SMICROSPHERE'S: A PROMISING DRUG CARRIER

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Abstract: The targeted drug delivery is designed for endeavoring to concentrate the drug in the tissues of curiosity while reducing relative concentration of medication in the remaining tissues. There for drug is localized on the targeted site. Hence, surrounding tissues are not affected by the drug. Controlled drug delivery system can overcome the problems of conventional drug therapy and gives better therapeutic efficacy of a drug. 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. Microspheres has a drug located centrally within the particle, where it is encased within a unique polymeric membrane. In future various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene and genetic materials, safe, targeted and effective in vivo delivery and supplements as miniature versions of diseased organ and tissues in the body.

Keywords: Microspheres, Controlled release, Therapeutic efficacy, Novel drug delivery

Introduction:

Microspheres are spherical particles that range in diameter from 10 µm to 1000 µm. Microspheres are essential for improving the way conventional drugs are absorbed and lessening their side effects. The controlled release of the medicinal content is the primary benefit of using microspheres as a drug delivery mechanism. By postponing the medication's release from dose forms, microencapsulation reduces adverse effects and enhances patient adherence. This method uses emulsion solvent diffusion evaporation to coat an aqueous insoluble coat (polymer) over an aqueous insoluble core (drugs) to create a sustained release drug delivery system. There are several methods for creating microspheres, such as phase separation, spray-dry, and emulsification using single or double solvent evaporation systems.

One method for creating microspheres is to dissolve the precursor components in volatile solvents and then disperse them in a different solvent that isn't miscible with the first one. A fine powder known as microspheres that is soluble in water will be produced when the last solvent has completely evaporated. Medication with a brief half-life that is merely transferred from the gastrointestinal tract (GIT) is instantly eliminated from the bloodstream[1]. In order to circumvent this issue, oral sustained or controlled release (CR) has also been created. This method will gradually release the drug into the gastrointestinal tract and maintain a constant level of medicine intensity in the plasma for an extended amount of time. A dose formulation that achieves the necessary plasma therapeutic drug concentration and stays stable over the course of the treatment is considered appropriate. This can be accomplished by administering a conventional dosage form at a predetermined frequency and dose. They have the advantage of not being microcarriers since nanoparticles act locally by migrating into the interstitium within the lymphatic system's 100 nm range.

Most likely, hazardous materials can be carried. Encapsulated, the dried microparticles may be referred to as solids instead of liquids. The intake dose is administered as a series of discrete, small multiarticulate particles, each of which retains and releases a portion of the dosage; hence, the failure of one subunit has no effect on the overall dosage failure. In order to facilitate the release of medication into the skin, microparticles are employed in skin applications. This helps to ensure that the drug stays localized at the application site and does not unnecessarily reach the systemic circulation. They serve as a reservoir that releases an active ingredient gradually over time to keep medication items at an appropriate concentration in the skin while minimizing unwanted side effects. As a result, there are fewer cycles of over- and under-medication. In the treatment of infectious diseases, it is particularly pertinent to the decrease of antibiotic resistance. Additionally, by integrating the product into the proper vehicle, these distribution methods can improve product safety[2].

Materials used:

Polymers are typically utilized as microspheres. They fall into two categories.

1. Synthetic polymers
2. Natural polymers

Synthetic polymers are divided into two types.

1] Non-biodegradable polymers:

- Poly methyl methacrylate (PMMA)
- Acrolein
- Glycidyl methacrylate

- Epoxy polymers

2] Biodegradable polymers:

- Lactides, Glycosides & their co polymers
- Poly alkyl cyano Acrylates
- Poly anhydrides[3,4]

Natural polymers obtained from different sources like Proteins, carbohydrates and chemically modified Carbohydrates.

A] Proteins:

- Albumin
- Gelatin
- Collagen

B] Carbohydrates:

- Agarose
- Carrageenan
- Chitosan
- Starch

C] Chemically modified carbohydrates:

- Poly dextran
- Poly starch [5,6]

Advantages of Microspheres:

1] Reduction in size leads to an increase in surface area and can boost the strength of the poorly soluble substance.
2] Reducing dose and risk.
3] Maintaining a constant level of medication in the body to enhance patent compliance.
4] Polymer-based drug packaging keeps the medication from undergoing enzymatic cleavage while allowing it to be used with a drug delivery system.
5] Shorter dosage intervals increase patient compliance[7].

Disadvantages of Microspheres:

1] The modified formulation-based releases.
2] The controlled dosage process's release rate, which varies depending on a number of variables including nutrition and levels of transfer via the intestines.
3] Differences in the rate of discharge between doses.
4] Chewing or breaking these dosage forms is not permitted.
5] There is less reproducibility[8].

Pre-requisites for ideal micro particulate carriers:

The material utilized for the preparation of micro particulate should ideally fulfill the following prerequisites.

- Longer duration of action
- Control of content release
- Increase of therapeutic efficiency
- Protection of drug
- Reduction of toxicity
- Biocompatibility
- Sterilizability
- Relative stability
- Water solubility or dispersability
- Target ability
- Polyvalent[9]

Types of Microspheres:

Microspheres are classified into different types. They are of following

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

I. Biodegradable polymeric microspheres
II. Synthetic polymeric microspheres

1] Bioadhesive microspheres:

Adhesion is the process by which a medication sticks to a membrane by the use of a water-soluble polymer that has the ability to stick. Bio adhesion is the phrase used to describe the adherence of a medication delivery device to a mucosal membrane, such as the nasal, rectal, ophthalmic, or buccal. These microspheres produce superior therapeutic activity because they stay longer at the application site, form close contact with the absorption site, and have a longer residence time. To have a way to give the drug delivery system and the absorbent membranes close contact, it would be beneficial to manufacture bioadhesive microspheres. Because of its superior bioadhesive qualities, polycarbophil (Noveon® AA1) was choosen as the polymer for the creation of bioadhesive microspheres.[10].

2] Magnetic microspheres:

This type of drug delivery system, which targets the exact location of the sickness, is crucial. A smaller quantity of a medicine with magnetic targeting can take the place of the greater amount of the drug that is freely circulating. Incorporated materials used to create magnetic microspheres respond magnetically to a magnetic field through magnetic carriers. medicines that dissolve in water (lipophilic medicines also require the dispersing agents) and 10 nm magnetite (Fe3O4) particles are combined in an aqueous solvent of the matrix material to create magnetic microspheres. After that, the oil is used to emulsify this combination. To create particles in the appropriate size range, ultrasonication or shearing are used. The matrix is then heated or chemically cross-linked to stabilize it.

I] Therapeutic magnetic microspheres
II] Diagnostic microspheres[11].

3] Floating microspheres:

Because the bulk density of floating kinds is lower than that of gastric fluid, they float in the stomach without slowing down the pace at which the stomach empties. The medication is released gradually at the desired pace if the stomach material is floating in the system, lengthening the duration of gastric residency and causing more variations in plasma concentration. By producing a sustained therapeutic impact, this

approach lowers the frequency of dose. Sink particles will disperse over a wide region of absorption sites with each consecutive gastric emptying, improving the likelihood of a more or less predictable drug release profile and absorption. Furthermore, there is less chance of dosage dumping because each dose is made up of several subunits[12].

4] Radioactive microspheres:

The 10–30 nm-sized microspheres used in radioembolization treatment are bigger than capillaries and are tapped into the first capillary bed they come across. They are injected into the arteries that supply the target tumor. Therefore, in all of these circumstances, radioactive microspheres give specific regions a strong radiation dose without endangering the healthy tissues nearby. There are three different types of radioactive microspheres: those that emit α, β, and γ. The subset of microspheres that interact radioactively is usually treated similarly to non-radioactive microspheres. However, the radioactive microsphere always contains one or more radio-nuclides in addition to the matrix material that gives the microsphere its targeting capabilities in a particular tissue or organ. Radioactive microspheres can deliver high radiation doses to a particular area in small quantities as well without harming the surrounding natural tissue. [13, 14]

5] Polymeric microspheres:

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

I] Biodegradable polymeric microspheres:

Because natural polymers like starch are biodegradable, biocompatible, and bioadhesive, they are employed. When biodegradable polymers come into touch with mucous membranes, they stay longer because of their high degree of swelling property with aqueous medium, which causes gel to form. The polymer concentration and the sustained release pattern regulate the drug's release rate and extent. The primary disadvantage is the complexity and difficulty in controlling drug release associated with the drug loading efficiency of biodegradable microspheres in clinical settings. On the other hand, they offer a broad range of applications in microsphere-based therapy[15].

II] Synthetic polymeric microspheres:

Synthetic polymeric microspheres are widely used in clinical application, but the main disadvantage of these kind of microspheres, are tend to migrate away from injection site and lead to potential risk, embolism and further organ damage[16].

Method of Preparation:

Certain requirements should be met when preparing microspheres.

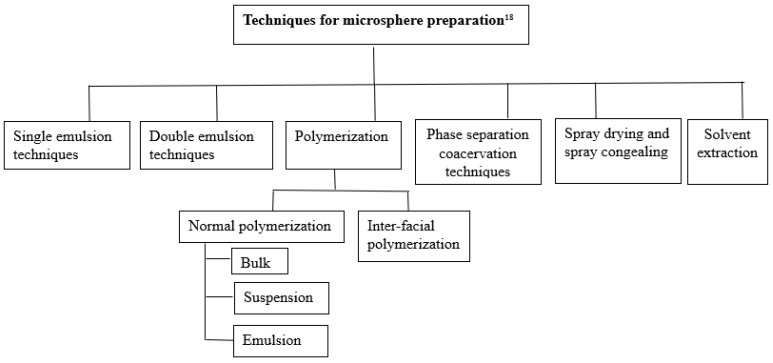
1]The ability to incorporate drug at reasonable concentrations

2] stability of the preparation following synthesis with a clinically acceptable shelf-life

3] Controllable particle size and dispensability in aqueous vehicles for injection

4] Good control over the release of the active agent over an extended period of time

5] Biocompatibility with controlled biodegradability, and susceptibility to chemical modification are the six factors that need to be considered.[17].



1] Single emulsion technique:

There are several natural polymers for ex-carbohydrates and proteins that act as microparticulate carriers and are prepared by single emulsion technique. In which the natural polymers are dissolved or dispersed in the non-aqueous medium e.g. oil. In next step, cross linking is carried out by either of two following methods;

I] Cross linking by heat:

Cross linking by heat is carried out by adding the dispersion, to previously heated oil. Heat denaturation is however, not suitable for the thermolabile drugs.

II] Chemical cross linking:

Chemical cross liking is done with the help of agents such as glutraldehyde, Formaldehyde, terephthaloyl chloride, diacid chloride, etc. This method suffers from disadvantage of excessive exposure of active ingredients to chemicals if added at the time of preparation, chitosan solution (in acetic acid) by adding to liquid paraffin containing a surfactant resulting in the formation of w/o emulsion. Metformin hydrochloride microsphere are prepared by using glutaraldehyde 25% solution as a cross linking agent[19].

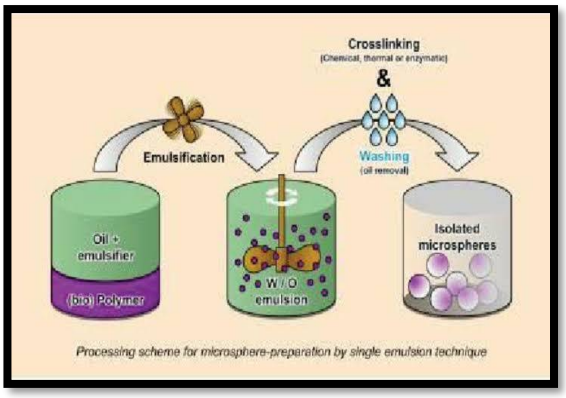


Fig 1: Single emulsion technique

2] Double emulsion technique:

The method of double emulsion solvent evaporation/extraction is ideal for incorporating water-soluble drugs, peptides, proteins, and vaccines into microspheres. It involves dispersing a protein solution in a lipophilic organic continuous phase, homogenizing it, and adding polyvinyl alcohol to form a double emulsion. The emulsion is then removed by solvent evaporation or extraction, resulting in solid microspheres. This method has been successfully used to incorporate hydrophilic drugs, vaccines, proteins/peptides, and conventional molecules.

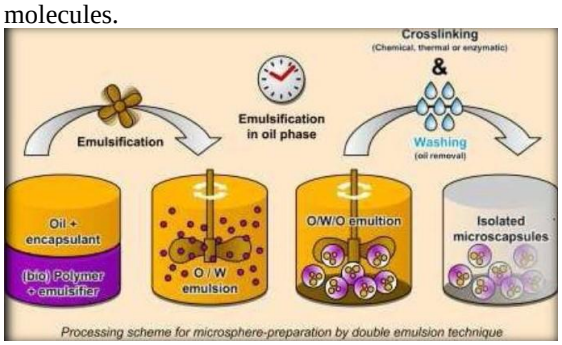


Fig 2: Double emulsion technique

3] Polymerization technique:

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

I] Normal polymerization

II] Interfacial polymerization

I] Normal polymerization:

1] Bulk polymerization:

To start the polymerization and complete the process, a monomer or a combination of monomer and initiator is often heated. To help or quicken the pace of the reaction, the catalyst or initiator is introduced to the reaction mixture. The resulting polymer can be broken up into microspheres or molded. Adsorptive drug loading or drug addition during the polymerization process are two possible approaches for drug loading.

2] The suspension polymerization:

Heating the monomer or combination of monomers containing active ingredients (drugs) as droplets dispersing in a continuous aqueous phase is how it is done. Other additives and an initiator could also be included in the droplets.

3] The emulsion polymerization:

Nonetheless, is distinct from suspension polymerization since the initiator is present in the aqueous phase and diffuses to the micelle or emulsion globule surface afterwards[17].

II] Interfacial polymerization:

The interfacial polymerization process involves two reactive monomers, one dissolved in the continuous phase and the other distributed there. The second monomer is emulsified during the continuous phase, often aqueous. The monomers diffuse quickly and polymerize quickly at the interface. The polymer's solubleness in the emulsion droplet can affect the carrier form. Temperature, vehicle composition, monomer concentration, and reactivity can affect polymerization. Particle size can be regulated by adjusting the size of dispersed phase droplets or globules. Controlling the polymerization process requires maintaining monomer concentration.

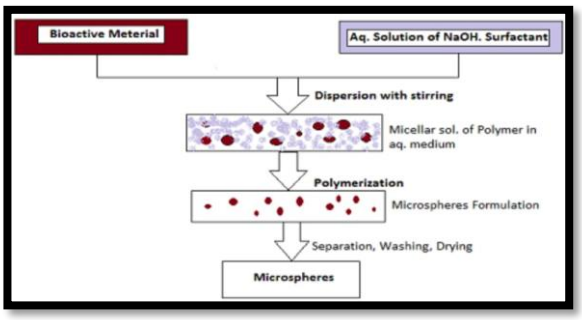


Fig 3: Polymerization technique

4] Phase separation coacervation technique:

specifically made to prepare the reservoir type of the system, that is, to encapsulate pharmaceuticals that are soluble in water, like as proteins and peptides, and medications that are hydrophobic, like steroids. The medication or protein in a matrix-type device is soluble in the polymer phase. The method works on the basis of reducing the polymer's solubility in the organic phase to influence the development of the coacervates, a polymer-rich phase. The creation of two phases, one of which is the supernatant depleted of polymer, can be caused by adding a third component to the system, therefore exacerbating the situation. This method involves dissolving the polymer in an appropriate solvent first, and then dispersing the drug if hydrophilic in an aqueous solution or if hydrophobic by dissolving it in the polymer solution itself. Next, phase separation is achieved by adjusting the conditions of the solution[21,18.]

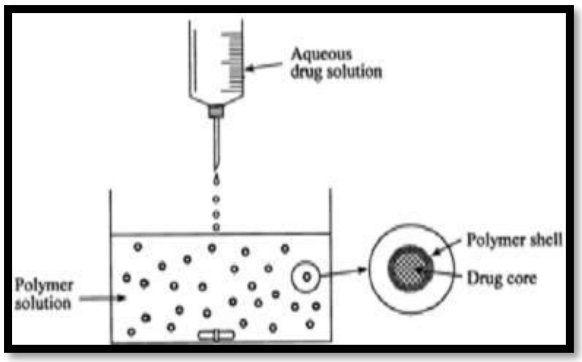


Fig 4: Phase separation coacervation technique

5] Spray drying and spray congealing:

Spray drying process concept The two processes are spray drying and spray congealing, and they rely on whether the solvent is removed or the solution cools down. The fundamental process of spray drying is evaporation, while the mechanism of spray congealing is a phase inversion from a liquid to a solid. With the exception of energy flow, both procedures are comparable. The most used industrial method for drying and forming particles is spray drying. Because of this, spray drying is the best method when the final product needs to meet exacting requirements for bulk density, particle shape, residual moisture content, and particle size distribution.

Principle: Three steps involved in spray drying :

I] Atomization: the transformation of a liquid stream into tiny droplets.

II] Mixing: this process includes directing a hot gas stream through spray droplets, causing liquids to evaporate and leaving behind dry particles.

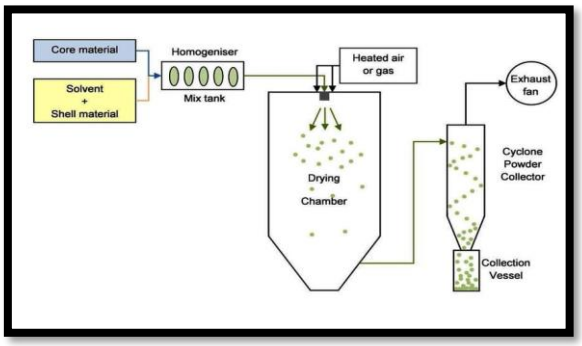
III] Dry: The powder is collected after being dried and removed from the gas stream.

The method of double emulsion solvent evaporation/extraction is ideal for incorporating water-soluble drugs, peptides, proteins, and vaccines into microspheres. It involves dispersing a protein solution in a lipophilic organic continuous phase, homogenizing it, and adding polyvinyl alcohol to form a double emulsion. The emulsion is then removed by solvent evaporation or extraction, resulting in solid microspheres. This method has been successfully used to incorporate hydrophilic drugs, vaccines, proteins/peptides, and conventional molecules.

Fig 5: Spray drying and spray congealing

6] Solvent extraction:

For the emulsion to develop between the polymer solution and an immiscible continuous phase in both the non-aqueous (w/o) and aqueous (o/w) phases. In their 2000 study, Bogataj et al. used the evaporation technique to create microspheres utilizing liquid paraffin and acetone as solvents. After dispersing the medication solution (in acetone) in chitosan solution, the combination was emulsified in liquid paraffin and agitated. The microsphere suspension underwent filtration, washing, and drying. Additionally, magnesium stearate was used as an agglomeration-preventing agent. The findings demonstrated that as the amount of magnesium stearate utilized to prepare the microspheres increased, the average particle size dropped.



examined the comparison between hyaluronic acid and gelatin microcapsules made by complicated coacervation and mucoadhesive microspheres of hyaluronic acid, chitosan glutamate, and a mixture of the two made by solvent evaporation[24,25].

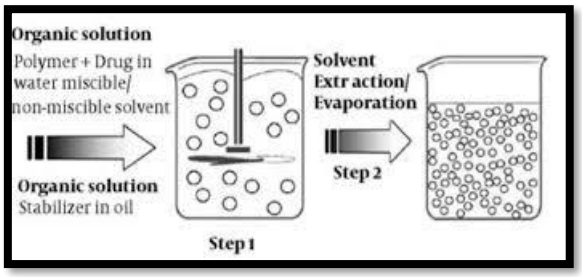


Fig 6: Solvent Extraction Technique

Evaluation of Microspheres:

1] Particle size and shape:

Scanning electron microscopy (SEM) and conventional light microscopy (LM) are commonly used to study microparticles, revealing their external structure and form. LM allows control over coating settings, while SEM offers higher resolution. Conflocal fluorescence microscopy characterizes multiple-walled microspheres, while laser light scattering and multisize Coulter counter can also be used[26].

2] Electron spectroscopy for chemical analysis:

Conflocal fluorescence microscopy is used to evaluate the structural properties of multiple walled microspheres. Apart from instrumental methods, the size, shape, and morphology of the microspheres may be evaluated using multisize Coulter counter and laser light scattering[27]

3] Attenuated total reflectance Fourier Transform-Infrared Spectroscopy:

The carrier system's polymeric matrix degradation is assessed using FT-IR. Alternate total reflectance (ATR) is used to measure the surface of the microspheres. Infrared spectra of the sample's surface material were mostly obtained by many

reflections of the IR beam that passed through the ATR cell. ATR-FTIR analysis yields surface composition information about the microspheres based on circumstances and production processes.

4] Density determination:

A multivolume pycnometer can be used to measure the density of microspheres. The multi volume pyrometer is filled with a precisely weighed sample that is placed in a cup. The chamber is filled with constant pressure helium, which is then allowed to expand. The pressure inside the chamber decreases as a result of this expansion. There are two sequential pressure decrease readings recorded, each at a different beginning pressure. Two pressure readings are used to calculate the volume and, consequently, the density of microsphere carriers[28].

5] Isoelectric point:

An instrument called a micro electrophoresis is used to evaluate the electrophoretic mobility of microspheres in order to identify their isoelectric point. Particle movement over a distance of 1 mm is timed to determine the mean velocity at various pH levels between 3 and 10. This information may be used to calculate the particle's electrical mobility. The surface contained charge, ionisable behavior, or ion absorption nature of the microspheres can all be connected to the electrophoretic mobility[27].

6] Drug entrapment efficiency:

A measured quantity of microspheres are removed and broken apart. then, with the aid of a stirrer, dissolved in buffer solution and filtered. Using a calibration curve, the filtrate is tested at a certain wavelength using a UV spectrophotometer.

Drug Entrapment efficiency =

$$\frac{\text{Actual weight of microspheres}}{\text{Theoretical wt. of drug and polymer}} \times 100$$

7] Percentage yield:

It is computed by dividing the total weight of the medicine and polymer needed to make each batch by the weight of microspheres that were obtained from it, then multiplying the result by 100

8] Swelling index:

It is ascertained by measuring the degree of microsphere swelling in a certain solvent. Five milligrams of dried microspheres are placed into five milliliters of buffer solution and left overnight in a measuring cylinder to reach the equilibrium swelling degree of the microspheres. It is computed using the provided formula.

Swelling index =

$$\frac{\text{Mass of swollen microspheres} - \text{Mass of dried microspheres}}{\text{Mass of dried microspheres}} \times 100$$

9] In vitro methods:

This technique makes it possible to determine a drug's permeability across a membrane as well as its release properties. The in vitro approach is used in product development, pharmaceutical manufacturing, and other areas as a quality control procedure. It is essential to have sensible and repeatable release data that are generated from settings that are chemically, physically, and hydrodynamically characterized[26, 28].

10] Beaker method:

Using an overhead stirrer, the dosage form is made to stick at the bottom of the beaker holding the medium in this procedure, and the mixture is agitated evenly. The studies' literature uses a range of volumes for the medium (50–500 ml) and stirrer speeds (60–300 rpm).

11] Interface diffusion method:

Dearden and Tomlinson devised this methodology. There are four sections in it. Compartment A, which symbolizes the oral cavity, started out with a suitable amount of medication in a buffer. One octanol is found in compartment B, which represents the buccal membrane, and 0.2M HCl is found in compartment C, which represents bodily fluids. One octanol is also present in compartment D, which symbolizes protein binding. The 1-octanol and aqueous phases are saturated with one another before to use. The samples are taken out and placed back into compartment A using a syringe[18].

13] In vivo method:

Techniques that provide the biological reaction of the organism locally or systemically, as well as those that include direct local assessment of absorption or accumulation of substances at their surface, are used to evaluate the permeability of intact mucosa. A common approach to doing in vivo investigations is the use of animal models and buccal absorption tests [20].

14] Animal models:

Its primary uses include screening a range of chemicals, looking into their mechanisms, and assessing a number of formulations. There are reports on animal models, including pigs, lambs, dogs, and rats. The process usually entails anesthetizing the animal, giving the dosage, taking blood samples at various intervals, and analyzing[22].

15] Buccal absorption test:

For both single- and multi-component medication mixes, it is the most appropriate and trustworthy technique for determining the amount of drug loss from the human oral cavity. The relative significance of drug structure, contact time, initial drug concentration, and solution pH while the drug is retained in the oral cavity have all been effectively investigated using this assay. Human volunteers swirl a 25 ml sample of the test solution for 15 minutes, after which they expect the solution, in order to determine the kinetics of drug absorption. To calculate the amount of medication absorbed, it

is then necessary to calculate the amount of drug that is still present in the ejected volume.[25]

Applications of microspheres:[29,30]

1] Microspheres in vaccine delivery:

A vaccination requires immunity to the microbe or any of its harmful byproducts. The perfect vaccination should meet the following criteria: it should be affordable, safe, easy to use, and effective. Safety and minimizing negative responses are two complicated issues. The technique of administration has a direct bearing on both the safety factor and the level of antibody response. One potential solution to address the shortcomings of traditional vaccines is the use of biodegradable delivery vehicles for parenteral vaccinations. Parenteral (subcutaneous, intramuscular, and intradermal) carriers are of interest because they provide a number of benefits, such as:

- Improved antigen city by adjuvant action
- Modulation of antigen release
- Stabilization of antigen.

2] Targeting using micro particulate carriers:

Targeting, or site-specific medication delivery, is a well-established idea that is receiving a lot of attention. The drug's ability to specifically engage and get access to its target receptors determines how effective it is as a treatment. The drug action is mediated by the employment of a carrier system, which allows the drug to exit the pool in a repeatable, effective, and targeted manner.

3] Monoclonal antibodies facilitated microspheres targeting:

Immunological microspheres are those that are targeted by monoclonal antibodies. Selective targeting to particular places is accomplished using this targeting. The molecules known as monoclonal antibodies are very selective. Monoclonal antibodies (Mabs) with their high specificity can be used to direct microspheres containing bioactive compounds to specified locations. By covalent coupling, mab spheres may be directly linked to the microspheres. The antibodies can be attached to the free aldehyde, amino, or hydroxyl groups on the microspheres' surface. Microspheres can be equipped with maps using any of the following techniques:

- Nonspecific adsorption and specific adsorption
- Direct coupling
- Coupling via reagent

4] Imaging:

The microspheres have been utilized for targeting and have undergone substantial research. Radiolabelled microspheres can be used for imaging a variety of cells, cell lines, tissues, and organs. When it comes to imaging specific areas, the microspheres' variety of particle sizes is crucial. The intravenous particles will become caught in the lung's capillary bed if they are injected somewhere other than the portal vein. This phenomenon is used to create labeled human serum albumin microspheres for scintigraphic imaging of lung tumor masses.

5] Topical porous microspheres:

Porous microspheres with several interconnected gaps ranging in particle size from 5 to 300 µm are known as microsponges. These porous microspheres with active ingredients can be added to formulations like creams, lotions, and powders. These microsponges are used as topical carriers because they can entrap a wide range of active ingredients like emollients, fragrances, essential oils, etc. Microsponges are made of non-collapsible structures with porous surfaces that allow for the regulated release of active substances.

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