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Review Article

Nanoparticle Drug Delivery System and their Applications

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Abstract

Targeting cells or specific tissue by the means of individually designed carriers that are attached to the drugs could be a more reliable approach in the drug delivery system. Such an approach is understood as cell or tissue-specific targeting. These methods make the nanostructures favorable material for biomedical applications and thus acquire significant importance in pharmaceutical sciences.

Key words: nanoparticles; tumor targeting; zeta potential; drug content

Introduction

Targeting cells or specific tissue by the means of individually designed carriers that are attached to the drugs could be a more reliable approach in the drug delivery system. Such an approach is understood as cell or tissue-specific targeting. These methods make the nanostructures favourable material for biomedical applications and thus acquire significant importance in pharmaceutical sciences. Additionally, these methods help in reducing toxicity, enhancing release, improving solubility and bioavailability, and providing better formulation opportunities for drugs [1,2].

Nano word originated from the Latin word which implies dwarf ideal size range offered by nanotechnology refers to the one-thousandth millionth of a particular unit. Thus nanometer is one thousand millionth of a meter (1nm= 10^{-9}nm). The branch of nanotechnology is the science that deals with the processes that occur at a molecular level and of nano-length scale size. Nanotechnology offers drugs within the nanometer size range which enhances and reinforces the performance in a variety of dosage forms. Various advantages of nano sizing include decreased fed/fasted variability, decreased patient-to-patient variability, enhanced solubility, increased oral bioavailability, increased rate of dissolution, increased surface area, less amount of dose required, and more rapid onset of therapeutic action. Various polymers have been used in the formulation of nanoparticles for drug delivery research to increase therapeutic benefits while minimizing side effects. The most important goal in designing nanoparticles as a delivery system is to control particle size, surface properties, and release of pharmacologically active agents to achieve the site-specific action of the drug at a therapeutically optimal rate and dose regimen. Though other colloidal carriers are used as potential carriers with unique advantages including protecting drugs from degradation, targeting site to action, and reducing the toxicity or side effects, their applications are limited because of inherent problems such as low encapsulation efficiency, rapid leakage of water-soluble drugs within the presence of blood components and poor storage stability [3,4].

Polymeric nanoparticles (PNPs)

Polymeric nanoparticles are colloidal particles composed of a biocompatible or biodegradable lipid matrix. These are transport carrier compartment for drugs or other active molecules of non-liposomal character having size ranging from 10-1000nm(1µm). This bioactives are entrapped in the polymer matrix as particulates enmeshed or solid solutions or may be bound to the particle surface by adsorption or chemically. The nanoparticles loaded bioactives could not only deliver drugs to specific organs but delivery rate in addition could be controlled as being bystanders, burst, controlled, pulsatile or modulated. Depending on the process used for the preparation, two types of nanoparticles can be obtained nanospheres or nanocapsules. Nanospheres may be defined as solid core spherical particulates, which are nanometric in size, they contain drug embedded within the matrix or adsorbed on to the surface, nanocapsules are vesicular system in which drug is essentially encapsulated within the central volume surrounded by an embryonic continuous polymeric sheet. In nanocapsules, the active drug is mainly encapsulated in solution systems [5,6].

Advantages of nanoparticles:

1. Particle size and surface characteristics of nanoparticles can be easily manipulated to achieve both active and passive targeting.
2. Release of the drug can be controlled or sustained so as to achieve in therapeutic efficacy of drug and reduction in side effects.
3. They are capable of being stored for a period of up to one year and hence have longer shelf stability.

4. They have the ability to incorporate both hydrophilic and hydrophobic drug molecules.
5. They have higher carrier capacity and drugs can be incorporated without any chemical reaction and hence preserving the drug activity
6. The system can be administered via different routes including oral, nasal, parenteral, etc.,
7. This have the potential to increase the bioavailability of the drugs.
8. They have longer clearance time.
9. Site specific targeting can be achieved by attaching targeting ligands to surface of particles or by using magnetic guidance.

Disadvantages of nanoparticles:

1. It involves higher manufacturing costs which may intern lead to increase in the cost of formulation.
2. They have low encapsulation efficacy.
3. Water soluble drugs can be rapidly leaked out in the presence of blood components.
4. Their small size and large surface area can lead to particle-particle aggregation, making physical handling of nanoparticles difficult in dry and liquid forms.
5. They may trigger immune response and allergic reaction.
6. They may involve use of harsh toxic solvents in the preparation process.

Polymers used in nanoparticles:

Polymers are the building blocks of Nano particulatecomposites, belong to either natural or semisynthetic or synthetic origins. The use of these polymers is often restricted by their bio acceptability. Generally, two types of polymers are used in the preparation of nanoparticles [7].

1. Natural hydrophilic polymers.

2. Synthetic hydrophobic polymers.

1) Natural hydrophilic polymers:

They are classified as proteins and polysaccharides.

Proteins: Gelatin , albumin, lectin, legumin, lecithin

Polysaccharides : Alginates, dextran, chitosan, Agarose.

2) Synthetic hydrophobic polymers:

These polymers used are hydrophobic in nature. The polymers used are either pre polymerised or synthesized before or during the process of nanoparticle preparation.

Pre polymerised: Poly (lactic acid) Poly (lactic co glycolide) Polystyrene.

Polymerised in process: Poly (Isobutyl cyano acrylate), poly (butyl cyano acrylates), polyhexylcyano acrylates, polymethyl (methyl acrylate).

Mechanism of drug release:

The polymeric drug carriers deliver the drugs at the tissue site by anyone of the three general physicochemical mechanisms [8]

1. By swelling of the polymer nanoparticles by hydration followed by release through diffusion.

2. By enzymatic action resulting in rupture or cleavage or degradation of the polymer at site of delivery, thereby releasing the drug rom the entrapped inner core.

3. Dissociation of the drug from the polymer and its de absorption/release from the swollen nanoparticles.

Different Techniques for The Preparation of Nanoparticles

1.Polymer precipitation methods

- Solvent extraction/evaporation
- Solvent displacement (Nano precipitation)
- Salting out

2. Polymerisation methods

- Emulsion polymerisation
- Dispersion polymerisation

3. Cross linking methods

- By cross linking of amphiphilic macromolecules
- Heat cross linking
- Chemical cross linking

4. Ionic gelation or coacervation of hydrophilic polymers.

5. Other methods such as,

Super critical fluid technology (SFT),

Rapid expansion of super critical solution (RESS),

Rapid expansion of super critical solution into liquid solvent (RESOLV),

Particle replication in non-wetting templates (PRINT)

1.4.1Polymer precipitation methods:

a. Solvent evaporation method

This is the common method for the preparation of solid polymeric nanoparticles.This technique is suitable for encapsulation of hydrophobic compounds. Briefly, the performed polymer and drug are dissolved in an organic solvent. This organic phase is emulsified with an aqueous phase containing surfactant to obtain o/w emulsion. The crude emulsion is then is passed through homogeniser to reduce the particle size. Then organic phase is evaporated by the aid of heat or vaccum. A modification of this procedure has lead to favour the encapsulation of hydrophilic drugs which is called as multiple emulsion technique. Poly vinyl alcohol (PVA), tween 80 and albumin are used as colloidal stabilisers.

Advantages and disadvantages:

In emulsification technique, mostly chlorinated solvents (chloroform, methylene chloride) are used because of their water insolubility, easy emulsification, solubilising property, low boiling point. But use of this solvents are attributed to its toxicity and adverse effects.

b. Emulsification/solvent diffusion method

This is a modified version of solvent evaporation method. The polymer is dissolved in a partially water-soluble solvent such as propylene's and is saturated with water. To promote the diffusion of solvent of the dispersed phase, dilution was made with an excess of water. The saturated polymer-water solvent phase is emulsified in the aq. solution that contains stabiliser, leading to the solvent diffusion into the external phase and formation of nanospheres or nanocapsules, according to the oil-polymer ratio, finally the solvent is eliminated by evaporation or by filtration [9].

Advantages

High encapsulation efficiency

High batch-batch reproducibility

Ease of scale up and narrow size distribution.

Disadvantages

Large amounts of water have to be eliminated from the suspensions. The leakage of water soluble drug in to the saturated aqueous external phase during emulsification reduces encapsulation efficiency.

c. Solvent displacement/Nanoprecipitation

This technique involves the use of an semi polar organic solvent that is completely miscible with the aqueous phase typically (acetone, ethanol or methanol) in this case the polymer precipitation is induced in the aq. medium (Non solvent) by the addition under the stirring of polymer solution. This method is opted or used for the drugs which are highly soluble in the polar solvents. This method has been applied to various polymeric materials such as PLGA, PLA, PCL and poly (methyl vinyl ether-co malic anhydride), (PVM/PVA).

Advantages

This technique is very simple, does not involve use of high homogenisers and hence can be easily scaled up in an industrial step.

Disadvantages

A major drawback of this technique is the difficulty to choose drug/polymer/solvent/non-solvent in which nanoparticles are formed and the drug is efficiently entrapped [10].

Characterisation of Nanoparticles

Characterisation of nanoparticles is based on the size, morphology and surface charge, using advanced microscopic techniques as atomic force microscopy (AFM), Scanning electron microscopy (SEM), and TEM,etc. Properties such as the size distribution, average particle size diameter, charge affect the physical stability and the in vivo distribution of nanoparticles [11].

1) Study of drug-excipient interactions
2) Particle size analysis and stability
    i. Particle size
    ii. Zeta potential
3) Surface Morphology (SEM)
4) Drug content
5) Entrapment efficiency EE & Loading capacity LC
6) In-vitro drug release studies.

1. Study of drug – excipient interactions

There are several methods available to determine the drug-excipient interactions. The most commonly used process is as follows:

i. Differential scanning calorimetry (DSC)
ii. X-Ray diffraction method.
iii. FTIR.

These techniques are able to detect the physicochemical states and interactions of the drug and the polymers in pharmaceutical and nanotechnology.

i. Generally, DSC detects phase transition such as glass
ii. Crystalline and amorphous states of the drug molecules arer determined by XRD techniques.
iii. FTIR is a modern and modified form of infrared spectroscopy based on mathematical formula, that is able to determine the structure of the drug molecule and the physical interactions between drug and polymers. FT-IR spectroscopy is a form of vibrational spectroscopy, and the spectrum reflects both molecular structure and the molecular environment. In this technique, the sample is irradiated with IR radiation from an IR source and the absorption of this radiation stimulates vibrational motions by depositing quants of energy into vibrational modes. Therefore, a molecule, when exposed to radiation produced by the thermal emission of hot source, absorbs only at frequencies corresponding to its molecular modes of vibration in the region of electromagnetic spectrum between the visible and short waves. These changes in vibrational motion give rise to the bands in the vibrational spectrum, each spectrum band is characterised by its frequency.

2. Particle size analysis and stability

Most of the properties of nanoparticles like drug loading and release pattern, in vivo distribution, targeting, etc. are concerned with the size and size distribution of nanoparticles so they had become an important parameter in characterisation of product.

Particle size analysis and stability studies are generally determined by zeta sizer. The zeta sizer nano range instruments provide the ability to measure three characteristics of particles or molecules in a liquid medium. The three parameters are particle size, zeta potential and molecular weight. The zeta sizer range features prealigned optics and programmable measurement position plus the precise temperature control necessary for reproducible, repeatable and accurate measurements. In addition facility is included for measurements of other key parameters such as pH and concentration. The zetasizer was designed with simplicity in mind, so that the minimal amount of interaction is necessary to attain best results.

Zeta potential: The equation for zeta potential is

Stokes-Einstein Equation

$$D = KT/6\pi\eta R$$

D- Diffusion constant, K – Boltzmann constant, T-Temperature,

D- Viscosity, R- Hydrodynamic radius. Nanoparticles with zeta potential above (+/-) 30mV have been shown to be stable in suspension, as the surface charge prevents the aggregation of the particles. The zeta potential may be utilised to determine whether a charged active material encapsulated within the pore of nano capsule or absorbed on the surface.

3. Particle surface morphology-Scanning electron microscopy

Particles surface morphology of the formulation is generally determined by SEM, a type of electron microscope that images the sample by scanning it with a high beam of electron in faster scan pattern. The electrons interact with the atoms that make up the sample producing the signals that contain information about the surface topography, composition and other properties such as electrical conductivity. Due to very narrow electron beam, SEM micrographs have a large depth of field yielding characteristic three-dimensional appearance that is useful for the understanding the surface structure of a sample.

4. Drug content

The polymeric nanoparticles are evaluated for the drug content in order to know the amount of drug present in the formed nanoparticles. Drug content is an assay procedure conducted to know the actual amount of drug present in the product.

5. Entrapment efficiency and loading capacity

Entrapment efficiency and loading capacity:

$$\% E.E = \frac{\text{Total drug added - un entrapped drug}}{\text{Total drug added}} * 100$$

$$\%L.C = \frac{\text{Total drug added-un entrapped drug}}{\text{Weight of nanoparticles taken for test.}} * 100$$

6. In vitro drug release

In vitro release kinetics of a drug entrapped in nanoparticles can be evaluated by several experimental methods:

i. Side by side diffusion cells with artificial or biological membranes
ii. Dialysis bag diffusion technique
iii. Reverse dialysis sac technique
iv. Ultracentrifugation
v. Ultra filtration
vi. Centrifugal ultra-filtration technique
vii. Orbitary shaker technique.

There are several factors that affect the release rate of entrapped drug. Larger particles have a smaller initial burst and longer sustained release than the smaller particles. Drug release depends on

i. Structure of nanoparticles.
ii. Type and length of polymers
iii. Degradation of erosion.

In vitro drug release kinetics was performed by means of orbitary shaker. 50mg of each accurately weighed formulation was transferred into 250ml conical flask containing 50ml pH 7.4 phosphate buffer solution. They were kept in an orbitary shaker at 100rpm maintained at 37°C. Aliquots of 5ml buffer were withdrawn at a predefined time intervals and the medium was replaced with same volume of buffer. The withdrawn samples were centrifuged at 3000rpm for 15min. The supernatant sample was collected. This study was carried out for a time period of 12hrs with all the prepared formulations. The concentration of drug release was estimated by determining the absorbance at respective wavelength using ELICO UV Spectrophotometer.

S.no.	Parameters	Characterisation method
1.	Particle size and size distribution	Scanning electron microscopy Transmission electron microscopy Photon correlation spectroscopy
2.	Charge determination	Zetasizer Laser Doppler anemometry
3.	Polymer drug interaction	Fourier transform infrared spectroscopy(FTIR) Differential scanning calorimetry
4.	Chemical analysis of surface	Static secondary ion mass spectrometry Sorptometer
5.	Drug stability	Bioassay of drug extracted from nanoparticles Chemical analysis of drug
6.	Nanoparticle dispersion stability	Critical flocculation temperature(CFT)
7.	Drug release profile	In vitro drug release characteristics under physiological and sink conditions

Table 1: various characterisation tools and methods for nanoparticles

Applications of Nanoparticles

Applications of Nano particulate drug delivery systems [12]

There are two major mechanisms

Passive targeting

Passive targeting is the accumulation of chemotherapeutic agents at the target site in solid tumours which results in the enhanced vascular permeability of the tumor tissues when compared with healthy tissue. In this, ligand-receptor interactions can be highly selective. Thus precise targeting at the site of action is possible. In the process targeting with nanoparticles encounters multiple obstacles on the way to their target. These include mucosal barriers, nonspecific delivery of the drug (as a result of uncontrolled release).

Active Targeting

Active targeting allows the surface functionalization of drug carriers with ligands which are selectively recognized by the receptors on surface of cells at the target site. Therefore, the two most important aspects of nanoparticle drug delivery must be:

Specific targeting of the diseased tissue with nanoparticles [13]: Appropriate size and functionalization with antibodies or the other means of selective binding provides means of enhanced delivery of drugs and reduced nonspecific toxicity. This issue can be resolved by functionalization of the nano particles with recognition elements on their surfaces towards receptors present on the particular diseased tissue. Conjugation with short chain variable fragments (scFvs) or antibodies will provide selective binding to the specifics cell's surface, and their endocytosis will be enhanced with suitably adjusted binding affinities.

Timed release of the drug: To prevent the nonspecific toxicity, drug should not diffuse out of the particle while it is still in the circulatory system, and has to remain encapsulated until that particle binds to the target receptor. Nanoparticles with multilayers can be engineered, in which each according with the appropriate timing of delivery of the drug for combination therapy.

Nanoparticles can be significally used in targeted drug delivery at the site of disease

- Improve the drug bioavailability
- Targeting of drugs to a specific site
- To improving the uptake of poorly water-soluble drugs.

Tumor Targeting using Nanoparticulate Delivery Systems [14]

The rationale of using nanoparticles for tumor targeting is based on one of the most efficiency of nanoparticles is delivery drug in the area of the tumor targets via the enhanced permeability and the retention effect. This can also be achieved by active targeting by ligands on the surface of nanoparticles. Nanoparticles limits the drug distribution to the target organ, hence reduces the drug exposure against healthy tissues. It was reported that mice treated with doxorubicin-based poly (isohexylcyanoacrylate) nano spheres showed higher concentrations of doxorubicin in the liver, spleen and lungs than in mice treated with free doxorubicin. It was also demonstrated that polymeric composition of nanoparticles such as biodegradation profile of the polymer along with the associated drug's molecular weight, polymer type, its localization in nanospheres and the method of incorporation technique, and hydrophobicity has the large influence on drug distribution pattern in in vivo. In addition, nanoparticles are advantageous in their rapid nanoparticles rate, within ½ h to 3 h, and it likely involves MPS and pharmacokinetics (PK) pattern of a cyclic RGD doxorubicin-nanoparticle formulation in tumor bearing mice. During this biodistribution study it was revealed that drug accumulation has been found in the liver, spleen and tumor. Maximum of the injected dose was observed in the liver (56%) and only 1.6% in the tumor at 48 h post injection. The study ensures that thenano particles have the greater tendency to be captured by liver. This and several studies indicates, the greatest challenge of using nanoparticles for tumor targeting is to avoid particle uptake by mononuclear phagocytic system in liver and spleen. Such tendency of mononuclear phagocytic system for endocytosis/phagocytosis of nanoparticles provides an opportunity to effectively deliver therapeutic agents to the cells. This bio distribution can be of benefit for the chemotherapeutic treatment of mononuclear phagocytic system rich organs/tissues localised tumours [16].

Conclusions

Targeting of the drug to the tissue or cells of choice is the potential area in the drug delivery. Branch of nanotechnology is anticipated to bring the fundamental transformation in manufacturing and have an enormous impact on life sciences especially in delivery, diagnosis, nutraceuticals and the production of biomaterials. In delivery systems targeting is the ability to direct the drug loaded system to the desired site. Recent advancement in nanotechnology has proven that nanoparticles acquire excellent potential as drug carriers.

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