INTERNATIONAL JOURNAL IN PHARMACEUTICAL SCIENCES

Journal Homepage: https://www.ijpsjournal.com

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Review Article

Formulation And Evaluation of Nanoparticles-A Review

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ARTICLE INFO

Received: 08 June 2023
Accepted: 05 July 2023
Published: 09 July 2023
Keywords:
Nanotechnology, Nanoparticles, Types, Preparation and Evaluation
DOI:
10.5281/zenodo.8127920

ABSTRACT

Nanotechnology is the study of manipulating matter at the atomic and molecular levels and deals with matter at a scale of 1 billionth of a metre. The quality of human life recently been altered and improved physically using particulate systems like nanoparticles. They have been used in vivo to maintain the drug entity in systemic circulation, prevent drug access to the targeted sites, and transport the drug to the site of action at a controlled and steady rate. In general, nanoparticles have one or more dimensions and range in size from 1 to 100 nm. Nanoparticles are the preparations having size in nanometres. In this various polymer are used in the formulation of nanoparticles for the drug delivery research to increase therapeutic benefit. This review mainly focussed on types, preparation methods such as cross-linking technique, polymerization-based methods, polymer precipitation methods, and evaluation parameters such as particle size, zeta-potential, particle shape, drug entrapment efficiency, scanning electron microscopy, transmission electron microscopy, Fourier transform infrared spectroscopy, X-ray diffraction, differential scanning calorimetry, surface hydrophobicity, invitro drug release of nanoparticles.

INTRODUCTION

Nanotechnology employs knowledge from the fields of physics, chemistry, biology, materials science, health sciences and human life. [1] Nanoparticles are particles between 1 and 100 nanometres in size and are made up of carbon, metal, metal oxides or organic matter. [2] In These properties of nanoparticles has led to its use various applications. The nanoparticles differ from various dimensions, to shapes and sizes apart from their material. [3] It can be spherical, cylindrical, tubular, conical, hollow cored, flat, etc. With single or multiple crystal solids that are either loose or agglomerated, certain nanoparticles are either crystalline or amorphous. [4]A drug's complex and large molecular structure is one of the key causes of its insolubility. Around 65% of new active pharmaceutical ingredients (APIs) are either not soluble in water or have poor solubility, according to reports. According to the Biopharmaceutics Classification System (BCS),

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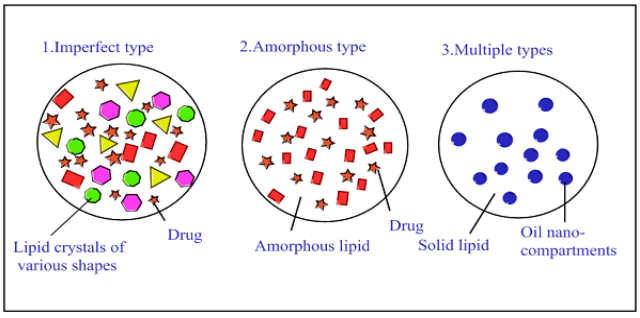
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

which states that the dissolution phase is the rate-limiting step in medication absorption, they are classified as class II due to their low water solubility and high permeability. [5] Both tiny medicinal molecules and macromolecules like nucleic acids, peptides, proteins, and hormones have been successfully delivered via nanoparticles. When given orally, macromolecules like peptides and proteins are protected from gastrointestinal enzymes and pH effects by being encapsulated since they have stability issues. Furthermore, it was shown that bioactive nanoparticles loaded with pharmaceuticals may not only control distribution but also deliver drugs to specific human part. [6] These days, nanoparticles are frequently used as a delivery system for drug molecules that have issues with solubility and poor bioavailability when administered orally. Nanoparticles are known to be an effective approach to achieve better pharmacokinetics profiles, reduced toxicity, and to increase the oral bioavailability of a number of drugs through specialised uptake mechanisms from gastrointestinal tract (GIT) through payer's patches via M cells of lymphatic system.[7] Moreover, nanoparticles have been employed in vivo to deliver drugs at a controlled and sustained rate to the site of action while protecting the drug entity from harm throughout its routine circulation. In order to maximise therapeutic effectiveness while avoiding side effects, several polymers have been used in the creation of nanoparticles for drug delivery research.



Structure of nanoparticles

Advantages of Nanoparticles

- Site-specific targeting is often achieved by attaching targeting ligands to the surface of particles.
- Drug release can be controlled or sustained which will increase the therapeutic efficacy of a drug.
- Side effects and toxicity shall be reduced.
- They have the ability to incorporate both hydrophilic and hydrophobic drug molecules.
- Passive and active drug targeting can be easily achieved by manipulating surface and particle size characteristics.
- The system can be administered via different routes including oral, nasal, parenteral etc.
- These have the potential to increase the bioavailability of drugs.
- They have longer clearance time.
- Site-specific targeting can be accomplished using magnetic guiding or by attaching targeting ligands to the surface of particles. [8]

Disadvantages of nanoparticles

- It involves greater manufacturing expenses, which could result in an increase in formulation costs.
- These have low encapsulation efficiency.
- Water-soluble drugs can be rapidly leaked out in the presence of blood components.
- Particle aggregation and physical handling of nanoparticles in dry and liquid form are difficult.
- They may trigger immune response and allergic reaction.
- It may involve use of harsh toxic solvents in the preparation process. [8]

Ideal properties of nanoparticles

- Stable in blood
- Non toxic
- Non thrombogenic
- Non immunogenic
- Non inflammatory

- No activation of neutrophils
- Biodegradable
- Avoidance of the reticulo-endothelial system
- Applicable to various molecules, such as small molecules, proteins, peptides or nucleic acids (platform technology).
- Inexpensive manufacturing process Because poly (butyl-cyano-acrylate) nanoparticles above properties and were reported to be useful tools to deliver the drugs in several experiments. In addition, they exhibit very low toxicity and are considered to be ideal. [9]

Applications of nanoparticles

1. For ocular delivery systems, to deliver pilocarpine and other miotic drugs.
2. For cytostatic medication targeting to lower toxicity and enhance therapeutic efficacy.
3. For targeted delivery of proteins and peptides.
4. In the form of solid nanoparticles for skin and hair care, the oily core of which comprises a wide range of various cosmetic oils and lipophilic substances.
5.To formulate sustained release preparations.
6. To deliver drugs across the blood brain barrier (BBB).
7. It is used in treatment of malignant tumours.
8. It improves the stability of drugs. [5,9]

Types of nanoparticles

1.Solid lipid nanoparticles
2.Polymeric nanoparticles
3.Polymeric micelles
4.Magnetic nanoparticles
5.Carbon nanotubes
6.Liposomes
7.Nano shells
8.Nanosuspensions and nanocrystals
9.Ceramic nanoparticles
10.Nano pores
11.Nano wires
12.Quantum dots
13.Nanofilms [10]

Methods for preparation of nanoparticle

1.Nanoparticles preparation by cross linking techniques

These amphiphilic macromolecules, proteins, and polysaccharides, which have high affinity for aqueous and lipid solvents, are used to make the nanoparticles. Amphiphiles are first gathered together in the procedure for their preparation, and then they are further stabilised either through heat denaturation or chemical cross-linking.

Using high pressure homogenization or high-frequency sonication, the procedure entails emulsifying bovine serum albumin/human serum albumin or protein aqueous solution in oil. the newly created w/o emulsion is then put into hot oil (heat cross-linking). The warmed oil is kept above 100 degrees Celsius and the suspension is kept stirring for the duration of the process in order to agglomerate and denature the protein content and evaporate water. The resulting particles were centrifuged to remove any remaining oil traces and then rinsed with a nature solvent. Chemical cross-linking is done for materials that are heat-sensitive. [8]

Cross linking can be done by two methods;

a) Heat denaturation method
b) Chemical cross-linking method

2. Polymerization based methods

They are three methods,

a) Emulsion polymerization
b) Dispersion polymerization
c) Interfacial polymerization

a) Emulsion polymerization

Emulsion with water, monomer, and surfactant are included in emulsion polymerization. The most typical form of emulsion polymerization, in which droplets of monomer are emulsified in a continuous stage of water, is an oil-in -water emulsion.one of the easiest ways to create nanoparticles is using emulsion polymerization. It entails dispersing the monomer into a solvent that it is not soluble in (non-solvent). In the initial

phases of polymerization, aggregation is avoided using surfactants or protective soluble polymers. Then, several mechanisms can be used to start the polymerization process, such as applying high energy radiation, such as uv or visible light, which can convert monomers into initiating radicals.

Initiation happens when a monomer contact one of these radicals. Phase separation and the creation of solid particles can happen either before or after the polymerization reaction has finished. [11]

b) Dispersion polymerization

It involves a homogenous system made of dissolved monomers, initiators, and stabilisers in a solvent that will produce polymer particles. The solvent utilised in this procedure is non-solvent.

And can be used to quickly dissolve the monomers and initiators. Direct induction of nucleation occurs in aqueous monomer solution. Hence, no stabiliser or surfactant is required. The same method used in high energy radiation-induced emulsion polymerization is used for initiation. Adding a catalyst causes polymerization to begin, and it continues through the nucleation stage, followed by the development stage. [12,13]

c) Interfacial polymerization

In this particular type of step-growth polymerization, polymerization occurs at the boundary between two immiscible phases (generally two liquids). It is one of the tried-and-true techniques used to create nanoparticles. It involves the polymerization of two reactive monomers or agents that are dispersed in two phases, namely the continuous phase and the dispersed phase, respectively. The reaction occurs at the interface of the two liquids. Oil-containing a very fine oil-in-water microemulsion was used to create Nanocapsule by polymerizing monomers at the oil/water interface. [14,15]

3) Polymer precipitation methods

They are four methods,

a) Solvent evaporation method

b) Double emulsion method

c) Emulsion-diffusion method

d) Salting out method

a) Solvent evaporation method

This technique involves dissolving polymers in an organic solvent like dichloromethane or chloroform before dispensing the medicine in this mixture. Aqueous phase containing a surfactant, such as sodium dodecyl sulphates, was used to emulsify the combination. You can create an oil-in-water emulsion by mechanically stirring, using sonication, or via micro fluidization (high-pressure homogenization).

The organic solvent is then evaporated using a combination of continuous stirring, increased temperature, and decreased pressure. By varying the stirring rate, the kind and quantity of the dispersant, the viscosity of the organic and aqueous phases, and the temperature, nanoparticle sizes can be regulated. This approach uses the polymers PLA, PLGA, cellulose acetate phthalate, and poly-hydroxybutyrate (PHB). [16]

b) Double emulsion method

This method is useful for incorporating hydrophilic drugs because of poor entrapment of hydrophilic drugs by emulsification and evaporation methods, so double emulsification technique is utilized.

This approach involves continuously agitating an organic polymer solution while adding an aqueous drug solution. The result is a w/o emulsion. To create a w/o/w emulsion, this created emulsion is then vigorously stirred into another aqueous phase. The organic solvent is then removed by high centrifugation. [16,17]

c) Emulsion-diffusion method

It is a modification of the solvent evaporation technique. This approach offers a substitute for the emulsification-evaporation procedures that have solvent-toxicity issues. It is highly reproducible and has a simple implementation. Many medications, including peptides and proteins, are also enclosed in it. In this procedure, the initial

thermodynamic equilibrium of the two liquids is made sure by dissolving the encapsulating polymer in a solvent that is only slightly water soluble, like propylene carbonate, and then saturating it with water. Following the emulsification of the polymer-water-saturated solvent phase in an aqueous solution containing a stabiliser, solvent diffusion to the exterior phase and the formation of nanospheres or nano capsules based on the oil-to-polymer ratio occur. Then finally, the solvent is eliminated by evaporation or filtration, according to its boiling point. [18,19]

d) Salting out method

The emulsification/solvent diffusion method is modified by the salting out process. The medication and polymer are first dissolved in a solvent. Toxic solvents are not employed in this procedure. Acetone is typically utilised since it is easily removed and miscible with water.

The aqueous gel created from the above mixture is then emulsified using a colloidal stabiliser and salting-out agents such electrolytes like magnesium chloride, calcium chloride, and magnesium acetate or non-electrolytes like sucrose (polyvinyl pyrrolidone or hydroxyethyl cellulose). The production of nanospheres is caused by diluting the oil/water emulsion with enough water or an aqueous solution to increase the diffusion of acetone into the aqueous phase. [20,21]

Evaluation of nanoparticle:

1.Particle size

The two most crucial factors in the characterisation of nanoparticles are the particle size distribution and shape. electron microscopy is used to measure size and morphology.

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. The majority of the drug that has been placed onto them will therefore be exposed to the particle surface, resulting in rapid drug release. Contrarily, medicines slowly spread across bigger particles. [22]

2. zetapotential

The surface charge property of nanoparticles is frequently described using the zeta potential of a nanoparticle. It exhibits how electrically charged particles are and is affected by both the particle's makeup and the medium in which it is disseminated. It has been demonstrated that nanoparticles having a zetapotential higher than () 30 mV are stable in suspension because the surface charge prevents the particles from aggregating. [23]

3. Particle shape

Before being evaluated, the nanosuspension is characterised by SEM and then lyophilized to produce solid particles. The solid particles have a platinum alloy coating, by means of a sputter coater. [24]

4. Drug entrapment efficiency

Ultracentrifugation was used to remove the nanoparticles from the aqueous medium for 30 minutes at 50C at 10,000 rpm. A decanter was used to collect the resultant supernatant solution. In phosphate buffered saline pH7.4 dispersed to thoroughly eliminate the unentrapped drug molecules. The technique was performed again. The difference between the total amount of drug used to generate the nanoparticles and the amount of drug present in the aqueous medium was used to calculate the amount of drug entrapped in the nanoparticle. [25] Drug entrapment efficiency is given by the following equation,

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

5.Scanning electron microscopy

Scanning electron microscopy (SEM) is giving morphological examination with direct visualization. The techniques based on electron

microscopy. To characterise nanoparticles using a SEM, the solution first needs to be turned into a dry powder and put on a sample holder. Employing a sputter coater to apply a conductive metal, such as gold, as a coating. Following that, a finely focused electron beam is utilised to scan the sample. The secondary electrons emitted from the sample. The polymer can be harmed by the electron beam, and the nanoparticles must be able to tolerate vacuum. The average size found by SEM is comparable to findings from dynamic light scattering. [26]

6.Transmission electron microscopy

Transmission electron microscopy (TEM) operates on different principle than SEM. yet it often brings same type of data. The sample preparation for TEM is complex and time consuming because of its requirement to be ultra-thin for the electron transmittance. The dispersion of nanoparticles is applied on films or grids of support. To enable and ensure that nanoparticles can withstand the instrument vacuum after treatment, they are either fixed by plastic embedding or a negative staining substance such phosphotungstic acid or its derivatives, uranyl acetate, etc. the sample can also be heated to liquid nitrogen temperatures after being embedded in vitreous ice. When a beam of electrons passes through an incredibly thin sample and interacts with it as it does so, the surface features of the sample are discovered. [27]

7.Fourier transform infrared spectroscopy

In the process of measuring the coherence of a radiative source using time-domain or space-domain measurements of electromagnetic radiation or another type of radiation, spectra are obtained using the Fourier transform spectroscopy method. It may be used with many other kinds of spectroscopy, including as optical spectroscopy, infrared spectroscopy, Fourier transform (FT), nuclear magnetic resonance, mass spectrometry, and electron spin resonance spectroscopy. There are several methods for measuring the temporal coherence of the light, including the continuous wave Michelson or Fourier transform spectrometer and the pulsed Fourier transform spectrograph. [28]

8. X-Ray Diffraction (Power X-ray Diffraction)

A solid's degree of crystallinity may be established by determining whether or not crystal planes are present in it by the geometric scattering of radiation from those planes. By lowering the wavelength and angle of incoming light on nanoparticles, order at the smaller scale may be studied. Due to the latter particle's shorter De Broglie wavelength, using electron or neutron beams enables decrease of the former value. [29]

9.Differential scanning calorimetry (DSC)

The type and variety of crystallinity inside nanoparticles may be determined using DSC, another technique that differs slightly from its application to bulk materials, by measuring the glass and melting point temperatures and their corresponding enthalpies. This method is frequently used as a complement to X-ray diffraction to assess the extent of multiple phases present inside or the degree of interaction between the various constituents, including the drug. [30]

10.Surface hydrophobicity

Many methods, including contact angle measurements, biphasic partitioning adsorption of probes, hydrophobic interaction chromatography, and others, may be used to detect the hydrophobicity of a surface. For the surface investigation of nanoparticles, a number of advanced analytical approaches have recently been published in the literature. Using X-ray photon correlation spectroscopy, it is possible to identify certain chemical groups that are present on the surface of nanoparticles. [31]

11. *Invitro* Drug release studies

Understanding how and how much drug molecules are released is crucial because delivering medicines is a major motivation for the

development of nanotechnology. The medication and its transport mechanism must typically be separated in order to acquire this information for the majority of release techniques. The quantity of drug bound per mass of polymer is the basic definition of the drug loading of the nanoparticles. It can also be expressed as a proportion relative to the polymer. Classical analytical techniques, such as UV spectroscopy or high-performance liquid chromatography (HPLC), are used for this study after ultra-centrifugation, ultra-filtration, gel filtration or centrifugal ultrafiltration. Quantification is carried out using HPLC or UV spectroscopy. Drug loading assays, which are evaluated over time to examine the mechanism of drug release, are comparable to drug release assays in this regard. [32]

CONCLUSION

Nanoparticles are now important in many industries, including energy, health care, the environment, agriculture, etc., because to their remarkable properties. Nanotechnology uses possess significant promise for transforming unstable, poorly soluble, and poorly absorbed physiologically active compounds into potential deliverable chemicals. From the above description we conclude that a new drug transport method that uses nanoparticles may be crucial in achieving therapeutic advantages that are efficient, improved bioavailability, and low toxicity. The current medical system has benefited greatly from it, and is expected to mark a turning point for the developing health care system.

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HOW TO CITE: Muni Raja Lakshmi K*, Lavanya E, Naseema Shaik, Vankata Rao Gadde, Formulation And Evaluation of Nanoparticles-A Review, Int. J. in Pharm. Sci., 2023, Vol 1, Issue 7, 196-204. https://doi.org/10.5281/zenodo.8127920