**Polymeric Nanoparticles for Targeted Drug Delivery**

**Biswajit Sarma\*, Anup Malakar, Kajal Dutta**

Dr. Biswajit Sarma, Associate Professor, Department of Chemistry, Royal School of Applied and Pure Sciences, Royal Global University, Guwahati-781035, Assam, India.

Dr. Anup Malakar, Assistant Professor, Department of Chemistry, Royal School of Applied and Pure Sciences, Royal Global University, Guwahati-781035, Assam, India.

Dr. Kajal Dutta, Assistant Assistant Professor, Department of Chemistry, Girijananda Chowdhury University, Assam, Azara, Guwahati -17

\*Corresponding Author E-mail: **Biswajit.Sarma@rgi.edu.in**

**Abstract:**

Polymeric nanoparticles are found to have high potential for drug delivery for the treatment of various diseases. Polymeric materials are suitable for drug delivery because of their high possibilities of surface modifications. Polymeric micelles, dendrimers, and vesicles etc. are used for polymeric drug delivery. Polymeric nanoparticles (NPs) have attracted considerable interest over recent years due to their properties resulting from their small size. Advantages of polymeric NPs as drug carriers include their potential use for controlled release, the ability to protect drug and other molecules with biological activity against the environment, improve their bioavailability and therapeutic index. The term “nanoparticle” comprises both nanocapsules and nanospheres, which differ with respect to their morphology. Because of their gene loading capacity, stability and tunable properties polymeric materials have emerged as potential carrier in formulating a efficient gene delivery system. To ensure appropriate release of the gene as well as easy removal of the carrier after gene release, selection of polymeric materials is vital. Because of their inherent competitive advantages, polymeric-based nanoparticles has astonishing potential to counteract the new coronavirus disease (COVID-19). Polymeric Nanoparticle because of their small size, have distinct properties compared to the bulk form of the same material, thus offering many new developments in the fields of biosensors, biomedicine, and bio nanotechnology. In this review article we have mainly discussed about the application of polymeric nanoparticles in the field of drug delivery for various common diseases.

**1.Introduction:**

Nanoscience is an emerging field in information technology, medical technology, biochemistry, synthetic chemistry, biotechnology, and medicine. Nanotechnology offers various applications in the field of health care and medicine such as for analytical purposes, diagnosis, treatment processes, targeted drug delivery, genetic engineering (Chandarana *et*.*al,* 2018). Nanomaterials can help in different ways in achieving therapeutic functions of drug molecules which are otherwise difficult to achieve with normal or traditional biomaterials. Nanomedicine is considered as a rapidly evolving field which are drawing significant attention of medical researchers. Nanomedicine is found to be a multidisciplinary research field. The field of Nanomedicine can be considered as an integrated field of biology, chemistry, biochemistry, pharmacology, biotechnology and material sciences. Various materials are used as sources for synthesize nanoparticles. Nanoparticles are generally composed of a surface layer, a core, and may exhibit various sizes and shapes. Surface of nanoparticles can be modified and functionalized with new side chains. Large surface area of small sized nanoparticles are suitable for interaction and binding. There are lots of advantages of using nanomaterials as carriers for drugs over conventional or traditional therapies. The use of nanotechnology can improve the process of drug delivery in various ways. Nanoformulations can increase the safety and tolerability of drugs. Nanoformulations may help to decrease the side effect of drugs and increase the homogenous drug absorption and distribution. There are high potential of preparation of nanoparticles from biocompatible as well as biodegradable materials. Nanocarrier mediated targeted drug delivery may be either by active or passive.

A wide range of drugs including hydrophilic drugs, biological macromolecules, hydrophobic drugs, vaccines, etc. can be can be delivered very much effectively using nanoparticulate carriers. Nanomaterial based drug delivery systems depend on the properties, characteristics and preparation methods of different nanomaterials, whereby suitable nanocarriers are selected and designed (Lee *et al.,* 2017). The efficacy of the nanoparticles as drug delivery materials depends on the structure, size and other properties of the nanoparticles. The drug’s absorption, distribution, cellular uptake of the drug molecules depends on surface topography of NPs. The shape and size of the nanoparticles is a crucial factor which ensures the safe travel of these nanoparticles in the bloodstream. Small sized nanoparticles can easily accumulate and extravasate into normal tissues. The shape of the nanoparticles has significant impact on cellular uptake as well as cytotoxicity (Jindal *et al.,* 2017). After the required action of the nanoparticles in the body, various organs easily clear them out these small nanoparticles. Surface characteristics of nanoparticles are very much important for the formation of interaction between the nanoparticle and the cellular components of a specific tissue. For proper effective interaction nanoparticles generally interact with extracellular fluids like blood, lymph etc. Various techniques like encapsulation, linking etc. are used for the loading of drug molecules into the nanoparticles (Jing Wang, *et al.,* 2017). Combined drug therapy is also possible where different drugs can be loaded with single nanocarrier. Micellar nanoparticles are reported to be loaded with two different drugs, bortezomib and doxorubicin, which are successfully used as antitumor agent on ovarian cancer (Wang *et al.,* 2017). Some nanoparticles have characteristic properties which can very effectively help to achieve targeted drug delivery. Targeted drug delivery depends on type of nano formulation. Nanoimaging is another area of application of nanotechnology in the field medicines. In nanoimaging nano formulation is used as detection agents. Few nanoparticles are found to have both pharmacological as well as imaging properties (Ventola *et al.,* 2017) [15]. Nanoparticles can improve the efficacy of the loaded detecting agent. Nanoimaging may also helpful in labelling the transplanted Stem cells.

During the last few years different types of nanotechnologies are developed for biomedicine with characteristics features and various degrees of benefits. Various types of nanoparticles have been synthesized for drug delivery applications. Different types of nano particles are developed such as polymeric NPs, organic NPs, inorganic NPs, lipid-based NPs, and micelles. Inorganic magnetic NPs have raised very much interest in the medical community. Magnetic NPs are generally made of metal compounds, metal oxides, carbon, silica, etc. Magnetic properties of these NPs may be used for both drug delivery as well as diagnostic tools.

In the recent decades, polymeric nanoparticles have got considerable interest due to their different important properties resulting from their nano range size (Cano *et*.*al,* 2019). Polymeric nanoparticles can be considered as nanoparticles made of polymers. Various polymeric materials make up the colloidal formations in the polymeric nanoparticles. Recently polymers are very commonly used as biomaterials due to their different suitable properties like excellent biocompatibility, a variety of structures as well as design quality, important bio-mimetic character, etc. Polymeric nanoparticle based nanomedicines has lots of advantages like high medication effectiveness, improved specificity, high tolerance, and excellent therapeutic index. Polymeric particles help in the stabilizing and protecting the medicine molecules from different environmental hazards degradation. Nanoparticles can be developed from the biodegradable polymers. Different types of natural and the synthetic polymers are used for these preparations. Some of the polymers which are suitable for controlled drug release applications are poly (lactic acid) (PLA), poly(caprolactone) (PCL), poly (amino acids), poly (D, Llactide-co-glycolide) (PLGA), etc. (Kumari *et*.*al,* 2010). Polymers are reported to be very much effective for the controlled release system of drug delivery. Some specific polymers have important physicochemical and biocompatibility properties. Polymeric drug delivery systems are found to be comparably stable as well as capable of high drug loading capacities. The smart drug delivery systems are developed effectively by using advances in polymer science and nanotechnology field. Encapsulation efficiency of polymeric nanoparticles are influenced by the molecular weight of the polymers and concentration of the polymer. Polymeric nanoparticles used in the area of drug delivery have different important properties like biodegradability, good shelf life, and water solubility. This review mainly summarizes the recent advances of ongoing research works on the role of polymeric nanoparticles in the drug delivery for various types of diseases.

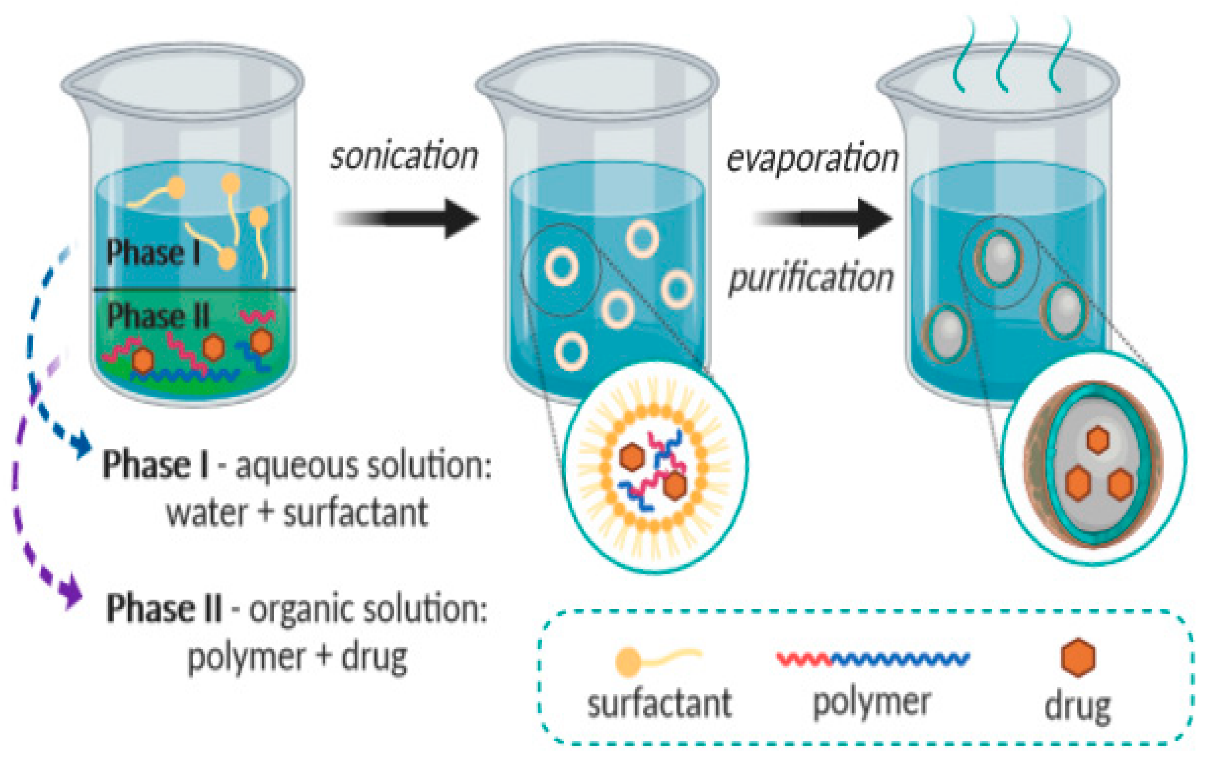
**2. Methods for Production of Polymeric Nanoparticles**

Preparation of polymeric nanoparticles with diversity in complex structures and functions has been drawing considerable attention during the past decade. This may be due to the reason that nanoparticles ranging in size from 10 nm to more than 100 nm offer improved physical, chemical, or biological properties when optimally structured. Finding economically viable processes for preparation of acceptable nanoparticles has been a challenging venture. Depending on the type of drug to be loaded and requirements for a specific administration route, variety of methods can be employed for the production of the polymeric nanoparticles (Jawahar *et al*., 2012). Two main strategies are employed in general for production of polymeric nanoparticles i.e., (i) dispersion of preformed polymers and (ii) the polymerization of monomers (Chander *et al*., 2019)

In majority of the techniques used for preparation of polymeric nanoparticles, organic solvents are generally used in the first step to dissolve the polymer (Chander *et al*., 2019). These solvents can lead to problems related to toxicity and environmental risk. Above all, solvent residues have to be removed from the final product, which is also challenging many a times. To load compounds in polymeric nanoparticles, techniques based on the polymerization of monomers leads to insertion with greater effeciency (Kamaly *et al*., 2016). Regardless of the method of preparation used, the products are generally obtained as aqueous colloidal suspensions (Jawahar *et al*., 2012)

**2.1. Solvent Evaporation**

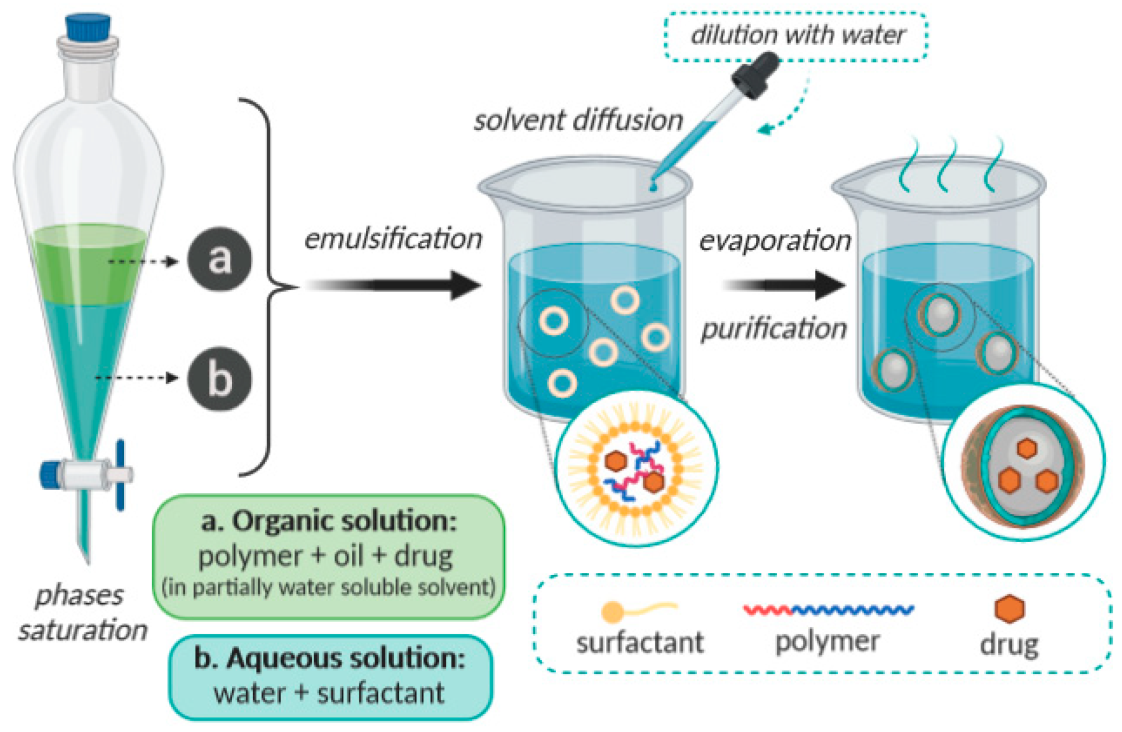
One of the initial methods for development of polymeric nanoparticles from a preferred polymer is solvent evaporation (Vieira *et al.,* 2019). Desgouilles *et al*., 2003 developed a method where an oil-in-water emulsion was initially prepared which leads to the production of nanospheres. In the beginning, an organic phase consisting of a polar organic solvent containing the dissolved polymer was taken. The active ingredient i.e., the drug is included through dissolution or dispersion. Earlier as solvents, dichloromethane and chloroform have been extensively employed. Due to their environmental toxicity, they have been replaced by ethyl acetate (Bohrey *et. al.,* 2016). Ethyl acetate shows improved toxicological profile, and thus it is better suited for biomedical applications (Vauthier *et al.,* 2017). An aqueous phase containing a surfactant such as polyvinyl acetate has also been employed frequently (Bohrey *et. al.,* 2016). The organic solution is made to undergo emulsification in the aqueous phase with a surfactant followed by processing with a high speed homogenization or ultrasonication to produce dispersion of nanodroplets (Sharma *et al.,* 2016). On evaporation of the polymer solvent, a suspension of nanoparticles was obtained, which was washed and collected by centrifugation. A schematic diagram of the solvent evaporation method is shown in **Figure 1**.



**Figure1**. Schematic representation of the solvent evaporation method (Open access: Zielińska *et al*., 2020).

**2.2 Emulsification/Solvent Diffusion**

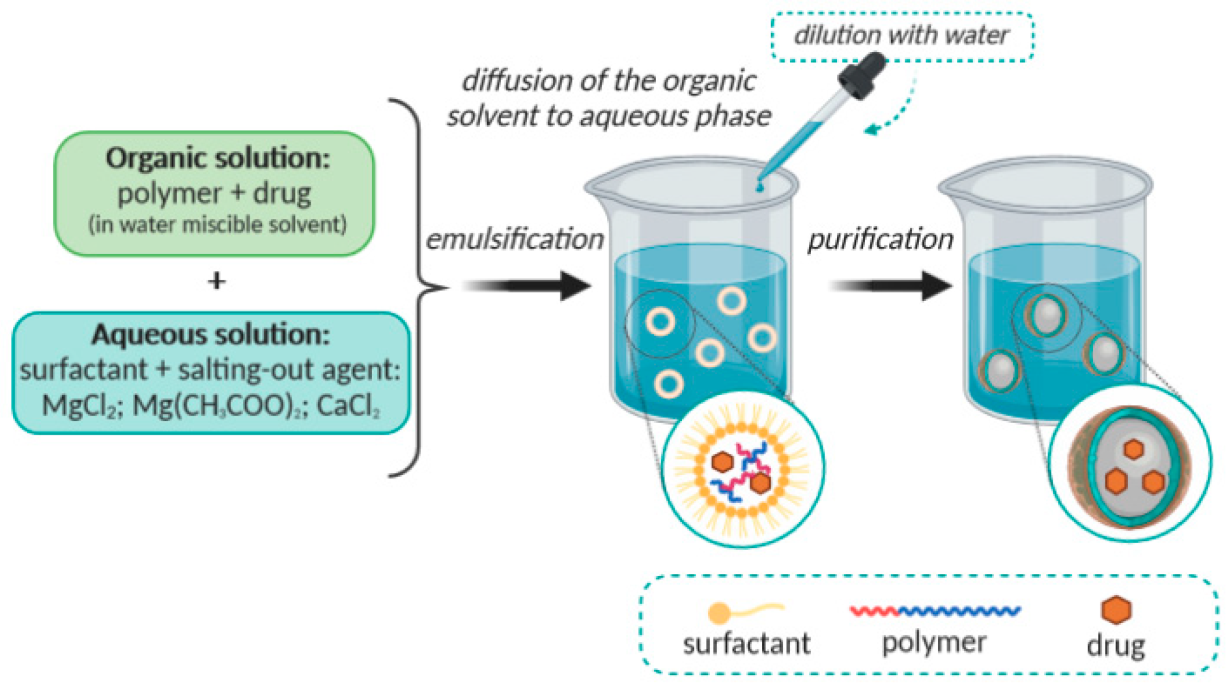
This method involves formation of an oil in water emulsion between a partially water-miscible solvent and an aqueous solution (Kumar *et al*., 2012). The partially water miscible solvent contains the polymer and the drug, while the aqueous solution contains the surfactant. The internal phase of this emulsion is made of a partly water-miscible organic solvent, i.e., benzyl alcohol or ethyl acetate. The emulsion is previously saturated with water so that an initial thermodynamic balance of both phases is maintained at room temperature (Souto *et al*., 2012) Although, this method is used in general to produce nanospheres, but nanocapsules can also be produced if a slight amount of oil is mixed with the organic phase. This method enables us to prepare nanoparticles with dimension ranging from 80 to 900 nm (Quintanar *et. al.,*1998). A schematic representation of the emulsification/solvent diffusion method is shown in **Figure 2**.



**Figure 2.** Schematic representation of the emulsification/solvent diffusion method. (Open access: Zielińska *et al*., 2020)

**2.3 Emulsification/Reverse Salting-Out**

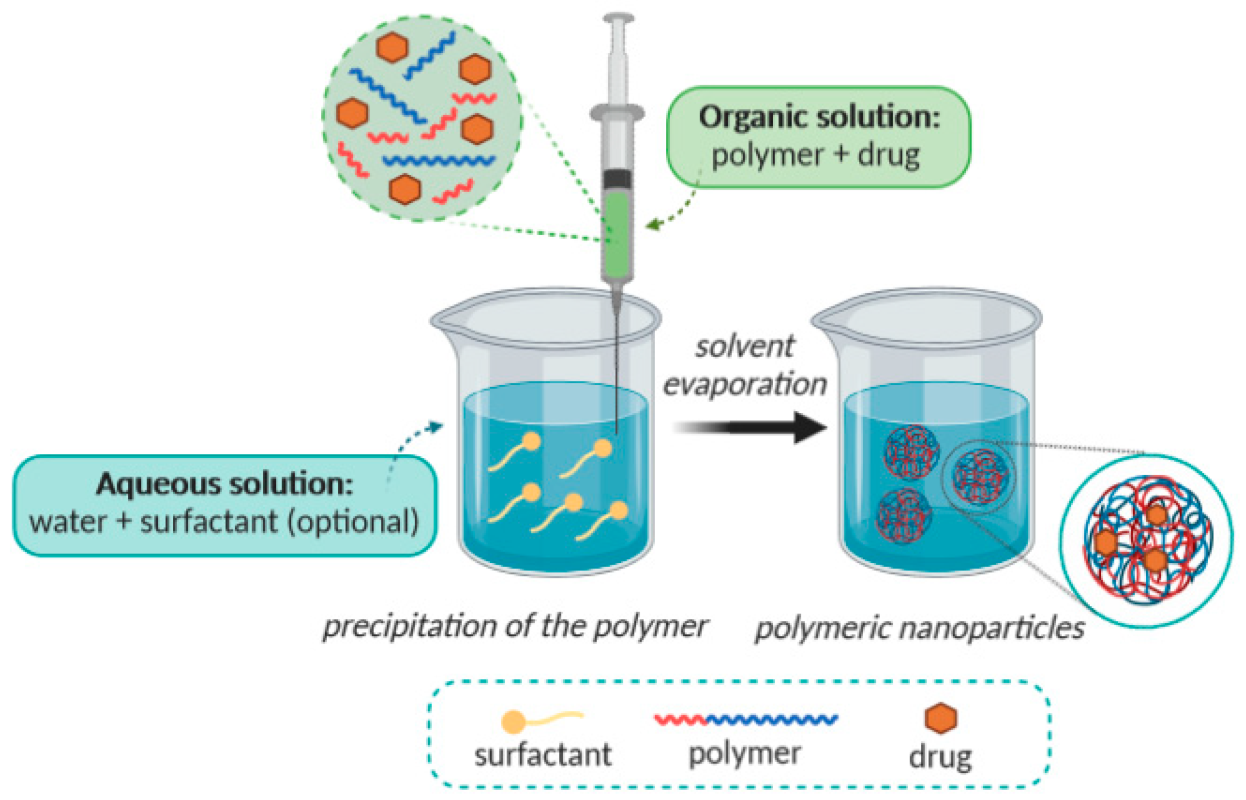
The emulsification/solvent diffusion method can be considered as a modified version of the emulsification/reverse salting-out method (Wang *et al.,* 2016). The prime difference is the composition of the oil in water emulsion, which is prepared from a water miscible polymer solvent. The aqueous phase is comprised of a gel, the salting-out agent and a colloidal stabilizer. Electrolytes, such as magnesium chloride, calcium chloride or magnesium acetate and non-electrolytes such as sucrose (Pal *et al*., 2011) are being applied as suitable salting-out agents (Vauthier *et al*., 2009). The oil in water emulsion is prepared under intense stirring, followed by dilution with deionized water or an aqueous solution so that there exist diffusion of the organic solvent to the external phase leading to the precipitation of the polymer and formation of nanospheres. Elimination of the remaining solvent and salting-out agent are done by cross-flow filtration. A schematic representation of the emulsification/reverse salting-out method is shown in **Figure 3**.



**Figure 3.** Schematic representation of the emulsification/reverse salting-out method. (Open access: Zielińska *et al*., 2020)

**2.4** **Nanoprecipitation**:

Nanoprecipitation or solvent displacement method uses two miscible solvents. A polymer dissolved in a miscible organic solvent, such as acetone or acetonitrile form the internal phase The principle of this technique relies on the interfacial deposition of a polymer after the movement of the organic solvent from a lipophilic solution to the aqueous phase (Salatin *et al*., 2017). In the first step, the polymer is dissolved in a water-miscible solvent of intermediate polarity followed by controlled addition of the solution into an aqueous solution leading to instantaneous formation of nanoparticles (Salatin *et al*., 2017). Diffusion of solvent from the nanodroplets leading to the precipitation of polymer in the form of nanocapsules or nanospheres. Although the addition of surfactants is not necessary for the formation of nanoparticles, their presence confirms the stability of the nanoparticles. (Bilati *et al*., 2005) Nanoprecipitation has been constantly used for the production of polymeric nanoparticles with around 170 nm dimensions (Chidambaram *et al.,* 2005). **Figure 4** depicts a schematic illustration of the nanoprecipitation method.



**Figure 4.** Schematic illustration of the nanoprecipitation method. (Open access: Zielińska *et al*., 2020)

**2.5 Dialysis**

A simple and effective method for the preparation of small and narrow-distributed polymeric nanoparticles is dialysis (Fessi *et al.,* 1989). In this method polymer dissolved in an organic solvent is kept inside a dialysis tube with proper molecular weight cut off. In general dialysis involves the gradual displacement of the solvent inside the membrane. This is followed by the gradual aggregation of polymer, which occurs due to a loss of solubility leading to the formation of nanoparticles. A good number of polymeric as well as copolymer nanoparticles have been reported to be prepared by this technique. Chécot*et al.,* 2008 and Ferranti *et al.,* 2008 reported preparation of Poly(benzyl-l-glutamate)-b-poly(ethylene oxide), Poly(lactide)-b-poly(ethylene oxide) nanoparticles by employing DMF as solvent. The morphology and particle size distribution of the nanoparticles have been influenced by the solvent used in the preparation of the polymer solution. Chronopoulou *et al*., 2009 reported a novel osmosis based method for the synthesis of both natural and synthetic polymeric nanoparticles. This method is based on the application of a physical barrier, specifically dialysis membrane or common semipermeable membranes which allow the passive transport of solvents. This leads to slowing down the mixing of the polymer solution with a non-solvent.

**2.6 Supercritical fluid technology**

Supercritical fluid technology has been emerging as an environmentally benign method for production of polymeric nanoparticles. The utility of supercritical fluids as environmental friendly solvents for production of highly pure polymeric nanoparticles and without organic solvent have gained immense popularity (York *et al*., 1999). Mostly two principles have been adopted for the production of nanoparticles using supercritical fluids:

**2.6.1** Rapid expansion of supercritical solution (RESS)

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

**2.6.1** **Rapid expansion of supercritical solution**

In conventional RESS, a solution is formed by dissolving the solute in a supercritical fluid. Rapid expansion of the solution has been done across an orifice or a capillary nozzle into ambient air. Higher super saturation along with fast reduction of pressure in the expansion process leads to the generation well-dispersed particles. RESS has been successfully employed for production of poly(perfluoropolyetherdiamide) droplets by Chernyak *et al.,* 2001*.* through rapid expansion of CO2 solutions. The RESS experimental set up is comprised of three major units: a high-pressure stainless steel mixing cell, a syringe pump, and a pre-expansion unit. At ambient temperature, a solution of polymer in CO2 is pumped to the pre-expansion unit and is heated at the same pressure to the pre-expansion temperature. This is followed by expansion of the supercritical solution through the nozzle at ambient pressure. For polymeric nanoparticles prepared by REES, the particle size and morphology is influenced by the concentration and degree of saturation of the polymer. Blasig *et al*., 2002 performed a RESS mediated process for synthesis of polymeric nanoparticles with poly(heptadecafluorodecyl acrylate). They have used a concentrations of 0.5–5 wt % in CO2. The RESS process has been used by the Lim *et. al*., 2005 for the synthesis of spherical nanoparticles of PSFTE (poly[2-(3-thienyl) acetyl-3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctanoate) having a size of 50–500nm from solutions (0.1–0.5 wt.% PSFTE) in CO2 at pre-expansion temperatures of 40◦C. In a characteristic experiment, CO2 was introduced into PSFTE through a syringe pump. After shifting the CO2 from pre-heater, PSFTE sample was collected by spraying particles through the nozzle onto a slide glass. Not only the concentration and degree of saturation, but also other factors like material properties, processing conditions, molecular mass of the polymer etc. play a vital role in determining the particle size. Sane *et al*., 2007 performed RESS mediated process with CO2 and THF solutions of PLLA, poly(l-lactic acid). They have also demonstrated that the solid-state diffusion coefficient of the solute is one of the prime factors for controlling the particle size during the RESS processing. In general, RESS products synthesized from PLLA consisted nanoparticles mainly 30–100nm in diameter. The particles have been dispersed with either micron sized particles or agglomerates of nano and submicron sized particles. Although this technique utilizes no organic solvent for the formation of polymeric nanoparticles, the products obtained using this technique are microscaled rather than nano-scaled. This is the main drawback of RESS.

**2.6.2** **Rapid expansion of supercritical solution into liquid solvent**

Rapid expansion of supercritical solution into liquid solvent (RESOLV) is a modification to RESS. It involvesexpansion of the supercritical solution into a liquid solventinstead of ambient air (Sun *et al*.,2002). The liquidsolvent suppresses the particle growth in theexpansion jet, thus making it possible to acquire primarilynanosized particles.Meziani *et al.,* 2004 synthesised PHDFDA (poly(heptadecafluorodecylacrylate)) nanoparticles with an average size of less than 50 nm. The water insoluble polymer is soluble in supercritical CO2. In a typical experiment, a CO2 solution of the polymerPHDFDA was pressurized in a syringe pump. It was thenpushed through the heating unit so that it reached the desired supercritical temperature. This is followed by passing the expanded solution passed through the nozzle into a water containing chamber. Due to its insolubility in water, the polymer got precipitated to form nanoparticles. However, larger particles were found to be formed in the aqueous suspension because of aggregation of the initially formed nanoparticles. Replacing water with aqueous NaCl solution at the receiving end of the expansion process stabilized the firstly formed nanoparticles. This happened due to the increased ionic strength in the suspension. For determining the product morphology, the polymer concentration in the pre-expansion supercritical solution plays prime role. Meziani *et al*., 2005, while synthesising RESOLV processed PMMA (poly(methylmethacrylate)) and the biodegradable polymer PLLA in supercritical CO2 co-solvent observed this effect. The co-solvent leads to increases in the polymer solubility. The quick enlargement of the polymer solutions in supercritical CO2 with low and high concentrations into an ambient aqueous NaCl solution leads to the production of nanoparticles and nanofibers. Although a lot number of supercritical fluids like carbon monoxide, n-pentane, water, ammonia, etc. are available, the main obstacle in employing the RESS and RESOLV technologies for the production of polymeric nanoparticles is the poor solubility or even non-solubility of polymers in these supercritical fluids. Schematic illustration of the RESOLV method is shown in **Figure 5**.

|  |
| --- |
| **Polymeric nanoparticles**  **Pre-expansion unit**  **Polymeric Solution in CO2**  .  **Pump** |

**Figure 5.** Schematic illustration of the RESOLV method

**3.1 Polymer nanoparticles for cardiovascular diseases**

Atherosclerosis is one of the prime causes of cardiovascular disease, it up-regulates immune response at infected sites leading to restricted blood flow from narrowed arteries formed by the formation of fatty plaque deposits along vessel walls (Alzalzalah *et al*., 2017). Aggravation of inflected endothelium due to macrophage recruitment in atherosclerotic vasculature results in destabilization of plaque leading to potential thrombosis, where these deposits can rupture and create blockages in the vasculature typical of stroke. Current treatments for atherosclerosis involves reducing lipid levels with statins or reducing immune response with anticoagulants (Lewis *et al*., 2011) However, this therapy for atherosclerosis may result in musclerelated myopathy and undesirable side effects (Nguyen *et al*., 2011). Polymeric nanoparticles have been employed in sustained delivery for long-term treatment of a active pharmaceutical ingredients (API). This becomes possible due owing to the flexibility in setting size and surface charge parameters that leads increased bioavailability. PLGA (Poly(lactic-co-glycolic acid)) nanoparticles have been employed to mimic the size and surface charge of high-density lipoprotein to target atherosclerotic tissue (Gaytan *et. al*., 2015).The dysfunctional endothelium in atherosclerosis can promote a similar enhanced permeation and retention (EPR) effect. EPR allows controlled nanoparticle accumulation in atherosclerotic build up . By employing this concept, Katsuki *et al*., 2014 developed pitavastatin-incorporated PLGA nanoparticles that have sustained uptake in plaque macrophages. This results in not only stabilization of remaining plaque, but also reduction of plaque area. Some other features of atherosclerosis like clotting factors and up-regulated cellular adhesive molecules on endothelial cells may also be used to deliver polymer-encapsulated APIs.

**3.2 Polymer nanoparticles for pulmonary diseases**

Respiratory diseases have been leading cause of morbidity globally. When compared with systemic or oral delivery of the same molecule, direct aerosol administration of aerosol to the lung can result approximately 100 times higher local drug concentrations. This leads to increase in effeciency. Intravenously administered nano-particles escape first-pass metabolism and can offer superior patient compliance by evading needles and cold chain storage (Patton *et al*., 2007). In spite of these advantages, lung administration is encouraged for most lung diseases, with commercial inhaled therapies have been employed to few small molecule drugs. Polymer nanoparticles have been increasingly investigated for pulmonary drug delivery (Mansour *et al*., 2009). Large porous polymer particles have been found effective in pulmonary API delivery by providing distinctive features of controlled API release. They have been successful in avoidance of macrophage clearance and lung penetration stemming from their low density and large geometric size of greater than 20 mm. Biodegradable polymers such as PLGA led to the initiation of inhalable insulin along with sustained release in the lungs. The concept of large porous polymer particles has also been converted to the delivery of polymer nanoparticles, with the large porous polymer particles offering efficient aerosol properties and the polymeric nanoparticles providing superior drug release and tissue penetration (Tsapis *et al*.,2002). Although particle sizes between 1 and 5 mm are conventionally thought to be ideal for pulmonary deposition, recent studies suggests that polymeric nanoparticles less than 100 nm have been efficient at deep lung deposition. Furthermore, nanoparticles smaller than around 6 nm in size have been successful in diffusing across the epithelium into circulation (Choi *et al*., 2010). With modification of size, nanoparticles can be effectively used for sustained and controlled release of a therapeutic payload for both local and systemic action. In summary polymer nanoparticles have been established to deliver a varied range of payloads for pulmonary applications that includes inhaled vaccines, insulin, antibiotics and chemotherapeutics.

**3.4 Polymeric Nanoparticle for Gene Therapy/Genetic Application**

Gene therapy, has emerged as a new and efficient method for treating acquired diseases, such as genetic disorders, cancer, cardiovascular diseases, neurological disorders, and diabetes mellitus in the recent decades (Marzbali *et.al*, 2017). Gene therapy has become a method for treatment of diseases that the conventional drug delivery systems have failed to deal with, such as the first human immunodeficiency virus (HIV) patient, Timothy Ray Brown, recovered from HIV by gene delivery. Gene therapy is useful for combating diseases caused by only the absence or extra of proteins though conventional methods are usually effective in treating a large percentage of diseases caused by numerous factors such as heart disease. Scientists see greater potential in gene therapy in treating such diseases in general because of the diminishing returns for the time and money investment in conventional drug for treating genetic disease. Gene therapy can also be used for treatment of other diseases such as viral infection and cancers (Sung *et.al*, 2019). Gene therapy is different from conventional drug delivery in terms of the properties of the materials that have therapeutic effect, such as hydrophobicity, and the delivery vehicle.

Gene therapy is a method in which the delivery of genomic materials such as small interfering RNA (siRNA) and DNA, utilizing viral vectors or nonviral vectors takes place. There are two types of gene delivery system - germline and somatic delivery system. somatic delivery system is more useful because of the unethicality of the germline delivery system. Viral vector is a delivery of the genomic materials, typically utilizing adenovirus as a vehicle for packing (Lundstrom *et.al*, 2018). But because of toxicity, cost, potential replication and carrying capacity of viral vectors, gene delivery utilizing non-viral vectors are more useful. Non-viral vector uses polymeric materials as delivery vehicle (Marzbali *et.al*, 2017).

Because of their gene loading capacity, stability and tunable properties polymeric materials have emerged as potential carrier in formulating a efficient gene delivery system. To ensure appropriate release of the gene as well as easy removal of the carrier after gene release, selection of polymeric materials is vital. Usually, biodegradable and biocompatible polymers are utilized rather than other materials (Ullah *et.al*, 2017). Polymers selected for nanoparticles production banks on the desired size and surface characteristics of the particle and nature of the genes or active ingredients. The fabrication process used to form matrix-based nanoparticles depends upon the physicochemical properties of the polymer.

Two types of polymers are commonly used for preparing nanoparticles in gene therapy.

a) Natural or bio polymers-these polymers are hydrophilic in nature

b) Synthetic polymers- these polymers are hydrophilic in nature

The structure, molecular weight, and surface charge of cationic polymers affects their gene transfection efficacy. Synthetic polymers such as poly (l-lysine), poly (l-ornithine), linear and branching polyethyleneimine, poly (amidoamine) dendrimers, diethylaminoethyl-dextran, and poly (amidoamine) dendrimers are some most common examples of polymers that found application in the previous decade for use in gene therapy (dimethylaminoethyl methacrylate). Natural polymers include polymers like dextran, chitosan, gelatin, and pullulan as well as synthetic analogues with advanced properties like guanidinylated bio-reducible polymers (Vangala *et.al*, 2021).

There are various hurdles to gene transfer in biological systems that gene therapy can help overcome. The effectiveness of the delivery vehicle or vector is one of the most critical difficulties. Because of their low toxicity, potential for targeted administration, long-term stability, absence of immunogenicity, and low production cost, non-viral delivery methods have gotten a lot of attention in recent decades. Because of their ease of synthesis and flexibility, cationic polymers have became attractive options for nonviral gene delivery systems. These polymers can be conjugated with genetic material via electrostatic attraction at physiological pH, thereby facilitating gene delivery (Pullela *et.al*, 2021).

Many factors like entrapment efficiency, particle size, and surface chemistry of the NP/gene complexes have an effect on overall efficiency of a gene delivery vehicle. The process parameters involved in synthesis also play an important role. Each synthetic approach is unique in providing specific entrapment efficiency for water-soluble or water-insoluble therapeutic moieties (Rai *et.al*, 2019). Besides, most polymeric nano particles are designed in house for applications including gene therapy. Therefore, it is imperative to discuss these synthetic approaches utilized for designing common polymeric gene carriers.

**3.5 Polymeric Nanoparticle for Anti diabetic Drugs Application**

Diabetes Mellitus is a group of metabolic disorder considered by a whole lack of insulin, a comparative lack of insulin, or insulin resistance, which then results in hyperglycemia. (Deopa et al., 2013). The polymeric nanoparticles have several advantages with a novel delivery system and as such can be a effective method for the treatment of diabetes mellitus. The table.1 shows various polymeric anti-diabetic drugs and polymers used for the formulation.

Table 1: Polymeric Nanoparticles for diabetic treatment (Gopalasatheeskumar et al., 2017)

|  |  |  |
| --- | --- | --- |
| **Sl. No** | **Drug used** | **Polymer used** |
| 1 | Metformin | Ethylcellulose (EC), Poly (lacticco-glycolic acid) (PLGA), Poly (methyl methacrylate) (PMMA), and Chitosan |
| 2 | GLIPIZIDE | Polycaprolactone |
| 3 | Glipizide | Eudragit RL100 |
| 4 | Pioglitazone Hydrochloride | Chitosan |
| 5 | Glipizide | PLGA and Eudragit RS 100 |
| 6 | Glibenclamide | Poly (lactic-co-glycolic) acid |
| 7 | Insulin | Chitosan |
| 8 | Human insulin (Mw ~ 5800 Da) | PLGA |
| 9 | Human insulin 100 | polycaprolactonetriol |

These polymeric nanoparticles have the nature of bio-adaptability, bio-comptability and biodegradable. The drug is dissolved, entrapped, encapsulated to a nanoparticle medium. The nanoparticles, nano-spheres or nano-capsules are obtained by depending up on the preparation. In nano-capsule system, the drug is limited to a cavity enclosed by even polymer layer, while the nano-shell contains of medium, in which the drug is physically and uniformly dispersed (Ranjit et al., 2013, Yadav et al., 2013). The main advantages of the polymeric nanoparticles are the simplest preparation method, targeted delivery, the minimizing of the dose and high therapeutic efficiency.

**3.6 Polymeric Nanoparticle for treatment of Covid – 19**

Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus. COVID-19 outbreak has become one of the catastrophic health emergencies that could threaten public health worldwide through several hospitalizations and thousands of deaths, leading to boosting global concern intensive precautionary measurements. COVID-19 is an acute respiratory infection that has high transmissibility and global distribution, promoting massive death rates with signifcant economic losses (Gennaro et al., 2020).

Because of their inherent competitive advantages, polymeric-based nanoparticles has astonishing potential to counteract the new coronavirus disease (COVID-19). To counteract COVID-19 and future outbreaks, robust, repeatable, and cost- and time-efcient vaccines and and new drug platforms, as well as prophylactic methods, must be developed. To fight and prevent COVID-19 infection and considering this scenario, a large number of works involving nanotechnological approaches have been carried out worldwide (Singh et al., 2020). The versatility of polymeric-based nanoparticle engineering can provide (i) specifcity, (ii) tunable release kinetics, and (iii) multimodal drug composition, making it becomes possible to get the better of common limitations encountered during traditional drug development.

Advances in nanotechnology engineering have impressively leveraged diversifed areas of knowledge, such as materials, chemical, and tissue engineering as well as nanomedicine. Such advancements are strictly correlated with the nanometer scale of the materials (Chauhan et al., 2020). Compared with conventional therapeutic methods, nanostructured materials can overcome common limitations related to the specifcity of the target tissue, the release rate, and biodegradation of bioactive molecules as well as act as carries of hydrophobic and hydrophilic compounds with fewer side-efects. Moreover, sophisticated strategies to enhance the therapeutic potential of nanomedicines such as functionalization, passivation, and loading of multiple drugs in a single carrier can enable steadier biological responses compared with traditional methods (Zhou et  al., 2020).

Another advantage of using polymeric nanoparticles is their inherent colloidal stability and surface activity which enables nanomaterials to escape undesirable interactions with the immune system and extend their circulation time in the bloodstream. Otherwise, they can also be engineered to facilitate the interaction with the immune system, turning these materials into interesting tools to act as adjuvants and virus-like particles in vaccines (Zhou et al., 2020).

The high surface area of the polymeric NPs allows a highly efficient drug carrier, and the size becomes a determining characteristic at the moment of interaction with the cell membrane and in the penetration of physiological barriers (Kumari et al., 2010). In addition, these nanosystems have unique physical–chemical characteristics such as (i) prolonged blood circulation time; (ii) reduced adverse efects; (iii) ability to protect therapeutic agents from degradation, increasing the stability, bioavailability, and pharmacokinetics of drugs; (iv) ease of chemical modifcation; (v) controlled drug release; and (vi) improved therapeutic efects (Gao et  al. 2020; Yang 2021; Sun et al. 2021). Due to its advantages, nanostructured polymers have been considered as tools to fght against COVID-19 (Zhang et al., 2020). Among some of the advantages presented by polymeric NPs for use against the SARS-CoV-2 virus are the high stability of the systems, control of drug delivery, biocompatibility, manipulation and adequacy of physical and chemical properties, compatibility with hydrophilic and hydrophobic drugs, and also the preparation through simple and suitable methods (polymer, NP size, desired administration route, and the drug carried, among others) (Bhardwaj et al., 2020).

**3.7 Polymeric Nanoparticle for Anti Microbial (or Antibiotic) Therapy (or Application)**

Microorganisms are an important part of human existence. These are responsible for numerous and diverse processes, including nitrogen fixation, vitamin production, photosynthesis, and organic matter decomposition. However, when the balance between microorganisms and the immune system may shift in favor of microorganisms, immune deficiencies may arise (Chircov et al., 2019). Infectious diseases are caused by pathogenic microorganisms, such as bacteria, viruses, fungi, parasites, protozoa, or algae, can be directly or indirectly (vector-borne) transmitted from one individual to another (Tripathi et al., 2019). Despite many advancements in the pharmaceutical and medical fields and the development of numerous antimicrobial drugs, infectious diseases are still one of the major major health threat affecting millions of lives daily (Devrim et al., 2017). The major limitations of antimicrobial drugs include low transportation rate, water solubility, oral bioavailability and stability, inefficient drug targeting, considerable toxicity, and limited patient compliance. In addition, another cause for their inefficiency is the antimicrobial resistance of microorganisms.

For this reason, researchers have shifted their focus toward the discovery and development of novel and alternative antimicrobial agents that has the potential to overcome the challenges associated with conventional drugs. They see nanotechnology as a possible alternative. Polymeric nanoparticles have got significant attention as potential antimicrobial drug delivery agents because of their considerable advantages regarding their efficient cargo dissolving, entrapment, encapsulation, or surface attachment, the possibility of forming antimicrobial groups for specific targeting and destruction, biocompatibility and biodegradability, low toxicity, and synergistic therapy. Nanomaterials and nanoparticles in particular have proven a broad spectrum of antimicrobial activity against Gram-negative and Gram-positive bacteria, mycobacteria, viruses, fungi, bacteriophages, protozoa, and algae (Fernando et al., 2018). The two main strategies for using nanoparticles as antimicrobial agents involve combatting antimicrobial drug resistance themselves or acting as carriers for the delivery of conventional antimicrobials. Specifically, while the precise mechanisms are not completely understood, it has been demonstrated that nanoparticles can penetrate and disrupt the microbial cell membrane through membrane-damaging abrasiveness, induce intracellular antimicrobial effects such as the production of reactive oxygen species, interact with DNA/RNA and proteins, inactivate enzymes, increase efflux by overexpressing efflux pumps, decrease cell permeability, release metal ions, and hinder biofilm formation (Liu et al., 2019). The antimicrobial activity of nanoparticles is directly affected by variables such as chemistry, particle size and shape, surface-to-volume ratio, and zeta potential.

The fast growth of nanotechnology results in the production of numerous nanosystems shown to be effective antimicrobial agents for the treatment of bacterial and fungal infections. The design of PNPs containing conventional antibiotics as the therapeutic agents supported by the antimicrobial properties of nanosystems alone have the ability to overcome limitations facing conventional antibiotic therapy. Treatment of H. pylori with amoxicillin and pectin sulfate-loaded lipid PNPs significantly eradicates H. pylori in the biofilm form, inhibits bacteria from adhering to gastric cells and decreases the MIC value for amoxicillin, which increases its ability to inhibit bacterial colonization despite the well-known resistance of H. pylori to antimicrobial treatment (Cai et al., 2015). Strong antimicrobial potential of streptomycin-conjugated magnetic nanoparticles coated with chitosan against drug-sensitive S. aureus and its methicillin-resistant counterpart (MRSA), may be a promising strategy to fight drug-resistant infections, particularity those reported in the hospital environment (Hussein-Al-Ali et al., 2014). Recently, chitosancoated alginate (CS-ALG) nanoparticles were proposed for a facilitated ocular delivery system of daptomycin for the treatment of MRSA-originated endophthalmitis.

**3.8 Drug delivery in ocular diseases:**

Drug delivery processes to the eye entails are found to be very much challenging. The areas of the entire organs can be divided as anterior and posterior segments. The anterior segment is composed of conjunctiva, cornea, iris, lens, etc. The posterior segment—composed of neural retina, retinal pigment epithelium, vitreous humor etc. It is difficult for drug formulations to reach the posterior segment due to the presence of different barriers. Drug access is drastically reduced by the blood retinal barrier. Most of these limitations in the drug delivery of ocular therapy can be minimized by using nanotechnological systems. Dendrimeric nanocarriers are found to be very much useful as a drug delivery agent for ocular diseases. The archetypical dendritic polymer prepared for the drug delivery nanosystems of ocular diseases is based on polyamidoamines. Yang et al. [52] prepared PEGylated polyamidoamine based dendrimers as nano drug carriers for ocular diseases. He modified these dendrimers with cyclic arginine–glycine–aspartate hexapeptide (Yang *et.al*, 2019). Lancina et al. [53] synthesized a polyamidoamine based dendrimeric core from timolol analog (Lancina *et.al*, 2018). Timolol is commonly used as a drug for the ocular hypertension. Tai et al. [54] developed a complex based on polyamidoamine dendrimer and hyaluronic acid (Tai *et.al*, 2017). This complex was modified with penetratin as well as loaded with antisense oligonucleotides and applied for the control and management of ocular diseases. This system was found to effectively enhanced the eye permeability. Some polylysine (PLL) and phosphorous based dendrimers are also developed for the use of drug delivery nanosystems for ocular diseases.

Chitosan is one of the commonly used polymers used for the preparation of micelles for drug delivery of ocular disease. This polymer has excellent penetration properties which make it suitable for drug delivery in ophthalmic areas. Imam et al. developed micelles by using sodium tripolyphosphate (TPP) for the drug delivery for ocular infection treatment (Imam *et.al*, 2018). Formulation efficacy can be improved by the use of specific media with drug-loaded micelles. Wen et al. [49] modified a nano particle loaded gel for the drug delivery for ocular inflammation (Wen *et.al*, 2018). Cyclodextrins (CDs) is also reported to be used as polymeric nanocarriers. CDs are cyclic oligo- or polysaccharide having six or more glucose units connected by α-1,4 glycosidic linkages. They have special structural characteristics with an outer hydrophilic surface and an internal cavity having hydrophobic feature. These Cyclodextrins are useful as drug delivery agents for hydrophobic active ingredients. Rodriguez-Aller et al. prepared cyclodextrin derivative, propylamino-β-CD as nanocarriers of latanoprost for the treatment of glaucoma (Rodriguez-Aller *et.al*, 2015). This cyclodextrin showed better drug stability as well as drug availability. Lorenzo-Veiga et al. prepared a library of micelles and poly(pseudo)rotaxanes using soluplus, pluronic P103 and α-cyclodextrin (Lorenzo-Veiga *et.al*, 2019). These are found to be very effective candidates as they showed good diffusion as well as sclera permeability coefficients. PLGA and CH are commonly used polymers for the synthesis of nanoformulations for the drug delivery of ocular diseases. It was reported that nanoparticles was prepared by using Tween-80, polyoxyethylene stearate to encapsulate a drug called everolimus (40-*O*-(2-hydroxyethyl)-rapamycin).

**3.9 Polymeric nanoparticles for diagnosis of cancer:**

Cancer is considered as one of the major causes of death worldwide. Cancer has the very high rate of mortality nowadays. Ordinary diagnosis techniques are not so much effective to detect cancer at early stages. Many researchers and scientists are now trying to apply nanotechnology for the diagnosis and treatment of cancer. Polymeric NPs also have great potential as therapeutic and diagnostic agent of cancer. Computed tomography (CT) is commonly used for the diagnosis of cancer. Various researchers have investigated the role of metallic gold nanoparticles for the diagnosis and treatment of cancer. Gold nanoparticles are found to be nontoxic and their shape and surface can be comparatively easily modified. AuNPs can be used in bioimaging techniques to study the binding coefficient between nanoparticles and target cells. Wang et al. [79] developed polymeric NPs based on AuNPs for photoacoustic imaging (PAI) (Wang *et.al*, 2016). Magnetic resonance imaging (MRI) can be successfully used for the analysis of morphologic characteristics in tumors and clinical cancer diagnosis. Gadolinium-based contrast agents are also developed by using nanotechnology which can be successfully used for the diagnosis processes. Liu et al. [87] developed a new polymeric GdNPs-based material (Anti-VEGF PLA–PEG–PLL–GdNP) (Liu *et.al*, 2011). These nanomaterial systems were developed for the purpose of facilitates delivery to cancer cells and their detection in early phases. Gd ions based polymeric NPs was synthesized by using polymerization-induced self-assembly (PISA). Gadolinium was found to be useful for PAI technique. Wu et al. [97] synthesized special type Gd based nanoparticles which was designed for photothermal therapy (Wu *et.al*, 2018). It was mainly composed of Gd–PEG-coated Bi. These NPs has the capacity of producing the in vivo tumor ablation. Perfluorocarbons (PFCs) are structurally similar to that of alkanes. In perfluorocarbons hydrogen atoms are replaced with fluorine. PFCs are useful in the techniques to improve diagnosis as well as imaging effects. Pisani et al. [103] developed liquid PFCs based polymeric nanoparticles for the uses of ultrasound imaging (Pisani *et.al*, 2006). The produced a homogeneous PLGA–PVA polymeric shell using emulsion-evaporation methodology. Perfluorooctyl bromide (PFOB) and perfluorohexane (PFH) polymeric nanoparticles were developed for the applications of medicinal purposes.

PEGylated melanin-like nanoparticles are reported to be used in photoacoustic tomography. MNP–PEG analysed for biocompatibility and they were found to quite stable in biologic medium. Nano particles in the form of quantum dots (QDs) are used in this process. However, the efficiency of these agents in the cancer treatment were found to be very low mainly due to low solubility as well as low bioavailability. Zhou et al. [108] modified new imaging agents by using Gd and Au for targeting dual mode tumor CT/MR. In this study AuNPs was prepared by using folic acid and Gd chelators as matrix (Zhou *et.al*, 2018). Topete et al. [110] produced polymeric–gold nanohybrids for the applications in the fields of optical and magnetic resonance (Topete *et.al*, 2014). These folic acid-functionalized PLGA–Au nano particles were investigated in human cervical cancer cell line to study their physicochemical and theranostic characteristics. Polymer-modified iron oxide NPs are reported to be a very good contrast agents which are useful in cancer imaging.

**3.10 Polymeric nanoparticle-based cancer therapy approaches:**

Nontargeted treatments are found to be the main reasons of cancer-related deaths. Polymeric nanoparticle based nanoformulation may be useful for different types of cancer therapies including tumor-targeted medication delivery, photodynamic therapy, etc. (Prasad *et.al*, 2016). Nanomaterials based on Poly lactic-co-glycolic acid (PLGA) are reported to be are occasionally used in these fields. Nano-hydrogels are considered as one of the important polymeric nanoparticles useful in the area of cancer theranostics. Nano-hydrogels are mainly cross-linked hydrophilic nanoparticles having polymeric network. Nano-hydrogels are effective for drug delivery of both hydrophilic as well as hydrophilic drugs. Nano-hydrogels are reported to be very much effective in drug delivery for breast cancer due to their excellent biocompatibility and multifunctionality.

Cancer is considered as one of the world’s most deadliest disease. Main problem of cancer treatment is that drugs molecules does not only target cancer cells but also affect the normal healthy cells. Many chemotherapy drugs destroy healthy normal cells. Polymeric nanoparticles generally have a targeted mechanism of action. Polymeric nanoparticles are found to enter the tumor or other cancer cells more precisely and efficiently. With the use of polymeric nanoparticles anticancer can be precisely delivered into tumor structures and side effects of chemotherapy drugs can be significantly reduced. Polymers are used in nano-based cancer therapy approaches. Polymeric micelles are widely used as nanocarriers for drug delivery in the treatment of cancer. Polymeric micelles are used as nanocarriers for drug to tumors. Hydrophobic drugs are loaded into hydrophobic core of the nanoparticles to improve the solubility of these drugs. These nanoparticles have a hydrophilic shell. Genexol- polymeric micelles are used as nanocarriers. This polymeric micelles are used as carries for chemotherapy for tumors. Polymeric micelles may be of various shapes including rods, spheres, tubules, etc. Pharmacokinetic properties of micelles are highly affected by morphology of the micelles. Polyethylene glycol (PEG) is commonly used in the preparation of micelles used for the drug delivery purposes. PEG is a neutrally charged and water soluble molecule. PEG is suitable for the application of drug delivery. Polyvinylpyrrolidone (PVP) and poly(N-isopropylacrylamide) (pNIPAM) are also reported to be used for the synthesis of Polymeric micelles (Chung *et.al*, 1998). Poly (lactic acid) PLA and poly (beta-amino ester) are two other polymers used for the preparation of Polymeric micelles. Dendrimers also have significant role as polymeric drug delivery material in cancer nano therapy. Polyamidoamine, polyaryl ether etc. are commonly used macromolecules in this field of drug delivery.

Bioactive molecules are reported to be used in the drug delivery of cancer treatments. Biopolymers and some of their derivatives are used in the creation of hydrogels. Natural bioactive molecules have a strong impact on cell signaling pathways and they can be applied to management and cure of cancer. Biopolymers as nanoparticles are reported to be useful in the drug delivery for anticancer drugs of different types of cancers. A large number of biopolymer based nanomedicines are used in cancer therapy. Nanoformulation of 3, 3′-diindolylmethane are reported to show significant suppression of cell viability in pancreatic cancer (Mousa *et.al*, 2020). Biopolymeric formulations prevent nanoparticles from degradation and enhance stability. The size of polymeric nanoparticles have size range from 1 nm to 1000 nm. Nanocapsules and nanospheres are two main types of structural forms of polymeric nanoparticles. Drug is loaded with cross-linked polymer of nanospheres. Polymers used in the preparation of nanoparticles are mostly biodegradable and biocompatible. Chitosan or collagen are reported to be used in the Polymeric drug delivery systems. Synthetic polymers like poly (lactide) (PLA), poly (lactide-co-glycolide) (PLGA), etc. are currently used in drug delivery (Zhang, *et.al*, 2022).

The size, shape, zeta potential, stability, etc. of polymeric nanoparticles are mainly dependent on the method used to synthesize the polymeric nanoparticles. For effective drug delivery to vascularized tumors through polymeric nanoparticles its diameter should be of around 100 nm. The function and pharmacology of polymeric nanoparticles depends on the size of the particles. Single monomer units are polymerized through bottom-up techniques. Bottom-up techniques form nanoparticles from single monomers through polymers. Emulsion polymerization and recombination technology are used for the preparation of polymeric nanoparticles. Various top-down approaches of nanotechnology like nanoprecipitation, salting out, supercritical fluid method, etc. are also equally useful for the preparation of polymeric nanoparticles. Breast cancer is a common type of cancer among women. The role of polymeric nanocarrier in the treatment of breast cancer have been extensively studied in the last few years. Polymer conjugated with folate ligand (PFTTQ) was reported to have inhibition effect on positive folate receptor of tumor cells in breast cancer.

Different chemotherapy drugs are reported to be encapsulated with polymeric nanoparticles for the development of drug delivery systems. These polymers can encapsulate a drug molecule within their structure. Polymeric nanoparticle base drug delivery system can increase the antitumor efficacy, reduce the process of metastases, and decrease the side effects of chemotherapy drugs. In the early stages various non-biodegradable polymers like poly (methyl methacrylate), polystyrene, etc. are generally used to develop polymeric nanoparticles (PNs). Poly (alkyl cyanoacrylates) (PACA) are reported to be used for the development of nanocarriers. PACA are degraded by hydrolysis of the ester bonds. PACAs can retain significant quantity of drug. Polylactone-based polymers are also useful for the preparation of drug delivery nanoformulations. Poly(Ɛ-caprolactone) (PCL) may have high potential for anticancer drug development. Plant and animal derived natural biopolymers are also widely used in drug delivery research. Natural biopolymers have high biodegradability and low toxicity. Chemotherapeutics drug DOX was reported to be delivered by using Transferrin (Tf)-conjugated polymer NPs in cancer treatment (Soe *et.al*, 2019). This drug delivery is found to be very much effective in the treatment of breast cancer and reported to cause minimal damage to healthy cells. Another nanoformulation PLGA-PEG was used with Thymoquinone (TQ) nanoparticles for breast cancer. The drug showed selective cytotoxicity toward breast cancer cells (Ahmad *et.al*, 2020). Anticancer drug Losmapimod was encapsulated with poly (lactic-co-glycolic acid) NPs and was used against multiple myeloma (MM) cancer cells (Ye *et.al*, 2021). Lung cancer is also very much common in the society now a days. Paclitaxel-loaded polymeric nanoparticle was found to be effective in the preparation of nano-formulation for the drug delivery against A549 cancer lung cell. This nanosystem was reported to have high antiproliferation effect of paclitaxel on targeted cancer lung cells. Inhalable nanocarriers are also developed for the delivery of antineoplastic drugs.

**4. Advantages of Polymeric Nanoparticle Application**

Polymeric Nanoparticle because of their small size, have distinct properties compared to the bulk form of the same material, thus offering many new developments in the fields of biosensors, biomedicine, and bio nanotechnology. Nanotechnology is also being utilized in medicine for diagnosis, therapeutic drug delivery and the development of treatments for many diseases and disorders. Following are the advantages of PNPs in various applications (Sailaja et al., 2017).

* Increases the stability of any volatile pharmaceutical agents, easily and cheaply fabricated in large quantities by a multitude of methods.
* They offer a significant improvement over traditional oral and intravenous methods of administration in terms of efficiency and effectiveness.
* Ease of formulating smaller drug doses.
* Less toxicity
* Good control over size and size distribution.
* Protects the encapsulated drug from degradation.
* Stable dosage forms of drug which are either unstable or have unacceptably low bioavailability can be formulated as nanoparticles.
* Increased surface area results in a faster dissolution of active agents in an aqueous environment.
* Faster dissolution generally equates with greater bioavailability.
* Improving drug bioavailability through enhancing aqueous solubility
* Increasing the resistance time in the body (increasing the half-life for the clearance/ increasing specificity for its cognate receptor).
* Relatively higher intercellular uptake.
* Because of their small size, can penetrate through smaller capillaries and are taken up by cells, which allow efficient drug accumulation at the target sites
* Minimizes non-specific uptake, prevents undesirable off target and side effects
* The use of biodegradable materials for nanoparticle preparation allows sustained drug release within the target site over a period of days or even weeks.

**5. Toxicity of Polymeric Nanoparticles**

The field of nanotechnology is growing gradually and undergoing major changes in the drug delivery field. Nanotechnology is an emerging technology that involves the manipulation of material at the nanoscale. Nanoparticles (NPs) are utilized as carriers for delivery of the active agent and are stated as the ideal applicants to overcome the poor bioavailability of most drugs by increasing their solubility and permeability across a biological membrane. A number of nanomaterials based on different types of substances such as polymers, silicon, lipids, carbon, silica and metals are utilized for drug delivery. In comparison to the other nanomaterials, polymeric nanomaterials are widely choosen by researchers. With the increased understanding related to polymers and their properties, polymeric nanoparticles have been extensively used in the drug delivery system. But, due to various associated nanomaterial risks, there has been a considerable increase in the researchers’ focus on the safety aspects of polymeric nanoparticles. Special focus is paid to study the methodology, design, and morphology, which offer precious understanding into the complexities encountered in the nanomaterial approach and safety assessment (Sharma et al., 2012). One possible reason for this could be the lack of toxicity and safety information related to these nanosystems that are needed to exceed the regulatory requirement. The potential toxicity of polymeric NPs is the main problem concerning their use in medicine. Polymeric nanoparticles are a subset of nanomedicines that are continuously developing in order to improve the specificity and efficacy of drug delivery.

Nanoparticles (NPs) hold the promise to be a universal tool for drug delivery into the brain. This has been a research topic for more than a decade, but unfortunately, successful pharmaceutical developments are still rare. This can be explained in part by toxicity concerns which have not been considered sufficiently. In fact, during the recent years, we have witnessed an increasing public concern regarding the potential toxicity of NPs and there are ongoing international efforts to develop tests to evaluate the safety and tolerability of NPs after exposure of biological systems, and the mechanisms of action are now partially understood (De Jong et al., 2008). The focus of these efforts has been on the possible toxicity of NPs following inhalation or food intake, and therefore predominantly lung and gastroenteral toxicities have been investigated. However, only a minority of the studies focused on brain cells. It was suggested that—in contrast to chemical toxicity, where purity and concentration are the main determinants— in the area of ’nanotoxicity’ also particle size, shape, surface and charge need to be taken into account. The literature shows that NPs can cause inflammation, DNA damage and destruction of membranes and production of reactive oxygen species. However, specific hazards are associated with specific particles, i.e. DNA damage and production of reactive oxygen species are predominantly associated with metal (oxide) NPs, whereas, membrane leakage has been observed after application of polymeric NPs. To test nanotoxicity, in vitro test systems have been largely used, and the MTT-test of viability is recommended for this purpose. However, in vitro experiments may be insufficient as a strategy for testing the safety of NPs, and data regarding the correlation of in vitro and in vivo studies are entirely missing (Dhawan et al., 2010).

Owing to their fascinating characteristics, including systemic stability, solubility, and focus on a particular site, NPs have revolutionized biomedicine, particularly in the field of drug administration. However, they can be beneficial and hazardous depending on the characteristics of the surroundings, highlighting the importance of conducting nanotoxicology studies before their use in humans. Smart medication delivery uses poly-NPs synthesized from synthetic or natural polymers. In-depth research is being conducted on these materials as carriers for controlled and sustained drug release in DDSs. However, the activity of these nanopharmaceuticals is limited by safety, toxicity risks, insufficient biocompatibility, and physiological limitations. The disadvantages of these NPs include hazardous disintegration, leftover material linked to them, and damage to monomer aggregation.

**6. Challenges of Polymeric Nanoparticles**

The application of nanomedicine will assures an encouraging advance in the next decade. Treatments will become more efficient and safer due to the enormous variety of NP design and functionalization. The lists of potential applications progress to the point where the nanocarrier can be customized to best adjust to a certain active ingredient, a specific environment and then provide fitting drug location at the site of action, in a controlled manner. However, it is relevant to mention that NP-based treatments are not perfect and have challenges to conquer. First, the number of polymeric materials currently available for their utilization as DDS is still limited although the R&D has been moved in the last decade, exceeding expectations, from the micro- to the nanosize scale. The ideal adjustment to the delivery conditions, such as transportation to the site of action, specific targeting or adequate delivery profile, among others, for each type of disease, requires the development of new polymers that can fit these requisites. Although selective targeting supposed a great improvement in comparison to non-encapsulated drugs, it is a very complex mechanism and represents a challenge itself. Overexpression of a specific surface protein is not enough to assure selective targeting as they are also normally expressed in Nanomaterials 2020, 10, 1403 25 of 38 normal cells. This point is more critical in cancer treatments, where administered drugs usually possess higher toxicity that could lead to numerous undesirable secondary effects compared to drugs used in other diseases treatments. Most the assays have been developed in small animal models showing promising results, but the translation from animal results into clinical success has been limited. More clinical research and data are needed to fully comprehend the mechanism of these nanocarriers. In addition, limitations include the uncertain future of pharmaceutical companies which face high expenses concerning clinical trials and decreasing success rates in the flow of novel entities in the R&D pipeline. Examples of polymeric NPs that do not fulfil all the regulatory requirements for clinical evaluations and which had a harmful economic impact for their pharmaceutical companies are Livatag Conceiving new methods for the manufacture of NPs at reasonable costs is an important part of this challenge because there are only a small number of them that fulfill the appropriated requirements to reach the target and to subsequently deliver the drug in a suitable manner. It is also mandatory for these polymeric NPs to be biodegradable or to possess a high capacity to be eliminated outside the body avoiding accumulation, being nontoxic and non-immunogenic. It is remarkable to point out the role that copolymers could play in tuning or modulating the interactions with mucosa or blood proteins in order to control their in vivo fate or to stabilize NPs without the need of surfactants entities. It would be also interesting for the near future research in this field to include stimuli responding polymers which can confer triggered release properties. From a manufacturing point of view, nanospheres and nano capsules could be easily obtained by applying the existing methods, but new structures like polymerases, are still waiting for better synthesis to join the family of nanoparticulate DDS. The need for developing NPs with many capabilities (targeting, image contrast enhancement), named as multifunctional NPs, means more synthetical steps, more regulatory hurdles and higher expenses. Conquering these objectives may seem very difficult, but there is hope of reaching a better scenario (Begines et al., 2020).

Over the last few years, there has been a global transformation in the field of nanomedicine, which has led to a multidisciplinary and collaborative approach with promising results and success. The future path of collaborations between theoretical and experimental scientists as well as the pharmaceutical industry, physicians and the regulatory agencies, will be crucial and will allow us to implement the laboratory results into the clinic and therefore, initiate the next generation of clinical therapies.

**7. Future Prospect of Polymeric Nanoparticles**

Polymeric nanoparticles (NPs) are one of the most studied organic strategies for nanomedicine. Intense interest lies in the potential of polymeric NPs to revolutionize modern medicine. Even though regulatory mechanisms for nanomedicines along with safety/toxicity assessments will be the subject of further development in the future, nanomedicine has already revolutionized the way we discover and administer drugs in biological systems. Tanks to advances in nanomedicine, our ability to diagnose diseases and even combining diagnosis with therapy has also became a reality (Patra et al., 2018). Nanoparticles are intended to maximize the benefit/risk ratio of therapies. Rather than causing many debilitating symptoms in the hopes of curing one disease, like current cancer treatments, nanoparticles are designed to minimize any side effects while treating that same disease. More research is needed and more money must be spent on analyzing both the effectiveness of nanomedicine as well as the long-term effects on the body.

While lipid-based nanoparticles are the most promising prospect because they are made of natural elements and have more advantages than other types of nanoparticles, they are not yet a perfect solution for drug delivery. We need more significant investments in clinical trials in both the government and private sectors to advance the technology. Nanomedicine is used to treat a variety of different diseases and conditions, but it is in the oncology segment where nanoparticles see the most use and the most promise. To date, there are 51 nano pharmaceuticals approved for use in clinical practice. More are being studied in clinical trials for cancer and other diseases.

**8. Conclusion:**

Nanotechnology has been considered as very much effective as well as attractive therapy in the medical field. The uses of polymeric nanoparticles in the field of drug delivery will improve efficacy of traditional therapies. Various parameters of nano-systems can be easily modulated as per the requirements. The efficiency of nano-formulation for the drug delivery of various diseases depends on various parameters like particle size, shape, drug encapsulation efficacy, distribution in the body. The advanced research works on polymeric nanoparticles in clinical studies may improve the treatment processes of various diseases. Nano particle mediated drug delivery processes have lots of advantages such as reduced toxicity, higher bioavailability of the drug, targeted delivery, higher solubility, enhanced permeability, etc. Polymeric nanoparticles are found to be very good nanocarriers and will offer a new strategy for drug delivery of ocular diseases. Biodegradable nano polymers are effective in the drug delivery because they work through a mechanism of controlled-release systems (CRS). Various types of polymers like protein-based polymers, carbohydrate-based polymers, synthetic polymers, natural polymers, etc. are used for the preparation of different types of nano-formulations for drug delivery applications. Polymeric nanoparticle based therapeutic systems are reported to be useful for the treatment of various critical diseases. For the development of effective nanocarriers, proper study of nanoparticles and nanoecotoxicology is very much essential.

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