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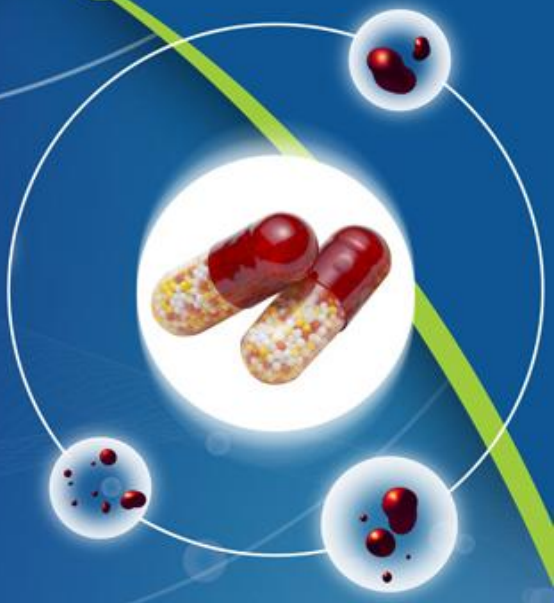

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Review Article

ADVANCES IN NOVEL DRUG DELIVERY SYSTEM EMPHASISING FLOATING MICROSPHERES FOR ULCER TREATMENT

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ABSTRACT

The purpose of writing this review on novel drug delivery system with special focus on Floating microspheres was to compile the recent literature on method of preparing the floating microspheres. Ulcers are lesions which is a discontinuity of gastrointestinal mucosa. Various medications are used to treat mild to moderate ulcers. Drugs used to treat ulcers are called anti-ulcer drugs. Floating microspheres prepared by solvent-evaporation method using polymers and solvents whose particle size analysis, scanning electron microscopy, encapsulation efficiency and drug loading, in-vitro release study, stability studies characterization was carried out which showed an improved absorption and bioavailability by retaining the system in stomach for a prolonged period of time. Significant attempts have been made worldwide to explore these systems according to patient requirements, both in terms of therapeutic efficacy and compliance. Floating microspheres as gastro retentive dosage forms precisely control the release rate of target drug to a specific site and facilitate an enormous impact on health care. This review briefly emphasizes on Gastro Retentive Drug Delivery system of anti-ulcer drug. Various categories like antacids, antidiabetic, antifungal and anticancer drugs are formulated into Floating Drug Delivery System. These systems also provide tremendous opportunities in the designing of new controlled and delayed release oral formulations, thus extending the frontier of futuristic pharmaceutical development. In the present review preparation methods, characterization, advantages, applications are discussed.

Key words: *Floating microspheres, Novel drug delivery system, Solvent evaporation method, Ulcers.*

INTRODUCTION

Conventional drug delivery system introduces therapeutic agents into the body mostly through mouth but come across various limitations of unfavorable biodistribution, low bioavailability, poor delivery to target site, low therapeutic response, toxicity, side effects, drug resistance, overcome barriers in the body (e.g. Blood Brain Barrier). Thus, these limitations lead to the development of novel drug delivery systems (NDDS)[1].

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NOVEL DRUG DELIVERY SYSTEM (NDDS)

Modern medicines treat a disease by targeting the particular affected area of the patient and transport the drug directly to that area. There are drugs which have an optimum concentration range which gives maximum result and above or below this concentration produce no or toxic effect. Also on the other hand, the very slow progression of therapy of a severe disease suggested the need for multidisciplinary approach for delivering the agent to target site. Thus, new strategy called drug delivery system (DDS) developed from ideas by controlling pharmacokinetics, pharmacodynamics, non- specific toxicity, immunogenicity etc, which combined polymer science, pharmaceutics, bioconjugate chemistry and molecular biology[2]. Drug

delivery is the process of administering a pharmaceutical compound to achieve therapeutic effect. Novel drug delivery is a vital research area which aims to achieve a programmed delivery of the therapeutic agent obtaining the beneficial effect and avoiding side effects of drugs. Novel drug delivery system provide an opportunity for formulation scientists in overcoming many challenges associated with a drug therapy, thereby improving the management of patients. Novel Drug Delivery System is an advanced drug delivery system having improved solubility, absorption, bioavailability, drug potency, control drug release to give a sustained therapeutic effect and is a desired target oriented system with a better patient compliance. This system has got a novel approach of drug delivery that mentions the limitations of the traditional drug delivery system.

TYPES OF NOVEL DRUG DELIVERY SYSTEMS:

- Sublingual that is, a drop under the tongue.
- Self adhesive patch on skin.
- Pump e.g. Insulin pump.
- Special pervious plastic injected below skin e.g. Norplant.

Drug Delivery Carries

Colloidal drug carrier systems such as micellar solutions, vesicle and liquid crystal dispersions, as well as nanoparticle dispersions consisting of small particles of 10–400 nm diameter show great promise as drug delivery systems. When developing these formulations, the goal is to obtain systems with optimized drug loading and release properties, long shelf-life and low toxicity. The incorporated drug participates in the microstructure of the system, and may even influence it due to molecular interactions, especially if the drug possesses amphiphilic and/or mesogenic properties [3,4].

RECENT DEVELOPMENTS

In recent years nanostructured carrier system like liposomes, Solid Lipid Nanoparticle's, nanoemulsion , polymeric micelles, microspheres etc have been investigated for their aim of delivering anti- cancer drugs by oral route. Oral route is a great potential of delivering cytotoxic agents and thus attention has been focused on the development of oral chemotherapy in oncology[5].

MICROSPHERES

Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers having a particle size ranging from 1-1000 µm.

FLOATING MICROSPHERES

Floating microspheres (Hollow Microspheres) are 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 micrometer. 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. Floating microspheres to improve patient compliance by decreasing dosing frequency, better therapeutic effect of short half-life drugs can be achieved. Floating microspheres are prepared by solvent diffusion and evaporation methods to create the hollow inner core[6,7,8].

METHOD OF PREPARATION

There are various methods of preparation of floating microspheres of which 2 methods are described here:

- ***Emulsion Solvent Evaporation technique***: Measured proportion of drug and polymer was weighed and dissolved in a mixture of measured ratio of solvents at room temperature. This was poured into specified volume of water containing surfactant maintained at the specified temperature and was stirred to allow the volatile solvent to evaporate. The microspheres formed were filtered washed and dried in vacuum[9].

- ***Emulsion Solvent Diffusion technique***: The drug polymer mixture was dissolved in a mixture of solvents was dropped into 0.2% surfactant (specified volume). The solution was stirred with a propeller-type agitator at room temperature for specified time and rpm. The formed floating microspheres were filtered, washed with water and dried at room temperature in a desicator[10].

Advantages:[11]

- Uniform drug release.
- No risk of dose dumping.
- Avoidance of gastric irritation.
- Improved receptor activation selectivity.
- Flexibility in dosage form design
- Gastric retention time is increased
- Sustained drug delivery.
- Reduced frequency of dosing
- Site-specific drug delivery to stomach can be achieved.
- Targeted therapy for local ailments in the upper GIT.

Disadvantages:[12]

- Drugs having irritant effect on gastric mucosa are not suitable candidates for FDDS. e.g.NSAIDs
- Drugs which are absorbed along the entire GIT and which undergo first pass metabolism may not be desirable e.g. nifedipine.
- They are not suitable candidates for drugs with stability or solubility problem in stomach. eg.ranolazine
- FDDS require sufficiently high level of fluid in stomach so that the system can float and thus sufficient amount of water (200-250 ml of water to be taken together with FDDS.

Characterization of floating microspheres

- Particle size determination: carried out using an optical microscope and mean particle size calculated by counting 100 particles with a calibrated coulometer.
- Bulk density: determined by three-tap method by using a graduated measuring cylinder.
- Tapped density: using tapped density apparatus of either 100 tap or 1000 tap

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

- Compressibility index and Hausner ratio: can be determined by using the following equations

$$\% \text{ Compressibility Index} = \frac{\text{Tapped density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100$$

$$\text{Hausner Ratio} = \frac{\text{Tapped density}}{\text{Bulk Density}}$$

- Angle of Repose (θ): $\tan\theta = 2H/D$ where, θ measures the resistance to particle flow and 2H/D is the surface area of the free standing height of the microspheres heap that is formed after making the microspheres flow from the glass funnel[13].
- Yield of Microspheres : was calculated using the equations
- % Yield = (Actual weight of product /Total weight of excipients and drug) x100
- Optical microscopy: is used to determine the particle size.
- Entrapment Efficiency: Drug loaded floating microspheres were crushed and dissolved in distilled water using stirrer for 3 hrs and assayed by uv-vis spectroscopy. Entrapment efficiency is equal to ratio of actual drug content to theoretical drug content.
- FT-IR (Fourier Transform Infra Red) : The drug polymer interaction and also degradation of drug while processing for microencapsulation can be determined by FTIR.
- Floating behavior: Floating microspheres should be placed in 100 ml of the simulated gastric fluid containing 0.02% w/v Tween 80. The mixture was stirred at 100 rpm with a magnetic stirrer. After 8 hours, the layer of buoyant microspheres was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in a desiccators until constant weight was achieved. Both the

fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles. Buoyancy (%) = Wf / Wf + Ws Where, Wf and Ws are the weights of the floating and settled microparticles[14]

- *In-vitro* release studies: using USP apparatus XXIII basket type. 50 mg of weighed equivalent drug was placed in a hard gelatin capsule and carried out the experiment in simulated gastric fluid containing 0.02%Tween 80 maintained at 37^0C at specified rpm. 12 hrs studies were carried out and 5ml was withdrawn at 30min intervals and read spectroscopically replacing with 5ml fresh dissolution fluid. All experiments were run in triplicate [15].

STOMACH ULCER

Stomach ulcers are painful sores that can be found in the stomach lining or small intestine. Stomach ulcers are the most visible sign of peptic ulcer disease. They occur when the thick layer of mucus that protects your stomach from digestive juices is reduced, thus enabling the digestive acids to eat away at the lining tissues of the stomach [16].

Causes

- *Helicobacter pylori* (*H. pylori*) infection long-term use of NSAIDs(non-steroidal anti-inflammatory drugs), such as aspirin and ibuprofen
- Excess acid in the stomach, which is related to genetics, lifestyle (stress, smoking),
- Certain foods Zollinger-Ellison syndrome, a rare disease that makes the body produce excess stomach acid.

Symptoms

- A burning sensation or pain in the area between your chest and belly button which will be severe when stomach is empty and lasts from few seconds to hrs.
- Nausea ,vomiting
- Weight loss
- Bloating
- Heart burn.

Treatment of stomach ulcers

- Surgical treatment
- Non surgical treatment-includes
  - **H2 blockers**: to prevent your stomach from making too much acid
- **proton pump inhibitors:** blocks the cells that produce acid
- **over-the-counter antacids**: to help neutralize stomach acid
- **cytoprotective agents:** to protect the lining of the stomach and small intestine, such as Pepto-Bismol[17].

Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Floating microspheres of anti-ulcer drug were prepared by solvent evaporation method using polymer combinations and solvents. Thus, the formulated anti-ulcer drug loaded floating will have a good buoyancy and release the drug in a sustained manner for a prolonged period of time thereby treating the condition. The low bioavailability and short biological half life of anti-ulcer drug, following oral administration favors development of a sustained release Formulation thereby giving enhanced floatability and bioavailability [23].

APPLICATIONS [18-20]

- Floating microspheres are very effective approach in delivery of drugs that have poor bioavailability because of their limited absorption in the upper GIT. These systems efficiently maximize their absorption and improve the bioavailability of several drugs. e.g Furosemide, Riboflavin etc.
- Gastro retentive floating microspheres are very effective in the reduction of major adverse effect of gastric irritation; such as floating microspheres of nonsteroidal anti inflammatory drugs i.e.Indomethacin are beneficial for rheumatic patients.
- Provide sustained drug release behavior and release the drug over a prolonged period of time.
- Floating microspheres are especially effective in delivery of sparingly soluble and insoluble drugs
- The floating microspheres can be used as carriers for drugs with so- called absorption

windows eg:antifungal, anti-viral, antibiotics etc are taken up only from very specific sites of the GI mucosa.

- These systems are particularly advantages for drugs that are specifically absorbed from stomach or the proximal part of the small intestine e.g. riboflavin frusemide and misoprostol. By targeting slow delivery of misoprostol to the stomach, desired therapeutic level could be achieved and drug waste could be reduced.
- Hollow microspheres can greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentrations at the gastric mucosa, thus eradicating *Helicobacter pylori* from the sub-mucosal tissue of the stomach and making it possible to treat stomach and duodenal ulcers The development of such systems allow administration of nonsystemic, controlled release antacid formulations containing calcium carbonate and also locally acting antiulcer drugs in the stomach; e.g. Lansoprazole. Buoyant microspheres are considered as a beneficial strategy for the treatment of gastric and duodenal cancers.
- The drugs recently reported to be entrapped in hollow microspheres include prednisolone, lansoprazole, celecoxib, piroxicam, theophylline, diltiazem, verapamil and riboflavin, aspirin, griseofulvin, ibuprofen, terfenadine.

CONCLUSION

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. Floating controlled drug delivery systems are employed to solve this problem [21]. Floating microspheres have been showing high potential for gastro retention and provide an efficient means of enhancing bioavailability and controlling the release of anti-ulcer drug thereby proving it to be efficient [22].

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