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Microspheres: A Short Overall Review

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ABSTRACT

Microspheres are having free flow powder uniqueness, which are consisting of synthetic polymers and proteins. These are biodegradable in nature have particle size smaller than 200um. Microspheres are the multiparticulate system of drug delivery which having natural and synthetic material. Microsphere inhances bioavailability, stability and target the drug to definite site at prearranged rate. Types of microspheres are as bioadhesive, floating, and radioactive, polymeric and biodegradable microspheres. Microspheres are mainly used in novel drug delivery system.

Keywords: New drug delivery system**,** microsphere, advantages, types, method of preparations.

INTRODUCTION (9, 17, 20, 21, 25, 27, 28)

Drug delivery system which target drug to the specific body site, having a number of impacts on the healthcare system. The perfect drug delivery system delivers the drug at rate decided by requirement of body all through the period of treatment so carrier technology find out the smart approach for drug delivery by coupling the drug to carrier particles example, microspheres, nanoparticles,liposomes oral route of drug administration is most preferable route for taking medication. Microspheres are small spherical particles which having diameter 1um to 100um. They are free flowing particle which are consisting of proteins or synthetic polymers this are biodegradable in nature. There are two types of microspheres

- Microcapsule-entrapped matter distinctly enclosed by distinct capsule wall
- Micromatricess-entrapped matter is dispersed all through the matrix

Controlled drug delivery system defeat the problems of conventional therapy and increase therapeutic efficacy of given drug7 to obtain maximum therapeutic efficacy it becomes necessary to deliver the agent. Microspheres are used in progress of new drug delivery system for controlled release of drug.

Microspheres Advantages

- They decrease concentration of drug at site other than the tissue or the target organ.
- They offer protection before after administration for unstable drug.
- Cut dose and toxicity.
- Particle size lessening for increasing solubility of poorly soluble drugs.
- Offer constant and prolonged therapeutic effect.

Preparation Of Microspheres ShouldSatisfy Certain Criteria: (11)

- The ability to incorporate reasonably high concentrations of the drug.
- Stability of the preparation after synthesis with a clinically acceptable shelf life.
- Controlled particle size and dispersibility in aqueous vehicles for injection.
- Release of active reagent with a good control over a wide time scale.
- Biocompatibility with a controllable biodegradability and
- Susceptibility to chemical modification.

Microspheres Types

- ➢ Bioadhesive microspheres
- ➢ Magnetic microspheres
- ➢ Floating microspheres
- ➢ Radioactive microspheres
- ➢ Polymeric microspheres
- ❖ Biodegradable polymeric microspheres
- ❖ Synthetic polymeric microspheres

➢ Bioadhesive Microspheres (17,25,28)

The adhering of drug to membrane by using the adhering property can be defined ticking to of water soluble polymers. These types of microspheres exhibit a prolonged habitation time at the site of application. Adhesion of the drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc.

➢ Magnetic Microspheres

This delivery system is very much important for localizes the drug to the disease site. In which bigger amount of freely circulating drug can be substitute by small amount of magnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic field.

➢ Floating Microspheres

In the floating microspheres the bulk density is very less than the gastric fluid therefore it leftovers buoyant in stomach without affecting on gastric emptying rate. Drug is released slowly at the desired rate of the site. it also reduces chances of striking and dose dumping Produces.

➢ Radioactive Microspheres (25)

In Radio emobilisation therapy microspheres sized 10-30 nm are of larger than capillaries. They are injected to arteries which lead to tumor of interest. These radioactive microspheres deliver high radiation dose to targeted areas without damaging the normal tissues. Different types of radioactive microspheres are α emitters, β emitters, γ emitters. (3)

➢ Polymeric Microspheres

The Polymeric Microspheres Are Classified Into Two Types As

❖ Biodegradable Polymeric Microspheres (9,25)

In this type Natural polymers such as starch are used as concept that they are biodegradable, biocompatible, and also Bioadhesive in nature. These polymers prolongs the residence time when contact with mucous membrane due to its high degree of swelling property with aqueous medium, results get gel formation.

❖ Synthetic Polymeric Microspheres (2, 22, 24, 4)

In Synthetic polymeric microspheres are widely used in clinical application, that are also used as bulkiness agent, fillers, embolic particles and drug delivery vehicles etc. and proved to be safe and biocompatible but the disadvantage of these kind of microspheres, are tend to migrate away from injection site and lead to potential risk, embolism ,further organ damage.

- **Proteins**

Albumin, Gelatin, Collagen

- **Carbohydrates**

Agarose, Carrageenan, Chitosan, Starch **(11)**

- **Chemically Modified Carbohydrates**

Poly dextran**,** Poly starch

Prepration Methods Of Microsomes

a. Spray Drying
b. Solvent Evaporation
c. Single emulsion technique
d. Double emulsion technique
e. Phase separation coacervation technique
f. Spray drying and spray congealing
g. Solvent extraction
h. Quassi emulsion solvent diffusion
i. Ionic gelation
j. Hydroxyl appetite (HAP) microspheres in sphere morphology

a. Spray Drying 1

In Spray Drying technique, polymer is primarily dissolved in volatile organic solvent such as dichloromethane, acetone, etc. The drug in solid form is then dispersed in to polymeric solution with the high-speed homogenization. This dispersion is then atomized in hot air stream. The atomization leads to the form the small droplets from which the solvent evaporates instantly leads the formation of the microspheres in the size range 1-100µm. Micro particles are separated from hot air by the cyclone separator while the trace of solvent is removed by vacuum

drying. Main advantages of this process are feasibility of operation under aseptic conditions.

b. Solvent Evaporation: (1,5,6,15)

This process carried out in a vehicle phase of liquid manufacturing. The coating of microcapsule is dispersed in the volatile solvent which immiscible with the vehicle phase of liquid manufacturing. A core material which is microencapsulated is dissolved in the coating polymer solution. Stir With the core material mixture is dissolved in the liquid manufacturing vehicle phase to obtain appropriate size microcapsule. Then the mixture is heated if necessary to evaporate and the solvent for the polymer of the core material are dissolved in the polymer solution, around the core polymer shrinks. If the core material is dissolve in the coating polymer solution, matrix type microcapsules are formed. The core materials are either water soluble or soluble materials.

c. Single Emulsion Technique (28)

The micro particulate carriers of the natural polymers i.e. proteins and carbohydrates are formulated by the single emulsion technique. Natural polymers are been dissolved in aqueous medium which is followed by a dispersion in non-aqueous medium like oil. In next step, the cross linking of dispersed globule is carried out. The cross linking can be achieved by the heat or by using the chemical cross linkers. The chemical cross linking agents used are glutaraldehyde, formaldehyde, acid chloride. Heat denaturation is not suitable for the hermolabile substance. Chemical cross linking having the disadvantage of excessive exposure of active ingredient to chemicals if added at time of preparation and then subjected to centrifugation, washing, separation ,nature of the surfactants used to stabilize the emulsion phases can greatly influence by the size, size distribution, surface morphology and loading drug release, and bio per-formance of the final multiparticulate product.

d. Double Emulsion Technique: (14)

In This method of microspheres preparation involves formation of multiple emulsions or double emulsion of type w/o/w and is best suited to the water soluble drugs, peptides, proteins and vaccines. The method can be used with the both natural as well as synthetic polymers. The aqueous protein solution is dispersed in the lipophilic organic continuous phase. This protein solution may contain the active constituents.

e. Phase Separation Coacervation Technique: (28)

This process is based on the principle of the decreasing the solubility of polymer in organic phase which have an effect on the formation of polymer rich phase called the coacervates. In this method, drug particles are dispersed in a solution of polymer and an incompatible polymer is added to system which makes first polymer for the phase separation.

f. Spray Drying And Spray Congealing: (10)

These are the methods based on the drying of the mist of polymer and drug in the air. Depending upon removal of the solvent or cooling of the solution, these two processes are named spray drying and spray congealing.

g. Solvent Extractions: (28)

In this Solvent evaporation method is used for the manufacturing of microparticles & includes removal of the organic phase by extraction of the non-aqueous solvent. This method involves the water miscible organic solvent which is iso-propanol.

h. Quassi Emulsion Solvent Diffusion (10,31)

A new quasi-emulsion solvent diffusion method which is used for the manufacturing of the controlled release microspheres of drugs with acrylic polymers has been reported in the literature. Microsponges can be manufactured by the quassi emulsion solvent diffusion method by using external phase which contsains distilled water and polyvinyl alcohol. The internal phase consist the drug, ethanol and polymers. Firstly the internal phase is manufactured at 60ºC and after then added to the external phase at room temperature. Then emulsification the mixture is continuously stirred for 2 hours. Then the mixture can be filtered for separate the microsponges.

i. 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 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. **(15)**

j. 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.**(19)**

Microspheres Physicochemical Evaluation

Characterization

The characterization of microparticulate carrier is a important phenomenon, which helps to design a appropriate carrier for the proteins, drug or antigen delivery. These microspheres have diverse microstructures. These microstructures verify the release and the stability of the carrier**.**

Particle shape and size

The most largely used procedures to visualize microparticles are conventional light microscopy (LM) and scanning electron microscopy (SEM). These 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.(**32)**

Electron spectroscopy for chemical analysis

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

Attenuated total reflectance Fourier Transform Infrared Spectroscopy

This FT-IR is used to identify the degradation of the polymeric matrix of the carrier system. The surface of the microspheres is investigated measuring alternated total reflectance (ATR). The ATRFTIR provides information about the surface composition of the microspheres based upon manufacturing procedures and conditions.

Determination of Density

The density of microspheres can be measured by using a multi-volume pychnometer. Precisely weighed sample in a cup that is placed into the multi volume pychnometer. Helium is introduced at a steady pressure in the chamber and allowed to expand. This expansion results in a reduce in pressure within the chamber. Two consecutive readings of reduction in pressure at different initial pressure are noted. From two pressure readings the volume and hence the density of the microsphere carrier is determined.

Iso-electric point

The micro electrophoresis is a special apparatus that 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 residue of carboxylic acid

The surface carboxylic acid residue can measured by using radioactive glycine. The radioactive glycine conjugates are 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 residue of amino acid

Surface linked 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.

Efficiency of Capture

Capture efficiency of the microspheres or the percent trap 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:

% Entrapment = Actual content/Theoretical content x 100

Contact Angle

The angle of contact can 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

The In vitro drug release studies have been employed as a quality control process in pharmaceutical production, in product development etc. Sensitive and reproducible release data derivative from physic-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**.(8)**

Beaker method

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

Interface diffusion system

This is a method that developed by Dearden & Tomlinson. It consists of 4 compartments. A represents the oral cavity, and initially contained an suitable 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 taken and returned to compartment A with a syringe.(**29**)

Modified Keshary Chien Cell

Its a specialized apparatus that 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**. (26)**

Dissolution apparatus

A 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. **(13)**

In vivo methods

These 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 gathering of penetrate 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

These animal models are used mostly 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, 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**.(2)**

Test for Buccal absorption

The buccal absorption test that was developed by Beckett & Triggs in 1967. It is a very 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)**

A In vitro-In vivo correlations

These 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.

Peak Plasma Concentration Vs Percent of Drug Dissolved *In Vitro*

It is one of the way 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 attained by them and then to check the correlation between them.

Percent of Drug Absorbed Vs Percent of Drug Dissolved

Dissolution rate is the limiting step in the absorption of the drug, and is absorbed entirely 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.

Absorption Rate Vs Dissolution Rate

Absorption rate is usually harder to determine than the absorption time. As 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 faster 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.

Serum Drug Concentration Vs Percent of Drug Dissolved

For those drugs whose absorption from GIT is dissolution speed 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 the Dose Excreted in urine Vs Percent of Drug Dissolved

The % of a drug dissolved and the percent of drug absorbed are linearly correlated. There exists a correlation between the quantity 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. **(23)**

ADVANTAGES of MICROSPHERES

- ❖ Reliable means to convey the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects.
- ❖ Solid biodegradable microspheres these have the potential throughout the particle matrix for the controlled release of drug.
- ❖ Microspheres established much attention not only for prolonged release, but also for Targeting of anticancer drugs to the tumour**. (23)**
- ❖ The size, surface charge and surface hydrophilicity of microspheres have been found to be important in determining the fate of particles *in vivo*.
- ❖ Studies on the macrophage uptake of microspheres have established their potential in targeting drugs to pathogens residing intracellularly.
- ❖ Blood flow determination: This study has been carried out using radiolabelled microspheres.

APPLICATIONS OF THE MICROSPHERES

▪ Into vaccine delivery

An ideal vaccine that must fulfill the requirement of efficacy, safety, convenience in application and cost. Biodegradable delivery systems for vaccines that are administeredd 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:

- ➢ Improved antigenicity by adjuvant action
- ➢ Modulation of antigen release
- ➢ Stabilization of antigen.

▪ Targeting with microparticulate carriers

The concept of the targeting, i.e. site specific drug delivery is a well established dogma, which is receiving 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 reproducible, efficient and specific manner is center to drug action mediated by use of a carrier system.

▪ Monoclonal antibodies mediate microspheres targeting

Monoclonal antibodies targeting microspheres are the immune microspheres. This type of targeting is 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

- ➢ Non specific adsorption and Specific adsorption
- ➢ Direct coupling
- ➢ Coupling via reagents

▪ Chemo-embolisation

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

▪ Imaging

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

▪ Topical porous microspheres

Mostly Microsponges are porous microspheres having myriad of inter-connected voids of particle size that range 5-300µm. These microsponges having capacity to entrap large range of active ingredients such as emollients, fragrances, essential oils etc., are used as the topical carries system. **(16)**

▪ Medical application

- ✓ In therelease of proteins, hormones and peptides over extended period of time.
- ✓ In Gene therapy with DNA plasmids and also delivery of insulin.
- ✓ In Vaccine delivery for treatment of diseases like hepatitis, influenza, pertusis, ricin toxoid, diphtheria, birth control.
- ✓ In Passive targeting of leaky tumour vessels, active targeting of tumour cells, antigens, by intra arterial/ intravenous application.
- ✓ In Tumour targeting with doxorubicin and also
- ✓ In Treatments of leishmaniasis.
- ✓ In Magnetic microspheres can be used for stem cell extraction and bone marrow purging.
- ✓ Its Used in isolation of antibodies, cell separation and toxin extraction by affinity chromatography.
- ✓ Its Used for various diagnostic tests for infectious diseases like bacterial, viral, and fungal. (7)

▪ Application of Radioactive microsphere(12)

- ✓ It can be used for radio embolisation of liver and spleen tumours.
- ✓ It is used for radio synvectomy of arthiritis joint, local radiotherapy, interactivitytreatment.
- ✓ Used in imaging of liver, spleen, bone marrow, lung and even imaging of thrombus in deep vein thrombosis can be done.

CONCLUSION

This review article shows that the microspheres are better choice as a drug delivery system than many other types of drug delivery system. In future aspects by combining a variety of other strategies, microspheres will

find the central and important place in new drug delivery, predominantly 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 parts.

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