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MICROSPHERE: A GENERAL OVERVIEW

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Abstract:

Microspheres are a type of solid particles that are made up of synthetic polymers or proteins which are biodegradable in nature. They have a number of appealing biological properties, including improved bio adhesion and permeability. These make microsphers as excellent alternate to conventional dosage form. The microspheres can be encapsulated in aqueous media, and they can be dispersed in vehicles for injection. The control of the size and dispersibility of such material is important for the effective use of medicines.microsphere have vast application in drug delivery.

Keywords — Microspheres , Microcapsule, micromatrix, polymeric microspheres.

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Introduction:

Oral administration is the preferable route for taking medications because of its ease of administration, reduced therapy costs, and patient compliance. However, the short half-life, high first-pass metabolism, and limited absorption of many drugs limit the therapeutic potential of these drugs. The pharmacokinetic limitation often results in frequent dosing of medication to achieve a therapeutic effect. A rational approach to enhancing bioavailability and improving pharmacokinetic and pharmacodynamics profiles is to release the drug in a controlled and site-specific manner, which can be achieved by microsphere [2]

As the name suggests, a microsphere is a solid Sphere with a size of 1 µm to 1000 µm, with free-flowing properties, and is made up of synthetic polymer or proteins which are biodegradable in nature.[1] microcapsules and microspheres this two-term are often used interchangeably with each other.[1]

There are two types of microspheres:

1. **Microcapsules** are those in which a clearly defined capsule wall surrounds an enclosed Drug

2. **Micromatrix** is those in which drugs are dispersed uniformly in Matrix.[2]

Ideal characteristics of microspheres:

1. Microspheres Should have the ability to deliver a large amount of drug
2. Microspheres Should have a clinically acceptable half-life
3. Microspheres Should have appropriate dispersibility for reconstitution of aqueous injection.
4. It should be biocompatible and biodegradable .
5. Susceptibility to chemical modification.[2][4]

Advantages

1. The reduction of size helps increase the surface area and can increase the solubility.
2. Provide a constant amount of medications in the body that can improve the compliance of patients.
3. Reduce dose and toxicity
4. Drug packaging with polymers prevents the drug from enzymatic degradation.
5. Less dosing duration contributes to higher patient compliance.
6. The effective use of medicines can improve bioavailability and reduce harmful effects.
7. A liquid can be administered in a solid form by using microspheres, which provides a taste-masking effect, beneficial for bitter and unpleasant taste drugs.
8. Morphology of the microsphere allows control and constant degradation of biodegradable polymer and release of the drug.
9. Protect the git from the irritating effects of some git irritant drugs.
10. Biodegradable microspheres have a great advantage over implants because they don't require surgical procedures to implant or remove devices.
11. Biodegradable microspheres provide a controlled release of drugs, thus decreasing toxic side effects and eliminating The disadvantage of repeated injections.

Limitation

1. The material and processing cost is much higher than the traditional dosage form.
2. The release rate of the microsphere is affected by several factors like diet, the content of food, and transfer levels through the gut.
3. The reproducibility is lower.
4. Process conditions such as temperature change, pH, the addition of solvents, and evaporation/agitation can influence the stability of the drug core to be encapsulated.
5. Controlled release formulations generally have a greater dose to load and, therefore, any lack of quality of the release properties of the drug can contribute to potentially dangerous.
6. Microspheres shouldn't be chewed or crushed. [2]

Polymer used for the preparation of Microsphere

Polymers which is used can be classified into two class:

1. **Natural polymer:** this polymer is obtained from various natural sources such as Carbohydrate, chemically modified carbohydrates, and protein
For example :
A. Carbohydrates: Chitosan, Starch, Agarose, Carrageenan.
B. Modified carbohydrate: Poly dextran, Poly starch.
C. Proteins: Albumin, Gelatin, and Collagen.

2. **Synthetic Polymer:** can be further classified into :
A. Non-biodegradable Polymer: e.g Glycidyl methacrylate, Epoxy polymers, Acrolein and Poly methyl methacrylate.
Non-biodegradable Polymer, when Parenterally administered, the Polymer remains in the body after the drug is completely released Possibility of bearer toxicity for a long period.

B. Biodegradable polymer: e.gPoly-lactide acid, poly(lactic-co-glycolic acid, Poly alkyl cyanoacrylates, and Poly anhydride.
biodegradable polymer degrades in the biological Environment products, so there is no Polymer toxicity problem, and is more suitable for parenteral applications.

Ideal properties of the polymer carrier

- Should provide a Longer duration of action
- Should Provide protection of the drug from enzymatic degradation and the environment
- Can be easily sterilized.
- Should have sufficient Water solubility and Water dispersibility
- Should be nontoxic
- Should be Bioresorble and biocompatible [4]

METHOD OF PREPARATION

Choosing the method of preparation depends mainly on the character of a polymer that has been used, the drug, also depends on many formulations and technological factors.[3]

The most important physical factor which should be considered while choosing a method of preparation for a microsphere are as follow

1. Desired particle
2. Polymer to-drug ratio
3. The total mass of drug and polymer
4. The molecular weight of the polymer
5. Have good stability
6. Controlled particle size and dispersibility in aqueous vehicles for injection
7. The final product should be non-toxic and non-irritant.
8. Reproducibility
9. Release of drug with control over a long period of time [4]

General Methods Of Preparation :

1. Single Emulsion Technique
2. Double Emulsion Technique
3. Polymerization Techniques

A. Normal polymerization

- ✓ Bulk
- ✓ Emulsion
- ✓ Suspension

B. Interfacial polymerization

4. Phase separation coacervation technique
5. Spray drying and Spray congealing.
6. Solvent Extraction.[5]
7. Quassi emulsion solvent diffusion[2]

1. **Single Emulsion Technique :**There are several proteins and carbohydrates, which are prepared by this technique. Inthgis technique the natural polymers are dissolved in aqueous environment and followed by Dispersion in then non- aqueous phase, Which is generally oil .This is the first step methods and second step can be carried out by following two methods :

1) Cross linking by heat: by adding the dispersion into heated oil, this method is not suitable for thermoliable drug.

2) Chemical cross linking : by using chemical agents such as glutaraldehyde, formaldehyde, di acid chloride, etc in this method drug have excessive exposure to chemicals .[6]

2**.Double Emulsion Technique**

In double emulsion technique there is formation of multiple emulsion (w/o/w).which is best suited for water soluble drugs that are soluble in water, such as peptides, proteins, and the vaccines.

This approach is applicable to both

both synthetic and natural polymers. The aqueous phase is distributes in oily/organic phase. This protein solution may contain drug in it .after formation of primary emulsion it is first subjected to homogenization or sonication . after that add aq solution PVA(poly vinyl alcohol).

This result in formation of final double emulsion. Then this double emulsion is subjected to separation washing and drying to obtain microsphere .[4][5]

3.**Polymerization techniques**

Polymerization technique which is used for microsphere preparation are classified into two .

a.Normal polymerization : it is carried out and proceed using different technique such as

Bulk
Suspension
Emulsion [5]

In bulk polymerization, the polymerization process is often started by heating a monomer or combination of monomers combined with an initiator or catalyst. The resulting polymer can be moulded into microspheres. [4]The process of suspension polymerization, also known as bead or pearl polymerization, involves heating a monomer combination containing the active ingredient and dispersing it as droplets in a continuous aqueous phase.

The size of the microspheres produced by these techniques is less than 100 m.

Emulsion polymerization differs from suspension polymerization with respect to the presence of an initiator in the aqueous phase. It is also carried out at low temperature because the external phase of suspension in the latter two procedures is often water, allowing for easy heat dissipation. These methods enable the production of higher polymers at a faster rate, but they also raise the possibility of polymer association with unreacted monomers and other additives.

b. Interfacial polymerization

In this polymerization technique Various monomers react at the boundary between the two immiscible liquid phases to create a polymer film that effectively envelops the dispersed phase. This method uses two reactive monomers, one of which dissolves in continuous phase and the other of which disperses in continuous phase. Due to the produced polymer's solubility in the emulsion droplet, two circumstances occur .If the polymer is soluble in a droplet, the carrier will develop as a monolith. If the polymer is insoluble in a droplet, the capsule type is generated.[4][5]

4. Phase separation coacervation.

Phase separation cocervation technique is specially designed for reservoir type of system i.e microcapsule. In this technique there is formation of coacervates.which is polymer rich phase and based on decreasing the solubility of polymer to form this coacervates [7]. Coacervation can be brought by various methods such as addition os non solvent, addition of incaompatible polymer,or change in temperature or pH,Etc.[5]

In this method the polymer is dissolved in a solvent of choice and then the drug is added in polymer solution and dispressed to make it aqueous solution . the phase sepration is done by above mention method . this precess is carried out under constant stirring to control size of microcapsule [5][7]

5. Spray drying and Spray congealing.

These techniques rely on the drying of the drug and polymer mist in the atmosphere. Spray drying and spray congealing are two different techniques that are distinguished by the elimination of the solvent or chilling of the solution, respectively. First, a volatile organic solvent, such as dichloromethane,acetone, or another, is used to dissolve the polymer. The medication is subsequently dissolved in the polymer solution while being homogenised at a high speed. Then, a jet of hot air is used to atomize this dispersion. The process of atomization produces tiny droplets or a fine mist, from which the solvent instantly evaporates, resulting in the creation of microspheres with a size range of 1 to 100 m.By using a cyclone separator, microparticles are separated from the heated air, and vacuum drying removes any remaining solvent. Operating the procedure successfully in aseptic circumstances is one of its main benefits. The different penicillins are encapsulated using the spray drying method. Spray congealing is used to encapsulate thiamine mononitrate and sulpha ethylthiadizole in a combination of mono- and diglycerides of stearic acid and palmitic acid.

However, extremely quick solvent evaporation results in the creation of porous microparticles.[2][5]

6. Solvent extraction :

Solvent evaporation in this involves removal of the organic phase by extraction of the or non aqueous solvent.

It uses organic solvents that are water soluble, such as isopropanol. Water extraction can be used to get rid of the organic phase. The microspheres' hardening time is decreaseb by this procedure. The rate of solvent removal by extraction method depends on the water's temperature, the volume of the emulsion in relation to the water, and the polymer's solubility profile.[2][5]

7.Quassi emulsion solvent diffusion

A novel technique is reported in literature which is quasi-emulsion solvent diffusion method for preparation of controlled release microspheres of several drugs with acrylic polymers.A quasi emulsion solvent diffusion method using an external phase containing dil water and polyvinyl alcohol (PVA) can be used to make microsponges. The internal phase is made up of the drug, ethanol, and polymer. The polymer concentration is

increased to improve plasticity. The internal phase is first produced at 60oC before being combined with the external phase at room temperature. The mixture is continuously stirred for 2 hours after the emulsification process. The microsponges can then be separated by filtering the mixture. After that, the product is washed and dried in a vacuum oven at 40□ for a day[4][8]

Characterization of Microspheres

1. **Particle size and shape** :The two most common methods for visualising microparticles are conventional light microscopy (LM) and scanning electron microscopy (SEM).[2]Both are capable of determining the shape and outer structure of microparticles.In the case of double-walled microspheres, LM allows for control over coating parameters. The structures of the microspheres can be seen before and after coating, and the difference can be measured microscopicallyIn comparison to the LM, the SEM has a higher resolution. SEM can be used to investigate the surfaces of microspheres and, after particles have been cross-sectioned, it can also be used to investigate double-walled systems.[8]
Nevertheless they have there certain limitation when used for analysis of internal structure of microspheres. Confocal laser scanning microscopy is used as a non-destructive visulaization techniquefor microparticles ,and also allows characterization and visualization of both surface and inside of particle .[5]In addition to using experimental approaches, characterization of the microspheres' size, shape, and morphology can also be done using laser light scattering and a multi size coulter counter.[8]

2. Surface chemistry:Electron spectroscopy for chemical analysis (ESCA) can be used to determine the surface chemistry of the microspheres . ESCA allows for the determination of the surface's atomic composition. The ECSA spectra can be used to calculate the surfacial degradation of biodegradable microspheres.[5].

3. Density determination :
A multi volume pycnometer can be used to determine the density of the microspheres.[2].

Micro electrophoresis is used to determine the isoelectric point by measuring the electrophoretic mobility of microspheres.[2]

5. **Degradation of the polymeric matrix :**
FT-IR is used to assess the degradation of the carrier system's polymeric matrix. The surface of the microspheres is investigated using alternated total reflectance measurements (ATR). The IR beam reflected many times through the sample as it passed through the ATR cell, providing IR spectra primarily of surface material. Depending on the manufacturing procedures and conditions, the AT-FTIR provides information about the surface composition of the microspheres.[8]

6. Angle of contact:
The angle of contact is used to assess a micro particulate carrier's wetting property. It determines whether microspheres are hydrophilic or hydrophobic in nature.[8]

7. **Capture efficiency:**
By allowing washed microspheres to lyse, the capture efficiency or percent entrapment of the microspheres can be determined.

Following equation is used to calculate the percent entrapment efficiency

% Entrapment = Actual content/Theoretical content x 100. [8]

8. **In vitro release :**
In vitro drug relase of microsphere can be determined by using different apparatus such as

- Beaker method: In This method's dosage form is designed to adhere to the bottom of the medium-containing beaker and uniformly stirred with an over-head stirrer the amount of the research medium used in the literature

varies50-500 mL and a stirrer speed of 60-300 rpm. [8]

- Interface diffusion system :It contain 4 compartments. Compartment A represents the oral cavity and was initially filled with a suitable concentration of drug in a buffer. 1-octanol was present in compartment B, which represented the buccal membrane, and 0.2 M HCl was present in compartment C, which represented body fluids. 1-octanol was also present in compartment D, which represented protein binding. The aqueous phase and 1-octanol were saturated with each other prior to use. With a syringe, samples were drawn and returned to compartment A.[8]

- Dissolution apparatus : standard USP and BP apparatus 1 and 2 are used generally for microspheres.[8]

- Other methods : various other methods are also used such as Modified Keshary Chien Cell, plexi glass sample blocks placed in flasks,agar gel method etc , although many method are reported in literaturefor to study drug release study only method which are able to maintain sink condition are used . [8]

Applications :

- **Microspheres in vaccine delivery :**

A vaccine must provide protection against the microorganism or its toxic product.Biodegradable vaccine delivery systems for parenteral administration may overcome the problem associate with conventional vaccines. Using microspheres with parenteral carriers has several advantages such as :

1. Adjuvants improve antigenicity
2. stabilizing the antigen
3. And by modulating antigen release.[1][8]

- **Chemoembolization:** Chemoembolisation is an endovascular therapy that combines selective arterial embolisation of a tumour with concurrent or subsequent local delivery of a chemotherapeutic agent. Theoretically, such embolisations will not only provide vascular occlusion but will also result in sustained therapeutic levels of chemotherapeutics in tumour areas. Chemoembolisation is a technique that builds on traditional percutaneous embolisation techniques.[9]

- **Imaging**: Radiolabeled microspheres can be employed to image various cells, cell lines, tissues, and organs.diameter of microsphers plays important role in imaging. Particles injected intravenously other than through the portal vein will become entrapped in the lungs' capillary bed. Using labelled human serum albumin microspheres, this phenomenon is used for scintigraphic imaging of tumour masses in the lungs.
- **Monoclonal antibodies** mediated microspheres targeting: microspheres with monoclonal antibody are used for active targeting and such microsphere is know as immunomicrosphere .In this molocolnal antibody is attached to microsphere by following method :

I. Non specific adsorption
II. Specific adsorption
III. Coupling via reagents
IV. Direct coupling.[9][1]

The specificity of monoclonal antibody used to delivered mactive molecule to predetermined targeted site.[4]

- **Nasal drug delivery :**

Polymer-based drug delivery systems, such as microspheres, has been shown high bio adhesive properties and swell when comes in contact with the nasal mucosa, thereby increasing drug bioavailability and nasal cavity residence time.[1]

- Ophthalmic Drug Delivery:

Polymer-based microspheres have a number of appealing biological properties, including improved bio adhesion and permeability.these make polymeric microsphers as excellent alternate to conventional dosage form. [1]

Pharmaceutical application

1. For Taste and odour masking
2. Separation of incompatible substances
3.Delay the volatilisation
4. Improvement of flow properties of powders
5. Improve the solubility of water-insoluble substances by incorporating dispersion of such material in aqueous media.
6. Safe handling of toxic substances.[1]

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