e-ISSN: 2961-6204, p-ISSN: 2961-6123

Available online on http://www.ijhacr.com

International Journal of Health Advancement and Clinical Research (tz) 2023; 1(4); 65-70

Review Article

An Overview on Microparticle Drug Delivery Systems

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Received: 12-08-2023 / Revised: 19-09-2023 / Accepted: 28-10-2023
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Conflict of interest: Nil

Abstract:

To improve effectiveness, tolerance, and patient compliance, microparticles are used as multiunit drug delivery methods with well-defined physiological as well as pharmacokinetic advantages. They have a diameter between 0.1 µm and 200 µm. This review explores the key aspects of microparticulate drug delivery systems, their advantages as well as disadvantages. There are various methods like Single Emulsion Process, Phase Separation, Fluidized Bed Coating, Double Emulsion Process, Spray Drying and Solvent / Emulsion Extraction Process which can be used for the manufacturing of microparticles and various evaluation parameters. There are many challenges with microparticles which we have discussed here and potential application of microparticles in pharmaceutical industry.

Key Words: Microparticles, Pharmacokinetic, Fluidized Bed Coating, Spray Drying.

Introduction

Microparticles were initially characterized in 1967 by Peter Wolf, who discovered platelet membrane fragments within human plasma as well as linked them to inflammation. [1]

One method for delivering drugs over lengthy periods of time in a regulated and sustained manner is the microparticulate drug delivery system. They have a diameter between 0.1 µm and 200 µm and are composed of tiny solid particles or liquid droplets that are encased in walls made of synthetic and natural polymer films that vary in thickness and degree of permeability. [2]

Microparticulate drug delivery systems have emerged as a groundbreaking advancement in the field of pharmaceuticals, promising more efficient and targeted drug delivery for a wide range of medical conditions. This review explores the key aspects of microparticulate drug delivery systems, their advantages, disadvantages, methods of manufacturing, challenges, and potential application of microparticles.

Advantages of Microparticles [3,4]

a. Targeted Drug Delivery: Microparticles enable site-specific drug delivery,

reducing systemic side effects and enhancing therapeutic outcomes.

b. Controlled Release: They offer precise control over drug release kinetics, ensuring prolonged therapeutic effects and reduced dosing frequency.

c. Improved Bioavailability: Microparticulate systems protect drugs from degradation and enhance their absorption, leading to increased bioavailability.

d. Reduced Toxicity: By minimizing exposure to healthy tissues, these systems often result in lower toxicity profiles compared to conventional drug delivery methods.

e. Effective distribution of water-insoluble or sparingly soluble drugs.

f. They also reduced the local adverse reactions of medicines, such as GI discomfort, when taken orally.

g. They may also be utilized to manufacture amorphous medicines with appropriate physical characteristics.

Disadvantages of Microparticles [5]

a. The material and processing costs of controlled release formulations are higher than those of standard formulations.

b. There is minimal repeatability.

c. The temperature, pH, as well as the incorporation of solvents may all have an impact on the drug's stability.

Because of their small size and large surface area, particles aggregate, resulting in physical handling of the micro particles within liquid as well as dry forms difficult.

Methods of Microparticle Preparation:

There are different methods which are employed for the manufacturing of microparticles like:

- Single Emulsion Process
- Phase Separation
- Fluidized Bed Coating
- Double Emulsion Process
- Spray Drying
- Solvent / Emulsion Extraction Process

A. Phase Separation

A third component is added to the polymer solution in order to reduce the polymer solution's solubility of the encapsulating polymer. The process yields two aqueous phases: a coacervate phase containing polymers and a supernatant phase depleted of polymers. [6]

The coacervate covers the drug once it has been dispersed or dissolved in the solution of polymers. The coacervation process consists of three steps:

i. Phase separation of the polymer solution,

ii. Coacervate adsorption around the drug particle.

iii. Solidification of the microspheres.

B. Single Emulsion Process

This process employs oil-in-water (o/w) emulsification. The O/W emulsion system's organic phase is composed of up of a volatile solvent comprising dissolved polymer together with the drug that is encapsulated, along with a dissolved surfactant.

A surfactant in the aqueous phase prevents organic droplets from coalescing after they have formed. To create an o/w, The polymer - solvent medicine solution is emulsified (together with the appropriate agitation and temperature). The emulsion is created by combining both aqueous and organic phases with the aid of a propeller/magnetic bar. [7]

C. Fluidized Bed Coating

Top, bottom, & tangential are three prominent fluidized bed coating processes. Although granules often have a porous

surface as well as an interstitial void region, the granules created have a low bulk density. Tangential-spray coating produces a product having a high bulk density but significant interstitial void space by combining centrifugal, high-density mixing, and fluid bed drying efficiency. It produces particles which are less friable yet more spherical. In the bottom spray technique, the solid core particles are fluidized by air pressure, and a solution is sprayed onto the particles through the bottom of the fluidization chamber (which is comparable to the air stream).

The spraying nozzle, that is suspended in the air, sprays the coating ingredients into the fluidized particles. The film is more uniformly spread because the coating sol. droplets travel a short distance before hitting with the solid particles. The coated particles are then lifted into the air stream, where they dry. The particles that were lifted into the air stream settle, and a new cycle starts. [8]

D. Double Emulsion Process

The double emulsion method is often employed for medications that are insoluble in organic solvents. If the drug's form is small enough, it might be encapsulated using a solid-in-oil-in-water emulsion (s/o/w). To prevent enormous bursts caused by larger crystal dissolution, the drug crystal needs to be at least an order of magnitude smaller than the intended microparticle diameter.

Smaller crystals would evenly distribute throughout the organic droplet of the emulsion. This method has had been utilized to encapsulate hydrophilic drugs (such as cisplatin and doxorubicin).

E. Spray Drying

Spray drying is a standard practice in the pharmaceutical business, and many researchers have investigated it as a method of producing biodegradable microparticles. It is simple, rapid, and simple to scale up, needs only moderate conditions, and relies less on drug & polymer solubility variables.

In this method, the drug is generally dissolved/suspended in a polymer solution. The solution/suspension is then fed through the nozzle into the spray drying apparatus, when the polymer/drug solution is swiftly mixed with air and forced via a tiny diameter hole. At nozzle 25, the polymer/drug solution is nebulized, and the resultant droplet is quickly evaporated before being collected. [9]

F. Solvent / Emulsion Extraction Process

In this technique for producing micro particles, the organic phase is eliminated by extracting the organic solvent. This technique employs water miscible organic solvents such as isopropanol. The organic phase is extracted using water as a solvent. As a consequence of this technique, the hardening time of the microspheres is decreased. Polymer dissolution in a solvent is necessary for the production of micro particles. The solution is then emulsified in vegetable oil, and an amphiphilic agent is added to help with solvent extraction, resulting in the creation of micro particles. [10].

Evaluation of Microparticles [11, 12,13,14]

The following are the numerous assessment procedures for microparticle preparation:

a) Particle shape & size determination

Microscopy, sieve analysis, laser light scattering, the coulter counter technique, and photon correlation spectroscopy can be utilized for the assessment of particle size and shape.

b) Bulk and tapped densities

We used a graduated cylinder with a 10 mL capacity to measure the bulk and tapped densities. The sample that had been put into the cylinder was mechanically tapped 200 times before the tapped volume, bulk density, alongside tapped density were

determined. Each micromeritic characteristics investigation was carried out in triplicate.. The formula for calculating bulk density is as follows.

$$Bulk\ Density = \frac{Powder\ blend's\ weight\ (gm)}{Bulk\ volume\ of\ the\ Granule's\ (ml)}$$

$$Tapped\ Density = \frac{Mass\ of\ sample\ (gm)}{Tapped\ volume\ of\ \ the\ sample\ (ml)}$$

c) Angle of repose

Angle of repose of different formulations was measured according to fixed funnel standing method.

$$\theta\ =\ tan-1\ h\ /\ r$$

Where θ is the angle of repose, r is the radius, and h is the height

d) Carr's index

Compressibility index (Ci) or Carr's index value of microparticles was computed according to the following equation:

Carr's index (%) = (Tapped density – bulk density) / Tapped density x 100

e) Hausner's ratio

Hausner's ratio of microparticles was determined by comparing the tapped density to the bulk density using the equation:

Hausner's ratio = Tapped density / Bulk density.

f) In vitro drug release study

The USP method II or dissolution test technique was used to assess the drug release investigations. The release media was heated to 37±0.5 C and analyzed spectrophotometrically.

g) Kinetics study of Drug release

Models were fitted to the dissolution data of improved formulations using linear regression analysis to explain the kinetics of the drug release process in the various formulations.

- **Zero order kinetics**

The following equation may be used to depict drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the medication slowly, provided that area does not change and no equilibrium requirements are followed.

$$\mathbf{Q_t = Q_0 + K_0 t}$$

Qt is the amount of drug dissolved in time t

Q0 is the initial amount of drug in solution

K is the zero-order release constant

- **First order kinetics**

The use of this model in drug dissolution research to characterize drug absorption and/or excretion. The release rate data had been fitted to the following equation to analyze the first order release rate kinetics.

$$\mathbf{Log\ Qt = Log\ Q_0 + K_1 t\ /\ 2.303}$$

Qt - is the amount of drug released in the time t

Q0-is the initial amount of drug in the solution

K1 -is the first order release constant

- **Higuchi model**

Higuchi created many theoretical models to investigate the release of water soluble as well as poorly soluble medicines embedded in semisolid and/or solid matrixes. For drug particles distributed in a uniform matrix acting as a diffusion medium, mathematical formulas were developed. The formula is

$$\mathbf{Qt = KH\ t^{1/2}}$$

Qt is the amount of drug released in time t

KH is the Higuchi dissolution constant

- **Korsmeyer and Peppas Model**

This model is used to assess the release of pharmacological polymeric dosage forms when the release mechanism is unknown or when many types of release phenomena are present. The formula is

$$\mathbf{Mt\ /\ M = K.t\ n}$$

Mt /M is the fraction of drug release

K is the release constant

t is the release time

n is the diffusion exponent for drug release that is depend on the shape of matrix dosage form.

Challenges:

a) **Formulation Complexity:** Developing microparticulate drug delivery systems can be challenging due to the need for biocompatible materials and precise control over particle size and drug loading.

b) **Regulatory Hurdles:** Regulatory approval for these novel systems can be complex, requiring extensive testing and documentation to ensure safety and efficacy.

c) **Cost of Production:** The production of microparticulate systems can be more expensive than conventional formulations, affecting drug pricing.

d) **Limited Drug Compatibility:** Not all drugs are suitable for microparticulate delivery, as some may degrade or lose efficacy during the formulation process. [15]

Applications [16,17]

- **Oral Drug Delivery**
- Improved drug stability and bioavailability
- Gastrointestinal targeting
- **Pulmonary Drug Delivery**
- Inhalable microparticles for lung diseases
- Localized drug delivery to the respiratory tract
- **Transdermal Drug Delivery**
- Enhanced skin penetration
- Prolonged drug release for topical applications
- **Targeted Drug Delivery**
- Ligand-conjugated microparticles for site-specific drug delivery
- Reduced systemic side effects

Conclusion

Microparticles drug delivery systems offer a promising avenue for improving drug efficacy and patient compliance. Their versatility in terms of materials and fabrication techniques, along with their ability to provide controlled release and targeted delivery, makes them a valuable tool in the pharmaceutical industry. However, addressing challenges related to regulatory approval and ensuring patient safety will be crucial for the successful translation of microparticle-based drug delivery systems from the laboratory to clinical practice. With ongoing research and innovation, microparticles hold the potential to revolutionize drug delivery and improve healthcare outcomes.

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