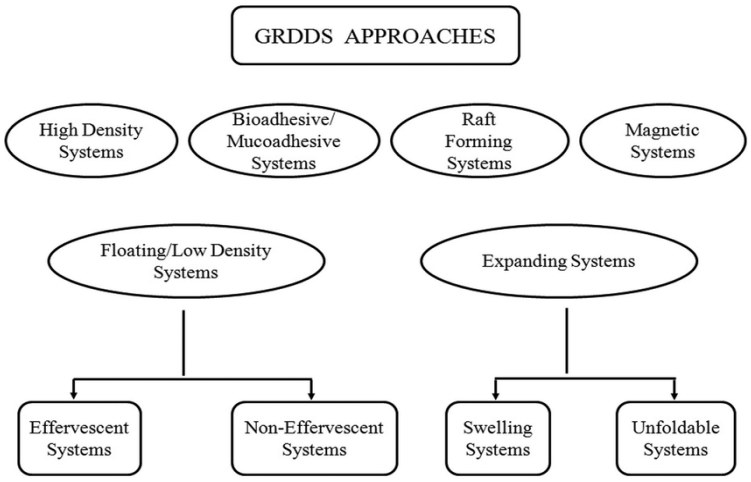
## Introduction

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, low density (floating) systems that causes buoyancy in gastric fluid mucoadhesive systems that causes bioadhesion to stomach mucosa, unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach, superporous hydrogel systems, magnetic systems etc.

## Advantages of gastro-retentivedrug delivery systems

- The bioavailability of therapeutic agents can be significantly enhanced especially for those which get metabolized in the upper GIT by this gastroretentive drug delivery approach in comparison to the administration of non gastroretentive drug delivery. There are several different factors related to absorption and transit of the drug in the gastrointestinal tract (GIT) that act concomitantly to influence the magnitude of drug absorption.
- For drugs with relatively short half- life, sustained release may result in a flip- flop pharmacokinetics and also enable reduced frequency of dosing with improved patient compliance.

- They also have an advantage over their conventional system as it can be used to overcome the adversities of the gastric retention time (GRT) as well as the gastric emptying time (GET). As these systems are expected to remain buoyant on the gastric fluid without affecting the intrinsic rate of employing because their bulk density is lower than that of the gastric fluids.
- Gastroretentive drug delivery can produce prolong and sustain release of drugs from dosage forms which avail local therapy in the stomach and small intestine. Hence they are useful in the treatment of disorders related to stomach and small intestine.
- The controlled, slow delivery of drug form Gastroretentive dosage form provides sufficient local action at the diseased site, thus mini mizingor eliminating systemic exposure of drugs. This site-specific drug delivery reduces undesirable effects of side effects.
- Gastroretentive dosage forms minimize the fluctuation of drug concentrations and effects. Therefore, concentration dependent adverse effects that are associated with peak concentrations can be presented. This feature is of special importance for drug with a narrow therapeutic index.
- Gastroretentive drug delivery can minimize the counter activity of the body leading to higher Drug efficiency.
- Reduction of fluctuation in drug concentration makes it possible to obtain improved selective receptor activation.
- The sustained mode of drug release from Gastroretentive doses form enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the chemical outcomes.




**Microsphere**

Microspheres are defined as "Monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles" (or) can be defined as structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level. Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 μm to 1000 μm). Microspheres are sometimes referred to as microparticles. Biodegradable synthetic polymers and modified natural products such as starches, gums, proteins, fats and waxes. The natural polymers include albumin and gelatin, the synthetic polymer include poly lactic acid and polyglycolic acid. The solvents used to dissolve the polymeric materials chosen according to the polymer and drug solubility and stabilities, process safety and economic considerations. Microspheres for oral use have been employed to sustain the drug release, and to reduce or eliminate gastrointestinal tract irritation. In addition, multiparticulate delivery systems spread out more uniformly in the gastrointestinal tract. This results in more reproducible drug absorption and reduces local irritation when compared to single-unit dosage

forms such as no disintegrating, polymeric matrix tablets. Unwanted intestinal retention of the polymeric material, which may occur with matrix tablets on chronic dosing, can also be avoided.

**Advantages**

1. Microspheres provide constant and prolonged therapeutic effect.
2. Reduces the dosing frequency and thereby improve the patient compliance.
3. They could be injected into the body due to the spherical shape and smaller size.
4. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
5. Microsphere morphology all owes a controllable variability in degradation and drug release.

**Mechanism of Microsphere Floating**

They communicate with the acid in the stomach after administration of the dosage type, since the outer layer of the floating microspheres includes polysaccharides, polymer hydrates and forms a colloidal gel barrier that governs the movement of the drug and the gastric fluid in and out of the microspheres. The air molecule traps inside it because of this membrane, because it lowers its bulk density and lets it swim across the gastric fluid surface. For the floatation of the floating dosage type, a smaller amount of gastric fluid is required for maximum cases. Mechanism of drug release form microspheres following method.

1. Erosion
2. Diffusion
3. Osmosis

**Limitation**

Some of the disadvantages were found to be as follows:

1. The modified release from the formulations.
2. The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit though gut.
3. Differences in the release rate from one dose to another.
4. 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.
5. Dosage forms of this kind should not be crushed or chewed 21.

**Criteria for microsphere preparation:**

Incorporation of solid, liquid or gases into one or more polymeric coatings can be done by micro encapsulation technique 22. The different methods used for various microspheres preparation depends on particle size, route of administration, duration of drug release and these above characters related to rpm, method of cross linking, drug of cross linking, evaporation time, co-precipitation etc23. Preparation of microspheres should satisfy certain criteria 24:

1. The ability to incorporate reasonably high concentrations of the drug.
2. Stability of the preparation after synthesis with a clinically acceptable shelf life.
3. Controlled particle size and dispersability in aqueous vehicles for injection.
4. Release of active reagent with a good control over a wide time scale.
5. Biocompatibility with a control lable biodegradability.
6. Susceptibility to chemical modification.

**Method of Preparation of Floating Microspheres**

Wide ranges of developmental techniques are available for the preparation of Gastroretentive floating microspheres. However, solvent evaporation technique and ionotropic gelation method have been extensively employed by large number of scientific investigators worldwide to explore the different vistas of floating microspheres. During the preparation of floating controlled release microspheres, the choice of optimal method has utmost relevance for the

efficient entrapment of active constituents. Selection of fabrication technique generally depends upon the nature of the polymer, the drug, and their intended use.

**Solvent Evaporation Technique**

This technique is widely employed by large number of pharmaceutical industries to obtain the controlled release of drug. This approach involves the emulsification of an organic solvent (usually methylene chloride) containing dissolved polymer and dissolved/dispersed drug in an excess amount of aqueous continuous phase, with the aid of an agitator. The concentration of the emulsifier present in the aqueous phase affects the particle size and shape. When the desired emulsion droplet size is formed, the stirring rate is reduced and evaporation of the organic solvent is realized under atmospheric or reduced pressure at an appropriate temperature. Subsequent evaporation of the dispersed phase solvent yields solid polymeric microparticles entrapping the drug. The solid microparticles are recovered from the suspension by filtration, centrifugation, or lyophilisation. For emulsion solvent evaporation, there are basically two systems which include oil-in-water (o/w) and water-in-oil (w/o) type.

**Oil-In-Water Emulsion Solvent Evaporation Technique**

In this process, both the drug and the polymer should be insoluble in water while a water immiscible solvent is required for the polymer. In this method, the polymer is dissolved in an organic solvent such as dichloromethane, chloroform, or ethyl acetate, either alone or in combination. The drug is either dissolved or dispersed into polymer solution and this solution containing the drug is emulsified into an aqueous phase to make an oil-in water emulsion by using a surfactant or an emulsifying agent. After the formation of a stable emulsion, the organic solvent is evaporated either by increasing the temperature under pressure or by continuous stirring. Solvent removal from embryonic microspheres determines the size and morphology of the microspheres. It has been reported that the rapid removal of solvent from the embryonic microspheres leads to polymer precipitation at the o/w interface. This leads to the formation of cavity in microspheres, thus making them hollow to impart the floating properties. Oil-in-water emulsion is widely used than water-in-oil due to simplicity of the process and easy cleans up requirement for the final product.

**Oil-in-Oil Emulsification Solvent Evaporation Technique**

This oil-in-oil (sometimes referred as water-in-oil) emulsification process is also known as non aqueous emulsification solvent evaporation. In this technique, drug and polymers are codissolved at room temperature into polar solvents such as ethanol, dichloromethane, acetonitrile etc. with vigorous agitation to form uniform drug–polymer dispersion. This solution is slowly poured into the dispersion medium consisting of light/heavy liquid paraffin in the presence of oil soluble surfactant such as Span. The system is stirred using an overhead propeller agitator at 500 revolutions per minute (rpm) and room temperature over a period of 2–3 h to ensure complete evaporation of the solvent. The liquid paraffin is decanted and the microparticles are separated by filtration through a Whitman filter paper, washed thrice with n-hexane, air dried for 24 h and subsequently stored in desiccators [34-38]. Span 60 is generally used which is non- ionic surfactant. Span 60 has an HLB value of 4.3 and acts as a droplet stabilizer and prevents coalescence of the droplets by localizing at the interface between the dispersed phase and dispersion medium.

**Ionotropic Gelation Method**

In this method, cross linking of the polyelectrolyte takes place in the presence of counter ions to form gel matrix. This technique has been generally employed for the encapsulation of large number of drugs. Polyelectrolyte such as sodium alginate having a property of coating on the drug core and acts as release rate retardant contains certain anions in their chemical structure. These anions forms meshwork structure by combining with polyvalent cations and induced. gelation. Microspheres are prepared by dropping drug loaded polymeric solution using syringe into the aqueous solution of polyvalent cations. The cations diffuses into the drug loaded lymeric drops, forming a three dimensional lattice of ionically cross linked moiety. Microspheres formed left into the original solution for sufficient time period for internal gelification and they are separated by filtration. Natural polymers such as alginates can be used to improve drug entrapment and are widely used in the development of floating microspheres.

**Polymers Used in Floating Microspheres**

A number of different substances both biodegradable as well as nonbiodegradable have been investigated for the preparation of microspheres; these materials include polymers of natural origin or synthetic origin and also semisynthetic substances. Microspheres can be prepared by using both hydrophilic and hydrophobic polymers.

**Hydrophilic polymers**

These are includes gelatin, agar, egg albumin, starch, chitosan, cellulose derivatives; HPMC, DEAE cellulose.

**Hydrophobic polymers**

These are include ethyl cellulose, polylactic acid, PMMA, acrylic acid esters etc.

**Biodegradable polymers**

These materials also slowly disappear from the site of administration; however it occurs in response to a chemical reaction such as hydrolysis.

*Example:* Polylactic acid (PLA), poly glycolic acid (PGA), Polycaprolactone (PCL) and several generic classes such as the poly anhydrides and poly orthoesters.

**Non-Biodegradable Hydrophobic Polymers**

These materials are inert in the environment of use, are eliminated or extracted intact from the site of administration.

*Example:* Polyethylene vinyl acetate (EVA), Polydimethyl siloxane (PDS), Polyether urethane (PEU), Ethyl cellulose (EC), Cellulose acetate (CA), Polyethylene (PE) and Polyvinyl chloride (PVC), Acrycoat, Eudragit S etc.

**Reference**

[1]. Streubel A, Siepmann J, Bodmeier R. Multiple unit Gastroretentive drug delivery: a new preparation method for low density microparticles. J Microencapsul 2003; 20: 329-47.

[2]. Goole J, Vanderbist F, Aruighi K. Development and evaluation of new multiple-unit levodopa sustained-release floating dosage forms. Int J Pharm 2007; 334: 35-41.

[3]. Shrma S, Pawar A. Low density multiparticulate system for pulsatile release of meloxicam. Int J Pharm 2006; 313: 150-58.

[4]. Santus G, Lazzarini G, Bottoni G, Sandefer EP, Page RC, Doll WJ, Ryo UY, Digenis GA. An in vitro- in vivo investigation of oral bioadhesive controlled release furosemide formulations. Eur J Pharm Biopharm 1997;44: 39-52.

[5]. Klausner EA, Lavy E, Friedman M, Hoffman A. Expandable gastroretentive dosage forms. J Control Release 2003; 90: 143-62.

[6]. Deshpande AA, Shah N, Rhodes CT, Malik W. Development of a novel controlled-release system for gastric retention. Pharm Res 1997; 14: 815-19.

[7]. Park K. Enzyme-digestible swelling as platforms for long-term oral drug delivery: synthesis and characterization. Biomaterials 1988; 9: 435.

[8]. Fujimori J, Machida Y, Nagai T. Preparation of a magnetically-responsive tablet and configuration of its gastric residence in beagle dogs. STP Pharma Sci 1994; 4: 425-30.

[9]. Amit Kumar Nayak, RumaMaji, Biswarup Das; Gastroretentive Drug Delivery Systems: A Review; Asian Journal of Pharmaceutical and Clinical Research, 2010;3(1):2-10

[10]. Klusner EA, Eyal S, Lavy E, Friedman M, Hoffman A; Novel Levodopa Gasrtroretentive Dosage form: In Vivo Evaluation in Dogs; J Control Release 2003; 88: 117-26.

[11]. Hoffman A; Pharmacodynamic aspects of sustained release preparation; A Drug Delivery; Rev 1998; 33:185-99.

[12]. Devkant Sharma, Anjali Sharma; Gastroretentive Drug Delivery System - a mini review; Asian pacific Journal of Health Sciences, 2014; 1(2): 80-89.

[13]. Robinson J, Lee R. Controlled Drug Delivery, 2nd edition, 1987: pg 418.

[14]. Bardonnet PL, Faivre V, Pugh WJ, Piffaretti JC, Falson F; Gastroretentive Dosage Forms; Journal of Controlled Release, 2006; 111:1-18.

[15]. Arora S, Javed A, Ahuja A, Khar RK, Baboota S; Floating Drug Delivery System: A Review; AAPS Pharm Sci Tech, 2000;6(3):372-390.
[16]. Patel GM, Patel HR, Patel M.; Floating drug delivery system an innovative approaches to prolong gastric retention; Pharmainfo.net 2007.
[17]. Vedha Hari; The Recent Developments on Gastric Floating Drug Delivery Systems: An Overview; Int Journal pharmtech Res.2010; 2(1): 524-534.
[18]. A. Badoni, A. Ojha, G. Gnanarajani, P. Kothiyali; Review on Gastro Retentive Drug Delivery System; The Pharma Innovation. 2012; 1(8): 32-42.
[19]. Mathew Sam T., Devi Gayathri S., PrasanthV.V., Vinod B; NSAIDs as microspheres, The Internet Journal of Pharmacology.6(1), 2008, 67-73.
[20]. Vyas SP, Khar RK. Targeted and Controlled drug delivery., 7th Edition; Vallabh Prakashan, New Delhi India , 420-445.
[21]. Ghulam M., Mahmood A., Naveed A., Fatima R.A., Comparative study of various microencapsulation techniques. Effect of polymer viscosity on microcapsule charecterestics, Pak.J.Sci. 22 (3), 2009, 291-300.
[22]. Li, S.P., Kowalski C.R., Feld K.M., Grim W.M., Recent Advances in Microencapsulation Technology and Equipment, Drug Dev Ind Pharm. 14, 1988, 353-376.
[23]. Alagusundaram. M, Madhu Sudana Chetty.C, Umashankari.K, Attuluri Venkata Badarinath, Lavanya.C and Ramkanth.S. Microspheres as a Novel Drug Delivery System – A Review. International Journal of ChemTech Research. 1(3), 2009, 526-534.
[24]. Banker, S.G., Rhodes, T.C., and Kumar Vijay. 1996. Target-oriented drug delivery systems, In: Modern Pharmaceutics. Marcel Dekker. Inc. 72, 651- 652.
[25]. Benita, S. (1996). ―In: Microencapsulation‖, Marcel Dekker, New York, 1996, 1-21.
[26]. Okada, H., Toguchi, H. (1995). Biodegradable microspheres in drug delivery, Critical Reviews in Therapeutics Drug Carrier Systems, 12(1), 1-99.
[27]. Vyas. In Jain, N. K. (2006). Pharmaceutical Product Development‖, 1st ed., CBS Publishers, New Delhi, 112-138.
[28]. Li, M., Rouaud, O., Poncelet, D. (2008). Microencapsulation by solvent evaporation: State of the art for process engineering approaches, ―International Journal of Pharmaceutics‖, 363(1-2), 26-39.
[29]. Watts, P. J., Davis, M. C., Melia, C. D. (1990). Microencapsulation using emulsification/solvent evaporation: an overview of techniques and applications,
[30]. Critical Reviews in Therapeutics Drug Carrier Systems‖, 7(3), 235-259.
[31]. Jalil, R., Nixon, J. R. (1990). Biodegradable poly(lactic acid) and poly(lactide-co-glycolide) microcapsules: problems associated with preparative techniques and release properties, Journal of Microencapsulation, 7(3), 297-325.
[32]. Soppimath, K. S., Kulkarni, A. R., Rudzinski, W. E., Aminabhavi, T. M. (2001). Microspheres as floating drug-delivery systems to increase gastric retention of drugs, Drug Metabolism Reviews‖, 33(2), 149-160.
[33]. Lee, J. H., Park, T. G., Choi, H. K. (1999). Development of oral drug delivery system using floating microspheres, Journal of Microencapsulation, 16(6), 715-729.
[34]. Garg, R., Gupta, G. D. (2010). Gastroretentive Floating Microspheres of Silymarin: Preparation and in-vitro Evaluation, Tropical Journal of Pharmaceutical Research, 9(1), 59-66.
[35]. Rao, M. R. P., Borate, S. G., Thanki, K. C., Ranpise, A.A., Parikh, G.N., (2009). Development and in vitro evaluation of floating rosiglitazone maleate microspheres, Drug Development and Industrial Pharmacy, 35(7), 834-842.
[36]. Huang, H. P., and Ghebre-sellassie, I. (1989). Preparation of microspheres of water-solublepharmaceuticals, Journal of Microencapsulation, 6 (2), 219-225.
[37]. Hincal, A. A., and Calis, S. (2005). ―Handbook of Pharmaceutical Controlled Release Technology‖, 1st ed., Marcel Dekker, Inc, New York, 2005, 329-343.