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Herbal Nanoparticles Drug Delivery System - An Overview

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Abstract: ***For the past few decades, there has been a considerable research interest in the 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. 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 nanoparticles for drug delivery research to increase therapeutic benefit, while minimizing side effects. Here, we review various aspects of nanoparticles formulation, characterization, effect of their characteristics and their applications in delivery of drug molecules and therapeutic genes.***

Keywords: Nanoparticles, Drug delivery, Targeting, Drug release

1. Introduction

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. Though liposomes have been used as potential carriers with unique advantages including protecting drugs from degradation, targeting to site of action and reduction toxicity or side effects, their applications are limited due to inherent problems such as low encapsulation efficiency, rapid leakage of water-soluble drug in the presence of blood components and poor storage stability. On the other hand, polymeric nanoparticles offer some specific advantages over liposomes. For instance, they help to increase the stability of drugs/proteins and possess useful controlled release properties [1].

Nanoparticles 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 nanoparticles matrix. Depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained. Nanocapsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed. In recent years, biodegradable polymeric nanoparticles, 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 [2].

2. Advantages

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 [3].
5) The system can be used for various routes of administration including oral, nasal, parentral, intra-ocular etc. In spite of these advantages, nanoparticles do have limitations. For example, their small size and large surface area can lead to particle particle aggregation, making physical handling of nanoparticles difficult in liquid and dry forms.

3. 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: (a) size of nanoparticles required; (b) inherent properties of the drug, e.g., aqueous solubility and stability; (c) surface characteristics such as charge and permeability; (d) degree of biodegradability, biocompatibility and toxicity; (e) drug release profile desired; and (f) Antigenicity of the final product. Nanoparticles have been prepared most frequency by three methods:
(1) Dispersion of preformed polymers
(2) Polymerization of monomers and
(3) Ionic gelation or coacervation of hydrophilic polymers.

However, other methods such as supercritical fluid technology and particle replication in non-wetting templates have also been described in the literature for production of nanoparticles. The latter was claimed to have absolute control of particle size, shape and composition, which could

set an example for the future mass production of nanoparticles in industry [4].

1. 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)[8,9]. This technique can be used in various ways as described below.

2. 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 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. [5].

3. Spontaneous emulsification or solvent diffusion method: This is a modified version of solvent evaporation method. 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. Both solvent evaporation and solvent diffusion methods can be used for hydrophobic or hydrophilic drugs. In the case of hydrophilic drug, a multiple w/o/w emulsion needs to be formed with the drug dissolved in the internal aqueous phase [6].

4. 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 in an isotonic surfactant-free medium. This technique has been reported for making polybutylcyanoacrylate or poly (alkylcyanoacrylate) nanoparticles[7]. Nanocapsules formation and their particle size depend on the concentration of the surfactants and stabilizers used.

5. Coacervation or ionic gelation method

Much research has been focused on the preparation of nanoparticles using biodegradable hydrophilic polymers such as chitosan, gelatine and sodium alginate. Calvo and co-workers developed a method for preparing hydrophilic chitosan nanoparticles by ionic gelation. 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.

6. Production of nanoparticles using supercritical fluid technology

Conventional methods such as solvent extraction-evaporation, solvent diffusion and organic phase separation methods require the use of organic solvents which are hazardous to the environment as well as to physiological systems. Therefore, the supercritical fluid technology has been investigated as an alternative to prepare biodegradable micro- and nanoparticles because supercritical fluids are environmentally safe. A supercritical fluid can be generally defined as a solvent at a temperature above its critical temperature, at which the fluid remains a single phase regardless of pressure. Supercritical CO_2 (SC CO_2) is the most widely used supercritical fluid because of its mild critical conditions (Tc = 31.1 °C, Pc = 73.8 bars), no toxicity, non-flammability, and low price. This technique is clean because the precipitate is basically solvent free. RESS and its modified process have been used for the product of polymeric nanoparticles. Supercritical fluid technology technique, although environmentally friendly and suitable for mass production, requires specially designed equipment and is more expensive (Thote and Gupta, 2005).

4. Effect of Characteristics of Nanoparticles on Drug Delivery

a) Particle size

Particle size and size distribution are the most important characteristics of nanoparticles systems. They determine the in vivo distribution, biological fate, toxicity and the targeting ability of nanoparticles systems. In addition, they can also influence the drug loading, drug release and stability of nanoparticles. Many studies have demonstrated that nanoparticles of sub-micron size have a number of advantages over microparticles as a drug delivery system. 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 nanoparticle dispersion. It is always a challenge to formulate nanoparticles with the smallest size possible but maximum stability. Polymer degradation can also be affected by the particle size. For instance, the rate of PLGA polymer degradation was found to increase with increasing particle size in vitro. It was thought that in smaller particles, degradation products of PLGA 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, prepared PLGA particles with different size ranges and found that the polymer degradation rates in vitro were not substantially different for different size particles. Currently, the fastest and most routine method of determining particle size is by photon-correlation spectroscopy or dynamic light scattering. Photon-correlation spectroscopy requires the viscosity of the medium to be known and determines the diameter of the particle by

Brownian motion and light scattering properties[27]. The results obtained by photon-correlation spectroscopy are usually verified by scanning or transmission electron microscopy (SEM or TEM).

b) Surface properties of nanoparticles

When nanoparticles are administered intravenously, they are easily recognized by the body immune systems, and are then cleared by phagocytes from the circulation. Apart from the size of nanoparticles, their surface hydrophobicity determines the amount of adsorbed blood components, mainly proteins (opsonins). This in turn influences the in vivo fate of nanoparticles. Binding of these opsonins onto the surface of nanoparticles called opsonization acts as a bridge between nanoparticles and phagocytes. The zeta potential of a nanoparticle is commonly used to characterise the surface charge property of nanoparticle. It reflects the electrical potential of particles and is influenced by the composition of the particle and the medium in which it is dispersed. Nanoparticles with a zeta potential above (+/-) 30 mV have been shown to be stable in suspension, as the surface charge prevents aggregation of the particles. The zeta potential can also be used to determine whether a charged active material is encapsulated within the centre of the nanocapsule or adsorbed onto the surface.

c) Drug loading

Ideally, a successful nanoparticulate 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 nanoparticles production (incorporation method)
- Absorbing the drug after formation of nanoparticles by incubating the carrier with a concentrated drug solution (adsorption /absorption technique). 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.

d) Drug release

To develop a successful nano 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 nanoparticle matrix; (4) nanoparticle matrix erosion/degradation; and (5) combination of erosion/diffusion process. Thus solubility, diffusion and biodegradation of the matrix materials govern the release process. In the case of nanospheres, where the drug is uniformly distributed, the release occurs by diffusion or erosion of the matrix under sink conditions. (Sun and Mezian, 2005)

5. Characterisation of Nanoparticles

1) Flocculation studies: Nanoparticles after preparation were subjected to flocculation studies by allowing them to stand over 24hrs. at RT and sampled at 0 hr, 4hr, 8hr and 24hr intervals for particle size analysis.
2) Particle size, charge, and morphology of nanoparticles: Measurement of particle size, and polydispersity (size distribution) of nanoparticles were performed using zetasizer nano ZS90 by dynamic light scattering technique. Measurements were carried out in dil. Acetic acid medium. The morphological examination and particle size of the freeze dried nanoparticles were determined by TEM. The lyophilized particles (100 microgram) were diluted with deionized water and sonicated for 2 mins.
3) Fourier transform infrared (ftir) and differential scanning calorimetry (dsc): FTIR analysis for nanoparticles was performed using a FTIR spectrophotometer. Freeze dried sample (7.0-9.0 mg) was placed on IR crystal window and subjected to light within the infrared region. DSC analysis of nanoparticles prepared were carried out using Perkin Elumer DSC 7, USA, calibrated with indium (5mg) was placed onto a standard aluminium pan, crimped and heated from 60 to 400C at a constant rate of 10C per min under conditions purging of nitrogen. An empty sealed pan was used as a reference. All samples were run in triplicate and the mean average values were calculated.
4) Determination of entrapment efficiency, loading efficiency and % yield: The drug content in nanoparticles was calculated from the difference between the total amount of drug added in the nanoparticles preparation and the amount of unentrapped drug in the aqueous medium. The content of drug added was analysed by modified Folin Ciocalteu (FC) method. In brief , 200 micro litre of samples were mixed with 140 micro litre of 0.2 N FC reagent , 2.4 ml of deionised water and 420 micro litre of sodium carbonate (20%). The mixture was placed in dark at ambient condition for 1 hr, to which 910 micro litre of deionized water was added and absorbence was measured using UV – vis –spectrophotometer. Encapsulation efficiency (EE) was calculated using equation :

EE (%) = TC- FC/ TC * 100

Where TC is the total amount of drug and FC is the free amount of drug in the supernatant.

Loading capacity was articulated as:

LC (%) = TC – FC / wt. of the nanoparticles retrieved * 100

% yield (w/w) was calculated from the wt. of dried nanoparticles recovered (W1), and the sum of the initial dry wt. of starting materials (W2) as:

$$\% \text{ yield} = W1/W2 * 100.$$

5) Swelling studies: Water sorption capacity of nanoparticles was determined by swelling the nanoparticles in media of 1.2 (HCl; potassium chloride), 4 (acetate buffer) and 6.8 (phosphate buffer) at RT for 24 hrs. The pre weighed nanoparticles were placed in each media and analysed at 0hr, 4hr, 12hr or 24hr intervals. Samples were centrifuged (74,088 * g at RT) for 2 hrs in pre weighed centrifuge tubes and the wet weights were determined after decanting the supernatant. The %

swelling of nanoparticles was then calculated gravimetrically using the following formula:
E (%) = W2 – W1/ W1 * 100
E = % swelling of nanoparticles
W1 = initial wt. of nanoparticles
W2 = wet weight

6. Applications of Nanoparticulate Delivery Systems

1. Tumor targeting using nanoparticulate delivery systems
The rationale of using nanoparticles for tumor targeting is based on 1) nanoparticles will be able to deliver a concentrate dose of drug in the vicinity of the tumor targets via the enhanced permeability and retention effect or active targeting by ligands on the surface of nanoparticles; 2) nanoparticles will reduce the drug exposure of health tissues by limiting drug distribution to target organ. Verdun et al demonstrated in mice treated with doxorubicin incorporated into poly (isohexylcyanoacrylate) nanospheres that higher concentrations of doxorubicin manifested in the liver, spleen and lungs than in mice treated with free doxorubicin. Studies show that the polymeric composition of nanoparticles such as type, hydrophobicity and biodegradation profile of the polymer along with the associated drug's molecular weight, its localization in the nanospheres and mode of incorporation technique, adsorption or incorporation, have a great influence on the drug distribution pattern in vivo. Their biodistribution studies revealed decreasing drug concentrations over time in the heart, lung, kidney and plasma and accumulating drug concentrations in the liver, spleen and tumor. The majority injected dose appeared in the liver (56%) and only 1.6% in the tumour at 48 hrs post injection, confirming that nanoparticles have a great tendency to be captured by liver.

2. Long circulating nanoparticles
To be successful as a drug delivery system, nanoparticles must be able to target tumors which are localized outside MPS-rich organs. In the past decade, a great deal of work has been devoted to developing so-called "stealth" particles or PEGylated nanoparticles, which are invisible to macrophages or phagocytes. A major breakthrough in the field came when the use of hydrophilic polymers (such as polyethylene glycol, poloxamines, poloxamers, and polysaccharides) to efficiently coat conventional nanoparticle surface produced an opposing effect to the uptake by the MPS. These coatings provide a dynamic "cloud" of hydrophilic and neutral chains at the particle surface which repel plasma proteins. As a result, those coated nanoparticles become invisible to MPS, therefore, remained in the circulation for a longer period of time. Hydrophilic polymers can be introduced at the surface in two ways, either by adsorption of surfactants or by use of block or branched copolymers for production of nanoparticles. Studies show nanoparticles containing a coat of PEG not only have a prolonged half-life in the blood compartment but also be able to selectively extravasate in pathological sites such as tumors or inflamed regions with a leaky vasculature.

3. Reversion of multidrug resistance in tumour Cells
Anticancer drugs, even if they are located in the tumour interstitium, can turn out to be of limited efficacy against numerous solid tumour types, because cancer cells are able to develop mechanisms of resistance. These mechanisms allow tumours to evade chemotherapy. Multidrug resistance (MDR) is one of the most serious problems in chemotherapy. MDR occurs mainly due to the over expression of the plasma membrane pglycoprotein (Pgp), which is capable of extruding various positively charged xenobiotics, including some anticancer drugs, out of cells. In order to restore the tumoral cells' sensitivity to anticancer drugs by circumventing Pgp-mediated MDR, several strategies including the use of colloidal carriers have been applied. The rationale behind the association of drugs with colloidal carriers, such as nanoparticles, against drug resistance derives from the fact that Pgp probably recognizes the drug to be effluxed out of the tumoral cells only when this drug is present in the plasma membrane, and not when it is located in the cytoplasm or lysosomes after endocytosis.

4. Nanoparticles for oral delivery of peptides and proteins
Significant advances in biotechnology and biochemistry have led to the discovery of a large number of bioactive molecules and vaccines based on peptides and proteins. Development of suitable carriers remains a challenge due to the fact that bioavailability of these molecules is limited by the epithelial barriers of the gastrointestinal tract and their susceptibility to gastrointestinal degradation by digestive enzymes. Polymeric nanoparticles allow encapsulation of bioactive molecules and protect them against enzymatic and hydrolytic degradation.

5. Targeting of nanoparticles to epithelial cells in the GI tract using ligands
Targeting strategies to improve the interaction of nanoparticles with adsorptive enterocytes and M-cells of Peyer's patches in the GI tract can be classified into those utilizing specific binding to ligands or receptors and those based on nonspecific adsorptive mechanism. The surface of enterocytes and M cells display cell-specific carbohydrates, which may serve as binding sites to colloidal drug carriers containing appropriate ligands. For this intrinsic process, mucoprotein is required, which is prepared by the mucus membrane in the stomach and binds specifically to cobalamin. The mucoprotein completely reaches the ileum where resorption is mediated by specific receptors.

6. Absorption enhancement using non-specific interactions
In general, the gastrointestinal absorption of macromolecules and particulate materials involves either paracellular route or endocytotic pathway. The paracellular route of absorption of nanoparticles utilises less than 1% of mucosal surface area. Using polymers such as chitosan, starch or poly(acrylate) can increase the paracellular permeability of macromolecules. Endocytotic pathway for absorption of nanoparticles is either by receptor-mediated endocytosis, that is, active targeting, or adsorptive endocytosis which does not need any ligands. This process is initiated by an unspecific physical adsorption of material to the cell surface by electrostatic forces such as hydrogen bonding or hydrophobic interactions.

Table 1: Selected Nanoparticle Based Therauptics Approved by the FDA

Product /Brand Name	Nanoparticle Drug Delivery Component/ Active Ingredients	Delivery Route	Company Alliance	Fda Approval Date	Fda Approved Indications
Doxil Caelyx (Outside The Us)	Pegylated Doxorubicin (Adriamycin) Hcl Liposomes	IV	Ortho Biotech Schering Plough	November 1995	Metastatic ovarian cancer and aids related kaposis sarcoma
Abraxane	Paclitaxel (Taxol) Bound Albumin Nanoparticles (~130nm)	IV	Abraxis Bioscience Astra Zeneca	January 2005	Metastatic breast cancer patients who have failed combination therapy
Ambisome	AMPHOTERICIN B LIPOSOMES (~45-80nm)	IV	Gilead Sciences	August 1997	Fungal infections
Renagel	Cross Linked Poly (Allylamine) Resin (Sevelamer Hcl)	Oral Tablets (Capsules Discontinued)	Genzyme	October 1998	Control of serum phosphorus in patients with chronic kidney disease on dialysis
Diprivan	Propofol Liposomes	IV	Zeneca Pharma	October 1989	Anaesthetic
Triglide	Nano Crystalline Fenofibrate	Oral Tablets	Skye Pharma First Horizon	May 2005	Lipid disorders markedly reduces elevated plasma concentrations of triglyeride, LDL and total cholesterol and raises abnormally low levels of HDL

7. Conclusion

The foregoing show that 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 reticular-endothelial system. To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and particle engineering, is still required. Further advances are needed in order to turn the concept of nanoparticle technology into a realistic practical application as the next generation of drug delivery system.

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