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Emerging Trend in Developing Mesalamine Loaded Microspheres for Targetting Colon

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Abstract

Microspheres being novel drug delivery system with several advantages which mostly has importance in every type of disease we are facing today. Mesalamine belongs to BCS Class-IV drug used for treating several inflammatory bowel diseases. Drug loaded microspheres are target specific, they protect drug and show their activity thoroughly. In the current review we proposed about microspheres, their advantages, disadvantages, types, methods of preparation, evaluation, applications and final conclusion.

Keywords: Inflammatory bowel diseases, microspheres, colon, target-specific.

INTRODUCTION

Microspheres are small spherical or spherical like particles which consists of drug dissolved and (or) dispersed homogenously throughout a polymer material with particle size ranging 0.01-500µm.Now-a-days, microspheres are effectively used in the treatment of ulcerative colitis because they are safe, target specific and release the drug dosage in controlled manner. Thus, it will provide prolong, constant and better therapeutic effect. Microspheres also give protection of drug against enzymatic metabolism. They are used for controlled and sustained drug delivery system to deliver drugs, antigens and even DNA. They also have potential applications as injection or inhalation products.

After cancer colon disease is second most cause of increasing death rates. Some of the colon diseases are ulcerative colitis, cirrhosis disease, amoebiasis, colonic cancer, irritable bowel syndrome, Crohn's disease etc., To treat these diseases several approaches have to be followed like targeted delivery, controlled and sustained delivery, pH dependent delivery of drug in order to reach colon. These approaches have showed successful results. Drug to reach colon first it should cross GIT (stomach, small intestine, large intestine) and then colon. The main limitation of colon drug delivery system is the drug may get absorbed in GIT resulting in failure of drug reaching colon. There are over 50,000 deaths per year due to inflammatory bowel diseases among them ulcerative colitis and Crohn's disease are most common and affective. There is no permanent treatment available for these IBDs up to date so patients have to be treated constantly. This treatment is based on disease severity. It has been observed in a few studies that Mesalamine when combined with pH dependent delivery system showed better results.[1,2]

Microspheres received more attention for colon drug delivery because of its several advantages as mentioned before. They are novel based drug delivery system. The main disadvantage in delivering drugs to the colon is the absorption and degradation pathways in the upper GIT. The pathologies of colon range from constipation, diarrhea, inflammatory bowel diseases and colon cancers which should be treated with targeted drug delivery disease site with lower dosing and reduced systemic side effects. The lower portion of colon is regarded as the perfect site for colon targeted delivery of drugs having less hostile environment, less diversity and intensity of activity than the stomach and small intestine. Therefore, microspheres can be used for colon drug delivery as it has lot of benefits related to colon diseases so as mesalamine.

ADVANTAGES AND DISADVANTAGES

They have gained importance because of its several advantages such as protection of drug, longer duration of action, dose reduction thereby increasing patience compliance, masks bitter taste, protect GIT from drug irritation, toxicity reduction, increased therapeutic efficiency, water solubility, bio-compatibility and controlled release of drugs. Even though along it has several benefits they also have some of the disadvantages such as low reproducibility, high cost, degradation of product due to environmental changes, release rate difference from one dose to another. Leaving aside its advantages and disadvantages one of the main characteristics of microspheres is its ability to incorporate high concentrations of drug. There are different types of microspheres such as bioadhesive microspheres, magnetic microspheres, floating microspheres, radioactive microspheres, polymeric microspheres where these are of two subtypes such as biodegradable and synthetic polymeric microspheres.[3]

METHODS OF PREPARATION

- Single emulsion method
- Double emulsion method
- Heat stabilization method
- Chemical stabilization method
- Ionotropic gelation
- Polymerization
- Spray drying
- Solvent extraction
- Phase separation (co-acervation)
- Solvent evaporation
- Salting out

Single Emulsion method:

In this technique first polymers are dissolved in aqueous phase and then dispersed in oil phase. The obtained medium is subjected for cross-linking and this is done by two methods such as heat cross-linking and chemical cross-linking.

Heat stabilization and chemical stabilization methods

Heat cross-linking us carried out using heated oil and chemical cross-linking is carried out by addition of chemicals such as formaldehyde, chloric acid etc. After cross-linking they are centrifuged, washed and filtered.

Double emulsion method

This method is same as single emulsion method but involves preparation of multiple emulsions like oil in water in oil (O/W/O) or water in oil in water (W/OW) emulsions. In this method aqueous solution and active ingredient are added to organic phase (polymeric solution) this mixture is known as primary emulsion. The obtained solution is again added to aqueous solution such as Poly vinyl alcohol this result in formation of double emulsion. Organic solvent is removed by solvent evaporation. Microspheres are obtained.[4]

Ionotropic gelation method

In this method sodium alginate and drug are added to distilled water and heated on water bath. A thick slurry is obtained and allowed to cool. Then calcium chloride is dissolved in distilled water in a beaker. Prepared polymeric drug slurry was added drop wise using syringe from a height of 5cm from the beaker containing calcium chloride solution. Microspheres are formed which are then washed filtered and subjected for drying.

Polymerization

In this method microspheres are prepared by using monomers. Monomer/monomers with drug are heated by using bioreactor or initiator. Then microspheres are obtained from this polymeric mixture by moulding.There are different types of polymerizations such as emulsion polymerization (dispersing drug in emulsion), suspension polymerization(dispersing drug in suspension),interfacial polymerization (formation of polymeric film at the interface).

Spray drying

In this method first polymer us dissolved in a suitable volatile organic solvent. Then drug is dispersed in this polymeric solution and subjected for homogenization. This drug-polymeric solution is atomized in spray drying chamber which results in the formation of small droplets (microspheres). These microspheres are separated by cyclone separator.

Solvent extraction

In this method first polymer is added to chloroform and then drug is added to this polymeric solution. This solution is added to aqueous phase which contain polyvinyl alcohol. The above mixture was agitated at 500 rpm where fine droplets of this solution are solidified into microspheres by solvent evaporation. This is followed by washing, filtering, drying and storing them at room temperature.[4]

Phase separation (Co-acervation)

Coacervation phase separation means formation of different phases from single homogenous mixture. Polymer can be either dissolved in aqueous or organic solvent then drug is added to it. Polymeric rich droplets are formed which are hardened in aqueous or organic phase. Hardened microspheres are separated, washed and dried in the oven at 50ºC.[4]

Solvent evaporation

In this method organic phase and aqueous phases are prepared and mixed. Polymer is added to organic solvent, then drug is added this is organic phases whereas aqueous phase is prepared by dissolving aqueous protein in water. These two phases are subjected for homogenization/sonication. Then organic solvent is subjected for solvent evaporation where microspheres harden and can be separated by washing and filtration.

Salting out method

In this method aqueous phase is prepared by using electrolytes such as magnesium acetate, magnesium chloride and polyvinyl alcohol (stabilizing agent). Then organic phase is prepared by adding polymer to the acetone solution. Both phases are mixed and vigorously stirred. As aqueous phase contains saturated electrolytes there will be no miscibility of both phases. Then addition of pure water results in the formation of spherical particles known as microspheres.

EVALUATION

Evaluation methods for microspheres include determination of particle size, particle shape, density entrapment efficiency, FTIR, *in-vitro* drug release studies.[5]

Particle size and particle shape

Particle size and shape can be determined by using scanning electron microscopy, confocal laser scanning microscopy, confocal fluorescence microscopy, laser light scattering microscopy and multi size coulter counter. The size range of microspheres is 0.01-500µm.Density is determined by using multivolume psychrometer.

Entrapment efficiency

Entrapment efficiency is percentage of drug that is successfully entrapped within microspheres. About 10mg of drug loaded microspheres were accurately weighed, transferred to a beaker containing 10 ml phosphate buffer pH 7.4 and sonicated for one hour at room temperature. The drug content in the microspheres was determined by measuring the absorbance of entrapped product at specific wavelength UV spectrophometrically using

$$\text{Drug loading (\%)} = \frac{weight\ of\ the\ drug\ in\ specific\ amount\ of\ microspheres}{weight\ of\ microspheres} X100$$

$$\%\text{Entrapment efficiency} = \frac{Actual\ loading}{Theoretical\ loading}\ X\ 100$$

FTIR

Fourier Transform Infrared Spectroscopy (FTIR) identifies chemical bonds in a molecule by producing an infrared absorption spectrum. The common use of FTIR is identification of unknown materials and its confirmation. It is also used to check drug-excipient compatibility. From the FT-IR spectra of the pure drug and the combination spectra of drug with the excipients drug excipient compatibility is known.

In-vitro drug release studies

In-vitro drug release studies can be performed by two methods for microspheres such as dissolution and dialysis method. Dissolution method is performed by using USP type-II dissolution test apparatus. Dried microspheres were suspended in 500 mL of either 0.1NHCl solution of pH 1.2 or phosphate buffer saline solution of pH 7.4. The dissolution media was maintained at 37°C±0.5 under continuous stirring at 50 rpm. At predetermined intervals, the sample was withdrawn, and the concentration of released drug in the media was determined by analyzing at specific using a UV spectrophotometer. Dialysis method is performed by placing microspheres in biological (dialysis) membrane with one end opened and other end closed. This whole membrane is placed in beaker containing phosphate buffer and allowed for drug release. For each selected time intervals samples were withdrawn and fresh buffer is added. These samples are analyzed using UV spectrophotometer for determining drug concentration.[5]

APPLICATIONS

Inflammatory bowel diseases

IBDs such as ulcerative colitis, colon inflammations, Crohn's disease has become serious issues now-a -days. There is no permanent treatment for these diseases so the patient has to take treatment constantly. Even though it cannot be cured it can be controlled. Microspheres has been vastly increasing in the treatment of colon diseases because they are target-specific, protects the drug and release drug in controlled manner. By using various approaches such pH dependent, time dependent approaches when combined with microsphere drug delivery showed successive results in drug release in controlled and protected manner. For example, pH dependent meloxicam loaded microspheres which contains Eudragit pH dependent reabsorbable co-polymers showed quick drug release at 7.4 pH, reduced the inflammation in colon and their release was sustained up to 24 hours. Therefore, microspheres drug delivery count has been increasing widely for treated IBDs. [17,18]

Cancer therapy

Microspheres in cancer technology play a major role in cancer therapy. These formulations provide maximum therapeutic effect and less side effects. Cancer is a deadly disease in which the tumour cells and normal cells are hard to differentiate because they have minimum genetic and functional change with just minute genetic or functional change. These tumour cells are difficult to target. So, microsphere technology mostly is only method which has site specific activity and also protects normal cells by producing less side effects. Some of the examples are Paclitaxel-loaded PLGA microspheres have been significantly effective in inhibiting lung tumour without any clinical toxicity in the patients, sustained release of 5-fluorouracil was achieved with the help of polymeric microspheres for local delivery of antineoplastic agents in the brain which showed long-term delivery of the drug to the tumour site. They are used in treating brain cancer, lung cancer, colon cancer, prostate cancer (Leuprolide acetate microspheres), pancreatic cancers etc. In the future there will also be much more significance for microspheres in cancer technology.[17]

Genital infections

When chitosan, PLGA microspheres modified with thioglycolic acid in their primary amino groups can be used for treatment of genital infections. Gelatin is also one of the polymers used for treating these infections.[17]

Diagnosis

It has several diagnostic applications such as gated blood pool study,blood flow measurements, lung scintigraphy, liver, spleen, bonemarrow, tumour imaging, infection localization.[18]

Gene and vaccine delivery

Microspheres are used as oral gene carriers due to their advantageous transport properties through GIT. Chitosan and gelatinare commonly used as carriers for gene delivery. They are used for vaccine delivery. Biodegradable polymeric microspheres have been encapsulated with several parenteral vaccines such as tetanus and diphtheria.

CONCLUSION

It has been concluded that there has been increase in the use of mesalamine microspheres for colon targeted drug delivery systems in recent years and it is also a promising approach for treating colon diseases. As microspheres ensure balance between efficiency, target-specificity, cost, and patient compliance it is best option to use this drug delivery system for treating colon diseases. There are nearly over 50,000 deaths per year due to these diseases. So, using this novel drug delivery may show impact and reduce the symptoms and death rates.

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