IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Floating Microspheres Review Article

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Abstract:

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. FDDS can be divided into non-effervescent and gas-generating system. The floating microspheres (Hollow Microspheres) are the gastro-retentive drug delivery systems based on non-effervescent approach. Hollow microspheres are in strict sense, spherical empty particles without core, free flowing powders consisting of proteins or synthetic polymers, ideally having a size in the range 1-1000 micro meter. Gastro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. The drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration.

Keywords: Microsphere, Gastro retentive, Hydrogels, Floating drug delivery system.

INTRODUCTION

The aim of any drug delivery system is to offer a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration. Oral drug administration is by far the most preferable route for taking medications. Oral route has been received more consideration in the pharmaceutical field because of the more flexibility in the designing of dosage form than drug delivery design for other route.[1] However, most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit, variable gastric emptying lead to nonuniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach.[2] These physiological restrictions limit the therapeutic potential of many drugs. Such a pharmacokinetic limitation leads in many cases to frequent dosing of the medication to achieve therapeutic effect.[3] This results in pill burden and consequently, patient complains. The gastric emptying of dosage form in humans is affected by several factors because of which wide inter and intra-subject variations are observed. Since many drugs are well absorbed in the upper part of the gastrointestinal tract, such high variability may lead to non-uniform absorption and makes the bioavailability unpredictable.[4] Hence a beneficial delivery system would be one which possesses the ability to control and prolong the gastric emptying time and can deliver drugs in higher concentrations to the absorption site (i.e. upper part of the small intestine) Further incomplete release of the drug and a shorter residence time of dosage forms in the upper gastrointestinal tract (prominent site for absorption of many drugs) will lead to lower bioavailability.[5]

The Floating drug delivery system (FDDS) is of special interest in improving the bioavailability of drugs that are poorly soluble or unstable at higher pH of the intestinal or colonic environment1. In order to obtain local and sustained drug delivery in the stomach and proximal parts of the small intestine, it is desired to have prolonged gastric retention of the drug. This helps to have improved bioavailability and therapeutic efficacy which may also results in the reduction in dosing frequency of the dosage form.2-6 The diminished efficacy of the administered dose may be observed due to inter-subject variability and short time of gastric emptying which may results because of incomplete drug release from the drug delivery system above the absorption zone (stomach ,upper part of small intestine).[6] Moreover, it has been reported that drug delivery system is one of the commercial system which is attributed to obtain the higher bioavailability than that of the non floating system.[7] The FDDS system is widely useful for the drugs which effectively act in the stomach and have absorption window in stomach.[8.] To formulate FDDS the drug moiety should have good solubility at acidic pH and absorption window in upper GIT. In the present study, an attempt was made to develop GRDDS for CP using Ethyl cellulose and HPMC as a release retarded material by solvent evaporation technique.[9] The prepared CP microspheres were evaluated for drug content, particle size, percentage yield, entrapment efficiency, particle size distribution, surface morphology, in vitro drug release and stabilities studies[10]

PHYSIOLOGY

The stomach is J-shaped organ situated in the upper left hand portion of the abdomen, just below the diaphragm.[11] It occupies a portion of the epigastric and left hydrochondriac region. The main function of the stomach is to store the food temporarily, grind it and then release it slowly into the duodenum. Very little absorption takes place from the stomach due to its small surface area. It provides barrier to the delivery of drugs to small intestine. Stomach is a collapsed bag with a residual volume of 50 ml and contains a small amount of gastric fluid (pH 1-3) and air under fasting condition.[12] Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions 3-5. Gastric emptying occurs during fasting as well as fed states.[15] The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases.[13] An entire cycle of these four phases has an average duration of 90 to 120 minutes.[14] Phase III has a housekeeping role and serves to clear all indigestible materials from the stomach and the small intestine. Therefore, any controlled release gastrointestinal drug delivery system designed to stay during the fasted state should be capable of resisting the house keeping action of phase III, if one wants to prolong the GI retention time. Scintigraphic studies involving the measurements of gastric emptying rates in healthy human subjects have revealed that an orally administered controlled release dosage form is mainly subject to two physiological adversities:[15]

1. Short gastric retention time (GRT)

2. Unpredictable gastric empty time (GET)

Under physiological conditions, the gastric absorption of the most drug is insignificant due to its limited surface area (0.1-0.2 m2) covered by a thick layer of mucous coating, the lack of villi on the mucosal surface, and the short residence time of most drug in the stomach. Oral route is considered to be highly suitable route and frequently used for delivery of drug due to ease of administration, patient compliance and flexibility of formulation. The success of oral controlled delivery system depends on the fact that the drug can be better absorbed from GI tract. But the main problem with conventional delivery is to maintain the drug concentration within the therapeutic effective concentration level, [16] which can be achieved only when taken several times a day. Although attempts have been made to develop controlled release delivery

systems for oral route but various limitations like variable drug absorption, uncontrolled gastric transit time have established the need of more intelligent drug delivery systems, which can prolong the transit time of drug, or provide effective concentration locally.[17] The gastro retentive drug delivery system can be retained in the stomach and help in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the GI tract. Various methods have been designed to increase the gastric residence time (GRT) which include: floating drug dosage systems (FDDS), swelling or expanding systems, mucoadhesive systems and high-density systems.[18] These system give advantage in improving bioavailability of drugs that have a narrow absorption window, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It also has applications for local drug delivery to the stomach and proximal small intestines. Floating microspheres are gastroretentive drug delivery systems based on non-effervescent approach. They are spherical empty particles without core.[21] These microspheres are characteristically free flowing powders consisting of protein or synthetic polymers with diameters 1 μm to 1000 μm. Hydro dynamically controlled drug delivery systems (Floating drug delivery system) are low density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.[19] The sustained release of drug from floating systems improves the gastric retention of drugs and reduces the fluctuations in plasma drug concentration. Commonly used polymers to prepare floating microspheres include polycarbonate, HPMC, cellulose acetate, calcium alginate, Eudragit S, chitosan etc. Thus floating microspheres are considered as one of most promising buoyant systems.[20]

Novel drug delivery system delivers a therapeutic substance to the target site in a well-controlled and sustained model.1 Microspheres or microparticles are defined as a free-flowing spherical articles consisting of polymer matrix and drug. They consist of proteins or synthetic polymers which are biodegradable in nature having a particle size less than 200μm.2 Microspheres.[21] The dug should be delivered to specific targetsites at a rate and concentration that permit optimal therapeutic efficacy while reducing side effect to minimum and patient compliance during therapy. Site specific delivery with absolute accuracy can be achieved by attaching bioactive molecule to liposome, bioerodible polymer, implants monoclonal antibodies and various particulate carriers (Ex. Nanoparticles and microspheres etc) the micro particulate delivery system if modified then maintains the desired concentration at the site of interest without side effect. The term microcapsule is defined as a spherical particle with size varying from 50 nm to 2nm containing a core substance.[22] Alternate terminology for the microsphere is microbeads and
-beads are used alternatively.

History: between 1940s and 1960s, the concept of chemical microencapsulation technology began as an alternative means of delivering drugs. In continued quest for the more refined systems' in 1980s polymer/Membrane technology came to be known at forefront The polymers and other material utilized for the preparation of microsphere should give following **characteristics:**

Target ability, Polyvalent, Biocompatibility, Longer duration of action, Sterlizability, Relative stability, Water solubility, Control of content release, Bioresobability, Water solubility and dispensability, Reduction of toxicity, Protection of drug.

ADVANTAGES [23]

1. Microspheres provide constant and prolonged therapeutic effect.
2. Reduces the dosing frequency and there by 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 allows a controllable variability in degradation and drug release.

Polymer used in preparation of floating microspheres.[24]

Materials used in the formulation of microsphere. Microspheres are usually made of polymers, they are classified as follows.

Synthetic Polymers Natural polymers

i. Non-biodegradable polymers Poly methyl methacrylate (PMMA) **Acrolein**

Glycidyl methacrylate Epoxy polymers

ii. Biodegradable polymers5, 6 Lactides, Glycolides & their co polymers Poly alkyl cyano Acrylates

Poly anhydrides

Natural polymers obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates.

A] Proteins:

Albumin Gelatin9 Collagen

B] Carbohydrates:

Agarose Carrageenan Chitosan10 Starch

C] Chemically modified carbohydrates:

Poly dextran11 Poly starch

TYPES OF MICROSPHERES

Microspheres are classified into different types. They are of following

1. Bioadhesive microspheres
2. Magnetic microspheres
3. Floating microspheres
4. Radioactive microspheres
5. Polymeric microspheres

I. Biodegradable polymeric microspheres

II. Synthetic polymeric microspheres

1. Bioadhesive microspheres

Sticking of drug to the membrane by using the water soluble property of the water-soluble polymers is called adhesion. Sticking or adhesion of drug delivery system to the mucosal membrane such as buccal, nasal, ocular, rectal etc can be termed as bioadhesion. This type of microsphere provides prolonged residence time at the target site and provide better therapeutic action.

2. Magnetic microspheres

This type of delivery system localizes drug to the target site. In this type of delivery system, a drug or therapeutic radioisotope bound to a magnetic component is injected in the systemic circulation, which is then stopped with powerful magnetic field in the disease/target site. Magnetic microspheres are molecular particles which are small enough to move across capillaries without creating an esophageal occlusion(<4μm) but are extremely sensitive (ferromagnetic) to be trapped in micro-vessels and drawn by a magnetic field through neighbouring tissues. Here larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug. There are different kind of magnetic microsphere. They are • Therapeutic microsphere- They are used to target anticancer agents to liver tumors. This helps in tumor cell eradiation without harming the nearby cells. • Diagnostic microsphere- They are used for

imaging liver metastases and also can be used to distinguish bowel loops from other abdominal structures by forming nano size particles supramagnetic iron oxides.

3. Floating microspheres

In floating type, the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, and the system is found to be floating on gastric contents and decrease gastric residence and increases fluctuation in plasma concentration. Moreover, it also reduces chances of dose dumping. It produces prolonged effect and so reduces dosing frequencies.

4. Radioactive microspheres

Radio embolization therapy microspheres sized 10-30nm are of larger than the diameter of the capillary bed when they come across. They are injected in the arteries that lead them to tumour of interest so all these conditions radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues. Here radioactivity is not released from microsphere but acts within a radioisotope in typical distance. The different types of radioactive microspheres are α emitters, β emitters and ϒ emitters.

5. Polymeric microspheres

Polymeric microspheres can be classified as biodegradable polymeric microsphere and synthetic polymeric microspheres

METHOD OF PREPARATION

The choice of technique depends upon the nature of polymer as well as nature of drug and the duration of therapy. The most important physical and chemical factors that may be controlled in microsphere manufacture are

- The particle size requirement
- Molecular weight of polymer
- Polymer to drug ratio
- Stability problem
- Reproducibility
- Total mass of drug and polymer
- Dispersibility in aqueous vehicle

CRITERIA FOR MICROSPHERE PREPARATION

Incorporation of solid, liquid or gases into one or more polymeric coatings can be done by micro encapsulation technique. 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, coprecipitation etc. Preparation of microspheres should satisfy certain criteria

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 controllable biodegradability. Susceptibility to chemical modification.

TECHNIQUES FOR MICROSPHERE PREPARATION

1. Solvent evaporation
2. Single emulsion technique
3. Double emulsion technique
4. Phase separation coacervation technique
5. Spray drying and spray congealing
6. Solvent extraction
7. Quassi-emulsion solvent diffusion

1. Solvent evaporation

Solvent evaporation is carried out in a manufacturing vehicle phase. The microcapsule coating is first dispersed in A volatile solvent which is immiscible with the liquid manufacturing vehicle phase. In a coating polymer solution, a core material to be microencapsulated is dissolved or dispersed. To obtain acceptable size microcapsule, agitation is performed so that the core material mixture is dispersed in the liquid manufacturing vehicle phase. If necessary, the mixture is heated to evaporate the solvent. If the core material is dissolved in the coating polymer, matrix-type microcapsules are formed. The core material may be either water soluble or water insoluble material. Solvent evaporation involves the formation of an emulsion between polymer solution and an immiscible continuous phase whether aqueous (o/w) or non-aqueous.

2. Single emulsion technique

The microparticulate carriers of natural polymers i.e. those of proteins and carbohydrates can be prepared by single emulsion technique. The natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in non-aqueous medium such as oil. In the next step, cross linking can be achieved either by means of heat or by using the chemical cross linkers. The chemical cross-linking agents used are glutaraldehyde, formaldehyde, acid chloride etc. Heat denaturation is not suitable for thermolabile substances. Chemical cross linking suffers the disadvantage of excessive exposure of active ingredients to chemicals if added at the time of preparation. It is then subjected to centrifugation, washing and separation. The nature of the surfactants used to stabilize the emulsion phases can greatly influence the size, size distribution, surface morphology, drug loading, drug release and bio performance of the final multiparticulate product

3. Double emulsion technique

Double emulsion method of microsphere involves the formation of the multiple emulsion or double emulsion of type w/o/w and is best suited for water soluble drugs, peptides, proteins and the vaccines. This method can be used with both the natural as well as synthetic polymers. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. The continuous phase generally consists of the polymer solution that eventually encapsulates protein contained in dispersed aqueous phase. The primary emulsion is then subjected to the sonication before addition to the aqueous solution of the polyvinyl alcohol (PVA). This results in the formation of a double emulsion. The emulsion is then subjected to a solvent removal either by solvent evaporation or by solvent extraction. A number of hydrophilic drug like luteinizing hormone (LH-RH) agonist, vaccines, proteins/peptides and conventional molecules are successfully incorporated into the microspheres using method of double emulsion solvent evaporation/extraction.

4. Phase separation coacervation technique

This technique is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase called coacervates. In this process, the drug particles are dispersed in a polymer solution and an incompatible polymer is added which makes the first polymer to phase separate and engulf the drug particles. In order to avoid agglomeration stirring should be done.

5. Spray Drying and spray congealing

These processes are based on the drying of the mist of the polymer and drug in the air. Depending upon the removal of the solvent or cooling of the solution, two processes are named spray drying and spray congealing respectively. In spray drying, the polymer is dissolved in a volatile organic solvent such as dichloromethane, acetone etc. The drug in solid form is dispersed in the polymer solution with highspeed homogenization. This dispersion is then subjected to atomization in a stream of hot air. The atomization leads to the formation of small droplets or the fine mist from which the solvent evaporates instantaneously leading to the formation of the microspheres in a size range 1-100µm. Microparticles are separated from the hot air with the help of cyclone separator while the trace of solvent is removed by vacuum drying. One of the major advantages of this process is feasibility of operation under aseptic conditions.

6. Solvent extraction

Solvent evaporation has been extensively used for the preparation of PLA and PLGA microspheres which contain various drugs. Several variables are identified that can significantly affect microspheric characteristics, such as solubility of drug, internal morphology, type of solvent, diffusion rate, temperature, polymer composition, viscosity, and drug loading. The efficacy of this method relies on the effective entrapment of the active substance into the particles, and therefore this procedure is particularly efficient with drugs that are either insoluble or partially soluble in the liquid medium.

7. Quassi emulsion solvent diffusion

Quasi-emulsion solvent diffusion method is used for the manufacturing of the controlled release microspheres of drugs with acrylic polymers. Microsponges can be manufactured by this method by using external phase which contains distilled water and polyvinyl alcohol. Internal phase consists of the drug, ethanol and polymers. Firstly, the internal phase is heated at 60ºC and added to the external phase in the room temperature. The mixture is stirred continuously for 2 hours. Then the mixture can be filtered for separation of the microsponges.

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