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Review Article

Recent Trends of Nanotechnology In Drug Delivery And Their Application-An Overview

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ABSTRACT

Controlled drug delivery systems (DDS) have several advantages compared to the traditional dosage forms. From the last few decades, there has been a considerable research on the basis of Novel drug delivery system, using particulate drug delivery systems as such drug carriers for small and large molecules. Nanoparticles, Liposomes, Microspheres, Niosomes, Pronisomes, Ethosomes, and Pro-liposomes have been used as drug carrier in vesicle drug delivery system. Various polymers have been used in the formation of Nanocarriers. Nanocarriers are colloidal particulate systems with size ranging between 10-1000 nm. This are used for the diagnosis, treatment and monitoring of various diseases and physical approach to alter and improve the pharmacokinetic and pharmacodynamics properties of various types of drug molecules. Controlled and targeted delivery is one of the most valuable requirements from a carrier, which involves multi-disciplinary site specific or targeted approach. Nanoparticulate drug delivery system may offer plenty of advantages over conventional dosage forms, which includes improved efficacy, reduced toxicity, enhanced biodistribution and improved patient compliance.

Key-words: Nanocarriers, Nanoparticles, drug delivery system,

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Introduction:

According to the definition from NNI (National Nanotechnology Initiative), nanoparticles are structures of sizes ranging from 1 to 100 nm in at least one dimension. However, the prefix "nano" is commonly used for particles that are up to several hundred nanometres in size. Nanoparticles are nothing to the particulate dispersions or solid particles. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation, nanoparticles, Nano spheres or Nano capsules can be obtained. Nanoparticles, particularly those coated with hydrophilic polymer such as poly (ethylene glycol) (PEG) known as long-circulating particles, used as a 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 [1-4].

The main aim in designing nanoparticles as a drug 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 technology enables the delivery of drugs that are poorly water soluble and can provide means of bypassing the liver, thereby preventing the first pass metabolism Nanotechnology increases oral bioavailability of drugs due to their specialized uptake mechanisms such as absorptive endocytosis and are able to remain in the blood circulation for a long time, releasing the incorporated drug in a controlled fashion, leading to less plasma fluctuations and minimized side-effects [5-7].

Advantages / Why Nanoparticles?

- Greater surface area/volume ratio = more exposed surface = faster dissolution
- Greater bio-availability, small drug doses and less toxicity
- Small enough to avoid removal by MPS
- Large enough to avois rapid renal filtration
- Can cross cell membranes
- Interact on cell surface (receptors).
- Site-specific targeting can be achieved by attaching targeting ligands to surface of particles.
- can be used for various routes of administration including oral, nasal, parenteral, intra-ocular etc.

These different types of nanoparticles are prepared according to prerequisite and straightforwardly reaches to the desired site to deliver bioactive therapeutic and diagnostic agents. Although opportunities to develop nanotechnology-based efficient drug delivery systems

extend into all therapeutic classes of pharmaceuticals, many therapeutic agents have not been successful because of their limited ability to reach to the target tissue.

In spite of these advantages, nanoparticles have some limitations. For example, their small size & large surface area can lead to particle-particle aggregation, making physical handling in liquid and dry dosage forms. In addition, small particles size and large surface area readily result in limited drug loading and burst release. The present review details the latest development of nanoparticulate drug delivery systems, surface modification issues, drug loading strategies, release control and potential applications of nanoparticles.

Classification of Nanoparticle:

Nanostructure/Category	Example Material or Application
Nanotubes	Carbon, (fullerenes).
Nanowires	Metals, semi conductors, oxides, sulfides, nitrides.
Nano crystals, quantum dots	Insulators, semiconductors, metals, magnetic materials.
Other nanoparticles	Ceramic oxides, metals.

Preparation of Nanoparticles:

Nanoparticles are prepared from various materials such as proteins, polysaccharides and synthetic polymers. The selection of matrix materials is dependent on various factors such as [8]

- 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.

Mostly Nanoparticles are prepared by three methods such as dispersion of preformed polymers, polymerization of monomers; and ionic gelation or coacervation of hydrophilic polymers. Also, supercritical fluid method [9] has been described in the literature for production of nanoparticles.

Dispersion of preformed polymers [10-12]

Dispersion of preformed polymers is a common technique used to prepare polymeric biodegradable nanoparticle from poly (lactic acid) (PLA); poly (D,L-glycolide), PLG; poly (D,L-

lactide-co-glycolide) (PLGA) and poly(cyanoacrylate) (PCA), This technique can be used in various ways as described below.

1. **Solvent evaporation method:**

In this method, the polymer is dissolved in varrious 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. Particle size was found to be influenced by the type and concentrations of stabilizer, homogenizer speed and polymer concentration [12-13]. In order to produce small particle size, often a high-speed homogenization or ultrasonication may be employed.

2. **Spontaneous emulsification or solvent diffusion method:**

This is a modified version of solvent evaporation method [14]. 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 these methods are 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.

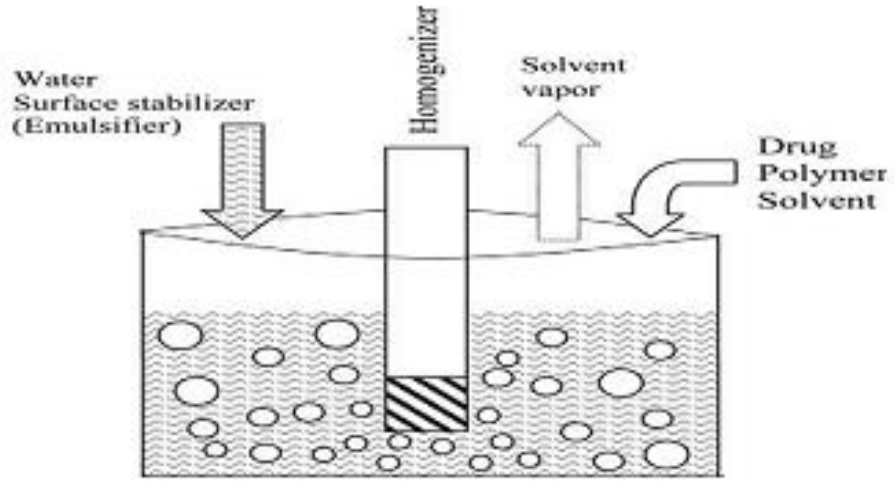

Fig. 2: Spontaneous emulsification or solvent diffusion method for particle formation.

Polymerization method [15-17]

In this method, monomers are polymerized to form nanoparticle 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.

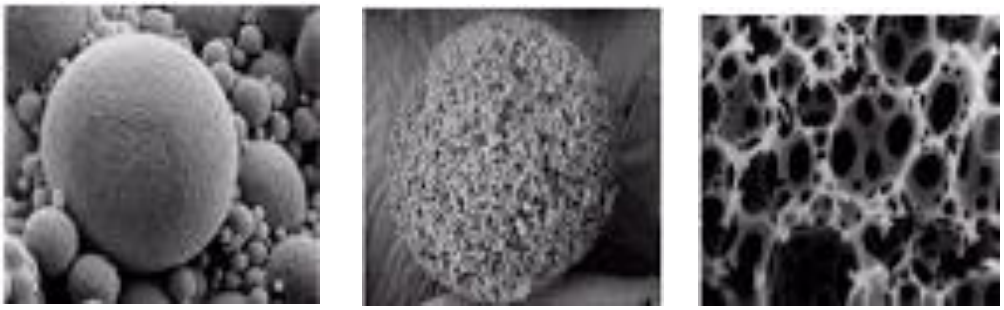

Fig. 1: Polymeric Nanoparticles

Coacervation or ionic gelation method [18]

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. 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.

Supercritical fluid method:

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 **[19].** Supercritical CO_2 ($SCCO_2$) is the most widely used supercritical fluid because of its mild critical conditions (Tc = 31.1 °C, Pc = 73.8 bars), non-toxicity, non-flammability, and low price. The most common processing techniques involving supercritical fluids are supercritical anti-solvent (SAS) and rapid expansion of critical solution (RESS). The process of SAS employs a liquid solvent, eg methanol, which is completely miscible with the supercritical fluid (SC CO_2), to dissolve the solute to be micronized; at the process conditions, because the solute is insoluble in the supercritic al fluid, the extract of the liquid solvent by supercritical fluid leads to the instantaneous precipitation of the solute, resulting the formation of nanoparticles. Thote and Gupta (2005) reported the use of a modified SAS method for formation of hydrophilic drug dexamethasone phosphate drug nanoparticles for microencapsulation purpose **[20].**

Effect of Characteristics of Nanoparticles on Drug Delivery:

Particle size:

Drug release is affected by particle size. Smaller particles have larger surface area; therefore, most of the drug associated would be at or near the particle surface, leading to fast drug release. Whereas, larger particles have large cores which allow more drug to be encapsulated and slowly diffuse out **[21].**

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.

Surface properties:

Surface hydrophobicity determines the amount of adsorbed blood components, mainly proteins (opsonins). This in turn influences the in vivo fate of nanoparticles [22-23]. Binding of these opsonins onto the surface of nanoparticles called opsonization acts as a bridge between nanoparticles and phagocytes. The association of a drug to conventional carriers leads to modification of the drug bio distribution profile, as it is mainly delivered to the mononuclear phagocytes system (MPS) such as liver, spleen, lungs and bone marrow. Indeed, once in the blood stream, surface non-modified nanoparticles (conventional nanoparticles) are rapidly opsonized and massively cleared by the macrophages of MPS rich organs [24]. Generally, it is IgG, compliment C3 components that are used for recognition of foreign substances, especially foreign macromolecules.

It is necessary to minimize the opsonization and to prolong the circulation of nanoparticles in vivo. This can be achieved by (a) surface coating of nanoparticles with hydrophilic polymers/surfactants; (b) formulation of nanoparticles with biodegradable copolymers with hydrophilic segments such as polyethylene glycol (PEG), polyethylene oxide, polyoxamer, poloxamine and polysorbate 80 (Tween 80).

Drug loading:

The PEG moiety has no or little effect on drug loading [25]. 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 [26-27].

Drug release:

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. in the case of nanospheres, where the drug is uniformly distributed, the release occurs by diffusion or erosion of the matrix under sink conditions. If the diffusion of the drug is faster than matrix erosion, the mechanism of release is largely controlled by a diffusion process. The rapid initial release or 'burst' is mainly attributed to weakly bound or adsorbed drug to the large surface of nanoparticles.

Evaluation of Nanoparticles:

1. **Drug Entrapment Efficiency:**

The nanoparticles were separated from the aqueous medium by ultracentrifugation at 10,000 rpm for 30 min at 5^0c. Then the resulting supernatant solution was decanted and dispersed into phosphate buffer saline pH 7.4. Thus the procedure was repeated twice to remove the unentrapped drug molecules completely. The amount of drug entrapped in the nanoparticles was determined as the difference between the total amount of drug used to prepare the nanoparticles and the amount of drug present in the aqueous medium[28].

$$\text{Drug Entrapment efficiency (\%)} = \frac{\text{Amount of released from the lysed nanoparticle}}{\text{Amount of drug initially taken to prepare the nanoparticles}} \times 100$$

2. **Particle Shape:**

The nanoparticles were subjected to microscopic examination (SEM) for characterization size. The nanosuspension was characterized by SEM before going for evaluation; the nanosuspension was lyophilized to form solid particles. The solid particles were coated with platinum alloy using a sputter coater [29].

3. **Particle size:**

Particle size and size distribution are the most important characteristics of nanoparticle systems. They determine the in vivo distribution, biological fate, toxicity and targeting ability of nanoparticle system. Currently, the faster and most routine method of determining particle size is by photon-correlation spectroscopy or dynamic light scattering. The results obtained by photon-correlation spectroscopy are usually verified by scanning or transmission electron microscopy (SEM or TEM) [30].

4. **Zeta potential:**

The Zeta potential of a nanoparticle is commonly used to characterize the surface charge property of nanoparticles. 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 [31].

Turbidimetry:

For nonabsorbing particles, turbidity is the complement to light scattering because it represents the amount of incident radiation not reaching a detector, that is, light lost to scattering. Hence the turbidity spectrum is also described by Mie theory and thus can be used to determine particle size as long as the data are normalized for concentration. This approach requires tiny amounts of sample and

can be easily executed using a spectrophotometer. However, it suffers the ills common to all ensemble methods and the lack of commercial implementation requires the investigator to carry out the appropriate calculations on their own. [32]

Nuclear Magnetic Resonance:

Nuclear magnetic resonance (NMR) can be used to determine both the size and the quality of nanoparticles. The selectivity afforded by chemical shift complements the sensitivity to molecular mobility to provide information on the physicochemical status of components within the nanoparticle. For example, the mobility of Miglyol 812 within solid lipid nanoparticles confirmed the liquid-like nature of the interior, though it was more limited than the same oil in an o/w emulsion. Pulsed field gradient methods allow diffusivity of the entire particle to be quantified and compared to produce 2-D, diffusion ordered plots in which colloidal behaviour and chemical speciation are leveraged simultaneously. [32]

Other Forms of Microscopy:

Various types of microscopy also used for the evaluation of nanomaterial's such as Optical Microscope, Electron Microscopy, Atomic Force Microscopy (AFM), other than this techniques The size resolution of TEM can be leveraged for morphological studies by restring the sample across a well-defined electron beam (STEM), and high resolution and some chemical information can be extracted if X-rays are substituted for electrons (STXM). While these methods have not been applied to pharmaceutically relevant nanoparticles, studies of related samples suggest that they may be worth investigating for this purpose. Also Filtration, Field-Flow Fractionation, Hydrodynamic Chromatography, Hydrophobic Interaction Chromatography commonly used for the evaluation of nanomaterial's. [32]

Applications of Nanotechnology [33]:

- Tumor targeting using Nanoparticulate delivery system.
- Nanoparticles for Gene delivery.
- Nanotechnology in Medicine as a Cell Repair.
- Nanotechnology in Medicine as Anti-Microbial Techniques.
- Nanoparticles for oral delivery of peptides and proteins.
- Nanoparticles for drug delivery into the brain.
- Fluorescent biological labels.
- Bio detection of pathogens.
- Detection of proteins.
- Probing of DNA structure.

- Tissue engineering.
- Tumour destruction via heating (hyperthermia).
- Separation and purification of biological molecules and cells.
- MRI contrast enhancement.
- Phagokinetic studies.
- Targeted drug delivery
- Alternative drug and vaccine delivery mechanisms (e.g. inhalation, oral in place of injection).
- Bone growth promoters
- Cancer treatments
- Biocompatible coatings for implants
- Sunscreens (e.g. using ZnO and TiO2) / cosmetics
- Biolabeling and detection (e.g. using Au)
- Carriers for drugs with low water solubility
- Fungicides (e.g. using ZnO)
- MRI contrast agents (e.g. using super paramagnetic iron oxide)
- New dental composites
- Biological binding agents (e.g. for high phosphate levels)
- Antiviral, antibacterial (e.g. Ag), anti-spore non-chemical creams and
- powders (using surface tension energy on the Nano scale to destroy biological particles)

Conclusion:

Nanotechnology is expected to bring a fundamental change in manufacturing in the next few years and will have an great impact on life sciences, including drug delivery, diagnostics, nutraceuticals and production of biomaterials. he use of Nanotechnology in medicine and drug delivery is spread rapidly. From decades various researchers have using nanoparticles to reduce toxicity and side effects of drugs. And Nano particulate systems have great potentials, being able to convert poorly soluble, or absorbed and labile biological active substance into promising deliverable drugs.

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