REVIEW ARTICLE ON MICROPARTICLES

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ABSTRACT

Recent drug discovery using advanced techniques such as genomics, combinatorial chemistry, high throughput screening and in silico three dimensional drug design has yielded drug candidates with low water solubility and thus an inherently low mucosal permeability which makes the development of pharmaceutical formulations difficult. To overcome these, particulate systems like microparticles have been used as a physical approach to alter and improve the pharmacokinetic and pharmacodynamics properties of various types of drug molecules. They have been used in vivo to protect the drug entity in the systemic circulation, restrict access of the drug to the chosen sites and to deliver the drug at a controlled and sustained rate to the site of action. Various polymers have been used in the formulation of microparticles for drug delivery research to increase therapeutic benefit, while minimizing side effects. The review embraces various aspects of microparticle formulations, characterization, effect of their characteristics and their applications in delivery of drug molecules and therapeutic genes.

KEY WORDS: Microparticles, Absorption, Low solubility

INTRODUCTION

Microparticles are defined as particulate dispersions or solid particles with a size in the range of 1-1000 µm. The drug is dissolved, entrapped, encapsulated or attached to a microparticle matrix. Depending upon the method of preparation, microparticles, microspheres or microcapsules can be obtained. Microcapsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while microspheres are matrix systems in which the drug is physically and uniformly dispersed. In recent years, biodegradable polymeric microparticles, particularly those coated with hydrophilic polymer such as poly (ethylene glycol) (PEG) known as long-circulating particles, have been used as potential drug delivery devices because of their ability to circulate for a prolonged period time target a particular organ, as carriers of DNA in gene therapy, and their ability to deliver proteins, peptides and genes. Microparticles offers easy administration to deliver macromolecules by a variety of routes and effectively control the release of drugs over the periods ranging from few hours to months, because of effective protection of encapsulated drug against degradation (e.g. enzymatic). Controlled drug delivery systems could be extremely useful in providing the optimal therapy for a given drug molecule. Each drug has a characteristic ‘minimum effective concentration’, below which no therapeutic effect is observed and a characteristic ‘minimum toxic concentration’ above which undesired side effects occur. The range in
between is called the ‘therapeutic range’ or ‘therapeutic window’.

ADVANTAGES OF MICROPARTICLES
1. Particle size and surface characteristics of microparticles can be easily manipulated to achieve both passive and active drug targeting after parenteral administration.
2. They control and sustain release of the drug during the transportation and at the site of localization, altering organ distribution of the drug and subsequent clearance of the drug so as to achieve increase in drug therapeutic efficacy and reduction in side effects.
3. Controlled release and particle degradation characteristics can be readily modulated by the choice of matrix constituents. Drug loading is relatively high and drugs can be incorporated into the systems without any chemical reaction; this is an important factor for preserving the drug activity.
4. Site-specific targeting can be achieved by attaching targeting ligands to surface of particles or use of magnetic guidance.
5. The system can be used for various routes of administration including oral, nasal, parenteral, intraocular etc.

LIMITATIONS OF MICROPARTICLES
1. Their small size and large surface area can lead to particle aggregation, making physical handling of microparticles difficult in liquid and dry forms.
2. In addition, small particles size and large surface area readily result in limited drug loading and burst release.
3. These practical problems have to be overcome before microparticles can be used clinically or made commercially available.

PREPARATION OF MICROPARTICLES
SOLVENT EVAPORATION AND EXTRACTION BASED PROCESSES
SINGLE EMULSION PROCESS
The process involves oil-in-water (o/w) emulsification. The o/w emulsion system consists of an organic phase comprised of a volatile solvent with dissolved polymer and the drug to be encapsulated, emulsified in an aqueous phase containing a dissolved surfactant. A surfactant is included in the aqueous phase to prevent the organic droplets from coalescing once they are formed. The polymer-solvent-drug solution is emulsified (with appropriate stirring and temperature conditions) to yield an o/w emulsion. The emulsion is created by using a propeller or magnetic bar for mixing the organic and aqueous phases. Surfactants are used to stabilize the dispersed phase droplets formed during emulsification and inhibit coalescence. Surfactants are amphiphatic in nature and will align themselves at the droplet surface promoting stability by lowering the free energy at the interface between the two phases. The surfactant also confers resistance to coalescence and microsphere flocculation. PVA is one of the widely used surfactants for producing the microparticles.

DOUBLE EMULSION PROCESS
A double emulsion process is usually employed for drugs not soluble in an organic solvent. A solid-in-oil-in-water emulsion (s/o/w) process could be used to encapsulate a drug provided its form is of small size. The size of the drug crystal should be at least an order of magnitude smaller than the desired microparticle diameter in order to avoid large bursts associated with dissolution of larger crystals. Smaller crystals will be homogeneously distributed throughout the organic droplets created in emulsion. Hydrophilic drugs (cisplatin, doxorubicin) have been encapsulated using this method. The problem with encapsulating hydrophilic drugs is the loss of drug to the external aqueous phase during the formation of the microparticle. Along with the loss of drug to the external phase, the remaining drug may migrate to the surface of the droplet before solidifying. To minimize these problems, the organic droplets should be solidified into microparticles as quickly as possible following their formation. This is achieved by using a viscous organic solution of polymer and drug and a large secondary volume of water that attracts the organic solvent into the aqueous phase immediately, thus leaving the microparticle with the encapsulated drug. The viscous dispersed phase minimizes the volume of organic solvent, facilitating its quick removal from the droplet and also makes it more difficult for the solid drug particles/crystal to migrate to its surface, resulting in a more homogeneous distribution of the drug within the particle.

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PHASE SEPARATION
The process consists of decreasing the solubility of the encapsulating polymer by addition of a third component to the polymer solution. The process yields two liquid phases: the polymer containing coacervate phase and the supernatant phase depleted in polymer. The drug which is dispersed /dissolved in the polymer solution is coated by the coacervate. Thus the coacervation process consists of the following three steps:

i) Phase separation of the coating polymer solution,
ii) Adsorption of the coacervate around the drug particles, and

iii) Solidification of the microspheres.7

The polymer is first dissolved in an organic solution. The water-soluble drugs like peptides and proteins are dissolved in water and dispersed in the polymer solution (w/o emulsion). Hydrophobic drugs like steroids are either solubilized or dispersed in the polymer solution. An organic non-solvent is then added to the polymer-drug-solvent system with stirring, which gradually extracts the polymer solvent. As a result, the polymer is subjected to phase separation and it forms soft coacervate droplets that entrap the drug. The system is then transferred to a large quantity of another organic non-solvent to harden the microdroplets and form the final microspheres which are collected by washing, sieving, filtration, or centrifugation, and are finally dried.

SPRAY DRYING
Spray-drying is a widely used method in the pharmaceutical industry and has been investigated by several researchers as a method for formulating biodegradable microparticles. It is rapid, convenient, easy to scale-up, involves mild conditions, and is less dependent on the solubility parameters of the drug and the polymer. The method typically uses drug dissolved or suspended in a polymer solution (either organic or aqueous solvent, depending on the polymer used). The solution/suspension is then fed into the spray drying apparatus through the most important component is the nozzle and polymer/drug solution is mixed rapidly with air and forced through a small diameter orifice. Nebulization of the polymer/drug solution occurs at the nozzle 25 and the resultant droplets are very quickly dried by evaporation (under high-pressure air) before collection.8

FORMULATION CONSIDERATIONS FOR MICROPARTICLE PREPARATION
STABILIZER
Stabilizer plays an important role in the formulation of microparticles. In the absence of an appropriate stabilizer, the high surface energy of micro-sized particles can induce agglomeration or aggregation of the drug crystals. The main functions of a stabilizer are to wet the drug particles thoroughly, and to prevent Ostwald’s ripening and agglomeration of microparticles in order to yield a physically stable formulation by providing steric or ionic barrier. The type and amount of stabilizer has a pronounced effect on the physical stability and in-vivo behavior of microparticles. In some cases, a mixture of stabilizers is required to obtain stable microparticles. The drug-to-stabilizer ratio in the formulation may vary from 1:20 to 20:1 and should be investigated for a specific case.9 Stabilizers that have been explored so far include cellulosics, poloxamers, polysorbates, lecithins and povidones. Lecithin is the stabilizer of choice if one intends to develop a parenterally acceptable and autoclavable microparticles.

ORGANIC SOLVENTS
Organic solvents may be required in the formulation of microparticles if they are to be prepared using an emulsion or microemulsion as a template. As these techniques are still in their infancy, elaborate information on formulation considerations is not available. The acceptability of the organic solvents in the pharmaceutical arena, their toxicity potential and the ease of their removal from the formulation need to be considered when formulating microparticles using emulsions or microemulsion as templates. The pharmaceutically acceptable and less hazardous water-miscible solvents, such as ethanol and isopropanol, and partially watermiscible solvents, such as ethyl acetate, ethyl formate, butyl lactate, triacetin, propylene carbonate and benzyl alcohol, are preferred in the formulation over the conventional hazardous solvents, such as dichloromethane. Additionally, partially watermiscible organic solvents can be used as the internal phase of the microemulsion when the microparticles are to be produced using a microemulsion as a template.10
CO-SURFACTANTS
The choice of co-surfactant is critical when using microemulsion to formulate microparticles. Since co-surfactants can greatly influence phase behavior, the effect of cosurfactant on uptake of the internal phase for selected microemulsion composition and on drug loading should be investigated. Although the literature describes the use of bile salts and dipotassium glycerrhizinate as co-surfactants, various solubilizers, such as Transcutol, glycofurol, ethanol and isopropanol, can be safely used as co-surfactants in the formulation of microemulsions.

OTHER ADDITIVES
Microparticles may contain additives such as buffers, salts, polyols, osmogent and cryoprotectant, depending on either the route of administration or the properties of the drug moiety.

CHARACTERIZATION OF MICROPARTICLES
The essential characterization parameters for microparticles are as follows.

MEAN PARTICLE SIZE AND PARTICLE SIZE DISTRIBUTION
The mean particle size and the width of particle size distribution are important characterization parameters as they govern the saturation solubility, dissolution velocity, physical stability and even biological performance of microparticles. It has been indicated by that saturation solubility and dissolution velocity show considerable variation with the changing particle size of the drug. Photon correlation spectroscopy (PCS) can be used for rapid and accurate determination of the mean particle diameter of microparticles. Moreover, PCS can even be used for determining the width of the particle size distribution (polydispersity index, PI). The PI is an important parameter that governs the physical stability of microparticles and should be as low as possible for the longterm stability of microparticles. A PI value of 0.1–0.25 indicates a fairly narrow size distribution whereas a PI value greater than 0.5 indicates a very broad distribution. No logarithmic normal distribution can definitely be attributed to such a high PI value. Although PCS is a versatile technique, because of its low measuring range (3 nm to 3 µm), it becomes difficult to determine the possibility of contamination of the microparticles by microparticulate drugs (having particle size greater than 3 µm). Hence, in addition to PCS analysis, laser diffractometry (LD) analysis of microparticles should be carried out in order to detect as well as quantify the drug microparticles that might have been generated during the production process. Laser diffractometry yields a volume size distribution and can be used to measure particles ranging from 0.05–80 µm and in certain instruments particle sizes up to 2000 µm can be measured. The typical LD characterization includes determination of diameter 50% LD (50) and diameter 99% LD (99) values, which indicate that either 50 or 99% of the particles are below the indicated size. The LD analysis becomes critical for microparticles that are meant for parenteral and pulmonary delivery. Even if the microparticles contains a small number of particles greater than 5–6 µm, there could be a possibility of capillary blockade or emboli formation, as the size of the smallest blood capillary is 5–6 µm. It should be noted that the particle size data of a microparticles obtained by LD and PCS analysis are not identical as LD data are volume based and the PCS mean diameter is the light intensity weighted size. The PCS mean diameter and the 50 or 99% diameter from the LD analysis are likely to differ, with LD data generally exhibiting higher values. The microparticles can be suitably diluted with deionized water before carrying out PCS or LD analysis.

CRYSTALLINE STATE AND PARTICLE MORPHOLOGY
The assessment of the crystalline state and particle morphology together helps in understanding the polymorphic or morphological changes that a drug might undergo when subjected to microsizing. Additionally, when microparticles are prepared drug particles in an amorphous state are likely to be generated. Hence, it is essential to investigate the extent of amorphous drug microparticles generated during the production of microparticles. The changes in the physical state of the drug particles as well as the extent of the amorphous fraction can be determined by X-ray diffraction analysis and can be supplemented by differential scanning calorimetric In order to get an actual idea of particle morphology, scanning electron microscopy is preferred.

SATURATION SOLUBILITY AND DISSOLUTION VELOCITY
The determination of the saturation solubility and dissolution velocity is very important as these two parameters together help to anticipate any change in the in-vivo performance (blood profiles, plasma peaks and bioavailability) of the drug. As microparticles are known to improve the saturation solubility of the drug, the determination of the saturation solubility rather than an increase in saturation solubility remains an important investigational parameter. The saturation solubility of the drug in different physiological buffers as well as at different temperatures should be assessed using methods described in the literature. The investigation of the dissolution velocity of microparticles reflects the advantages that can be achieved over conventional formulations, especially when designing the sustained release dosage forms based on microparticulate drugs. The dissolution velocity of drug microparticles in various physiological buffers should be determined according to methods reported in the pharmacopoeia.

IN-VIVO BIOLOGICAL PERFORMANCE

The establishment of an in-vitro/in-vivo correlation and the monitoring of then-vivo performance of the drug is an essential part of the study, irrespective of the route and the delivery system employed. It is of the utmost importance in the case of intravenously injected microparticles since then-voor behavior of the drug depends on the organ distribution, which in turn depends on its surface properties, such as surface hydrophobicity and interactions with plasma proteins. In fact, the qualitative and quantitative composition of the protein absorption pattern observed after the intravenous injection of microparticles is recognized as the essential factor for organ distribution. Hence, suitable techniques have to be used in order to evaluate the surface properties and protein interactions to get an idea of in-vivo behavior. Techniques such as hydrophobic interaction chromatography can be used to determine surface hydrophobicity, whereas 2-D PAGE can be employed for the quantitative and qualitative measurement of protein adsorption after intravenous injection of drug microparticles in animals.

EFFECT OF CHARACTERISTICS OF MICROPARTICLES ON DRUG DELIVERY

PARTICLE SIZE

Particle size and size distribution are the most important characteristics of microparticle systems. Drug release is affected by particle size. Smaller particles have larger surface area, therefore, most of the drug associated would be at or near the particle surface, leading to fast drug release. Whereas, larger particles have large cores which allow more drug to be encapsulated and slowly diffuse out. Smaller particles also have greater risk of aggregation of particles during storage and transportation of microparticle dispersion. It is always a challenge to formulate microparticles with the smallest size possible but maximum stability. Polymer degradation can also be affected by the particle size. For instance, the rate of polymer degradation was found to increase with increasing particle size in vitro. It was thought that in smaller particles, degradation products of formed can diffuse out of the particles easily while in large particles, degradation products are more likely remained within the polymer matrix for a longer period to cause autocatalytic degradation of the polymer material. Therefore, it was hypothesized that larger particles will contribute to faster polymer degradation as well as the drug release. However, Panyam et al prepared particles with different size ranges and found that the polymer degradation rates in vitro were not substantially different for different size particles. Hence, to increase the likelihood of the success in drug targeting by microparticles, it is necessary to minimize the opsonization and to prolong the circulation of microparticles in vivo. This can be achieved by:

a) Surface coating of microparticles with hydrophilic polymers/surfactants
b) Formulation of microparticles with biodegradable copolymers with hydrophilic segments such as Polyethylene glycol (PEG), polyethylene oxide, polyoxamer, poloxamine and polysorbate 80 (Tween 80).

DRUG LOADING

Ideally, a successful micro particulate system should have a high drug-loading capacity thereby reduce the quantity of matrix materials for administration. Drug loading can be done by two methods:

• Incorporating at the time of microparticles production (incorporation method)
Absorbing the drug after formation of microparticles by incubating the carrier with a concentrated drug solution (adsorption/absorption technique).

Drug loading and entrapment efficiency very much depend on the solid-state drug solubility in matrix material or polymer (solid dissolution or dispersion), which is related to the polymer composition, the molecular weight, the drug polymer interaction and the presence of end functional groups (ester or carboxyl). The PEG moiety has no or little effect on drug loading. The macromolecule or protein shows greatest loading efficiency when it is loaded at or near its isoelectric point when it has minimum solubility and maximum adsorption. For small molecules, studies show the use of ionic interaction between the drug and matrix materials can be a very effective way to increase the drug loading.

DRUG RELEASE
To develop a successful micro particulate system, both drug release and polymer biodegradation are important consideration factors. In general, drug release rate depends on:
1. Solubility of drug
2. Desorption of the surface bound/adsorbed drug
3. Drug diffusion through the microparticle matrix
4. Microparticle matrix erosion/degradation
5. Combination of erosion/diffusion process.
Thus solubility, diffusion and biodegradation of the matrix materials govern the release process. In the case of microspheres, where the drug is uniformly distributed, the release occurs by diffusion or erosion of the matrix under sink conditions. If the diffusion of the drug is faster than matrix erosion, the mechanism of release is largely controlled by a diffusion process. The rapid initial release or ‘burst’ is mainly attributed to weakly bound or adsorbed drug to the large surface of microparticles. It is evident that the method of incorporation has an effect on release profile. If the drug is loaded by incorporation method, the system has a relatively small burst effect and better sustained release characteristics.

APPLICATIONS OF MICROPARTICLES IN DRUG DELIVERY
ORAL DRUG DELIVERY
The oral route is the preferred route for drug delivery because of its numerous well-known advantages. The efficacy or performance of the orally administered drug generally depends on its solubility and absorption through the gastrointestinal tract. Hence, a drug candidate that exhibits poor aqueous solubility and/or dissolution-rate limited absorption is believed to possess low and/or highly variable oral bioavailability. Owing to low oral bioavailability, such a drug candidate would have to be administered in a larger excess than actually required if it were completely bio-available in order to achieve a therapeutically active concentration, thus making the therapy costly. Orally administered antibiotics such as atovaquone and bupravaquone reflect this problem very well. Microsizing of such drugs can lead to a dramatic increase in their oral absorption and subsequently bioavailability. The amelioration in oral bioavailability can be attributed to the adhesiveness of the drug microparticles, increased surface area (due to reduction in particle size by 10–50-fold), and increased saturation solubility, leading to an increased concentration gradient between the gastrointestinal tract lumen and blood, and increased dissolution velocity. The enhancement in bioavailability will lead to a subsequent reduction in drug dose, rendering the therapy cost-effective and obliterating any undue drug dumping in the body. Apart from improving oral absorption, microparticles offer the following advantages:
• Improved dose proportionality
• Reduced fed/fasted state variability
• Reduced inter-subject variability.

PARENTERAL DRUG DELIVERY
The parenteral route is an invasive route. Parenteral administration of drugs is critical and often associated with the problems such as the limited number of acceptable excipients, restrictions on the quantities of excipients approved for parenteral use, the stringent requirements of the aseptic production process, safety issues, patient noncompliance and biological problems such as allergic reactions and thrombophlebitis. Despite all these limitations, the parenteral route still retains its value because of its special advantages, such as quick onset of action in case of emergency, reduction in dose of the drug and the ability to target the drug quickly to the desired site of action, especially in the case of severe infections. The parenteral route is often employed as an
alternative when the drug is either not absorbed through the gastrointestinal tract or undergoes extensive first-pass metabolism. For administration by the parenteral route, the drug either has to be solubilized or have particle/globule size below 5m to avoid the capillary blockade. The current approaches for parenteral delivery include salt formation, solubilization using co-solvents, micellar solutions, complexation with cyclodextrins and recently liposomes. However, there are limitations on the use of these approaches because of limitations on their solubilization capacity and parenteral acceptability. In this regard, liposomes are much more tolerable and versatile in terms of parenteral delivery. However, they often suffer from problems such as physical instability, high manufacturing cost and difficulties in scale-up.

OCULAR DRUG DELIVERY

Micro suspensions can prove to be a boon for drugs that exhibit poor solubility in lachrymal fluids. For delivery of such drugs, approaches such as suspensions and ointments have been recommended. Although suspensions offer advantages such as prolonged residence time in a cul-de-sac (which is desirable for most ocular diseases for effective treatment) and avoidance of the high tonicity created by watersoluble drugs, their actual performance depends on the intrinsic solubility of the drug in lachrymal fluids. Thus, the intrinsic dissolution rate of the drug in lachrymal fluid governs its release and ocular bioavailability. However, the intrinsic dissolution rate of the drug will vary because of the constant inflow and outflow of lachrymal fluids. Hence, suspensions may fail to give consistent performance. However, micro suspensions, by their inherent ability to improve the saturation solubility of the drug, represent an ideal approach for ocular delivery of hydrophobic drugs. Moreover, the microparticulate nature of the drug allows its prolonged residence in the cul-de-sac, giving sustained release of the drug.

CONCLUSION

The microparticles drug delivery system is a physical approach to alter and improve the pharmacokinetic and pharmacodynamics properties of various types of drug molecules. They have been used in vivo to protect the drug entity in the systemic circulation, restrict access of the drug to the chosen sites and to deliver the drug at a controlled and sustained rate to the site of action with enhanced therapeutic benefit, while minimizing side effects. The review embracing various aspects of microparticle formulations, characterization, effect of their characteristics and their applications in cell specific delivery of drug molecules and therapeutic genes will give the researchers and academicians a better insight of microparticulate drug delivery arena for better management of life threatening diseases.

REFERENCES