A BRIEF REVIEW OF MICROPARTICLE DRUG DELIVERY SYSTEM

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ABSTRACT

Microparticles are recently being focused as novel drug delivery systems, especially for suitability for their wider field of application. The particles range from one micron to few mm. Micro particles are mainly used for the protection of drug from degradation and for local and control drug delivery systems. These microparticles are 2 types’ microreservoir and micromatrix. The main drawback of this system is dose-dumping of drug occurs in device. Different types of methods are used for the preparation of microparticles like solvent extraction, double emulsion, water-in-oil systems, phase separation and chemically and therapeutic methods like hot melt techniques. While preparing the device the selection of polymer and suitability of therapeutic agents are also to be considered. Microparticulate drug delivery dosage form are having a wide range of applications such as a drug carries in vaccine delivery, oral drug delivery, chemotherapy, drug targeting to organs, vaccines, ocular drug delivery, enhancement of bioavailability and Transdermal drug delivery systems.

KEYWORDS: Microparticles, Microspheres, Solvent extraction, Phase separation.

INTRODUCTION

Microparticles are a type of drug delivery systems where the particle size ranges from one micron to few mm generally them ranges form 1-200µm.[1] microparticles are a method of delivering macromolecules by a variety of routes and effectively control the release of drugs. They may also be used in the delivery of vaccines and molecules such as DNA for use in gene therapy. Microparticles have been an ideal way of preparing sustained and controlled release dosage forms. These provide a constant drug concentration in the blood or to target drugs to specific cells or organs.[2]
Microparticles are offers protection of the microparticle drug agent against degradation and posse’s local and control delivery of the drug.\(^3\) Drug is gradually released on erosion and diffusion from the particles. Microparticles are generally injected either intra peritoneal, intramuscularly or directly into the target organ.\(^4\)

Microparticles can be manufactured from various natural and synthetic materials. The release rate may be increased by decreasing the molecular weight of the polymer, particle size and also by controlling the nature of the polymer. In the preparation of microparticles polymers such are natural polymers like dextran and albumin synthetic polymers like HPMA and poly (L-glutamic acid) are often used as drug carries.\(^5\)

These are mainly of two types’ i.e microparticles and microspheres. The microparticles can be embedded within a polymer or proteinic matrix network in either as solid aggregated state or a molecular dispersion thus will produce microspheres. Polyethylene and polystyrene microspheres are two mainly used polymers for microspheres.\(^6\) Microcapsules are containing core material is completely surrounded by a polymer shell. The shell is continuous, porous and sometimes non porous polymeric type.\(^1\)

**Advantages of microparticulate drug delivery systems**

1. Effective delivery of agents which are insoluble or sparingly soluble in water.
2. Microparticles increase the relative bioavailability of drugs.
3. They provide the sustained release formulation with lower dose of drug to maintain plasma concentration and improved patient compliance.
4. They provide protection against local side effect i.e gastrointestinal irritation of drugs on oral administration.
5. The pH trigged microparticles are used in immunization transition and gene therapy.
6. Targeted release for encapsulated material.
7. Taste and odor masking of some nauseating drugs.
8. Parenteral microparticles have the advantage of administering high concentration of water soluble drugs without severe osmotic effects at the site of administration.
9. They reduce the dosage frequency and toxicity of numerous drugs.
10. They are useful in administrating of effervescent dosage form of medicament to individual who are having difficulty in swollen of larger particles.\(^7, 8\)
Disadvantages
1. In microparticle drug delivery systems dose dumping occurs.
2. Slow absorption may delay the onset of activity.

Polymers used in microparticle drug delivery systems
For preparation of microparticles using biodegradable polymers, it is important to choose a system that meets the following requirements:
- The process of manufacture should be continuous and avoid harsh environment.
- Encapsulating and yield of microparticles should be high for scale-up.
- The process should be free flowing microparticles so that it is easy to prepare a uniform suspension of microparticles.\(^9\)

Polymer used for preparation of microparticles is either synthetic or natural polymers. The amount of polymer various from 3% to 30% from the total weight, which correspond to a dry film thickness is 1-100\(\mu\)m.

Natural polymers like starch, amylopectin, amylodextrin, gelatin etc. Which act as a hydrophilic colloids.

Synthetic hydrophilic colloids include poly acrylic acid, poly acryl methacrylate, poly (lactic acid), waxes, cellulose derivatives, cellulose acetate phthalate, hydroxy ethyl cellulose, hydroxy propyl methyl cellulose, polyvinyl alcohol, polyvinyl pyrrolidone and shellac.\(^2\)

METHODS OF PREPARATION
The preparation methods for microparticles are varied but most are based on solvent evaporation or extraction technique. The methods involve dissolving the polymer in an appropriate organic solvent and suspending this solution in an aqueous continuous phase that contains an appropriate surfactant. Continuous stirring then allows for evaporation of the organic solvent and Harding of microparticles. The key factors in the size as well as the size distribution of these particles are the polymer concentration in the solvent. The amount and type of surfactant and stirring rate is an important factor in this method.

The solvent evaporation method is most appropriate for incorporating drugs that are soluble in the organic solvents. In this case, the drug and polymer are dissolved together in the
organic solvent and molecular mixture of polymer and drug will exist in the resulting microparticles.

These solvents used with these techniques include dichloromethane, acetone, methanol, ethyl acetate, acetonitrile, chloroform and carbon tetrachloride. Polymer concentration of 125-110 mg/mL will usually yield microparticles in the size of 10-150µm.

Variations on this basic solvent evaporation technique includes
a) Solvent extraction
b) Double emulsion
c) Oil-in-oil system
d) Phase separation or coaservation.\(^\text{[10]}\)

**Solvent extraction method**
This method has been primarily used to encapsulate hydrophobic drugs through oil in water [o/w] emulsification process. The polymer is dissolved in a water – immiscible /volatile organic solvent the resulting mixture is emulsified in a large volume of water in the presence of an emulsifier the solvent in the emulsion is removed by either evaporation at elevated temperature or extraction in a large amount of water resulting in formation of compact microparticles. Process is shown in Fig.1.

**Double emulsion method**
Most water soluble drugs have been encapsulated by water in oil in water (W/O/W) method. The aqueous solution of water soluble drug is added to the polymer dissolved oily solution to
form primary emulsion i.e w/o emulsion, emulsification is done by using high speed homogenizers. The primary emulsion is added to the excess amount of water containing emulsifier with continuous stirring resultant solution is known as w/o/w emulsion. Then the solvent is removed by either evaporation or extraction process.\(^{[11]}\)

**Water-in-oil emulsification**

It is also called as solvent evaporation or water in oil system. It is mainly employed for highly water soluble drugs. In this method polymer and drug contained in a polar solvent such as acentonitrile are emulsified into oil in presence of surfactant such as spans. In this method the main demerit is using an oil external phase is cleaning up the final product. It can be removed by using n-Hexane timolol maleate, Adriamycin, diphenyl hydramine are the drugs that are prepared by this method.\(^{[2]}\)

**Phase separation or co-acervation method**

In this method, the drug is dissolved or dispersed in a polymer solution, organic solvents like liquid paraffin, vegetable oil, silicon oil is added to this mixture while it is stirred continuously. Next the polymer solvent is gradually extracted and soft coacervate droplets containing drug is coated. Exposing these droplets into an excess amount of another non solvent like hexane, heptanes are harden the coacervate phase. The process parameters that control the release of drug from these microparticles include the rate of non solvent addition to extract the polymer solvent and the viscosity non solvent along with formulation parameters.\(^{[9]}\)

Other techniques may include.

**Spray drying process**

Compare to other methods spray drying offers several advantages. It is rapid, convenient, easy to scale up, involves mild conditions and it is less dependent on the solubility parameters of the drug and the polymer.\(^{[12]}\)

The drug is dissolved or suspended in a suitable solvent containing polymer material. The solution or suspension is atomized into a drying chamber and microparticles from as the atomized droplets are dried by heated carrier gas. The results of this process heavily dependent on the material properties. The process is shown in Fig.2
Significant advantage of this method includes high encapsulation efficiencies and no residual surfactant on the surface of the microparticles. Parameters that affect the microparticle size and morphology are temperature, pressure, nozzle diameters, volume of mixture, polymer or drug concentration. Spray drying technique produce particle having size of 10µm.

![Spray drying process of microparticles](Fig 2)

*Fluidized bed coating*

This method is used for encapsulating of solids core materials including liquids that are absorbed into porous solid. Particles of the drug are to be covered by a spray of liquid polymeric material. The capsules are then solidified by cooling, or solvent evaporation. The process is repeated until particles having desired thickness.

*Chemical and thermal method*

From the natural polymers microparticles are prepared by a cross-linking process. Natural polymers like gelatin, starch, albumin and dextrin. Drug is incorporated into the solution of polymer act as a water phase thus a formation of W/O emulsion, where the oil phase is suitable vegetable oil or oil organic solvent mixture containing an oil- soluble emulsifier. Then water soluble polymer is solidified by some kind of cross-linking process. It involves the addition of a chemical cross linking agent such as glutaldehyde to form a stable chemical cross link such as in albumin, gelatin or dextrin.

*Hot melt technique*

It involves dispersion of polymer in a suitable vehicle and slowly cooled to form the microparticle.
Other techniques

Other techniques for preparation of microparticles include melt solidification, polymer precipitation, co-extrusion, layer-by-layer deposition, supercritical fluid expansion and spinning disk methods.

APPLICATIONS

Microparticles in vaccines delivery

Poly (ethylene glycol) - dextran (PEG-DEG) conjugates have been used as a combined stabilizer and surface modifier to produce resorbable poly (DL-lactide-co-glycolide) microparticles by an emulsification or solvent evaporation technique. This approach offers opportunities for attaching hydrophilic species such as targeting moiety to biodegradable microparticles to improve the interaction of vaccines with the specific tissue sites.\textsuperscript{[14]} Sean M. Geary et al (2015) studied the characteristics and immunostimulatory capacity, \textit{in vivo} of antigen and adjuvant co-loaded into microparticles made form a novel diaminosulfide polymer, poly (4, 4-trimethylene di piperdyl sulfide) (PNSN) and to assess their potential as cancer vaccine vectors. PNSN microparticles co loaded with the antigen, ovalbumin (OVA) and adjuvant, CpG1826, (PNSN(OVA+CpG)) were fabricated and characterized it was shown that of all vaccination formulations tested PNSN(OVA+CpG) was the most protective against subsequent challenge with an OVA-expressing tumor cell line, E.G7. Thus, microparticles made from poly(diaminosulfide) based macromolecules possess promising potential as vaccine vectors and may have impact as cancer vaccines in particular.\textsuperscript{[20]}

Antigens such as staphylococcus enterotoxin B, diphtheria toxoid, hepatitis surface antigen and tetanus toxoid are formulated into microspheres by using thermoplastic polyesters of PLA and (glycolic acid) and their copolymers poly(lactides coglycolides).\textsuperscript{[22]}

In Oral drug delivery

Orally administered drugs generally depend on its solubility and absorption. These drugs which exhibits poor aqueous solubility and low bioavailability microsizing of such drugs leads to increase the oral absorption and bioavailability. Microparticles are having in achieving quick onset of action for drugs that are completely but slowly absorbs.\textsuperscript{[15]} Hai-feng Cheng et al (2015) done a research on floating microparticulate oral diltiazem drug delivery system, microparticles were prepared by using cellulose acetate and Eudragit R5100. Drug release from the microparticulate was found to be 77.62 ± 2.12 to 97.50 ± 1.04 at the end of
12 hr. the research conclude that microparticulate floating oral drug delivery system of diltiazem may be an effective alternative to conventional oral tablets for cardiac delivery.[18]

**Ocular drug delivery systems**
Polymer shows favorable biological behavior such as bioadhesion, permeability-enhancing properties and interesting physico-chemical characteristics, which makes it single materials for the design of ocular drug delivery vehicle. Due to the elastic properties of polymer, polymer hydrogels offers better acceptance with solid or semi solid i.e ointments and suspensions. It contrast, polymer based colloidal conjunctival epithelia or corneal epithelia, via facilitating the transport of drugs to the inner eye.[16] Microspheres show promising drug carriers for ophthalmic applications. The ocular bioavailability of a number of drugs is significantly enhanced in comparison to normal aqueous eye drop solutions. Generally, smaller particles are better tolerated by the patients than larger particles. For this reason especially microspheres may be preferred for long acting ocular drug delivery systems, although larger microparticles showed elimination kinetics from the precorneal compartment.[19]

**Transdermal drug delivery system**
If polymer has good film forming properties the drug release from the device affected by the membrane thickness and cross linking of the film. For treatment of local inflammation drugs like prednisolone are prepared as microparticles which show more drug release and therapeutic efficacy. A study conducted by Dr. Tarl Prow and Dr. Anthony Raphael, they a method of improving the delivery of topical treatments by combining them with elongated microparticles (EMPs). The EMP was free particles that can be massaged into the skin and work by piercing through the outer skin layer, allowing topical treatment passage to the deeper layer. Clinical studied that EMPs formulated with the fluorescent dye, fluorescein can increase dermal drug delivery by more than three times and acute no adverse reactions.[23]

**Microparticles in Cancer therapy**
Cancer microsphere technology is the more useful in now a day. Cancer is the diseases in which a malignant growth or tumor resulting from an uncontrolled division of cells. Anticancer drugs having a major drawback of their selectivity for tumor tissues alone, which severe side effects and low cure rates. By conventional method of drug delivery is fail to target only abnormal cells. Microsphere technology is probably the only method that can be used for site specific actions, without any significant side effects on normal cells.[24]
A microsphere based system has been developed to deliver therapeutic agents to brain tumors. The polymethylidene-malonate polymer is used to prepare 5-fluorouracil-loaded sustained release biodegradable microspheres for treatment of malignant brain tumors. The polymer slowly degraded and results in long term local delivery of drug i.e 5-fluorouracil.\[^{[4]}\]

**Enhance bioavailability**

Microparticles increase the bioavailability of poorly soluble drugs. Several research studies that drug in the form microparticulate shows the good results than that of drug alone. Zhang et al. (2015) described the use of carboxylated mesoporous carbon microparticles (cMCMs) to increase the oral bioavailability of carvediol, a poorly water soluble beta blocker. The microparticles were prepared by adsorption and solvent evaporation technique. The study concluded that the use of the cMCMs can enhance the bioavailability of carvedilo by 179.3%. Khonsari et al. prepared gastric Mucoadhesive disk microparticles of metformin by emulsification solvent evaporation using different ratios of carbomer 934P and ethyl cellulose. Drug release was observed 82.22% at 8 hours. It conforms that the use of microparticles as a drug delivery system to enhance oral bioavailability of drug molecules.\[^{[21,24]}\]

**Other applications**

- Air filled microparticles are used in echocardiography and other ultrasonic imaging technique. They are also used in cosmetics as opacifiers.
- Solid microspheres are of particles used in nasal delivery of drugs including peptides, proteins like insulin, stomatostatin, metoloproteins etc.
- pH triggered microparticles have been used to deliver drugs by various means by IV injection, intra dermal injection, orally, mucosal delivery systems.\[^{[2]}\]
- Imaging: various cells, cell lines, tissues and organs can be imaged using radiolabeled microspheres. Labeled human serum albumin microspheres can be used for scintigraphic imaging of the tumor masses in lungs.
- Magnetic microspheres: Magnetic monitoring has the advantage of being efficient in allowing high local concentration of therapeutic agents. For instance, amphoteresin B magnetic microspheres are used in the treatment of pulmonary aspergillosis. Interleukin-2 magnetic microspheres are used to target the antiulcer tumor response of the macrophages.\[^{[22,26,27]}\]
CONCLUSION
The microparticles provide increase bioavailability, taste masking, improve stability, having good handling property, protections, controlled release of active ingredient. The methods of preparation of microparticles are taking short time with fewer steps. Microparticles are the best choice of drug carriers in various drug delivery systems. That’s why now days most of the companies focused on microparticle drug delivery system.

REFERENCES


