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Nanoparticles: A Novel Approach for Targeted Delivery of Medicines

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ABSTRACT

The utilization of nanotechnology in medicine and all the more explicitly tranquilize conveyance is resolved to spread quickly.Right now numerous substances are under scrutiny for medication conveyance and all the more explicitly for disease treatment Strangely pharmaceutical sciences are utilizing nanoparticles to lessen lethality and reactions of medications and up to as of late did not understand that bearer frameworks themselves may force dangers to the patient.The sort of risks that are presented by utilizing nanoparticles for medication conveyance are past that presented by customary perils forced by synthetic concoctions in established conveyance frameworks. For nanoparticles the learning on molecule danger as got in inward breath poisonous quality tells the way the best way to examine the potential risks of nanoparticles. The toxicology of particulate issue contrasts from toxicology of substances as the making chemical(s) could conceivably be dissolvable in natural frameworks, therefore impacting extraordinarily the potential presentation of different inside organs. This may differ from a fairly high neighborhood introduction in the lungs and a low or neglectable presentation for other organ frameworks after inward breath. Be that as it may, ingested species may likewise impact the potential harmfulness of the breathed in particles. For nanoparticles the circumstance is distinctive as their size opens the potential for intersection the different organic boundaries inside the body. From a positive perspective, particularly the possibility to cross the blood cerebrum hindrance may open new ways for medication conveyance into the mind. Likewise, the nanosize additionally takes into consideration access into the cell and different cell compartments including the core. A large number of substances are right now under scrutiny for the arrangement of nanoparticles for medication conveyance, differing from organic substances like egg whites, gelatin and phospholipids for liposomes, and more substances of a concoction nature like different polymers and strong metal containing nanoparticles. Clearly the potential communication with tissues and cells, and the potential harmfulness, significantly relies upon the real creation of the nanoparticle plan. This paper gives a diagram on a portion of the right now utilized frameworks for medication conveyance.

Keywords: Nanoparticles, explicitly lethality, customary perils

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INTRODUCTION

Targeted drug delivery is a method of delivering medication to a patient in a manner that increases the concentration of the medication in some parts of the body relative to others. Targeted drug delivery seeks to concentrate the medication in the tissues of interest while reducing the relative concentration of the medication in the remaining tissues. This improves efficacy.[1] The ultimate goal of drug delivery research is to help patients by developing clinically useful formulations. During the last several decades controlled drug delivery technology has advanced significantly, leading to the development of various clinical formulations improving patient compliance and convenience. Current technologies allow delivery of drugs at desired release kinetics for extended periods of time ranging from days to years. Oral & transdermal drug delivery systems routinely deliver drugs for 24hrs, substantially improving drug efficacy & minimizing side effects. Implantable systems can locally deliver drugs for months, even years. While significant advances have been made, there are still areas where substantial improvements need to be made to reach the next level of clinical relevance. One such area is targeted drug delivery to solid tumors. The clinically significant impact of targeted drug delivery lies in the ability to specifically target a drug or drug carrier to minimize drug-originated systemic toxic effects.[3] Drug targeting is the delivery of drugs to receptors or organs or any other specific part of the body to which one wishes to deliver the drugs exclusively. The drug's therapeutic index, as measured by its pharmacological response and safety, relies in the access and specific introduction of the drug with its candidate receptor, whilst minimizing its introduction with non –target tissue. The desired differential distribution of drug its targeted delivery would spare the rest of the body and thus

significantly reduce the overall toxicity while maintaining its therapeutic benefits The targeted or site- specific delivery of drugs is indeed a very attractive goal because this provides one of the most potential ways to improve the therapeutic index of the drugs.[1]NPs have a relatively large (functional) surface which is able to bind, adsorb and carry other compounds such as drugs, probes and proteins. However, many challenges must be overcome if the application of nanotechnology is to realize the anticipated improved understanding of the patho-physiological basis of disease, bring more sophisticated diagnostic opportunities, and yield improved therapies. (2)

1.1 CLASSIFICATION OF TARGETED DRUG DELIVERY.

- Systemic targeting based on blood circulation and extravasation a). Ligand–receptor interaction mediated

b). Locally-activated delivery

i). Self-triggered release of the drug at the target cells

ii). Externally-activated release of the drug at the target cells

- Intracellular targeting

a). Low-pH activation technologies that use default pathway delivery to lysosomes b). Mechanisms that avoid (default) lysosomal delivery.[3]

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.[4]

1.2 ADVANTAGES

1. Particle size and surface characteristics of nanoparticles can be easily manipulated to achieve both passive and active drug targeting after parenteral 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 ofthe 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. Drug loading is relatively high and drugs can be incorporated into the systems without any chemical reaction; this is an important factor for preserving the drug activity.
4. Site specific targeting can be achieved by attaching targeting ligands to surface of particles or use of magnetic guidance.
5. One fundamental advantage of nanoparticles with regard to other colloidal drug delivery systems (liposomes, niosomes, microemulsions etc.) and a fortiori to nanoemulsions, is their great kinetic stability and rigid morphology.
6. The system can be used for various routes of administration including oral, nasal, parenteral, intra ocular etc.
7. The Drug loading efficiency of nanoparticles is more than other targeted drug delivery systems.

1.3 LIMITATIONS

1. Their small size and large surface area can lead to particle aggregation, making physical handling of nanoparticles difficult in liquid and dry forms.
2. In addition, small particles size and large surface area readily result in limited drug loading and burst release. These practical problems have to be overcome before nanoparticles can be used clinically or made commercially available.
3. Sometime special storage conditions require. Example: PCL nanoparticle required to be stored at low temp. Because at higher temperature it get soften and loses its shape.
4. Special instrument require like freeze dryer for solvent evaporation, centrifugation for nanoparticle separation.
5. High pressure induced drug degradation.
6. Coexistance of several colloidal species.[5]

1.4 TYPE OF NANOPARTICLES

According to the structural organization biodegradable nanoparticles are classified as nanocapsule & nanosphere. The drug molecules are either entrapped inside or adsorbed on the surface.

According to material used for synthesis of nanoparticle five types of particle are:

a. Polymeric Nanoparticle
b. Solid Lipid Nanoparticle
c. Pegylated Nanoparticle
d. Magnetic Nanoparticle
e. Metallic Nanoparticle

Polymeric Nanoparticle

Polymeric nanoparticles are nanoparticles which are prepared from polymers. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticles and depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained. Some of the polymeric materials are used for synthesis like Cellulosic, Poly (vinyl alcohol), Poly (acrylic acid), Polyacrylamide, Poly capro lactone[6]

The selection of the appropriate method for the preparation of nanoparticles depends on the physicochemical characteristics of the polymer and the drug to be loaded. The methodologies are classified as follows

1.5 PREPARATION METHODS OF POLYMERIC NANOPARTICLES

There are several methods on the preparation of polymeric nanoparticles and incorporation of bioactive compounds into them. In general, one of the two principles methods is utilized: controlled precipitation or controlled dispersion of the polymer. Few of the popular methods include solvent

displacement, salting-out, emulsion-solvent-evaporation, emulsion-solvent- diffusion and supercritical fluid technology.

1.5.1 Solvent displacement method

It is the simplest method compare to other methods, the polymer is dissolved in a good solvent that maybe partially-polar and water-miscible solvent such as ethanol or acetone. When the drug is to be incorporated into the particles, it can be dissolved in the same phase along with the polymer. This polymer phase is introduced into a non-solvent aqueous phase containing a stabilizer (generally a hydrophilic surfactant) at a controlled rate under continuous mixing. As the partially-polar solvent diffuses rapidly into the aqueous phase (i.e. as the partially-polar phase is displaced by the polar phase), the polymer starts precipitating due to changes in its solubility, resulting in the formation of nanoparticles. The surfactant present in the aqueous phase helps in preventing particle aggregation. Choice of a drug/polymer/solvent/non-solvent system is the major limitation of this method and hence its applicability is confined to hydrophobic drugs and polymers.[7]

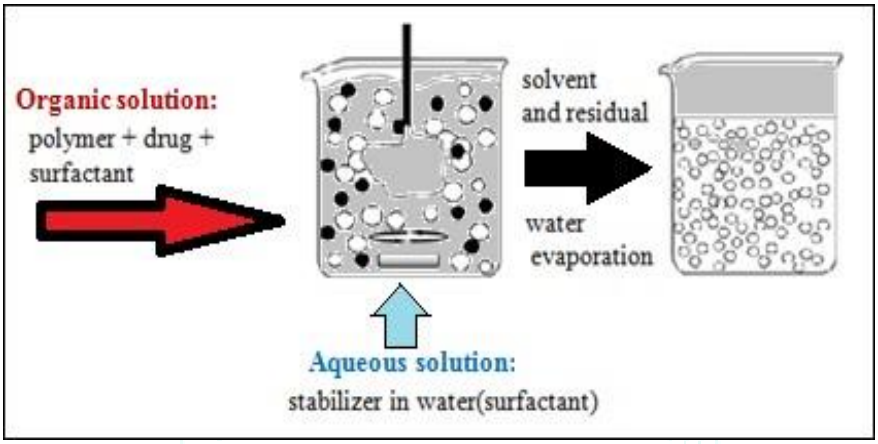

Figure 1: Schematic representation of the solvent displacement technique

1.5.2 Salting out method

Salting out technique is generally used for the preparation of drug-loaded biodegradable nanoparticles. This method was first applied to pseudolatexes.[7] It is based on the separation of water-miscible solvent from aqueous solutions by a salting out effect. An o /w emulsion is formed by adding a solution of the polymer and the drug in a water miscible solvent into an aqueous gel containing a salting-out agent and a colloidal stabilizer. Water is added to dilute this mixture, as a result of which nanoparticles are formed. Solvent and salting-out agents are then removed by cross-flow filtration. The use of this method results in a very high loading efficiency along with high yield and also the scale-up is fairly easy, but this method can only be used for the loading of lipophilic drugs.

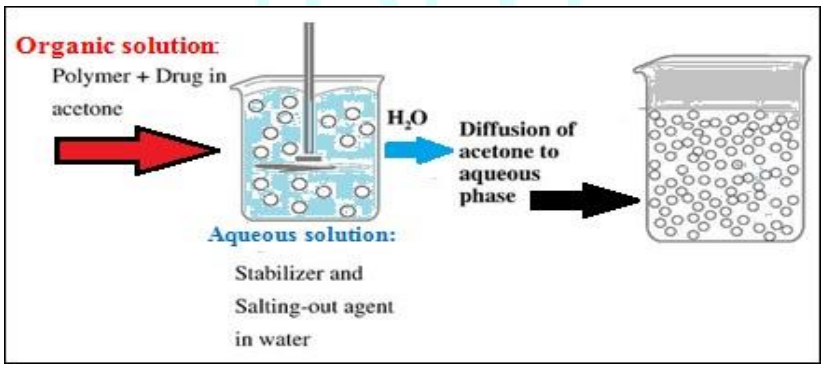

Figure 2: Schematic representation of the salting out technique

1.5.3 Emulsification-solvent-evaporation

It is based on the formation of a biphasic (o/w or w/o) or triphasic (w / o /w or o/w/o) emulsion.[6] Generally, a preformed polymer is dissolved in an organic solvent which is water immiscible along with the drug, and is emulsified in an aqueous solution (o/w emulsion). The formed emulsion is then exposed to high energy mixers (e.g. high-speed or high-pressure homogenizers, colloidal mills or ultra-sonic devices) to reduce globule size. The organic solvent is removed either by using heat or vacuum or even both at times. Nanoparticles are obtained as fine aqueous dispersions which can be collected and purified. The process variables involved in this method are complex and manifold, and the nanoparticles obtained are often polydisperse. However, this method is very popular for preparing polymeric microparticles rather than nanoparticles, as it facilitates industrial applicability and scalability.

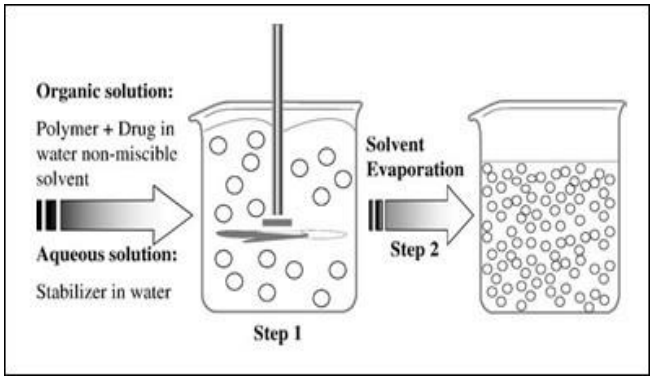

Figure 3: Schematic representation of the solvent-evaporation technique.

1.5.4 Emulsion-solvent-diffusion method

It is another method which is used for nanoparticles preparation. It is a modified salting-out technique and differs mainly in the organic solvent which is partially miscible with water in this case.[8] This solvent is pre-saturated with water to achieve initial thermodynamic equilibrium between water and the organic phase. Solvent diffuses out upon addition of water and results in the formation of nanoparticle suspension. Controlled complexation induced by electrostatic interactions between oppositely charged polymers can yield stable colloidal dispersions. The interacting polymers could be therapeutically active (e.g. oligonucleotides and plasmid DNA) or may have tailored properties (e.g. pH-sensitivity).[9,10] A wide variety of Charge bearing polymers can be utilized to manufacture composite nanoparticles and varying physico-chemical properties.[11]

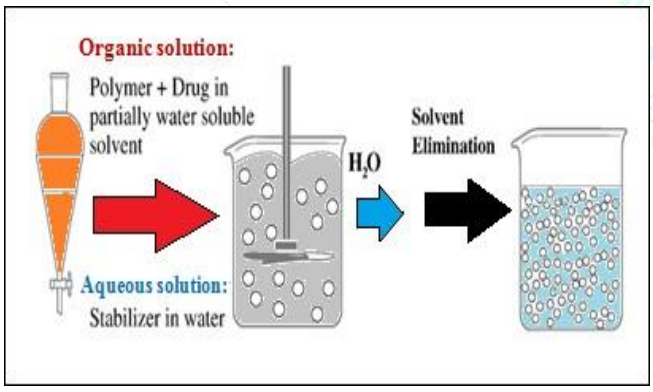

Figure 4: Schematic representation of the emulsification/solvent diffusion technique

1.5.5 Supercritical fluid technology

It is an emerging science for the production of micro and nanoparticles. In this method, an organic liquid solution of the polymer and the active moiety is sprayed through a nozzle into a chamber containing a gas that is miscible with the solvent, but in which the polymer and the active compound are not soluble. The gaseous phase in this case is a super critical fluid (e.g. supercritical C02). The dispersion of the liquid solution in such a condition generates a high degree of super-saturation, leading to the formation of fine, uniform colloidal particles. The particles can be recovered from the solution by depressurizing the chamber and allowing the gas to escape.[12-15]

1.5.6 Emulsion polymerization method

The most popular example for this method of synthesis is the nanoparticles made from poly(methylmethacrylates), poly(alkylcyanoacrylates) and poly(methylidenemalonates).[15] Generally, a water insoluble monomer is dispersed in an aqueous medium containing a colloidal stabilizer, and the polymerization is induced and controlled by the addition of a chemical initiator or by variations in physical parameters such as pH or radiation. Both hydrophilic and lipophilic drugs can be entrapped in the polymeric wall when added to the polymerization medium or adsorbed on preformed particles. While each of the above mentioned nanoparticle preparation method has its advantages and disadvantages, they can all be fine-tuned to encapsulate variety of drugs. The literature evidence shows that the nanoparticles are mostly employed to incorporate hydrophobic drugs, simply because the majority of the techniques facilitate encapsulation of lipophilic compounds with very high loading (approximately up to 40% by weight) and capturing efficiencies (nearly 100%). When hydrophilic drugs are to be incorporated, *in situ* polymerization or complexation remains the most accepted method. The collective advancements in nanotechnology and engineering sciences are expected to contribute major breakthroughs for bulk manufacturing of polymeric nanoparticles. In the highly competitive pharma/biotech industry, the formulation scientist can concentrate towards development of novel products, irrespective of complexities involved in the procedures. As in most cases, majority of the scaleup issues can be addressed and solved with the help of parallel advancements in high-technology engineering.

1.6 CHARACTERIZATION OF NANOPARTICLES

1.6.1 Particle size

Most of the properties of nanoparticle like drug loading and release pattern , in vivo distribution, tissue targeting, toxicity and biological fate are concerned with the size and size distribution of Nanoparticles so they had become an important parameter in characterization of product. It has been reported that micro particles are less effective drug delivers than particle having size ranging in between nanometers for e.g Nanoparticles having size range greater than 230 nm acquire in the spleen shown by body distribution studies.[16] Drug release is depend upon surface area larger the surface area more is the diffusion and less the surface area less is diffusion and surface area depend upon particle size i.e smaller the size greater is the surface area and vice –versa. Also large particle has large core which fills more drug and they diffuse out slowly. [17] It has been seen that aggregation occurs with small particle size. So it was considered that large particles will assist fast drug release and polymer degradation. [19]

Method of determining particle size is by [19]

1. Photon-correlation spectroscopy.
2. Dynamic light scattering.
3. Brownian motion and light scattering properties.
4. Scanning or transmission electron microscopy (SEM or TEM).

1.6.2 Surface Properties Of Nanoparticles

The nature and intensity of the surface charge of nanoparticle is very important as it determine their interaction with its biological environment as well as their electrostatic interaction with bioactive compounds. After the intravenous administration of nanoparticles, body immune system recognizes these, followed by phagocytic removal from body by blood circulation. After the recognization by body, delivered to the mono nuclear phagocytes system (MPS) of body which degrade them .The MPS system of body involves parts such as liver, spleen, lungs and bone marrow.

And if once, surface non-modified nanoparticles (conventional nanoparticles) reached in the blood stream they undergo rapid opsonization and cleared by the macrophages of MPS rich organs. [20]

Phagocytes can be prevented by-

(1) Coating the surface of nanoparticles with by using hydrophilic polymers/surfactants which coat the surface of nanoparticle.

(2) With the help of biodegradable copolymers having hydrophilic segments like polyethylene glycol (PEG), polyethylene oxide, poloxamine and polysorbate 80 (Tween 80) which are used to prepare Nanoparticles. For the characterization of surface property of nanoparticle determination of zeta potential is commonly employed.[21] Zeta potential reflects the electrical potential hold by particle and factor which affect its value are composition of particle and solvent in which it isdispersed.

1.6.3 Drug loading [22]

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:

a) Incorporation method: - In this drug is incorporated during the formation of nanoparticle.

b) 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 take place.

1.6.4 Drug release

Another Factor for a formulation of successful nanoparticulate system, study of parameter such as both drug release profile and polymer biodegradation is concern.

In general, drug release rate depends on:

(a) Solubility of drug.

(b) How far the Drug is diffused through the nanoparticle matrix.

(c) Combination of erosion/diffusion process.

(d) Degree of material matrix erosion/degradation and

(e) Time taken by the drug for desorption through surface.

Loading of drug by incorporation method produce system which has small burst effect and good sustained release characteristics. [23] Coating the nanoparticle with polymer, release is affected by movement of drug from core across the polymeric membrane. In this case polymeric membrane becomes release determing factor because it affects the solubility and diffusivity of drug. A number of methods can be used to determine in vitro release of drug

(24,25)

(a) Reverse dialysis bag technique

(b) Dialysis bag diffusion technique.

(c) centrifugal ultra-filtration techniques

(d) Agitation.

(e) Using biological or artificial membrane i.e. Side-by-side diffusion of cells.

1.6.5 Stability Study

The stability study of optimized formulation was carried out as per ICH (International Conference on Harmonization) guidelines at 4° C and at room Temperature for three months. Samples were withdrawn monthly and were determined for drug content by the method discussed previously in entrapment efficiency section.[26]

Table 1: Methods used in Characterization of Nanoparticless

S.No	PARAMETER	CHARACTERIZATION METHODS
1	Yield / Nanoparticle recovery	Chemical drug assay employing a suitable UV spectrophotometric (or) HPLC method.
2	Drug incorporation efficiency	
3	Surface morphology	Scanning electron microscopy (SEM), Transmission electron microscopy (TEM), Atomic force microscopy (ATM), Photon correlation spectroscopy (PCS), Laser defractometry& Mercury porositometry.
4	Particle size & size distribution	
5	Surface charge	Laser Doppler Anemometry (Zeta potentiometer).
6	Residual solvent	X-ray photoelectron spectroscopy (XPS) or Gas Chromatography (GC).
7	Ease of reconstitution	Particle aggregation studies on the basis of a numerical scale.
8	Intravenous admixture studies	Visual inspection for physical changes such as precipitation and pH determination.
9	Sterility	Sterility testing method as per IP 1996.
10	Drug stability	As per ICH Tripartite Guidelines.
11	Targeting potential	*In-vivo* tissue distribution studies in an animal model (rat).

Drugs incorporated into nano particles for targeted drug delivery

Table 2: List of Drugs incorporated in Nanoparticles (NPs)

Drug	Class	Target organ/cells	Technology	References
Camptothein[26]	Chemotherapeutic	Solid tumour	PEG – PLA nano particles	G.Maruthi(2011)
Paclitaxel[28]	Chemotherapeutic	Arterial neoinlima	Albumin nano particles	Shikanov A(2004)
SN-38[29]	Chemotherapeutic	Tumour	Crystalline nano particles	YunHwan ju(2011)
Indinavil[26]	Antiviral	Brain	Crystalline nano particles	G.Maruthi(2011)
Doxorubicin[30]	Chemotherapeutic	Brain	Poly sorbate coated nano particles	Robhash Kusam Subedi(2011)
Itraconazole[31]	Antifungal	Macrophages	Crystalline nano particles	A.A badawi(2011)

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