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A Review on Microspheres: Types, Methods of Preparation, Effects of Process Variables and Applications.

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ABSTRACT

Microspheres are small particles of spherical form with form below 200 μm. The analysis is concerned with the microspheres of its benefits, demerits, forms, planning, results and implementation of process variables. Here, in this article it is one of the novel drug delivery system. It overcame a number of problems regarding other forms of dosage. In order to improve bioavailability, the different types of microspheres are used in various ways to provide greater therapeutic efficacy. The effects of process variables on drug trapping, drug release, and particle size are being investigated. Microspheres are typically free flowing powders consisting of naturally biodegradable synthetic polymers. A microsphere has a drug in the middle of the molecule, where it is contained inside a special polymeric membrane.

Keywords: Microspheres, Drug Delivery, Particle Size, Controlled Release.

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INTRODUCTION

The oral route represents one of the most successful drug delivery routes.[1] It has a short circulating half-life and limited absorption through a defined segment of intestinal limits.[2] It leads to frequent dosage of medication to achieve therapeutic effect due to such pharmacokinetic demerit.[2] Improving pharmacokinetic and pharmacodynamic profile leads to increased bioavailability. The drug therapy's effectiveness is described as achieving the drug's desired concentration in blood or tissue. Good nature of the dosage scheme helps achieve goal[3].

Tiny spherical particles with a diameter (typically 0.1-200 μm) in the microsphere micrometer selection. Those are made of biodegradable and non-biodegradable compounds that can be inserted with 18 or 20 needle numbers.[4] They are also known as microparticles. Those methods help to solve the stability issues of these materials.[5]

Microsencapsulation technique is used to slow down drug release and to reduce or remove gastrointestinal tract inflammation. It is evenly distributed in the gastrointestinal tract. A low microsphere scale that increases drug absorption and minimizes side effects including gastric irritation.[6]

IDEAL CHARACTERISTICS OF MICROSPHERES[7,8]

- Clinically acceptable shelf life with better stability after synthesis
- Appropriate particle size and dispersability in aqueous vehicles for injection.
- Release of drug with a good control over a long period of time.
- Good Biocompatibility with a controllable biodegradability.

ADVANTAGES OF MICROSPHERES [9,10,11]

- Microspheres provide prolonged and constant therapeutic effect.
- Improve the patient compliance with reduced dosing frequency and better bioavailability
- Reproducible drug absorption.
- Drug discharge in stomach is hindered.
- Better therapeutic effect with short half life
- Decrease dose dumping.
- Protection of drugs against destructive environment.
- Mask the taste and odor.
- Surpasses the first pass metabolism.

LIMITATIONS OF MICROSPHERES [12]

- The modified release from the formulations.

- Variation in release of drug from different formulations through the GIT.
- Differences in the release rate from one dose to another.
- Non uniform release of drug may lead to toxicity.
- No crushing or chewing of tablet.

TYPES OF MICROSPHERES:

Bioadhesive microspheres

Magnetic microspheres

Radioactive microspheres

Floating microspheres

Polymeric microspheres

Biodegradable polymeric microspheres

Synthetic polymeric microspheres

Bioadhesive microspheres [13,14]

Adhesion can be described as sticking of drug to membrane by using the sticking property of water soluble polymers. Adherence to the drug delivery device's mucosal membrane, such as buccal, ocular, rectal, nasal, etc. can be considered bio adherence. Such kinds of microsphere exhibit a prolonged period of residence at the application site and induce intimate interaction with the absorption site and yield better therapeutic action. Mucoadhesive microspheres provide extended contact time at the application or absorption site and help to encourage intimate contact. The underlying surface where absorption is supposed to occur, thereby enhancing or improving the therapeutic efficacy of the drug.

Magnetic microspheres [15,16]

Microspheres are usually free moving small spherical particles consisting of proteins or synthetic polymers, of a biodegradable nature, varying in particle size from 1-1000μm.

They are considered as one of the essential approaches for delivering therapeutic substance in a safe and controlled manner for release to the target site.

The different types of

a) Therapeutic magnetic microspheres

Known for the application of chemotherapy to liver tumor. This device can also target medicinal products such as proteins and peptides.

b) Diagnostic Microspheres

Used for visualization of liver metastases and can also be used to separate intestines loops of other abdominal structures by the production of supramagnetic iron oxides particulate nanometer.

Radioactive microspheres [17]

Microsphere size of radio embolization therapy 10-30 nm greater than the capillary diameter and will be placed into the first capillary bed as they pass. These are placed into the arteries that lead to a tumor of interest and induce elevated radioactivity in each of these conditions. Microspheres to target areas without harming the usual tissues surrounding them. This varies from the drug delivery mechanism, as radioactivity is not emitted from microspheres but operates from within a distance typical of a radioisotope, and the different types of radioactive microspheres are α emitters, β emitters, π emitters.

Floating Microspheres [18,19]

The bulk density of floating forms is smaller than the gastric fluid, and therefore stays buoyant in the stomach without impacting the rate of gastric emptying. The drug is released at the target rate gradually, as the body floats on gastric content and decreases gastric residence and plasma concentration fluctuation. This also reduces the risk of hitting and dose dumping. One way it creates sustained therapeutic effect and therefore reduces the frequency of dosing.

Polymeric microspheres [17]

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

Biodegradable polymeric microspheres [21]

Natural polymers like starch are used with the idea that they are naturally biodegradable, biocompatible and even bioadhesive. Biodegradable polymers extend the duration of residence in contact with the mucous membrane due to its high swelling properties with aqueous medium. The rate and degree of drug release is sustainably regulated by polymer concentration and release pattern. The key downside is that the reliability of biodegradable microspheres in clinical use is complicated and the release of drugs is difficult to regulate. They do however offer a wide variety of applications treatment centered in a microsphere.

Synthetic polymeric microspheres [22,23]

Synthetic polymeric microspheres are commonly used in therapeutic applications, in addition to the fact that they are often used as bulking agents, fillers, embolic particles, drug delivery vehicles etc. and have proven safe and biocompatible, but the main drawback of these microspheres is that they appear to migrate away from the injection site and lead to potential harm, embolism and further damage to organs.

METHODS OF PREPARATION

Solvent Evaporation Technique [24,25,26,27]

In an organic solvent the polymer is dispersed, and the drug is either dissolved / dispersed in the polymer solution. The solution containing the product is then emulsified into an aqueous phase containing the necessary additives (surfactants / polymer) in water emulsion to form oil. The organic solvent is evaporated after emulsion formation either by increasing the temperature under pressure, or by continuous stirring. The removal of solvent leads to precipitation of the polymer at droplet oil / water interphase, forming cavity.

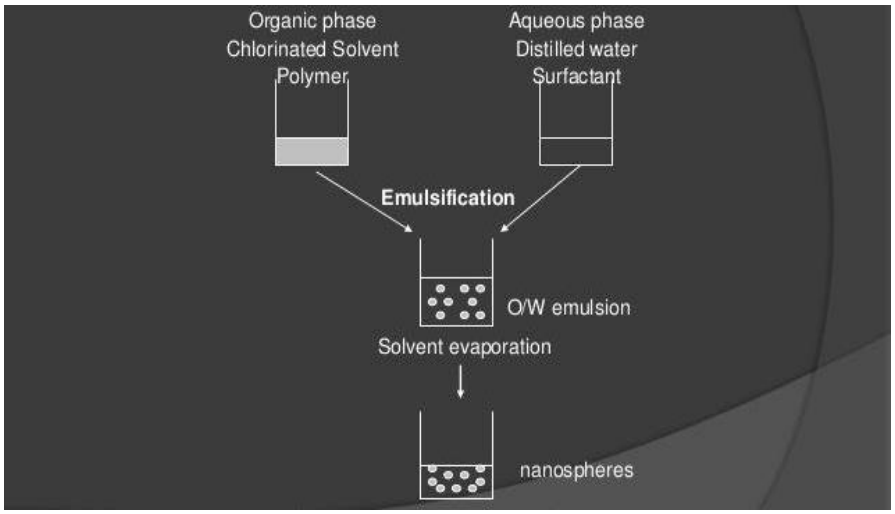

Figure 1: Solvent Evaporation Technique

Phase Separation Coacervation Technique [28, 29]

It is a simple process in which a micro molecular solution is separated into two immiscible liquid phases. The co-conservation principle involves decreasing solubility of polymer in organic phase affecting the formation of polymer-rich phase called coacervates. In this method, the formation of the dispersion of drug particles in a polymer solution and an incompatible polymer added to the system, which separates the first polymer and envelops the drug particle.

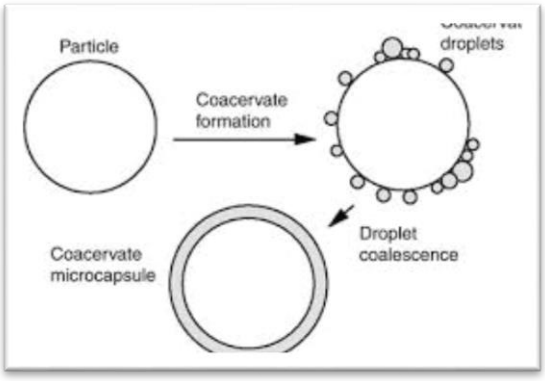

Figure 2: Formation of coacervates around the core material

Spray Drying Technique [30]

Through this procedure, the polymer is dissolved through volatile organic solvents such as

dichloromethane, acetone, etc. and then, under high-speed homogenization, the product (solid form) is distributed in a polymer solution. Dispersion is then atomized in the hot air stream, and atomization contributes to the creation of small droplets from which solvent evaporates instantaneously. Prepared micro particles are separate by hot air by the help of cyclone separator and solvent traces is removed by vacuum drying.

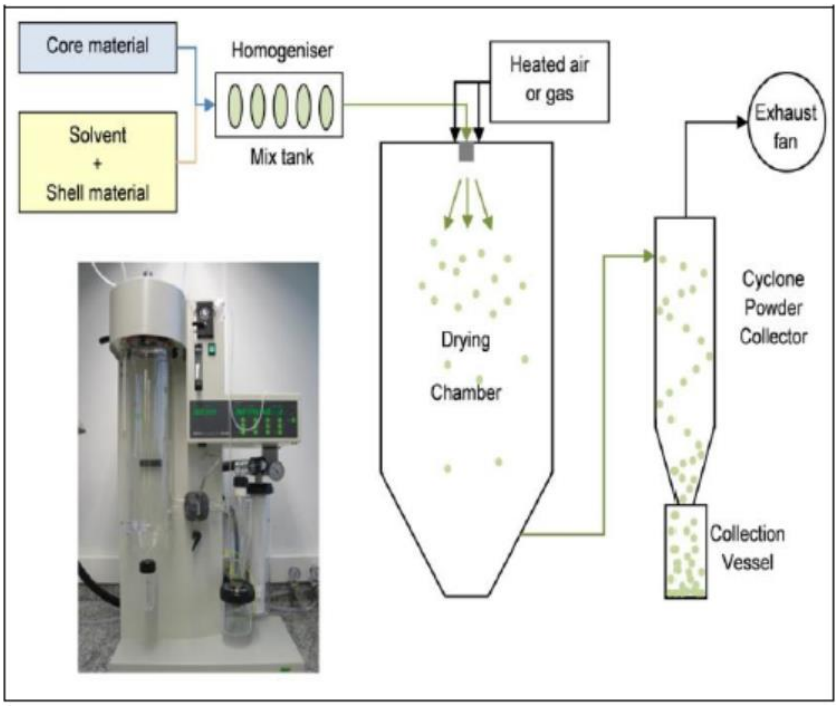

Figure 3: Spray Drying Technique

Principle:

1. Atomization: Liquid feed changed into fine droplets.

2. Mixing: It involves passing through spray droplets of hot gas stream which leads to liquid evaporation leaving dry particulates.

3. Drying: Dry powder is separated from the gas stream and collected.

Single emulsion technique [31]

Natural polymers micro particulate carriers i.e. those of proteins and carbohydrates are prepared by a single emulsion technique. The natural polymers are dissolved or dispersed in aqueous media accompanied by dispersion in non-aqueous medium such as oil. The cross linking of the dispersed globule is accomplished in the next step. The cross-linking can be achieved either by heat or through the use of the chemical cross linkers. Glutaraldehyde, formaldehyde, acid chloride etc., are the chemical cross linking agents used. Thermo-labile compounds are not suitable for heat denaturation. When applied at the time of preparation and then subjected to centrifugation, drying, isolation, chemical cross-linking, the drawback of prolonged exposure of the active ingredient to chemicals.

The existence of the surfactants used to stabilize the phases of emulsion will greatly affect the final multiparticulate product's size, size distribution, surface morphology, packaging, drug release and bio-performance.

Double emulsion technique [31]

Dual microspheric emulsion preparation process requires the creation of several emulsions or dual emulsions of type w / o / w and is ideally suited for water-soluble medications, peptides , proteins and vaccines. This approach is ideal for use with both natural and synthetic polymers. The solution of the aqueous protein is distributed in a continuous lipophilic organic flow. The active constituents can contain this protein solution. In general, the continuous phase consists of the polymer solution which eventually encapsulates the protein contained in the dispersed aqueous phase. The primary emulsion is then subjected to homogenization or sonication before the polyvinyl alcohol (PVA) aqueous solution is added. Which results in a double emulsion being produced. The emulsion is then subjected to removal of the solvent either by evaporation with solvent or by extraction with solvent. A variety of hydrophilic drugs such as agonist luteinizing hormone releasing hormone (LH-RH), vaccines, proteins / peptides, and traditional molecules are successfully introduced into the microspheres using the process of evaporating / extracting double emulsion solvent.

Hot Melt Microencapsulation [32]

The polymer is first melted and then combined with product solid particles which have been sieved to below 50 μm. The mixture is suspended in a non-miscible solvent (similar to silicone oil), continuously stirred and heated to 5 ° C above the polymer's melting point. Once the emulsion is stabilized, it is refrigerated until the particles of the polymer solidify. The resulting microspheres are washed off with petroleum ether by decantation. The primary objective of developing this approach is to establish a process of microencapsulation suitable for water-labile polymers, for example polyanhydrides. It is possible to obtain microspheres with a diameter of 1-1000 μm, and the size distribution can be easily managed by adjusting the stirring rate. The only downside to this approach is the moderate temperature at which the medication would be exposed.

EFFECTS OF FORMULATION VARIABLES

Effect of formulation variables on drug release

a. Effect of Stirring Speed on Drug Release

Various methods of micro and nanospheric preparation require the use of stirrers. It is usually more common in solvent evaporation or the evaporation technique of emulsion solvents. The average diameter of the microspheric network was clarified using stirring rate. The vulnerability of polymer erosion to the degree of agitation that affect the ability of the polymer to give reproducible and

agitation-independent release in the gastrointestinal tract 's complex hydrodynamic environment as opposed to more rigid non-eroding matrix materials.[33]

b. Effect of concentration of surfactant on Drug Release

Usually the introduction of higher amounts of surfactant is not a good idea for designing the regulated or sustained microparticulate release system because it has been found that the surfactant increases the rate and quantity of the microparticulate release from the system. The basic explanation for understanding this phenomenon is improved wettability and greater penetration of solvents within the matrix structure. Increased concentration of surfactants is also thought to increase the drugs deposited at the surface of those microspheric matrix systems.[34]

The involvement of the surfactants also influences the alteration of encapsulated products such as insulin and results in a continuous release profile from the microspheric matrices. In a research involving the encapsulation of bovine insulin with poly (lactide co-glycolide) using different concentrations of non-ionic surfactants such as poloxamer 188, polysorbate 20 and sorbitan monooleate 80, it was observed that during the time of sustained release, insulin was changed to a high-molecular weight product and its quantity was linked to the surfactant used. For all the surfactants used, polysorbate 80 was found to have strong insulin loading and slow drug release at 3 % w / v concentration.[35]

c. Effect of Temperature Programming on Drug Release

Temperature has a very important role in defining drug release in all microsphere preparation methods which involve evaporation of the volatile component. Normally, an sudden increase in temperature during the manufacture or use of very high temperatures induces the rapid expansion of methylene chloride from the microsphere body and causes the development of a hollow center and a small, permeable organism.[36]

It was found that the sum of the continuous step and the micro / nanoparticle: bulk fluid ratio influences the system 's drug release behavior. The method of solvent evaporation is usually uncomfortable for water soluble drug micro / nano spherical systems because there is a risk of drug loss from emulsified polymeric phase before polymer solidification in microsphere.[37]

Drug release is also substantially faster in the higher particle mass: bulk fluid volume ratio in the case of non-porous and initially porous systems that should be taken into account when determining the experimental conditions for measuring drug release from this type of advanced drug delivery systems.[38]

Effect of formulation variables on drug entrapment

a. Effect of Polymer Concentration on Drug Entrapment

A higher molecular weight polymer has a greater degree of embroidery and thus decreases the area of molecular diffusion and drug permeation through the matrix gel. As the concentration of polymers increases, the viscosity of the polymer gel increases, resulting in a longer diffusion path.[39]

It triggers a drop in the drug's diffusion coefficient, and a decrease in the drug's release rate. To reach a constant zero order or continuous release the polymer should be easily hydrated to form a gel layer before dissolving the contents of the tablet matrix. They are more resistant to dilution and corrosion for the greater viscosity gels[40].

On the other hand, the polymer forming the loose network in the matrix reduces the release rate and encapsulation efficiency, since the network allows the drug particles to leach out during the production of the microsphere.[41]

It was found and commonly recognized that an increase in polymer concentration increases the drug's encroachment within micro and nanospheric structures. With the help of the following points the main reason for this phenomenon can be explained.

b. Effect Due to Increase in Viscosity

As explained earlier, the high concentration of the polymer used to formulate the microsphere systems causes the solution's increased viscosity and delays the diffusion of drugs within the polymer droplets.

c. Effect of Increase in Velocity of Precipitation

As the polymer concentration increases or the drug / polymer ratio decreases, the polymers appear to precipitate more readily on the surface of the dispersed product.

d. Effect of Increase in Size

The size of the microsphere increases with the rise in polymer concentration. This allows the microspheres surface area to decrease and the exposure to water to decrease. Therefore the degradation of the product due to diffusion from the gel layer decreases as well. Decreasing the polymer concentration often leads to loading efficiency reduction due to the maximum drug: polymer ratio and limited size of microspheres are obtained resulting in surface drug loss during microspheric washing. In a Saravananet et al trial where they formulated the floating microspheres of ranitidine hydrochloride with ethyl-cellulose as a polymer, they observed that increase in the polymer concentration increased the drug entrapment with maximum entrapment seen at a drug: polymer ratio 1:3[42]

e. Effect of Interaction between Drug and Polymer on Drug Entrapment

The interaction between drug and polymer may be hydrophilic or hydrophobic, and can result in micro or nanospheric system release and trapment of drugs. The product is ideally encapsulated for

hydrophobic interactions in polymers containing end groups of free carboxylic acids. For hydrophobic interactions, relatively hydrophobic end-capped polymers can increase the encapsulation or trap efficiency.[43,44]

It is also observed that when formulated with hydroxylpropyl cyclodextrine (g-HPCD), the encapsulation of tetanus toxoid microsphere shaped with PLGA increased. The g-HPCD is expected to enhance the interaction by entering the toxoid's side amino acid group into its cavity and interacting with PLGA by Vander Waals and hydrogen bonding forces simultaneously.[45]

It is also observed that the Complexation between the drug and the polymer in releasing the drug from the matrix system will affect. In a study of 23 drugs with varying solubility and molecular weight, matrixed with HPMC and sodium carboxy methylcellulose, it was observed that very soluble and soluble drugs such as beta-blockers and soluble vitamins (thiamine hydrochloride) were released more slowly in a matrix of HPMC and sodium carboxymethylcellulose due to complex formation between cationic drug and anionic polymer.[46]

f. Effect of Stirring Rate on Drug Entrapment

Different experiments took into account the observation of the stirring rate and its effect on the imprisonment of the drug within the microspheric matrix systems. It was found that the mean particle size decreases with the rise in the stirring rate, and the formation of the hollow spheres occurs due to the rapid evaporation of the solvent from the matrix system during manufacture. The formation of the solid and irregular microsphere type occurs in the lower stirring rate such as 300 rpm.

But as the rpm increases to 1000 or 1500, in the process of formulation, various hollow spheres begin to form but the microspheres are of a spherical nature. This forming property of the hollow microsphere of the spherical shape can be taken as an characteristic for the drug's entanglement to move within the narrow capillary space. In an experiment of formation of the microspheres of Diltiazem HCl using Eudragit RS100 and Eudragit RL 100 in which the stirring speed had been applied between 300 to 1000 rpm, solid and irregular microparticles were seen at a lower stirring rate while at 600 rpm particles size and drug entrapment efficiency were 82% and 210 μm, respectively, and at 1000 rpm spherical shape of microspheres was observed but particles coalesced to beaker wall and also decrease with decreased particle size.[47]

g. Effect of Surfactant Concentration on Drug Entrapment

It has been observed that surfactant in the microspheric system affects both the release of drugs and the drug treatment. Increased surfactant concentration results in decreased microspheric encapsulation efficiency because an increase in surfactant concentration results in stabilization of

small droplets and results in smaller microspheres. Loss of medication from the surface of small microspheres during washing is greater than that of larger microspheres.[48]

h. Effect of Temperature on Drug Entrapment

Temperature plays a major role in influencing the drug's morphology, trapping, and rate of release from microspheric structures. It was observed that the microspheres have hollow core and porous walls at higher temperatures due to the fact that the volatile components such as methylene chloride used in microspheric formulation evaporate rapidly at higher temperatures. It has also been observed that the core size and the thickness of the wall depend on the ramp. A rapid rise in temperature results in a thin wall and a large hollow core whereas a gradual rise in temperature (15 to 25, then 40oC) leads to a reduced core size.[49]

Effects of formulation variables on microsphere size

a. Effect of Polymer Concentration on Microsphere Size

It is widely observed phenomenon that microspheric particle size increases as the polymer ratio increases in the microspheric system due to increased polymer viscosity resulting in the formation of larger emulsion droplets and consequently larger microspheric size. The theories had been well tested by Patel *et al* in an experiment where the particle size of aspirin loaded microspheres was analyzed by optical microscopy. Microspheres average particle size was found to be in the range of 328 to 990 µm. In SEM the polymer solution with increased concentration showed greater scale.[50]

b. Effect of Surfactants on the Microsphere Size

- **Effect of Surfactants of Different HLB Values on the Size of Microspheres**

The particle size of the microsphere decreases with the surfactant being used increasing the HLB value. Microspheres prepared using surfactants with a higher HLB value are larger in size and have a higher trap efficiency competitively, which is due to the fact that the trap efficiency decreases with the rise in microspheral size. Similar results were obtained in an experiment which studied the effect of surfactants such as span 80 and span 20 on particle sizes and tramadol loaded PCL microspheres. Results showed that the microspheres which were prepared using span 80 were smaller than the span 20. And the surfactant mixture reveals still smaller microsphere.[51]

- **Effect of Surfactant Concentration on the Size of Microspheres**

It was found that an increase in the concentration of the surfactant used to create the microsphere causes a decrease in the size of the microsphere as an increase in the concentration of the surfactant causes a decrease in the interfacial energy between the two droplets and the presence of the emulsifying agent in the cross-link medium, allowing the stability of the preformed microsphere to retain its size until the cross-link reaction is complete. Similar results were obtained in the

experiments of Patel *et al* in preparation and evaluation of ethyl cellulose microspheres by emulsification-solvent evaporation method where increase in concentration of the emulsifying agent caused decrease in the particle size of the microspherical system.[52]

- **Effect of Stirring Rate on the Microsphere Size**

Due to the turbulence produced, stirring speed also affects percentage yield and mean microparticle size. In the higher stirrer rate (1500 rpm), there was froth and adhesion output in the container walls which consequently decrease the microsphere's mean particle size. An optimal spherical form and condition free of aggregation to the stirring speed of 1000 rpm was obtained. An rise in particle size at low stirring velocity (500 rpm) can be explained by the globules' propensity to aggregate and coalesce.[53]

- **Effect of Viscosity of the Dispersed and Continuous Phase on the Microsphere Size**

The viscosity of the dispersed and the continuous process have been found to significantly influence the size of the microsphere. Microspheres were prepared in an experiment using a method of extraction of the hydrocarbon-perfluorocarbon solvent. It was observed that when the viscosity of the dispersed phase was reduced smaller microspheres were formed at the same mixing rate. Increased continuous viscosity of the phase reduced droplet coalescence and therefore smaller microspheres were created. The mean microsphere size was first found to decrease as the volume ratio of the dispersed phase to the continuous phase increased but the mean microsphere size was found to increase following further increase.[54]

APPLICATIONS OF MICROPSHSRES

In Vaccine Delivery

Defense against the microorganism or its toxic product is a precondition of a vaccine. The deficiency of conventional vaccines may be overcome by a biodegradable delivery system for vaccines given by the Parentral route. Several parenteral vaccines, including tetanus and diphtheria vaccines, were encapsulated in biodegradable polymeric microspheres.[55]

Targeting Drug Delivery

The idea of site-specific drug targeting is a well-established theory which is gaining full attention. The drug's therapeutic efficacy depends on its proximity to and precise interaction with its receptor.[56]

Radioactive Application

It may be used for liver and spleen tumor embolisation. This can be used for arthritis joints radio synvectomy, local radiotherapy, interactivity diagnosis, liver imaging, spleen, bone marrow, lung and even thrombus imaging in deep vein thrombosis.[57]

Topical Porous Microspheres

Micro sponges are porous microspheres with numerous size range of interconnected voids 5 to 300µm. These sponges are capable of absorbing the various active ingredients such as emollients, fragrances, essential oils used for topical use.[58]

Imaging

Particle size plays a significant role in determining the imagery of specific sites. Particles injecting intravenously apart from the portal vein will get trapped in the lungs' capillary bed. Using labeled human serum albumin microspheres, this phenomenon is exploited for scintiographic imaging of tumor masses in lungs.[59]

Hejazi and Amiji (2003) prepared microsphere by ionic crosslinking and precipitation method. The gastric residence time of chitosan microspheres charged by tetracycline was observed. After their oral administration in gerbils, suspension of the chitosan microsphere in the nonacid-suppressed and acid-suppressed states. Animals were slaughtered at various points of time, and tissue and fluid radioactivity was measured with a gamma counter.[60]

Other potential applications include [61]

- Conversion of oil and other liquids to solids for ease of handling
- Taste and odor masking
- To delay the volatilization
- Safe handling of toxic substance

CONCLUSIONS

Microspheres are used to deliver the drug with the site specificity. A microsphere has a drug placed centrally within the particle bounded by polymers. A microsphere type of dosage form can be a novel technique in the long run for treatment of a number of diseases with better effectiveness.

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