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A NOVEL DRUG DELIVERY SYSTEM

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Abstract: Microspheres are one of the particulate delivery systems has wide range of applications such as used to achieve sustained or controlled drug delivery, improve bioavailability and stability and target drug to specific sites. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200µm.It also has advantage over liposomes as its is physicochemical more stable. The purpose of the review is to compile various types of microspheres, different methods to preparation, its applications and also various parameters to evaluate their efficiency.

Keywords: Microspheres, types of microspheres, characterization of microspheres, novel drug delivery.

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INTRODUCTION

Novel drug delivery systems have several advantages over conventional multi dose therapy Recent trends indicate that micro particulate drug delivery systems are especially suitable for achieving controlled or delayed release oral formulations with low risk of dose dumping, flexibility of blending to attain different release patterns as well as reproducible and short gastric residence time.[1] Microspheres have been widely accepted as a means to achieve oral and parental controlled release drug delivery system. The microspheres require a polymeric substance as a carrier and a core material. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature and ideally having a particle size less than 200µm. This is the important approach in delivering therapeutic substance to the target site in sustained and controlled release fashion.[2]

Advantages of microspheres[1]:

1. Protection of unstable, sensitive materials from their environments prior to use.
2. Better processability (improving solubility, dispersibility, flowability).
3. Self-life enhancement by preventing degradative reactions.
4. Safe and convenient handling of toxic materials.
5. Masking of odor or taste.
6. Enzyme and microorganism immobilization.
7. Controlled and targeted drug delivery.
8. Handling liquids as solids.
9. To improve bioavailability
10. To improve the stability
11. Limiting fluctuation within therapeutic range
12. Decreasing dosing frequency
13. Improving patient compliance.

MATERIALS USED:

Microspheres used usually are polymers.

They classified into two types:

1. Synthetic Polymers:

a. Non- biodegradable polymers.

Eg. Poly methyl methacrylate (PMMA), Acrolein, Glycidyl methacrylate, Epoxy polymers

b. Biodegradable polymers

Eg. Lactides, Glycolides & their copolymers, Poly alkyl cyano acrylate, Poly anhydrides

2. Natural Polymers can be obtained from different sources like proteins, Carbohydrates and chemically modified carbohydrates.

Proteins: Albumin, Gelatin and Collagen

Carbohydrates: Agarose, carrageenan, Chitosan, Starch

Chemically modified carbohydrates: Polydextran, Poly starch

Types of microspheres:

Bioadhesive microspheres

Adhesion can be defined as sticking of drug to the membrane by using the sticking property of the water soluble polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc can be termed as bioadhesion. These kinds of microspheres exhibit a prolonged residence time at the site of application and causes intimate contact with the absorption site and produces better therapeutic action.[4]

Magnetic microspheres

Magnetic microspheres are supramolecular particles that are small enough to circulate through capillaries without producing embolic occlusion (<4μm)but are sufficiently succeptible (ferromagnetic) to be captured in microvessels and dragged into the adjuscent tissues by magnetic field of 0.5-0.8 tesla.[5]

Floating Microspheres:

In floating microspheres 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, if the system is floating on gastric content and increases gastric residence and increases fluctuation in plasma concentration. Moreover it also reduces chances of striking and dose dumping. One another way it produces prolonged therapeutic effect and therefore reduces dosing frequencies. Drug (ketoprofen) given through this form.[6]

Radioactive Microspheres :

Radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues. They are injected to the arteries that lead to tumour of interest. The different kinds of radioactive microspheres are α emitters, β emitters and γ emitters.[7]

Mucoadhesive microspheres:

Mucoadhesive microspheres which are of 1-1000mm in diameter and consisting either entirely of a mucoadhesive polymer or having an outer coating of it. Microspheres in general, have the potential to be used for targeted and controlled release drug delivery but coupling of mucoadhesive properties to microspheres has additional advantages, *e.g.* efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer, specific targeting of drug to the absorption site achieved by anchoring plant lectins, bacterial adhesions and antibodies, *etc.* on the surface of the microspheres. Mucoadhesive microspheres can be tailored to adhere to any mucosal tissue including those found in eye, nasal cavity, urinary and

gastrointestinal tract, thus offering the possibilities of localized as well as systemic controlled release of drugs.[10]

Polymeric microspheres

The different types of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and Synthetic polymeric microspheres[8].

Biodegradable polymeric microspheres

Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible, and also bio adhesive in nature. Biodegradable polymers prolongs the residence time when contact with mucous membrane due to it's high degree of swelling property with aqueous medium , results gel formation. The rate and extent of drug release is controlled by concentration of polymer and the release pattern in a sustained manner. The main drawback is, in clinical use drug loading efficiency of biodegradable microspheres is complex and is difficult to control the drug release. However they provide wide range of application in microsphere based treatment.

Synthetic polymeric microspheres

The interest of synthetic polymeric microspheres are widely used in clinical application, moreover that also used as bulking agent, fillers, embolic particles, drug delivery vehicles etc and proved to be safe and biocompatible.11But the main disadvantage of these kind of microspheres, are tend to migrate away from injection site and lead to potential risk, embolism and further organ damage.

Methods of preparation:

Solvent evaporation and solvent extraction: There are different methods to use microencapsulation by solvent evaporation technique. The choice of the method that will give rise to an efficient drug encapsulation depends on the hydrophilicity or the hydrophobicity of drug. For insoluble or poorly water-soluble drugs, the oil-in-water (o/w) method is frequently used. This method is the simplest and the other methods derive from this one.

It consists of four major steps.

(1) Dissolution of the hydrophobic drug in an organic solvent containing the polymer

(2) Emulsification of this organic phase, called dispersed phase, in an aqueous phase called continuous phase

(3) Extraction of the solvent from the dispersed phase by the continuous phase, accompanied by solvent evaporation, transforming droplets of dispersed phase into solid particles

(4) Recovery and drying of microspheres to eliminate the residual solvent.

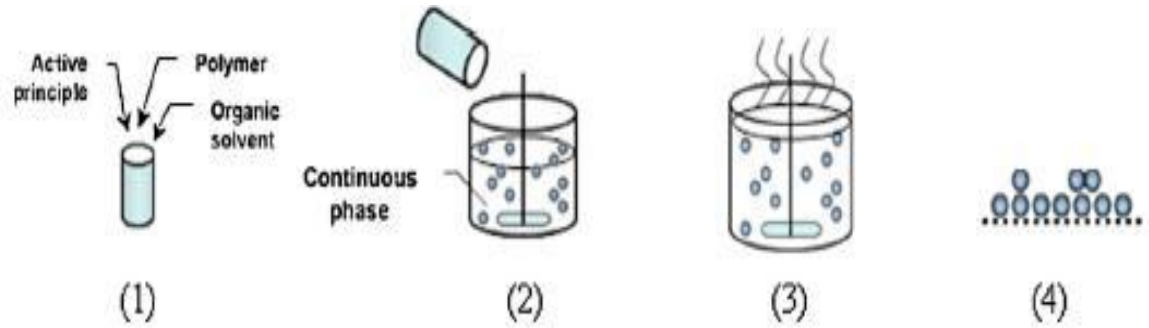

Fig. 1. Basic steps of microencapsulation by solvent evaporation.

The above mentioned method is not suitable for the encapsulation of high hydrophilic drugs. There are two main reasons:

(1) The hydrophilic drug may not be dissolved in the organic solvent

(2) The drug will diffuse into the continuous phase during emulsion, leading to a great loss of drug.

Emulsion cross linking method

In this method drug was dissolved in aqueous gelatine solution which was previously heated for 1 hr at 40 0C. The solution was added drop wise to liquid paraffin while stirring the mixture at 1500 rpm for 10 min at 35 ^{0}C , results in w/o emulsion then further stirring is done for 10 min at 15 0C. Thus the produced microspheres were washed respectively three times with acetone and isopropyl alcohol which then air dried and dispersed in 5mL of aqueous glutaraldehyde saturated toluene solution at room temperature for 3 hrs for cross linking and then was treated with 100mL of 10mm glycine solution containing 0.1%w/v of tween 80 at 37 ^{0}C for 10 min to block unreacted glutaraldehyde.

Examples for this technique is Gelatin A microspheres.

Co-acervation method

Co-acervation thermal change method was performed by weighed amount of ethyl cellulose was dissolved in cyclohexane with vigorous stirring at 80 ^{0}C by heating. Then the drug was finely pulverised and added with vigorous stirring on the above solution and phase separation was done by reducing temperature and using ice bath. Then above product was washed twicely with cyclohexane and air dried then passed through sieve (sieve no. 40) to obtain individual microcapsule. Co-acervation non solvent addition: Developed by weighed amount of ethyl cellulose was dissolved in toluene containing propylisobutylene in closed beaker with magnetic stirring for 6 hr at 500 rpm and the drug is dispersed in it and stirring is continued for 15 mins. Then phase separation isdone by petroleum benzoin 5 times with continuous stirring.[1] After that the microcapsules were washed

with n-hexane and air dried for 2 hr and then in oven at 50oc for 4 hr.

Spray drying technique

This was used to prepare polymeric blended microsphere loaded with ketoprofen drug. It involves dispersing the core material into liquefied coating material and then spraying the mixture in the environment for solidification of coating followed by rapid evaporation of solvent.4 Organic solution of poly (epsilon-caprolactone) (PCL) and cellulose acetate butyrate (CAB), in different weight ratios and ketoprofen were prepared and sprayed in different experimental condition achieving drug loaded microspheres. This is rapid but may loose crystalinity due to fast drying process.

Emulsion-solvent diffusion technique

In order to improve the residence time in colon floating microperticles of ketoprofen were prepared using 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 dropwise to sodium lauryl sulphate (SLS) solution. The solution was stirred with propeller type agitator at room temperature at 150 rpm for 1 hr. Thus the formed floating microspheres were washed and dried in a dessicator at room temperature. The following microperticles were sieved and collected.

Multiple emulsion method

Oral controlled release drug delivery of indomethacin was prepared by this technique. In the beginning powder drug was dispersed in solution (methyl cellulose) followed by emulsification in ethyl cellulose solution in ethyl acctate. The primary emulsion was then re emulsified in aqueous medium. Under optimised condition discrete microspheres were formed during this phase.

Ionic gelation

Alginate/chitosan particulate system for diclofenac sodium release was prepared using this technique. 25 % (w/v) of diclofenac sodium was added to 1.2 % (w/v) aqueous solution of sodium alginate. In order to get the complete solution stirring is continued and after that it was added dropwise to a solution containing Ca2+ /Al3+ and chitosan solution in acetic acid. Microspheres which were formed were kept in original solution for 24 hr for internal gellification followed by filteration for separation. The complete release was obtained at pH 6.4-7.2 but the drug did not release in acidic pH.

Hydroxyl appetite (HAP) microspheres in sphere morphology

This was used to prepare microspheres with peculiar spheres in sphere morphology

microspheres were prepared by o/w emulsion followed by solvent evaporation. At first o/w

emulsion was prepared by dispersing the organic phase (Diclofenac sodium containing 5% w/w of EVA and appropriate amount of HAP) in aqueous phase of surfactant. The organic phase was dispersed in the form of tiny droplets which were surrounded by surfactant molecules this prevented the droplets from co solvencing and helped them to stay individual droplets .While stirring the DCM was slowly evaporated and the droplets solidify individual to become microspheres.

Characterization of microspheres:

Percentage yield

The dried microspheres were weighed and percentage yield of the prepared microspheres was calculated by using the following formula[11]

Percentage yield = (Weight of microspheres\Weight of polymer + drug) × 100

Micromeritic properties

The microspheres were characterized by their micromeritic properties such as particle size, bulk density, tapped density, compressibility index and flow properties. The size was measured using optical microscope, and the mean particle size was calculated by measuring 200-300 particles with the help of calibrated ocular micrometer. The tapping method was used to determine the tapped density and percent compressibility index. Bulk density (ρb) was measured by tapping method[12].

$$\text{compressibility index} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100$$

ρb, bulk density = mass of microsphere/ bulk volume of the microsphere

ρt, Tapped density = mass of microspheres/volume of microspheres after tapping

Angle of repose, θ of the microspheres, which measures the resistance to particle flow, was determined by a fixed funnel method.

Entrapment efficiency:

100 mg of microspheres were accurately weighed. They were dissolved in minimal amount of dichloromethane and the drug was extracted into pH 7.4 buffer by evaporating dichloromethane. The volume was adjusted to 100 ml with buffer. The resulting solution was then suitably diluted and analyzed for drug content spectrophotometrically using pH 7.4 buffer as blank. And entrapment efficiency was calculated.[11]

Swelling index:

This technique was used for Characterization of sodium alginate microspheres were performed with swelling

index technique Different solution (100mL) were taken such as (distilled water, buffer solution of pH(1.2, 4.5, 7.4) were taken and alginate microspheres (100mg) were placed in a wire basket and kept on the above solution and swelling was allowed at 37 ^{o}C and changes in weight variation between initial weight of microspheres and weight due to swelling was measured by taking weight periodically and soaking with filter paper.[13]

FTIR studies:

FTIR study is carried out by KBr pellet method for drug excipients interactions study.

Differential scanning calorimetry:

The DSC analysis of pure drug, drug-loaded microspheres and blank microspheres without drug were carried out using Shimadzu DSC 60 to evaluate any possible drug polymer interaction. The analysis was performed at a rate 10 ^{0}C min^{-1} from 20 ^{0}C to 300 ^{0}C temperature range under nitrogen flow of 25 ml min^{-1}.[11]

Scanning electron microscopy:

A scanning electron microscope was used to characterize the surface morphology of the microspheres . A scanning electron photomicrograph of drug-loaded microspheres was taken. A small amount of microspheres was spread on glass stub. Afterwards, the stub containing the sample was placed in the scanning electron microscope chamber. The scanning electron photomicrograph was taken at the acceleration voltage of 10 kV, chamber pressure of 0.6 mm Hg, original magnification 500.[11]

***IN VITRO* RELEASE:**

The in vitro dissolution studies were carried out in 900 ml of phosphate buffer, pH 7.4, maintained at 37±0.5 ^{0}c and 100 rpm by using USP type II dissolution test under sink conditions. Accurately weighted samples of the microspheres were added to the dissolution medium and at preset time intervals; 5 ml aliquots were withdrawn and replaced with an equal volume of fresh dissolution medium. After suitable dissolution, the amount of drug released was calculated using standard calibration curve.[11]

Stability studies:

Stability studies were carried out as per ICH Guidelines. The microspheres were stored at 40°C ± 2°C/75% RH ± 5% RH for 6 months. The formulations were analyzed for appearance, entrapment efficiency and drug content.[12]

APPLICATIONS OF MICROSPHERES:

Medical application[4]

1. Release of proteins, hormones and peptides over extended period of time.
2. Gene therapy with DNA plasmids and also delivery of insulin.

3. Vaccine delivery for treatment of diseases like hepatitis, influenza, pertusis, diphtheria, birth control.
4. Passive targeting of leaky tumour vessels, active targeting of tumour cells, antigens, by intraarterial/intravenous application.
5. Tumour targeting with doxorubicin and also treatments of leishmaniasis.
6. Magnetic microspheres can be used for stem cell extraction and bone marrow purging.
7. Used in isolation of antibodies, cell separation, and toxin extraction by affinity chromatography.
8. Used for various diagnostic tests for infectious diseases like bacterial, viral, and fungal.

Radioactive microsphere application:

1. Can be used for radioembolisation of liver and spleen tumours.
2. Used for radiosynvectomy of arthiritis joint, local radiotherapy, interactivity treatment.
3. Imaging of liver, spleen, bone marrow, lung etc and even imaging of thrombus in deep vein thrombosis can be done.

Other applications:

1. Fluorescent microspheres can be used for membrane based technologies for flow cytomettry, cell biology, microbiology, Fluorescent Linked Immuno-Sorbent Assay.
2. Yttrium 90 can be used for primary treatment of hepatocellular carcinoma and also used for pretransplant management of HCC with promising results.

Table 1: Lists of drug and vaccines given as microspheres

DRUG	REASON	FORMULATION
Glipizide[11]	It has short biological half life of 3.4+/- 0.7hr and is rapidly eliminated because of its short half life and chronic use attempts are made to control release parental in the form of microspheres.	Microspheres
Diclofenac pottasium[14]	It has short biological half life of 1-2hr and is rapidly eliminated because of its short half life and Gastrointestinal side effects such as bleeding, ulceration or perforation of intestinal wall are commonly seen.	Microspheres
Vaccines[15]	1. Microspheres can deliver the antigen to the targeted site at the predetermined rate and duration so optimum response can be achieved. 2. The carrier will also prevent degradation of vaccines. 3.It reduces systemic side effects	Microspheres
Ketorolac tromethamine[16] **NSAID(S)**	NSAID(S), may produce gastrointestinal side effects. After oral administration it is rapidly eliminated from blood exhibiting a short biological half life of 4-6 hr.	Microspheres

CONCLUSION:

Microsphere is having a micron size but it is having wide applications in novel drug delivery systems in compare to other drug delivery system. Most important are the targeted drug delivery (Bioadhesive microspheres-nasal, ocular, buccal, rectal etc., Magnetic microspheres and radioactive micospheres – For tumours), Controlled and sustained drug delivery (Polymeric microspheres, Floating microspheres). Microspheres have central place in novel drug delivery mainly particularly in cell sorting, diagnostics and Genetic engineering. From the study it is proved that Microspheres act as effective carriers for the novel drug delivery system.

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