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AN OVERREVIEW ON MICROSPHERES PREPARATION AND EVALUATION METHODS

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ABSTRACT

The concept of targeted drug delivery is designed for attempting to concentrate the drug in the target tissues of interest while reducing the relative concentration of the medication in the remaining tissues i.e., other than target tissues, so that the drug is localized on the targeted site. Hence, other/surrounding tissues are not affected by the drug. So, carrier technology offers an intelligent approach for drug delivery systems by coupling the drug into carrier particles such as microspheres, nanoparticles, liposomes, niosomes etc., which modulate the release and absorption characteristics of the drugs. 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 200 μm . It is the reliable means to deliver the drug to the target site with specificity, if modified and to maintain the desired concentration at the site of interest without untoward effects. Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumour. In future by combining various other strategies, microspheres will find the central place in novel drug delivery systems, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective *in-vivo* delivery and supplements as miniature versions of diseased organ and tissues in the body.

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INTRODUCTION

Drug delivery systems (DDS) that can precisely control the release rates or target drugs to a specific body site have had an enormous impact on the health care system. The ideal drug delivery system delivers drug at a rate decided by the need of the body throughout the period of treatment and it provides the active entity solely to the site of action. So, carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, nanoparticles, liposomes, etc., which modulates the release and absorption characteristics of the drug.¹

Types of drug delivery system are: Liposome, Niosome, Nanoparticle and Microsphere.

MICROSPHERE:

Microspheres are solid spherical particles ranging in size from 1 – 1000 μm. They are spherical free flowing particles consisting of proteins or synthetic polymers. The microspheres are free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature. There are 2 - types of microspheres; Microcapsules and Micromatrices.

Microcapsules are those in which entrapped substance is distinctly surrounded by distinct capsule wall and micromatrices in which entrapped substance is dispersing throughout the microspheres matrix. Solid biodegradable microspheres incorporating a drug dispersed or dissolved through particle matrix have the potential for the controlled release of drug. They are made up of polymeric, waxy or other protective materials, that is, biodegradable synthetic polymers and modified natural products.²

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 membranes such as buccal, ocular, rectal, nasal etc., can be termed as bioadhesion. The term “bioadhesion” describes materials that bind to biological substrates, such as mucosal membranes. Adhesion of bioadhesive drug delivery devices to the mucosal tissue offers the possibility of creating an intimate and prolonged contact at the site of administration. This prolonged residence time can result in enhanced absorption and in combination with a controlled release of drug also improved patient compliance by reducing the frequency of administration. Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, nanospheres, liposomes, nanoparticles, etc., which modulates the release and absorption of the drug. Microspheres constitute an important part of these particulate drug delivery systems by virtue of their small size and efficient carrier capacity.³

Magnetic microspheres:

This kind of delivery system is very much important which localises the drug to the disease site. In this larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran etc.,⁴ The different types are Therapeutic magnetic microspheres are used to deliver chemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be targeted through this system.⁵

Magnetic drug transport technique is based on the fact that the drug can be either encapsulated into a magnetic microsphere or conjugated on the surface of the microsphere. The accumulation of the carrier at the target site allow them to deliver the drug locally.⁷

Diagnostic microspheres:⁶

Floating microspheres:

In floating types 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, increases gastric residence and fluctuation in plasma concentration. It also reduces chances of striking and dose dumping and produces prolonged therapeutic effect.

Example; Drug (ketoprofen) given through this form.⁸

Radioactive microspheres:

Radio embolisation therapy microspheres sized 10-30 nm are of larger than capillaries and gets trapped in 1st capillary bed when they come across. They are injected to the arteries that lead to tumour of interest. So these radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues. It differs from drug delivery system, as radio activity is not released from microspheres but acts from within a radioisotope typical distance and the different kinds of radioactive microspheres are α -emitters, β - emitters, γ - emitters.⁹

Mucoadhesive microspheres:

Mucoadhesive microspheres which are of 1 – 1000 μm in diameter and consisting either entirely of a mucoadhesive polymer or having an outer coating of it and coupling of mucoadhesive properties to microspheres has additional advantages, eg; 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.¹

Polymeric microspheres:

The different types of polymeric microspheres can be classified as:

Biodegradable polymeric microspheres:

Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible and also bioadhesive in nature. Biodegradable polymers prolongs their residence time when contact with mucous membrane due to its 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.¹⁰

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. But 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.¹¹

Materials and methods:

Microspheres used usually are polymers. They are classified into 2 - types: Synthetic Polymers and Natural polymers.

Synthetic polymers are divided into 2 – types;**i) Non-biodegradable polymers –**

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

ii) Biodegradable polymers –

Lactides, Glycolides & their co polymers, Poly alkyl cyanoacrylates, Poly anhydrides.

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

Proteins:

Albumin, Gelatin, Collagen.

Carbohydrates:

Agarose, Carrageenan, Chitosan, Starch.

Chemically modified carbohydrates:

Poly dextran, Poly starch.¹²

METHODS OF PREPERATION: 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 dispersibility 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 and
6. Susceptibility to chemical modification.

Emulsion solvent evaporation technique:

In this technique the drug is dissolved in polymer which was previously dissolved in chloroform and the resulting solution is added to aqueous phase containing 0.2 % sodium of PVP as emulsifying agent. The above mixture was agitated 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 demineralised water and desiccated at room temperature for 24 hrs. Aceclofenac microspheres were prepared by this technique.¹¹

Emulsion cross linking method:

In this method drug was dissolved in aqueous gelation solution which was previously heated for 1 hr at 40°C. The solution was added drop wise to liquid paraffin while stirring the mixture at 1500 rpm for 10 min at 35°C, results in w/o emulsion then further stirring is done for 10 min at 15°C. 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°C for 10 min to block unreacted glutaraldehyde.¹³ Examples for this technique is Gelatin A microspheres.

Coacervation method:**i. Coacervation thermal change:**

Performed by weighed amount of ethylcellulose was dissolved in cyclohexane with vigorous stirring at 80°C by heating. Then the drug was finely pulverized 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 twice with cyclohexane and air dried then passed through sieve (sieve no. 40) to obtain individual microcapsule.

ii. Coacervation non - solvent addition:

Developed by weighed amount of ethylcellulose 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 is done by petroleum benzoin¹⁴ times with continuous stirring. After that the microcapsules were washed with n-hexane and air dried for 2 hr and then in oven at 50°C 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. 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 lose crystallinity due to fast drying process.¹⁵

Emulsion-solvent diffusion technique:

In order to improve the residence time in colon floating microparticles 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 drop wise 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 desiccator at room temperature. The following microparticles were sieved and collected.¹⁵

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 acetate. The primary emulsion was then reemulsified in aqueous medium. Under optimized condition discrete microspheres were formed during this phase.¹⁵

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 drop wise to a solution containing Ca^{2+} / Al^{3+} and chitosan solution in acetic acid. Microspheres which were formed were kept in original solution for 24 hr for internal gelification followed by filtration for separation. The complete release was obtained at pH 6.4-7.2 but the drug did not release in acidic pH.¹⁵

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 1st 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-solvening and helped them to stay individual droplets. While stirring the DCM was slowly evaporated and the droplets solidify individual to become microspheres.¹⁶

PHYSICOCHEMICAL EVALUATION:**Characterization:**

The characterization of the microparticulate carrier is an important phenomenon, which helps to design a suitable carrier for the proteins, drug or antigen delivery. These microspheres have different microstructures. These microstructures determine the release and the stability of the carrier.²²

Particle size and shape:

The most widely used procedures to visualize microparticles are conventional light microscopy (LM) and scanning electron microscopy (SEM). Both can be used to determine the shape and outer structure of microparticles. LM provides a control over coating parameters in case of double walled microspheres. The microspheres structures can be visualized before and after coating and the change can be measured microscopically. SEM provides higher resolution in contrast to the LM. SEM allows investigations of the microspheres surfaces and after particles are cross-sectioned.¹⁷

Electron spectroscopy for chemical analysis:

The surface chemistry, atomic composition of surface and surface degradation of biodegradable microspheres can be determined using the electron spectroscopy for chemical analysis (ESCA).

Attenuated total reflectance Fourier Transform Infrared Spectroscopy:

FTIR is used to determine the degradation of the polymeric matrix of the carrier system. The surface of the microspheres is investigated measuring attenuated total reflectance (ATR). The ATRFTIR provides information about the surface composition of the microspheres depending upon manufacturing procedures and conditions.

Density determination:

The density of the microspheres can be measured by using a multi volume pycnometer. Accurately weighed sample in a cup is placed into the multi volume pycnometer. Helium is introduced at a constant pressure in the chamber and allowed to expand. This expansion results in a decrease in pressure within the chamber. 2 - Consecutive readings of reduction in pressure at different initial pressure are noted. From 2 - pressure readings the volume and hence the density of the microsphere carrier is determined.

Isoelectric point:

The micro electrophoresis is an apparatus used to measure the electrophoretic mobility of microspheres from which the isoelectric point can be determined. The electrophoretic mobility can be related to surface contained charge, ionisable behaviour or ion absorption nature of the microspheres.

Surface carboxylic acid residue:

The surface carboxylic acid residue is measured by using radioactive glycine. The radioactive glycine conjugate is prepared by the reaction of C¹⁴-glycine ethyl ester hydro chloride with the microspheres. The radioactivity of the conjugate is then measured using liquid scintillation counter. Thus the carboxylic acid residue can be compared and correlated.

Surface amino acid residue:

Surface associated amino acid residue is determined by the radioactive C¹⁴-acetic acid conjugate. The carboxylic acid residue is measured through the liquid scintillation counter and hence the amino acid residue can be determined indirectly.

Capture efficiency:

The capture efficiency of the microspheres or the percent entrapment can be determined by allowing washed microspheres to lyse. The lysate is then subjected to the determination of active constituents as per monograph requirement. The percent encapsulation efficiency is calculated using following equation:

$$\% \text{ Entrapment} = \text{Actual content} / \text{Theoretical content} \times 100$$

Angle of contact:

The angle of contact is measured to determine the wetting property of a micro particulate carrier. It determines the nature of microspheres in terms of hydrophilicity or hydrophobicity. The angle of contact is measured at the solid/air/water interface.

Drug release**In vitro methods –**

In vitro drug release studies have been employed as a quality control procedure in pharmaceutical production, in product development etc., Sensitive and reproducible release data derived from physico-chemically and hydro dynamically defined conditions are necessary, however no standard in vitro method has yet been developed. Different workers have used apparatus of varying designs and under varying conditions, depending on the shape and application of the dosage form developed.¹⁸

Beaker method –

The dosage form in this method is made to adhere at the bottom of the beaker containing the medium and stirred uniformly using overhead stirrer. Volume of the medium used in the literature for the studies varies from 50-500 ml and the stirrer speed from 60-300 rpm.

Interface diffusion system –

This method is developed by Dearden & Tomlinson. It consists of 4 - compartments. A represents the oral cavity and initially contained an appropriate concentration of drug in a buffer. The compartment B representing the buccal membrane, contained 1-octanol and compartment C representing body fluids, contained 0.2 M HCL. The compartment D representing protein binding also contained 1-octanol. Before use, the aqueous phase and 1-octanol were saturated with each other. Samples were withdrawn and returned to compartment A with a syringe.¹⁹

Modified Keshary Chien Cell:

A specialized apparatus was designed in the laboratory. It comprised of a Keshary Chien cell containing distilled water (50ml) at 370 C as dissolution medium. TMDDS (Trans Membrane Drug Delivery System) was placed in a glass tube fitted with a 10# sieve at the bottom which reciprocated in the medium at 30 strokes per min.²⁰

Dissolution apparatus:

Standard USP or BP dissolution apparatus have been used to study in-vitro release profiles using rotating elements, paddle and basket. Dissolution medium used for the study varied from 100- 500 ml and speed of rotation from 50- 100 rpm.²¹

In vivo methods:

Methods for studying the permeability of intact mucosa comprise of techniques that exploit the biological response of the organism locally or systemically and those that involve direct local measurement of uptake or accumulation of penetrates at the surface. The most widely used methods include in-vivo studies using animal models, buccal absorption tests and perfusion chambers for studying drug permeability.

Animal models:

Animal models are used mainly for the screening of the series of compounds, investigating the mechanisms and usefulness of permeation enhancers or evaluating a set of formulations. Animal models such as the dog, rats, rabbits, cat, hamster, pigs and sheep have been reported. In general, the procedure involves anesthetizing the animal followed by administration of the dosage form. In case of rats, the oesophagus is ligated to prevent absorption pathways other than oral mucosa. At different time intervals, the blood is withdrawn analyzed.²²

Buccal absorption test:

The buccal absorption test was developed by Beckett & Triggs in 1967. It is a simple and reliable method for measuring the extent of drug loss of the human oral cavity for single and multi-component mixtures of drugs. The test has been successfully used to investigate the relative importance of drug structure, contact time, initial drug concentration and pH of the solution while the drug is held in the oral cavity.²³

In-vitro and In-vivo correlations:

Correlations between in-vitro dissolution rates and the rate and extent of availability as determined by blood concentration and or urinary excretion of drug or metabolites are referred to as "*in-vitro-in vivo* correlations". Such correlations allow one to develop product specifications with bioavailability.

Percent of Drug Dissolved In-Vitro Vs Peak Plasma Concentration:

One of the ways of checking the in-vitro and in-vivo correlation is to measure the percent of the drug released from different dosage forms and also to estimate the peak plasma concentrations achieved by them and then to check the correlation between them.

Percent of Drug Dissolved Vs Percent of Drug Absorbed:

If the dissolution rate is the limiting step in the absorption of the drug, and is absorbed completely after dissolution, a linear correlation may be obtained by comparing the percent of the drug absorbed to the percent of the drug dissolved. If the rate limiting step in the bioavailability of the drug is the rate of absorption of the drug, a change in the dissolution rate may not be reflected in a change in the rate and the extent of drug absorption from the dosage form.

Dissolution Rate Vs Absorption Rate:

The absorption rate is usually more difficult to determine than the absorption time. Since the absorption rate and absorption time of a drug are inversely correlated, the absorption time may be used in correlating the dissolution data to the absorption data. In the analysis of in vitro and in vivo drug correlation, rapid drug absorption may be distinguished from the slower drug absorption by observation of the absorption time for the dosage form. The quicker the absorption of the drug the less is the absorption time required for the absorption of the certain amount of the drug. The time required for the absorption of the same amount of drug from the dosage form is correlated.

Percent of Drug Dissolved Vs Serum Drug Concentration:

For drugs whose absorption from GIT is dissolution rate limited, a linear correlation may be established between the percent of drug dissolved at specified times and the serum drug concentrations at corresponding times.

Percent of Drug Dissolved Vs Percent of the Dose Excreted in urine:

The percent of a drug dissolved and the percent of drug absorbed are linearly correlated. There exists a correlation between the amount of drug in body and the amount of drug excreted in the urine. Therefore, a linear relation may be established between the percent of the drug dissolved and the percent of the dose excreted in the urine.²⁴

Advantages:

1. Reliable means to deliver the drug to the target site with specificity, if modified and to maintain the desired concentration at the site of interest without untoward effects.
2. Solid biodegradable microspheres have the potential throughout the particle matrix for the controlled release of drug.
3. Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumour.²⁵
4. The size, surface charge and surface hydrophilicity of microspheres have been found to be important in determining the fate of particles in-vivo.
5. Studies on the macrophage uptake of microspheres have demonstrated their potential in targeting drugs to pathogens residing intracellularly.
6. Blood flow determination: This study has been carried out using radiolabelled microspheres.

APPLICATIONS:**Microspheres in vaccine delivery -**

An ideal vaccine must fulfill the requirement of efficacy, safety, convenience in application and cost. Biodegradable delivery systems for vaccines that are given by parenteral route may overcome the shortcoming of the conventional vaccines. The interest in parenteral (subcutaneous, intramuscular, intradermal) carrier lies since they offer specific advantages including:

1. Improved antigenicity by adjuvant action
2. Modulation of antigen release
3. Stabilization of antigen.

Targeting using microparticulate carriers –

The concept of targeting, i.e., site specific drug delivery is a well-established dogma, which is gaining full attention. The therapeutic efficacy of the drug relies on its access and specific interaction with its candidate receptors. The ability to leave the pool in a reproducible, efficient and specific manner is center to drug action mediated by use of a carrier system.

Monoclonal antibodies mediated microspheres targeting –

Monoclonal antibodies targeting microspheres are immune microspheres. This targeting is a method used to achieve selective targeting to the specific sites. Monoclonal antibodies are extremely specific molecules. Mabs can be directly attached to the microspheres by means of covalent coupling. The Mabs can be attached to microspheres by any of the following methods;

1. Nonspecific adsorption and Specific adsorption
2. Direct coupling and
3. Coupling via reagents.

4. Chemoembolisation –

Chemoembolisation is an endovascular therapy, which involves the selective arterial embolisation of a tumour together with simultaneous or subsequent local delivery of the chemotherapeutic agent.

5. Imaging –

The particle size range of microspheres is an important factor in determining the imaging of particular sites using radiolabelled microspheres. The particles injected intravenously apart from the portal vein will become entrapped in the capillary bed of the lungs. This phenomenon is exploited for the scintigraphic imaging of the tumour masses in lungs using labeled human serum albumin microspheres.

6. Topical porous microspheres –

Microsponges are porous microspheres having myriad of interconnected voids of particle size range 5 – 300µm. These microsponges having capacity to entrap wide range of active ingredients such as emollients, fragrances, essential oils etc., are used as the topical carrier system.²⁶

7. Medical application;

- Release of proteins, hormones and peptides over extended period of time.
- Gene therapy with DNA plasmids and also delivery of insulin.
- Vaccine delivery for treatment of diseases like hepatitis, influenza, pertussis, ricintoxoid, diphtheria, birth control.
- Passive targeting of leaky tumour vessels, active targeting of tumour cells, antigens, by intra-arterial/intravenous application.
- Tumour targeting with doxorubicin and also
- Treatments of leishmaniasis.
- Magnetic microspheres can be used for stem cell extraction and bone marrow purging.
- Used in isolation of antibodies, cell separation and toxin extraction by affinity chromatography.
- Used for various diagnostic tests for infectious diseases like bacterial, viral and fungal.²⁷

8. Radioactive microsphere's application:⁴

- Can be used for radio embolisation of liver and spleen tumours.
- Used for radio synectomy of arthritis joint, local radiotherapy, interactivity treatment.
- Imaging of liver, spleen, bone marrow, lung and even imaging of thrombus in deep vein thrombosis can be done.

CONCLUSION

The present review article shows that microspheres are better choice of drug delivery system than many other types of drug delivery system. In future by combining various other strategies, microspheres will find the central and significant place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted, specific and effective *in vivo* delivery and supplements as miniature versions of diseased organ and tissues in the body.

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