INTRODUCTION

The concept of drug delivery has been revolutionized with the advancement in drug delivery systems, especially those offering a sustained and controlled action of drug to desired area of effect. These novel drug delivery systems are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic action, and/or targeting the delivery of drug to a specific site.

A well designed controlled drug delivery system offers several potential advantages over traditional method of administration such as:- 1. Drug release rates can be tailored to the needs of specific application, for example, providing a constant rate of drug delivery or pulsatile release. 2. Controlled release systems provide protection of drugs, especially proteins that are otherwise rapidly destroyed by the body. 3. Controlled release system can increase patient comfort and compliance by replacing frequent (e.g. daily) doses with infrequent (once per month or less) injection.

Microspheres as drug carriers are one of the most effective novel approach in sustaining and controlling the action of drug to a specific site (e.g tissue). They are characteristically free flowing powders of spherical shape, consisting of proteins or synthetic polymers, which are either biodegradable or non-biodegradable in nature and ideally having a particle size ranging from 1 – 1000 μm. There are two types of microspheres:

- Microcapsules
- Micromatrices

Each type is described as, microcapsules are those in which entrapped substances is distinctly surrounded by distinct capsule wall whereas in micromatrices the entrapped substance is dispersed or dissolved through the particle matrix, having the potential for the controlled release of drug.
1. Synthetic polymers: They are employed as carrier materials and are divided into two types:-

(A) Non-biodegradable polymers: for ex- Poly methyl methacrylate, Acrolein, Glycidyl methacrylate, Epoxy polymers.3

(B) Biodegradable polymers: for ex- Lactides and Glycolides and their copolymers, Poly alkyl cyano acrylates, Poly anhydrides and Poly-ε-caprolactone(PCL).3

2. Natural polymers: They are obtained from different sources like proteins, carbohydrates, and chemically modified carbohydrates.3

(A) Proteins- Albumin, Gelatin, Collagen.

(B) Carbohydrates- Agarose, Gelatin, Starch, Chitosan, Carrageenan.

(C) Chemically modified carbohydrates- Poly(acryl) dextran, Poly(acryl) starch, DEAE cellulose.

### IDEAL MICROPARTICULATE CARRIERS

The material utilized for the preparation of microparticulates should have the following properties5,4,11:

- Longer duration of action.
- Provide protection of drug.
- Sterilizability.
- Water solubility or dispersability.
- Non-toxic.
- Relative stability.
- Biodegradable.
- Increase of therapeutic efficiency.
- Control of content release.

### TYPES OF MICROSHERES

#### Bioadhesive microspheres

Adhesion is the sticking of drug to the membrane by using water soluble polymer which posses sticking property. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc can be termed as bio adhesion. 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. Preparation of bioadhesive microspheres would be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membranes. Polycarbophil (Noveon® AA1) selected as polymer in the production of bioadhesive microspheres due to its excellent bioadhesive properties.5,9

#### Magnetic microspheres

This kind of delivery system is very much important which localizes the drug to 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. Magnetic microspheres are prepared by mixing water soluble drugs(for lipophilic drugs, along with the dispersing agents) and 10nm magnetite(Fe3O4) particles in an aqueous solvent of matrix material. This mixture is then emulsified in the oil. Ultrasonicication or shearing is done to produce particle of suitable size range. The matrix is then stabilized by chemical cross linking or heating.3,8

#### 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 gasteric contentand, increases gastric residence and increases fluctuation in plasma concentration. This system produces prolonged therapeutic effect and therefore reduces dosing frequencies. On each subsequent gastric emptying, sink particles will spread out over a large area of absorption sites, increasing the opportunity for drug release profile and absorption in a more or less predictable way. Moreover, since each dose consists of many subunits, the risk of dose dumping is reduced.9,11

#### Radioactive microspheres

Radio emobilisation therapy microspheres sized 10-30 nm are of larger than capillaries and gets tapped in first capillary bed when they come across. They are injected to the arteries that lead to tumour of interest. So in all these conditions radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues. Different kinds of radioactive microspheres are α emitters, β emitters, γ emitters.9,12

#### Polymeric microspheres

The different types of polymeric microspheres can be classified on the basis of biodegradable and non-biodegradable polymers into:-

- **Biodegradable polymeric microspheres**

Natural polymers such as starch are used because of their biodegradable, biocompatible, bio adhesive property. Biodegradable polymers prolongs the residence time when comes in contact with mucous membrane due to its high degree of swelling property with aqueous medium which results in formation of gel. Concentration of polymers controls the release of drug.13

- **Synthetic polymeric microspheres**

Synthetic polymeric microspheres are widely used in clinical application, 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.14

### METHOD OF PREPARATION

The preparation of microspheres should satisfy certain criteria.13 They are:
(i) The ability to incorporate reasonably concentrations of the drug,
(ii) Stability of the preparation after synthesis with a clinically acceptable shelf-life,
(iii) Controllable particle size and dispensability in aqueous vehicles for injection,
(iv) Release of active agent with good control over a wide time scale,
(v) Biocompatibility with a controllable biodegradability, and
(vi) Susceptibility to chemical modification.

Techniques for microsphere preparation
The techniques are as follows 3,16
1. Single emulsion techniques
2. Double emulsion techniques
3. Polymerization
   a. Normal polymerization
      i. Bulk
      ii. Suspension
      iii. Emulsion
   b. Inter-facial polymerization
4. Phase separation coacervation technique

Double emulsion techniques
Involves the formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited to the water-soluble drugs, peptides, proteins and the vaccines. This method can be used with both the natural as well as the synthetic polymers. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This 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 then subjected to the homogenization or the sonication before addition to the aqueous solution of the polyvinyl alcohol (PVA). This results in the formation of the double emulsion. The emulsion is then subjected to the solvent removal either by solvent evaporation or by solvent extraction process. The solvent evaporation is carried out by maintaining emulsion at reduced pressure or by stirring the emulsion so that the organic phase evaporates out. In the latter case, the emulsion is added to the large quantity of water (with or without surfactant) into which organic phase diffuses out. The solid microspheres are subsequently obtained by filtration and washing. A number of hydrophilic drugs like luteinizing hormone releasing hormone (LH-RH) agonist; vaccines, proteins/peptides and conventional molecule are successfully incorporated in to the microspheres using the method of double emulsion solvent evaporation/extraction. 3,20,21
Polymerization technique

The polymerization techniques used for the preparation of the microspheres are mainly classified as:

- Normal polymerization
- Interfacial polymerization

Normal polymerization

1) Bulk polymerization:
   A monomer or a mixture of monomer along with the initiator is usually heated to initiate the polymerization and carry out the process. The catalyst or the initiator is added to the reaction mixture to facilitate or accelerate the rate of the reaction. The polymer so obtained may be molded or fragmented as microspheres. For loading of drug, adsorptive drug loading or adding drug during the process of polymerization may be adopted.

2) The suspension polymerization:
   It is carried out by heating the monomer or mixture of monomers with active principles (drugs) as droplets dispersion in a continuous aqueous phase. The droplets may also contain an initiator and other additives.

3) The emulsion polymerization:
   However, differs from the suspension polymerization as due to presence of the initiator in the aqueous phase, which later on diffuses to the surface of the micelles or the emulsion globules.

Interfacial polymerization

In Interfacial polymerization technique two reacting monomers are employed; one of which is dissolved in the continuous phase while the other being dispersed in the continuous phase. The continuous phase is generally aqueous in nature through which the second monomer is emulsified. The monomers present in either phase diffuse rapidly and polymerize rapidly at the interface. Two conditions arise depending upon the solubility of formed polymer in the emulsion droplet. If the polymer is soluble in the droplet it will lead to the formation of the monolithic type of the carrier on the hand if the polymer is insoluble in the monomer droplet, the formed carrier is of capsular (reservoir) type. The degree of polymerization can be controlled by the reactivity of the monomer chosen, their concentration, and the composition of the vehicle of either phases and by the temperature of the system. Controlling the droplets or globules size of the dispersed phase can control the particle size. The polymerization reaction can be controlled by maintaining the concentration of the monomers, which can be achieved by addition of an excess of the continuous phase.

Phase separation coacervation technique

Specially designed for preparing the reservoir type of the system, i.e., to encapsulate water soluble drugs e.g. peptides, proteins, matrix type particularly, when the drug is hydrophobic in nature e.g., steroids. In matrix type device, the drug or the protein is soluble in the polymer phase. The process is based on the principle 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 addition of the third component to the system which results in the formation of the two phases, one i.e. supernatant, depleted of the polymer.3,22

In this technique, the polymer is first dissolved in a suitable solvent & then drug is dispersed by making its aqueous solution, if hydrophilic or dissolved in the polymer solution itself, if hydrophobic. Phase separation is then accomplished by changing the solution conditions.3,22 (figure-4)

Spray drying and spray congealing

Concept of spray drying technique (fig 1) depending upon the removal of solvent or the cooling of solution the two processes are spray drying & spray congealing. Evaporation is the basic mechanism in spray drying, whereas in spray congealing it is that of a phase inversion from a liquid to a solid. Both processes are similar, except for energy flow1. Spray drying is the most widely used industrial process involving particle formation and drying. Therefore, spray drying is an ideal process where the end-product must comply with precise quality standards regarding particle size distribution, residual moisture content, bulk density, and particle shape.23,24,25

Principle: Three steps involved in spray drying:

a.) Atomization: of a liquid feed change into fine droplets.

b.) Mixing: it involves the passing of hot gas stream through spray droplets which result in evaporation of liquids and leaving behind dried particles.

c.) Dry: Dried powder is separated from the gas stream and collected.

In this technique polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high-speed homogenization. This dispersion is then atomized in a stream of hot air, this form small droplets or the fine mist, from which the solvent evaporates instantaneously leading the formation of the microspheres. The size range is 1-100 µm. By using hot air separate of Microparticle by means of the cyclone separator while the traces of solvent are removed by vacuum drying. Advantages of the process are feasibility of operation. This technique is very useful to encapsulate various penicillins. Thiamine mononitrate and sulpha ethylhiadizole are encapsulated in a mixture of mono- and diglycerides of stearic acid and palmitic acid using spray congealing. Very rapid solvent evaporation, however leads to the formation of porous microparticles. The sprays are produces by either rotary (wheel) or nozzle atomizers. Evaporation of moisture from the droplets and formation of dry particles proceed under controlled temperature and airflow conditions. The microsphere size is controlled by the rate of spraying, nozzle size, temperature (in drying and collecting chambers.) and the feed rate of polymer drug solution. The quality of product is improved by addition plasticizer spray flow rate should kept constant around 6ml/min2. Spray drying technique is also useful for preparing chitosan microsphere, In 1999 He et al. Used formaldehyde as a crosslinking agent and also reported a novel method in which cimetidine and famotidine were entrapped in microspheres prepared by spray drying of multiple emulsion (o/w/o or w/o/w). They found that the release of the drugs from microspheres by this novel method was significantly sustained as compared to those prepared by conventional spray drying or o/w emulsion method. In 1994 Giunchedi et al. was used spray drying used for the preparation of PCL microspheres of ketoprofen. He used the organic solution of the drug and two polymers, cellulose acetate butyrate and PCL was made in a mixture of dichloromethane and chloroform (1:1). The prepared solution was sprayed through a nozzle in a spray-drier under different experimental conditions. Solid microspheres were collected into final bottom vessel spray-drier.23-25

Solvent extraction

For the formation of the emulsion between polymer solution and an immiscible continuous phase in aqueous (o/w) as well as non-aqueous phase (w/o) . Bogataj et al. (2000) prepared microsphere by using liquid paraffin/ acetone as the solvents by evaporation method. The drug solution (in acetone) was dispersed in chitosan solution and this mixture was
emulsified in liquid paraffin and stirred. The suspension of microspheres was filtered, washed and dried. Magnesium stearate was also added for preventing agglomeration as a Agglomeration preventing agent. The results showed that average particle size decreased with increasing amount of magnesium stearate used for microsphere preparation. Lim et al. (2000) investigated the comparison of mucoadhesive microspheres of hyaluronic acid, chitosan glutamate and a combination of the two prepared by solvent evaporation with microcapsules of hyaluronic acid and gelatin prepared by complex coacervation. 20,21

**Quasi emulsion solvent diffusion**

A novel quasi-emulsion solvent diffusion method to prepare the controlled release microspheres of drugs with acrylic polymers has been reported in the literature. Microsponges can be prepared by a quasi-emulsion solvent diffusion method using an external phase containing distilled water and polyvinyl alcohol (PVA). The internal phase is consisting of drug, ethyl alcohol and polymer is added at an amount of 20% of the polymer in order to facilitate the plasticity. At first, the internal phase is prepared at 60°C and added to the external phase at room temperature. After emulsification, the mixture is continuously stirred for 2 hours. Then the mixture can be filtered to separate the microsponges. The product is then washed and dried by vacuum oven at 40°C for 24 hours. Example: - Ibuprofen. 16

**EVALUATION OF MICROSPHERES**

**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, it can also be used for the investigation of double walled systems. Confocal fluorescence microscopy is used for the structure characterization of multiple walled microspheres. Laser light scattering and multi size couler counter other than instrumental methods, which can be used for the characterization of size, shape and morphology of the microspheres. 3,17,26-29

**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. 3,17,26-29

**Attenuated total reflectance Fourier Transformed-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. 3,17,26-29

**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. 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. 3,17,26-29

**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, ionisable behaviour or ion absorption nature of the microspheres. 3,17,26-29

**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) carbodiimide (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. 3,17,26-29

**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 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. 3,17,26-29
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:

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\% \text{ Entrapment} = \frac{\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. 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 20°C within a minute of deposition of microspheres.

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.

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.

IN-VITRO-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. 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.

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.
APPLICATIONS

1 Microspheres in vaccine delivery

The prerequisite of a vaccine is protection against the microorganism 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 issue. 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 vaccines. The interest in parenteral (subcutaneous, intramuscular, intradermal) carrier lies since they offer specific advantages including:

i. Improved antigenicity by adjuvant action
ii. Modulation of antigen release
iii. Stabilization of antigen.

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 immunomicrospheres. 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:

i. Non specific adsorption
ii. Specific adsorption
iii. Direct coupling
iv. 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. 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 labeled microspheres. The particle size 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 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 interconncted 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 carriers. These 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:

i. Antibodies and their fragments
ii. Proteins
iii. Mono-, oligo- and polysaccharides
iv. Chelating compounds (EDTA, DTPA or Desferroxamine)
v. Synthetic soluble polymers

Such modifications are provided surface of microspheres in order to achieve the targeting to the discrete organs and to avoid rapid clearance from the body.

CONCLUSION

Due to the recent advances in the technology of novel drug delivery system, the microsphere is becoming a widely accepted method for delivering therapeutic agents. Development in the polymer science has made it possible to synthesize different biodegradable and non-biodegradable polymers which can be used for the preparation of microspheres with different...
characteristics by using different available techniques. The foregoing shows that microsphere as drug carrier has great potentials, being able to use not only for delivering drugs but also as diagnostic tools. Although considerable research is needed to make easy-to-manufacture microsphere based pharmaceutical products, which comply with quality control requirements, they are very attractive systems, considering their advantages leading to a rapid development in this field.

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ACKNOWLEDGEMENT
The authors express their sincere thanks to Prof. R.M. Dubey, Vice Chancellor, IFTM University, Moradabad, Uttar Pradesh, India, for his constant encouragement and support to carry out this work.

CONFLICTS OF INTEREST
The author declares no conflicts of interest.

How to cite this article: Microspheres: a promising drug carrier, Rastogi V, Shukla Shiv S, Singh R, Niharika L, Yadav P., Journal of Drug Delivery & Therapeutics. 2016; 6(3):18-26