JOURNAL OF PHARMACEUTICAL SCIENCE AND BIOSCIENTIFIC RESEARCH (JPSBR)

(An International Peer Reviewed Pharmaceutical Journal that Encourages Innovation and Creativities)

Gastro Retentive Floating Microsphere: A Review

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Article history:

Received 02 March 2019
Accepted 02 April 2019
Available online 30 April 2019

Citation:
Kumar L., Sharma A. Gastro Retentive Floating Microsphere: A Review **J Pharm Sci Bioscientific Res**. 2019. 9(2):142-148

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(www.jpsbr.org)

ABSTRACT:

Drug delivery system should release the drug according to the body requirement during treatment and to the target site. With the passage of time and development in medical segment research was done in field floating microspheres which reduce the dosage form drawbacks like low gastric residence time and unpredictable gastric emptying time. Floating microspheres is a technique of the gastro retentive drug delivery system having both effervescent and non-effervescent mechanism. Due to their low density they offer enough buoyancy to float over the gastric fluids for longer period of time and thus increase the gastro retention time. Floating microspheres also maintains desire drug concentration with minimum interval of frequency of drug dosing thus they can either be formulated as sustained release or controlled release. The main property of floating microspheres is that they buoyant over the surface of gastric fluid for more than 12 hrs. This review article comprises the detailed study of the property, classification, method of preparation as well as the characterization of floating microspheres.

KEY WORDS: Gastro retentive drug delivery system, Floating microspheres, Buoyant, Gastric residence time.

INTRODUCTION:

Most common route for the drug administration is oral route. This route is convenient, flexible, safe, cost effective and most natural. Due to its ease of administration the major goal of any drug delivery system is to provide the therapeutic amount of drug in the body that reaches the site and maintain the desired drug concentration to give its max therapeutic effect with minimum side effect [1,2].

Drugs having shorter half-life and the drug which are easily absorbed in GIT are quickly eliminated from the blood circulations. Oral controlled drug delivery system have been developed to overcome these problems because they release the drug slowly into the GIT and maintain a constant drug concentration in the serum for longer period of time [3-5]. Gastro-retentive dosage forms are one of the widely used oral controlled drug delivery system which prolong the duration of drug in stomach and improve its bioavailability. These microspheres are spherical free flowing property mainly consist of synthetic polymer or protein which are biodegradable in nature [9-11]. The outer layer of the solid microspheres is biodegradable in nature that has the drug dispersed or dissolved in the matrix and control the release of the drug [12].

ADVANTAGES OF MICROSPHERES

- Reduction in particle size enhances solubility
- Provide prolonged therapeutic effect
- Minimum adverse drug reaction and side effect
- Provide protection of the drug from physicochemical effects
- Provide constant and controlled release of the drug in the systemic circulation

LIMITATIONS OF MICROSPHERES

- Manufacturing cost is high
- Factors like change in pH, temperature, agitation may influence the core particle stability

- Polymer may degrade in response to oxidation, hydrolysis and some biological agents [11]

TYPES OF MICROSPHERES

- Floating microspheres
- Bio-adhesive microspheres
- Radioactive microspheres
- Polymeric microspheres
- Magnetic microspheres

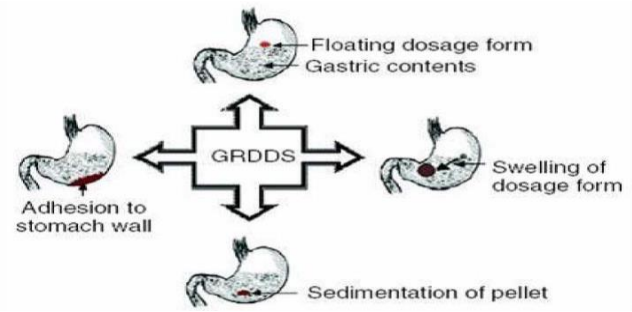

Figure 1: Types of gastro retentive drug delivery system

Floating microspheres

This system was first introduced in year 1968 by Davis. The name suggests the property of these microspheres. Due to their low bulk density than the gastric fluids it remains buoyant in stomach without affecting gastric emptying rate. Floating microspheres also help in the reduction in dose dispose from the body. It also helps in the reduction of dosing frequency by increasing the therapeutic effect time. The drug release slowly when the drug float on the gastric content which gives the desired rate from the drug systems and after removal of drug residual system is eliminated from the stomach. The above-mentioned process leads to increase in gastric residence time and better control in drug plasma core [17-19].

Advantages of floating microspheres

- Less frequent dosing
- Ease for better patient compliances and administration
- Mucosal irritation of drug is minimized.
- Drug absorption is improved due to increase in gastric residence time [30].

Disadvantages of floating microspheres

- These are not applicable for drugs having stability and solubility issues in gastric fluids
- Retention of drug in stomach is influenced by factors such as gastric motility, presence of food and pH
- Drugs causing irritation in gastric mucosa are not suitable for this type of drug delivery system [31-33]

Bio-adhesive microspheres

In these microspheres the water-soluble polymer has the sticking or the adhesion property. This property helps the microspheres to stick to the walls of the mucosal layer or to the absorption site for the better drug release as well as the therapeutic action [13, 14]

Radio-active microspheres

These microspheres have radioactive property. These having diameter ranging in between 10-30nm that are larger than the capillary. These microspheres are injected to halt tumor via blood supply and these only effects the cancer cells and don't affect the nearby tissue [8, 20].

Polymeric microspheres

These microspheres matrix is made either from synthetic polymeric material or the biodegradable polymer material and the medication is released in the body from one of this material [20]. Polymeric microspheres further divided in biodegradable polymeric microspheres (swelling property with aqueous medium) and synthetic polymeric microspheres (used as filters, bulking agent, embolic particles, drug vehicle etc.) [21, 22].

Magnetic microspheres

In this kind of drug delivery system, free circulating drug is replaced by the magnetic carrier that receives magnetic response and act at target sites [15, 16].

Mechanism of Floating microspheres

The microspheres having outer surface is formed of gel, carbohydrate and polymer. After their administration they came in contact with the acid in stomach due to which the outer layer of the floating microspheres hydrates and form a colloidal gel barrier that regulates the flow of the drug as well as the gastric fluid in and out of the microspheres. Due to this barrier the air molecule traps inside it, thus decreasing its bulk density and help it to float over the surface of the gastric fluid. For maximum cases a minute amount of gastric fluid is necessary for the floatation of the dosage form.

Diffusion: the movement of the gastric fluid starts inside the microsphere thus entrapping air inside it and helps it to float.

Erosion: this steps place takes with the passage of time. The acid help in the erosion of the outer shell of the dosage form.

Osmosis: this is the movement of the drug from the higher concentration to the lower concentration. The aqueous fluid in GIT comes inside and leads to increase the concentration in the interior of the particle that helps in the movement of drug to the adsorption site [26-28].

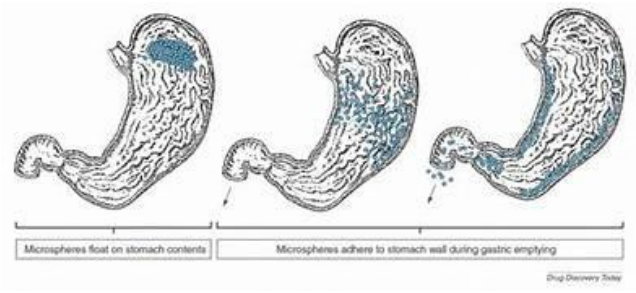

Figure 2: Mechanism of gastro retention of floating microspheres [27]

CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEM

- Effervescent system
- Non-effervescent system

Effervescent system

In this system generation of carbon dioxide bubbles leads to the bouncy of the drug. This system consists of the carbonate or bicarbonate that reacts with the natural acid present in the stomach or with the tartaric acid which leads to the formation of carbon dioxide. Effervescent is further classified as
A: volatile liquid containing system
B: gas generating system

Volatile liquid containing system

This system comprises of deformable unit that expands from the collapsed position and then return to collapsed position from expanded position to increase the period of time for the drug delivery [34].

Gas generating system

In this system the matrix is incorporated with bicarbonate material when react with acid environment leads to the formation of carbon dioxide thus decreasing their bulk and help them to float over the gastric fluid [35, 36].

Non-effervescent system

In this system when the drug is swallowed, it reacts with gastric fluids and swells thus decreasing its bulk density and prevents it's existed from the stomach thus increasing its residual time in stomach. It is of different type-

- Micro porous compartment system
- Floating micro-balloon
- Colloidal gel barrier system
- Alginate beads

Micro porous compartment system

In this the drug is placed inside the micro porous compartment having pores along its bottom and top wall. The floatation chamber entraps the air and then the system starts floating over the gastric fluids.

Floating micro-balloon

They have the diameter ranging from 10-300µm. They are made from synthetic form or light weight concrete and are hollow glass microspheres in nature [29].

Colloidal gel barrier system

This type of system contains hydro-colloidal gel form which helps the drug to remain floating on the gastric content.

Alginate beads

These types of dosage form are developed by freeze drying of calcium alginate having a diameter of approximately 2-5mm that are prepared by dropping sodium alginate into aqueous solution of calcium chloride this formation of the precipitate of calcium alginate. When administered it leads to the formation of porous system that helps it to buoyant over the gastric fluid for over 12hours [37].

Factors affecting gastric residence time

- Density of dosage form
- Shape and size
- Food intake and its nature
- Effect of gender and age

Density of dosage form

Dosage form must have the density lower than that of gastric content which allow them to float to the surface otherwise dosage form sink to the bottom due to high

density of dosage form determines the location of system in the stomach and also effect the gastric emptying rate. The dosage form should have density <1.0gm/cm^3 to show buoyant property.

Shape and size

The drugs or the dosage form having larger size will have greater gastric retention time than that of smaller size dosage forms. Larger size dosage form would float due to their less density and would not allow them to pass quickly into the intestine. Ring shape dosage forms have high gastric residual time.

Food intake and its nature

Presence of food increases the gastric residual time in the stomach due to their absorption of drug increase at the site of absorption.

Effect of gender and age

Young people have faster gastric emptying rate and time while the elderly people have slower gastric emptying time. As in the case of gender male have faster gastric emptying rate then female.

Method of preparation of gastro-retentive floating microspheres

- Spray drying methods
- Solvent evaporation methods
- Single emulsion technique
- Double emulsion method
- Solvent extraction method
- Quasi emulsion solvent diffusion method

Spray drying methods

The polymer is dissolved in volatile organic solvent such as acetone and dichloromethane. Solid form of drug is obtained which is then dispersed in the polymer solution with homogenization at higher speed. Then the material is passed through the stream of hot air which helps in dispersion at atom level. This leads to the formation of fine mist or the small droplets. Which result in the formation of microspheres which are then separated by cyclone separator with the help of hot air. After the traces of solvent is removed from the microspheres using vacuum drying method [31-33].

Solvent evaporation method

The creation of hollow inner core is done by the solvent evaporation and solvent diffusion method. The core material is dispersed in coating polymer solution that helps its micro encapsulation. Core material is dispersed with the help of agitation process in vehicle phase to obtain micro capsule. Then the mixture is heated which leads to the shrinkage of the polymer around the core [20, 23].

Single emulsion technique

The micro particles are dissolved in natural polymer. These polymers are then dispersed in aqueous medium after that dispersion is dissolved in non-aqueous medium which help in cross linkage. Cross linkage can also be achieved by means of heating.

Double emulsion method

Double emulsion method contains w/o/w type which is suitable for vaccine; protein etc. method is useful for both synthetic and natural polymer. It involves the dispersion of the protein solution in lipophilic organic phase. This phase is then dispersed in aqueous phase. Then it is dried and micro sphere is obtained [7].

Solvent extraction method

It is achieved by the removal of the organic phase by the extraction off non aqueous solvent. With the help of heat organic phase can be removed from the solution. Hardening time of microspheres is decreased. Thus, micro particle is prepared. [7, 24, 25].

Quasi emulsion solvent diffusion method

Micro-sponges contain internal and external phase. The internal phase consists of drug and external phase consists of distilled water and polyvinyl alcohol. Internal phase is manufactured at 60^0c and allows cooling till it attains normal room temperature. It is the added to external phase. Emulsification process is achieved by continuous stirring for 2 hrs. Filter separation of micro sponges can be achieved by filtration. The filtered particles are then washed and dried by vacuum oven for 24 hrs at 40 $^{\circ}$C [24, 25].

EVALUATION OF GASTRO RETENTIVE FLOATING MICROSPHERES

- Fourier Transform Infra-Red (FTIR) spectroscopy study
- Angle of Repose
- Bulk Density

- Hausner's Ratio
- Buoyancy Lag Time/ Duration of Buoyancy
- Compressibility Index
- Surface Morphology
- *In-vitro* Release study
- *In-vivo* Evaluation

Fourier Transform Infra-Red (FTIR) spectroscopy study

It is used to determine the chemical interaction of the polymeric material with that of the drug during the manufacturing of the microspheres.

Angle of Repose

It is the steepest angle at which a sloping surface formed of loose material is stabled. It is also known as the critical angle of repose that range in between 0^0-90^0. It is measured by height of the pile to the radius of the pile.

It is calculated by formula:

$$\theta = \tan^{-1} h/r$$

Where, θ = angle of repose
h = height of pile
r = radius of pile

Table 1 **Relationship between angle of repose and static cohesive index.**

Flow	Repose Angle (^{O})	Static Cohesive Index
Excellent	25-30	<0.2
Good	31-35	0.3-0.5
Fair	36-40	0.6-0.8
Passable	41-45	0.9-1.2
Poor	46-55	1.3-1.7
Very Poor	56-65	1.8-2.4
Very -Very Poor	>65	>2.5

Bulk density

It is determined by the weight of the microspheres in gram divided by the bulk volume of the microspheres in milliliter.

Bulk density = weight of microspheres (gm) / bulk volume of microspheres (ml)

Hausner's Ratio

This ratio is named after engineer Henry H Hauser. It is calculated by Tapped density by Bulk density.

Buoyancy Lag Time/ Duration of Buoyancy

It was determined by the floating lag time method that was given by Dave B.S. In this method 300mg of microspheres rises to the surface and the float was determined. It is the time between introduction of microspheres at its buoyancy in 0.1N HCL and the time during which microspheres remain buoyant was determined. The process is performed in USP Type II Dissolution apparatus (paddle system) by visual method.

Compressibility Index

Compressibility index is determined by given mathematical formula:

Compressibility index = [(tapped volume – bulk volume) / tapped volume] *100

Surface morphology

It is part of analytical imaging where high spatial resolution image of product are produced using sophisticated microscope that cannot be seen with the naked eye. These images are originating from the exposed of surface of the sample product.

***In-vitro* drug release study**

This study is done using the USP Type-I Dissolution Apparatus. The apparatus is adjusted at 37 $\pm$ 0.5 $^{\circ}$C at 100 RPM. The dissolution media used in this experiment is 0.1N HCL (900ml) having 1.2 pH. After each given interval 5ml sample is taken out and replaced from the dissolution media of equal volume in each interval. Then the sample absorbance is determined at given wavelength using UV spectrophotometer.

In-VIVO evaluation (Gamma Scintigraphy)

It helps to predict the position of dosage form in GIT tract and also determine the gastric emptying time with its passage. The radio opaque material that is used in solid dosage form can be seen using X-rays [44,45].

CONCLUSION

Among the ADME process the absorption of the drug take place in the GI tract when administer orally. The absorption process shows high variance in the GI tract. Floating microspheres type of dosage form that is commonly used worldwide as these shows major usefulness according to patient required in term of usage and therapeutic action. Floating microspheres are used in the case of gastric retention dosage form. These prolong the duration of the

drug absorption. These also helps in drug absorption on the upper part of the GI tract i.e. stomach, duodenum & jejunum. Major companies are advancing their research as well as increasing their focus in the manufacturing of floating microspheres.

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