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The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.23
TPI 2022; 11(4): 837-840

www.thepharmajournal.com
Received: 01-01-2022
Accepted: 06-03-2022

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A review on microparticles: Preparation techniques and evaluation

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Abstract
There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres as carriers for drugs. The micro particles are physical approach to alter and improve the pharmacokinetic and pharmacodynamics properties of various drugs. They have particles range between 0.1 and 100µm in size. A recent study showed that negative charged, immune-modifying and infused micro particles could have better therapeutic index and is used in diseases caused by inflammatory monocytes. Both natural and synthetic materials can be used for preparation of micro particles. Now days, micro particles are constituted from polymers, ceramic and glass. In comparison with liposome, micro particles are more stable in the biological environment. Micro particles can be designed as surface-linked targeting moiety. Therefore this system is used for targeted drug delivery. Micro particles are also used for controlled and long-term release. In micro particles, macromolecules are encapsulated inside a system to treat different diseased conditions such as ocular diseases, cancer, cardiac diseases, and inflammation. This review is concerned with micro particles as novel drug delivery system, its advantages, disadvantages and method of preparations, so that targeted, controlled and sustained release effect is achieved.

Keywords: Micro particles, target drug delivery system, microencapsulation, preparation of micro particles, novel drug delivery

Introduction
Microspheres are small spherical micro particles that can be used as drug carrier. Micro particles are the solid particles or small droplets of liquid which are protected or surrounded by polymer film. They have size in the range of 1-1000 µm (1mm) [1].
There is micro particle matrix, in which drug can be encapsulated, dissolved, attached or entrapped. Micro particles help in easy administration to deliver macromolecules by a various routes and control the release of drugs effectively. It provides effective protection to encapsulated drug against any kind of degradation [2].

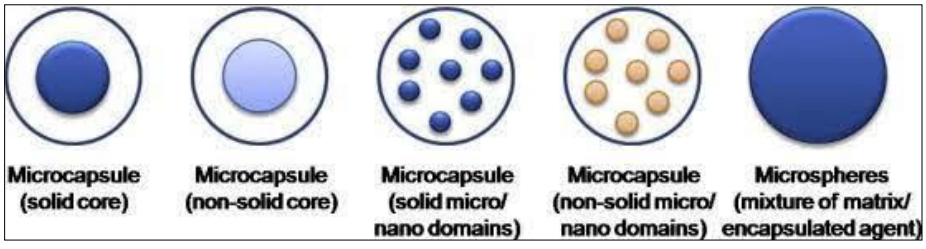

Fig 1: Microsphere

Micro particles offers a variety of opportunities such as masking of taste and odor, increase bioavailability of drug, protection of drug, controlled release, improves stability, decrease dose dumping, reduce dissolution rate etc. [3]
The substances used in the formulation are biodegradable, synthetic polymers, and natural products. The polymers used to manufacture microspheres are chosen according to their solubility, stability profile, safety, and economic suitability [4].

- There is micro particle matrix, in which drug can be encapsulated, dissolved, attached or entrapped. Micro particles help in easy administration to deliver macromolecules by a various routes and control the release of drugs effectively. It provides effective protection to encapsulated drug against any kind of degradation [5].

- It provides protection to the encapsulated drug against degradation, such as enzymatic degradation [6].
- Micro particles are also used to produce amorphous drug (desirable physical properties).
- Also leads to reduction of the local side effects of drugs on oral ingestion e.g. GI irritation [7].
- Micro particles drug delivery system offers great therapeutic effect to patients in term of effectiveness, patient compliance and safety. To ensure equilibrium between target specificity, price, effectiveness and patient compliance, it arrives that combination of conventional and novel drug approaches, is the key to the development of controlled drug delivery system. It helps in improving bioavailability of drug and also in controlled release of drugs [8].

Advantages of microparticles [9]

1. It provides protection to the encapsulated drug against degradation, such as enzymatic degradation.
2. It is easy to administer.
3. This technique helps in masking taste.
4. They help in increasing the relative bioavailability of drugs.
5. This technique is flexible in targeting the delivery of drug to specific sites.
6. The micro particles provide reduced toxicity of various drugs.
7. Micro particles are also used to produce amorphous drug (desirable physical properties).
8. Also leads to reduction of the local side effects of drugs on oral ingestion e.g. GI irritation.
9. This technique provides the sustained release formulation and lower dose of drug which also helps in maintaining plasma concentration & improves patient compliance.
10. The pH triggered micro particles are used in vaccination, transfect ion & gene therapy.
11. High concentration of water soluble drugs can be administered using parenteral micro particles without severe osmotic effects at site of administration.
12. They can also be stored for longer period in the form of dry particle or suspension.
13. These micro particles are provided in a tablet with an effervescent disintegration agent, which is useful for individual unable to chew.

Disadvantages [10]

Although the micro particles are impressive but it also have some disadvantages, which are as follow:

1. The costs of the materials & processing of controlled release preparation is higher than standard formulations.
2. The fate of polymer matrix and its effect on the environment.
3. The fate of polymer additives such as plasticizers, stabilizers, antioxidants and fillers.
4. Less reproducibility.
5. Some conditions like change in temperature, pH, and solvent addition may influence the stability of drug.
6. Due to their small size and large surface area, aggregation of particle occur which makes difficulty in physical handling of micro particles difficult in liquid and dry forms.
7. These problems have to be overcome before micro particles can be used clinically.

Method of preparations [11].

There are various techniques for the preparation of micro particles. Some of them are listed below:

1. Emulsions-solvent evaporation (o/w, w/o, o/o)
2. Phase separation technique (non solvent addition and solvent partitioning)
3. Interfacial polymerization
4. Spray drying
5. Hot melt microencapsulation
6. Solvent / Emulsion extraction process
7. Fluidized bed coating

1) Emulsions solvent evaporation

Single Emulsion Process

(a) Oil in water

This process involves oil-in-water emulsification (o/w). This type of emulsion consists of an organic phase comprised of a volatile solvent having dissolved polymer and the drug which is encapsulated, emulsified in an aqueous phase. A surfactant is also used in the aqueous phase to prevent the organic droplets from merging once they are formed. Surfactants are used to stabilize the dispersed phase droplets. The polymer-solvent drug solution is emulsified to produce an o/w emulsion. Propeller or magnetic bars are used for mixing of organic and aqueous phases. Surfactants are amphipathic in nature. They align themselves at the droplet surface with a property of promoting stability by lowering the free energy at the interface between the two phases. The surfactants are included in aqueous phase so as to provide resistance to coalescence and microsphere flocculation. The mostly widely used surfactants for producing the micro particles are PVA [12].

(b) Oil-in-Oil or Water-in-Oil

Oil-in-oil emulsification process was for the encapsulation of highly water soluble drugs. In this system, polymer and drug are contained in a polar solvent which are emulsified into lipophilic phase (with light mineral oil) in the presence of an oil-soluble surfactant like Span. An important drawback of using oil as external phase is cleaning up the final product. The oil is needed to be removed using organic solvents. Some drugs which can be encapsulated by this technique are Diphenhydramine hydrochloride, mitomycin C, Adriamycin, phenobarbitone etc. [13]

In this process, the solubility of the encapsulating polymer is decreased by adding third component to the polymer solution which gives two liquid phases (coacervate phase and the supernatant phase) depleted in polymer. The drug which is to be dispersed or dissolved in the polymer solution is coated by coacervate. The coacervation process includes three steps.

1. Phase separation of coating polymer solution is done,
2. Then adsorption of the Coacervate is done around the drug particles,
3. Finally solidification of the micro particles is done [14].

First of all, polymer is dissolved in an organic solution. Then water- soluble drugs are dissolved in water and are dispersed in the polymer solution (w/o emulsion). Hydrophobic drugs can either be solubilise or dispersed in the polymer solution [15]. Then an organic non- solvent is added to the polymer-drug-solvent system with continuous stirring, which leads to extraction of the polymer solvent. As a result, the phase separation of polymer is done which yields in formation of

soft coacervate droplets in which drug is entrapped. Then the system is transferred to a large quantity of another organic non-solvent, to harden the micro droplets and form the final micro particles which can be collected by washing, sieving, filtration, and centrifugation and then finally dried [16].

2) Interfacial polymerization

In this technique, there is reaction of various monomers between the two immiscible liquid phases which forms a film of polymer in which dispersed phase is enveloped. In interfacial polymerization technique, two monomers (oil-soluble and water-soluble) are used and a polymer is formed on the droplet surface. This method involves the reaction of various monomer units located at the interface existing between core material substance and a continuous phase in which the core material is dispersed [17].

3) Spray drying

Spray drying is used to protect any substances, which is sensitive, from oxidation. It is based on atomization of a solution by compressed air and drying by a current of warm air. In this technique, micro particles are prepared by dispersing core material in a coating solution, in coating solution, coating substance must be dissolved and the core material is insoluble. Then atomise the mixture into an airstream. Due to hot air, solvent is removed from the coating solution thus forms micro particles [18].

4) Hot Melt Microencapsulation

In this technique, the polymer is first melted and then acid (solid drug or liquid drug) are mixed. This mixture is then suspended in an immiscible solvent and then heated to the temperature which is above the melting point of the polymer (50°C) with continuous stirring. Then the emulsion is cooled below the melting point to found solid droplets [19].

5) Solvent / Emulsion extraction process

This method is used for the preparation of micro particles, involves removal of the organic phase by extraction of the organic solvent. The method involves water miscible organic solvents e.g. isopropanol. The organic phase is removed by extraction using water as solvent. This process results in decreasing the hardening time of the microspheres. The preparation of micro particles involves dissolving of polymer in solvent. The solution is then emulsified in a vegetable oil and then amphiphilic agent was added into the emulsion which helps in extraction of solvent and hence micro particles are formed [20].

This technique involves three consecutive steps as follows

a. Melting (for placebo micro particles)
b. Drug (for drug loaded micro particles), and pre grinding
c. Jet milling step for the reduction of the particle size and smoothening of the micro particle surface [21].

Step 1-Melting

In case of drug loaded micro particles, melting of polymer and dispersion/dissolving of drug was done in a beaker on a hot plate. The temperature is dependent on the physicochemical nature of polymer and drug. Temperature was adjusted slightly higher than the melting point of the polymer to be used. A low viscous solution/suspension is to be obtained which is then transferred into another beaker so that on cooling it became congeal [22].

Step2-Pregrinding

In this step, pre grinding is done using a rotor speed mill at 18 000 rpm.

In a second step a breaker plate of 500 m is placed around the rotor [23].

Step 3-Jet Milling

The micro particles are formed in a Jet Mill. The nitrogen 5.0 is used for this technique. It is a process of size reduction [24].

7) Fluidized Bed Coating (Air Suspension Technique)

Three commonly used fluid-bed process are top, tangential and bottom spray methods. Usually granules have a porous surface and an interstitial void space, therefore, the bulk density of granules produced is usually low. In tangential-spray coating method, combination of centrifugal, high-density mixing and efficiency of fluid bed drying, gives a product having high bulk density but it still have some interstitial void space. It produce particle which are less friable and more spherical in shape. In bottom spray method, the solid core particles are fluidized by air pressure and a solution is sprayed from the bottom of the fluidization chamber (which is parallel to the air stream to the particles [25].

The spraying nozzle is in the air and sprays the coating materials into the fluidized particles. As the coating solution droplets travel only a short distance before contacting the solid particles, it results in more evenly film. The coated particles are then raised on the air stream, which dries the coating of particles. The particles lifted on the air stream are then settled down, and then another cycle begins [26].

Evaluation of microspheres [27, 28]

- **Particle Size and shape:** The most widely used procedures to visualize micro particles are conventional light microscopy (LM) and scanning electron microscopy (SEM).
- **Electron spectroscopy for chemical analysis:** The surface chemistry of the microspheres can be determined using electron spectroscopy for chemical analysis (ESCA).
- **Density determination:** The density of the microspheres can be measured by using a multi-volume pycnometer.
- **Isoelectric point:** The micro electrophoresis is used to measure the electrophoretic mobility of microspheres from which the isoelectric point can be determined.
- **The angle of contact:** The angle of contact is measured to determine the wetting property of a micro particulate carrier.
- ***In vitro* methods:** Release studies for different types of microspheres are carried out by using different suitable dissolution media, mostly by rotating paddle apparatus (USP /BP).
- **Drug entrapment efficiency:** Drug entrapment efficiency can be calculated using the following equation, % Entrapment = Actual content/Theoretical content x 100.
- **Swelling index:** The swelling index of the microsphere was calculated by using the formula, Swelling index= (mass of swollen microspheres – a mass of dry microspheres/mass of dried microspheres) 100.

Conclusion

The present review article shows that microspheres are better choice of drug delivery system than many other types of drug delivery system. With rising new technologies, an important growth has been made in producing a truly stable approach for targeting drug delivery or sustained release drug delivery. In future by combining various other strategies, microspheres will find the central and significant place in novel drug delivery. The progression of micro particles drug delivery has attained growing attention among formulation scientist on current years. As discussed above, micro particles drug delivery system offers great therapeutic effect to patients in term of effectiveness, patient compliance and safety. To ensure equilibrium between target specificity, price, effectiveness and patient compliance, it arrives that combination of conventional and novel drug approaches, is the key to the development of controlled drug delivery system. It helps in improving bioavailability of drug and also in controlled release of drugs.

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