10.37021/ijper.v7i2.01

REVIEW ARTICLE

Polymeric Nanoparticles: An Overview of Preparation, Characterization, Applications, and Future Perspectives

Randhawan Bhagyashri[*], Dr. Hapse Sandip[1]

ABSTRACT

Polymeric nanoparticles (NPs) are tiny particles with a size between 10 and 1000 nm, with the ability to contain or have active substances surface-adsorbed onto the polymeric core. Both nanospheres and nano capsules are under the umbrella of "nanoparticles," which are distinguished by the morphological organisation. For the targeted delivery of medications used to treat a variety of disorders, polymeric NPs have demonstrated considerable promise. We go through the most popular techniques for creating and characterising polymeric NPs, the effectiveness of the active ingredient's connection with the polymeric core, and in vitro release mechanisms in this review. Due to their adaptability and broad range of features, polymeric nanoparticles have recently gained more potential usage as carriers for a variety of pharmaceuticals in therapeutic applications. Due to the drawbacks of conventional pharmacological therapy, there will be a higher risk of unpleasant responses. These days, nanoparticles are becoming more and more significant since they enable activity at specific locations. These nanoparticles enable the precise targeting of different cells or receptors. Cellular absorption and internalisation are both regulated in a number of different ways.

Keywords: Polymeric nanoparticles, Nanospheres, Nano capsules, Targeted drug delivery.

How to cite this article: Bhagyashri R, Sandip H.Polymeric Nanoparticles: An Overview of Preparation, Characterization, Applications, and Future Perspectives. Int. J. Pharm. Edu. Res. 2025;7(2):1-10.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

The drug is dissolved, entrapped, encapsulated, or linked to a nanoparticle matrix in the form of polymeric nanoparticles (PNPs), which range in size from 10 to 1000 nm and are made from biocompatible and biodegradable polymers. Depending on the method of preparation, nanospheres and nano-capsules can be created. In Nano capsules, the drug is physically and evenly distributed throughout the matrix, but in nanospheres, the drug is contained within a hollow that is surrounded by a special polymer membrane. With applications in medicine, biotechnology, and environmental technology, the field of polymeric nanoparticles (PNPs) is expanding quickly. PNPs are appealing drug delivery systems because some PNP methods (eg., emulsion polymerization) can be complex. They carriers designed to deliver medications to certain targets. (Singh and Lillard, 2009)

Polymer-based nanoparticles effectively carry drugs, proteins, and DNA to target cells and organs. Their nanoscale size enables effective cell membrane penetration and circulatory stability. Polymers are extremely helpful components when building various molecular patterns that can be combined to create distinctive nanoparticle shapes with various potential medical applications. Over the past two decades, a number of techniques for producing PNPs have been developed. These techniques are divided into three categories based on how the particle is formed: through a polymerization reaction, directly from a macromolecule or pre-made polymer, or through an ionic gelation technique. (Yadav et al .2012)

METHOD OF PREPARATION OF POLYMERIC NANOPARTICLES

Depending on the intended use, different polymeric nanoparticles are created using different processes.

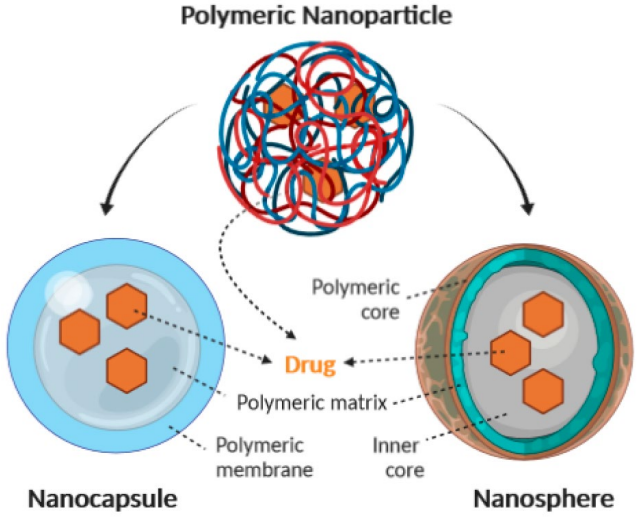

Figure 1: Structure of a nanocapsule and a nanosphere.

[*]Research Scholar, Shubham University, Bhopal, MP

[1]Assistant Professor, Dr.V.V.P.F's College of Pharmacy, Vilad Ghat, Ahilyanagar, MS

Corresponding Author: Hapse Sandip, Assistant Professor, Dr.V.V.P.F's College of Pharmacy, Vilad Ghat, Ahilyanagar, MS, E-mail: sandiphapse@gmail.com

Polymerization and drug dispersion in prepared polymers are the two most common processes for producing PNPs in drug delivery methods. There are advantages to polymerization processes, such precise control over size, architecture, and functionality of nanoparticles. The release-defining properties, chemical make-up, charge, hydrophilicity/hydrophobicity, swelling/de-swelling ability, reactivation, and pH dependence/independence can all have an impact on the choice of polymer. (Bock et al., 2011; Bruschi et al., 2002; Jyothi et al., 2010)

Methods for preparation of nanoparticles from the dispersion of preformed polymer

- Solvent evaporation
- Nanoprecipitation
- Emulsification/solvent diffusion
- Salting out
- Dialysis
- Supercritical fluid technology (SCF)

Methods for preparation of nanoparticles from polymerization of monomers

- Emulsion
- Mini emulsion
- Micro emulsion
- Interfacial polymerization
- Controlled/Living radical polymerization(C/LRP)

Ionic gelation or coacervation of hydrophilic polymers

Solvent Evaporation

The first technique created to create polymeric NPs from a premade polymer was solvent evaporation. In order to produce nanospheres using this approach, an oil-in-water (o/w) emulsion must first be prepared. The process begins with creating an organic phase, which consists of a polar organic solvent in which the polymer is dissolved and the active ingredient (such as a medication) is added through dissolution or dispersion. Chloroform and dichloromethane are frequently utilised, albeit more so in the past. They have been replaced by ethyl acetate, which exhibits a superior toxicological profile and is more appropriate for biomedical applications, due to its toxicity. The preparation of an aqueous phase containing a surfactant, such as polyvinyl acetate (PVA), is also common. The organic solution is treated by high-speed homogenization or ultrasonication after being emulsified in the aqueous phase using a surfactant. This results in a dispersion of nanodroplets. The polymer solvent evaporates while being allowed to diffuse into the continuous phase of the emulsion, resulting in a suspension of NPs. When utilising more non-polar to

Figure 2: Schematic representation of the solvent evaporation method.

moderately polar solvents, such as dichloromethane and chloroform, for example, the solvent is either slowly evaporated under reduced pressure or by continuous magnetic stirring at ambient temperature. The nanoparticles can then be cleaned, recovered by centrifugation, and freeze-dried for prolonged storage after the solvent has evaporated. (Ahmed and Aljaeid, 2016)

Nanoprecipitation

This procedure, also known as the solvent displacement procedure, calls for two miscible solvents. A polymer that has been dissolved in an organic miscible solvent, such as Acetone or acetonitrile. They are easily eliminated by evaporation because they are immiscible in water. The basis of this method is the interfacial deposition of a polymer once the organic solvent is displaced from a lipophilic solution to the aqueous phase. The polymer is dissolved in an intermediate polarity water-miscible solvent, and this solution is dropped-wise or at a regulated rate sequentially into an aqueous solution while being stirred. The nanoparticles form instantly to escape the water molecules as a result of the rapid spontaneous diffusion of the polymer solution into the aqueous phase. The polymer precipitates as nano capsules or nanospheres as the solvent diffuses from the nanodroplets. While adding the organic phase to the aqueous phase is customary, the technique can also be reversed without negatively impacting the creation of nanoparticles. Although their presence is not necessary to ensure the creation of nanoparticles, surfactants can typically be added to the process to maintain the stability of the colloidal suspension. The resultant nanoparticles typically have a narrow size distribution and a well-defined size, which distinguishes them from those made by the emulsification solvent evaporation process. (Beyer et al., 2015)

One of the most well-liked and repeatable methods for laboratory drug encapsulation is nanoprecipitation. It is founded on the use of a non-solvent, which must be miscible with the solvent but is insoluble for the drug

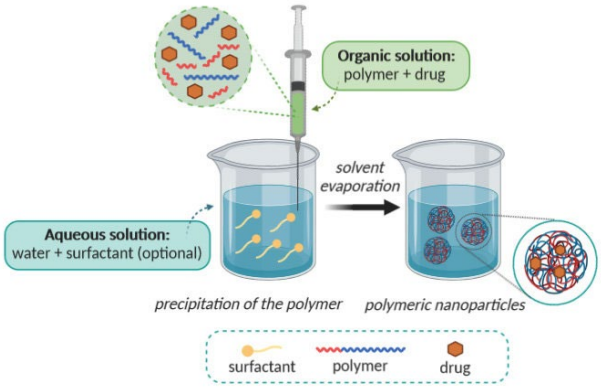

Figure 3: Schematic representation of the nanoprecipitation method.

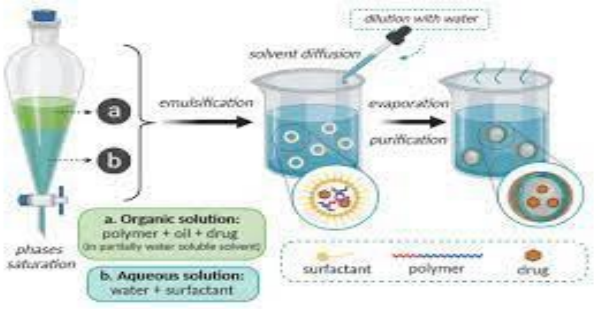

Figure 4: Schematic representation of the emulsification/

and polymer, and a solvent in which the polymer and drug are soluble. Following contact between the two solutions, a spontaneous diffusion of the polymer-drug solution occurs in the direction of the non-solvent, resulting in simultaneous polymer precipitation and API encapsulation. Nanoprecipitation is typically used to produce NPs with a low polydispersity index and a size range of 100 to 300 nm. The water, whether or not it contains a stabiliser, is employed as a non-solvent, and the most used solvents are ethanol, acetone, and tetrahydrofuran. Solvent type, polymer concentration, solvent/non-solvent ratio, non-solvent addition flow rate, and stirring rate are frequently examined for process optimization. One of the most often used techniques for creating PLGA NPs is nanoprecipitation. The efficiency of the mixture and the precipitation can make the scale-up problematic, despite the fact that it is fairly reproducible at the laboratory scale. Because they enable better control of the factors involved in precipitation processes and can generate the formulations on a medium scale, microreactors have thus been utilised to aid the process. (Roberge et al., 2009; Zhao et al., 2011)

Emulsification/solvent diffusion

This technique involves creating an o/w emulsion between an aqueous solution containing a surfactant and a somewhat water-miscible solvent containing a polymer and medicament. This emulsion's internal phase is made up of a somewhat hydro-miscible organic solvent, like benzyl alcohol or ethyl acetate, that has already been saturated with water to provide an initial thermodynamic equilibrium between the two phases at room temperature. Colloidal particles are created as a result of solvent diffusion from the dispersed droplets into the external phase, which is caused by the following dilution with a high amount of water. Usually, this process is used to create nanospheres, but if a small amount of oil (such as triglycerides: C6, C8, C10, C12) is added to the mixture, nano capsules can also be created. (Archana et al.2013)

Salting out

The separation of a water miscible solvent from an aqueous solution is the basis for the salting-out effect. You can think of the salting-out method as an emulsification/solvent diffusion method modification. The salting-out agent (electrolytes such as magnesium chloride, calcium chloride, and magnesium acetate, or non-electrolytes like sucrose) and a colloidal stabiliser like polyvinylpyrrolidone or hydroxyethyl cellulose are used to emulsify the polymer and medication after being first dissolved in acetone. In order to improve acetone penetration into the aqueous phase, this oil/water emulsion is thinned out with just enough water or aqueous solution to produce nanospheres. The effectiveness of the drug's encapsulation can be significantly impacted by the salting-out agent, so it should be carefully chosen. The solvent and salting-out agent are both removed via cross-flow filtration. The process used to create PLA, or poly (methacrylic acid), nanospheres is highly effective and simple to scale up. Reduced protein encapsulant stress is the main advantage of salting out. When processing heat-sensitive materials, salting out may be advantageous since it doesn't call for a temperature rise. The most notable limitations are

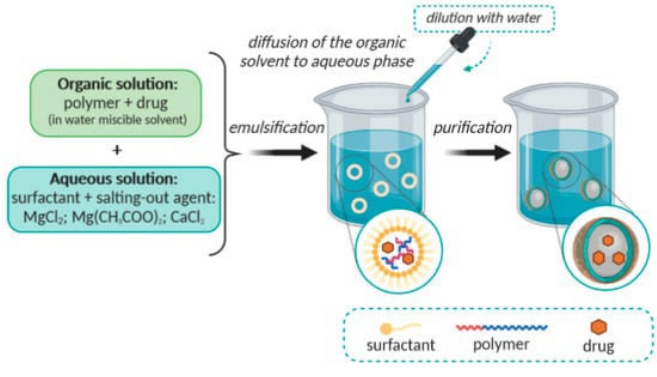

Figure 5: Schematic representation of the salting-out method

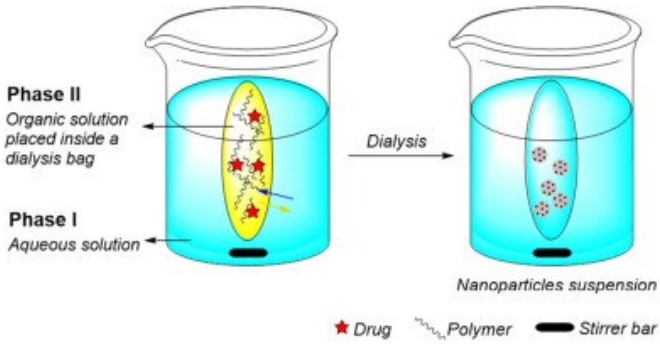

Figure 6: Schematic representation of the dialysis method.

the extensive nanoparticle cleaning operations and the restricted use to lipophilic drugs. (Lambert G et al, .2001)

Dialysis

The creation of the dialysis procedure served as the culmination of efforts to investigate a nanoparticulate framework free of surfactants. The dialysis approach is one of the most often used methods because of its many benefits, including its ease of use and effectiveness in producing polymeric nanoparticles with a uniform size distribution. Dialysis offers a straightforward, practical method for producing tiny, homogenous PNPs that is free of surfactants. The dialysis tube is filled with polymer that has been dissolved in an organic solvent and has a specific molecular weight cut-off. Due to a reduction in solvability and the onset of homogeneous nanoparticle suspensions, the withdrawal of the solvent from inside the film causes vanguard polymer buildup. The polymer solvent used affects the nanoparticles' morphology and size. (Lee J et al.2004)

Supercritical fluid *technology (SCF)*

It should be emphasised that the techniques covered in the previous sections call for the use of organic solvents and surfactants, both of which pose risks to human health and the environment. On the other hand, if solvent contaminants from the original solvent are still present in the drug-loaded PNPs, they become toxic and may cause the drug to break down in the polymer matrix. Another difficulty is coming up with accurate, adaptable production techniques for nanomedicines that could be easily scaled up. Research efforts have been focused on developing environmentally sound PNP production techniques in order to address these obstacles. A SCF is a fluid that has been heated and compressed above its critical pressure (Pc) and temperature (Tc) (Pc). Its physicochemical characteristics in these circumstances fall between a gas and a liquid. This is a novel state of matter where the fluid has the density and solvating properties of a liquid while also behaving like a gas. The most popular SCF is supercritical carbon dioxide (scCO2) because it possesses moderate critical conditions, is plentiful, affordable, non-flammable, nontoxic, and environmentally safe. (Kawashima, 2001; York, P., 1999)

Methods for preparation of nanoparticles from polymerization of monomers

Emulsion Polymerization

One of the quickest methods for producing nanoparticles is polymerization, which may be categorised into two forms depending on whether an organic or an aqueous continuous phase is utilised. Monomer dispersion into an emulsion or suspension is mastery of the continuous organic phase process, as in Inverse microemulsion or any nonsolvent. If enough energy is applied, the monomer can also be changed into an initiating radical. When this radical monomer strikes another monomer, the chain propagates, and phase separation and the formation of solid particles can happen before or after termination. In the beginning, surfactants and other soluble polymers were used to prevent the particles from clogging during the polymerization process. However, this procedure is no longer used because dangerous chemicals were used at various stages. (Kreuter, 1982; Reis et al., 2006)

Mini-emulsion polymerization

For mini-emulsion polymerization processes, free radical producers (initiators) and radical polymerizable monomers, dispersion media (often water), surfactants, and organic solvents. The emulsion polymerization medium is typically deionized water. A 50–500 nm homogeneous emulsion or settling scatterings of monomer nanodroplets are used in the mini-emulsion polymerization process. Under constant mixing, an organic solvent containing an initiator and a dissolver is combined with a watery stage containing surfactant and water. This results in a conventional emulsion. A high-energy mechanical source, like an ultrasonicator, is used to create nanodroplets. During the mechanical unsettling process, the monomer beads rapidly change in size until they finally find a balancing state with a negligible attainable nano-molecule size. (Bardajee et al., 2007; Baruch-Sharon and Margel, 2010)

Micro emulsion technique

In a microemulsion, a water-solvent initiator is added to a miniaturised-scale emulsion fluid that contains a volatile organic solvent and monomer and has been thermodynamically tuned. The surfactant-containing water is added, and as soon as it is, the polymerization process begins. This process depends on a substantial amount of surfactant framework, which reduces interfacial tension to almost zero. These emulsions

can be made by combining two immiscible oil/water phases; ultrasonication is not necessary. Additionally, due to the usage of a considerable amount of surfactant, nanoparticles are completely submerged in surfactant. The resulting particles are between 5 and 50 nm in size. This method can be used to create polymer nanoparticles with a variety of morphologies, such as core-shell, hollow spherical, moonlike, etc. (Prasad Rao and Geckeler, 2011)

Interfacial polymerization

A general preparation method for getting PNPs is interfacial polymerization. Polymerization in steps is another name for it. In this method, the two miscible liquid phases' interfacial region serves as the site of polymerization. This method can be used to create a variety of polymer nanoparticles, including ultra-thin films, nano capsules, and nanofibers. Liquid-solid interfaces, liquid-liquid interfaces, and liquid-in-liquid emulsion interfaces are among the many types of interfacial polymerization that exist. Two immiscible (consistent and dispersed) fluid phases of two reactive monomers are scattered. The immiscible stages' interfacial limit is where the response occurs. Momentarily, the latex nanoparticles scatter in the fluid stage. A number of polymers, including polyaniline (PANI), polypyrene (PPy), poly(3,4-ethylenedioxythiophene), and polythiophene (PTh), have been developed. (Shrivastav P.S et al.2019)

Controlled or living radical polymerization (C/LRP)

Using the aforementioned polymerization techniques, radical polymerization courses introduced new methodologies to PNPs that had been obtained. This is among the most helpful techniques for making polymers. It entails the polymer undergoing free radical generation, which can be produced in several ways, for example, by adding an initiator. Particularly in the context of emulsion polymerization, radical polymerization takes place in a continuous or dispersed framework and is sustained by the ongoing expansion of free radical components. The profitable component of the plan is to adjust the polymer's key features, resulting in the creation of PNPs with the appropriate molecular size and size distribution, design, and utility. Numerous radical polymerization techniques have been proposed in the literature, including nitroxide-mediated polymerization, atom transfer radical polymerization, and currently developed reversible addition and fragmentation transfer chain polymerization. (Dire et al., 2009; Farcet et al., 2002; Nicolas et al., 2007)

Ionic gelation or coacervation of hydrophilic polymers

Polymeric nanoparticles are created using biodegradable hydrophilic polymers like chitosan, gelatin, and sodium alginate. Ionic gelation is a technique developed by Calvo and colleagues for creating nanoparticles of hydrophilic chitosan. Amir Dustgani et al. used ionic gelation to create chitosan nanoparticles that were loaded with dexamethasone sodium phosphate in their study. Chitosan, a diblock co-polymer of ethylene oxide or propylene oxide (PEO-PPO), and poly anion sodium tripolyphosphate are the two aqueous phases combined in the method. In this method, the negatively charged tripolyphosphate and the positively charged amino group of chitosan interact to produce nanometre-sized coacervates. In contrast to ionic gelation, which takes place when a substance changes from a liquid to a gel as a result of ionic interaction circumstances at room temperature, coacervates are produced when two aqueous phases interact electrostatically. (Agazzi et al., 2016; Ahmed and Aljaeid, 2016)

Characterization of Polymeric Nanoparticles

Morphology

The size and shape of polymeric NPs have been extensively studied using scanning and transmission electron microscopy (SEM and TEM). To undertake the NPs' morphology analysis, they are typically paired with cryofracture techniques. The commonly used TEM can measure the thickness of the nano capsule wall, distinguish between nano capsules and nanospheres, and distinguish between them. Nano capsules are created by wrapping an oily core in a thin (5 nm) polymeric envelope, as opposed to nanospheres, which have a spherical shape and a solid polymeric structure. Atomic force microscopy (AFM) has also been utilised to describe the surface morphology of polymeric NPs. It offers high-resolution data in three formats. It can also discern surface details at the atomic level and in nanometric dimensions. By using this method, a complex topography on the nanoparticles' surfaces has been seen, and by examining sample slices, the existence of tiny cavities and pores has also been made clear. (Kreuter et al., 2003; Kroll et al., 1998)

Particle Size Distribution

The average diameter of polymeric NPs produced using various techniques might range from 100 to 300 nm. The size distribution should be unimodal, and the polydispersity should be as low as possible (preferably, close to zero). It is also possible to obtain particles with dimensions between 60 and 70 nm or even less than 50 nm. The most often used methods for measuring nanoparticle size are dynamic (DLS) and static (SLS) light scattering, while TEM, SEM, and AFM are also frequently employed. Depending on the technique, different sizes can be measured; for instance, electron microscopy shows

a particle separated from its surroundings, whereas DLS enables measurement of the hydrodynamic radius of suspended particles. Additionally, because it can measure larger sizes, DLS is a crucial addition to TEM. Observing variations in particle size distribution can provide details on the aggregation state of a nanoparticle in solution. Many factors, including the qualitative and quantitative composition, can affect the size of polymeric NPs. For instance, when producing nano capsules, the type of oil used as the core can affect the particle diameter because of variations in viscosity, hydrophobicity, or interfacial tension between the various liquid phases. The amount of medicine may result in larger particles with a wider size distribution, which can also affect the nanoparticles' average diameter. (Singh and Lillard, 2009)

Chemical Composition and Crystal Structure

The idea of atomic absorption, which states that ground-state electrons of atoms can leap to an excited state by absorbing a given amount of energy from light with a particular wavelength, is the basis for one of the most widely used ensemble techniques, atomic absorption spectroscopy. The sample mass concentration can be determined by comparing the signal with calibration standards at known concentrations, since the amount of energy absorbed depends on the type and quantity of atoms in the light path. Time-of-flight mass spectrometry (TOFMS), which involves ionising small to large organic analytes into the gas phase with minimal fragmentation and their subsequent separation/detection using a time-of-flight mass spectrometer, is one method used to determine the chemical composition of a single particle. A nanoparticle's arrangement of constituent atoms can either be amorphous or structured into a crystal form. In most cases, Powder X-ray diffraction (PXRD) or selective area electron diffraction using a transmission electron microscope are methods for determining structure. While single particles can be used for electron diffraction, a gram of material must be supplied for X-ray diffraction. (Chowdhury et al., 2016; Souris et al., 2010)

Molar Mass Distribution of the Polymer

Determining the polymer's molar mass distribution can reveal details about the formulation's impact on the polymerization process, the occurrence of chemical interactions between the drug and the polymer, as well as the polymer's degradation. Size-exclusion chromatography is the method most frequently employed to determine the polymer molar mass distribution (SEC). Additionally, static light scattering (SLS) has been utilised to assess the amount of light that the polymeric NPs scatter. (Swarbrick and Boylan, 2002)

Surface Area and Chemistry

The surface area of the NPs is significant because it affects reactivity and surface interactions with ligands. Surface area is measured using various techniques. Adsorption of an inert gas, such as N2, under various pressure circumstances results in the formation of a monolayer of gas coverage, which is used to directly estimate the surface area of the nanoparticle. The "total surface area" is inversely proportional to the number of gas molecules required to create a monolayer and the cross-sectional area of the adsorbate gas molecule. Due to the gas's ability to bind to internal pores and crevices, this approach is also used to assess the morphology of porous materials. The elemental or molecular chemistry of a particle surface is referred to as surface chemistry. Due to their increased area-to-volume ratio, nanoparticles have a higher percentage of atoms on their surfaces, where they are in direct contact with solvents and have an impact on how other molecules interact with them. Some nanoparticles, like nano capsules, have a core-shell structure in which the atoms on the exterior surface and the inside core are unlike. The surface chemistry of nanoparticles can be characterised using a variety of methods, such as secondary ion mass spectroscopy and X-ray photoelectron spectroscopy. (Brigger et al., 2002; Muller et al., 1996)

Zeta Potential

The surface charge of the particles is represented by the zeta potential, which is affected by changes in the interface with the dispersing medium, changes brought on by the dissociation of functional groups on the particle's surface, or by the adsorption of ionic species present in the aqueous dispersion medium, as well as the solvation effect. The zeta potential is estimated from the electrophoretic mobility of particles in a particular solvent, and this parameter is evaluated using Doppler techniques to quantify the particle velocity as a function of voltage. The major elements of polymeric NPs are phospholipids, poloxamers, and polymers, and when included in formulations, they have the power to alter the zeta potential. For the colloidal solution to be physicochemically stable, a relatively high zeta potential value, defined as | 30 mV|, is necessary because strong repulsive forces tend to prevent aggregation due to sporadic collisions with nearby nanoparticles. Zeta potential measurements help understand the way that medications bind to nanoparticles. Understanding the loading of albumin into nanospheres made from chitosan and a diblock copolymer of ethylene oxide and propylene oxide required the use of the zeta potential (PEO-PPO). We have noticed how the zeta potential values are impacted by the composition of the various formulations. Thus, by adding surfactants or other coatings to the surface of NPs, such as poly-ethylene-glycol (PEG) of varied molecular weights, the zeta potential of NPs can be adjusted for a particular application. (Muller et al.,

1996; Singh and Lillard, 2009)

pH of Suspension

Monitoring pH as a function of time allows for the collection of pertinent data regarding the stability of nanoparticulate suspensions. For instance, a change in pH could be a sign of polymer breakdown, suggesting alterations in particle surface protonation. In a study, it was discovered that suspensions of nano capsules and nanospheres had less molar mass after six months of storage, which led to a drop in the pH of these formulations. However, depending on how hydrophobic the polymer is, the rapid reduction in pH values of suspensions can be due to both the ionisation of carboxylic groups present in the polymer, which releases protons into the surrounding media. (Couvreur et al., 2002)

Stability of Polymeric NPs Suspensions

Because the sedimentation process is sluggish for submicrometric particles and further slowed down by the Brownian movement, colloidal suspensions typically do not phase separate until a few months after preparation. The processes of particle agglomeration and sedimentation, however, might take place gradually. The adsorption of active molecules onto the surface of the nanoparticles and the presence of adsorbed surfactants are two aspects that can affect the stability of colloidal suspensions. Particle size, zeta potential, polymer molar mass distribution, drug content, and pH are a few physicochemical variables that can be used to track the stability of polymeric colloidal suspensions. However, issues with low physicochemical stability, especially lengthy storage periods, can limit the commercial utilisation of polymeric NPs dispersed in aqueous fluids. Particle aggregation, chemical stability of the polymer, drugs, or other raw materials utilised in the manufacture of NPs, as well as the early release of the active ingredient, are the key drawbacks. In addition, it's critical to stress that preservatives are necessary for liquid dosage forms because they are susceptible to microbial growth. Drying techniques like lyophilization (freeze-drying) or spray drying are typically advised in order to postpone or prevent these physicochemical and microbiological issues. Lyophilization, which involves evaporating water, has been used extensively for drying suspensions of nanospheres. (Bhadra et al., 2002; Olivier, 2005; Villa Nova et al., 2015)

Determination of the Drug Association

Due to their small size, which makes it challenging to distinguish the free fraction of the drug from the associated fraction, determining the amount of drug associated with nanoparticles is particularly complicated. Ultracentrifugation is a separation method that is frequently employed. After centrifugation, the free medication that is present in the suspension is found in the supernatant. The complete dissolving of a portion of the nanoparticles in an appropriate solvent often yields the whole drug concentration. Consequently, the difference between the concentrations of total and free drug is used to compute the drug concentration associated with the nanoparticles. Another technique that has been applied is ultrafiltration-centrifugation, which uses a membrane to separate a portion of the colloidal suspension from the dispersion aqueous phase. The ultrafiltrate is used to measure the free drug concentration, and the drug fraction bound to the nanostructures is derived by deducting the total and free concentrations. (Calvo et al., 1997)

Pharmaceutical In Vitro Release Kinetics

Drug release from polymeric nanoparticles has been characterised by techniques such as diffusion from dialysis bags and separation based on ultracentrifugation, low-pressure filtration, or ultrafiltration-centrifugation. Previous research has shown that the drug release from nanospheres typically takes the shape of an exponential (first order), which may be because the drug diffuses from the polymeric matrix to the environment or because the polymeric matrix erodes, releasing the drug. The medicine contained in the oily nucleus of the nano capsule would potentially be released from this vesicular structure upon diffusion through the polymeric wall, presenting zero-order kinetics. (Magenheim et al., 1993)

Applications of Nanoparticulate Delivery Systems

Nanoparticle as Drug Delivery Systems

Due to physiological hurdles cellular mechanisms confront, drug resistance at the target level commonly restricts the use of pharmacological drugs. Additionally, many medications have low bioavailability, poor solubility, and are swiftly eliminated from the body by the reticuloendothelial system. Furthermore, dose-dependent side effects frequently limit the efficiency of other medications, such as chemotherapeutic medicines. (Archana et al., 2013)

Gastrointestinal tract:

The GI and Skin are other entrance points. It is well established that cellular trafficking, post-translocation processes, and diffusion and accessibility through mucus, initial contact with enterocytes, all affect the rates of particle uptake in the gastrointestinal system. The quicker the particles could diffuse through the GI secretion to reach the target organ, the smaller their

diameter. Intestinal enterocytes Nanoparticles can go to the bloodstream after GI tract absorption and disperse throughout the body. Targeting techniques use specific binding to ligands or receptors and nonspecific adsorptive mechanisms to enhance the interaction of nanoparticles with adsorptive sites (enterocytes and M-cells of Peyer's patches) in the GI tract. Cell-specific carbohydrates are visible on the surface of enterocytes and M cells, and they can act as drug-binding sites for nanoparticles. (Herrero-Vanrell et al., 2005; Vauthier et al., 2003)

Brain

The blood-brain barrier (BBB), which regulates the transit of endogenous and exogenous substances and serves the neuroprotective function, makes the brain one of the least accessible organs for the delivery of medications. Drugs that bind to the surface-modified poly (butyl cyanoacrylate) (PBCA) nanoparticles may be able to pass the BBB and reach the brain. (Moghimi et al., 2001)

Tumor cell targeting

Anticancer medications, which often have wide distribution, are harmful to both healthy and cancerous cells. Miniaturizing the delivery systems so that they are significantly smaller than their targets is therefore necessary for precise medication release into highly specific targets. Personalized medicine, which minimises the treatment's impact on other locations while optimising its therapeutic benefit, is now a possibility because of the application of nanotechnology in drug molecule targeting to the site of action. The fact that these particles are so small allows them to pass through various barriers, tiny capillaries, and individual cells to accomplish this purpose. (Schaffazick and Gutterres, 2003)

Respiratory tract

The respiratory tract is one of the most common entrance points for nanoparticles. Nanoparticles could get past the typical phagocytic defences in the respiratory tract, enter the bloodstream, and possibly even reach the central nervous system. For the delivery of medicinal chemicals, aerosol therapy employing nanoparticles as drug carriers is becoming more and more important. Due to non-invasive administration through inhalation aerosols, avoiding first-pass metabolism, direct delivery to the site of action for the treatment of respiratory diseases, and the availability of a significant surface area for local drug action and systemic drug absorption, the lung is an appealing target for drug delivery. (Damge C.et al.1990)

Nanoparticles for gene delivery

Nanoparticles containing plasmid DNA may also be used as efficient sustained release gene delivery agents because they may quickly transition from the lysosomal degradation compartment to the cytoplasmic compartment. According to Hedley et al., nanoparticles may continuously release DNA upon intracellular uptake and end lysosomal escape. After intracellular uptake and endosomal escape, nanoparticles might release DNA at a steady rate, leading to permanent gene expression. By using PLGA nanoparticles that express therapeutic genes like bone morphogenic protein, this gene delivery method could be used to facilitate bone repair. (Hedley M et al 1998)

3) Nanoparticles for diagnosis and bioimaging

There are several molecular imaging methods, including optical imaging (OI) and magnetic resonance imaging (MRI), and it has been reported that imaging of biological specimens in vitro and in vivo can be done using MRI, ultrasonic imaging, positron emission tomography, and other techniques. Bioimaging technologies are being advanced by the present development of luminous and magnetic nanoparticles. Luminescent nanoprobes for OI and magnetic nanoparticles for MRI are two separate types of nanoparticles that have been extensively employed for imaging. Additionally, dual-mode nanoparticles are available for simultaneous OI and MRI imaging. (Desai et al., 1997; Panyam et al., 2003)

Future perspectives

Applications for polymer-based nanomedicine are numerous and have a long history. The transition from lab-scale proof of concept research to reproducible, with precisely controlled physicochemical features and high-yield manufacture of practical nanomaterials is likely one of the most significant problems related to nanoparticles. This is a crucial element that is frequently overlooked in the literature. Additionally, certain nanomaterials will never be tested in human studies. If the key characteristics that make a polymer suitable for biological use (biodegradable, stable, non-cytotoxic, and well defined) and the regulatory requirements for clinical trials were taken into consideration, this may be somewhat overcome. The designed polymer also needs to be affordable to manufacture as a nanomedicine. Numerous techniques have been widely used to create PNPs. The size distribution is typically fairly wide, and the mean particle size isn't necessarily ideal for applications involving medication delivery. The most researched techniques use emulsion-based systems. Longer periods of sonication exposure are known to cause surfactant degradation due to radicals that develop during the thermal decomposition of water. As an alternative, nanoprecipitation has rapidly gained attention in the literature in recent years.

CONCLUSION

Since various medications and macromolecules (such

as proteins, peptides, vaccines, hormones, and genes) can be delivered via these systems, polymeric NPs have demonstrated promising potential for diagnostic and therapeutic applications for a variety of disorders. The usage of NPs has been linked to improvements in bioavailability, stability, solubility, cellular permeability, absorption, biodistribution, and targeting to particular locations. Additionally, they can provide the formulation through more practical means, improving patient compliance. The basics of the most popular preparation techniques mentioned in the literature, as well as the natural and synthetic polymers that are available to prepare polymeric NPs. It was shown that the method and materials utilised to create the NPs may have an impact on the particle size, size distribution, surface charge, drug loading, and drug release, all significant factors to take into account during the development. To make it easier for these formulations to reach the market, innovation in recent decades has primarily concentrated on enhancing current techniques and using approaches that enable the reproducible manufacture of vast numbers of particles. Polymeric NPs are anticipated to fulfil the needs of appropriate drug delivery systems to consistently improve therapeutics and diagnosis.

REFERENCES

1. Soppimath, K.S.; Aminabhavi, T.M.; Kulkarni, A.R.; Rudzinski, W.E. Biodegradable polymeric nanoparticles as drug delivery devices. J. Control. Release 2001, 70, 1–20.
2. Crucho, C.I.C.; Barros, M.T. Polymeric nanoparticles: A study on the preparation variables and characterization methods. Mater. Sci. Eng. C Mater. Biol. Appl. 2017, 80, 771–784.
3. George, P.A. Shah, P.S. Shrivastav, Natural biodegradable polymers based nano formulations for drug delivery: A review, International Journal of Pharmaceutics (2019).
4. Nagwarma BVN, Hemant K.S. Yadav, Ayaz A, Vasudha L.S, Shivkumar H.G, Different Techniques for Preparation of Polymeric Nanoparticles-A Review, Asian Journal of Pharmaceutical and Clinical Research (2012).
5. Barbara Luppi, Federica Bigucci, Giuseppe Corace, Alice Delucca, Teresa Cerchiara, Milena Sorrenti et al. Albumin nanoparticles carrying cyclodextrins for nasal delivery of the anti-Alzheimer drug tarcine. Eur J Pharm Sci 44(2011) 559565.
6. Nasir, A.; Kausar, A.; Younus, A. A Review on Preparation, Properties, and Applications of Polymeric Nanoparticle-Based Materials. Polym. -Plast. Technol. Eng. 2015, 54 (4), 325–341. DOI: 10.1080/03602559.2014.958780.
7. Karlsson, J.; Vaughan, H. J.; Green, J. J. Biodegradable Polymeric Nanoparticles for Therapeutic Cancer Treatments. Annu. Rev. Chem. Biomol. Eng. 2018, 9(1), 105–127. DOI: 10.1146/annurev-chembioeng-060817- 084055.
8. Wang, X.; Hall, J. E.; Warren, S.; Krom, J.; Magistrelli, J. M.; Rackaitis, M.; Bohm, G. G. A. Synthesis, Characterization, and Application of Novel Polymeric Nanoparticles. Macromolecules. 2007, 40(3), 499–508. DOI: 10.1021/ma0613739.
9. Takami A., Masanori B., Mitsuru A., Preparation of nanoparticles by organisation of polymers consisting of hydrophobic and hydrophilic segments: Potential applications, Polymer,2007,48,6729-6747.
10. Kwon H-Y., Preparation of PLGA nanoparticles containing estrogen by emulsification–diffusion method, Colloids Surf. Release, 2001,182,123–30.
11. Karan Gulati, Moom Sinn Aw, Dusan Losic, Nanoengineered drug-releasing Ti wires as an alternative for local delivery of chemotherapeutics in the brain, Int J Nanomedicine, 2012, 7, 2069–2076.
12. Schadler, L.; Kumar, S.; Benicewicz, B.; Lewis, S.; Harton, S. Designed Interfaces in Polymer Nanocomposites: A Fundamental Viewpoint. MRS. Bull. 2007, 32(4), 335–340.
13. Srikanth, H.; Hajndl, R.; Chirinos-Garcia, C.; Sanders, J.; Sampath, A.; Sudarshan, T. Magnetic Studies of Polymer-coated Fe Nanoparticles Synthesized by Microwave Plasma Polymerization. Appl. Phys. Lett. 2001, 79(21), 3503.
14. Ali, U.; Karim, K. J. Bt. A.; Buang, N. A Review of the Properties and Applications of Poly (Methyl Methacrylate) (PMMA). Polym. Rev. 2015, 55(4), 1–28.
15. Mu L, Feng SS. A novel controlled release formulation for the anticancer drug paclitaxel (Taxol(R)), PLGA nanoparticles containing vitamin E TPGS. Journal of Control Release. 2003; 86:33-48.
16. Betarcourt T., Byrne J.D., Sunaryo N., Crowder S. W, Kadapakkam, Patel S., CasciatoS., Pepp asL., Pegylation strategies for active targeting of PLA/PLGA nanoparticles, J. Biomed, Mater Res.,2009,91,263-276.
17. Tahara K., Sakai T., Yamamoto H., Takeuchi H., Hirashima N., Kawashima Y., Improved cellular uptake of chitosan-modified PLGA nanospheres by A549 cells, Int. J. Pharm. ,2009,382,198–204.
18. Lambert G, Fattal E, Coureurs P. Nanoparticulate system for the delivery of antisense oligonucleotides. Adv Drug Deliv Rev 2001; 47:99 – 112.
19. Bardajee, G.R., Vancaeyzeele, C., Haley, J.C., Li, A.Y., Winnik, M.A., 2007. Synthesis, characterization, and energy transfer studies of dye-labeled poly (butyl methacrylate) latex particles prepared by mini-emulsion polymerization. Polymer 48, 5839–5849.
20. Mohanraj VJ., Chen Y. Nanoparticles: a review. Tropical Journal of Pharmaceutical Research, 2006; 5:561-573.
21. Kohler M., Fritzsche W. Nanotechnology, an introduction to nano structuring. Wiley-VCH 2007, 2.
22. Goldberg M., Langer R., Jia X. Nanostructured materials for applications in drug delivery and tissue engineering. Journal of Biomaterials Science, Polymer. 2007; 18:241-268.
23. Kreuter J. Nanoparticles. In Colloidal Drug Delivery Systems, J.K., Ed. Marcel Dekker New York, 1994, 219-342.
24. Krishnamoorthy, K.; Mahalingam, M. Selection of a suitable method for the preparation of polymeric nanoparticles: multi-criteria decision-making approach. Adv. Pharm. Bull. 2015, 5, 57.
25. Kamiya, H.; Gotoh, K.; Shimada, M.; Uchikoshi, T.; Otani, Y.; Fuji, M.; Matsusaka, S.; Matsuyama, T.; Tatami, J.; Higashitani, K. Characteristics and behaviour of nanoparticles and their dispersion systems. In Nanoparticle Technology Handbook; Elsevier: London, UK, 2008; pp. 113–176.
26. Shen, J.; Burgess, D.J. In vitro dissolution testing strategies for nanoparticulate drug delivery systems: Recent developments and challenges. Drug Deliv. Transl. Res. 2013, 3, 409–415.
27. Gupta, R.; Xie, H. Nanoparticles in daily life: Applications, toxicity and regulations. J. Environ. Pathol. Toxicol. Oncol.

2018, 37, 209–230.
28. Fam, S.Y.; Chee, C.F.; Yong, C.Y.; Ho, K.L.; Mariatulqabtiah, A.R.; Tan, W.S. Stealth Coating of Nanoparticles in Drug-Delivery Systems. Nanomaterials 2020, 10, 787.
29. Palanikumar, L.; Al-Hosani, S.; Kalmouni, M.; Nguyen, V.P.; Ali, L.; Pasricha, R.; Barrera, F.N.; Magzoub, M. pH-responsive high stability polymeric nanoparticles for targeted delivery of anticancer therapeutics. Commun. Biol. 2020, 3, 1–17.
30. Moscatelli, D.; Sponchioni, M. Bioresorbable Polymer Nanoparticles in the Medical and Pharmaceutical Fields. Bioresorbable Polymers for Biomedical Applications, 2017, 265–283.
31. Carmonaribeiro, A.; Biomimetic Lipid Polymer Nanoparticles for Drug Delivery. Methods in Molecular Biology (Clifton, N.J.). 2020, 2118, 45–60.
32. Wang, H.; Rempel, G. pH-Responsive Polymer Core-Shell Nanospheres for Drug Delivery. Journal of Polymer Science Part A: Polymer Chemistry. 2013, 51 (20), 4440–4450.
33. Bozkir, A.; Saka, O. M. Chitosan Nanoparticles for Plasmid DNA Delivery: Effect of Chitosan Molecular Structure on Formulation and Release Characteristics. Drug Deliv. 2004, 11, 107–112.
34. Kumari, A.; Yadav, S. K.; Yadav, S. C. Biodegradable Polymeric Nanoparticles Based Drug Delivery Systems. Colloids Surf. B 2010, 75(1), 1–18.
35. Damge C., Michel C., Aprahamian M., Couvreur P., Devissaguet J.P., Nanocapsules as carriers for oral peptide delivery. J. Control. Release,13,1990, 233- 239.
36. Leroux J-C., Biodegradable nanoparticles from sustained release formulations to improved site-specific drug delivery. J Control Release 1996,39,339–50.
37. Verma A., Stellai F., Effect of surface properties on nanoparticles cell-interactions Small,2010,6,12-21.
38. Devika C., Ghazani A., Chan W., Size and shape dependence of nanoparticles on cellular uptake, Nano lett,2006,6,662-68.
39. Govender T., PLGA nanoparticles prepared by nanoprecipitation: drug loading and release studies of a water-soluble drug. J Control Release 1999,57,171–85.
40. Cho C.S., Kabayashi A., Takei R., Ishihara A., Maruyama A., Akaike T., Receptor–mediated cell-modulated delivery to hepatocytes using nanoparticles coated with carbohydrates carrying polymers, Biomaterials,22,2001,45-51.
41. Vasir J.K., Labhasetwar V., Quantification of the force of nanoparticle–cell membrane interactions and its influence on intracellular trafficking of nanoparticles, Biomaterials, 2008,29 4244–4252.
42. Manguian, M., Save, M., Charleux, B., 2006. Batch emulsion polymerization of styrene stabilized by a hydrophilic macro-RAFT agent. Macromol. Rapid Commun. 27, 399–404.
43. Jung SW, JeongYI, KimYH, KimSH. Self-assembled polymeric nanoparticles of poly (ethylene glycol) grafted pullulan acetate as a novel drug carrier. Arch Pharm Res 2004; 27:5629.
44. Carolina MM, Angélica PM., Renata L, André HR, Eneida P Leonardo FF. Initial development and characterization of PLGA nanospheres containing Ropivacaine. The Journal of Biological Physics 2007; 33:455-461.
45. Hariharn S., Bhardwaj V., Sitterberg J., Bakowsky U., Ravikumar MN. Design of Estradiol-loaded PLGA nanoparticulate formulations: A potential oral delivery system for hormone therapy. Pharmaceutical Research. 2006; 23:184-195.
46. Govender T, Stolnik S., Garnett MC, Illum L, Davis SS. PLGA nanoparticles prepared by nanoprecipitation: drug loading and release studies of a water-soluble drug. Journal of Control Release, 1999, 57:171-185.
47. Maria GC., Paola MP, Luygi L. Release of Dexamethasone from PLGA nanoparticles entrapped into Dextran Poly (Vinyl alcohol) hydrogels. Journal of Materials Science: Materials in Medicine. 2002; 13-265-269.
48. Molpeceres J., Aberturas MR., Guzman M. Biodegradable nanoparticles as a delivery system for cyclosporine; preparation and characterization. Journal of Microencapsulation. 2000; 17:599-614.
49. Zhang Q, Shen Z, Nagai T. Prolonged hypoglycemic effect of insulin-loaded polybutylcyanoacrylate nanoparticles after pulmonary administration to normal rats. International Journal of Pharmaceutics 2001, 218:75-80.
50. Calvo P., Remunan-Lopez C., Vila-Jato JL. Novel hydrophilic chitosan- polyethylene oxide nanoparticles as protein carriers. Journal of Applied Polymer Science, 1997, 63:125-132.
51. Maurya, A.; Singh, A.K.; Mishra, G.; Kumari, K.; Rai, A.; Sharma, B.; Kulkarni, G.T.; Awasthi, R. Strategic use of nanotechnology in drug targeting and its consequences on human health: A focused review. Interv. Med. Appl. Sci. 2019, 11, 38–54.
52. Morshed, N.; Polymeric Nanoparticles for Targeted Delivery in Cancer Treatment: An Overview. Int. J. Pharma. Sci. Rev. Res. 2018, 52(1), 101–111.
53. Mehta, R. C.; Jayanthi, R., Calis, S.; Thanoo, B.C.; Burton, K. W.; De Luca, P. P. Biodegradable Microspheres as Depot System for Parenteral Delivery of Peptide Drugs. J. Controlled Release 1994, 29(3), 375–384.
54. Lepeltier, E.; Bourgaux, C.; Couvreur, P. Nanoprecipitation and the "Ouzo Effect": Application to Drug Delivery Devices. Adv. Drug Delivery Rev. 2014, 71, 86–97.
55. Srinivasan, S.; Gajbhiye, K.; Paknikar, K.; Gajbhiye, V. Conjugated Polymer Nanoparticles as a Promising Tool for Anticancer Therapeutics. Methods in Molecular Biology (Clifton, N.J.). 2019 2019, 257–280.
56. Francis, R.; Joy, N.; Aparna, E.; Vijayan, R. Polymer Grafted Inorganic Nanoparticles, Preparation, Properties, and Applications: A Review. Polym. Rev. 2014, 54(2), 268–347.
57. Tuncel, D.; Demir, H. Conjugated Polymer Nanoparticles. Nanoscale. 2010, 2(4), 484–494.
58. Wang, H.; Rempel, G. Introduction of Polymer Nanoparticles for Drug Delivery Applications. J Nanotechnology. 2015, 2, 008.
59. Kreuter J Physicochemical characterization of polyacrylic nanoparticles. International Journal of Pharmaceutics 1983; 14:43 -58.
60. Ghosh. PK Hydrophilic polymeric nanoparticles as drug carriers. Indian J Biochem Biophys 2000 (37), 273-282.