

**Solvent evaporation matrix erosion method: a novel approach for floating microsphere development**Rajesh Asija^{1*}, Deepak Sharma¹, Kalu Ram Mali¹

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ABSTRACT

Floating drug delivery system is one of the novel drug delivery system. Floating drug delivery system has a bulk density less than gastric fluids and thus it remains buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. Atrovastatin is a competitive inhibitor of HMG-CoA reductase with half life 14hr. HMG-CoA reductase catalyzes the reduction of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to the mevalonate, which is rate-limiting step in hepatic cholesterol biosynthesis. Inhibition of the enzyme decreases *denovo* cholesterol synthesis, increasing explanation of low density lipoprotein receptors (LDL receptors) on hepocytes. This increases LDL uptake by the hepatocytes, reducing the amount of low density lipoprotein-cholesterol in the blood. Atrovastatin also reduces blood levels of triglycerides and slightly increases levels of HDL-cholesterol. The floating microspheres of Atrovastatin is being prepared by solvent evaporation method by using ethyl cellulose as a polymer and ethanol as a solvent and after the preparation of microsphere; it's evaluated for particle size, percentage yield, micromeritic properties, in vitro drug and in-vitro buoyancy release of microsphere, drug polymer compatibility, scanning electron microscopy, incorporation efficiency.

Key words: Atrovastatin, Ethyl cellulose, Floating microspheres

INTRODUCTION:

The oral route is increasingly being used for the delivery of therapeutic agents because the low cost of the therapy and ease of administration lead to high levels of patient compliance. More than 50% of the drug delivery systems available in the market are oral drug delivery systems¹. Controlled-release drug delivery systems (CRDDS) provide drug release at a predetermined, predictable, and controlled rate. Controlled-release drug delivery system is capable of achieving the benefits like maintenance of optimum therapeutic drug concentration in blood with predictable and reproducible release rates for extended time period; enhancement of activity of duration for short half-life drugs; elimination of side effects; reducing frequency of dosing and wastage of drugs; optimized therapy and better patient compliances.^{2,3}

Recent advances in novel drug delivery system to enhance the safety and efficacy of the drug molecule by formulating a dosage form being suitable for regulation. The high level of patient assent has been observed in taking oral dosage forms is due to the ease of administration and handling of dosage forms. There are lot of improvement has been seen in oral controlled drug delivery system in the last few years, this system has been of limited success in case of drugs with a poor absorption window throughout the GIT (Gastro Intestinal

Tract). To modify the GIT time is one of the main challenge in the development of oral controlled drug delivery systems. Gastric emptying of dosage forms is quite variable process and ability to prolong and control the emptying time is valuable asset for dosage form, which reside in stomach for a long time than conventional dosage forms. Several difficulties are look towards in designing controlled released systems for better absorption and enhanced the bioavailability⁴. Conventional oral dosage forms such as capsules, tablets provide specific drug concentration in systemic circulation without offering any control over drug delivery and also cause great fluctuations in plasma drug levels. Although single unit floating dosage form have been broadly studied, these single unit dosage form have the disadvantage of a release all or nothing emptying process while the multiple unit particulate system pass through the GIT to avoid the vagaries of gastric emptying and thus release the drug more consistently. The uniform distribution of these multiple unit dosage forms along the GIT could result in more reproducible drug absorption and reduced risk of local irritation; this gave birth to oral controlled drug delivery and led to development of Gastro-retentive floating microspheres.

Microspheres can be explained as solid, around spherical particles ranging in size from 1 to 1000 μm . The

Microspheres are generally free flowing powders consisting of proteins or synthetic polymer, which are biodegradable in nature. Solid biodegradable microspheres integrate a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drug. Microspheres are small in size and therefore have large surface to volume ratios. The use of microspheres in pharmaceuticals have a number of advantages Viz., odor and taste masking, conversion of oils and other liquids to solids for facilitate, protection of drug against environment (moisture, heat, light and oxidation), separation of incompatible materials, to increase flow of powders, production of controlled release and targeted medications. The most significant physico-chemical characteristics that may be controlled in microspheres manufacture are; particle size and distribution, ratio of drug to polymer, polymer molecular weight, and various attempts have been done to retain the dosage form in the stomach as a way of increasing retention time.

OBJECTIVE OF FORMULATION OF FLOATING MICROSPHERE:⁵

The purpose of this research was to formulate and evaluate Floating microspheres of Atorvastatin calcium. As the bioavailability of Atorvastatin Calcium is 13% to 14% owing to major hepatic first pass metabolism. It has an elimination half life of 13hr and has an absorption zone from the upper intestinal tract. Efficacy of the administered dose may get diminished due to the incomplete drug release from the device above the absorption zone. Atorvastatin Calcium requires twice a day drug dosage in order to maintain adequate plasma concentration. Because of poor bioavailability and rather high first pass metabolism, it is necessary to develop floating preparation with extended clinical effect.

- To Prepare and characterize novel Floating Microspheres for gastro retentive drug delivery of drug name
- To encapsulate drug name to achieve a uniform concentration of the drug at the absorption site and to reduce the frequency of administration.
- To increase the poor oral bioavailability of the drug
- To study various formulation variables those ultimately affect the release of the drug

Classification of Gastro-retentive Drug Delivery System (GRDDS):

Gastroretentive drug delivery system is classified as:

1. Bio/Mucoadhesive system
2. Floating system
3. Swelling system
4. Sedimentation system

1. Bio/Mucoadhesive system:

The term bioadhesion can be defined as the state in which two materials, at least one biological in nature, stand together for an extended period of time by interfacial forces⁶. Adhesion of bio-adhesive drug delivery devices to the mucosal tissue offers a possibility of creating an intimate and prolonged contact at the site of absorption. This longed contact time can result in the enhanced absorption and in combination with a controlled release of drug also improved patient compliance by reducing the frequency of administration. The adhesive properties of mucin towards epithelial membrane have been applied in the development of gastro retentive drug delivery systems^{7, 8}. Be classified into 3 types:

- **Type 1:** Adhesion between two biological phases. Example: wound healing and Platelet aggregation.
- **Type 2:** Adhesion of a biological phase to an artificial substrate. Example: biofilm formation on prosthetic devices and inserts.
- **Type 3:** Adhesion of an artificial material to a biological substrate. Example: Adherence of synthetic hydrogel to soft tissues and adhesion of sealants to dental enamel.

2. Floating Systems:

Floating systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for extending period. While the system floats over the gastric content, the drug is discharge slowly at the predetrmined rate, which results in expand gastro-retention time and reduces fluctuation in plasma drug concentration⁹⁻¹¹.

3. Swelling Systems:

These are capable of swelling to a size that prevents their passage through the pylorus; therefore, the dosage forms are retained in stomach for a longer period of time. Upon coming in contact with gastric fluid, the polymer absorbs water and swells.

Floating Drug Delivery System:

Floating system was first described by Davis in 1968. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach for a prolonged period without affecting the gastric emptying rate. During this time the system is floating on the gastric contents, the drug is delivering slowly at the predetermined rate from the system and the residual system is discharge from stomach. This results in an elevated Gastric Residence Time (GRT) and a better control of the fluctuations in plasma drug profile. However, as well as minimum gastric content needed to allow the proper achievement of the buoyancy principle, a minimal level of floating force (F) is also required to

keep the dosage form reliably buoyant on the dosage form reliably buoyant on the exterior of the meal. To measure the floating force kinetics, a novel equipment for determination of resultant weight (RW). The RW equipment operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the immerse object. The object floats better if resultant weight (RW) is on the higher positive side. This equipment helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intra-gastric buoyancy capability variations¹².

$RW \text{ or } F = F \text{ buoyancy} - F \text{ gravity} = (D_f - D_s) gV$

Where, RW - total vertical force

D_f - fluid density

D_s - Object density

V - volume

g - Acceleration due to gravity.

Types of Floating Drug Delivery System:

FDDS can be divided into two systems:

1. Effervescent systems
2. Non-effervescent systems

1. Effervescent Systems:

A. Volatile liquid containing systems:

The GRT of a drug delivery system can be sustained by incorporating an inflatable (expansive) chamber, which contains a liquid e.g. cyclopentane, ether, that gasified at body temperature to cause the inflation (expansion) of the chamber in stomach. The device may also contains a bioerodible plug made up of Polyethylene, PVA, etc. that slowly dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach.¹³

B. Gas-generating Systems:

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to release CO₂, which gets entice in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme^{17, 18}.

These buoyant systems can be developed by using swellable polymers like methocel (cellulose ethers are water-soluble and (HPMC), polysaccharides like Deacetylchitin, effervescent components like citric acid, tartaric acid, and sodium bicarbonate or chambers containing a liquid that gasifies at body temperature. The optimal stoichiometric proportion of citric acid and sodium bicarbonate for gas formation is noted to be 0.76:1. The common advance for developing these systems involves resin beads loaded with bicarbonate and coated with EC. The coating, which is insoluble but

permeable and allows permeation of water. Thus, CO₂ is liberating, causing the beads to be buoyant in stomach. Other advances and materials that have been reported are highly swellable hydrocolloids and light mineral oil, a mixture of sodium bicarbonate and sodium alginate, multiple units floating pill that release CO₂ when swallowed, floating minicapsules with a core of lactose, sodium bicarbonate, and PVP coated with HPMC, and floating systems based on ion exchange resin technique.

2. Non-Effervescent Systems:

This type of system, after ingestion, swells uncontrolled via absorption of gastric fluid to an extent that it prevents their exit from stomach. These systems may be indicated as the 'plug type systems' since they have a tendency to remain lodged near the pyloric sphincter. The formulation methods of such dosage form involves the mixing of a gel with drug, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous boundary. The air ambushed by the swollen polymer confers buoyancy to these dosage forms.

A. Colloidal gel barrier systems:

Hydro-dynamically balanced system (HBS) systems contains drug with gel forming hydrocolloids meant to remain buoyant on the stomach content. This system contains a high level of one or more gel forming highly swellable cellulose type hydrocolloids e.g. NaCMC, HEC, HPMC, Polysaccharides and matrix forming polymers such as polystyrene, polyacrylates and polycarbophil, incorporated either in capsules or in tablets. When this system come in contact with gastric juice, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around the gel surface. The air confined by the swollen polymers maintains a density less than unity and confers buoyancy to this dosage forms.¹⁴⁻¹⁸

B. Microporous Compartment System:

This technology is based on the encapsulation of drug reservoir inside a microporous compartment with perforation along its bottom and top wall. The outside walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the undissolve drug. In the stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the perforation, dissolves the drug, and carries the dissolve drug for continuous transport across the intestine for absorption.

C. Alginate beads:

Multiple unit floating dosage forms have been developed from freeze-dried Ca-alginate. Spherical beads of

generally 2.5 millimeter in diameter can be prepared by dropping a sodium alginate solution in to aqueous solutions of CaCl_2 , causing precipitation of Ca alginate. The beads are then separated snap and frozen in liquid nitrogen, and freeze dried at -40° for 24 hr, leading to the formation of porous system, which can maintain a floating force(F) over 12 hr.

D. Hollow microspheres:

Hollow microspheres loaded with ibuprofen in their outer polymer shells were prepared by a novel emulsion-solvent diffusion process. The dichloromethane, ethanol, solution of the drug and an enteric acrylic polymer was poured in to an agitated aqueous solution of PVA that was thermally controlled at 40° . The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed in internal cavity in microspheres of the polymer with drug. The microspheres (microballons) floated continuously over the surface of acidic dissolution media containing surfactant for greater than 12 hr in vitro.

Floating microspheres:¹⁹

Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Hollow microspheres are spherical empty particle lacking of core. These microspheres are typically free flowing powders consisting of synthetic polymers or proteins, ideally having a size less than $200\ \mu\text{m}$. Solid biodegradable microsphere contains a drug dispersed or dissolved throughout particle matrix have the potential for controlled delivery of drug.

The floating microspheres have been utilized to obtain prolonged and uniform release in the stomach for development of a once daily formation. When microspheres come in contact with gastric fluid the polymers, polysaccharides, and gel former hydrate to form a colloidal gel barrier that control the rate of fluid penetration into the device and consequent drug releases. As the outer surface of the dosage form dissolve, the gel layer is sustained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymers lower the density and confers buoyancy to the microsphere. However minimum gastric contents needed to allow proper acquirment of buoyancy. Hollow microspheres of Cellulose acetate, PMMA, Eudragit, and acrylic resins; Polystyrene floatable shells; polycarbonate floating balloons and gelucire floating granules are the recent development.

Development of Floating Microspheres:²⁰⁻²¹

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core. These microspheres are typically free flowing powders consisting of synthetic polymers or proteins, ideally having a size less than $200\ \mu\text{m}$. Solid biodegradable microspheres integrate a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs²⁵. Gastro-retentive floating microspheres are low density systems that have sufficient buoyancy to float over gastric content and remain in stomach for long time. As the systems float over gastric contents, the drug is released gradually at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration.

Mechanism of Floating Microspheres:

When microspheres come in contact with gastric fluid the gel formers, polymers and polysaccharides hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the outer surface of the dosage forms dissolve, the gel layer is sustained by the hydration of the adjacent hydrocolloid layers. The air confined by the swollen polymers lower the density and confers buoyancy to the microspheres. However a minimum gastric content needed to allow proper achievement of buoyancy. Hollow microspheres of cellulose acetate, polyethylene oxide, Eudragit, and acrylic resins; polystyrene floatable shells; polycarbonate floating balloons and gelucire floating granules are the recent developments.

Criteria for selection of Drug candidate for GRDF:²²

- ❖ Drugs that are easily absorbed from the gastrointestinal tract (GIT) and having a short half – life are eliminated quickly from the blood circulation.

- ❖ Absorption from upper GIT:

Drugs have a particular site for maximum absorption. E.g. Ciprofloxacin, whose maximum absorption is in the stomach. The absorption of Metformin HCL is confined to the small intestine only and the conventional sustained release dosage form may be poorly BA since absorption appears to diminish when the dosage form pass into large intestine.

- ❖ Drugs insoluble in intestinal fluids (acid soluble basic drugs):e.g. Chlordiazepoxide, diltiazem, chlorpheniramine.

- ❖ Drugs that are abnormally absorbed due to variable gastric emptying time.

- ❖ Drugs which get metabolized in the colon or having high first pass metabolism.

Method of preparation for floating microspheres:

Floating microspheres should satisfy certain conditions, they are following:

1. The ability to incorporate reasonably high concentration of drug.

2. Stability of the preparation after synthesis with a clinically acceptable shelf-life.
3. Release of active agent with good control over a wide time scale.
4. It must maintain specific gravity lower than gastric content(1.004-1.01g/cc)
5. Biocompatibility with a controlled biodegradability.
6. Susceptibility to chemical modification.

Selection of excipients is an important strategic consideration for designing a dosage forms with consistence and controlled residence in the stomach. High molecular weight and less hydrophilic polymers are expected to improve floating properties of delivery system. The polymer studied for the development of such systems include cellulose acetate, chitosan, eudragit acrycoat, methocil, polyacrylate, polyvinylacetate, carbopol, agar, polyethylene oxide, and polycarbonate.

Various procedures are used for the development of the floating microsphere is:

Hollow microspheres are prepared by solvent diffusion and evaporation methods to create inner core. The polymer is dissolved in an organic solvent and the drug is either dissolved or dispersed in polymer solution. The solution containing the drugs is then emulsified into an aqueous phase containing polyvinyl alcohol to form an o/w emulsion. After the forming of a stablised emulsion, the organic solvent is evaporated (vaporized) either by continuous stirring or by increasing the temperature under pressure. The solvent removal results to polymer precipitation at o/w interface of the droplet, forming the cavity and thus making them hollow to import the floating properties.

B. Solvent evaporation:

In this method drug and polymers (HPMC and Ethylcellulose) were dissolved in a mixture of ethanol and dichloromethane at room temperature. This was poured into 250mL water containing 0.01% Tween 80 maintained at a temperature of 30-40° C and subsequently stirred at ranging agitation speed for 20 min to allow the volatile solvent to evaporate. The prepared microsphere filtered, washed with water and dried in vacuum.

C. Spray drying:

In Spray drying the polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane and acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high-speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization results to the formation of the fine mist or the small drops from which the solvent, evaporate immediately results in the formation of the microspheres in the size range of 1-

100µm. Micro particles are separated from the hot air by means of the cyclone separator while the trace of solvent is removed by vacuum drying. The major advantages of this process are feasibility of operation under septic conditions. This process is rapid and this lead to the formation of porous microparticle.

Advantages of Floating Microspheres:²³⁻²⁶

- Better to single unit floating dosage form as such microsphere release drug uniformly and there is no risk of dose dumping.
- Prevention of gastric irritation, because of sustained release effect, floatability and uniform release of drug through multi particulate system.
- Increased receptor activation selectivity
- Extended time over critical (effective) concentration
- Lesser inter and intra-subject variability.
- Flexibility in dosage form design.
- Increase patient assent by reduction in dose frequency.
- Excellent therapeutic effect of short half-life drugs can be achieved.
- GRT is increased because of buoyancy.
- Drug releases in controlled manner for long time.
- Increased first-pass biotransformation
- Reduced frequency of dosing
- Targeted therapy for local disorders in the upper GIT
- Site specific drug delivery to the stomach can be obtained.
- Increased absorption of drugs which solubilize only in the stomach.
- Desirable plasma drug concentration is sustained by continuous drug release.

Disadvantages:²⁷⁻³⁰

This requires sufficiently high levels of fluids in the stomach, for enabling the system to float and to work efficiently.

- Floating microspheres are not suitable candidates for drugs with stability or solubility problem in the stomach.
- A drug with irritant effect on gastric mucosa also limits the applicability of floating microspheres

Application of floating microspheres:

- Floating microspheres are especially effective in delivery of sparingly soluble and insoluble drugs.
- Drugs that have poor bioavailability because of their limited absorption to the upper gastrointestinal tract can also be delivered efficiently thereby maximizing their absorption and improving the bioavailability.

CONCLUSION:

Floating drug delivery system is one of the novel drug delivery system. Floating drug delivery system has a bulk

density less than gastric fluids and thus it remains buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time.

REFERENCES:

1. Arora S, Ali A, Ahuja A, Khar RK, Baboota S, Floating drug delivery systems, A Review AAPS Pharm SciTech 2005; 6(3): E372- E390.
2. Chien YW, Rate-control drug delivery systems: controlled release vs. sustained release, Med Prog. Techn. 1989; 21-46.
3. Chien YW, Oral drug delivery in novel drug delivery systems, ed. 50, Marcel Dekker Publication, New York, 1992; 43-47.
4. Jain NK, Controlled novel drug delivery, 1st Eds, CBS Publishers and Distributors, New Delhi. 2002; 236-55.
5. Ikeda K, Murata K, Kobayashi M, Noda K, Enhancement of bioavailability of dopamine via nasal route in beagle dogs, Chem Pharm Bull 1992; 40: 2155-2158.
6. Good WR, Transdermal nitro-controlled delivery of nitroglycerin via the transdermal route, Drug Dev Ind Pharm. 1983;647-70.
7. Nagai T, Nishimoto Y, Nambu N, Suzuki Y, Sekine K, Powder dosage form of Insulin for nasal administration, J Control Release 1981; 15-22.
8. Illum L, Furraraj N, Critcheley H, Davis SS, Nasal administration of gentamycin using a novel microsphere delivery system, Int J Pharm 1998; 46,261-265.
9. Schaefer MJ, Effect of isopropyl myristic acid ester on the physical characteristics and in – vitro release of etoposide from PLGA microspheres, AAPS Pharm Sci Tech 2005;1(4): E370-E380.
10. Hannah B, Novel bioadhesive formulation in drug delivery, 2003; 16-19.
11. Chawla G, Gupta P, Koradia V, Bansal AK, Floating drug delivery system, Pharm Tech 2001; 27(7):50-51,
12. Chickering DE, Jacob JS, Matho WE, Reactive Polymers in novel drug delivery system, 1995 ;(25):189-206.
13. Seng CH, Novel drug delivery system, J Pharm Sci 1995; 74(4):399-405.
14. Cremer K, Non effervescent drug delivery system, Pharm. J 1997; 19(108):259.
15. Garg S, Sharma S, Gastro-retentive drug delivery system, Pharm. Tech 2003;13(1):160.
16. Singh BN, Kim KH, Controlled drug delivery system, J. Controlled Release 2000; 63(12):235-259.
17. Timmermans J, Moes AJ, How well does a floating dosage form float, Int J Pharm 1990; 62:207-216.
18. Yyas SP, Khar RK, Controlled drug delivery concepts and advances, 1st Edition, New Delhi, 2002; 196-217.
19. Chawla C, Gupta P, Koradia V, Bansal AK, Gastroretention: A means to address regional variability in intestinal drug absorption, Pharmaceutical technology, 2003; 27(2):50-68.
20. Sangekar S, Evaluation of effect of food and specific gravity of the tablets on gastric retention time, Int J Pharm 1987; 35(3):34-53.
21. Jain NK, Progress in controlled and novel drug delivery systems, 1st Ed. CBS Publishers and Distributors, New Delhi, 2004; 84-85.
22. Debjit B, Chiranjib B, Margret C, Jayakar B, Floating Drug Delivery System: A Review. Der Pharmacia Lettre, 2009; 1(2): 199-218.
23. Chawla G, Gupta P, Koradia V, Bansal AK, Floating drug delivery systems: An approach to Gastro retention, Pharm. Tech, 2003; 27(2): 50-68.
24. Garg R, Gupta GD, Progress in controlled Gastro-retentive delivery systems, Trop. J. Pharma. Res, 2008; 7(3): 1055-1066.
25. Hoffman A, Expandable gastro retentive dosage forms, 1998, 185-199.
26. Hoffman A, Stepensky D, Floating multiparticulate oral sustained release drug delivery system, Crit. Rev. Ther. Drug Carrier Syst, 1999; 571-639.
27. Sangekar S, Review on Stomach specific drug delivery systems: Development and Evaluation, Int. J. Pharm ,1987; 35(3): 34-53.
28. Mojaverian P, Vlasses PH, Kellner PE, Rocci ML, Floating drug delivery system: An innovative acceptable approach in gastro-retentive drug delivery, Pharm. Res, 1988; 10(2): 639-664.
29. Vyas SP, Khar RK, Targeted and Controlled Drug Delivery Novel Carrier System, 1st Ed., CBS Publishers and Distributors, New Delhi, 2002; 417-54.
30. Mayavanshi AV, Gajjar SS, Floating drug delivery system to increase gastric-retention of drug, A Review, Research J. Pharm and Tech. 2008; 1(4): 345-358.
31. Hoffman A, David SA, Earn LB, Sara EA, Pharmacokinetic and pharmacodynamic aspect of gastroretentive dosage form, 141-153.