Review Article

Nanoparticles: A Review

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ABSTRACT

Nanotechnology is commonly used for delivery of small and large drug molecules to the particulate targeted area. Nanoparticles have been used to improve the pharmacokinetic and pharmacodynamic properties of various drug molecules. Several methods have been developed like Solvent evaporation method, Spontaneous emulsification or solvent diffusion method, Double emulsification method, Salting out technique and Polymerization method to make nanoparticles. Advantages and disadvantages of these methods will be presented so as to facilitate selection of an appropriate method according to a particular application. In recent years, the number of patents and products in this nanotechnology field is increasing significantly.

Keywords: Nanoparticles, Targeted area, Nanospheres, Solvent evaporation method, Drug loading.

INTRODUCTION

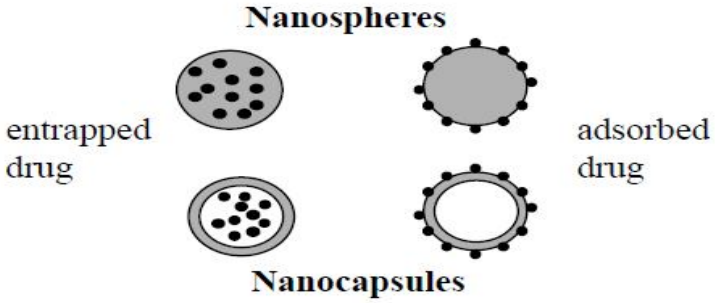
The objective in designing sustain or control release system is to reduce the frequency of dosing or to increase effectiveness of drug by localisation at the site of action, providing uniform drug delivery, or reducing the dose required. From the last 30 years, complications as well as expence had been increased in marketing new drug entities, sustain or control drug delivery system has been raised as an alternative due to recognition of their therapeutic advantages

1. For ideal drug delivery system, two prerequisites would be required-Drug would be given in single dose for the full duration of treatment, whether it will be for days or weeks, according to infection, or for the life time of patient, as in case of diabetes or hypertension.
2. Active ingredient should be directly delivered to the site of action which will minimise or eliminate side effects.

Nanoparticles have been extensively used as control or sustain drug delivery system[1.] Nanoparticles are colloidal solid particles there diameter range from 1 to 1000 nm. These particles can be used therapeutically as additive in drug carriers or vaccines in which active entity is either entrapped, dissolved, adsorbed, chemically attached or encapsulated.

Nanoparticles can be of two types depending upon the method of preparation-

1. Nanospheres – These have monolithic type system (matrix) in which drugs are either adsorbed or dispersed.
2. Nanocapsules – in these drugs are adsorbed on to their exterior or entrapped in the core also these particles exhibit a membrane wall structure[2.]



Advantages

1. Nanoparticles because of their ultra small volume can easily pass through tiny capillary vesicles.
2. They have prolonged duration in blood stream as they avoid rapid clearance by phagocytes.
3. Passive and active targeting can be achieved by easily manipulated surface characteristics or particle size after parenteral administration.
4. Nanoparticles also have control release property.
5. They can be easily administered by various routes including nasal, oral, parenteral etc.
6. Drug loading in nanoparticles is relatively high as compared to other dosage forms.
7. Reduction in toxicity is also an important advantage of nanoparticles.
8. Use of nanoparticle can reduce dosing frequency thus increasing bioavailability of drug[4].

Nanoparticles can be prepared from various materials like proteins, polysaccharides and synthetic polymers.

Many factors are responsible for the selection of matrix material -

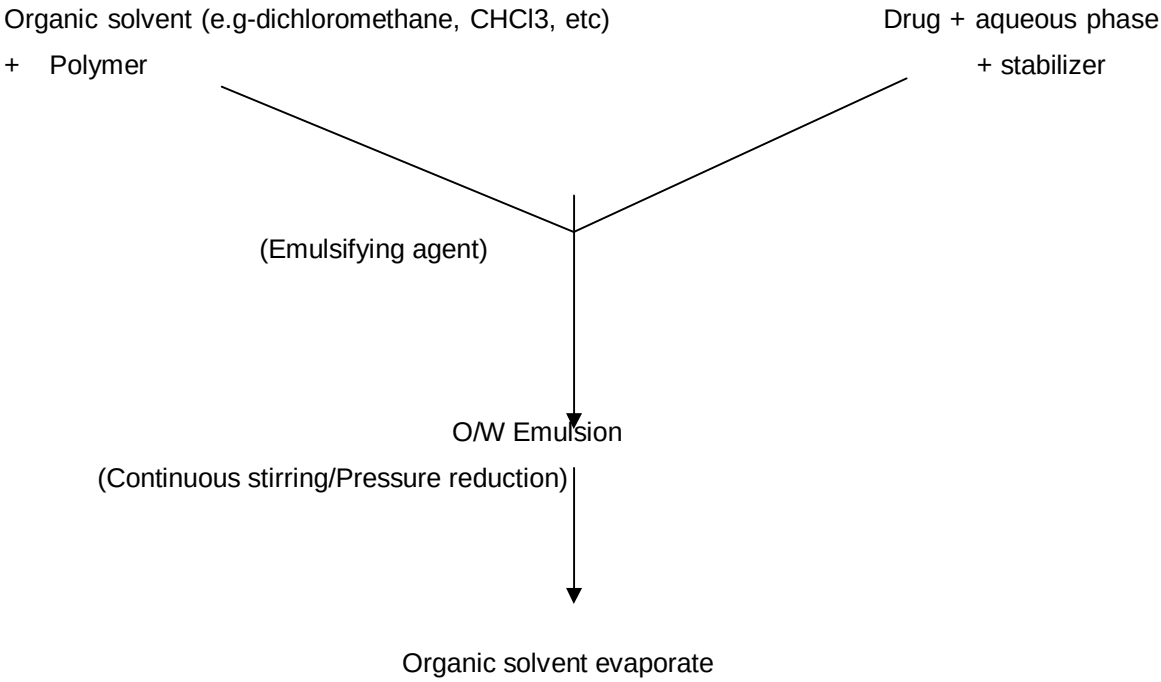
1. Required size of nanoparticles.
2. Properties of drug e.g- aqueous solubility, stability etc.
3. Surface characteristics like surface charge and permeability
4. Amount of biodegradability, toxicity and biocompatibility
5. Desired drug release profile
6. Final product's antigenicity

Nanoparticles are prepared by various types of methods.

- Solvent evaporation method
- Solvent diffusion method
- Phase inversion temperature method
- Super critical fluid method
- Salting out
- Spray drying
- Polymerization method
- Emulsification method

Method of preparation

1. **Solvent evaporation method**



Nanoparticle size is affected by homogenizer speed, concentration and nature of stabilizer and also by property of polymer. Nanoparticle size is reduced by using high speed Homogenizer or Ultrasonication. This method cans only b applicable to lipid soluble drugs.

2. Solvent diffusion method

This is modified form of Solvent Evaporation Method. In this method both Water miscible as well as small amount of Water immiscible solvents are used as an Oil phase. Interfacial turbulence is created between the two phases when the two solvents get diffused and produce small particles. Particle size can be

decreased by increasing the Water miscible solvent. This method can be used for Hydrophilic as well as Hydrophobic drugs. In case of Hydrophilic drug, multiple emulsion (w/o/w) is formed in which drug is dissolved in internal aqueous phase.

There are several advantages of this Technique like High encapsulation efficiency, High batch to batch reproducibility, No need for homogenization, Simplicity, Ease of scale up and Narrow size distribution. Disadvantage of this technique is water soluble drugs will leak in the saturated external aqueous phase during emulsification which reduces the encapsulation efficiency[6].

3. Phase inversion method

In this process droplets of nanoemulsion are used to desolubilise the polymer to produce nanoparticles. In this method oil is substituted by volatile solvent, in which polymer had been introduced earlier to produce nano – emulsion. After that solvent evaporation takes place below PIT to produce nanoparticles. Main advantage of this method is that organic solvent is lost there is no other interest to change the Phase Inversion Temperature.

4. Super critical fluid method

Various conventional approaches like solvent diffusion, solvent extraction Evaporation, etc. Require the use of organic solvent is hazardous to the environment as well as the physiological systems. This method had been used as an alternative to prepare biodegradable nanoparticles. In this method both the drug and polymer are dissolved in a suitable organic solvent and are atomized through a nozzle into supercritical CO_2. The dispersed organic solvent phase and the anti solvent CO_2 phase diffuse into each other and since CO_2 is miscible only with the solvent, the solvent gets extracted causing the supercritical fluid (insoluble solid) to precipitate as nanoparticles. When the density of CO_2 decreases, the atomization of the spray is increased, resulting in faster mass transfer rates associated with high surface area of the associated droplets, thus rapid nucleation and smaller particle sizes. The dry, micronized powder is then collected following the depressurization of CO_2[8].

5. Salting out

In this method, polymer is dissolved in water miscible organic phase (Acetone, THFetc.). Organic phase is emulsified in an aqueous phase, under strong mechanical shear stress. The aqueous phase contains high concentration of salt and emulsifier which are not soluble in organic phase. Mostly, the salts used are 60% w/w of magnesium chloride hex hydrate or magnesium acetate tetra hydrate in a ratio of 1:3 polymers to salt. Unlike emulsion diffusion method, there is no diffusion of the solvent due to the presence of salts. The fast addition of pure water, to the o/w emulsion, under mild stirring, reduces the ionic strength and leads to the migration of the water-soluble organic solvent to the aqueous phase inducing nanoparticle formation. The final step is purification by cross flow filtration or centrifugation to remove the salting out agent. Common salting out agents are electrolytes (sodium chloride, magnesium acetate, or magnesium chloride) or non-electrolytes, such as sucrose[9].

- Important parameters to be considered are-
- polymer concentration and molecular weight stirring rate and time
- nature and concentration of surfactant and solvent
- cryoprotectans

6. Spray drying

This method is to improve the entrapment efficiency of hydrophilic drugs. An emulsion is formed between the organic phase and water. The organic phase, consists of a mixture of dichloromethane and chloroform, containing the polymer, and lipophilic surfactant L- α-phosphatidylcholine. The aqueous phase contained the drug. The final emulsion was injected from a standard 0.7 mm nozzle into a chamber containing liquid nitrogen overlaying frozen ethanol , frozen at -80°C and lyophilized. The liquid nitrogen is evaporated, whereupon the melting liquefied ethanol extracts the organic solvent from the frozen droplets causing the particles to harden. The nanoparticles are filtered and dried under vacuum.

The mean size obtained was 257 nm (182-417 nm) and 240 nm (182-417 nm) respectively.

7. Polymerization method

Three different techniques are used for the preparation in aqueous solution -

- Emulsion polymerization
- Dispersion polymerization
- Interfacial polymerization

Drug particles can be incorporated in nanoparticle either by dissolving the drug in polymerization medium or by adsorption onto nanoparticle. Suspension of nanoparticles is formed, which contain surfactants and stabilizers which have to be removed by method like ultracentrifugation or by

suspending them in isotonic medium which is free of surfactant. Main advantage of this method is that it form well controlled polymeric shell nanoparticles, by close monitoring of drug polymer ratio[11].

8. Emulsification evaporation method

This is the oldest method used to prepare nanoparticles. This method is based on the emulsification of an organic solution of the polymer in an aqueous phase followed by the evaporation of the organic solvent. The polymer is dissolved in a suitable solvent (e.g., ethyl acetate, chloroform, ethylene chloride). The organic phase or aqueous phase is poured into the continuous phase (aqueous or organic phase) in which a surfactant is dissolved to impart stability to the emulsion. High shear stress is used for emulsification to reduced the size of emulsion droplets. Emulsification is followed by evaporation of the organic solvent under vacuum, which leads to polymer precipitation and nanoparticle formation[12].

- Two methods are used for emulsification
- Single emulsion method (o/w or w/o emulsions are formed)
- Double emulsion method (w/o/w or o/w/o emulsions are formed)

Table 1: Various processes in preparation of Nanoparticle

S. No.	Process	Types of particle produced	Particle size
1.	Single emulsion	Polymeric nanoparticles	Depends on size of emulsion used
2.	Double emulsion	Polymeric nanoparticles	100 - 1000nm
3.	Spray drying	Polymeric or lipidic	Less than 200 nm
4.	Nano precipitation	Polymeric or crystalline nanoparticle	Down to 100nm
5.	Wet milling	Crystalline nanoparticle	Down to 100 nm
6.	Micro precipitation	Crystalline nanoparticle	Down to 100 nm
7.	High pressure homogenisation	Polymeric, lipidic or crystalline nanoparticle	Less than 100 nm
8.	High gravity precipitation	Polymeric nanoparticle	Down to 100 nm

Drug Loading

A high drug- loading capacity is the measure of successful nanoparticulate system because it reduces the amount of matrix material for administration. Drug loading can be done by two methods:

1. Incorporation method

In this drug is incorporated during the formation of nanoparticle. Loading of drug by incorporation method produce system which has small burst effect and good Sustained release characteristics.

2. Adsorption/absorption method

In this method drug is made to be adsorbed on nanoparticle.

In this formed nanoparticle is kept in concentrated solution of drug and adsorption phenomenon takes place.

Nanoparticles (circle) and pharmaceutical surface of nanoparticles

Compounds absorbed on the active compounds

Drug loading of nanoparticles by adsorption

Drug Release

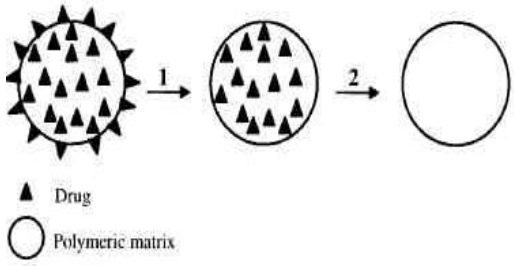
Five possible methods for drug release:

1. Desorption of drug bound to the surface
2. Diffusion through the nanoparticles matrix
3. Diffusion through the polymer wall of nanocapsules
4. Nanoparticles matrix erosion
5. Combined erosion- diffusion process

The pharmacokinetic analysis of drug release from nanoparticles can be described by a biexponential function

$$Ct = Ae^{-at} + Be^{-\beta t}$$

Where C = Conc of drug remaining in the nanoparticles at time, t
A & B are system characterstic constants
a&ß are rate constants



1. Initial rapid desorption of drug from the nanoparticles surface
2. Controlled release of drug by diffusion the nanoparticles matrix and polymer wall.

Application

1. Targeted Drug Delivery

Targeting is the ability to direct the drug-loaded system to the site of interest. Two major mechanisms can be distinguished for addressing the desired sites for drug release:
(i) Passive and (ii) active targeting.
An example of passive targeting is the preferential accumulation of chemotherapeutic agents in solid tumors as a result of the enhanced vascular permeability of tumor tissues compared with healthy tissue. A strategy that could allow active targeting involves the surface fictionalization of drug carriers with ligands that are selectively recognized by receptors on the surface of the cells of interest.
Two most important aspects of nanoparticle drug delivery must be:

- The specific targeting of the diseased tissue with nanoparticles.
- The timed release of the drug.

2. Long circulation of nanoparticles

Basically nanoparticles are able to target tumors which are localized outside MPS (Mononuclear Phagocytic system). For long circulation of nanoparticles a major break came in the field when hydrophilic polymer (PEG, Poloxamine and Polysaccharides) is coated to the surface of nanoparticles by which opposite effect is produced to the uptake by the MPS.
The coating provides a cloud of hydrophilic and neutral chain at the particle surface which repels plasma proteins. As a result coated nanoparticles become invisible to MPS and remain for a longer duration during circulation

3. Nanoparticles for Gene Delivery

Polynucleotide 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. Such vaccines produce both humoral and cell-mediated immunity because intracellular production of protein, as opposed to extracellular deposition, stimulates both arms of the immune system

4. Nanoparticles for Oral Delivery

It is very difficult to use the bioactive molecules (peptides and proteins) with suitable carriers. These suitable carriers remain a challenge due to the fact that bioavailability of these molecules is limited and they get degraded by enzymatic action. So the polymeric Nanospheres allow encapsulation of bioactive molecules and protecting them against enzymatic degradation.

5. Nanoparticles for Drug Delivery in Brain

In central nervous system the most important factor is Blood brain barrier (BBB) for the development of new drugs and it is characterized by impermeable endothelial cells with tight junction, enzyme activity and active transport systems. Basically the BBB only permits selective transport of molecules. So if we use Nanospheres as targeted drug delivery it will interact with specific receptor-mediated transport system in BBB. E.g. Polysorbate 80/LDL is capable for delivery. So the drugs which cannot easily cross the BBB can pass easily with the help of Nanoparticles.[14].

Table: list of some marketed products

Company	Trade Name	Composition	Indication	Administration
Enzon	Abelect	Liposomal amphotericin B	Fungal infection	Intravenous
Novavax	Estrasorb	Micellular estradiol	Menopausal therapy	Topical
Genzyme	Renagel	Poly(allylamine hydrochloride)	End-stage renal disease	Oral
Berna Biotech	Epaxal	Liposomal IRIV vaccine	Hepatitis A	Intramuscular
Elan, Merck	Emend	Nanocrystalline aprepitant	Antiemetic	Oral
Elan, Abbott	Tricor	Nanocrystalline fenofibrate	Anti-hyperlipidemic	Oral

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