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Nanoparticles-in-microparticles systems (NiMS): An overview

Parijat Pandey, Harish Dureja*

Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak-124001, India

Abstract: Nanoparticles-in-Microparticles System (NiMS) is defined as novel drug delivery system in which particles of nano- and micro- ranges are combined for the delivery of drug (s) or gene in specific regions of the body. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticles matrix. The NiMS can be designed to control particle size, surface properties and release of therapeutic agent to achieve the site specific delivery of drug (s) at optimal rate and dose regimen. NiMS can be prepared by applying the various methods like ionic gelation, emulsion cross-linked method, coacervation/ precipitation, nanoprecipitation, spray-drying, emulsion-droplet coalescence, salting-out method, emulsification diffusion method. These NiMS can be further utilized for the development of new drug loaded orally disintegrating tablets (ODTs). The aim of the present study is to overview the preparation and evaluation of NiMS for further application in drug delivery.

Keywords: Nanotechnology, Drug, Salting-out, Nanoprecipitation, Tablets, Cross-linked

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In past few years, considerable attention has been focused on the development of novel drug delivery systems (NDDS). NDDS is novel and safe due to its capability of controlling the rate of drug delivery, sustaining the duration of action and targeting the diseased tissue, thereby leading to better therapeutic effects with minimum side effects. The delivery of the drug to the site of action without any significant immune-genicity reactions, biological inactivation or the potential side effect to the critical tissues such as lungs, liver, kidney or bone marrow are the major reasons behind the development of NDDS. The therapeutic efficacy safety of the existing drugs can be improved by altering the bio-distribution pattern of the drugs and reducing the amount and frequency of dosing by developing a NDDS (Longer and Robinson, 1990). NDDS possesses numerous advent-ages as multiple unit drug delivery system over the conventional dosage form (single unit system) (Longer and Robinson, 1990; Lordi, 1986). These advantages are tabulated in Table 1. Nanotechnology plays an important role in advancement of biology and medicine research particularly in the development of site specific delivery with lower drug toxicity and greater efficiency (Bhowmik et al. 2009). Nanotechnology is the science and technology of precisely manipulating the structure of matter at the molecular level. At this size, atoms and molecules work differently, and provide useful uses. With advancement in nano science and technology, a large number of materials and improved products may be available with a change in the physical properties. A number of nano- based systems allow delivery of insoluble drugs, allowing the use of previously rejected drugs or drugs which are difficult to administer (Bhowmik et al. 2009).The advantages of nanotechnology are tabulated in Table 2.

Nanoparticles-in-Microparticles System (NiMS) is the delivery system in which the particles of nano- and micro-ranges are ensembled for drug and gene delivery in specific parts of the body. The drug can be dissolved, entrapped, encapsulated or attached to a nanoparticles matrix (Li et al. 2011). The major goals in designing NiMS as delivery system are to control particles size, surface properties and release of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen (Lee et al. 2013). Despite the more complex and onerous production of the multiple-unit drug delivery

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Corresponding Author:
Dureja H, (✉) Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak-124001, India
Email: harishdureja@gmail.com

Table 1 Advantages of NDDS over convential dosage form (Lordi, 1986)

- Improved patient compliance due to decreased dosing frequency.
- Enhanced efficacy at desired site by modifying the carrier to the target site.
- Improved chemotherapy of disease due to decreased fluctuation in blood vessel.
- Fewer side effects due to controlled delivery of the drug to the target tissues and thus avoiding the toxicity to the normal cells.
- Reduced health care cost due to reduced dosing frequency and overall dose administered.
- Reduction in the total amount of dose as a result of targeting.

Table 2 Advantages of nanotechnology (Jin and Ye, 2007; Sahoo et al. 2007; Jain et al. 2010)

- Reduce the number of doses required.
- Improved products may be available with a change in the physical properties.
- Improve the oral bioavailability of the agents that are not effectively used orally.
- Nano-based systems allow delivery of insoluble drug.
- Make treatment a better experience and reduce treatment expenses.
- Allowing the use of previously rejected drugs or drugs which are difficult to administer.
- Drug targeting can be achieved by taking advantage of the distinct pathophysiology features of diseased tissues.
- An ideal targeting system should have long circulating time; it should be present at appropriate concentrations at the target site.
- Nanotechnology offers a solution for using the numerous chemical entities for treating brain disorders that are not clinically useful because of the presence of the blood-brain barrier.
- Nanotechnology-based delivery systems can also protect drugs from degradation.
- Passive targeting of drugs to the macrophages present in liver and spleen.

systems they have several advantages over the single-unit systems (Husen and Siddiqi, 2014). NiMS, offers the possibility of dual or multiple functionalities within a formulation. NiMS can be used therapeutically as adjuvant in vaccines or drug carriers, in which the active ingredient is dissolved, entrapped, encapsulated, adsorbed or chemically attached. The synthetic and natural polymers can be used to formulate NiMS. The NiMS can be developed into ODTs. NiMS have been successfully formulated for the development of orally disintegrating tablets of Scopolamine and box behnken designed nanoparticles-in-microparticles system (NiMS) for formulating mouth dissolving tablets of acetazolamide ((Li et al. 2011; Li et al. 2010). The aim of the present review is to highlight the preparation and evaluation of nanoparticles-in-microparticles system (NiMS) for further applications in drug delivery.

Methods of preparation of NiMS

NiMS can be prepared from a variety of materials such as proteins, polysaccharides and synthetic polymers. The selection of matrix materials is dependent on many factors including: size of nanoparticles required; inherent properties of the drug, e.g., aqueous solubility and stability; surface characteristics such as charge and permeability; degree of biodegradability, biocompatibility and toxicity; drug release profile desired and antigenicity of the final product (Martena et al. 2012).

The methods used for the preparation of NiMS are as:

- Ionic gelation
- Emulsion cross-linked method
- Coacervation/ precipitation
- Nanoprecipitation
- Spray-drying
- Emulsion-droplet coalescence
- Salting-out method
- Emulsification diffusion method

The method being utilized for the preparation of nanoparticles can also be used for the development of NiMS, which are:

Ionic gelation

Calvo and Co-workers, in 1997 developed nanoparticles using Ionic gelation method. This method involves preparation of two aqueous phases. One phase contains polysaccharides dissolved in water or in weak acidic medium and other phase contains a polyanion dissolved in water. These solutions are then added dropwise under constant stirring. When electrostatic interaction take place between two aqueous phases coacervates are formed, and when two molecules interact due to ionic force, it results in transition from liquid phase to gel phase at room temperature. The beads particles of nano range/ micro range are removed by filteration or centrifugation washed with distilled water and dried using lyophilizer (Calvo et al. 1997).

The advantages of this method includes, reversible physical crosslinking by electrostatic interaction occur instead of chemical crosslinking; absence of organic solvents avoids the possible toxicity of reagents and other undesirable effects and distribution can be easily monitored by changing the amount of counter ions (Agnihotri et al. 2004).

The limitation of this method is that it can only be used for ionic species and not for neutral particles; the size of particles will only be depends on physical interaction and not any involvement of chemical reaction and only water soluble substances are used for this method (Patil et al. 2011).

Emulsion cross-linked method

In this method, water-in-oil (w/o) emulsion is prepared by emulsifying the polymer solution in oil phase. Aqueous droplets are stabilized using a suitable surfactant, the stable emulsion is cross-linked by appropriate cross-linking agent such as glutaraldehyde to harden the droplets, and the particles are filtered and washed repeatedly. In this method, the particle size can be controlled by controlling the size of aqueous droplets. However, the particle size of the final product depends upon the extent

of the cross-linking agent used while hardening in addition to the speed of stirring during the formation of emulsion. The drawback of this method involves tedious procedure as well as use of harsh cross-linking agents, which might possibly induce chemical reaction with agents, however complete removal of the un-reacted cross-linking agent may be difficult in this process (Agnihotri et al. 2004; Banerjee et al. 2010).

Coaceravation/ precipitation

This method utilizes the physiochemical property of polymer. Since polymer is insoluble in alkaline pH and as it comes in contact with alkaline solution, it precipitates or coaceravates. Particles are produced by blowing the chitosan solution into the alkaline solution using a compressed air nozzle to form coacervates droplets. Separation and purification can be done by filteration/ centrifugation followed by successive washing with hot and cold water (Aggarwal et al. 2011).

The advantages of this technique include high yield and encapsulation efficiency; however, it involves complex and multi-step manufacturing procedures (Majeti, 2000).

The major disadvantages of coacervation method include the difficulties in scaling-up and the use of large amount of organic solvent (Li et al. 2008).

Nanoprecipitation

The nanoparticles formation by nanoprecipitation is instantaneous and the entire procedure is carried out in only one step. Ideally, both the polymer and the drug must dissolve in the first one (the solvent), but not in the second system (the non-solvent). Nanoprecipitation occurs by a rapid desolvation of the polymer when the polymer solution is added to the non-solvent (Reis et al. 2006).

The advantage of this method is that it is a single step not requiring extended shearing/ stirring rates, sonification, or high temperatures (Bilati et al. 2005; Perez et al. 2002). This method is mostly suitable for hydrophobic compounds that are soluble in ethanol or acetone (Barichello et al. 1999).

The limitations of this method are poor aqueous solubility, lack of site specific targeting, rapid systemic clearance, intestinal metabolism and systemic toxicities (Moorthi and Kathiresan, 2012; Kesisoglou et al. 2007).

Spray-drying

In this method, polymer is first dissolved in a solvent, drug is dissolved or dispersed in solution and then, suitable cross-linking agent is added, this solution or dispersion is then atomized in a stream of hot air. Atomization leads to the formation of small droplets, from which solvent evaporates leading to the formation of free flowing powders. The particle size depends upon size of the nozzle, spray flow rate, atomization pressure, and inlet air temperature and extent of cross-linking (Sahoo and Labhasetwer, 2002).

The advantage of this method is that the both hydrophilic and hydrophobic polymer can be used with proper selection of the solvent (Giunchedi and Conte, 1995). Spray drying is useful for encapsulating even heat-sensitive drugs, such as proteins or peptides, because it involves mild temperature (Yeo et al. 2001).

The limitation of this method is that the considerable amounts of the material can be lost during the process due to sticking of the nanoparticles/ microparticles to the wall of the drying chamber (Pavantto et al. 1992).

Emulsion-droplet coalescence

In this method, instead of cross-linking the stable droplets, precipitation is induced by allowing the coalescence of polymer droplets with NaOH droplets. Firstly, a stable emulsion containing aqueous solution of chitosan along with drug is produced using paraffin oil and then, another stable emulsion containing aqueous solution of NaOH is produced in same manner. When both the emulsion are mixed under high speed stirring, droplets of each emulsion would collide at random and coalesce, thereby precipitating chitosan droplets to small size particles. The advantages of this technique include high yield and encapsulation efficiency. The limitations of this method are poor aqueous solubility, lack of site specific targeting (Sahoo and Labhasetwer, 2002).

Salting-out method

In this method, acetone is used as the water-miscible organic solvent. This method consists of the addition of water soluble polymer in a highly concentrated salt solution in water (aqueous phase) to a polymer solution in acetone (organic phase). Although acetone is miscible with pure water in all ratios, the high salt concentration of the aqueous phase prevents mixing of the phase. After emulsification, the addition of pure water in a sufficient quantity causes acetone to diffuse into the aqueous phase, resulting in the formation of nanoparticles (Vandervoort and Ludwig, 2002).

The major advantages of this technique are the possible incorporation of high amounts of polymer and drug, excellent yields and the easy scale up in an industrial setup (Vandervoort and Ludwig, 2002). This technique is limited to lipophilic drugs, salting out agents that enable phase separation without precipitation and soluble stabilizers that are compatible with saturated aqueous solutions and do not coacervates in the presence of the solvent. Also, the process requires intense purification to ensure complete removal of the electrolytes (Vandervoort and Ludwig, 2002).

Emulsification diffusion method

In this method, polymer is dissolved in measured amount of solvent. This organic phase is added into required amount of aqueous phase containing the stabilizer. After mutual saturation of organic and continuous phase, the mixture is emulsified with a high speed homogenizer. For full diffusion into water phase, excess amount of water is added to the oil in water emulsion under magnetic stirring, leading to the nanoprecipitation of the polymer (Sahoo and Labhasetwer, 2002).

This technique presents several advantages, such as high encapsulation efficiencies (generally >70%), no need for homogenization, high batch-to-batch reproducibility,

ease of scale-up, simplicity, and narrow size distribution (Mohanraj and Chen, 2002). Disadvantages are the high volumes of water to be eliminated from the suspension and the leakage of water-soluble drug into the saturated-aqueous external phase during emulsification, reducing encapsulation efficiency (Reis et al. 2006).

CHARACTERIZATION OF NiMS

The NiMS are generally characterized for size, morphology, electrophoretic mobility, angle of contact and specific surface area, *in vitro* release, encapsulation efficiency, drug loading etc (Janes et al. 2001; Douglas et al. 1987.

Size and morphology

The particle size and morphology is one of the most important parameters of NiMS. Two main techniques are being used to determine the particle size distribution which includes photon correlation spectroscopy (PCS) and electron microscopy (EM) (Reis et al. 2006). This latter includes scanning electron microscopy (SEM), transmission electron microscopy (TEM). The size evaluation of NiMS dispersion demonstrates better results with freeze-fracturing microscopy and photon correlation spectroscopy as quantitative methods (Douglas et al. 1987)

The electron microscopy however, could be adopted as an alternative option, which measures individual particles for size and its distribution, it is relatively less time consuming. In combination with freeze-fracture procedures, TEM permits differentiation among nano-capsules, nanoparticles and emulsion droplets. On the other way SEM is much less time consuming. However, since particles are based on organic and non-conductive material, they require gold coating (Gref et al. 1994).

Specific surface

The specific surface area of freeze-dried NiMS is generally determined with the help of Sorptometer (Kreuter et al. 1983). The equation (1) can be used in the calculation of specific surface area.

$$A = 6/\theta.d \qquad \text{eq (1)}$$

Where A is the specific surface area. θ is density and d is the diameter of the particles.

Surface charge and electrophoretic mobility

The nature and intensity of the surface charge of NiMS is very important as it determines their interaction with the biological environment as well as their electrostatic interaction with bioactive compounds. The surface charge of NiMS can be determines by measuring the particle velocity in an electric field. Laser light scattering technique has become available as fast and high resolution technique for the determination of NiMS velocities (Sreeramoju and Libutti, 2010).

Surface hydrophobicity

The surface hydrophobicity of NiMS has an important influence on the interaction of colloidal particles with the biological environment. The hydrophobicity and hydrophilicity collectively determine the bio-fate of NiMS and their contents. Several methods, including hydrophobic interaction chromatography, two-phase partition, adsorption of hydrophobic fluorescent of radio-labeled probes, and contact angle measurements have been adopted to evaluate surface hydrophobicity (Liu et al. 2010).

NiMS recovery and drug incorporation efficiency:

The encapsulation efficiency, drug loading and % yield were calculated according to the following equations (Elzoghby et al. 2012);

Loading Capacity (%) = (Mass of drug in NiMS)/ (Mass of NiMS recovered)×100 eq (2)

Incorporation Efficiency (%) = (Mass of drug in NiMS)/ (Mass of drug used in formulation) ×100 eq (3)

Percentage yield (%) = (Total NiMS weight)/ (Total solid weight) ×100 eq (4)

In vitro release

In vitro release profile can be determined using standard dialysis, diffusion cell of recently introduced modified ultra filtration technique. In vitro release from the NiMS can be evaluated in acidic medium as well as in neutral medium utilizing double chamber diffusion cells on a shaker stand. A Millipore hydrophilic low protein binding membrane is placed between two chambers. The donor chamber is filled with nanoparticulate suspension and the receptor chamber with plain buffer. The receptor chamber is assayed at different intervals for the released drug sing standard procedures. Modified ultra filtration technique can also be used to determine in vitro release behaviour of the NiMS. The NiMS suspension is added directly into a stirred ultra filteration cell containing buffer. At different time intervals aliquots of the dissolution medium are filtered through the ultra filteration membrane using less than and assayed for the released drug using standard procedures (Jia et al. 2010).

Conclusion

NiMS have caused a fundamental change in manufacturing and have an enormous impact on drug delivery, diagnostics, nutraceuticals and production of biomaterials. They have advantages over conventional drug delivery systems and can increase the solubility, bioavailability, and permeability of many potent drugs. NiMS based drug delivery systems will also reduce the drug dosage frequency and will increase the patient compliance. Moreover, NiMS can be used to alter the kinetic profiles of drug release leading to more sustained release of drugs. There are now numerous simple, safe and reproducible preparation methods available for producing NiMS, and important technological advances have been achieved. In future, NiMS based drug delivery systems can be used for exploiting many therapeutically active agents which have poor aqueous solubility, permeability and less bioavailability. Overcoming the

obstacles in conventional drug delivery systems, NiMS will have better application and effective drug delivery and would ultimately enhance treatment and patient compliance.

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