**Polymeric nanoparticles in drug delivery**

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**Abstract:**

Nanoparticles have shown encouraging outcomes as carriers for drug delivery systems. Nanoparticles like liposomes, polymeric nanoparticles, and inorganic nanoparticles are widely used to carry drug molecules. Polymeric nanoparticles have become popular as drug carriers due to their versatility, biocompatibility, and ability to encapsulate a wide range of drugs. The drug is dissolved, entrapped, encapsulated, or linked to a nanoparticle matrix in the form of polymeric nanoparticles (PNPs). Polymeric nanoparticles of size from 10 to 1000 nm can be prepared by a variety of techniques based on whether a polymerization reaction is involved in the particle formation or whether nanoparticles form directly from macromolecules, preformed polymers, or the ionic gelation method. The present review aims to review and summarize the methods for the preparation of polymeric nanoparticles.

*Keywords: Drug delivery, nanoparticles, polymeric nanoparticles, polymers, drug release*

**Introduction:**

Drug delivery is one of the many industries that have been transformed by nanotechnology. It entails working with objects and structures at the nanoscale level, which typically falls between 1 and 100 nanometers (Blanco et al., 2015). Researchers can create drug delivery systems with greater efficiency, specificity, and targeted delivery by using nanotechnology, which will boost therapeutic outcomes. Drug compounds are frequently transported using nanoparticles including liposomes, polymeric nanoparticles, and inorganic nanoparticles (like gold or iron oxide). These particles have the ability to encapsulate medicines, preventing drug deterioration and enabling regulated medication release (Dreaden et al., 2012). Additionally, nanoparticles can increase the stability, bioavailability, and solubility of drugs. Nanoparticles can be made functional by adding ligands or antibodies that selectively bind to the sick cells' or tissues' molecular targets (Allen & Cullis, 2013). With this focused strategy, drug exposure to healthy tissues is minimised, adverse effects are decreased, and therapeutic efficacy is increased. While passive targeting relies on the leaky nature of tumour vasculature to collect nanoparticles in tumour tissues, active targeting systems actively direct nanoparticles to the desired site. Drugs can be released from nanoparticles in a regulated and continuous manner (Siepmann & Siegel, 2012). Drug release can be activated by a variety of stimuli, including pH, temperature, enzymes, or external energy sources like light or magnetic fields, by modifying the nanoparticle composition, size, surface features, or integrating stimuli-responsive components. As a result, therapeutic concentrations at the target site can be optimised by the use of precise drug release patterns. Some medications are intrinsically prone to instability and deterioration. These medications can be shielded against deterioration by being enclosed within nanoparticles that have a stable carrier matrix (Patel et al., 2012). This could increase therapeutic efficacy, prolong shelf life, and improve medication stability. The simultaneous distribution of several medications or therapeutic agents within a single carrier system is made possible by nanotechnology. As a result, medicines with various modes of action can be used in combination therapy to achieve synergistic effects, combat drug resistance, or target various disease-progression pathways. The present review aims to review and summarize the methods for the preparation of polymeric nanoparticles.

**Polymeric nanoparticles**

Polymeric nanoparticles (PNPs) in the size range of 10-1000 nm are prepared by either dissolving the drug or linking the drug with a nanoparticle matrix. The formation of nanoparticles, nanospheres, or nanocapsules largely depends upon the choice of the method of preparation while all are made from biocompatible and biodegradable polymers. While in polymeric nanospheres the drug is physically and uniformly spreaded, in nanocapsules the drug is restricted to a cavity surrounded by a specific polymer membrane (Babak et al., 2001). Finally, these polymeric nanoparticles have been subjected to use in a variety of fields including electronics, photonics, biosensors, healthcare, and environmental technology (Schmidt et al., 2004). By allowing for simple production of carriers with the goal of delivering the pharmaceuticals to a specified target, TPNPs are potential drug delivery systems. A benefit like this raises drug safety (Shokri et al., 2011). Drugs, proteins, and DNA can be successfully delivered to target cells and organs by polymer-based nanoparticles (Allemann et al., 1998). Their nanoscale size encourages stability in the bloodstream and efficient diffusion through cell membranes. Ingenious nanoparticle structures with numerous potential medical uses can be created using polymers, which are particularly practical materials for the production of innumerable and diverse molecular designs (Peer et al., 2007). PNPs have been prepared using a variety of techniques over the past 20 years. These techniques are categorised based on whether a polymerization reaction is involved in the particle formation or whether nanoparticles form directly from macromolecules, preformed polymers, or the ionic gelation method (Aleksandra et al., 2020).

The primary features of a polymer to be used as drug carrier is its biocompatibility, adaptability, non-antigenicity, and biodegradability. A number of natural polymers like Chitosan, Gelatin, Sodium alginate, and Albumin are used commonly for the preparation of polymeric nanoparticles (Daljeet et al., 2021). Similarly, synthetic polymers can also be used for the same like Polylactides (PLA), Polyglycolides(PGA), Poly(lactide co-glycolides) (PLGA), Poly malic acid, Poly(N-vinyl pyrrolidone) and similar ones . The drug is released at the tissue location either through hydration-induced swelling of nanoparticles followed by drug diffusion, enzymatic rupture, or drug de-adsorption from the swollen nanoparticles ([Chizhu Ding](https://pubmed.ncbi.nlm.nih.gov/?term=Ding+C&cauthor_id=28482511) et al., 2017).

**Techniques of preparation**

The choice of method of preparation of polymeric nanoparticles completely depends upon the specific application. A range of methods have been developed and are described below (Carina et al., 2017).

*Nanoparticles preparation from dispersion of preformed polymer:*

A typical method for creating biodegradable nanoparticles is to disperse the medication in premade synthetic polymers by following methods (Thiruchelvi et al., 2022).

**(I) Solvent evaporation**

This was one of the earliest methods developed to design PNPs. Initially the premade synthetic polymers were dissolved in volatile solvents like dichloromethane and chloroform, however these solvents were quickly replaced by ethyl acetate due to toxicity reasons. While the solvent was allowed to evaporate, the suspension of nanoparticles were maintained into the continuous phase of the emulsion (Tyagi and Pandey, 2016). The emulsions are created either through single-emulsions, such as oil-in-water (o/w) or double-emulsions, such as (water-in-oil)-in-water, (w/o)/w. These conventional procedures primarily used acetone (8:2, v/v) as the solvent system and PVA as the stabilising agent. These are the two primary techniques utilised in the for the formation of emulsions (Song et al., 2017). The usual particle size of these nanoparticles is between 60 and 200 nm. It was discovered that factors like type and concentration of stabiliser as well as polymers, speed of homogenization and ultrasonication significantly influences the particle size with inverse connections.

**(II) Nanoprecipitation**

Another name for nanoprecipitation is solvent displacement technique. According to Fessi et al. (1989), it entails the precipitation of a preformed polymer from an organic solution and the diffusion of the organic solvent in the aqueous medium with or without the presence of a surfactant. A water-miscible solvent with an intermediate polarity is recommended for the dissolution of polymer in-order to facilitate precipitation of nanospheres. 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 (Quintanar-Guerrero et al., 1998). Phase separation is carried out using a fully miscible solvent (Vauthier et al., 2003). A small addition of nontoxic oil to the organic phase allows the formation of nanocapsules using solvent displacement approach. When nanocapsules are manufactured, high loading efficiencies for lipophilic medicines are typically observed due to the oil-based central chambers of the nanocapsules. This straightforward method is only effective with water-miscible solvents because the diffusion rate is high enough to result in spontaneous emulsification in these solvents (Quintanar-Guerrero et al., 1998). Although, water-miscible solvents often lead to partial instability when combined with water, spontaneous emulsification is not seen if the droplets' coalescence rate is high enough (Dimitrova et al., 1988). High coalescence rate and increase in the mean particle size is achieved through dichloromethane which certainly dissolve and increase the entrapment of medicines. However, considering its categorization as an ICH-class 2 hazardous agent it’s use is restricted only for the encapsulation of lipophilic pharmaceuticals (Wehrle et al., 1995). The process remains useless for the water-soluble medications due to the solvent's miscibility with the aqueous phase. Polymers like PLGA, PLA, PCL, and poly (methyl vinyl ether-comaleic anhydride) (PVM/MA), have been used for the synthesis of polymeric nanoparticles using this approach (Barichello et al., 1999). In case of cyclosporin A, entrapment efficiencies as high as 98% were attained using this approach (Allemann et al., 1998). This solvent displacement approach was also utilized for the delivery of poorly soluble antifungal medications Bifonazole and Clotrimazole where these drugs were loaded in nanoparticulate systems based on amphiphilic h-cyclodextrins (Memisoglu et al., 2003).

**(III) Emulsification/solvent diffusion (ESD)**

The method is the modification of solvent evaporation method (Niwa et al., 1993) involving dissolution of the encapsulating polymer in a partly water-soluble solvent, such as propylene carbonate followed by saturation with water. In-order to facilitate the precipitation of polymeric nanoparticles, it is necessary to allow the diffusion of the dispersed phase's solvent through dilution with an excess of water. This should be done when the organic solvent is partially miscible with water. The diffusion of the solvent as an exterior layer occurs during the emulsification of the polymer-water saturated solvent phase with stabiliser in an aqueous solution. The solvent is allowed to evaporate leading to the formation of nanospheres or nanocapsules. The advantages of this method include excellent encapsulation efficiency (often >70%), the absence of homogenization, excellent batch-to-batch consistency, ease of scaling up, simplicity, and limited size distribution. On the contrary, the primary disadvantages include need of removal of excessive amount of water and the outflow of a medication (Catarina et al., 2006). This method, like some of the others, works well to encapsulate medicines that are lipophilic like mesotetra(hydroxyphenyl)porphyrin-loaded PLGA (p-THPP) nanoparticles, doxorubicin-loaded PLGA nanoparticles, plasmid DNA-loaded PLA nanoparticles, coumadin-loaded PLA nanoparticles, indocyanine (Quintanar-Guerrero et al., 1998).

**(IV) Salting out**

The salting out method minimizes the problem of unfolding or inactivation of protein during encapsulation. In this method the water-miscible solvent in which the polymer and protein are dissolved separates from the aqueous solution on addition of salts such as magnesium chloride, calcium chloride, etc. The emulsification/solvent diffusion process can be thought of as being modified by the salting out process. The production of nanospheres is induced by diluting this oil/water emulsion with an adequate amount of water or aqueous solution to improve acetone's ability to diffuse into the aqueous phase (Catarina et al., 2006). The choice of the salting out agent is crucial since it can have a significant impact on how effectively the medicine is encapsulated. Cross-flow filtration is then used to remove both the solvent and the salting out agent. This method, which is used to make PLA, or poly (methacrylic acid), nanospheres, is highly effective and simple to scale up. According to (Jung and Fessi, 2006), the fundamental benefit of salting out is that it reduces stress on protein encapsulants. When heat-sensitive materials need to be processed, salting out may be advantageous because it doesn't require a rise in temperature (Lambert et al., 2001). The most significant drawbacks are the exclusive use of lipophilic medicines and the lengthy nanoparticle cleaning procedures (Couvreur et al., 1995).

**(V) Dialysis**

This method is used to develop small and narrow-distributed polymeric nanoparticles (Jeong et al., 2001). The polymeric substance appropriately dissolved in an organic solvent is filled in a dialysis tube followed by the dispersion of the solvent inside the membrane. The polymer progressively aggregates due to loss of solubility thereby forming a homogeneous suspension of nanoparticles. While, the mechanism of formation of PNP through this approach is not completely understood, it is hypothesized that the process similar to nanoprecipitation might be involved (Fessi et al. in 1989). A range of polymer and copolymer nanoparticles were produced through this technique where DMF was used as the solvent to create poly(benzyl-l-glutamate)-b-poly(ethylene oxide) and poly(lactide)-b-poly(ethylene oxide) nanoparticles (Lee et al., 2004). A strong impact was incurred by the polymer dissolving solution over the shape and particle size distribution of the nanoparticles. A unique osmosis-based technique for the synthesis of different natural and synthetic PNP was disclosed by Chronopoulou et al. (2001). The authors used physical barrier in the form of dialysis semi-permeable membrane containing the polymer solution. The semi-permeable membrane allows the passive transit of solvents to slow down the mixing of the polymer solution with a non-solvent.

**(VI) Supercritical fluid technology**

The need for the exploration of environmentally friendly solvents that can led to the development of highly pure PNPs with complete absence of organic solvent has driven the use of supercritical fluids for PNPs development (York P, 1999). Technology based on supercritical fluid and dense gas is anticipated to provide an environt-friendly method of particle creation while avoiding the majority of the disadvantages of conventional approaches.

Supercritical fluids have been used to create nanoparticles, and two principles have been established:

1. Rapid expansion of supercritical solution into liquid solvent (RESOLV).

2. Rapid expansion of supercritical solution (RESS).

1. **Rapid expansion of supercritical solution**

In the conventional RESS process, a supercritical solution is rapidly expanded through a nozzle to precipitate the solute as microparticles. The well-dispersed particles are developed through the process of homogeneous nucleation carried by super saturation and the quick pressure reduction in the expansion. In the expansion jet, nanoparticles of both nanometer- and micrometer-sized particles can be found, according to the findings of mechanistic investigations of various model solutes for the RESS process (Weber et al., 2002). Several research on the creation of PNPs utilising RESS have been conducted. Droplets of poly (perfluoropolyetherdiamide) are created when CO2 solutions rapidly expand. The experimental RESS apparatus consists of a pre-expansion unit, a syringe pump, and a high-pressure stainless steel mixing chamber. At room temperature, a polymer and CO2 solution is formed. The particle size and morphology of the particles for RESS are significantly influenced by the polymer's concentration and saturation level (Chernyak et al., 2001).

1. **Rapid expansion of supercritical solution into liquid solvent**

This is the modified method of RESS where a liquid solvent was replaced by the supercritical solution (Sun et al., 2002). Poly (heptadecafluorodecyl acrylate) nanoparticles with an average size of less than 50 nm were prepared, according to Meziani et al. (2004). While the use of supercritical solution is an advantage, the main disadvantage is the formation of microscaled rather than nanoscaled PNPs. However, this limitation was overcomed in the improved RESOLV technology where particle growth is limited in the expansion jet thereby leading to the formation of mostly nanosized particles (Meziani et al., 2005).

 *Preparation of nanoparticles by polymerization of monomer*

In these methods nanoparticles are designed during the polymerization of monomers according to the specific application.

**(I) Emulsion polymerization**

Emulsion polymerization is one of the rapid and most adaptable processes for producing nanoparticles. The method of emulsion polymerization can be divided into two groups, depending on whether the continuous phase is organic or aqueous. When the continuous organic phase approach is adopted, a monomer must be dispersed into an emulsion or a nonsolvent. In this technique, polyacrylamide nanospheres were created (Ekmam et al., 1978). Surfactants or protective soluble polymers were utilised as one of the first techniques for producing nanoparticles to stop aggregation in the early phases of polymerization. Due to the need for hazardous organic solvents, surfactants, monomers, and initiators that are afterwards removed from the produced particles, this technique has lost some of its significance. Alternative approaches were explored due to the non-biodegradable nature of this polymer and the challenging procedure. Later, nanoparticles made from poly (methylmethacrylate, or PMMA), poly (ethylcyanoacrylate, or PECA), and poly (butylcyanoacrylate, or PBC, were created by dispersing them in organic phase solvents such cyclohexane (ICH class 2, n-pentane (ICH class 3), and toluene (ICH class 2). Surfactants or emulsifiers are not required in the aqueous continuous phase, when the monomer is dissolved in a continuous phase that is typically an aqueous solution. Several mechanisms can start the polymerization process. The collation between the monomer molecule dispersed in the continuous phase with an initiator ion or a free radical can initiate the process. The initiating radicals can also be generated alternatively through powerful ultraviolet or visible light, and high-energy radiation. The process is known as anionic polymerization reaction where chain development begins when started monomer ions or radicals strike additional monomer molecules. Before or after the polymerization reaction is completed, phase separation and the creation of solid particles can occur (Kreuter et al., 1982).

**(II) Mini-emulsion polymerization**

Recent years have seen a significant growth in the number of publications on mini-emulsion polymerization and the creation of numerous practical polymer compounds. Water, a monomer combination, a co-stabilizer, a surfactant, and an initiator make up a typical formulation used in mini-emulsion polymerization. The employment of a high-shear device (ultrasound, etc.) and a low molecular mass substance as the co-stabilizer are the two main differences between emulsion polymerization and mini-emulsion polymerization. Mini-emulsions have an interfacial tension much above zero, are highly stabilised, and need strong shear to attain a steady state. As described in the literature (Ham et al., 2006), the Mini-emulsion approach was used to create the different polymer nanoparticles.

**(III) Micro-emulsion polymerization**

In micro-emulsion polymerization, both particle size and the average number of chains per particle are much smaller. Even while both emulsion and micro-emulsion polymerization techniques can create colloidal polymer particles with high molar masses, they are completely different kinetically. The reaction involved the addition of thermodynamically stable micro-emulsion with swollen micelles to the aqueous phase of micro-emulsion along with a water-soluble initiator. This thermodynamically stable, spontaneously produced state serves as the starting point for polymerization, which depends on large amounts of surfactant systems with low interfacial tension at the oil/water contact. Use of large amount of surfactant results in the coverage of the particles with surfactant. Since the initiation cannot occur simultaneously in all microdroplets, polymer chains initially only form in part of the droplets. The resulting micro-emulsions are later destabilised by the elastic and osmotic impact of the chains thereby increasing the particle size, the generation of empty micelles, and subsequent nucleation. Factors impacting the micro-emulsion polymerization kinetics and the characteristics of PNP include types and concentrations of initiators, surfactants, monomers, and reaction temperature (Puig et al., 1996).

**(IV) Interfacial polymerization**

It is among the tried-and-true techniques for making polymer nanoparticles ([Yongyang Song](https://pubs.rsc.org/en/results?searchtext=Author%3AYongyang%20Song) et al., 2017). The reaction takes place at the interface of the two liquids and involves the step polymerization of two reactive monomers or agents that are dissolved in two phases (i.e., continuous and dispersed). By using interfacial cross-linking processes like polyaddition and polycondensation (Danicher et al., 2000) or radical polymerization (Scott et al., 2005), nanometer-sized hollow polymer particles have been created. By polymerizing monomers at the oil/water interface of a very fine oil-in-water micro-emulsion, oil-containing nanocapsules were created (Khoury-Fallouh et al., 1986). The interfacial polymerization of the monomer was thought to take place at the surface of the oil droplets that formed during emulsification because the organic solvent, which was totally miscible with water, served as a carrier for the monomer (Gallardo et al., 1993). Aprotic solvents like acetone and acetonitrile should be used to encourage nanocapsule development. Protic solvents were discovered to cause the development of nanospheres in addition to nanocapsules, including ethanol, n-butanol, and isopropanol (Puglisi et al., 1995). As an alternative, interfacial polymerization of monomers in water-in-oil micro-emulsions can be used to create water-containing nanocapsules. According to (Gasco et al. 1986), in these situations, the polymer precipitated locally at the water-oil interface to create the nanocapsules' shell.

**(V) Controlled/living radical polymerization (C/LRP)**

The lack of control over the molar mass, molar mass distribution, end functions, and macromolecular architecture are the main drawbacks of radical polymerization. The unavoidable quick radical-radical termination reactions are what lead to the restrictions. The recent introduction of numerous 'controlled' or 'living' radical polymerization (C/LRP) techniques has created a new field for an established polymerization method (Matyjaszewski et al., 2001). Increased environmental awareness and a fast increase in the use of hydrophilic polymers in pharmaceutical and medical applications are the main drivers of this development in the C/LRP process. These factors have given rise to "green chemistry" and increased demand for solvents like water and supercritical carbon dioxide that are safe for the environment and human health. Industrial radical polymerization, specifically emulsion polymerization, is frequently carried out in aqueous dispersion systems. Controlling the polymer's properties in terms of molar mass, molar mass distribution, architecture, and function was the main objective. Future commercial success of C/LRP depends on its application in the industrially significant aqueous dispersion systems, which produces polymeric nanoparticles with precise control over particle size and size distribution (Nicolas et al., 2005). Nitroxide-mediated polymerization (NMP) (Dire et al., 2009), atom transfer radical polymerization (ATRP) (Min et al., 2006), and reversible addition and fragmentation transfer chain polymerization (RAFT) (Zhou et al., 2007) are among the successful and in-depth methods for controlled/living radical polymerization that are currently available (Braunecker et al., 2005). In addition to temperature, other important factors that affect PNP size include the kind and concentration of the control agent, monomer, initiator, and emulsion type. The type of control agent is one of them that has a significant impact on the final product's particle size.

*Ionic gelation or coacervation of hydrophilic polymers*

Hydrophilic polymers like alginate, chitosan, and gelatin are used for the development of nanoparticles using ionic gelation method. By using ionic gelation, Calvo Calvo et al. (1997) created a technique for producing hydrophilic chitosan nanoparticles. Ionic gelation was used by (Amir et al. 2008) to create Dexamethasone Sodium Phosphate loaded chitosan nanoparticles. Chitosan and poly anion sodium tripolyphosphate are the two aqueous phases that are combined in the procedure. By interacting with the negatively charged tripolyphosphate, the positively charged amino group of chitosan forms coacervates that have a size in the nanometer range. Unlike ionic gelation where transition from a liquid to a gel occurs because of ionic interaction conditions at ambient temperature, coacervates are formed as a result of electrostatic interaction between two aqueous phases.

**Conclusion:**

Overall, polymeric nanoparticles incur several advantages. They provide a considerable improvement over conventional oral and intravenous ways of delivery in terms of efficiency and effectiveness. They increase the stability of any volatile pharmacological substances, which are easily and inexpensively manufactured in large quantities by a variety of methods. Transports a greater quantity of the medicinal agent to the desired spot. Polymeric nanoparticles are the perfect vehicle for the delivery of vaccines, contraceptives, and targeted antibiotics due to the polymer they were chosen for and the flexibility of their drug release. Polymeric nanoparticles are simple to incorporate into other drug delivery-related processes, like tissue engineering (Adelina et al., 2021). Nevertheless, personalised treatment, targeted therapy, and better patient outcomes are all made possible by the use of nanotechnology in drug delivery. Prior to extensive clinical translation, more study is required to optimise the design of nanomaterials, their safety, scalability, and regulatory considerations.

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