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REVIEW ARTICLE

MICROSPHERE: A REVIEW

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ABSTRACT

Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers having a particle size ranging from 1-1000 µm. 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. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres as carriers for drugs also known as microparticles. It is the reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest. Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs. 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.

KEY WORDS: Microsphre , Novel Drug Delivery ,Methods of Preparation , Digital holographic microscopy

INTRODUCTION:

Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 µm to 1000 µm). Microspheres are sometimes referred to as microparticles. Microspheres can be manufactured from various natural and synthetic materials. Glass microspheres, polymer microspheres and ceramic microspheres are commercially available. Solid and hollow microspheres vary widely in density and, therefore, are used for different applications. Hollow microspheres are typically used as additives to lower the density of a material. Solid microspheres have numerous applications depending on what material they are constructed of and what size they are. Polyethylene and polystyrene microspheres are two most common types of polymermicrospheres.Polystyrene microspheres are typically used inbiomedical applications due to their ability to facilitate procedures such as cell sorting and immune precipitation.

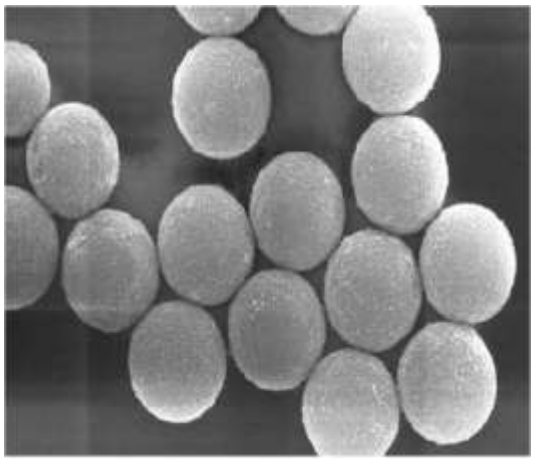

Figure 1: Microsphere

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METHOD OF DRUG INCORPORATION:

Drugs are incorporated into the microspheres either during their synthesis or after the microspheres are formed. High loading can be achieved by in situ loading if the drug is insoluble in the dispersion medium employed for microsphere stabilization. Washing the microspheres after their preparation to remove surfactants, oils, other impurities etc., using solvents in which the drug solubility is high may result in poor loading efficiency. In situ loading can not be employed for drugs which are affected by temperature of microsphere preparation, solvents employed, cross-linked agents etc. if the drug is heat sensitive, the resulting drug-loaded microspheres can not be sterilized by heat.Loading into preformed microspheres incorporated.

The microsphere is swollen in a suitable solvent containing high concentration of the drug. The drug molecules diffuse into the matrix which is then dried to obtain drug-loaded microspheres. The method is best suited for cross-linked microspheres which do not dissolve but only swell when equilibrated in a suitable solvent. A high payload of water soluble drugs can be obtained if the microspheres are hydrophilic and swells to a high degree in aqueous solution. The method allows the most native form of the drug to be incorporated into the matrix.

MATERIALS USED IN THE PREPARATION OF MICROSPHERE:

Microspheres used usually are polymers. They are classified into two types:

1. Natural polymers
2. Synthetic Polymers

1. Natural polymers obtained from different sources Like carbohydrates proteins and chemically modified Carbohydrates.

Carbohydrates**:** Agarose, Carrageenan, Chitosan,Starch

Proteins**:** Albumin, Collagen and Gelatin

Chemically modified carbohydrates: Poly dextran, Polystarch.

2. Synthetic polymers are divided into two types.

Biodegradable polymers

E.g. Lactides, Glycolides & their co polymers,Poly anhydrides,Poly alkyl cyano acrylates

Non-biodegradable polymers

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

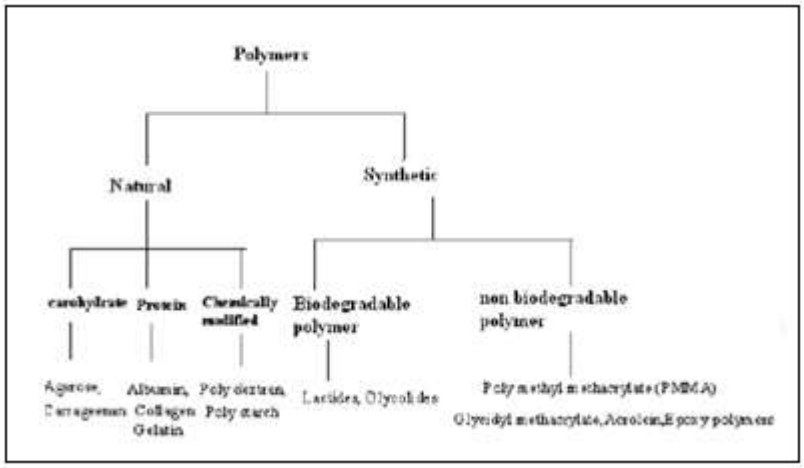

Figure 1: Flow chart of types of Polymers used in preparation of microsphere

ROUTE OF ADMINISTRATION:

Microspheres can be used for the delivery of drugs via different routes. Route of administration is selected depending on the drug properties, disease state being treated and the age and condition of the patient. Desirable properties of the microspheres to be used for the delivery will also change depending on the route of administration.

(a) ORAL DELIVERY:

Oral delivery is the simplest way of drug administration. In oral drug delivery, the microspheres have to pass through frequently changing environment in the GI tract. There is also patient to patient variation in GI content, stomach emptying time and peristaltic activity. Although constants of the oral route are numerous, on the whole, it offers less potential danger than the parenteral route. The relatively brief transit time of about 12 h through the GI tract limits the duration of action that can be expected via the oral route. Bioavailability of drugs with limited solubility in the stomach or intestine and small absorption rate constant can be increased by increasing the retention time in the stomach.

(b) PARENTERAL DELIVERY:

Most of the microsphere base controlled delivery systems are developed with the purpose of using them for

parenteral administration. Microspheres used for parenteral delivery should be sterile, free from impurities and should be dispersible in a suitable vehicle . Hydrophilic microspheres have the potential advantage of aqueous dispersibility as opposed to hydrophobic microspheres for reconstituting them for injection. Surfactants in small concentrations are necessary for reconstituting hydrophobic particles for injection in aqueous vehicle which are reported to cause adverse tissue reaction and affect the release of the incorporated drug.

TYPES OF MICROSPHERES:

(1) BIO ADHESIVE MICROSPHERES:

Adhesion of drug delivery device to the mucosal membrane such as rectal, nasal , buccal, ocular can be called as bio adhesion. These kinds of microspheres exhibit a prolonged residence time at the site of application which causes intimate contact with the absorption site and produces desire therapeutic action on specific part of body.

(2) MAGNETIC MICROSPHERES:

Magnetic carriers receive magnetic responses towards a magnetic field from incorporated materials magnetic microspheres They are used to deliver chemotherapeutic agent to liver tumour.

(3) FLOATING MICROSPHERES:

In floating types the bulk density of microsphere is less than the gastric fluid and so remains buoyant in stomach. Releasing drug becomes slowly at the desired rate. It also reduces chances of dose dumping. ketoprofen given through this form.

(4) RADIOACTIVE MICROSPHERES:

They are injected to the arteries that lead to tumors . In these conditions radioactive microspheres deliver high radiation dose to the targeted areas which doesn't damaging the normal surrounding tissues.The different kinds of radioactive microspheres are α emitters, β emitters, γ emitters. Biodegradable polymeric microspheres Natural polymers prolongs the residence time with in body parts when contact with aqueous medium, results gel formation. The rate and extent of drug release is controlled by concentration of different types of hydrophilic and hydrophobic polymers.

(5) SYNTHETIC POLYMERIC MICROSPHERES:

These microspheres are broadly applicable in clinical application and proved to be safe and biocompatible. But the main disadvantage of these kinds of microspheres, are tend to migrate away from injection site and lead to potential risk just like organ damage.

METHODS USE OF PREPARATION OF MICROSPHERES:

1. Solvent evaporation method,
a) Single emulsion technique.
b) Double emulsion technique.
2. Coacervation phase separation method.
3. Spray drying and spray congealing method.
4. Polymerization method.

1. SOLVENT EVAPORATION METHOD:

A) SINGLE EMULSION TECHNIQUE:

The microparticulate carriers of natural polymers which are proteins & carbohydrates are prepared by single emulsion technique. The natural polymers are dissolved/ dispersed in aqueous medium followed by dispersion in the non aqueous medium. Ex: oil. In the next step, cross linking of the dispersed globule is carried out either by means of heat or by using chemical cross linkers. The chemical cross linking agents used –gluteraldehyde, formaldehyde, terephthalate chloride, diacidchloride. Crosslinking by heat is effected by adding the dispersion to previously heated oil. Heat denaturation is not suitable for the thermolabile drugs while the chemical cross-linking suffers disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation.

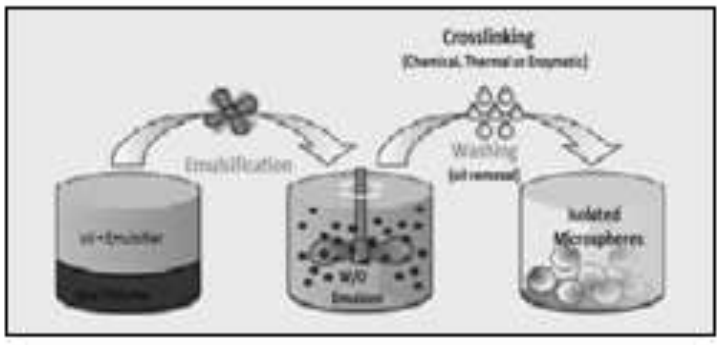

Figure 2: Processing scheme for microspheres-preparation by single emulsion technique

b) DOUBLE EMULSION TECHNIQUE:

This process consume formation of the multiple emulsions or the double emulsion of type w/o/w & is best suited to the water soluble drugs, peptides, proteins & the vaccines. The aqueous protein solution is dispersed in a lipophilic organic continuous phase which is generally consisted of polymer solution that eventually encapsulates protein contained in dispersed aqueous phase. The primary emulsion is then subjected to the homogenization before addition to aqueous solution of PVA .this results in formation of double emulsion which is then subjected to solvent removal by solvent evaporation maintaining the emulsion at reduced pressure or by stirring so that organic phase evaporates out.

Examples: hydrophilic drugs like LHRH agonist, vaccines and proteins.

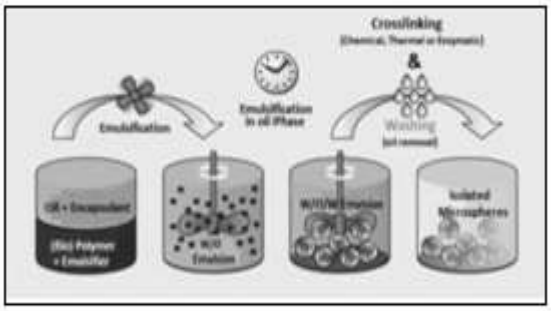

Figure 3: Processing scheme for microspheres-preparation by double emulsion technique

2. COACERVATION PHASE SEPARATION METHOD:

This method is used preparing the reservoir type of the system to encapsulate water soluble drugs like 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. 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 t he polymer solution itself, if hydrophobic. Phase separation is then accomplished by changing the solution conditions.

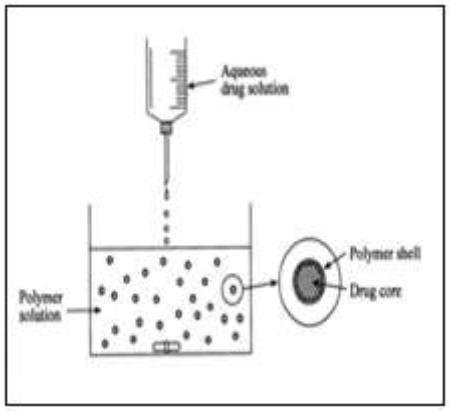

Figure 4 : Processing scheme for microspheres-preparation by Coacervation phase separation method

3. SPRAY DRYING AND SPRAY CONGEALING:

These methods are based on the drying of the mist of the polymer and drug in the air. Depending upon the removal of the solvent or cooling of the solution . Two processes are named spray drying and spray congealing respectively. The 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. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporates instantaneously leading the formation of the microspheres in a size range 1- 100 µm. Microparticles are separated from the hot air by means of the cyclone separator while the traces of solvent are removed by vacuum drying. One of the major advantages of the process is feasibility of operation under aseptic conditions.

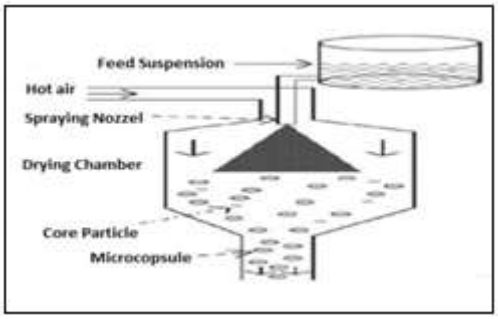

Figure 5: Processing scheme for microspheres-preparation by Spray drying and spray congealing

4. POLYMERIZATION METHOD

I. Normal polymerization

II. Interfacial polymerization.

NORMAL POLYMERIZATION:

Proceeds using techniques like bulk, suspension precipitation, emulsion & micellar polymerization processes. In bulk polymerization, a monomer with initiator is heated to start polymerization. Initiator is added to accelerate the rate of reaction. Drug is added during process of polymerization. The polymer so obtained is fragmented to microspheres.

SUSPENSION POLYMERIZATION:

Suspension polymerization is carried out by heating the monomer or mixture of monomers with active principles(drug) as droplets dispersion in a continuous phase. The droplets may also contain an initiator & other additives. The emulsion polymerization, differs from the suspension polymerization as due to presence of initiator in the aqueous phase, which later on diffuses to the surface of the micelles or the emulsion globules. The suspension & emulsion polymerization can be carried out at lower temperature, since continuous external phase is normally water through which heat can easily dissipate.

INTERFACIAL POLYMERIZATION:

Involves reaction of various monomers at the interface between the 2 immiscible liquid phases to form a film of polymer that essentially envelopes the dispersed phase. In this 2 reacting monomers are employed one of which is dissolved in the continuous phase while the other being dispersed in the continuous phase. Monomer present in either phases diffuse rapidly 7 polymerize rapidly at the interface. If the polymer is soluble in the droplet it will lead to the formation of monolithic type of the carrier on the other hand if 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 monomer chosen, their concentration, the composition of the vehicle of either phases & by the temperature of the system. The particle size can be controlled by controlling the droplets or globule size of the disperse phase. The polymerization reaction can be controlled by maintaining the concentration of the monomers, which can be achieved by the addition of an excess of the continuous phase.

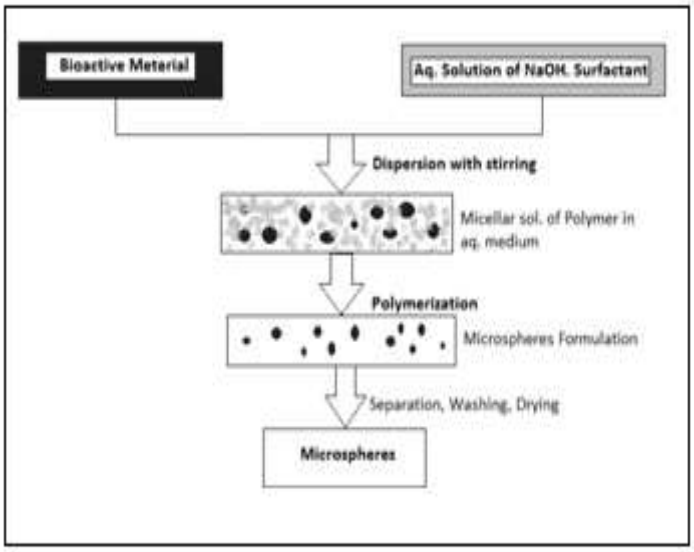

Figure 6: Processing scheme for microspheres-preparation by Polymerization method

COACERVATION METHOD:

Coacervation thermal change: Performed by weighed amount of ethyl cellulose was dissolved in cyclohexane with vigorous stirring at 80oC by heating. Then the drug was finely pulverized and added with vigorous stirring on the above solution and phase separation was done by reducing temperature and using ice bath. Then above product was washed twice with cyclohexane and air dried then passed through sieve (sieve no. 40) to obtain individual microcapsule. Coacervation non solvent addition: Developed by weighed amount of ethyl cellulose was dissolved in toluene containing propylisobutylene in closed beaker with magnetic stirring for 6 hr at 500 rpm and the drug is dispersed in it and stirring is continued for 15mins. Then phase separation is done by petroleum benzoin. 14 times with continuous stirring. After that the microcapsules were washed with n-hexane and air dried for 2 hr and then in oven at 50oC for 4 hr.

SPRAY DRYING TECHNIQUE:

This was used to prepare polymeric blended microsphere loaded with ketoprofen drug. It involves dispersing the core material into liquefied coating material and then spraying the mixture in the environment for solidification of coating followed by rapid evaporation of solvent. Organic solution of poly (epsilon caprolactone) (PCL) and cellulose acetate butyrate (CAB), in different weight ratios and ketoprofen were prepared and sprayed in different experimental condition achieving drug loaded microspheres. This is rapid but may loose crystalinity due to fast drying process.

EMULSION-SOLVENT DIFFUSION TECHNIQUE:

In order to improve the residence time in colon floating microparticles of ketoprofen were prepared using emulsion solvent diffusion technique. The drug polymer mixture was dissolved in a mixture of ethanol and dichloromethane (1:1) and then the mixture was added drop wise to sodium lauryl sulphate (SLS) solution. The solution was stirred with propeller type agitator at room temperature at 150 rpm for 1 hr. Thus the formed floating microspheres were washed and dried in a dessicator at room temperature. The following microparticles were sieved and collected.

MULTIPLE EMULSION METHOD:

Oral controlled release drug delivery of indomethacin was prepared by this technique. In the beginning powder drug was dispersed in solution (methyl cellulose) followed by emulsification in ethyl cellulose solution in ethyl acetate. The primary emulsion was then re emulsified in aqueous medium. Under optimized condition discrete microspheres were formed during this phase.

IONIC GELATION:

Alginate/chitosan particulate system for diclofenac sodium release was prepared using this technique. 25% (w/v) of diclofenac sodium was added to 1.2% (w/v) aqueous solution of sodium alginate. In order to get the complete solution stirring is continued and after that it was added drop wise to a solution containing Ca2+ /Al3+ and chitosan solution in acetic acid. Microspheres which were formed were kept in original solution for 24 hr for internal gellification followed by filteration for separation. The complete release was obtained at pH 6.4-7.2 but the drug did not release in acidic pH.

HYDROXYL APPETITE (HAP) MICROSPHERES IN SPHERE MORPHOLOGY:

This was used to prepare microspheres with peculiar spheres in sphere morphology microspheres were prepared by o/w emulsion followed by solvent evaporation. At first o/w emulsion was prepared by dispersing the organic phase in aqueous phase of surfactant. The organic phase was dispersed in the form of tiny droplets which were surrounded by surfactant molecules this prevented the droplets from co-solvencing and helped them to stay individual droplets .While stirring the DCM was slowly evaporated and the droplets solidify individual to become microspheres.

MECHANISM OF DRUG RELEASE:

The release of drugs from biodegradable microspheres can be classified into four different categories. But in actual practice, the mechanism is more complex and an interplay of different mechanisms may operate. In degradation controlled monolithic microsphere systems, the drug is dissolved in the matrix and is distributed uniformly throughout. The drug is strongly to the matrix and is released only on degradation of the matrix. The diffusion of the drug is slow compared with the degradation of the matrix. When degradation is by homogeneous bulk mechanism, drug release is initially becomes slow and increases rapidly when rapid bulk degradation starts. Drug release from such type of devices is independent of the geometry of the device. Release from a sphere is governed by the equation, where Mt is the amount of the agent released at time t, M∞ is the amount at time t∞ is the time for total erosion. Progesterone release from poly (glycolic-co-lactic acid) polymer films containing 10 weight% steroids is an example of this type of release.

$$Mt / M8 = 1-[(1-t/ t8)]3$$

DIFFUSION CONTROLLED MONOLITHIC SYSTEM:

Active agent is released by diffusion prior to or concurrent with the degradation of the polymer matrix. Degeneration of the polymer matrix affects the rate of release. Rate of release also depends on whether the polymer degrades by homogeneous or heterogeneous mechanism.

DIFFUSION CONTROLLED RESERVOIR SYSTEMS:

Active agent is encapsulated by a rare controlling membrane through which the agent diffuses and the membrane erodes only after its delivery is completed. In this case, drug release is unaffected by the degradation of the matrix. Polymer that remains as such till the complete, release of drug and then degrades by homogenous mechanism so that the device is removed from the body is better for this type of delivery.

ERODIBLE POLY-AGENT SYSTEM:

Active agent is chemically attached to the matrix and the rate of biodegradation of the matrix is slow compared to the rate of hydrolysis of drug polymer bond. Diffusion of the active agent from the matrix to the surrounding is rapid, the limiting step is the rate of cleavage of the bond attaching drug to the polymer matrix.

EVALUATION PARAMETERS

1. PHYSICOCHEMICAL EVALUATION CHARACTERIZATION:

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

2. 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. 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 and morphology of the microspheres.

3. 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.

4. 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.

5. 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.

6. 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.

7. 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.

8. 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. 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 60-300 rpm.

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 with drawn 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, paddle25, 26, 27 and basket 28, 29. Dissolution medium used for the study varied from 100- 500 ml and speed of rotation from 50-100 rpm.

9. IN VIVO METHODS:

Methods used to study 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. Most widely used methods include in vivo studies using animal models, buccal absorption tests, and perfusion chambers for studying drug permeability.

10. 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.

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.

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.

11. SWELLING INDEX:

Swelling index was determined by measuring the extent of swelling of microspheres in the given buffer. To ensure the complete equilibrium, exactly weighed amount of microspheres were allowed to swell in given buffer. The excess surface adhered liquid drops were removed by blotting and the swollen microspheres were weighed by using microbalance.

The hydrogel microspheres then dried in an oven at 60° for 5 h until there was no change in the dried mass of sample. The swelling index of the microsphere was calculated by using the formula Swelling index= (mass of swollen microspheres – mass of dry microspheres/mass of dried microspheres) 100.

DIGITAL HOLOGRAPHIC MICROSCOPY:

It is commonly accepted that it is energetically favourable for particles to bind to fluid-fluid interfaces. The particle sits at an equilibrium position in between the two bulk phases, as predicted by Young's law. But how does a particle reach this equilibrium position from the bulk phase? In this paper, the authors examine the dynamics of how a particle reaches this position and find that the process is surprisingly slow and has parallels in ageing of glassy systems.

Digital Holographic Microscopy is used to capture the three-dimensional trajectory of the microspheres as they approach the interface at up to 5000 frames/sec. A high spatial precision of 2nm is achieved by refractive index matching the aqueous phase (~60% glycerol, 40% water, NaCl) to the decane. This minimises reflections within the sample, which would make hologram analysis much more complicated. Digital holographic microscopy is used to image the microsphere.

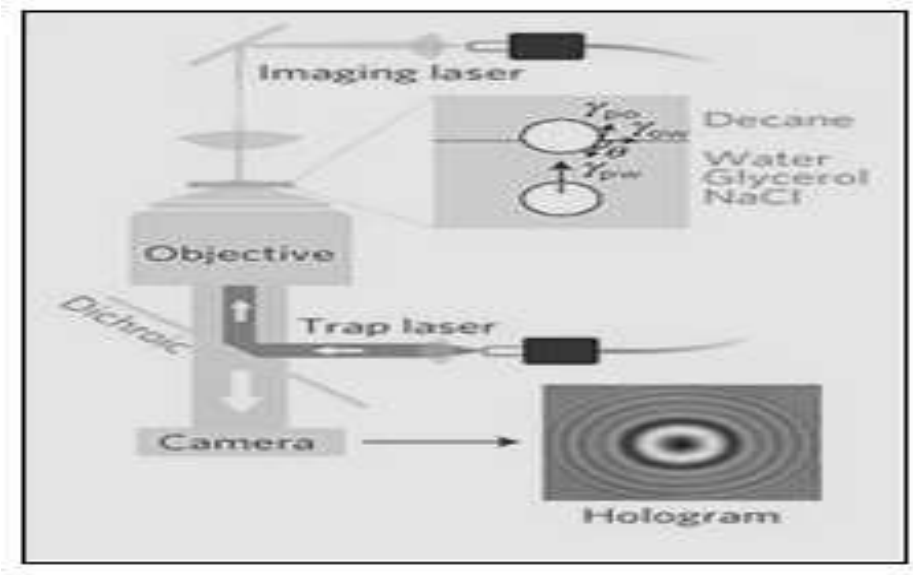

Figure 7: Digital Holographic Microscop

Table 1: Therapeutic applications of microspheres

Type of radioactive microspheres	Applications
^{90}Y-glass microspheres, ^{186}Re/^{188}Re-glass microspheres	Radioembolisation of liver and spleen tumors
^{35}S-colloid, ^{90}Y-resin microspheres, ^{169}Er.citrate	Radiosynovectomy of arthritis joints
^{90}Y-labeled poly(lactic acid) microspheres, ^{211}At-microspheres, ^{212}Pb-sulfur colloid	Local radiotherapy
Chromium ^{32}P-phosphate, ^{90}Y-silicate	Intracavity treatment

APPLICATIONS:

1. Release of proteins, hormones and peptides over extended period of time.
2. Gene therapy with DNA plasmids and also delivery of insulin.
3. Vaccine delivery for treatment of diseases like hepatitis, influenza, pertusis, ricin toxoid, diphtheria, birth control.
4. Passive targeting of leaky tumour vessels, active targeting of tumour cells, antigens, by intra arterial/ intravenous application.
5. Tumour targeting with doxorubicin and also Treatments of leishmaniasis.
6. Magnetic microspheres can be used for stem cell extraction and bone marrow purging.
7. Used in isolation of antibodies, cell separation and toxin extraction by affinity chromatography.
8. Used for various diagnostic tests for infectious diseases like bacterial, viral, and fungal.
9. Can be used for radio embolisation of liver and spleen tumours.
10. Used for radio synvectomy of arthiritis joint, local radiotherapy, interactivity treatment.
11. Imaging of liver, spleen, bone marrow, lung and even imaging of thrombus in deep vein thrombosis can be done.
12. Determining the imaging of particular sites using radio labbled microspheres.
13. In endovascular therapy

RESULT AND DISCUSSION:

The purpose of the present study is to enhance efficiency of formulayion of microsphere . Number of polymers are available for formulation of microsphere. Biodegradable polymer microspheres appear to have potential applications in controlled drug delivery. Development in polymer science has made it possible to synthesize polymers with a wide range of biodegradability. macrophage uptake of microspheres have demonstrated their potential in targeting drugs to pathogens residing intracellularly. This approach may prove to be potentially useful in the treatment of macrophage as, associated diseases.

CONCLUSION:

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

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