

NANOCARRIERS IN DRUG DELIVERY

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ABSTRACT

Nanotechnology is an advanced extension in the field of science. Introducing nanotechnology into drug delivery system has resulted in development of nanocarriers. Nanocarriers is a drug delivery approach sized in nanometers. Reduced size of the carrier lead to better targeting and improved efficacy. It enables the carrier to easily get into the tissues and reach the target site, overcoming the cellular obstacles like physical barriers. Despite of the cost of production and stability issue, nanocarriers are beneficial in terms of therapeutics. In the past two decades, nanocarriers are widely being used and approved by the regulatory bodies. Nanocarriers additionally offer the brightest advantage of being feasible to variety of routes of administration like topical, injectables and oral liquids. This chapter discusses in brief about the types of nanocarriers, preparation, evaluation, and their applications.

1. INTRODUCTION

Nanotechnology is a contemporary scientific field that has a significant impact on many elements of daily life. Nanotechnology is a fancy term revolving around the materials in nanometer range. The term "nanoparticle" refers to a particulate carrier system having a size between 1 and 1000 nm. Colloidal sub-nanoscale structures known as nanoparticles are made of synthetic or partially synthetic polymers. Chemicals can be delivered to the body's small units more effectively with nanoparticles.[1] Nanoparticles (NPS) are commonly used to carry medications, release medications at the target site, which typically results in degradation in biological fluids, and for medications that are unable to readily diffuse over a barrier. They are employed to regulate and control medications that are crucial for enhancing human health as well as biomolecules that are necessary for life and to enhance quality of life [2]. These systems have mainly been researched for regulated drug delivery, site-specific drug delivery, and improving the bioavailability and dissolving rate of medicines that are poorly water soluble. [3].

Nanoparticles carry several advantages like ease of particle size manipulation along with the surface modification. They are commonly involved in active and passive drug targeting. These nanocarriers can be modified to attain the most maximum therapeutic beneficence. Another advantage of the introducing nanotechnology in carrier system is that it can offer controlled release and minimize the degradation of the drug. A carrier must ensure high amounts of drug loading which directly contributes to the therapeutic efficacy.

A carrier is intended to achieve site specific drug delivery which is supported by the use of ligands or an external-stimuli. The polymer-based nanoparticles are usually biodegradable and are safe in general.

In contrast, small sized nanocarriers result in aggregation. Nanoparticles in the liquid and dry forms, this could result in compliance issues. [4] These carriers can be easily scavenged by RES leading to reduced half-life.

2.TYPES OF NANOCARRIERS

Nanocarriers are be broadly based on the structure and material used. Few such nanocarriers are listed in the table 1.

Table 1: Nano carriers in drug delivery

Sl.no	Type of Nanoparticles	Material used
1.	Nanosuspensions and Nanocrystals	Drug powder is dispersed in surfactant solution
2.	Solid lipid Nanoparticles	Melted lipid dispersed in aqueous surfactant
3.	Polymeric nanoparticles	Biodegradable polymers
4.	Polymeric micelles	Amphiphilic block co-polymers
5.	Magnetic Nanoparticles	Magnetite Fe ₂ O ₃
6.	Carbon Nanotubes	Metals, semiconductors or carbon
7.	Liposomes	Phospholipid vesicles
8.	Ceramic Nanoparticles	Silica,alumina,titania
9.	Nanopores	Aerogel,which is produced by cell gel chemistry
10.	Nano wires	Silicon, cobalt, gold or Copper based nanowires
11.	Quantum dots	cdSe-cdS core shell

2.1. Nano suspension

A suspension is a biphasic system in which the solid state is dispersed in liquid medium. When the size range of the solid phase is reduced to nanometer range, it is denoted as nanosuspension. The particle size lies in between 200 to 500nm. A nanosuspension

demonstrates increased solubility and dissolution. [5] Another noticeable phenomenon is that it can induce changes in crystalline structure which increases the amorphous fraction or conversion to crystalline structure. They also exhibit good adherence or adhesiveness to the human tissue. [6] Devising a nanosuspension for oral route offers improved absorption rate and bioavailability.

2.2. Solid lipid Nanoparticles (SLN)

Solid Lipid Nanoparticles are gaining a lot attention in the recent research. They are sub micron colloidal carriers (50-1000 nm). They are made up with lipids and surfactants. Lipids in lipids come with various disadvantages which can be overcome by the use of solid lipids. [7]

2.3. Polymeric nanoparticles

The components of polymeric nanoparticles include biodegradable, biocompatible, and non-toxic synthetic poly esters like poly(D, L-lactide), poly cyano acrylate, and related polymers like poly(lactide-co-glycolide), PLA, or poly(lactid acid), as well as advanced modifications of natural polymers. Chitosan, a natural polymer, is the one that is being utilized the most frequently. In addition to chitosan, numerous other substances, including sodium alginate and gelatin, help synthetic polymers overcome some toxicity issues. In terms of efficiency and effectiveness, natural polymer-based nanoparticles significantly outperform conventional oral and intravenous drug delivery system. [7]

2.4. Polymeric micelles

For the systemic distribution of medications that are not soluble in water, micellar systems are helpful. From stable dispersion in aqueous media, drugs can be partitioned in the hydrophobic cores of micelles and the outer hydrophilic layer, which can subsequently be delivered intravenously. Following intravenous administration, the distribution of drug-loaded polymeric micelles (less than 100 nm in diameter) has been shown to have a prolonged systemic circulation time due to their smaller size and hydrophilic shell, which reduces their uptake by the reticuloendothelial system. Medicines that are integrated into polymeric micelles have a restricted distribution in non-targeted locations and may accumulate into tumors to a larger extent than free medicines. [8]

2.5. Nanopores

Due to their exceptional qualities in terms of thermal insulation, controllable material separation and release, and their suitability as templates or fillers for chemistry and catalysis, materials with defined pore-sizes in the nanometer range are of particular interest for a wide range of industrial applications. Aerogel is a type of nanoporous material that is created using the sol-gel chemical process.

2.6. Nanowires

Nanowires are conductive or semi-conductive particles with a high length/diameter ratio and a crystalline structure of a few dozen nm. Nanowires made of silicon, cobalt, gold, or copper have already been created. In nanoelectronics, they are used to transport electrons and can be made of different metals, including oxides, sulfides, and nitrides.

2.7. Quantum dots

Quantum Dots are colloidal semiconductor nanocrystals with diameters between 2 and 10 nm. Colloidal synthesis or electrochemistry are two methods that can be used to create QDS from different kinds of semiconductor materials. The most often used QDS are indium phosphide (INP), indium arsenide (INAS), cadmium selenide (CDSE), and cadmium telluride (CDTE). The number of electrons in a quantum dot might range from one to thousands. To attach therapeutic molecules for simultaneous drug delivery and in vivo imaging, tissue engineering, and other applications, the size, shape, and number of electrons can be precisely controlled. [9]

3. PREPARATION OF NANOPARTICLES

The preparation technique for nanocarriers is based on the structure and complexity, which includes,

- Nano precipitation
- Solvent evaporation
- Solvent diffusion
- Salting out technique
- Super critical fluid
- Polymerization
- Ionic gelation technique
- Spray drying method

- Micro emulsion

3.1. Nanoprecipitation

Another name for nanoprecipitation is solvent displacement technique. The preformed polymer, typically PLA, is dissolved in a water-miscible solvent of intermediate polarity, causing the precipitation of nanospheres. This process also involves the diffusion of the organic solvent in the aqueous medium in the presence or absence of a surfactant. This phase is added to an aqueous solution that has been agitated and contains a stabilizer as a surfactant. Instantaneous development of a colloidal suspension results from polymer deposition on the interface between the organic solvent and water, which is brought on by fast solvent diffusion. Phase separation is carried out using a completely miscible solvent that is also a non-solvent of the polymer in order to aid the production of colloidal polymer particles during the first step of the method. When a little amount of nontoxic oil is added into the organic phase, the solvent displacement approach allows the creation of nano capsules. Given that the interior cavities of the nanocapsules are made of oil, high loading efficiencies. When nanocapsules are manufactured, high loading efficiencies for lipophilic medicines are typically observed due to the oil-based central chambers of the nano capsules. Only water-miscible solvents, where the diffusion rate is sufficient to achieve spontaneous emulsification, are suitable for using this straightforward procedure. Additionally, if the coalescence rate of the produced droplets is sufficiently high, spontaneous emulsification is not observed even if some water-miscible solvents exhibit considerable instability when mixed with water [10]

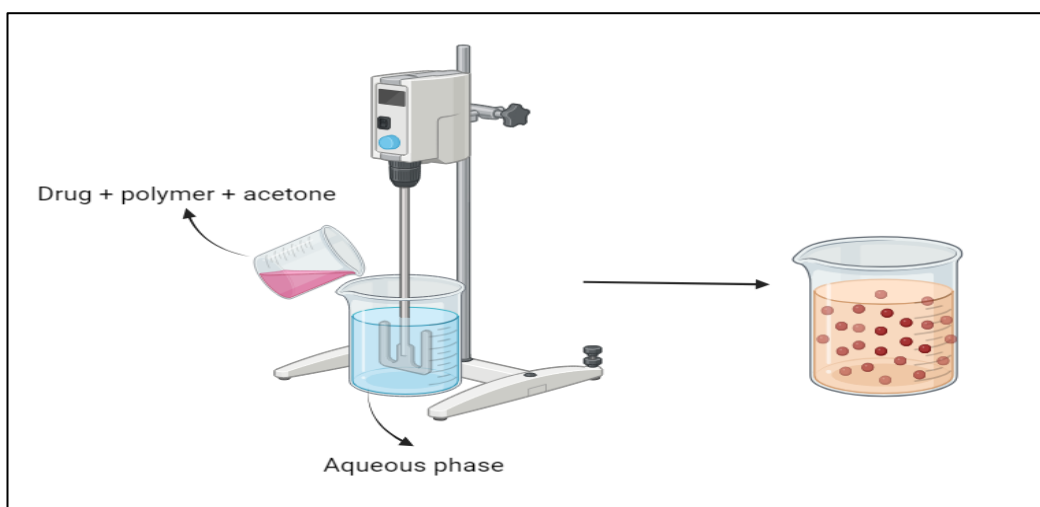


Figure 1: Nanoprecipitation method

3.2. Solvent evaporation

The first technique created to create polymeric nanoparticles was solvent evaporation. This technique involves creating polymer solutions in volatile solvents and creating emulsions. The hydrophobic medication is dissolved using organic solvents such as dichloromethane, chloroform, or ethyl acetate. To create an oil-in-water emulsion, the medication is first dissolved and dispersed in a polymer solution, which is then emulsified in an aqueous solution with a surfactant. [11]

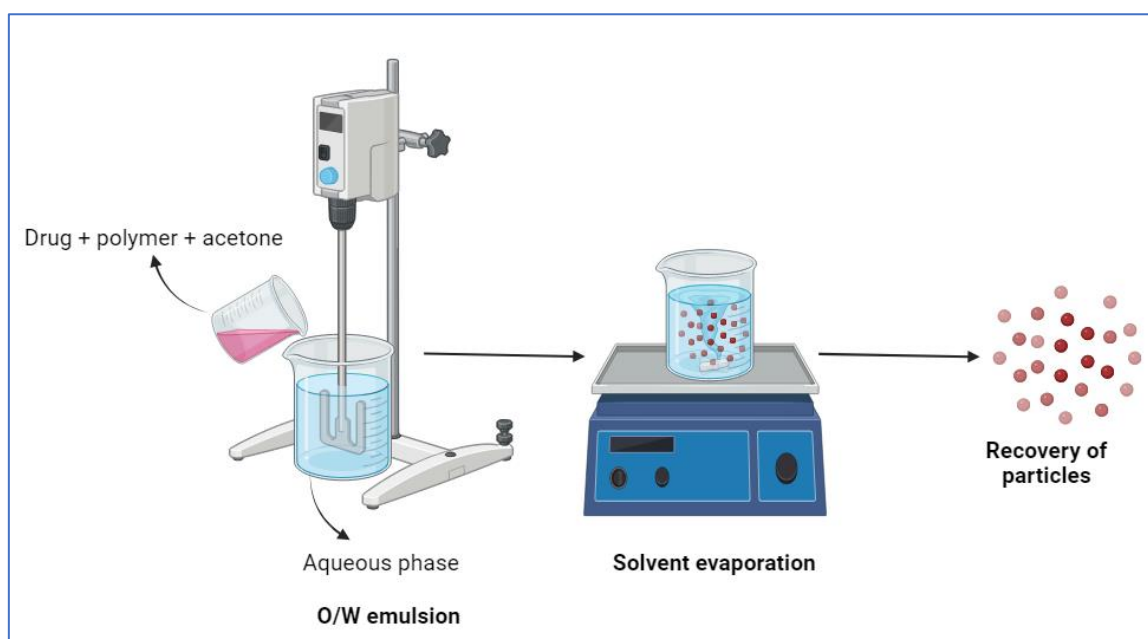


Figure 2: Solvent evaporation technique

3.3. Solvent diffusion

When an organic phase is added to a chitosan solution containing a stabilizing agent (i.e., polyoxamer) while being mechanically stirred, high pressure homogenization is used to create an o/w emulsion. This technique also uses a small amount of the water immiscible organic solvent as an oil phase. To overcome the miscibility of the organic solvent in water, the emulsion is subsequently greatly diluted with water. When an organic solvent diffuses into water, it causes the creation of nanoparticles, which leads to polymer precipitation. According to Alleman et al. (1993), this approach works well with hydrophobic drugs. [12]

3.4. Polymerization

In this procedure, monomers are polymerized to form nanoparticles in an aqueous solution in which drugs may be dissolved. Drugs may also be added by adsorption to the

suspension of nanoparticles, which is then purified by ultracentrifugation to remove various stabilizers and surfactants used for polymerization and resuspended in an isotonic surfactant-free medium. Making poly butyl cyano acrylate or poly alkyl cyano acrylate nanoparticles using this method has been documented. [13]

3.5. Ionic gelation

It is the simplest and most convenient approach for creating nanoparticles. Nanoparticle production is caused by electrostatic interactions between the cationic amino group of chitosan and the negatively charged anions of cross-linking agents like s-tpg. Acetic acid is used to dissolve chitosan to create a polymer solution. Water is mixed with a cross-linking agent to create a solution. The polyethylene glycol cross linking agent is added to the chitosan solution to instantly create the nanoparticles while stirring at room temperature, whether stabilizing chemicals like tween 80 are present or not. By adjusting the chitosan to stabilizer ratio, it is possible to change the size and surface charge of the particles. [14]

4. EVALUATION OF NANOCARRIERS

4.1. Visualization by SEM analysis

Analyze the size, morphologies, and shapes of newly produced nanoparticles. SEM provides the needed high resolution images of a sample's surface. Similar to an optical microscope, a scanning electron microscope examines dispersed electrons from the material rather than photons. An electric potential can accelerate electrons, which allows for a shorter wavelength than that of a photon. As a result, the SEM can magnify images up to 200,000 times. uses a conductive or sputter-coated sample, measures particle size and characterization, and has a sensitivity of 1 nm or less. [15]

4.2. Particle size analysis

The two most crucial factors in the characterization of nanoparticles are the particle size distribution and shape. Nanoparticles are primarily used for medicine delivery and targeting. The release of drugs has been found to be influenced by particle size. Larger surface areas are offered by smaller particles. Due to the majority of the medication that has been put onto them being exposed to the particle surface, rapid drug release results. [16]

4.3. Zeta potential

The nature and intensity of the surface charge of nanoparticles is very important as it their interaction with the biological environment as well as their electrostatic interaction with the bioactive compounds. The colloidal solubility is analyzed through zeta potential of nanoparticles, The potential is an indirect measure of the surface charge. It corresponds to potential difference between the outer Helmholtz plane and the surface of shear. The measurement of the zeta potential allows for predictions about the storage stability of colloidal dispersion. High zeta potential values, either positive or negative, should be achieved in order to ensure stability and avoid aggregation of the particles. The extent of surface hydrophobicity can then be predicted from the values of zeta potential. The zeta potential can also provide information regarding the nature of material encapsulated within the nano capsules or coated on to the surface.

4.4. Dynamic light scattering

Monochromatic light (laser) shining on a solution of spherical particles in Brownian motion causes a Doppler shift when the light hits the moving particles, changing the wave length of the incoming light. This method is widely used to determine the size of Brownian nanoparticles in colloidal suspensions in the nano and submicron ranges. The size of the particle has an impact on this alteration. By determining the particle's diffusion coefficient and utilizing the autocorrelation function, it is possible to extract the size distribution and provide a description of the motion of the particle in the medium. The most popular method for accurately estimating particle size and size distribution based on DLS is photon correlation spectroscopy (PCS). [17]

4.5. Yield

When manufacturing nanoparticles, the raw materials, active compounds, and other process parameters all play a role in the final result. Weighing the nanoparticles and calculating the weight of the medication and polymer that were utilized as additional materials yielded the results that were achieved. [18]

4.6. Entrapment efficiency

The amount of free drug in the dispersion was evaluated spectrophotometrically at max to determine entrapment efficiency (EE). The amount of drug that was successfully

entrapped inside the nanoparticles was calculated by subtracting this from the formulation's total drug concentration. [17]

4.7. Drug release

Understanding how and to what extent drug molecules are released is crucial because one of the main uses of nanotechnology is to deliver medications. Drug loading of nanoparticles is typically defined as the quantity of drug bound per mass of polymer (typically moles of drug per mg polymer or mg drug per mg polymer), though it can also be expressed as a percentage relative to the polymer. The technique used for this analysis is classical analytical methods like UV spectroscopy or high performance liquid chromatography (HPLC) after ultra-centrifugation, ultra filtration, gel filtration or centrifugal ultra filtration.

5. NANOCARRIERS IN CANCER

Nanocarriers are being used widely in clinical cases. The primary usage of nanoparticles in biomedical applications, including the delivery of drugs and genes, the development of diagnostic and therapeutic instruments for cancer, the production of food, etc.

Nanoparticle systems currently under investigation to be applied in biomedical with the emphasis on cancer therapeutics. Nanoparticle systems involved in drug delivery - the nanoparticle get entrapment of drugs are either enhanced delivery to, or uptake by, target cells, and/or a reduction in the toxicity of the free drug to non-target organs. In the fields of information and communication technology, power engineering, industrial engineering, environmental engineering, chemical industry, medicine, pharmaceuticals, and cosmetics, among others, a number of nanoparticle systems are now being researched and studied for biological application. Application of nanoparticles in food, often known as "nanofood," is a phrase used to describe foods that incorporate manmade nanomaterials into the growth, production, processing, or packaging of the food. The efficient introduction of a gene of interest to express its encoded protein in an appropriate host or host cell is made possible by the use of nanoparticles in gene delivery. Nanomedicine helps with disease early detection and prevention, improved diagnosis, and follow-up care. Gene sequencing has become easier thanks to the development of nanotechnology, such as gold nanoparticles. [19]

Silver nanoparticles are widely employed in the electronics sector, as an antibacterial agent in medicine, and other fields. Nanotechnology is a way to manipulate matter at the molecular level. Nanoparticles in nutritional aspects.

In colon targeting, since eudragit degrades in the colon, it was successfully used for colon medication administration. Compared to the uncoupled nanoparticles, these particles showed improved cellular absorption by ht-29 colon cancer cells. Nanoparticles designed for colon-targeted administration that have unique biodegradability and pH-sensitive characteristics. [20] In case of liver cancer, by using either active targeting based on identification between hepatic receptor and ligand-bearing particulates, or passive trapping of nanoparticles by reticuloendothelium, eudragit nanoparticles were employed for liver delivery. [21] Drug carrier conjugates made of chitosan have been utilized to target medications for the kidney. After being administered intravenously to mice, the low molecular weight chitosan (lmwc) specifically collected in the kidneys, notably in the renal tubes. [22] A lung cancer cell line (a549) significantly absorbed more of the nanoparticles in-vitro thanks to the chitosan modification. Chitosan nanoparticles changed their charge to become more positive in an acidic tumor environment, where they aggressively interacted with the tumor cells' negative charges. The acidic microenvironment promotes greater interactions between C-NPS and tumor cells. The blood brain barrier (BBB), which regulates the movement of endogenous and exogenous substances and serves the neuroprotective role, makes the brain one of the least accessible organs for the delivery of medications. Modified polybutylcyanoacrylate (PBCA) nanoparticles have the ability to transfer drugs to the brain after adhering to the surface. [23]

A. BIOSYNTHEZED NANOPARTICLES

In the recent research, biosynthesized nanoparticles are found to control the rapid tumor growth and induce apoptosis in cancer cells. They come with the advantage of easy internalization by tumor cells. Biogenic nanoparticles are made from biological sources like plants, animals, and microorganisms. Nanoparticles produced using bacteria like E.Coli demonstrated impressive results against ovarian cancer. Biological sources come with multiple targets and choosing a selective agent with high specificity towards each cancer type can be seen as a promising solution. [24, 25].

B. NANOCARRIES IN PHOTODYNAMIC THERAPY

Photodynamic therapy is a dual targeted drug delivery systems that uses energy in the form of light. A drug, also known as photosensitizer is administered into the body. Due to the affinity, the drug gets absorbed into the cancer cells. After incubation period, the patient is exposed to light at predetermined wavelength. The light activates the photosensitizer to produce oxygen which results in destruction of cancer cells. [26] This procedure is minimally invasive and provides targeted cytotoxicity. Clinical studies have shown that it is highly effective in early stages of cancer.

The anticancer effect occurs as a result of photochemical reaction between the light and the photosensitizer leads to formation of singlet oxygen which is highly toxic to the surrounding cancerous cells via necrosis and apoptosis. The photosensitizers are mostly based on tetrapyrrole. It is highly active in 600-800nm range. This light range is sufficient to activate the agent and produce oxygen singlet. [27, 28] Mixture of porphyrin, hematoporphyrin derivative was the first clinically used photosensitizer and still remains as the most widely used photo sensitizer. A light source is selected based on the extend of penetration. Blue lights are sufficient for topical or surface tissues while infrared lights are required for deeper tissue penetration. [29] The choice of the light is also dependent on the structure of the photosensitizer, target site and disease condition.

Liposomal carriers are being used as carriers for water-insoluble photosensitizers. The use of magnetic ceramic, metallic and polymeric nanoparticles, are used in this fashion. [30]

C. SELF THERAPEUTIC NANOCARRIERS

Most of the nanocarriers require an external stimuli to reach the target or for activation. Self therapeutic nanocarriers can directly exert anticancer effect without the use of external and even without an therapeutic agent. [31] These carriers rely on free radical generating species which can scavenge the tumor cells. Copper, silver and gold are good examples of self therapeutic carriers that possess impressive anticancer properties. [32] These metals act as deoxygenating agents that cut down the oxygen supply to the tumor site, restricting its growth. Majority of the self therapeutic system is based on peptides. One big example is (KLAKLAK)₂ (KLAK) is a popular peptide in anticancer self therapeutic therapy and an amphiphilic peptide with positive in vitro and in vivo results.

7. CONCLUSION

The modern medication is constantly working on the drug delivery systems to improve therapeutic action of the active pharmaceutical agent. Delivering a drug with effective delivery system enables better therapeutic outcome. By bringing the down the size of the carrier, an effective outcome can be achieved. Nanotechnology is the talk of the hour. Use of nanocarriers help overcome formulation hurdles like solubility. Nanocarriers offer enormous potential in targeting tumor cells and result in better outcome. We believe that further research in nanocarrier can lead to development of newer carriers which can be helpful in treating complex diseases.

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