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Floating Microballoon – A Novel Formulation For Gastrointestinal Diseases

Nithyashree RS[1], Shouvik Kumar D[1], Tanmoy Gosh[1], Ranjitha M[2], Uma[2], Sasi Priya SVS[3], Sundara Saravanan K[4], Mohammad Azamthulla*[2]

[1]Department of Pharmaceutics, [2]Department of Pharmacology,
[3]Department of Pharmaceutical chemistry, [4]Department of Pharmacognosy,
Faculty of Pharmacy, M. S. Ramaiah University of Applied Sciences, MSR Nagar, Bangalore, India -560054

Abstract

The microballoons are hollow microspheres which incorporates drug and the drug release can be controlled at a desired rate. Microballoons are floating microspheres which floats over the gastrointestinal fluid as the density of microballoons is less than the density of the gastrointestinal fluid. This floating system helps to treat many gastrointestinal diseases such as ulcers, GERD, Zollinger-Ellison diseases. Targeted drug delivery can be achieved with the use of microballoons. Therefore used for target specific drug delivery. Applications of microballoons are not only limited for treating of GIT disorders; it plays a major role in treating many other complications. Though the availability of products related to microballoons is many in the market, the research is going on to fill the lacuna. This article will provide sufficient information related to microballoon formulation.

Keywords: Antiulcer, Floating system, Gastrointestinal tract, Microballoons.

INTRODUCTION

Despite of the disadvantages, oral route of administration is the most popular and convenient route of administration in case of gastrointestinal route. The maximum utilization of the drug at different parts of gastrointestinal tract is achieved with oral route of administration, where targeted drug delivery can be achieved. Inadequate absorption window of the drugs can be seen with conventional pharmaceutical dosage forms in the upper gastrointestinal tract [1]. The great challenge is faced by the scientists to deliver the drug at a controlled rate due to its impotence to leash and concentrate the system in the selected area of the gastrointestinal tract. Floating delivery system has been developed which extends the gastric residence time. In floating delivery system, the drug remains buoyant and floats on the gastric fluid with sustained release of drug [2]. Several advantages of floating delivery system over immediate release dosage forms are reduction in alteration of plasma-level concentration, prolonged duration of residence at the site of action, advanced therapeutic potency and minimized side effects, reduction in the administration of the total dose and administration frequency, bioavailability is improved and the solubility of the drugs which are poorly soluble at higher pH values can be enhanced [3]. Some of the marked products of gastro retentive drug delivery system are showed in table 1.

Floating system is classified into two systems [4]:

Effervescent systems

- Volatile liquid containing systems
- Gas generating system

Non-effervescent system

- Colloidal barrier system
- Microporous compartment system
- Alginate beads
- Hollow microspheres

Advantages:

a. Patient compliance is improved with the reduction of dosing frequency.
b. The absorption of the drugs which will solubilize in the stomach is improved.
c. For a prolonged period of time, controlled release of the drug can be achieved.
d. Due to buoyancy, the gastric retention time of the microballoons is enhanced.
e. Target specific delivery can be achieved.
f. Due to sustained release of the drug, gastric irritation is prevented [5].

Disadvantages:

a. Factors like food and rate of transit through gut will affect the drug release in a controlled manner.
b. The release of the drug may differ from one dose to another.
c. Potential toxicity can be observed in case of any loss of virtue in the release of dosage form characteristics.
d. Chewing or crushing of the dosage form is not allowed.
e. High level of fluid is required for the microballoons to remain buoyant.
f. The drugs which undergo first pass metabolism are not good candidates for this system. Eg: Nifedipine.
g. Drugs with poor stability and solubility are not good candidates of this system.

Eg: Ranolazine

h. Drugs which have irritant effect on gastric mucosa are not suitable for FDDS.

Eg: NSAIDs, antibiotics, digoxin, theophylline, corticosteroids [6].

Floating systems:

Floating drug delivery system are different type of system shows that the bulk density of the dosage form is lower than that of gastric fluid which makes the system to float on the gastric fluid and remains buoyant for an extended period of time. The drug is released slowly at a desired rate potentially. Floating dosage forms are also assigned as low-density system [7]. The pharmacokinetic and pharmacodynamic assets of controlled release dosage form can be utilized with the incorporation of the drug into the floating dosage form [8]. The exertion of enteric polymers will gives prolonged drug release features to the floating drug delivery system [9].

The absorption of the drug from the gastrointestinal tract is a complex procedure and it is subjected to many variables. Hence, designing of the controlled release systems to constrain the dosage form in the target area of gastrointestinal tract becomes difficult [10].

Effervescent system

- Volatile liquid containing systems: The gastric retention time of the drug within the stomach can be sustained by the implementation of expandable chamber. This chamber contains liquid, Eg: ether, cyclopentane which vaporizes at room temperature and is responsible for the expansion of the chamber in the stomach.

Eg: Sevoflurane USP

This is further classified as:

- Intragastric floating gastrointestinal drug delivery system
- Expandable gastrointestinal drug delivery system
- Intragastric osmotically controlled drug delivery system

- Gas generating systems: By the generation of gas bubbles, the system is made to float in the stomach. With the incorporation of carbonates or bicarbonates, the carbon dioxide is generated in situ. The carbonates present in the system reacts either with the acid present in the stomach or co-formulate as citric or tartaric acid. The system is made to float on the gastric fluid by the generation of gas and the drug is released at the predetermined rate.

Eg: Cifran OD (Ciprofloxacin-1g)

The different types of gas generating system are:

- Floating capsules

Eg: Madopar (Levodopa-100mg + Benserazide-25mg)

- Floating pills

Eg: Gastric floating microcapsules of Metformin HCl

- Floating systems with ion exchange resins

Eg: Topalkan (Al-Mg antacid)

Non-effervescent systems

- Colloidal barrier systems
- Microporous compartment system
- Alginate beads
- Hollow microspheres

MATERIALS AND METHODS:

Materials: Drugs, polymers, solvents, processing medium, surfactant, cross linking agent, hardening agent.

Methods of preparation:

Solvent Evaporation Method: The polymer is dissolved in suitable solvent and the drug is added to the polymer solution to form a homogenous solution. At 1500rpm and at 35°C for 3 hours, the homogenous solution is poured into liquid paraffin resulting in the formation of an emulsion. The solvent is evaporated from the mixture after a stable emulsion has been formed. Due to evaporation, microspheres were solidified and were filtered using whattman filter paper [4].

Emulsion Solvent Diffusion Method: The polymer mixture is dissolved in organic solvent and then added to aqueous poly vinyl solution. At different ranges of temperature, the solution is stirred at 1500rpm for an hour [11].

Solvent Diffusion-Evaporation Technique: A moderate change in emulsion solvent evaporation method and emulsion solvent diffusion method gives solvent diffusion-evaporation method. At room temperature, drug, polymer and surfactant is mixed in organic solvents. This mixture is then introduced slowly into poly vinyl alcohol solution with stirring for an hour using a propeller agitator. The organic solvent is evaporated and then filtered [12].

Spray Drying: Slurry is prepared by dissolving polymer in a suitable organic solvent (dichloromethane, acetone) which is sprayed into drying chamber. Inside the small droplet, concentration gradient is formed and at the surface of the droplet, the highest concentration is maintained which is due to the reason that the diffusion of the solute is greater than that of the solvent from the droplets evaporating during the process of drying. Microspheres are formed with the appearance of solid shell which is isolated from the gases by means of cyclone separator. This is followed by the removal of traces of solvent by vacuum drying [13].

Factors affecting Physicochemical properties of Microballoons

- *Stirring rate:* The size of the microspheres is dependent on the stirring rate. With increase in agitation, there is a decrease in size of the microspheres though the increase in not significant statistically. The bulk of the polymers are not breakable into fine droplets within the range of the study [14].
- *Temperature of preparation:* At various temperatures like 20, 30, 40 and 50°C, the drug and the polymer solution is poured into aqueous solution of poly vinyl alcohol. The microspheres with greater porosity on the surface are obtained at 20 or 30°C. the size of the particle decreases with the increase in temperature. At the power of mixing input i.e., at higher temperature the viscosity of the emulsion is reduced and it is much easier for the breakdown of the emulsion [15].
- *Plasticizers:* The properties of elasticity and flexibility are given to the formulation with the addition of the plasticizers on to the walls of the material. The rupturing under pressure or brittleness is avoided with the addition of the plasticizers. With the increase in the concentration of the plasticizer the drug release increases significantly [16].

➢ *Volume of aqueous phase (continuous phase):* The buoyancy increases with increase in aqueous phase as the particle size decreases. The time required for stirring is reduced with increase in volume of aqueous phase. For example, the solubility of the dicholoromethane is 1% w/v in water. It is preferred to use 400 to 500ml of aqueous phase as the solidification of the particles occurs at a faster rate than 200ml of aqueous phase [17].

➢ *Solvent ratio:* Irregular shaped microspheres were formed with bridging of small volume of the solvent while the usage of large volume of liquid bridging prevents emulsion droplets solidification. A careful control over the volume of dichloromethane is required [18]. The morphology of the microspheres is affected by the ratio of dichloromethane and ethanol. The ratio must be optimized to give spherical shaped microspheres. The ratio of ethanol to dichloromethane is 2:1 gives spherical shaped microspheres [17].

➢ *Amount of polymer and viscosity:* At lower concentration of the polymer, smaller microballoons were formed and it is exposed to larger surface area which will give faster drug release [19].

➢ *Effect of solvent:* Dichloromethane is opted as the solvent for the preparation of microballoons as it is a good solvent for polymer and drugs. With the use of dichloromethane, the shape of the microspheres is not spherical in shape hence; methanol is used to solve this problem. Though the shape is spherical with the use of methanol, the texture was not smooth and hence methanol is replaced with ethanol to solve this problem [20].

➢ *Concentration of the emulsifier:* As the concentration of the surfactant reduces from 1% to 0.25%, there is an increase in the particle size and size distribution. Emulsifier plays a vital role in decreasing the interfacial tension between the dispersed droplets and continuous phase and also it protects the droplets from collision and coalescence [21].

Evaluation of floating microballoons:

➢ *Percentage yield:* The percentage yield of floating microballoons is calculated by the following equation:

$$Yield = \frac{M}{Mo} x\ 100$$

Where M – weight of the beads

Mo – total weight of drug and polymer expected

➢ *Micromeretic properties:* Micromeritic properties like particle size, tapped density, compressibility index, true density and flow properties are the characteristic features of microspheres. Optical microscopy is used to measure the particle size of the microspheres. The mean particle size is determined by measuring with the calibrated ocular micrometer about 200 to 300 particles. Liquid placement method is used to determine the true density; by measuring the change in volume using bulk density apparatus, tapped density and compressibility index are calculated; by using fixed funnel method, the angle of repose is calculated. By using scanning electron microscopy, the hollow nature of the microspheres is confirmed.

$$Tapped\ density = \frac{Mass\ of\ microspheres}{Volume\ of\ microspheres\ after\ tapping}$$

Compressibility index can be mathematically represented as

$$I = \frac{Vb - Vt}{Vb}\ x\ 100$$

Where V_b represents bulk volume

V_t represents tapped volume

By using helium densitometer, true density of the microspheres is determined. Porosity can be mathematically represented as:

$$e = \left\{1 - \left(\frac{tapped\ density}{true\ density}\right)\right\} x\ 100$$

➢ *In vitro buoyancy:* Into 100ml of simulated gastric fluid containing 0.02% w/v of tween 80, 50 milligrams of floating microspheres were placed and stirred at 100rpm with a magnetic stirrer. After 8 hours, the buoyant layer microsphere is pipetted out and is separated by filtration from the sinking particles. The obtained particles are dried in a desiccator until a constant weight is obtained. The obtained fractions of microspheres of both were weighed and by weight ratio of floating particles to the sum of floating and sinking particles buoyancy was determined [22].

$$Buoyancy(\%) = \left\{\frac{Wf}{(Wf + Ws)}\right\} x\ 100$$

Where W_f and W_s represents the floating and settled particles weights.

➢ *Scanning electron microscopy:* On an electron microscope brass stubb which is coated with gold ion sputter, dry microspheres were placed. By using spectro random scanning of the stub, images of the dry microspheres were captured and viewed at an accelerating voltage of 20KV [23].

➢ *In-vitro release studies:* The release rate of the floating microspheres is determined by using USP apparatus XXII (Basket type dissolution apparatus). The floating microspheres were weighed which is equivalent to the required amount of drug was filled in the hard gelatin capsule and is placed into the basket of dissolution apparatus which contains the dissolution medium. The temperature of the dissolution medium was set to 37 ± 1^0C and the rotation speed was set as specific rpm. At predetermined intervals of time, 5ml of the sample was withdrawn and passed through 0.25µm membrane filter and was analyzed by using LC/MS/MS method in order to determine the concentration present in the dissolution medium. To maintain sink conditions, 5ml of the dissolution medium is replaced back into the vessel.

➢ *In*-vivo studies: The hollow microspheres loaded with barium sulphates were ingested in to the beagle dogs and X-ray photography was taken to know the floating behavior of the microspheres. By using suitable in-vivo animal models, the plasma profile can be determined.

Table 1: Marketed products of gastro retentive drug delivery system:

Brand Name	Drug	Dosage form	Company
Nizatidine capsule 150 mg	Nizatidine	Capsule	Mylan
Protonix	Pantoprazole sodium	Tablet	Pfizer
Pepcid AC	Famotidine	Tablet and powder for suspension	McNeil Consumer Pharmaceuticals Co
Cytotec	Misoprstol	Tablet	Pfizer
Pro-Banthine	Propantheline	Tablet	Kyowa Kirin Ltd

Applications of Floating Microballoons

a. For the drugs to be absorbed at the absorption window of the gastrointestinal mucosa, floating microballoons were used as carriers.
   Eg: antiviral, antifungal and antibiotic agents
b. The major side effect of gastric irritation can be reduced with the controlled release of NSAIDs which were incorporated into the hollow microspheres [24].
c. The *Helicobacter pylori* is eliminated from the gastric mucosa with the implementation of hollow microspheres. With the use of hollow microspheres, the pharmacotherapy of the stomach is improved as the concentration of the drug is higher in the stomach which suppresses the *H.pylori* in the sub-mucosal layer. Stomach and gastric ulcers, gastritis and esophagitis can be treated with the suppression of *H. pylori*
   Eg: Lansoprazole [25].
d. Floating microspheres are very advantageous approach in drug delivery of drugs which have poor bioavailability as they have slender absorption in the upper gastrointestinal tract. The bioavailability of such drugs can be enhanced with maximum absorption at the targeted site.

Eg: Furosemide, Riboflavin.

e. The problem of short residence time which is detected with oral controlled release formulations can be reduced with the implementation of floating microspheres which releases the drugs over a long period of time at the specific site of absorption.

Other Applications:

a. Floating microballoons of pentoxifylline, a hemorheologic agent which is used in the treatment of peripheral arterial disease and intermittent claudication [26].
b. The floating microspheres of verapamil hydrochloride, a phenyl alkylamine derivative of the class IV calcium channel blockers were developed as antiarrhythmic agent [27].
c. The thiazide diuretic hydrochlorothiazide floating microspheres is used for the treatment of hypertension, congestive heart failure and edema.
d. The risperidone floating microparticles were developed to treat the positive as well as negative symptoms of schizophrenia [28].
e. Carvedilol floating microspheres were developed to treat hypertension by increasing its half-life.
f. Quercetin floating microspheres were used in the relaxation of cardiovascular smooth muscles (antihypertensive, antiarrhythmic effects) [29].
g. Curcumin floating microspheres were used as anticancer, antibacterial and as antifungal agents.
h. Resveratrol floating microspheres were used as an effective antioxidant, anti-inflammatory and antiproliferative agents.
i. Floating microspheres of *Cynara scolymus* is used in the phytotherapy preparations for hepatic infections, obesity and dyspeptic disorders.
j. Silymarin floating microspheres are used as hepatoprotective and as an antioxidant.
k. The extract of *Allium sativum* is used as an antibacterial agent and formulated as floating microspheres.
l. Camptothecin microspheres are potentially used in the treatment of abdominal metastases of colon carcinoma.

CONCLUSION:

Microballoons are important in treating the disorders associated with the stomach. It is used for target specific drug delivery. Applications of microballoons are not only limited for treating of GIT disorders; it plays a major role in treating many other complications. Though the availability of products related to microballoons is many in the market, the research is going on to fill the lacuna. This article will provide sufficient information related to microballoon formulation.

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Conflicts of Interest:

There are no conflicts of interest among the authors

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