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Review Article

Floating Microspheres: Recent Researchs

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Abstract

The purpose of writing this review on floating microspheres was to compile the recent literature with special focus on various gastro retentive approaches that have recently become leading methodologies in the field of orally controlled drug delivery to overcome physiological adversities such as short gastric residence times and unpredictable gastric emptying times. Floating microspheres enhances drug bioavailability; reduce drug excretion and controlled drug delivery and better patient compliance.

Keywords: Hydro dynamically controlled drug delivery systems; Microspheres; Gastroretentive

Introduction

The main purpose of nano drug delivery system is to provide a therapeutic amount of drug to the specific site of action in the body, to achieve desired effect and then maintain the desired drug concentration [1]. Oral controlled release drug delivery systems offer great advantages over the conventional dosage forms. Drugs with a narrow absorption window in the GIT, easily absorbable drugs and having a short half-life are eliminated quickly from the body. To avoid these problems various delivery systems have been developed as they release the drug slowly into the GIT and maintain a constant drug concentration in the body for prolonged period of time. A number of oral controlled release drug delivery systems such as hydro dynamically balanced drug delivery system (floating), oral osmotically driven drug delivery

systems and pH controlled drug delivery system, etc. This result in a higher bioavailability and better patient compliance [1,2].

Floating microspheres are gastro-retentive drug delivery system based on non-effervescent approach and characteristically free flowing powders consisting of proteins 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. While the dosage form floats on the gastric contents, the drug is released continuously at the desired rate from the system. This results in an increased Gastric retention time and a better control of the fluctuations in plasma drug concentration [3].

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Mechanism of Floating Microspheres

Floating systems or Hydro dynamically controlled

drug delivery systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in stomach for prolonged period. While the dosage form floats on the gastric contents, the drug is released continuously at the desired rate from the system resulting in increased gastric retention with reduced fluctuations in plasma drug concentration. When floating microspheres come in contact with gastric fluid all other ingredients 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 microspheres dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air entrapped by the polymer lowers the density and confers buoyancy to the microspheres but a minimal gastric content needed to allow proper achievement of buoyancy [3-5].

Techniques used in the preparation of microspheres

The different methods used for various microspheres preparation depends on route of administration, duration of drug release and particle size. The various methods of preparations are [1,4,6]

Emulsion solvent evaporation technique:

The drug is dissolved in chloroform and then dissolved in polymer and the resulting solution is added to aqueous phase containing 0.2% sodium of PVP as emulsifier. This mixture was stirred at 500 rpm then the drug and polymer (Eudragit) was transformed into fine droplet which solidified into rigid microspheres by solvent evaporation and then collected by filtration and washed with demineralized water and desiccated at room temperature for 24 hrs. For these techniques, there are basically two systems which include oil-in-water (o/w) and water-in-oil (w/o) type.

Oil in water solvent evaporation technique:

In this technique, both the drug and the polymer should be insoluble in water while a water immiscible solvent is required for the polymer. The polymer is dissolved in an organic solvent such as dichloromethane, methanol and chloroform. The drug is either dissolved or dispersed into polymer solution and this solution is emulsified into an aqueous phase to make an oil-in water

emulsion by emulsifying agent. After that the organic solvent is decanted and the micro particles are separated by filtration.

Water-in-oil emulsification solvent evaporation technique:

This water-in-oil emulsification process is also known as non aqueous emulsification solvent evaporation. Drug and polymers are co dissolved at room temperature with vigorous agitation to form uniform drug-polymer dispersion. This mixture is poured into the dispersion medium consisting of light / heavy liquid paraffin in the presence of oil soluble surfactant such as Span. Then this mixture is stirred using propeller agitator at 500 rpm over a period of 2-3 h to ensure complete evaporation of the solvent. The liquid layer is decanted and micro particles are separated by filtration through a Whitman filter paper, washed with n-hexane and dried for 24 h and subsequently stored in desiccators.

Emulsion-solvent diffusion technique:

The drug polymer mixture was dissolved in a mixture of ethanol and dichloromethane (1:1) and then the mixture was added drop wise to sodium lauryl sulphate solution. The solution was stirred with propeller type agitator at room temperature at 150 rpm for 1 hour and formed floating microspheres were washed and dried in a desiccator at room temperature.

Ionic gelation technique: The drug was added to 1.2% (w/v) aqueous solution of sodium alginate and continue stirring is preferred for complete solubility. After that it was added drop wise to a solution containing Ca^{2+} / Al^{3+} and chitosan solution in acetic acid. Microspheres were kept in original solution for 24 hr for internal gelification followed by filtration for separation. The maximum release of the drug was obtained at pH 6.4-7.2. Alginate/chitosan particulate system for diclofenac sodium release was prepared using this technique.

Single emulsion technique: Micro particulate carriers of natural polymers (proteins and carbohydrates) are prepared by single emulsion technique. The natural polymers (proteins and carbohydrates) are dispersed in aqueous media followed by dispersion in

non-aqueous medium like oil with the help of cross linking agent.

Double emulsion technique: Double emulsion technique is the formation of the multiple emulsions or the double emulsion such as w/o/w.

Coacervation phase separation technique: It is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase known as co-acervates. The drug was dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles.

Polymerization technique: The polymerization techniques conventionally are mainly classified as:

Normal polymerization: It is carried out using different techniques of polymerization like bulk, suspension, precipitation, emulsion and micellar polymerization processes.

Interfacial polymerization: This technique involves the reaction of a range of monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed.

Spray drying and spray congealing: These methods are based on the drying of the mist of the polymer and drug in the air. The polymer is dissolved in a suitable volatile organic solvent such as dichloromethane, acetone and methanol etc. The drug in the solid form is then dispersed in the polymer solution under high speed homogenization. This mixture is then atomized in a stream of hot air. The atomization prompts the formation of the small droplets or the fine mist from which the solvent evaporates instantaneously leading the formation of the microspheres in a size range 1-100 μm . Depending upon the removal of the solvent or cooling of the solution are named spray drying and spray congealing respectively.

Recent research on Fdds

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. FDDS guarantees to be a potential methodology for gastric maintenance. Dosage forms with a delayed GRT will bring about new and important therapeutic options. The currently accessible polymer-intervened Non effervescent and effervescent FDDS, outlined on the premise of delayed gastric emptying and buoyancy principles, appear to be a very much successful methodology to the modulation of controlled oral drug delivery [6].

Based on the literature surveyed, it may be concluded that gastro retentive drug delivery offers various potential advantages for drug with poor bioavailability due their absorption is restricted to the upper gastrointestinal tract (GIT) and they can be delivered efficiently thereby maximizing their absorption and enhancing absolute bioavailability [7].

Gastro-retentive floating drug delivery systems have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs. Administration of prolongs release floating dosage forms will result in dissolution of the drug in the gastric fluid. It is expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine [8].

The tablets prepared by combination of xanthan gum and guar gum could be more efficient on floating and sustained release of atenolol as compared to the tablets prepared by using natural gum alone. The natural hydrophilic polymer based matrix tablets as carrier for controlled release delivery has been widely and successfully use due to their ease of manufacturing, relatively low cost, favorable *in vivo* performance and versatility in controlling the release of drug with wide range of physicochemical properties [9].

Formulated sustained release microspheres of acarbose were prepared by emulsification solvent evaporation method to obtain high entrapment efficiency (88.9%). The drug release from the microspheres was

affected by the pH of the dissolution medium. *In vitro* drug release of 95.83% over the period of 12 h was obtained. The finding of every last one of the investigations have conclusively demonstrated that loading of acarbose into microspheres improves therapeutic response, patient compliance by reducing the dosing frequency and considerable reduction in side effects associated with the sudden release of drug from conventional dosage form in the systemic circulation by providing sustained release from the polymer matrix. From this study, it is concluded that acarbose can be loaded to sustained release microspheres for the treatment of diabetes with better patient compliance and improved efficacy [10].

Formulated hydro dynamically balanced tablet of an antibacterial drug clarithromycin can be formulated as an approach to increase gastric residence time and thereby improve its bioavailability. The drug release of formulation F3 was 82.56% up to 6 hrs as compared to other prepared formulation. It is useful for achieving controlled plasma level as well as improving bioavailability. Floating matrix tablets are designed to prolong the gastric residence time after oral administration at a particular site [11].

Formulated Hydrogel matrix tablets of Acarbose using hydroxypropyl methyl cellulose and guar gum with the aim to study of release kinetics and to attain a near zero order release. The release of drug followed a typical Higuchian pattern. *In vitro* dissolution studies were carried out using USP type 2 dissolution test apparatus. Matrix tablets formulated employing hydroxypropyl methyl cellulose and guar gum slow release of Acarbose over a period of 12 h and were found suitable for maintenance portion of oral controlled release tablets. Release of acarbose from these tablets was diffusion controlled and followed zero order kinetics after a lag time of 1 h [12].

Formulated Monolithic matrix tablets of Acarbose as controlled release tablets employing Hydroxypropyl methylcellulose and Eudragit in different concentrations and combinations, and investigated sustained release behavior of the fabricated tablets. Controlled released matrix tablets containing 350 mg Acarbose were developed using different drug:polymers combi-

nation. *In vitro* drug release was carried out using USP Type II at 50 rpm in 900 ml of acidic dissolution medium (pH 1.2) for 1 hr, followed by 900 ml alkaline dissolution medium (pH 7.4) upto 12 hr. Their result suggested that the drug release rate was strongly influenced by the type of polymer and concentration of polymer. To analyze the release mechanism Higuchi model, Kosmeyer-Peppas's model and zero model were used [13].

Kumar et al. [14] have developed Spectrophotometric Method for Acarbose from bulk and in its tablet dosage form. A simple rapid Spectrophotometric method has been developed for estimation of Acarbose from bulk drug and tablet dosage form by using potassium permanganate and sodium hydroxide. The technique is taking into account the formation of green colored complex of drug with 0.1 N antacid or alkaline potassium permanganate having absorbance maxima at 625 nm. The method is applied to the marketed tablet formulation. The developed method was found to be simple, sensitive and reproducible and can be used for routine analysis of Acarbose from bulk and tablet dosage form.

Mona et al. [15] have formulated floating microsphere of ofloxacin to develop gastroretentive formulation. These floating microspheres release the drug in the stomach and upper GIT and thereby improve the bioavailability.

Sharma et al. [16] have developed floating microspheres of Eudragit S100 containing Clarithromycin drug in it. For developing microspheres different process variables were optimized. Optimum surfactant concentration was found to be 0.75% w/v, optimum stirring speed was found to be 400 rpm, optimum temperature was found to be 37°C. The resulted Floating microspheres in sustained and prolonged release of drug in the GIT fluids. He concluded that more than 80% of entrapped drug was released in 24 hours.

Najmuddin et al. [17] have prepared floating microspheres of ketoprofen using Eudragit S 100 and Eudragit L 100 as polymer by emulsion solvent diffusion technique. The floating microspheres were assessed such as micromeritic properties, *in vitro* buoyancy, incorporation efficiency, drug polymer compatibility (IR study), scanning electron microscopy and drug release

of microspheres. The micromeritic properties were good and scanning electron microscopy confirmed their hollow structure with smooth and round surface. Formulation EU2 prepared with Eudragit S 100 drug:polymer ratio (1:2) which exhibited all excellent properties and percentage drug release 92.26% for a period of 12 hrs.

Kumar et al. [18] have prepared floating microsphere of curcumin by emulsion solvent diffusion method, using hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC), Eudragit S 100 polymer in varying ratios for prolonged gastric residence time and increased drug bioavailability. The floating microspheres showed excellent buoyancy, drug entrapment efficiency and yield in the ranges of 251-387 μm , 74.6-90.6%, and 72.6-83.5%, and 45.5-82.0%, respectively. The developed curcumin microsphere system is a promising floating drug delivery system for oral sustained administration of curcumin.

Pandey et al. [19] have prepared a floating drug delivery system of famotidine by solvent evaporation (Oil-in-water emulsion) technique using hydroxypropyl methylcellulose (HPMC) and Ethyl cellulose (EC) as the rate controlling polymers. Resulting microspheres showed that the polymer ratio and stirring speed affected the size, buoyancy and drug release of microspheres (> 12 h), floating time (> 12 hr) and the best results were obtained at the ratio of HPMC:EC (1:6).

Dharappa et al. [20] have formulated floating hollow microspheres of Rosiglitazone Maleate (RSM), which is soluble and shows better absorption in gastric pH. Microspheres were prepared by modified Quasi-emulsion diffusion technique using ethyl cellulose, eudragit S100, polyethylene oxide and Hydroxypropyl methyl cellulose (HPMC K15M) as polymers. The formulations were evaluated for micromeritic properties, *in vitro*, *in vivo* buoyancy, entrapment efficiency, *in vitro* and *in vivo* release studies. FT-IR and DSC studies indicated that there was no interaction between the drug and polymers and concluded that gastric floating hollow microspheres can be successfully used for the delivery of rosiglitazone maleate to control blood glucose level.

Irisappan et al. [21] have prepared floating microspheres of cefdinir for the prolongation of gastric residence time by using capillary extrusion method. And he

revealed that increase in concentration of gum karaya increased the drug release from the floating microspheres.

Rane et al. [22] investigated to formulate floating microspheres of Nateglinide in order to increase gastric residence time, expand bioavailability and to diminish dose frequency of drug atom. Novel o/w emulsion solvent diffusion technique was used to prepare microspheres of Nateglinide by using various polymers such as HPMC, Ethyl cellulose and Eudragit S100. Entrapment efficiency of drug was upto 69%. Eudragit S100 based microspheres which were found to be hollow cavity, spherical and porous nature from the results of scanning electron microscopy. Micromeritic profile of prepared microballoons was found attractive. From the results of FTIR spectroscopy it was detected that there is no drug- polymer interaction. Eudragit S100 based microspheres indicates good *in vitro* buoyancy and sustained release profile for longer period of time >14 hours. The formulation had followed first order kinetics as its release mechanism was diffusion controlled.

Fentie et al. [23] developed an optimized controlled release floating microspheres of furosemide capable of floating on the gastric fluid and delivering the drug over a period of 12 h. The floating microspheres were prepared by solvent evaporation method. Preliminary studies were conducted and, drug loading and EC/HPMC ratio were identified as the most important factors affecting the desired response variables: drug release rate and buoyancy. The effects of drug loading and EC/HPMC ratio were further studied and optimized. Simultaneous optimization of buoyancy and release rate was performed using central composite design and the most desirable optimal point was obtained at release rate of 27 h-1/2 and buoyancy of 58.45%, with corresponding levels of 344 mg furosemide and 4.84 EC/HPMC ratio. Evaluation of the optimized formulation showed high yield, good flow property, extended release and buoyancy over a period of 12 h and excellent drug entrapment efficiency. Comparison of the release profiles of the three different batches of the optimized formulation confirmed that there was no statistically significant difference ($p=0.302$) in the release profiles of the formulations.

Salunke et al. [24] developed floating tablets of Ciprofloxacin HCl which on oral administration prolongs its gastric residence time thereby increasing bioavailability, diminishing side effects and improved patient compliance. Ciprofloxacin an antibacterial having narrow absorption window in the upper part of gastrointestinal tract, Thus, Floating tablets were redied utilizing directly compression technique using polymers like Tamarind cmc, HPMC K4M, Ethyl Cellulose for their gel-framing properties. The HPMC alone polymer not able to controlled on release rate it release drug >90% in 12 hrs while in combination with Tamarind cmc it release >90% in 12 hrs. The results indicate that gas generated gastro retentive floating Tablets of Ciprofloxacin HCL containing Tamarind cmc and HPMCK4 provides a better option for controlled release action and improved bioavailability.

Gupta et al. [25] prepared microspheres of Ropinirole hydrochloride (RH) loaded with ethyl cellulose and carbopol 934P using solvent evaporation method. Formulations (RH1-RH5) with different ratios were evaluated for various parameters percentage yield, shape, particle size, entrapment efficiency, drug content, swelling ratio, powder X-ray diffraction studied (PXRD) and *in vitro* release studies. All the particles of formulated microspheres were in micrometric range (73.04-120.16 μm). Entrapment efficiency and percent drug content was found to be highest for formulation RH3. *In vitro* release studies revealed that all the formulations showed sustained release pattern with highest release in RH3 formulation (96.09%) and selected for further studies. Different kinetic models were connected and best fit with highest correlation coefficient (89.1/1.70) was observed in koresmeyer peppas model, showing diffusion controlled guidelines. Swelling ratio was highest for formulation RH 3 and revealed initial swelling followed by diffusion of drug from microspheres. Scaning Electron Microscopy (SEM) images of RH 3 showed that microspheres were smooth, non- porous, homogenous in size and spherical in shape. PXRD studies showed that drug was molecularly dispersed throughout the polymeric matrix. It is concluded that microspheres has improved residence time by enhancing its sustainability in body.

Conclusion and Discussion

As the floating dosage forms provides definite advantages on the bioavailability and controlled release of drug from the delivery system which are related with the polymer used which is mainly involved in controlling of drug release. Microspheres have better choice for drug delivery, particularly in diseased cell sorting targeted and effective *in vivo* delivery. Floating dosage forms have been showing high potential for gastro retention and provide an efficient means of enhancing bioavailability and controlling the release of many drugs.

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