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MICROSPHERE AS A NOVEL DRUG DELIVERY – A REVIEW

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ABSTRACT

Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers having a particle size ranging from1-1000um.The range of techniques for the preparation of microspheres offers a variety of opportunities to control aspects of drug administration and enhance the therapeutic efficacy of a given drug. Of the many polymeric drug delivery systems, biodegradable polymers have been used in the form of micro particles, from which the incorporated drug is released to the environment in a controlled manner. They can be employed to deliver the medication in a rate controlled and sometimes targeted manner. Medication is released from a microsphere by drug leaching from the polymer or by degradation of polymer matrix. This review discusses the characteristics and degradation behavior of biodegradable polymers which are currently used in drug delivery.

KEYWORDS: Microspheres, polymeric drug delivery systems, targeted manner, biodegradable polymers.

INTRODUCTION

Microspheres are multi particulate drug system which are prepared to obtain controlled or prolonged drug delivery to improve bioavailability, stability and to target the drug to specific site at a predetermined rate. These are characteristically free flowing powders consisting of proteins or synthetic polymers having a particle size ranging from 1-1000um.Microspheres received much attention not only for prolonged release, but also targeting of drugs. The therapeutic efficacy of microspheres containing drug depends upon their characteristics that can be altered in required terms by altering materials, methods, polymers or techniques used. These delivery systems offer numerous advantages compared to conventional dosage forms which include improved efficacy, reduced toxicity, improved patient compliance and

convenience. The target site drug deliver with specificity &maintain the concentration at site of interest without untoward effects. The rate of drug release from the microspheres dictates their therapeutic action. The process of targeting and site specific delivery with absolute accuracy can be achieved by attaching bioactive molecule to liposome, bio erodible polymer, implants, monoclonal antibodies and various particulate.

ADVANTAGES

1. Provide constant and prolonged therapeutic effect.
2. Reduces the dosing frequencing and thereby improve the patient compliance.
3. Particle size reduction for enhancing solubility of poorly soluble drug.
4. Microsphere morphology allows a controllable variability in degradation and drug release.
5. Protect the drug from enzymatic and photolytic cleavage hence found to be best for drug delivery.
6. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.

LIMITATIONS

1. Reproducibility is less.
2. The modified release from the formulations.
3. Differences in the release rate from dose to another.
4. The costs of the materials and processing of the controlled release preparation, are substantially higher than those of standard formulations.
5. The fate of polymer matrix and its effect on environment.
6. The fate of polymer additives such as plasticizers, stabilizers, antioxidants and fillers.

CRITERIA FOR MICROSPHERE PREPARATION

The different methods used for various microsphere preparation depends on particle size, route of administration, duration of drug release and the characters related to rpm, method of cross linking, drug of cross linking, evaporation time and co precipitation.

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 the clinically acceptable shelf life.
3. Controlled particle size and dispersability in aqueous vehicles for injections.

4. Susceptibility to chemical modification.
5. Release of active reagent with good control over a wide time scale.

TYPES OF MICROSPHERES

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

a. Bio degradable polymeric microspheres.
b. Synthetic polymeric microspheres.

1. BIOADHESIVE MICROSPHERES

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

2. MAGNETIC MICROSPHERES

This type of drug delivery is important which localizes drug release to disease site. In this freely circulating drug is replaced by 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. The different types are therapeutic magnetic microspheres and diagnostic microspheres.

- **THERAPEUTIC MAGNETIC MICROSPHERES**

It is used to develop the chemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be targeted through this system.

- **DIAGNOSTIC MICROSPHERES**

It can be used for imaging liver metastases can also be used to distinguish bowel loops from other abdominal structures by forming nano size particles super magnetic iron oxides.

3. FLOATING MICROSPHERES

In floating type, the bulk density is less than gastric fluid so remains buoyant in stomach without affecting gastric emptying rate. If the system is floating on gastric content and increases the gastric residence and increases the fluctuation in plasma concentration. Moreover it also reduces the chances of striking and dose dumping.

4. POLYMERIC MICROSPHERES

The different types of polymeric microspheres are classified as follows and they are biodegradable polymeric microspheres.

- **BIODEGRADABLE POLYMERIC MICROSPHERES**

Natural polymers such as starch are used as biodegradable, biocompatible and also bio adhesive in nature. These prolongs the residence time when contact with mucous membrane due to its high degree of swelling property with aqueous medium, results gel medium.

- **SYNTHETIC POLYMERIC MICROSPHERES**

These are used in clinical application, moreover used as bulking agent, fillers, embolic particles drug delivery vehicles etc and proved to be safe and biocompatible.

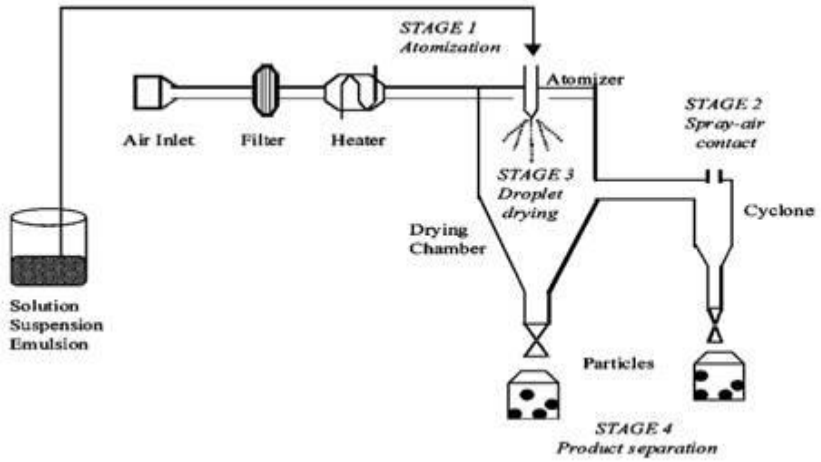
The main drawback is they migrate from injection site and lead to potential risk, embolism and further organ damage.

METHODS OF PREPARATION OF MICROSPHERES

1. Spray Drying.
2. Solvent Evaporation.
3. Single Emulsion Technique.
4. Double Emulsion Technique.
5. Phase Separation Co accervation Technique.
6. Spray Drying &Spray congealing.
7. Solvent Extraction.
8. Quassi Emulsion Solvent Diffusion.
9. polymerization technique.

SPRAY DRYING

In spray drying the polymer is dissolved in suitable volatile organic solvent such as dichloromethane, acetone etc. The drug in polymer form is then dispersed in polymer solution under high speed homogenization in a stream of hot air stream. Organic solution of poly and cellulose acetate butyrate in different weight ratios and ketoprofen were prepared and sprayed in different experimental condition achieving drug loaded microspheres. One of the advantage is feasibility of operation under aseptic conditions this process is rapid and leads to the formation of porous micro particles.

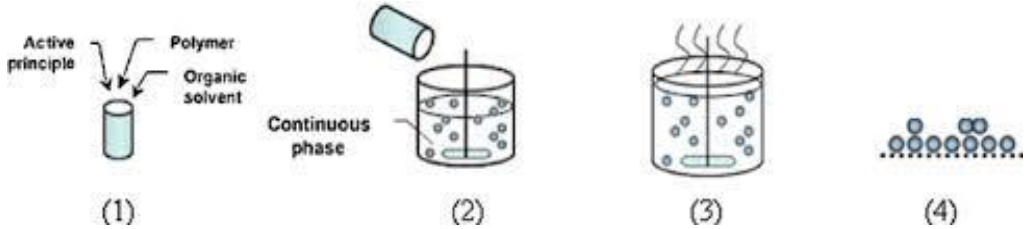


Microspheres by spray drying technique.

SOLVENT EVAPORATION TECHNIQUE

In this drug dissolved in polymer solution of chloroform resulting the solution is added to aqueous phase containing 0.2% sodium of PVP as emulsifying agent. The mixture was agitated at 500rpm to convert the polymeric solution to fine droplets which solidify into rich microspheres by solvent evaporation and then collected by filtration and at room temperature for 3hrs for cross linking then treated with 100ml of 10ml glycerine solution containing 0.1%w/v of tween80 at 37c for 10min to block unreacted glutaraldehyde.18.

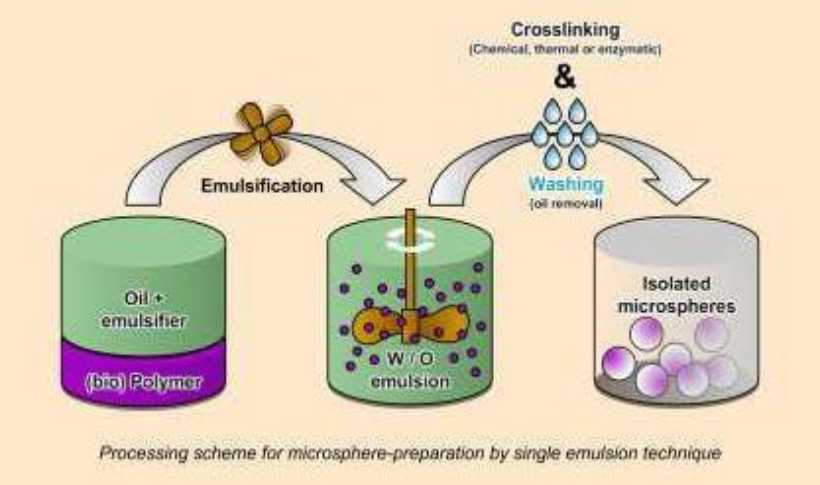
Ex: Gelatin A Microspheres.



SOLVENT EVAPORATION TECHNIQUE

SINGLE EMULSION TECHNIQUE

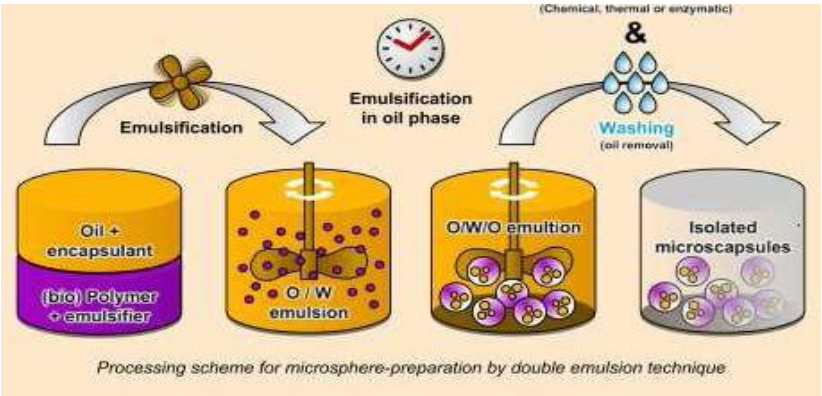
In single emulsion technique natural polymers like carbohydrates and proteins are used. The natural polymers are dissolved and dispersed in aqueous medium followed by dispersion in non aqueous medium ex: oil. Further cross linking of dispersed globules carried. The cross linking can be achieved either by means of heat or cross linking agents used include glutaraldehyde, formaldehyde, diacid chloride etc. cross linking by heat s affected by adding the dispersion to previously heated oil.



Microspheres by single emulsion technique.

DOUBLE EMULSION TECHNIQUE

Double emulsion method of microspheres involves the formation of multiple emulsions or double emulsion of type W/O/W and is best suited to water soluble drugs, peptides, proteins and vaccines. This method is suitable to both natural and synthetic polymers. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. The continuous phase generally consisted of a polymer solution the eventually encapsulates of the protein contained in dispersed aqueous phase. The primary solution is subjected to homogenization before the addition of PVA solution. The emulsion is subjected to solvent removal by solvent evaporation technique. ex: Leutinizing Harmone Releasing Harmone, vaccines, conventional molecules.



Microspheres by double emulsion technique.

PHASE SEPARATION AND COACCERVATION TECHNIQUE

This process is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase called co accervates. In this method, the drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles. The addition of non solvent results in solidification of polymer. Particle size and agglomeration of formed particles are responsible for the formation of coaccervates. The agglomeration is avoided by stirring the solution at specific rate.

%Entrapment=Actual content/ Theoritical content x 100

SPRAY DRYING AND SPRAY CONGEALING

The polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone etc. The drug in solid form is dispersed in the polymer solution under high speed homogenization. This atomized in a stream of cold air. This atomization leads to the formation of the small droplets or fine mist from which the solvent evaporates instantaneously leading to the formation of microspheres in a size range of 1-100um.

SOLVENT EXTRACTION

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

QUASSI EMULSION SOLVENT METHOD

Quassi emulsion solvent method involves the manufacture of micro sponges by using an external phase containing the distilled water and polyvinyl alcohol .T he internal phase is consisting of drug, ethanol and polymer is added at an amount of 20% of the polymer in order to enhance plasticity. At first, the internal phase is manufactured at 60c and then added to external phase at room temperature. The solution is stirred for 2hrs and filtered to separate micro sponges. The product is then washed and dried by vaccum- oven at 40c for a day.

POLYMERIZATON TECHNIQUE

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

1. Normal polymerization.
2. Interfacial polymerization.

1. Normal polymerization

It is carried out using different techniques as bulk suspension, precipitation, emulsion and micellar polymerization processes. In bulk, a monomer or a mixture 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 process of polymerization. Suspension polymerization also referred as bead or pearl polymerization. Here it is carried out by heating the monomer or mixture of monomers as droplets dispersion in a continuous aqueous phase. The droplets may also contain an initiator and other additives. Emulsion polymerization differs from suspension polymerization as due to the presence initiator in the aqueous phase, which later on diffuses to the surface of micelles. Bulk polymerization has an advantage of formation of pure polymers.

2. INTERFACIAL POLYMERIZATION

It involves the reaction of various monomers at the interface between the two immiscible phases to form a film of polymer that essentially envelopes the dispersed phase.

PHYSICOCHEMICAL EVALUATION

- **CHARACTERIZATION**

The characterization of the micro particulate carrier is an important phenomenon, which helps to design a suitable carrier for the proteins, drug or antigen delivery. The micro structures determine the release and stability of the carrier.

PARTICLE SIZE AND SHAPE

The most widely used procedures to visualize micro particles are conventional light microscopy and scanning electron microscopy. Both can be used to determine the shape and outer structure of micro particles. LM provides a controlled 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**33**. SEM allows investigations of the microspheres surfaces and after particles are cross-sectioned, it can also be used or the investigation of double walled systems. Conflocal fluorescence microscopy1 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 and morphology of the microspheres.

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.

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 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. Two consecutive readings of reduction in pressure at different initial pressure are noted. From two pressure readings the volume and hence the density of themicrosphere carrier is determined.

Iso electric Point

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Iso electric 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.

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) carbidimide (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 beam measured for hydrophobic or hydrophilic or any other derivatized type of the microspheres.

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.

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.

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 2000C 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 physic 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.

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 over head stirrer. Volume of the medium used in the literature for the studies varies from 50-500 ml and the stirrer speed form 60-300rpm.

Interface Diffusion System

This method is developed by Dearden & Tomlinson. It consists of four compartments. The compartment 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.

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.

Dissolution Apparatus

Standard USP or BP dissolution apparatus have been used to study *in vitro* release profiles using both rotating elements, paddle**41, 42, 43** and basket**44, 45**.m Dissolution medium used for the study varied from 100- 500 ml and speed of rotation from 50-100 rpm.

Other Methods

Few other methods involving plexi glass sample blocks placed in flasks**46**, agar gel method**47**, Valia- Chein cell USP n2 III dissolution apparatus**48, 49** etc have also been reported. Although a number of methods have been reported, the ideal method would be one where sink condition is maintained and dissolution time *in vitro* simulates dissolution time *in vivo.*

***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 them most widely used methods include *in vivo* studies using animal models, buccal absorption tests, and perfusion chambers for studying drug permeability**50**.

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. A number of animal models have been reported in the literature, however, very few *in vivo* (animal). Animal models such as the dog**51, 52**, rats**53**, rabbits**54, 55** cat**56**, hamster**57, 58**, pigs**59**, and sheep**60** 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 and analyzed.

***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"**61**. 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**62**.

APPLICATIONS

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 issue**64**. 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**65**. The interest in parenteral (subcutaneous, intramuscular, intra dermal) carrier lies since they offer specific advantages including:

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

2. Targeting using Micro particulate 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. Chemo embolisation

Chemo embolisation 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 them tumour. Chemo embolisation is an extension of traditional per cutaneous 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 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 scintio graphic imaging of the tumour masses in lungs using labelled human serum albumin microspheres.

6. Topical Porous Microspheres

Micro sponges are porous microspheres having myriad of interconnected voids of particle size range 5-300µm. These micro sponges 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. Micro sponges consist of non collapsible structures with porous surface through which active ingredients are released in a controlled manner **66**.

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-, oligo- and polysaccharides
4. Chelating compounds (EDTA, DTPA or Des ferrox amine)
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.

RECENT ADVANCEMENT IN MICROSPHERE

1. Important utilizations of chitosan polymer Cholesterol-lowering effects

2. Increase Stability of Drug
3. Orthopaedic Patients
4. Cosmetics industry
5. Dental Medicine
6. Chitosan as Permeation Enhancer
7. Chitosan as Muco adhesive Excipient
8. Effect of chitosan: citric acid ratio on drug Release
9. Chitosan as Permeation Enhancer
10. Enhanced Bone Formation by transforming growth factor (TGF-pl)
11. Direct Compressible Excipients and as Binder
12. Wound Healing Properties

FUTURE CHALLENGES

Future challenges of microspheres look bright particularly in the area of medicinal field because of its wide spectrum of application in molecular biology, eg: microsphere based genotyping platform is used to detect six single nucleotide polymorphism, yittrium-90 microspheres is used to prevent tumour after liver transplantation and it's advanced way in delivery of vaccines and proteins.

CONCLUSION

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. Microspheres by ionotropic gelation technique promises to be potential approach for gastric retention. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, 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. The prepared microspheres had good spherical geometry with smooth as evidenced by the scanningelectron microscopy.

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