EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 5
Issue: 3
799-802
Year: 2018

NANOPARTICLES ENHANCING DRUG THERAPEUTIC EFFICACY

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Article Received on 15/01/2018 **Article Revised on 05/02/2018** **Article Accepted on 26/02/2018**

ABSTRACT
From the last two decades, there has been a great interest in the research area of drug delivery using particulate delivery systems as carriers for small and large molecules. Particulate systems like nanoparticles have been used as a physical approach to alter and improve the pharmacokinetic and pharmacodynamic properties of various types of drug molecules. Nanoparticles formulations have many advantages over traditional dosage forms, such as increased dissolution properties and the potential for intracellular drug delivery. Specifically, pure drug nanoparticles, polymeric nanoparticles and polyelectrolyte complexes offer some encouraging results for delivering drugs to various organs and through various routes. Various polymers have been used in the formulation of nanoparticles for drug delivery to improve therapeutic benefit, while minimizing side effects.

KEYWORDS: nanoparticle formulations; drug delivery.

INTRODUCTION

Nanoparticles (NP) are defined as particulate dispersions or solid particles with a size in the range of 10-1000nm. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Nano-sized particles ranging below several 10 nm are of great interest, because of the chemical and physical behavior of the particles arising from the quantum size effect which are remarkably different from those in bulk form giving the great potential for use in applications in the electronic, chemical and mechanical industries, as well as in the related technologies using catalysts, drug carriers, sensors, pigments, also as well as in magnetic and electronic materials. The major goals in designing nanoparticles as a delivery system are to control particle 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.

The advantages of using nanoparticles as a drug delivery system include the following:

1. Particle size and surface characteristics of nanoparticles can be easily manipulated to achieve both passive and active drug targeting after parentral 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.
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, intra-ocular etc.

Preparation of Nanoparticles

Nanoparticles 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[1]:

- 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
- Antigenicity of the final product

Methods of preparation

Nanoparticles have been prepared most frequency by three methods:

- Dispersion of preformed polymers
- Polymerization of monomers
- Ionic gelation or coacervation of hydrophilic polymers

Dispersion of preformed polymers

Dispersion of preformed polymers is a common technique used to prepare biodegradable nanoparticles from poly (lactic acid) (PLA); poly (D,L-glycolide), PLG; poly (D, L-lactide-co glycolide) (PLGA) and poly (cyanoacrylate) (PCA).[2,3,4] This technique can be used in various ways as described below.

Solvent evaporation method: In this method, the polymer is dissolved in an organic solvent such as dichloromethane, chloroform or ethyl acetate which is also used as the solvent for dissolving the hydrophobic drug. The mixture of polymer and drug solution is then emulsified in an aqueous solution containing a surfactant or emulsifying agent to form an oil in water (o/w) emulsion. After the formation of stable emulsion, the organic solvent is evaporated either by reducing the pressure or by continuous stirring. Particle size was found to be influenced by the type and concentrations of stabilizer, homogenizer speed and polymer concentration.[5] In order to produce small particle size, often a high-speed homogenization or ultrasonication may be employed.[6]

Spontaneous emulsification or solvent diffusion method: This is a modified version of solvent evaporation method.[7] In this method, the water miscible solvent along with a small amount of the water immiscible organic solvent is used as an oil phase. Due to the spontaneous diffusion of solvents an interfacial turbulence is created between the two phases leading to the formation of small particles. As the concentration of water miscible solvent increases, a decrease in the size of particle can be achieved.

Polymerization method

In this method, monomers are polymerized to form nanoparticles in an aqueous solution. Drug is incorporated either by being dissolved in the polymerization medium or by adsorption onto the nanoparticles after polymerization completed. The nanoparticle suspension is then purified to remove various stabilizers and surfactants employed for polymerization by ultracentrifugation and re-suspending the particles inan isotonic surfactant-free medium. This technique has been reported for making polybutylcyanoacrylate or poly (alkylcyanoacrylate) nanoparticles.[8,9] Nanocapsule formation and their particle size depends on the concentration of the surfactants and stabilizers used.[10]

Coacervation or ionic gelation method

Much research has been focused on the preparation of nanoparticles using biodegradable hydrophilic polymers such as chitosan, gelatin and sodium alginate. Calvo and co-workers developed a method for preparing hydrophilic chitosan nanoparticles by ionic gelation.[11,12] The method involves a mixture of two aqueous phases, of which one is the polymer chitosan, a di-block co-polymer ethylene oxide or propylene oxide (PEO-PPO) and the other is a polyanion sodium tripolyphosphate. In this method, positively charged amino group of chitosan interacts with negative charged tripolyphosphate to form coacervates with a size in the range of nanometer. Coacervates are formed as a result of electrostatic interaction between two aqueous phases, whereas, ionic gelation involves the material undergoing transition from liquid to gel due to ionic interaction conditions at room temperature.

A successful NP system may be the one, which has a high loading capacity to reduce the quantity of the carrier required for administration. Drug loading into the NPs is achieved by two methods: one, by incorporating the drug at the time of NP production or secondly, by adsorbing the drug after the formation of NPs by incubating them in the drug solution. It is thus evident that a large amount of drug can be entrapped by the incorporation method when compared to the adsorption.[13,14] Adsorption iso-therms for the NP/drug delivery system give vital information on the best possible formulation, the drug binding capacity onto the surface of NPs and the amount of drug adsorbed. For instance, Couvreur et al[15] reported the adsorption of two antineoplastic drugs viz, dactinimycin and methotrexate onto poly (methylcyanoacrylate) and poly- (ethylcyanoacrylate). It was observed that methotrexate was bound to the NPs to a lesser extent than dactinimycin. Generally, in the case of poly (alkylcyanoacrylate), it is observed that longer the alkyl chain length higher the affinity for the drugs. The capacity of adsorption is thus related to the hydrophobicity of the polymer and the specific area of the NPs. In case of entrapment method, an increase in concentration of the monomer, increases the association of drug, but a reverse biotrend is observed with the drug concentration in the tech dispersed solution. This observation was further substantiated by Radwan[16] who studied the effect of monomer concentration on % drug loading. These results indicate that there is a need to optimize the amount of monomer available for the drug entrapment.

Drug release

Drug release from NPs and subsequent biodegradation are important for developing the successful formulations. The release rates of NPs depend upon:

- Desorption of the surface-bound /adsorbed drug
- Diffusion through the NP matrix
- Diffusion (in case of nanocapsules) through the polymer wall
- NP matrix erosion
- A combined erosion / diffusion process

Thus, diffusion and biodegradation govern the process of drug release.

Methods to study the in vitro release are:

- Side-by-side diffusion cells with artificial or biological membranes
- Dialysis bag diffusion technique
- Reverse dialysis sac technique
- Ultra centrifugation
- Ultrafiltration
- Centrifugal ultrafiltration technique

Despite the continuous efforts in this direction, there are still some technical difficulties to study in vitro drug release from NPs.[17,18] These are attributed to the separation of NPs from the release media. In order to separate NPs and to avoid the tedious and time-consuming separation techniques, dialysis has been used; here, the suspension of NPs is added to the dialysis bags/ tubes of different molecular mass cut-off. These bags are then incubated in the dissolution medium.[19]

APPLICATIONS OF NANOPARTICLES

Targeted Drug delivery

Nanotechnology will have a strong impact on Life Sciences, including drug delivery, diagnostics, nutriceuticals and the production of biomaterials. Site-specific-targeted drug delivery is important in the therapeutic modulation. Targeted encapsulated drug delivery using NPs is more effective for improved bioavailability, minimal side effects, decreased toxicity to other organs, and is less costly. NP-based drug delivery is feasible in hydrophobic and hydrophilic states through variable routes of administration, including oral, vascular, and inhalation.[20]

Stem cell therapy

Nanoparticles can be a proven effective tools for improving stem cell therapy. Chemical engineers have successfully used nanoparticles to enhance stem cells' ability to stimulate regeneration of damaged vascular tissue and reduce muscle degeneration in mice, they report in a study published online in *Proceedings of the National Academy of Sciences*. Scientists have suggested that after implantation into a living organism, cells may not continue to renew tissue effectively enough to keep the tissue alive long-term. The cells can be benefitted with performance-enhancing genes, which promote growth in the target tissue. Researchers can use nanoparticles as vectors to deliver these therapeutic genes to stem cells.

Reversion of multidrug resistance in tumour cells

Anticancer drugs, even if they are located around the tumour, can turn out to be of limited efficacy against numerous solid tumour types, because cancer cells are able to develop drug resistances.[21] These drug resistances allow tumours to evade chemotherapy. Multidrug resistance (MDR) occurs mainly due to the over expression of the plasma membrane p-glycoprotein, which is capable of extruding various positively charged xenobiotics, including some anticancer drugs, out of cells.[21] In order to regain the tumoral cells' sensitivity to anticancer drugs by circumventing p-glycoprotein-mediated MDR, several approaches including the use of colloidal carriers have been utilized. The reason behind the association of drugs with colloidal carriers, such as nanoparticles, against drug resistance derives from the fact that p-glycoprotein probably recognizes the drug to be effluxed out of the tumoral cells only when the drug is present in the plasma membrane.[22,23]

Gene delivery

Polynucleotide DNA vaccines work by delivering genes encoding relevant antigens to host cells where they are expressed, producing the antigenic protein within the vicinity of professional antigen presenting cells to initiate immune response.[24] However, there are some issues regarding the delivery of polynucleotides DNA vaccines including inefficient delivery and its localization to the nucleus of these target cells, along with integrity. Nanoparticles loaded with plasmid DNA could also serve as an efficient sustained release gene delivery system due to their fast escape from the degradative endo-lysosomal compartment to the cytoplasmic compartment.[25] Hedley et al[26] reported that nanoparticles capability of being escaped from endolysosomal area, they could release DNA at a sustained rate resulting in sustained gene expression. This effective gene delivery strategy could be applied to overcome such issues.

Drug delivery into the brain

Strategies for nanoparticle targeting to the brain rely on the presence of and nanoparticle interaction with specific receptor-mediated transport systems in the blood-brain barrier. For example, polysorbate 80/Low density lipoprotein, transferrin receptor binding antibody, lactoferrin, cell penetrating peptides and melanotransferrin have been shown capable of delivery of a self non transportable drug into the brain.[27-31]

CONCLUSION

Nanoparticulate systems have great potentials, being able to convert poorly soluble, poorly absorbed and labile biologically active substance into promising deliverable drugs. The core of this system can enclose a variety of drugs, enzymes, genes and is characterized by a long circulation time due to the hydrophilic shell which prevents recognition by the reticulo-endothelial system. To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and particle engineering, is still required.

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