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MICROPARTICLES IN DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Microparticles offer various significant advantages as drug delivery systems, including:(i) an effective protection of the encapsulated active agent against (e.g. enzymatic) degradation, (ii) the possibility to accurately control the release rate of the incorporated drug over periods of hours to months, and(iii) an easy administration (compared to alternative parenteral controlled release dosage forms, such as macro-sized implants). Desired, pre-programmed drug release profiles can be provided which match the therapeutic needs of the patient. This article gives an overview on the most important past, current and future strategies using drug-loaded microparticles to improve the efficiency of various medical treatments. Special emphasis laid on the different types of preparation techniques that are commonly used, the physicochemical properties of the devices and practical examples illustrating the considerable benefits of this type of advanced drug delivery systems. But also the major challenges and obstacles to be overcome during the development and production of these pharmaceutical dosage forms are pointed out.

INTRODUCTION

Microparticles are particles between 0.1 and 100 μm in size. Commercially available microparticles are available in a wide variety of materials, including ceramics, glass, polymers, and metals. Microparticles encountered in daily life include pollen, sand, dust, flour, and powdered sugar.[1]

Microparticles have a much larger surface-to-volume ratio than at the macroscale, and thus their behavior can be quite different. For example, metal microparticles can be explosive in air. Microspheres are spherical microparticles, and are used where consistent and predictable particle surface area is important.

Microparticulate drug delivery system is one of the processes to provide the sustained & controlled delivery of drug to long periods of time. They are small particles of solids or small droplets of liquids surrounded by walls of natural & synthetic polymer films of varying thickness & degree of permeability acting as a release rate controlling substance.[2]

Microparticles are small [0.2-5um], loded microspheres of natural or synthetic polymers. Microparticles were initially developed as carriers for vaccines and anticancer drug. [1]

ADVANTAGES OF MICROPARTICLES [3]

Recently, controlled release has become a very useful tool in pharmaceutical area, offering a wide range of actual and perceived advantages to the chronic diseases such as rheumatoid arthritis, osteoarthritis, and musculoskeletal disorders including degenerative joint conditions still demand long-term therapy. With the advent of microparticles following advantages were noted in the dosage forms-

1. Effective delivery of agents which re insoluble or sparingly soluble in water.
2. They give the products which exhibit immediate release properties & can give 80% or more of active agent in about 10 minutes or less. Ex. Nimesulide
3. The technique provides the way for improving taste of an active agent.
4. They increased the relative bioavailability of drugs.
5. The formulation of microparticles also provides the method of targeting the drug delivery to specific sites.

6. The microparticles hold great potential in reducing the dosage frequency & toxicity of various drugs.
7. Microparticles in the form of microcapsules can also be used as carrier for drugs & vaccines as diagnostic agents & in surgical procedures.
8. They can also be used to produce amorphous drugs with desirable physical properties.
9. They also caused the reduction of the local side effects ex. GI irritation etc of drugs on oral ingestion.
10. They provide the sustained release formulation with lower dose of drug to maintain plasma concentration & improved patient compliance.
11. The PH triggered microparticles are used in immunization, transfection & gene therapy.
12. Parenteral microparticles have the advantage of administering high concentration of water soluble drugs without severe osmotic effects at the site of administration.
13. They also have an advantage of being stored in dry particle or suspension form with little or no loss of activity over an extended storage period.
14. They are useful in administration of effervescent dosage form of medicaments to individual unable to chew. Ex. Debilitated patients having difficulty in swallowing solids &the elderly.
15. In contrast, smaller microparticles need to be prepared for application to other sites such as the eye, lung, and joints .[5]

PREPARATION OF MICROPARTICLES[3]:

There are innumerable methods for preparing microparticles for use in applications as diverse as carbonless paper to ion exchange resins to cosmetics to drug delivery. Here, we will concentrate on the materials, biodegradable and non biodegradable, which have been studied for drug delivery specifically for cancer treatment. An overwhelming majority of methods used for encapsulating drugs in a submillimeter spherical polymer matrix involve the use of liquid emulsions. A simple definition of an emulsion as applied to liquids is the dispersion and stabilization of one liquid within another to which it is immiscible. The most common emulsion type is oil-in-water, however, oil-in-oil and multiple emulsions (water-oil-water, oil-oil-water, solid-oil-water, and so on) are used

frequently (1–14). There are numerous materials available for creating these emulsions and we discuss a few specific examples here. The main criterion for creating an emulsion is that the dispersed phase (solution con-taining polymer and drug) must be immiscible (or nearly so) in the continuous phase (external phase containing dissolved surfactant).[6]

PREPARATION OF BIODEGRADABLE MICROPARTICLES:

1. Poly(lactic-co-glycolic Acid)[5,6]
2. Albumin-Containing Microparticles [6]
3. Fibrinogen Microparticles[6]

POLYMERS AND OTHER SUBSTANCES USED IN MICROPARTICLE PREPARATION:

Wall Materials-

The coating material can be selected from a wide variety of natural and synthetic polymers depending on the core material to be encapsulated and the desired characteristics. The amount of coating material used ranges from 3% to 30% of the total weight, which corresponds to a dry film thickness of less than 1–200 μm, depending on the surface to be coated.[3]

1. Natural or synthetic hydrophilic colloids:

Agar acrylicpolymers, polyacrylic acid, poly acrylmethacrylate, gelatin, poly(lactic acid),pectin(poly glycolic acid), waxes(poly hydroxyl butyrate-co-valerate), cellulose derivatives, cellulose acetate phthalate, Nitrate, Ethyl cellulose, Hydroxy ethyl cellulose, Hydroxypropylcellulose, Hydroxy propyl methyl cellulose, Hydroxy propyl methyl cellulose phthalate, Methyl cellulose, Sodium carboxymethylcellulose, Poly(ortho esters),Polyurethanes, Poly(ethylene glycol), Poly(ethylene vinyl acetate), Polydimethylsiloxane, Poly(vinyl acetate phthalate),. Soluble starch & its derivatives including Amylodextrin, Amylopectin, Carboxy methyl starch.[3]

2. **Biocompatible polymer:**

Poly (lactic) acid (PLA), poly (glycolic acid) (PLGA), Albumin Chitin Starch, Collagen Chitosan Dextrin, Gelatin, Hyaluronic acid, Dextran, Fibrinogen, Alginic acid ,Casein, Fibrin, Poly(ortho esters). Polyalkylcyanoacrylate, Polyanhydrides.

Table : A list of Polymers

Coating material	Solvent for coating material	Phasing out solvent (non-solvent)
Acrylonitrite styrene	Methyl ethyl ketone	Polybutadiene
Benzyl cellulose	Trichloroethylene	Propanol
Cellulose nitrate	Methyl ethyl ketone	Polybutadiene
Ethyl cellulose	Methyl ethyl ketone	Polydimethylsiloxane
Polyethylene	Xylene	Ethanol
Polystyrene	Xylene	Petroleum ether
Polyvinyl acetate	Chloroform	Isopropanol
Styrene maleic acid	Ethanol	Isopropyl ether

TECHNIQUES OF MICROPARTICLE PREPERATION[(9)]:

When preparing controlled release microspheres, the choice of the optimal method has utmost importance for the efficient entrapment of the active substance. Various pharmaceutically acceptable techniques for the preparation of microparticles have been given. Some of the methods include:

1. Emulsion–solvent evaporation (o/w, w/o, w/o/w).
2. Phase separation (nonsolvent addition and solvent partitioning).
3. Interfacial polymerization.
4. Spray drying.
5. Beaker method
6. Jet milling technique.

Methods:

1. Emulsion-solvent evaporation
   - A. Single-Emulsion Solvent Evaporation:
     - a). O/W Emulsion Solvent Evaporation Technique
     - b)Oil-in-Oil Emulsification–Solvent Evaporation Technique
   - B. Multiple-Emulsion Technique (w/o/w)
2. Coacervation/Phase Separation

A. Simple Coacervation
B. Complex Coacervation

3) Interfacial Polymerization Method

4) Spray drying

MATERIALS AND METHODS [11]

Materials

The PLG polymers were obtained from Boehringer Ingelheim. The PLG polymer used in this study was RG505, which has a copolymer ratio of 50/50 and a molecular mass of 65 kDa (manufacturer's data). The HIV-1 pCMVkm p55 gag plasmid was obtained by transforming *Escherichia coli* strain HB101 with the plasmid and fermenting under defined growth conditions. The plasmids were purified by using a proprietary Chiron process. The final product was endotoxin free (<2.5 units/ml). The pLUC plasmid was also similarly purified. All other chemicals and reagents were obtained from Sigma and used as shipped. ELISA microtiter plates were obtained from Nunc. [4]

The Preparation of Microparticles:

Cationic microparticles were prepared by using a modified solvent evaporation process. Briefly, the microparticles were prepared by emulsifying 10 ml of a 5% (wt/vol) polymer solution in methylene chloride with 1 ml of PBS at high speed using an Ika homogenizer (Ika-Werk Instruments, Cincinnati). The primary emulsion then was added to 50 ml of distilled water containing cetyltrimethylammonium bromide (CTAB) (0.5% wt/vol). The microparticles then were separated by centrifugation, the pellet was washed with Tris-EDTA buffer, and the microparticles were freeze-dried.[4]

Microparticle Characterization:

Size distribution of the microparticles is determined by using particle size analyzer (Malvern Instruments, U.K.) and the value was calculated by volume measurement.[4]

Plasmid Stability Evaluation:

Ten milligrams of PLG/CTAB-p55 DNA microparticles [0.85% (wt/wt) loading level] was incubated with 1 ml of PBS at 37°C. At each time point (days 1, 3, 7, and 14) the suspension was centrifuged and the supernatant was collected. One milliliter of PBS was added to the vial and the pellet was resuspended. The released DNA in the supernatants was run on a 1% agarose gel to evaluate plasmid integrity.

ENCAPSULATION AND *IN VITRO* RELEASE [12]

Hydrophilic Drugs:

Hydrophillic cellulose polymers are commonly used as the exipient base in tablet matrix system. The drug substance is combined and made into granuls with an excipient material that slowly erodes in body fluid. [6, 7]

Hydrophobic Drugs:

Hydrophobic drugs oft en present less of a challenge to formulate in slowly degrad-able microparticle systems, relative to hydrophilic drugs, as they are often soluble inthe organic solvents used, but are insoluble in water. Some hydrophobic anticancer agents that have been encapsulated in biodegradable microparticles include taxol, acla-cinomycin, and camptothecin (water-insoluble forms).[6]

EVALUATION OF MICROPARTICLES [14]

The various evaluation techniques for microparticlepreparation are as follows:

1. Particle shape & size determination:

It can be done by microscopy, sieve analysis, laser light scattering, coulter counter method, photon correlation spectroscopy.

- Crystallinity can be evaluated by differential scanning calorimetery analysis.
- Shape & surface morphology can be studied by freeze fracture microscopy & freezes etch electron microscopy.
- Laser diffractometer is also used to measure the size range of the microparticles.

2. Bulk & tap density:

Bulk & tap density of microparticles is also evaluated. Porosity, specific area can also be evaluated by Mercury or Helium intrusion potensiometry. Flow properties of microparticles can be evaluated by determining the angle of repose by fixed funnel & free standing cone method& the compressibility index by tapped density method.

3. The Thermal Properties:

These are detected by Differential Scanning Calorimetry, Thermo gravimetric analysis.

4. Thermogravimetric analysis or **thermal gravimetric Analysis;**

(TGA) is a type of testing that is performed on samples to determine changes in weight in relation to change in temperature.

4. Electrostatic interaction:

Which is detected by rheological& FTIR assays (Fourier Transform Infra-red spectroscopy) using potassium bromide pellets.

5. Peptide entrapment & entrapment efficacy:

It can be evaluated by HPLC.

6. The Drug release studies:

It was evaluated by USPmethod II or dissolution test method using phosphate buffer PH 6.8 with the temperature of release medium at 37 ±0.5 & then assaying spectophotometrically. Release kineticsto model the dissolution profile from the microparticles system two different mathematical differential equation can be used i.e.,

(1) First order equation;

(2) Higuchi's square root of time equation.

(3) First order model can be expressed as $Mt / M\infty = 1 - e^{-k1}$

(4) Higuchi's square root of time model is given by Mt / M0 = kH t1/2

Where, Mt is the amount of drug released at time t,

M∞ is the maximal amount of drug released at infinite time,

k1 and kH are the rate constants for first order and Higuchi model, respectively. [3],[7].

APPLICATIONS OF MICROPARTICLES

1. Application areas of microcapsules include pharmaceutical and biotechnology products, cosmetics, diagnostic aids, biological filtration devices, veterinary and zoo technical products, foods and food additives, flavors, fragrances, detergents, paints, agricultural chemicals, adhesives, industrial chemicals, household products, packaging, textiles, photographic and graphic arts materials.
2. These microcapsules are important in providing sustained and controlled release, improving drug stability, reducing vaporization of volatile oils, protecting moisture/light/oxidation–sensitive drugs, masking unpleasant taste and odor, converting liquids to powders,separating incompatible substances in a single system.
3. Amoxicillin, ampicillin, bacampicillin, cephalexin, cephradine, chloramphenicol, clarithromycin, eryithromycin, potassium pheneticillin, ofloxacin, and ciprofloxacin are some examples of the encapsulated antibiotics.

4. Anti-inflammatory drugs are another group in which microencapsulation is employed. Diclofenac sodium, flufenamic acid, glaphenine, hydrocortisone, ibuprofen, indomethacin, naproxen, oxyphenbutasone, and prednisone are examples of encapsulated drugs in this group.
5. Sulfadiazine, sulfamethizole, sulfamethoxazole, sulfamerazine, andsulfisoxazole are some representatives of sulfa drugs that are encapsulated.
6. Furosemide, chlorothiazide, and sulfonamide were encapsulated in order to prepare sustained release formulations that would offer the advantage of avoiding short periods of peak diuresis observed with the conventional formulations.
7. Isosorbide-5-mononitrate (IS-5-MN), dihydralazine sulfate, piretanide and propranolol HCl, captopril, nicardipin, and dipyridamole are examples of microencapsulated antihypertensives. Microcapsules were optimized to sustain the action and to overcome the tolerance developed in conventional preparations.
8. Vitamins A, B1, B2, B6, B12, C, D, were encapsulated to provide formation of smooth- and thick-walled microcapsules largely prevented the aggregation of microcapsules and showed low dissolution rate.
9. Converting Liquids to Free-Flowing Powders Citrus essential oil, cod liver oil, benzaldehyde, carbon tetrachloride, and oil droplets were coated and recovered as fine powders. The bulk droplet size of the encapsulated material appeared to be a factor in the strong capsule wall, which protects against vaporization and oxidation.
10. Air filled micro particles are used in echocardiography & other ultrasonic imaging techniques. They are also used as opacifier or reflectivity enhancers in cosmetics.
11. Solid microspheres are of particulars used in nasal delivery of drugs including polypeptides, insulin, somatostatin, metolopromide etc.
12. PH triggered micro particles have been used to deliver drugs by various means ex-by inject, intra dermal injections, rectally, orally, intra vaginally, mucosal delivery etc.
13. They are also used for administering. An antigenic epitote of a pathogen or a tumor.
14. The micro particles are useful in transfiting cells & gene therapy.
15. Condensed phase micro particles are used as stable strong kit for enzymes, antibodies, dye.[3]

FUTURE DIRECTIONS

Because it is clear that there is a great deal of potential for the use of microparticulate drug delivery formulations to treat cancer, only a few of these formulations have progressed enough in human studies to have proven their worth both in enhancing the efficacy of the drugs being delivered and in minimizing the undesirable side effects of traditional chemotherapy. Within the next 5–10 yr, we should certainly see some of the formulations currently in laboratories progress to the clinical setting and perhaps to a large number of cancer patients whose lives will be improved by using these advanced formulations. It should be emphasized that microparticulate formulations that provide controlled delivery can provide more than just a better-regulated chemotherapy regi-men. They may also deliver cell-specific drugs, based on biotechnology and DNA, directly to the site of interest. This element of intelligent engineering is present to a smaller degree in liposomal formulations but, especially in biodegradable particles, its promise has yet to be realized or even understood and in vivo distribution of fluorouracil following administration in poly (l-lactic acid) microspheres.

CONCLUSIONS

Microparticles can effectively be used as controlled drug delivery systems, allowing optimizing the resulting drug concentration-time-profiles at the sites of action in the human body and, thus, the therapeutic effects of the medical treatments. Furthermore, they can be directly injected into the target tissues. This reduces the drug concentrations in the other parts of the human body (and consequently the risk of undesired side effects) and permits to reach target tissues, which are normally not accessible for the drug (e.g., the Central Nervous System). Various process technologies can be used for the preparation of these advanced drug delivery systems and broad ranges of drug release patterns can be provided, matching the therapeutic needs of the patient. However, the development and production of drug-loaded microparticlesis not straightforward, because many physical and chemical processes can be involved in the control of drug release. Thus, great care has to be taken when identifying the optimal system design (composition and dimension) and preparation procedure.

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