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A Review Of Microsphere

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Abstract:

Controlled drug delivery systems are designed to overcome the limitations associated with conventional drug therapies, leading to improved therapeutic performance. Among various advanced delivery systems, microspheres represent a promising alternative to traditional single-dose or immediate-release formulations. Microspheres are free-flowing, spherical particles typically smaller than 200µm, composed of biodegradable natural or synthetic polymers. These systems offer several advantages, including enhanced bioavailability, improved drug stability, minimised side effects, reduced dosing frequency, and targeted delivery of drugs at a controlled rate. Depending on their functional characteristics, microspheres can be classified into several types, such as bio-adhesive, floating, radioactive, polymeric, and biodegradable microspheres. In the future, microsphere-based systems are expected to play a vital role in advanced drug delivery, particularly in areas like diagnostics, genetic material transport, and site-specific therapeutic applications.

Keywords:

Microsphere, Types, Preparation Methods, Characterisation, Application.

Introduction:

Microspheres are solid, spherical particles with sizes typically ranging from 1 to 1000µm. They are free-flowing powders composed of natural proteins or synthetic polymers, most of which are biodegradable in nature. Based on their internal structure, microspheres are generally categorised into two main types: 1) Microcapsules.

- 2) Micrometrics

In a microcapsule, the active ingredients are enclosed within a distinct polymeric shell that separates them from the external environment. In contrast, micrometrics are systems in which the drug or active substance is uniformly distributed throughout the polymer matrix. Biodegradable microspheres containing a drug either dispersed or dissolved within the matrix offer significant potential for controlled and sustained drug

release. These systems are commonly fabricated using polymeric, wax-based, or other protective materials, including biodegradable synthetic polymer and modified natural substances. [1]

Advantages:

- Microspheres offer a sustained and consistent therapeutic effect over an extended period.
- They decrease the frequency of drug administration, which in turn enhances patient compliance.
- Due to their small size and spherical morphology, microspheres can be easily administered through injection.
- They promote efficient drug utilisation, leading to improved bioavailability and a reduction in the severity and occurrence of side effects.[2]

Limitation:

Despite their numerous advantages, microsphere-based drug delivery systems also have certain drawbacks, including the following:

- The cost of raw materials and manufacturing processes for controlled-release formulation is generally higher compared to conventional dosage forms.
- The biodegradable behaviour of the polymer matrix and its potential environmental impact remain areas of concern.
- The presence of polymer additives such as plasticisers, stabilisers, antioxidants, and fillers may influence both the safety and performance of the formulation.
- Batch-to-batch reproducibility can sometimes be inconsistent.
- Processing parameters-including temperature, PH, solvent type, rate of evaporation, and encapsulation efficiency of the active core material.
- The degradation products of polymer matrices, formed through heat, oxidation, hydrolysis, sunlight, or biological action, may have undesirable environmental effects.[3]

Criteria for Microsphere Preparation:

- The process of microencapsulation allows the entrapment of solids, liquids, or gases within one or more polymeric coatings. The choice of preparation methods for microspheres depends on several factors, including desired particle size, route of administration, release duration, stirring speed(rpm), type of cross-linking, solvent evaporation time, and co-precipitation parameters.
- To achieve an effective microsphere formulation, the preparation should meet the following essential criteria:
- The system should have the capacity to encapsulate a high concentration of the active pharmaceutical ingredient (API).
- The formulation must exhibit adequate stability after synthesis, ensuring a clinically acceptable shelf life.
- Microspheres should possess uniform particle size distribution and good dispersibility in aqueous media for injectable use.
- The release profile of the active compound should be well-controlled over the intended duration.
- The material used must be biocompatible with adjustable biodegradability
- The polymer matrix should also allow chemical modification to optimise performance characteristics.[4]

Types of Microspheres:

Microspheres can be classified into several categories based on their composition and functional characteristics. The major types include bio-adhesive, magnetic, floating, radioactive, and polymeric microspheres.

1. Bio adhesive Microspheres Bio-adhesive microspheres are designated to adhere to biological membranes through the mucoadhesive property of water-soluble polymers. The term bioadhesion refers to the attachment of a drug delivery system to a mucosal surface, such as the buccal, ocular, nasal, or rectal mucosa. These microspheres enhance the residence time of the formulation at the absorption site, promoting closer contact with the mucosal surface and thereby improving the therapeutic efficacy of the drug.[5]

2. Magnetic Microspheres

Magnetic microspheres are an advanced form of targeted drug delivery systems that direct the drug specifically to a diseased site using an externally applied magnetic field. This approach minimises systemic exposure by replacing large amounts of circulating drug with smaller, magnetically directed doses. Materials such as chitosan and dextran are commonly used to prepare magnetic carriers.[5]

Therapeutic Magnetic Microspheres

These systems are employed to deliver anticancer agents, such as those targeting liver tumours, and can also be used for protein peptide drug delivery.

Diagnostic Magnetic Microspheres

These are utilised in medical imaging, for example, to visualise liver metastases or to differentiate intestinal loops from adjacent structures using superparamagnetic iron oxide nanoparticles.

3. Floating Microspheres

Floating microspheres possess a lower density than gastric fluid, allowing them to remain buoyant in the stomach for extended periods without interfering with gastric emptying. The drug is released gradually at a controlled rate while the microspheres float on gastric contents, thereby extending gastric retention time and ensuring sustained plasma drug levels. This reduces dose dumping and fluctuations in drug concentration, resulting in a prolonged therapeutic effect and decreased dosing frequency. Drugs such as ketoprofen have been effectively formulated using this system.[5]

4. Radioactive Microspheres

Radioactive microspheres are primarily used in radioembolization therapy for the treatment of tumours. These particles, typically sized between 10-30 µm, are larger than capillaries and thus become trapped in the encountered after injection. When administered through arteries supplying tumours, they deliver localized radiation doses directly to the cancerous tissue while minimising exposure to surrounding healthy structures. The radioactivity acts from within the microspheres rather than being released. Depending on the type of radiation emitted, they may be classified as alpha (α), beta(β), or gamma(γ) emitter microspheres. [6]

5. Polymeric Microspheres

Polymeric microspheres are broadly divided into two categories:

Biodegradable Polymeric Microspheres

These microspheres are typically prepared using natural polymers such as starch or other biopolymers known for their biocompatibility, biodegradability, and mucoadhesive nature. Due to their ability to swell in aqueous media, they form a gel-like structure that enhances mucosal adhesion and prolongs residence time. The rate and extent of drug release can be controlled by adjusting the polymer concentration. However,

drug loading efficiency and release control can be challenging to optimize during formulation. Despite these limitations, biodegradable microspheres offer great potential for sustained-release drug delivery.

Synthetic Polymeric Microspheres

Synthetic polymeric microspheres are widely applied in clinical and pharmaceutical fields as fillers, bulking agents, embolic materials, and drug delivery carriers. They are generally considered safe and biocompatible, but their tendency to migrate from the site of administration can cause complications such as embolism or organ damage.[6]

Methods Of Preparation:

1. Spray Drying Technique

The spray drying technique is employed for the preparation of polymeric blended microspheres containing ketoprofen. In this method, the core substance is dispersed within a liquified coating material and then atomized into a controlled environment, allowing the coating to solidify as the solvent rapidly evaporates. For the preparation, organic solutions containing poly(ε-caprolactone) (PCL), cellulose acetate butyrate (CAB) in varying ratios, and ketoprofen are prepared and then subjected to spray drying under different experimental conditions to obtain drug-loaded microspheres. This technique is relatively fast; however, it may lead to a partial loss of crystallinity due to the rapid drying process.[7]

2. Solvent Evaporation Technique

In this method, microencapsulation occurs within a liquid vehicle phase. The polymeric coating material is dissolved in a volatile solvent that is immiscible with the liquid manufacturing vehicle. The drug (core material) is then dissolved or dispersed within this polymer solution. Under continuous stirring, the drug-polymer solution is emulsified into the liquid vehicle phase, resulting in the formation of microdroplets of the desired size. The mixture is then gently heated, if required, to evaporate the solvent, leading to the solidification of the polymer shell around the core. When the drug is molecularly dispersed in the polymer, matrix-type microcapsules are obtained. This technique is suitable for encapsulating both water-soluble and water-insoluble substances. The solvent evaporation method thus involves forming an emulsion between the polymer solution and a continuous immiscible phase, followed by solvent removal and microcapsule formation.[8]

3. Single Emulsion Technique

The single emulsion technique is commonly used for preparing microparticulate carriers composed of natural polymers such as proteins and carbohydrates. In this approach, the polymer is first dissolved or dispersed in an aqueous phase and then emulsified into a non-aqueous medium, typically an oil phase. The emulsion droplets are subsequently cross-linked to stabilise the microspheres. Cross-linking can be achieved either thermally or chemically using agents such as glutaraldehyde, formaldehyde, or acid chlorides. Thermal cross-linking is unsuitable for thermolabile substances, whereas chemical cross-linking may cause prolonged exposure of the active ingredient to reactive agents. After cross-linking, the microspheres are washed, separated, and collected. The choice of surfactant used to stabilize the emulsion significantly affects particle characteristics such as size, morphology, drug entrapment efficiency, release behaviour, and overall performance of the microparticulate system.[9]

4. Double Emulsion Technique

The double emulsion method is one of the most widely used techniques for preparing microspheres, particularly suited for encapsulating water-soluble drugs, proteins, peptides, and vaccines. This technique involves forming a multiple emulsion, typically of the water-in-oil-in-water (w/o/w) type, and can be applied using both natural and synthetic polymers.

In this process, the aqueous phase containing the active ingredient (such as a protein or peptide) is emulsified into an organic solvent containing the polymer to form a primary water-in-oil emulsion. This primary emulsion is then subjected to homogenization or sonication to ensure uniform droplet size. The resulting emulsion is subsequently dispersed into an external aqueous phase containing an emulsifier such as polyvinyl alcohol (PVA), leading to the formation of the w/o/w double emulsion.

The solvent from the system is then removed by evaporation or extraction, resulting in the formation of microspheres that encapsulate the hydrophilic drug. This method has been successfully applied to incorporate several bioactive molecules, such as luteinizing hormone-releasing hormone (LH-RH) agonists, vaccines, peptides, proteins, and conventional hydrophilic drugs, using solvent evaporation or extraction approaches.[9]

5. Coacervation Method

1. **Coacervation by Thermal Change:**

In this variation, a measured quantity of ethyl cellulose is dissolved in cyclohexane and stirred vigorously at about 80°C. The drug, after being finely ground, is added to this hot polymer solution under continuous stirring. Phase separation occurs when the temperature is gradually reduced using an ice bath. The obtained product is washed twice with cyclohexane, air-dried, and passed through a sieve. 40 to collect discrete microcapsules**.**

2. **Coacervation by Non-Solvent Addition:**

Here, a weighed quantity of ethyl cellulose is dissolved in toluene containing propyl isobutylene under magnetic stirring at 500 rpm for six hours in a closed beaker. The drug is then dispersed into this solution, and stirring continues for 15 minutes. Phase separation is induced by adding petroleum benzoin (five times the volume) with constant stirring. The formed microcapsules are washed with n-hexane, air-dried for two hours, and then oven-dried at 50°C for four hours**. [10]**

6. Spray Drying and Spray Congealing

Both spray drying and spray congealing rely on atomizing a polymer-drug mixture into fine droplets and solidifying them rapidly. In spray drying, the solvent is removed by hot air, while in spray congealing, solidification occurs through cooling.

To begin, the polymer is dissolved in a volatile organic solvent such as acetone or dichloromethane. The drug is then uniformly dispersed into this polymer solution using high-speed homogenization. The resulting dispersion is atomized into a stream of hot air, forming a fine mist. Rapid evaporation of the solvent produces microspheres typically ranging from 1–100 am in size. The particles are then collected using a cyclone separator, and residual solvent is removed by vacuum drying.

This method allows for aseptic operation and is used to encapsulate compounds such as penicillin derivatives, thiamine mononitrate, and sulpha methylimidazole. In spray congealing, a mixture of mono- and diglycerides of stearic and palmitic acids is often employed as the coating material. However, the rapid solvent evaporation during the process can sometimes result in porous microspheres.[11]

7. Solvent Extraction Technique

The solvent extraction method, a modification of solvent evaporation, involves the removal of the organic phase through extraction using a suitable solvent. Typically, a water-miscible organic solvent such as isopropanol is used. The organic phase is extracted into water, thereby reducing the hardening time of the microspheres.

In one variation, the active ingredient is directly incorporated into the polymeric organic solution before emulsification. The efficiency of solvent removal depends on parameters such as the temperature of the extraction medium, the volume ratio of the emulsion to water, and the solubility characteristics of the polymer. This approach allows better control over particle solidification and reduces processing time.[12]

8. Quasi-Emulsion Solvent Diffusion Method

The quasi-emulsion solvent diffusion method is a modified technique designed to produce controlled-release microspheres, particularly with acrylic polymers. In this approach, an external aqueous phase containing distilled water and polyvinyl alcohol (PVA) is prepared. The internal phase, consisting of the drug, ethanol, and polymer (with ethanol added at about 20% of the polymer weight to improve plasticity), is prepared at 60°C. The internal phase is then introduced into the external phase at room temperature, and the system is emulsified under constant stirring for about two hours. The formed microspheres (or microsponges) are filtered, washed, and dried in a vacuum oven at 40°C for 24 hours to obtain the final product.[13]

9. Ionic Gelation Technique

Chitosan microspheres containing diclofenac sodium can be prepared by dissolving 25% (w/v) of diclofenac sodium in a 1.2% (w/v) aqueous solution of sodium alginate. The solution is stirred continuously until complete dissolution and then added dropwise into a gelling solution containing Ca^{2+}/Al^{3+} ions and chitosan dissolved in acetic acid. The microspheres are allowed to remain in the gelling solution for 24 hours to ensure complete internal gelation, followed by filtration and separation. The prepared microspheres demonstrate controlled release at a neutral to slightly basic pH range (6.4–7.2), with minimal or no release in acidic conditions.[14]

FACTORS AFFECTING PARTICLE SIZE, ENTRAPMENT EFFICIENCY, AND RELEASE CHARACTERISTICS:

The way a drug comes out of a formulation is affected by several factors.

These include the amount of drug in the micro particles, the type of polymer used, the physical form of the drug, the molecular weight of the polymer, the degree of cross-linking, the concentration of the copolymer, the type of any added excipients, and the size of the micro particles.

I) Drug content:

The amount of drug in the micro particles determines how quickly it is released.

As the amount of drug increases, the release also increases proportionally.[15]

ii) Nature of polymer:

The type of polymer used and how it breaks down affect how the drug is delivered.

Polymers can be divided into two main types: bulk-eroding and surface-eroding. In bulk-eroding polymers, the whole matrix breaks down as water moves into it. In surface-eroding polymers, the outer layer breaks down first because water has a hard time getting through.[16]

iii) Physical state of the drug:

How the drug is physically arranged in the micro particles affects how it is released.

The drug can be in different forms, such as completely mixed with the polymer or in a crystal-like structure.[16]

iv) Molecular weight of polymer:

The size of the polymer molecules plays a key role in how the polymer breaks down and how the drug is released.

Larger polymer molecules break down more slowly, leading to a slower drug release. The drug moves through water-filled spaces in the polymer, and this movement is slower when the polymer has a larger molecular weight.[17]

v) Density of cross-linking:

The amount of cross-linking in the polymer affects how quickly the drug is released.

If more cross-linking is present, the drug release is usually slower. This happens when the micro particles are made using a higher concentration of polymer or a polymer with a higher molecular weight, along with a lower drug content.[17]

vi) Copolymer concentration:

The amount of co-monomer in the copolymer affects how fast the drug is released.

Typically, a higher concentration of a polymer that breaks down quickly leads to a faster release. If the drug release is controlled by the polymer erosion, increasing the concentration of a more soluble or smaller monomer can increase the release rate.[18]

vii) Type of excipients:

Excipients are added to the micro particles to help preserve the drug. However, these can sometimes slow down the drug release. This might be due to the drug interacting with the excipients in ways like forming complexes, chelates, or changing isomerisation or racemisation.

viii) Micro particle size:

The size of the micro particles has a big impact on how the drug is released.

As the size gets smaller, the surface area of the particle increases, which allows the drug to diffuse out more quickly. Smaller particles also allow water to penetrate more easily, thereby speeding up the release process.[18]

Evaluation of Microspheres:

1. **Particle Size Analyser:**

Microspheres (50 mg) are mixed with 5 mL of distilled water that contains 2% w/v of Tween 80.

This helps prevent the microspheres from clumping together. The mixture is then sonicated in a water bath, and the average particle size is measured as the volume mean diameter in micrometres.

2. **Optical Microscopy:**

This method is used to check the size of the particles.

It involves using an optical microscope (Meizer OPTIK). Measurements are taken under 450x magnification, which is achieved using a 10x eyepiece and a 45x objective lens. A total of 100 particles is measured.

3. **Scanning Electron Microscopy (SEM):**

SEM is used to examine the surface shape and structure of the microcapsules.

The microcapsules are placed directly on a SEM sample holder using double-sided adhesive tape. They are then coated with a thin layer of gold under low pressure and analysed.

4. **Swelling Index:**

This method is used to study the properties of sodium alginate microspheres.

Different solutions (100 mL each) are prepared, such as distilled water and buffer solutions with pH values of 1.2, 4.5, and 7.4. A sample of 100 mg of microspheres is placed in a wire basket and submerged in each solution. The microspheres are left to swell at 37°C. The weight changes are measured regularly, and the swelling is calculated by comparing the starting weight with the weight after soaking, using filter paper.

5. **Entrapment Efficiency:**

Microspheres containing 5 mg of drug are crushed and dissolved in distilled water using an ultrasonic stirrer for 3 hours.

The mixture is filtered and then analysed using UV-Vi's spectroscopy. Entrapment efficiency is calculated by dividing the actual amount of drug found by the theoretical amount expected.

6. **X-ray Diffraction:**

This technique is used to check how the crystal structure of the drug changes.

Both the microspheres and their individual components are analysed using an XRD instrument, with the scanning range between 80°C and 70°C.

7. **Thermal Analysis:**

Thermal analysis of the microcapsules and their components is performed using Differential Scanning Calorimetry (DSC), Thermogravimetric Analysis (TGA), and Differential Thermometric Analysis (DTA).

The sample is weighed accurately, placed on an alumina pan, and heated at a constant rate of 10°C per minute under a nitrogen flow of 40 mL per minute.

8. **FTIR:**

FTIR is used to study how the drug interacts with the polymer and how the drug might break down during the microencapsulation process.

9. **Stability Studies:**

Stability studies are conducted by placing the microspheres in screw-capped glass containers and storing them under the following conditions:

- Ambient humid conditions

- Room temperature (27°C ± 2°C)

- Oven temperature (40°C ± 2°C)

- Refrigerator temperature (5°C ± 8°C)

These studies are carried out for 60 days, and the drug content of the microspheres is analysed.

10. Zeta Potential:

The polyelectrolyte shell is made by adding chitosan of different molecular weights into the W2 phase.

The resulting particles are analysed using zeta potential measurement.

Application of Microspheres:

1. Gene delivery
2. Eye drug delivery
3. Tumour and local drug delivery
4. Oral drug delivery
5. Nasal drug delivery
6. Buccal drug delivery
7. Gastrointestinal drug delivery
8. Peroral drug delivery
9. Vaginal drug delivery
10. Transdermal drug delivery
11. Colonic drug delivery
12. Multiarticulate delivery systems

Conclusion:

Microspheres are a short-term method but have a wide range of applications in drug delivery systems. Some of the most important applications are targeted drug delivery (bio-adhesive microspheres for nasal, ocular, buccal, rectal routes, magnetic and radioactive microspheres for tumours), and controlled and sustained release (polymeric and floating microspheres). By combining different approaches, microspheres will play a central role in new drug delivery systems, especially in areas like cell sorting, diagnostics, and genetic engineering. This study shows that microspheres can effectively act as carriers for new drug delivery systems.

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