**Polymeric nanoparticles in drug delivery**

**Sangita Saini, Shiva Sharma, Manisha Rastogi**

1School of Biomedical Engineering and Science, Shobhit Institute of Engineering and Technology (NAAC “A” Accredited Deemed to be University), Meerut, UP, India

\*Corresponding author: *manisha.rastogi@shobhituniversity.ac*.*in*

**Abstract:**

Nanoparticles have emerged as promising carriers in drug delivery systems due to their unique properties at the nanoscale. Nanoparticles like liposomes, polymeric nanoparticles, and inorganic nanoparticles are widely used to carry drug molecules. Polymeric nanoparticles have gained significant attention in the field of drug delivery 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), which range in size from 10 to 1000 nm and are made from biocompatible and biodegradable polymers. Polymeric nanoparticles 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**

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, one can produce nanoparticles, nanospheres, or nanocapsules. Nanospheres are matrix systems in which the drug is physically and uniformly spread, whereas nanocapsules are systems in which the drug is restricted to a cavity surrounded by a specific polymer membrane (Babak et al., 2001). According to Schmidt et al. (2004), the field of polymer nanoparticles (PNPs) is rapidly growing and playing a significant role in a variety of fields including electronics, photonics, conducting materials, sensors, medicine, biotechnology, pollution control, and environmental technology. 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).

 **Polymers used in preparation of nanoparticles**

The primary characteristic of a polymer to be used as drug delivery agent 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 enlisted below:

* Polylactides(PLA)
* Polyglycolides(PGA)
* Poly(lactide co-glycolides) (PLGA)
* Polyanhydrides
* Polyorthoesters
* Polycyanoacrylates
* Polycaprolactone
* Poly glutamic acid
* Poly malic acid
* Poly(N-vinyl pyrrolidone)
* Poly(methyl methacrylate)
* Poly(vinyl alcohol)
* Poly(acrylic acid)
* Poly acrylamide
* Poly(ethylene glycol)
* Poly(methacrylic acid)

**Mechanisms of drug release**

Any one of the three common physico-chemical methods is used by the polymeric drug carriers to deliver the drug at the tissue location.

1. By the polymer nanoparticles' hydration-induced swelling, which is followed by release through diffusion.

2. By an enzymatic process that causes the polymer at the point of delivery to rupture, cleave, or degrade, freeing the medication from the imprisoned inner core.

3. Drug de-adsorption/release from the swollen nanoparticles and polymer dissociation ([Chizhu Ding](https://pubmed.ncbi.nlm.nih.gov/?term=Ding+C&cauthor_id=28482511) et al., 2017).s

**Techniques of preparation**

Depending on the specific application, PNPs' attributes need to be optimised. The mode of preparation is essential in achieving the desired qualities. Consequently, it is very beneficial to have preparation methods on hand in order to create PNPs with the appropriate properties for a certain application. Various methods are employed, including polymerization, premade polymers, ionic gelation, etc. (Carina et al., 2017).

*Methods for preparation of nanoparticles from dispersion of preformed polymer:*

A typical method for creating biodegradable nanoparticles is to disperse the medication in premade polymers from poly (lactic acid) (PLA), poly (D, L-glycolide) (PLG), poly (D, L-lactide-co-glycolide) (PLGA) and poly (cyanoacrylate) (PCA). These can be accomplished by different methods described below (Thiruchelvi et al., 2022).

**(I) Solvent evaporation**

The first technique created to make PNPs from a was solvent evaporation. This technique involves creating polymer solutions in volatile solvents and creating emulsions. Dichloromethane and chloroform premade polymer were once frequently utilised, but ethyl acetate has now taken their place because of its superior toxicity profile. On the evaporation of the polymer's solvent, which is then allowed to seep into the continuous phase of the emulsion, the emulsion transforms into a suspension of nanoparticles (Tyagi and Pandey, 2016). The manufacture of single-emulsions, such as oil-in-water (o/w) or double-emulsions, such as (water-in-oil)-in-water, (w/o)/w, using acetone (8:2, v/v) as the solvent system and PVA as the stabilising agent are the two primary techniques utilised in the conventional procedures for the formation of emulsions. Song et al. (2017) created PLGA nanoparticles using dichloromethane and acetone (8:2, v/v) as the solvent system and PVA as the stabilising agent. The usual particle size of these nanoparticles is between 60 and 200 nm. It was discovered that the type and concentration of stabiliser, homogenizer speed, and polymer concentration all had an impact on particle size. Frequently, a high-speed homogenization or ultrasonication may be used to achieve small particle size.

**(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. The precipitation of nanospheres occurs when the polymer, typically PLA, is dissolved in a water-miscible solvent with an intermediate polarity. This phase is added to an aqueous solution that has been agitated and contains a stabiliser as a surfactant. Instantaneous development of a colloidal suspension results from polymer deposition on the interface between the organic solvent and water, which is brought on by fast solvent diffusion (Quintanar-Guerrero et al., 1998). Phase separation is carried out using a fully miscible solvent that is also a non-solvent of the polymer in order to enable the creation of colloidal polymer particles during the first step of the technique (Vauthier et al., 2003). When a little amount of nontoxic oil is added to the organic phase, the solvent displacement approach allows the creation of nanocapsules. 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). Then, even though some water-miscible solvents result in a certain amount of instability when combined with water, spontaneous emulsification is not seen if the droplets' coalescence rate is high enough (Dimitrova et al., 1988). Despite being used to dissolve and increase the entrapment of medicines, dichloromethane (ICH, class 2) is hazardous and increases the mean particle size (Wehrle et al., 1995). Due to the solvent's miscibility with the aqueous phase, this approach can only be used to encapsulate lipophilic pharmaceuticals and is ineffective for water-soluble medications. Many polymeric polymers, including PLGA, PLA, PCL, and poly (methyl vinyl ether-comaleic anhydride) (PVM/MA), have been subjected to this approach (Barichello et al., 1999). Because entrapment efficiencies as high as 98% were attained, this approach proved ideally suited for the inclusion of cyclosporin A (Allemann et al., 1998). The poorly soluble antifungal medications Bifonazole and Clotrimazole were made into highly loaded nanoparticulate systems based on amphiphilic h-cyclodextrins using the solvent displacement approach (Memisoglu et al., 2003).

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

The solvent evaporation method, as modified here (Niwa et al., 1993), is used. To ensure the initial thermodynamic equilibrium of both liquids, the encapsulating polymer is dissolved in a partly water soluble solvent, such as propylene carbonate, and saturated with water. In fact, it is necessary to encourage the diffusion of the dispersed phase's solvent by dilution with an excess of water when the organic solvent is partially miscible with water or with another organic solvent in the opposite case in order to produce the precipitation of the polymer and the subsequent formation of nanoparticles. Then, depending on the ratio of oil to polymer, the polymer-water saturated solvent phase is emulsified in an aqueous solution with stabiliser, causing solvent diffusion to the exterior phase and the creation of nanospheres or nanocapsules. Depending on its boiling point, the solvent is finally removed via evaporation or filtering. Figure 4 provides an illustration of the process. excellent encapsulation efficiency (often >70%), the absence of homogenization, excellent batch-to-batch consistency, ease of scaling up, simplicity, and limited size distribution are just a few benefits of this method. The enormous amounts of water that must be removed from the suspension and the leaking of a medication that is water-soluble into the saturated-aqueous exterior phase during emulsification are drawbacks (Catarina et al., 2006). This method, like some of the others, works well to encapsulate medicines that are lipophilic (Quintanar-Guerrero et al., 1998). The ESD method was used to create a number of drug-loaded nanoparticles, including mesotetra(hydroxyphenyl)porphyrin-loaded PLGA (p-THPP) nanoparticles, doxorubicin-loaded PLGA nanoparticles, plasmid DNA-loaded PLA nanoparticles, coumadin-loaded PLA nanoparticles, indocyanine.

**(IV) Salting out**

The principle behind salting out is the use of the salting out phenomenon to separate a water miscible solvent from aqueous solution. The emulsification/solvent diffusion process can be thought of as being modified by the salting out process. The salting-out agent (electrolytes, such as magnesium chloride, calcium chloride, and magnesium acetate, or non-electrolytes, such as sucrose) and a colloidal stabiliser, such as polyvinylpyrrolidone or hydroxyethylcellulose, are added to the polymer and drug after they have first been dissolved in a solvent, such as acetone. 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**

Small, narrow-distributed polymeric nanoparticles can be created using a simple and efficient approach called dialysis (Jeong et al., 2001). A dialysis tube is filled with a polymer that has been dissolved in an organic solvent and has had the appropriate molecular weight cut off. A non-solvent that is miscible with the former miscible is used for dialysis. Following the displacement of the solvent inside the membrane, the polymer gradually aggregates as a result of a loss of solubility, and homogeneous suspensions of nanoparticles form. Currently, the mechanism of PNP production by the dialysis approach is not completely known. It is believed that it might be based on a mechanism resembling the nanoprecipitation theory put forth by (Fessi et al. in 1989). By using this method, several polymer and copolymer nanoparticles were produced. 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). The shape and particle size distribution of the nanoparticles are influenced by the solvent that was used to make the polymer solution. A unique osmosis-based technique for the synthesis of different natural and synthetic PNP was disclosed by (Chronopoulou et al. in 2001) (Fig. 5). It is based on the employment of a physical barrier, specifically a dialysis membrane or typical semi-permeable membranes that allow the passive transit of solvents to slow down the mixing of the polymer solution with a non-solvent. The dialysis membrane contains the polymer solution.

**(VI) Supercritical fluid technology**

Research on the use of supercritical fluids as more environmentally friendly solvents, with the potential to manufacture PNPs with high purity and without any trace of organic solvent, has been inspired by the need to develop environmentally safer ways for the synthesis of PNP (York P, 1999). Technology based on supercritical fluid and dense gas is anticipated to provide an intriguing and efficient 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).

**(VII) Rapid expansion of supercritical solution**

Traditional RESS involves dissolving the solute in a supercritical fluid to create a solution, which is then rapidly expanded over an aperture or a capillary nozzle into the surrounding air. The creation of well-dispersed particles is caused by homogeneous nucleation, which is brought on by the high degree of super saturation and the quick pressure reduction in the expansion. Both nanometer- and micrometer-sized particles can be found in the expansion jet, 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. Three main components make up the RESS experimental apparatus: a pre-expansion unit, a syringe pump, and a high-pressure stainless steel mixing chamber. At room temperature, a polymer and CO2 solution is created. Syringe pumps are used to pump the solution to the pre-expansion unit where it is isobarically heated to the pre-expansion temperature before it leaves the nozzle. Now, at atmospheric pressure, the supercritical solution is permitted to expand through the nozzle. 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).

**(VIII) Rapid expansion of supercritical solution into liquid solvent**

Expansion of the supercritical solution into a liquid solvent rather than ambient air is a straightforward but important adjustment to the RESS process (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). Although there are no organic solvents utilised in the RESS process for the creation of PNPs, the fundamental disadvantage of RESS is that the primary products created using this technique are microscaled rather than nanoscaled. A new supercritical fluid technique called RESOLV has been created to get over this limitation. According to Meziani et al., 2005 the liquid solvent in RESOLV appears to inhibit particle growth in the expansion jet, allowing for the production of mostly nanosized particles.

 *Preparation of nanoparticles by polymerization of a monomer*

Designing appropriate polymer nanoparticles can be done during the polymerization of monomers in order to get the needed properties for a specific application. The procedures for creating PNPs by polymerizing monomers are explained below.

**(I) Emulsion polymerization**

One of the quickest and most scalable processes for producing nanoparticles is emulsion polymerization. Depending on whether an organic or an aqueous continuous phase is used, the approach is divided into two groups. In order to use the continuous organic phase approach, a monomer must be dispersed into an emulsion, an inverse microemulsion, or a nonsolvent—a substance in which the monomer is not soluble. By using 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 are of increased interest 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. When a monomer molecule dispersed in the continuous phase strikes an initiator molecule—which might be an ion or a free radical—initiation takes place. As an alternative, powerful ultraviolet or visible light, high-energy radiation, such as g-radiation, can convert the monomer molecule into an initiating radical. According to an anionic polymerization mechanism, 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**

A novel and successful method for producing nanosized polymer particles has gained a lot of attention: micro-emulsion polymerization. Even while both emulsion and micro-emulsion polymerization techniques can create colloidal polymer particles with high molar masses, they are completely different kinetically. In micro-emulsion polymerization, both particle size and the average number of chains per particle are much smaller. A thermodynamically stable micro-emulsion with swollen micelles is added to the aqueous phase of micro-emulsion polymerization together with an initiator, which is normally water-soluble. 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. Due to the application of a large amount of surfactant, the particles are also entirely covered in surfactant. Since the initiation cannot occur simultaneously in all microdroplets, polymer chains initially only form in part of the droplets. The delicate micro-emulsions are later destabilised by the elastic and osmotic impact of the chains, which typically result in a rise in particle size, the generation of empty micelles, and subsequent nucleation. In the finished product, the bulk of empty micelles coexist with very small latexes, 5–50 nm in size. Some of the key variables impacting the micro-emulsion polymerization kinetics and the characteristics of PNP are the 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*

Utilising biodegradable hydrophilic polymers like chitosan, gelatin, and sodium alginate, polymeric nanoparticles are created. By using ionic gelation, Calvo and colleagues created a technique for producing hydrophilic chitosan nanoparticles (Calvo et al., 1997). Ionic gelation was used by (Amir et al. 2008) to create Dexamethasone Sodium Phosphate loaded chitosan nanoparticles. Chitosan, a di-block co-polymer of ethylene oxide or propylene oxide (PEO-PPO), 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, which have a size in the nanometer range. In contrast to ionic gelation, which occurs when a substance changes from a liquid to a gel as a result of ionic interaction conditions at ambient temperature, coacervates are created as a result of electrostatic interaction between two aqueous phases.

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.

**References:**

* [Adelina-Gabriela Niculescu](https://pubmed.ncbi.nlm.nih.gov/?term=Niculescu%20AG%5BAuthor%5D) and [Alexandru Mihai Grumezescu](https://pubmed.ncbi.nlm.nih.gov/?term=Grumezescu%20AM%5BAuthor%5D) Polymer-Based Nanosystems—A Versatile Delivery Approach. 2021 Nov; 14(22): 6812.
* Ahmed Fadlelmoula, Diana Pinho, Vitor Hugo Carvalho,Susana O. Catarino and Graça Minas Fourier Transform Infrared (FTIR) Spectroscopy to Analyse Human Blood over the Last 20 Years: A Review towards Lab-on-a-Chip Devices. 2022  [Volume 13](https://www.mdpi.com/2072-666X/13)
* [Aleksandra Zielińska](https://pubmed.ncbi.nlm.nih.gov/?term=Zieli%C5%84ska%20A%5BAuthor%5D), [Filipa Carreiró](https://pubmed.ncbi.nlm.nih.gov/?term=Carreir%C3%B3%20F%5BAuthor%5D), [Ana M. Oliveira](https://pubmed.ncbi.nlm.nih.gov/?term=Oliveira%20AM%5BAuthor%5D), [Andreia Neves](https://pubmed.ncbi.nlm.nih.gov/?term=Neves%20A%5BAuthor%5D), [Bárbara Pires](https://pubmed.ncbi.nlm.nih.gov/?term=Pires%20B%5BAuthor%5D), [D. Nagasamy Venkatesh](https://pubmed.ncbi.nlm.nih.gov/?term=Venkatesh%20DN%5BAuthor%5D), [Alessandra Durazzo](https://pubmed.ncbi.nlm.nih.gov/?term=Durazzo%20A%5BAuthor%5D), [Massimo Lucarini](https://pubmed.ncbi.nlm.nih.gov/?term=Lucarini%20M%5BAuthor%5D), Polymeric Nanoparticles: Production, Characterization, Toxicology and Ecotoxicology 2020 Aug; 25(16): 3731.
* Allen, T. M., & Cullis, P. R. (2013). Liposomal drug delivery systems: from concept to clinical applications. Advanced Drug Delivery Reviews, 65(1), 36-48. doi:10.1016/j.addr.2012.09.037
* Allemann E., Leroux J.C., Gurny R. (1998). Polymeric nano-microparticles for the oral delivery of peptides and peptidomimetics. *Adv Drug Deliv Rev*, 34:171-189.
* Allemann E., Leroux J.C., Gurny R. and Doelker E. (1993). *Pharm. Res*., 10, 1732.
* Angel A. Justiz Vaillant; Roopa Naik. January 27, 2023. HIV-1 Associated Opportunistic Infections.
* [Aniket Nikam](https://pubmed.ncbi.nlm.nih.gov/?term=Nikam%20A%5BAuthor%5D),[Priya Ranjan Sahoo](https://pubmed.ncbi.nlm.nih.gov/?term=Sahoo%20PR%5BAuthor%5D), [Shubham Musale](https://pubmed.ncbi.nlm.nih.gov/?term=Musale%20S%5BAuthor%5D),[Roshani R. Pagar](https://pubmed.ncbi.nlm.nih.gov/?term=Pagar%20RR%5BAuthor%5D),[Ana Cláudia Paiva-Santos](https://pubmed.ncbi.nlm.nih.gov/?term=Paiva-Santos%20AC%5BAuthor%5D),and [Prabhanjan Shridhar Giram](https://pubmed.ncbi.nlm.nih.gov/?term=Giram%20PS%5BAuthor%5D) A Systematic Overview of Eudragit Based Copolymer for Smart Healthcare. 2023 Feb; 15(2): 587
* Archana M. and Jayanta K.P. (Fessi). Critical process parameters evaluation of modified nanoprecipitation method on Lomustine nanoparticles and cytostatic activity study on L132 human cancer cell line. *J Nanomed Nanotechol,* 3:149. doi:10.4172/2157-7439.1000149.
* Babak K., Katherine C., Keith L. Black, Vicky Y., Bhavraj K., Julia Y.Ljubimova (Soppimath). Nanoplatforms for constructing new approaches to cancer treatment, imaging, and drug delivery: *What should be the policy? Neuro Image* S106–S124.
* Barichello J.M., Morishita M., Takayama K., Nagai T. (1999). Encapsulation of hydrophilic and lipophilic drugs in PLGA nanoparticles by the nanoprecipitation method*. Drug Dev Ind Pharm*, 25:471- 476.
* Blanco, E., Shen, H., & Ferrari, M. (2015). Principles of nanoparticle design for overcoming biological barriers to drug delivery. Nature biotechnology, 33(9), 941–951. doi:10.1038/nbt.333
* Braunecker W.A., Matyjaszewski K. (2007). Controlled/living radical polymerization: features,developments, and perspectives. *Prog Polym Sci*, 32:93–146.
* Calvo P., Remunan-Lopez C., Vila-Jato J.L., Alonso M.J. (1997). Chitosan and chitosan/ethylene oxide-propylene oxide block copolymer nanoparticles as novel carriers for proteins and vaccines. *Pharm Res*, 14: 1431-1436.
* Campuzano A., Wormley F.L. Innate immunity against Cryptococcus, from recognition to elimination. *J. Fungi (Basel).*2018;4:33.
* Carina I.C. Crucho , Maria Teresa Barros , Polymeric nanoparticles: A study on the preparation variables and characterization methods [Volume 80](https://www.sciencedirect.com/journal/materials-science-and-engineering-c/vol/80/suppl/C), 1 November 2017,
* Catarina P.R., Ronald J.N., Antonio J.R., Francisco V. (2006). Methods for preparation of drug-loaded polymeric nanoparticles. *Nanomedicine: Nanotechnology, Biology and Medicine* 2, 8– 21.
* Chernyak Y., Henon F., Harris R. B., Gould R. D., Franklin R. K., Edwards J. R. (2001). Formation of perfluoro polyether coatings by the rapid expansion of Supercritical solutions(RESS) process Part1:experimental results*. Ind Eng Chem Res*, 40:6118–6126.
* [Chizhu Ding](https://pubmed.ncbi.nlm.nih.gov/?term=Ding+C&cauthor_id=28482511), [Zibiao Li](https://pubmed.ncbi.nlm.nih.gov/?term=Li+Z&cauthor_id=28482511) A review of drug release mechanisms from nanocarrier systems. 2017 Jul 1;76:1440-1453
* Chronopoulou L., Fratoddi I., Palocci C., Venditti I., Russo M.V. (2009). Osmosis based method drives the self-assembly of polymeric chains into micro and nanostructures. *Langmuir*, 25:119406.
* Couvreur P., Dubernet C., Puisieux F. (1995). Controlled drug delivery with nanoparticles: current possibilities and future trends. *Eur J Pharm Biopharm*, 41:2 - 13.
* Daljeet S. Dhanjal, ... Saurabh Satija, in [Modeling and Control of Drug Delivery Systems](https://www.sciencedirect.com/book/9780128211854/modeling-and-control-of-drug-delivery-systems), 2021
* Danicher L., Frere Y., Calve A.L. (2000). Synthesis by interfacial polycondensation of polyamide capsules with various sizes. Charecteristics and properties. *Macromol Sym,* 151:387–392.
* Dimitrova B., Ivanov I.B., Nakache E. (1988). Mass transport effects on the stability of emulsion films with acetic acid and acetone diffusing across the interface. *J Disp Sci Technol*, 9:321- 341.
* Dreaden, E. C., Alkilany, A. M., Huang, X., Murphy, C. J., & El-Sayed, M. A. (2012). The golden age: gold nanoparticles for biomedicine. Chemical Society Reviews, 41(7), 2740–2779. doi:10.1039/C1CS15237H
* Ekmam Meziani M.J., Pathak P., Wang W., Desai T., Patil A., Sun Y.P. (2005). Polymeric nanofibers from rapid expansion of supercritical solution. *Ind Eng Chem Res,* 44:4594–8.
* Fessi Jeon H.J., Jeong Y.I., Jang M.K., Park Y.H., Nah J.W. (2000). Effect of solvent on the preparation of surfactant free poly(dl-lactide-co-glycolide) nanoparticles and norfloxacin release characteristics*. Int J Pharm*, 207:99–108.
* [G.Kiran Kumar Reddy](https://pubmed.ncbi.nlm.nih.gov/?term=Reddy%20GK%5BAuthor%5D), [Alwar Ramanujam Padmavathi](https://pubmed.ncbi.nlm.nih.gov/?term=Padmavathi%20AR%5BAuthor%5D), and [Y.V. Nancharaiah](https://pubmed.ncbi.nlm.nih.gov/?term=Nancharaiah%20Y%5BAuthor%5D) (2022)  Apr27. doi: [10.1016/j.crmicr.2022.100137](https://doi.org/10.1016/j.crmicr.2022.100137) Fungal infections: Pathogenesis, antifungals and alternate treatment approaches.
* Gallardo M., Couarraze G., Denizot B., Treupel L., Couvreur P., Puisieux F. (1993). Study of the mechanisms of formation of nanoparticles and nanocapsules of poly(isobutyl-2-cyanoacrylate). *Int J Pharm*, 100:55–64.
* Gasco M., Trotta M. (1986). Nanoparticles from microemulsions. *Int J Pharm*, 29:267–268.
* Gelfuso G.M., Reis T.A., Matos B.N., Oliveira A.A., Gratieri T. (2002). Development of cationic nanoparticles encapsulating Fluconazole for improving the topical treatment of vaginal candidiasis.
* Ham H.T., Choi Y.S., Chee M.G., Chung I.J. (2006). Singlewall carbon nanotubes covered with polystyrene nanoparticles by in-situ miniemulsion polymerization. J Polym Sci Part A Polym Chem; 44:573–584.
* Hami Z. A Brief Review on Advantages of Nano-based Drug Delivery Systems. Ann Mil Health Sci Res. 2021;19(1)
* Hemul V.P., Mangesh R.S., Sanjay B.K., Naynika K.P. (2013). Spray dried microparticles for controlled delivery of Fluconazole using factorial Design, *International Journal of Research in Pharmaceutical and Biomedical Sciences, Vol. 4* (2), 582-590.
* Hokken M.W.J., Zwaan B.J., Melchers W.J.G., Verweij P.E. Facilitators of adaptation and antifungal resistance mechanisms in clinically relevant fungi. *Fungal Genet. Biol.*2019;132
* Jeong Y.I., Cho C.S, Kim S.H., Ko K.S., Kim S.I., Shim Y.H. (2001). Preparation of poly(dl-lactide- co-glycolide) nanoparticleswithout surfactant. *J Appl Polym Sci,* 80:2228–2236.
* [Jiri Housť](https://pubmed.ncbi.nlm.nih.gov/?term=Hou%C5%A1%C5%A5%20J%5BAuthor%5D), [Jaroslav Spizek](https://pubmed.ncbi.nlm.nih.gov/?term=Sp%C3%AD%C5%BEek%20J%5BAuthor%5D), and [Vladimir Havlicek](https://pubmed.ncbi.nlm.nih.gov/?term=Havl%C3%AD%C4%8Dek%20V%5BAuthor%5D)Antifungal Drugs2020 Mar; 10(3): 106.
* Jung Charcosset C., Fessi H. (2006). Amembrane contactor for the preparation of nanoparticles. *Desalination*; 200:568–569.
* Khoury-Fallouh A.N., Roblot-Treupel L., Fessi H., Devissaguet J.P., Puisieux F. (1986). Development of a new process for the manufacture of poly isobutylcyanoacrylate nanocapsules*. Int J Pharm*, 28:125–136.
* Khushwant S.Y., Krutika K.S. (2010). Modified nanoprecipitation method for preparation of Cytarabine-loaded PLGA nanoparticles, *AAPS PharmSciTech, Vol. 11, No. 3*, 1456-1466.
* Kreuter J. (1982). The mechanism of termination in heterogeneous polymerization. *J Polym Sci*, 20:543-555.
* Kreuter J. and Speiser P. (1976). *Infect. Immun.,* 13, 204.
* Lambert G., Fattal E., Alphandary H.P., Gulik A., Couvreur P. (2001). Poly isobutyl cyano acrylate nanocapsules containing an aqueous core for the delivery of oligonucleotides. *Int J Pharm*, 214:13–16.
* Lambert G., Fattal E., Couvreur P. (2001). Nanoparticulate system for the delivery of antisense oligonucleotides. *Adv Drug Deliv Rev*, 47:99-112.
* Lee J., Cho E.C., Cho K. (2004).Incorporation and release behaviour of hydrophobic drug in functionalized poly(d,l-lactide)-block-poly(ethylene oxide) micelles. *J Control Release,* 94:323–335.
* Lee P.P., Lau Y.-.L. Cellular and molecular defects underlying invasive fungal infections—revelations from endemic mycoses. *Front. Immunol.*2017;8:735.
* *Li Z., Lu G., Meng G. Pathogenic fungal infection in the lung. Front. Immunol. 2019;10:1524.*
* Matyjaszewski K., Xia J. (2001). Atom transfer radical polymerization. *Chem Rev*, 101:2921–2990.
* Memisoglu E., Bochot A., Ozalp M., Sen M., Duchene D., Hincal A. (2003). Direct formation of nanospheres from amphiphilic beta-cyclodextrin inclusion complexes. *Pharm Res*, 20:117- 125.
* Meziani M.J., Pathak P., Hurezeanu R., Thies M.C., Enick R.M., Sun Y.P. (2004). Supercritical fluid processing technique for nanoscale polymer particles. *Angew Chem Int Ed*, 43:7047.
* Meziani M.J., Pathak P., Wang W., Desai T., Patil A., Sun Y.P. (2005). Polymeric nanofibers from rapid expansion of supercritical solution. *Ind Eng Chem Res,* 44:4594–8.
* Mukesh C.G., Stavan N.A. (2009). Fabrication of modified transport Fluconazole transdermal spray containing Ethyl Cellulose and Eudragit® RS100 as film formers, *AAPS PharmSciTech, Vol*. 10, No. 2, 684-692.
* Nevine S.A., Shahira F El-Menshawe (2011). A new topical fluconazole microsponge loaded hydrogel: preparation and characterization, *Int J Pharm Pharm Sci, Vol 4, Suppl 1,* 460-468.
* [Niccolò Riccardi](https://pubmed.ncbi.nlm.nih.gov/?term=Riccardi%20N%5BAuthor%5D), [Gioacchino Andrea Rotulo](https://pubmed.ncbi.nlm.nih.gov/?term=Rotulo%20GA%5BAuthor%5D), and [Elio Castagnola](https://pubmed.ncbi.nlm.nih.gov/?term=Castagnola%20E%5BAuthor%5D) Definition of Opportunistic Infections in Immunocompromised Children on the Basis of Etiologies and Clinical Features 2019 Nov. doi: [10.2174/1573396315666190617151745](https://doi.org/10.2174/1573396315666190617151745)
* Nicolas J., Charleux B., Guerret O., Magnet S. (2005). Nitroxide-mediated controlled free-radical emulsion polymerization using a difunctional water-soluble alkoxyamine initiator. Toward the control of particle size, particle size distribution, and the synthesis of tri block copolymers. *Macromolecules*, 38:9963–9973.
* Nicolas J., Ruzette A.V., Farcet C., Gerard P., Magnet S., Charleux B. (2007). Nanostructured latex particles synthesized by nitroxide-mediated controlled/living free-radical polymerization in emulsion. *Macromolecules*, 48:7029–7040.
* Niwa T., Takeuchi H., Hino T., Kunou N., Kawashima Y. (1993). Preparation of biodegradable nanoparticles of water-soluble and insoluble drugs with D, Llactide/ glycolide copolymer by a novel spontaneous emulsification solvent diffusion method, and the drug release behavior. J. *Control.Release*, 25: 89-98.
* Patel, A., Patel, M., & Yang, X. (2012). Advances in anticancer protein drug delivery systems. AAPS PharmSciTech, 13(3), 899-906. doi:10.1208/s12249-012-9796-2
* Peer D., Karp J.M., Hong S., Farokhzad O.C., Margalit R., Langer R. (2007). Nanocarriers as an emerging platform for cancer therapy. *Nat. Nanotechnol. 2*, 761–770.
* Puglisi G., Fresta M., Giammona G., Ventura C.A. (1995). Influence of the preparation conditions in poly(ethylcyanoacrylate) nanocapsule formation. *Int J Pharm*, 125:283–287.
* Puig J.E. (1996). Microemulsion polymerization (oil-in water). In: Salamone JC, editor. Polymeric materials encyclopedia, (6) Boca Raton, *FL: CRC Press*, 4333–4341.
* Quintanar-Guerrero D., Allemann E., Fessi H., Doelker E. (1998). Preparation techniques and mechanism of formation of biodegradable nanoparticles from preformed polymers. *Drug Dev* *Ind Pharm*, 24: 1113-1128.
* Saeed Emami , Elham Ghobadi , Shahnaz Saednia , Seyedeh Mahdieh Hashemi. Current advances of triazole alcohols derived from fluconazole. [Volume 170](https://www.sciencedirect.com/journal/european-journal-of-medicinal-chemistry/vol/170/suppl/C), 15 May 2019, Pages 173-194
* [Sangita P. Shirsat](https://rjppd.org/search.aspx?key=Sangita%20P.%20Shirsat), [Kaveri P. Tambe](https://rjppd.org/search.aspx?key=Kaveri%20P.%20Tambe), [Ganesh G. Dhakad](https://rjppd.org/search.aspx?key=Ganesh%20G.%20Dhakad), [Paresh A. Patil](https://rjppd.org/search.aspx?key=Paresh%20A.%20Patil), [Ritik. S. Jain](https://rjppd.org/search.aspx?key=Ritik.%20S.%20Jain) Antifungal Agents [Volume - 13,   Issue - 4,   Year - 2021](https://rjppd.org/Issues.aspx?VID=13&IID=4)
* Schmidt G. (2004). Nanoparticles: from theory to applications. Weinheim, *Germany: Wiley-VCH Publishers.*
* Scott C., Wu D., Ho C.C., Co C.C. (2005). Liquid-core capsules via interfacial polymerization: a free-radical analogy of the nylon rope trick. *J Am Chem Soc*, 127:4160–4167.
* Shokri N., Akbari J.H., Fouladdel S., Khalaj A., Khoshayand M.R., Dinarvand R. (2011). Preparation and evaluation of poly (caprolactone fumurate) nanoparticles containing Doxorubicin Hcl. *DARU* (19) 1.
* Siepmann, J., & Siegel, R. A. (2012). Mathematical modeling of drug delivery. International journal of pharmaceutics, 437(1-2), 3-21. doi:10.1016/j.ijpharm.2012.07.012
* Singh A, Masih A, Khurana A, Singh PK, Gupta M, Hagen F, et al. High terbinafine resistance in Trichophyton interdigitale isolates in Delhi, India harbouring mutations in the Squalene epoxidase (SQLE) gene. *Mycoses.*2018;61:477–84
* Sun Y.P., Rolling H.W., Bandara J., Meziani J.M., Bunker C.E. (2002). Preparation and processing of nanoscale materials by supercritical fluid technology. In:SunYP, editor. Supercritical fluid technology in materials science and engineering: synthesis, properties, and applications*. NewYork: Marcel Dekker*, 491–576.
* **Swati Tyagiand Vinay Kumar Pandey.** Nanoparticles: An Overview of Preparation. **Published date:** 26/10/2016
* Thiruchelvi Pulingam, Parisa Foroozandeh, Jo-Ann Chuah and Kumar Sudesh Various Techniques for the Biological Synthesis of Polymeric Nanoparticles 2022, 12(3), 576
* Vauthier C., Dubernet C., Fattal E., Pinto A., Couvreur P. (2003). Poly(alkylcyanoacrylates) as biodegradable materials for biomedical applications. *Adv Drug Deliv Rev*, 55:519- 548.
* Weber M., Thies M.C. (2002). Understanding the RESS process. In: SunYP, editor. Supercritical fluid technology in materials science and engineering: synthesis, properties, and applications. *NewYork:Marcel Dekker*, 387–437.
* Wehrle P., Magenheim B., Benita S. (1995). Influence of process parameters on the PLA nanoparticle size distribution, evaluated by means of factorial design. *Pharm Biopharm,* 41:19-26.
* [Yongyang Song](https://pubs.rsc.org/en/results?searchtext=Author%3AYongyang%20Song),  [Jun-Bing Fan](https://pubs.rsc.org/en/results?searchtext=Author%3AJun-Bing%20Fan)  and  [Shutao Wang](https://pubs.rsc.org/en/results?searchtext=Author%3AShutao%20Wang) Recent progress in interfacial polymerization. 2017
* York P. (1999). Strategies for particle design using supercritical fluid technologies. *Pharm Sci Technol Today*, 2:430–440.
* Zhou X., Ni P., Yu Z. (2007). Comparison of RAFT polymerization of methyl methacrylate in onventional emulsion and miniemulsion systems. *Polymer*, 48:6262–6271.