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Microsphere; a Promising Drug Carrire

Dipali Hagir, Poonam Jadhav, Pooja Pote,
Navshyadri Institute of Pharmacy, Pune.

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ABSTRACT :
The target drug delivery system was designed forendeavoring to concentrate the drug in the tissue. Drug is localizedon the targeted site. Hence, drug does not affectsurrounding tissue. Microspheres are multiparticulate drug delivery system which are prepared to achieved prolonged and controlled drug delivery which is improve stability, bioavailability. Microspheres having a particle size ranging from 1-1000µm these are consisting proteins and synthetic these delivery system have numerous advantages as compared to conventional dosage form, the advantage is improved patient compliance, reduced toxicity, improved efficacy. Such system frequently usemacromolecules as carrier for the drug.
KEYWORDS : Microspheres, Type of microspheres , Method of preparation , Application of microspheres.

I. INTRODUCTION

"Microparticles"refers to the particles having the diameter range of 1-1000 um, irrespective of the precise exterior and/or interior structures.Microspheres are spherical particles, having with diameters 10µm to 1000µm. For retarding drug release from dosage form microcapsulation is used also they reduced adverse effects and improved patient compliance. Solid microspheres have many applications depending on what type of material materialthe are constructed of and what size they are.

Two most common type of polymer microspheres that are polyethylene and polystyrene microspheres. Polystyrene microspheres are commonly used in biomedical applications.

There are two types of microspheres:

- Microcapsules
- Micrometrics

Microcapsulesdefine as microparticles having a core surrounded by the coat or wallmaterial(s) distinctly different from that of the pay-load or nucleus or core, which may be solid, liquid and gas.

Classification of microcapsules **:**

-Mononuclear: Containing the shell aroundthe core.
-Polynuclear: In the shell many core are enclosed.
-Matrix type : Homogeneously distributed into the shell material [1]

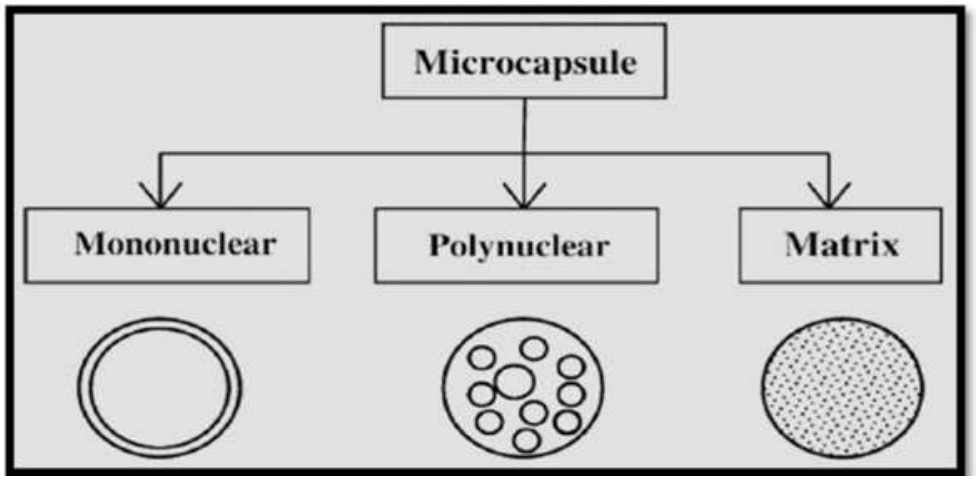

Fig.1: Classification of microcapsules

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By using various natural and synthetic material microspheres can be manufactured. Some microspheres are commercially available like polymer microspheres, glass microspheres, ceramic microspheres. The microspheres are preparedand fill this microspheres in hard gelatin and directly compress them. The microspheres which will get central place in novel drug delivery in future.

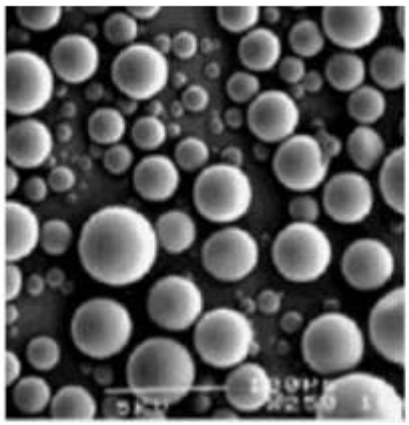

Fig.2Microspheres.

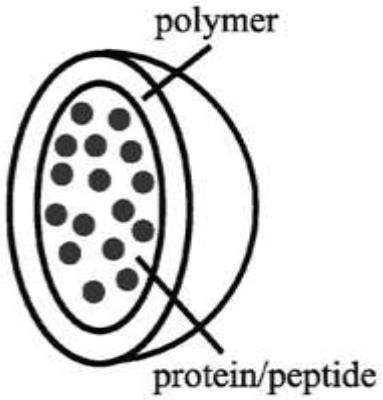

Fig.3Cross section of Microspheres

II.IDEAL CHARACTERISTICS OF MICROSPHERES

- Good Stability of the preparation after synthesis with clinical acceptable shelf-life
- Uniform particle size andfor injection soluble in aqueous vehicles.
- The ability to incorporate reasonably high concentration of the drug.
- Good Biocompatibility [2].

III. ADVANTAGE OF MICROSPHERES

- Reduced dose dumping.
- Drug absorption is reproducible.
- Achieved prolonged and controlled therapeutic effect.
- Improve patient compliance by providing constant drug concentration in blood.
- Decrease toxicity [3,5].
- Avoid hepatic first pass metabolism.
- Mask the odour and also taste.
- Decrease particle size for improve solubility of poorly soluble drug.
- Irritate effect of drug in GIT is absent
- Alter liquid to solid state and mask the unpleasant taste [4,6].

IV. DISADVANTAGE OF MICROSPHERES

- Toxicity is possible when inappropriate release of drugs.
- These dosage form must not be breaked.
- Reduced in Reproducibility [7,8].
- The cost of material is expensive.
- The polymer Matrix is effective and alsoit's impact on the environment.
- Not suitable for chewable tablet [9].
- They tend to migrate away from injection site and lead to potential risk, embolism and further organ damage[10].

V. TYPE OF MICROSPHERES:

1. Magnetic microspheres
2. Floating microspheres
3. Radioactive microspheres
4. Bioadhesive microspheres
5. Polymeric microspheres

a) Biodegradable polymeric microspheres
b) Synthetic polymeric microspheres

1. Magnetic microspheres:
Microspheres are contain proteins and synthetic polymers, of a biodegradable nature, which are generally free moving small spherical particles.Microshperes are different in particle size range from 1-1000 µm. It is essential for delivery system for directing the medication to the disease's source [11].

Two different types:

a) Therapeutic magnetic microspheres:These microspheres are commonly used for delivery of chemotherapeutic agent to liver tumors. Medicinal products like proteins and peptides can also targeted by this device.
b) Diagnostic microspheres:These microspheres used for diagnosis of liver metastases [12].

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2. Floating microspheres:

These microspheres have a bulk density lower than gastric fluids and thus remain float in the stomach for a prolonged period of time, withoutInfluence the gastric emptying rate and the drug is released slowly at a desired rate fromthe system, results in an greater in the gastric residence time and a better control offluctuations in the plasma drug concentrations and after complete release of the drug, theresidual system is emptied from the stomach[13,14].

3. Radioactive microspheres:

Size of microspheres of radio embolization therapy is normally 10-30 µm greater than capillary diameter. These type of Microshperes deliver to arteries that leads to a tumor of interest. So, that type of radioactive microspheres used foravoid Influence the normal surrounding tissue by deliver high radiation dose to targeted area.Their are different kinds of radioactive microspheres such as α emitters, β emitters, γ emitters [15].

4. Bioadhesive microspheres:

A novel electrobalance-based method to study adhesive interactions between individual microspheres and intestinal mucosa. Theterm"Bioadhesive" describes material which are bind or adhere to the biological substrate. The adherance to the drug delivery device's mucosal membrane ,the bioadherance can be considered like buccal, ocular, rectal nasal etc. Bioadhesive in between biological layer without the involvement of artificial material. Bioadhesive microspheres also called mucoadhesive microspheres. These mucoadhesive microspheres retard contact time at the absorption site [16].

5. Polymeric Microspheres:

There are different types of polymeric microspheres such as Biodegradable polymeric microspheres and Syntheticpolymeric microspheres**.**

a) Biodegradable polymeric microspheres:

Natural polymer such as gum tragacanth, sodium alginate, xanthan gum, gellan gumetc. also starch is natural polymer which are used with concept that they are biodegradable, biocompatible and also they are bioadhesive in nature. Biodegradable polymer retard the resistance time in contact with the mucus membrane due to it's better swelling property with aqueous medium [17].

b) Synthetic polymeric microspheres

In therapeutic applications synthetic polymeric microspheres are generally used. Also they are used as embolic particle, bulking agent, drug delivery vehicles, filtersetc.Themain limitation of these type of Microshperes are tends to migrate away from injection site and also lead to potential risk, emobilism and further organ damage.The example of synthetic polymer are following,

a) Cellulose derivative –Methyl cellulose (MC), Hydroxyethyl cellulose (HEC), Hydroxyl propylcellulose (HPC), Hydroxyl propyl methylcellulose (HPMC) etc.
b) Poly (Acrylic acid) polymers –Polycarbophil, Carbomers.
c) Poly vinyl alcohol (PVA) [18].

VI. METHODS OF PREPARATION OF MICROSPHERES:

1) Single Emulsion Technique
a) By heat
b) By Chemical Cross Linking Agents
2) Double Emulsion Technique
3) Polymerisation Technique
a) Normal Polymerisation
b) Interfacial polymerization.
4)Spray drying technique
5) Solvent Extraction
6)Phase separation co-acervation technique
7)Solvent evaporation technique

1) Single emulsion technique:

Several Carbohydrates and Proteins are mainly prepared by this technique. In this technique, natural polymers are first dissolved in aqueous medium and then dispersed in non-aqueous medium (oil phase) followed with next step crosslinking of dispersed globule; which can be achieved by 2 methods:

a) By Heat: Addition of dispersion into heated oil, but this method is not suitable for thermolabile drugs.

b) By Chemical Cross-linking Agent: Using glutaraldehyde, formaldehyde, acid chloride etc. as cross-linking agent. Chemical cross-linking suffers the disadvantage of excessive exposure [19].

2) Double emulsion technique:

Double emulsion method of microspheres preparation involves the formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited for water soluble drugs, peptides, proteins and the vaccines. This method can be used

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with both the natural as well as synthetic polymers. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. The protein solution may contain the active constituents. The continuous phase is generally consisted of the polymer solution that eventually encapsulates of the protein contained in dispersed aqueous phase. The primary emulsion is exposed then to the homogenization or the sonication before addition to the aqueous solution of the poly vinyl alcohol (PVA). The results in the formation of a double emulsion. The emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction. A number of hydrophilic drugs like luteinizing hormone releasing hormone (LH-RH) agonist, vaccines, proteins/peptides and conventional molecules are successfully incorporated into the microspheres using the method of double emulsion solvent evaporation/extraction.

3) Polymerizationtechniques:

The polymerization techniques conventionally used for preparing the microspheres are mainly classified as:

Normal polymerization

Interfacial polymerization

Normal polymerization: It is carried out by using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization methods. In bulk, a monomer or a combination of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer so obtained may be moulded as microspheres. Drug loading may be done during the polymerization process. Suspension polymerization also referred as bead or pearl polymerization. It is carried out by heating the monomer or composition of monomers as droplets dispersion in a continuous aqueous phase. Droplets may also contain an initiator and other additives. Emulsion polymerization deviates from suspension polymerization as due to the presence initiator in the aqueous phase, which afterwards diffuses to the surface of micelles. Bulk polymerization has merits of formation of pure polymers. Interfacial polymerization: This involves the reaction of various monomers at the interface between the two immiscible liquids to form a film of polymer that essentially envelops the dispersed phase [20].

5) Spray drying technique:

In this technique, the polymer is dissolved in volatile organic solvent like dichloromethane, acetone etc. and then drug (solid form) is dispersed in polymer solution under high speed homogenization. Dispersion is then atomized in the hot air stream, and atomization lead to the formation of small droplets from which solvent evaporates instantaneously; leading to formation of microsphere in a size range of 1-100 µm. Prepared micro particles are separated by hot air by the help of cyclone separator and solvent traces is removed by vacuum drying [21].

6) Solvent extraction:

Solvent evaporation method is used for manufacturing of micro particles, involves removal of the organic phase by extraction of the aqueous or non-aqueous solvent. This method involves water miscible organic solvents as isopropanol. Organic phase can be removed by extraction with water. This process decreases the hardening time for the microspheres. One variation of the process involves direct incorporation of the drug or protein to polymer organic solution. Rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion volume to the water and solubility profile of polymer

7) Phase separation co-acervation technique:

Phase separation method is mainly designed for preparing the reservoir type of the system. This method is used to encapsulate water soluble drugs e. g. peptides, proteins and some of preparations having matrix type particular, when the drug is hydrophobic in nature e. g. steroids. The process is based on the principal of decreasing the solubility of the polymer in the organic phase to affect the formation of the polymer rich phase called the coacervates. The coacervation can be brought about by the addition of the third component to the system which results in the formation of the two phases, one rich in polymer, while other not, i.e. supernant, depleted of the polymer. There are various methods which are effectively employed for coacervates phase separation. The methods are based on the salt addition, on-solvent addition, addition of the incompatible polymer [22].

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8) Solvent evaporation technique:

This is one of the earliest methods of microsphere manufacture. The polymer and drug must be soluble in an organic solvent, frequently methylene chloride.The solution containing the polymer and the drug may be dispersed in an aqueous phase to form droplets. Continuous mixing and elevated temperatures may be employed to evaporate the more volatile organic solvent and leave the solid polymer–drug particles suspended in an aqueous medium. The particles are finally filtered from the suspension [23].

VII. EVALUATION OF MICROSPHERES:

1) Particle size and shape:

The most widely used procedures to visualize microparticles are conventional light microscopy (LM)and scanning electron microscopy (SEM). Both can beused 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, it can also be used for the investigation of double walled systems. Conflocal fluorescence microscopy is used for the structure characterization of multiple walled microspheres. Laser light scattering and multi size coulter counter other than instrumental methods, which can be used for the characterization of size, shape andmorphology of the microspheres [24].

2) Electron spectroscopy for chemical analysis:

The surface chemistry of the microspheres can be determined using the electron spectroscopy for chemical analysis (ESCA). ESCA provides a means for the determination of the atomic composition of the surface. The spectra obtained using ECSA can be used to determine the surfacial degradation of the biodegradable microspheres.

3) Attenuated total reflectance Fourier Transfom-Infrared Spectroscopy:

FT-IR is used to determine the degradation of the polymeric matrix of the carrier system. The surface of the microspheres is investigated measuring alternated total reflectance (ATR). The IR beam passing through the ATR cell reflected many times through the sample to provide IR spectra mainly of surface material. The ATR-FTIR provides information about the surface composition of the microspheres depending upon manufacturing procedures and conditions.

4) Density determination:

The density of the microspheres can be measured by using a multi volume pychnometer. Accurately weighed sample in a cup is placed into the multi volume pychnometer. 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. 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 [25].

5) 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 mean velocity at different Ph values ranging from 3-10 is calculated by measuring the time of particle movement over a distance of 1 mm. By using this data the electrical mobility of the particle can be determined. The electrophoretic mobility can be related to surface contained charge, ionisablebehaviour or ion absorption nature of the microspheres.

6) Surface carboxylic acid residue:

The surface carboxylic acid residue is measured by using radioactive glycine. The radioactive glycine conjugates is prepared by the reaction of c14-glycine ethyl ester hydro chloride with the microspheres. The glycine residue is linked using the water soluble condensing 1-ethyl-3 (3 dimethyl amino propyl) carbidiimide (EDAC). The radioactivity of the conjugate is then measured using liquid scintillation counter. Thus the carboxylic acid residue can be compared and correlated. The free carboxylic acid residue can be measured for hydrophobic or hydrophilic or any other derivatized type of the microspheres.

7) 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. EDAC is used to condense the amino group and the c14 –acetic acid carboxylic acid residue. The method used for determining the free

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amino or the free carboxylic acid residues are based on indirect estimation, by measuring the radioactivity of the c14 having acetic acid or the glycine conjugate. The accuracy of the method however, depends on the time allowed for conjugation of the radioactive moiety and the reactivity of free functional group [26].

8) 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:

- % Entrapment = Actual content/Theoretical content x 100

9) 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. This thermodynamic property is specific to solid and affected by the presence of the adsorbed component. The angle of contact is measured at the solid/air/water interface. The advancing and receding angle of contact are measured by placing a droplet in a circular cell mounted above objective of inverted microscope. Contact angle is measured at 200C within a minute of deposition of microspheres [27].

10) In vitro methods:

There is a need for experimental methods which allow the release characteristics and permeability of a drug through membrane to be determined. For this purpose, a number of in vitro and in vivo techniques have been reported. 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. The influence of technologically defined conditions and difficulty in simulating in vivo conditions has led to development of a number of in vitro release methods for buccal formulations; 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.

11) 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 penetrants at the surface. Some of the earliest and simple studies of mucosal permeability utilized the systemic pharmacological effects produced by drugs after application to the oral mucosa. However the most widely used methods include in vivo studies using animal models, buccal absorption tests, and perfusion chambers for studying drug permeability.

12) In vitro in vivo correlation:

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 [25].

13) 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. It is expected that a poorly formulated dosage form releases amount of drug than a well formulated dosage form, and, hence the amount of drug available for absorption is less for poorly formulated dosage form than from a well formulated dosage form.

14) 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 [26,27].

15) Dissolution Rate Vs Absorption Rate:

The absorption rate is usually more difficult to determine than the absorption time.

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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.

16) 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.

17) 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 [28].

VIII. APPLICATION:

1) Microspheres in Vaccine Delivery:

The prerequisite of a vaccine is protection against the micro organism or its toxic product. An ideal vaccine must fulfill the requirement of efficacy, safety, convenience in application and cost. The aspect of safety and minimization of adverse reaction is a complex issue64 . The aspect of safety and the degree of the production of antibody responses are closely related to mode of application. Biodegradable delivery systems for vaccines that are given by parenteral route may overcome the shortcoming of the conventional vaccines65 . 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 [29].

2) 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 reproducible, efficient and specific manner is center to drug action mediated by use of a carrier system. Placement of the particles indiscrete anatomical compartment leads to their retention either because of the physical properties of the environment or biophysical interaction of the particles with the cellular content of the target tissue.

3) 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. This extreme specificity of monoclonal antibodies (Mabs) can be utilized to target microspheres loaded bioactive molecules to selected sites. Mabs can be directly attached to the microspheres by means of covalent coupling. The free aldehyde groups, amino groups or hydroxyl groups on the surface of the microspheres can be linked to the antibodies. The Mabs can be attached to microspheres by any of the following methods

1.Non specific adsorption
2. Specific adsorption
3.Direct coupling
4.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 the chemotherapeutic agent. The theoretical advantage is that such embolisations will not only provide vascular occlusion but will bring about sustained therapeutic levels of chemotherapeutics in the areas of the tumour. Chemoembolisation is an extension of traditional percutaneous embolisation techniques.

5) Imaging:

The microspheres have been extensively studied and used for the targeting purposes. Various cells, cell lines, tissues and organs can be imaged using radio labelled microspheres. The particle size

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range of microspheres is an important factor in determining the imaging of particular sites. 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 scintiographic imaging of the tumour masses in lungs using labelled human serum albumin microspheres.

6) Topical Porous Microspheres:

Microsponges are porous microspheres having myriad of interconnected voids of particle size range 5-300 µm. These microsponges having capacity to entrap wide range of active ingredients such as emollients, fragrances, essential oils etc., are used as the topical carries system further, these porous microspheres with active ingredients can be incorporated into formulations such as creams, lotions and powders. Microsponges consist of non collapsible structures with porous surface through which active ingredients are released in a controlled manner .

7) Surface Modified Microspheres:

Different approaches have been utilized to change the surface properties of carriers to protect them against phagocytic clearance and to alter their body distribution patterns .The adsorption of the poloxamer on the surface of the polystyrene, polyester or poly methyl methacrylate microspheres renders them more hydrophilic and hence decrease their MPS uptake. Protein microspheres covalently modified by PEG derivatives show decreased immunogenicity and clearance. The most studied surface modifiers are:

1.Antibodies and their fragments
2.Proteins
3.Mono, oligoand polysaccharides
4.Chelating compounds (EDTA, DTPA or Desferroxamine)
5.Synthetic soluble polymers Such modifications are provided surface of microspheres inorder to achieve the targeting to the discrete organs and to avoid rapid clearance from the body [30].

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