POLYMERIC NANOPARTICLES FOR TARGETED DRUG DELIVERY

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. Polymeric-based nanoparticles have an incredible potential to combat the novel coronavirus illness (COVID-19) due to their intrinsic competitive advantages. 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.

Keywords: Polymeric nanoparticles, Drug delivery, Nanoscience, Nanotechnology

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I. INTRODUCTION

Nanoscience is an emerging field in information technology, medical technology, biochemistry, synthetic chemistry, biotechnology, and medicine. Nanotechnology offers various applications in thefield of health care and medicine such as for analytical purposes, diagnosis, treatment processes, targeted drugdelivery, 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 ascytotoxicity (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 nanoformulation. Nanoimaging is another area of application of nanotechnology in the field medicines. In nanoimaging nanoformulation 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 interestdue 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.

II. METHODS FOR PRODUCTION OF POLYMERIC NANOPARTICLES

Over the past ten years, there has been a lot of interest in the creation of polymeric nanoparticles with a variety of complicated architectures and functions. This could be because, when properly arranged, nanoparticles with sizes ranging from 10 nm to more than 100 nm have enhanced physical, chemical, or biological capabilities. It has been difficult to find commercially feasible methods for creating suitable nanoparticles. A range of techniques can be used to produce the polymeric nanoparticles, depending on the kind of medication to be loaded and the specifications for a particular administration route (Jawaharet al., 2012). In general, two primary approaches are utilized to produce polymeric nanoparticles: the first involves dispersing premade polymers, and the second involves polymerizing monomers (Chander et al., 2019).

Organic solvents are typically employed in the first step of most procedures for creating polymeric nanoparticles in order to dissolve the polymer (Chander et al., 2019). These solvents may cause toxicity and environmental risk issues. Above all, and oftentimes a difficult task, solvent remnants must be eliminated from the finished product. Techniques based on the polymerization of monomers result in more effective insertion when loading chemicals into polymeric nanoparticles (Kamaly et al., 2016). The products are often produced as aqueous colloidal suspensions, regardless of the preparation method employed (Jawaharet al., 2012).

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. The dissolved polymer was first added to an organic phase made up of a polar organic solvent. The medicine, or active ingredient, is incorporated through dispersion or dissolution. Dichloromethane and chloroform were used widely as solvents in the past. They have been replaced by ethyl acetate due to their environmental toxicity (Bohrey et al., 2016). According to Vauthier et al. (2017), ethyl acetate has a superior toxicological profile and is therefore more appropriate for use in biological applications.It has also been common practice to use an aqueous phase with a surfactant, like polyvinyl acetate (Bohrey et al., 2016). In order to create a dispersion of nanodroplets, the organic solution is subjected to emulsification in the aqueous phase using a surfactant, which is then processed using high speed homogenization or ultrasonication (Sharma et al., 2016). A suspension of nanoparticles was produced when the polymer solvent evaporated; these were then cleaned and gathered using centrifugation. Figure 1 depicts a schematic diagram of the solvent evaporation process.
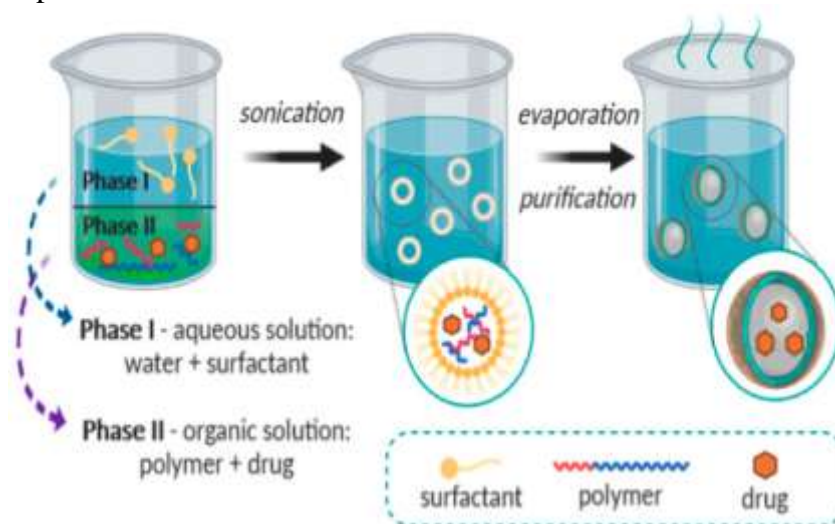
Figure 1: Schematic representation of the solvent evaporation method (Open access: Zielińska *et al*., 2020).

2. **Emulsification/Solvent Diffusion:** Using this technique, an aqueous solution and a somewhat water-miscible solvent combine to generate oil in water emulsion (Kumar et al., 2012). The medicine and polymer are present in the partly water miscible solvent, and the surfactant is present in the aqueous solution. An organic solvent that is partially water-

miscible, such as ethyl acetate or benzyl alcohol, makes up the internal phase of this emulsion. In order to preserve an initial thermodynamic equilibrium of both phases at room temperature, the emulsion is first saturated with water (Souto et al., 2012).While nanospheres are often generated using this process, nanocapsules can also be produced by mixing a little amount of oil with the organic phase.We may create nanoparticles using this technology that have sizes between 80 and 900 nm (Quintanar et al., 1998). Figure 2 illustrates the emulsification/solvent diffusion process schematically.
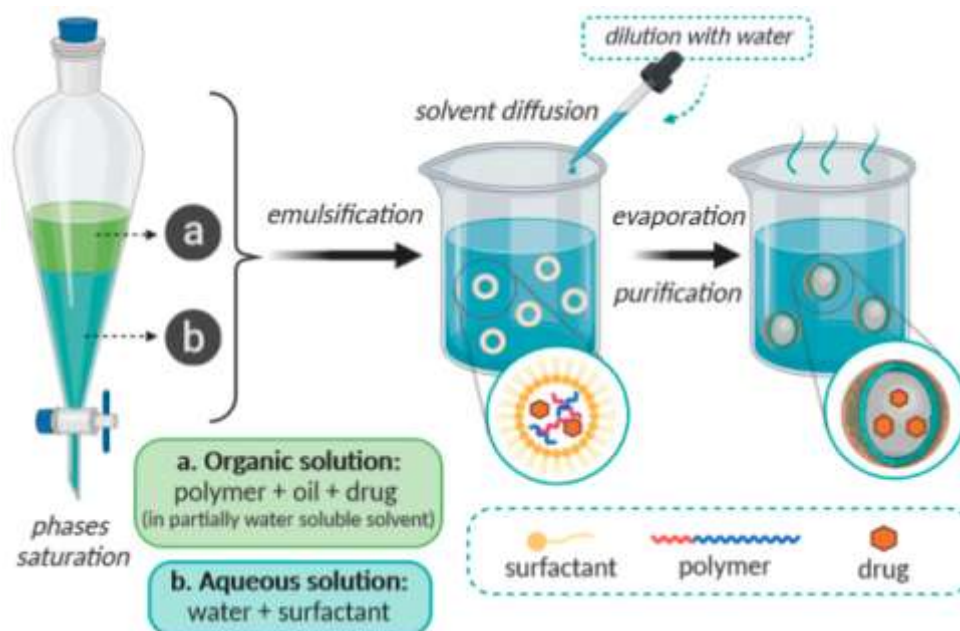

Figure 2: Schematic representation of the emulsification/solvent diffusion method. (Open access: Zielińska *et al*., 2020)

3. **Emulsification/Reverse Salting-Out:** An altered form of the emulsification/reverse salting-out approach is the emulsification/solvent diffusion method (Wang et al., 2016). The primary distinction is in the makeup of the oil in water emulsion, which is made using a polymer solvent that is miscible in water. The gel, the salting-out agent, and the colloidal stabilizer make up the aqueous phase. According to Pal et al. (2011), electrolytes such magnesium chloride, calcium chloride, or magnesium acetate, as well as non-electrolytes like sucrose, are used as appropriate salting-out agents (Vauthier et al., 2009). The preparation of the oil in water emulsion involves vigorous stirring, followed by dilution with deionized water or an aqueous solution. This allows for the organic solvent to diffuse to the exterior phase, causing the polymer to precipitate and the production of nanospheres. Cross-flow filtering is used to remove the salting-out agent and leftover solvent. Figure 3 illustrates the emulsification/reverse salting-out process schematically.
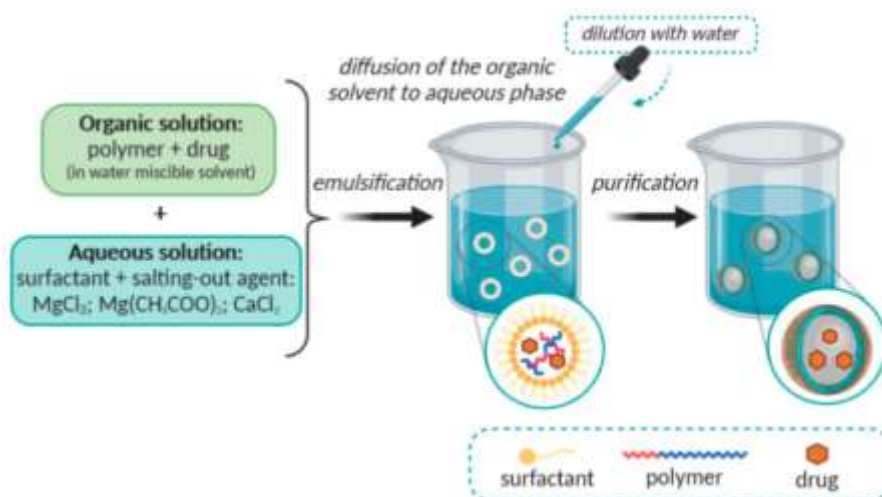
Figure 3: Schematic representation of the emulsification/reverse salting-out method. (Open access: Zielińska *et al*., 2020)

4. **Nanoprecipitation:** There are two miscible solvents used in the solvent displacement method, or nanoprecipitation. The internal phase is formed by a polymer dissolved in a miscible organic solvent, like acetone or acetonitrile. The technique's basic idea is based on the polymer's interfacial deposition that occurs when an organic solvent moves from a lipophilic solution into the aqueous phase (Salatin et al., 2017). The polymer is first dissolved in an intermediately polar water-miscible solvent. The solution is then carefully added to an aqueous solution, causing the nanoparticles to form instantly (Salatin et al., 2017). solvent from the nanodroplets diffusing, causing the polymer to precipitate as nanospheres or nanocapsules. Surfactants are not required for the production of nanoparticles, but their presence verifies that the nanoparticles are stable. (Bilati and others, 2005) The process of nanoprecipitation has been continuously employed to produce polymeric nanoparticles with a diameter of around 170 nm (Chidambaram et al., 2005). A schematic representation of the nanoprecipitation process is shown in Figure 4.
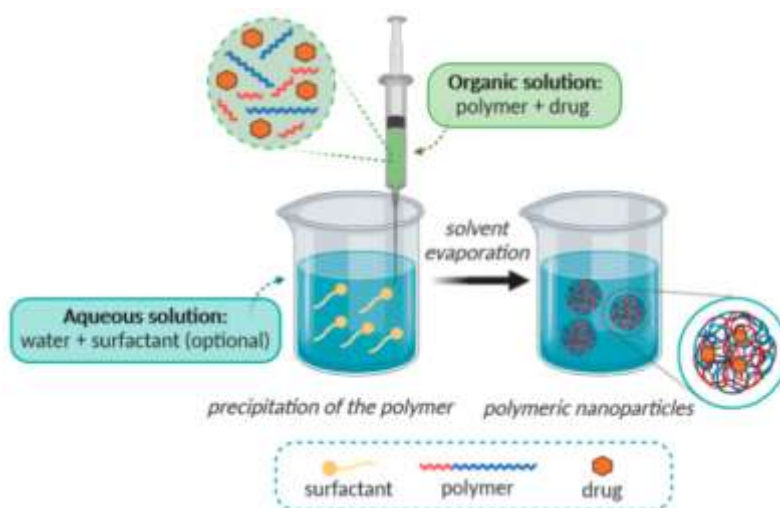
Figure 4: Schematic illustration of the nanoprecipitation method. (Open access: Zielińska *et al*., 2020)

5. **Dialysis:** Dialysis is a quick and easy way to prepare tiny, narrowly distributed polymeric nanoparticles (Fessi et al., 1989).Using an appropriate molecular weight cut-off, a polymer dissolved in an organic solvent is maintained within a dialysis tube using this technique. Dialysis generally entails the solvent inside the membrane being gradually displaced. Subsequently, the polymer gradually begins to aggregate as a result of a lack of solubility, which creates nanoparticles. Numerous reports of the synthesis of copolymer and polymeric nanoparticles using this method have been published. The synthesis of Poly(benzyl-l-glutamate)-b-poly(ethylene oxide) and Poly(lactide)-b-poly(ethylene oxide) nanoparticles using DMF as a solvent was reported by Chécotet al. (2008) and Ferranti et al. (2008). The solvent used to prepare the polymer solution has an impact on the nanoparticles' shape and particle size distribution. A novel osmosis-based technique for the creation of synthetic and natural polymeric nanoparticles was disclosed by Chronopoulou et al. in 2009. This technique is based on applying a physical barrier, such as a dialysis membrane or regular semipermeable membranes that permit solvent passive transport. The polymer solution's mixing with a non-solvent is slowed down as a result.

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:

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

- **Rapid Expansion of Supercritical Solution:** In the conventional RESS method, a solution is created by dissolving a solute in a supercritical fluid. This solution is then rapidly expanded through either an orifice or a capillary nozzle into the surrounding ambient air. The key factors contributing to the successful generation of well-dispersed particles in this process are higher supersaturation levels and the rapid reduction of pressure during expansion. Chernyak et al. (2001) effectively utilized the RESS technique to produce droplets of poly(perfluoropolyetherdiamide) by swiftly expanding CO_2 solutions. The RESS experimental setup consists of three primary components: a high-pressure stainless steel mixing cell, a syringe pump, and a pre-expansion unit. At ambient temperature, a polymer solution in CO_2 is pumped into the pre-expansion unit and heated to the desired pre-expansion temperature while maintaining the same pressure. This is followed by the expansion of the supercritical solution through the nozzle under ambient pressure conditions. When it comes to polymeric nanoparticles produced via the REES method, both particle size and morphology are affected by the polymer's concentration and degree of saturation. Blasig et al. (2002) conducted a RESS-mediated process to synthesize polymeric nanoparticles using poly(heptadecafluorodecyl acrylate), employing concentrations ranging from 0.5 to 5 wt% in CO_2. Lim et al. (2005) also employed the RESS process for synthesizing spherical nanoparticles of PSFTE (poly[2-(3-thienyl) acetyl-3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctanoate]) with sizes ranging from 50 to 500nm. They used solutions containing 0.1–0.5 wt% PSFTE in CO_2 at pre-expansion temperatures of 40∘C. In a typical experiment, CO_2 was delivered into PSFTE using a

syringe pump, and the PSFTE sample was obtained by spraying particles onto a glass slide through the nozzle after removing the CO2 in the pre-heater. Particle size is influenced by various factors, such as the degree of saturation, concentration, material properties, processing parameters, and the molecular mass of the polymer. In 2007, Sane et al. conducted a RESS-mediated process using CO2 and THF solutions of poly(lactic acid). They also demonstrated that an important determinant of the solute's solid-state diffusion coefficient is its capacity to regulate particle size during the RESS process. Typically, RESS products derived from PLLA exhibit nanoparticle diameters ranging from 30 to 100 nm. These particles tend to form agglomerates consisting of both nano and submicron-sized particles or micron-sized particles. Interestingly, products generated through this method are on a microscale rather than a nanoscale, despite not utilizing any organic solvents for the formation of polymeric nanoparticles. This constitutes the primary drawback of the RESS technique.

- **Rapid Expansion of Supercritical Solution into Liquid Solvent:** Rapid Expansion of Supercritical Solution into Liquid Solvent (RESOLV) represents a modification of the RESS method. In RESOLV, instead of expanding the supercritical solution into ambient air, it is expanded into a liquid solvent, as described by Sun et al. in 2002. The presence of the liquid solvent serves to suppress particle growth within the expansion jet, thereby enabling the production of primarily nanosized particles. Meziani et al. (2004) conducted a synthesis of PHDFDA (poly(heptadecafluorodecylacrylate)) nanoparticles with an average size of less than 50 nm using this method. The polymer, which is insoluble in water, is soluble in supercritical CO2.

  In a typical experiment, a CO2 solution of the polymer PHDFDA was pressurized using a syringe pump and then passed through a heating unit to reach the desired supercritical temperature. Subsequently, the expanded solution was directed through a nozzle into a chamber containing water. Due to its insolubility in water, the polymer precipitated, forming nanoparticles. However, in the aqueous suspension, larger particles were observed due to the aggregation of the initially formed nanoparticles. To address this issue, water was replaced with an aqueous NaCl solution at the receiving end of the expansion process, which stabilized the initially formed nanoparticles. This stabilization occurred as a result of the increased ionic strength within 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 CO_2 co-solvent observed this effect. The co-solvent leads to increases in the polymer solubility. The quick enlargement of the polymer solutions in supercritical CO_2 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 CO_2

Pump
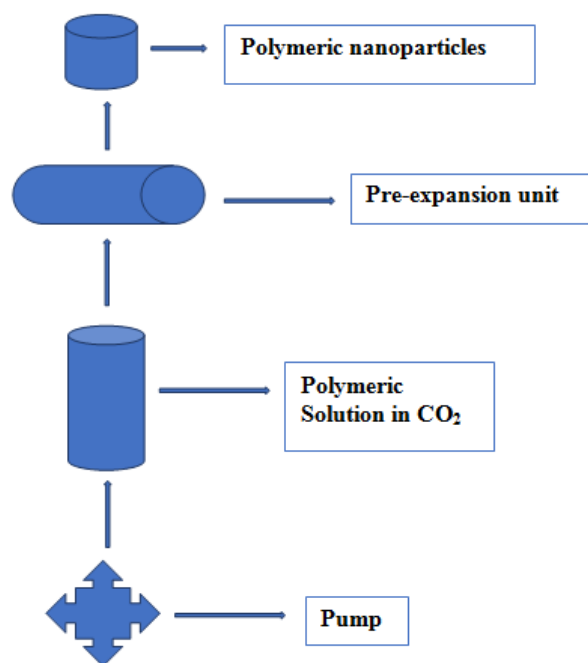
Figure 5: Schematic illustration of the RESOLV method

III. POLYMER NANOPARTICLES FOR CARDIOVASCULAR DISEASES

Atherosclerosis stands as a primary contributor to cardiovascular disease, inducing an up-regulation of immune responses at infected sites, which in turn leads to restricted blood flow due to the narrowing of arteries caused by the accumulation of fatty plaque deposits along vessel walls (Alzalzalah et al., 2017). This worsening of infected endothelium due to the recruitment of macrophages in atherosclerotic vasculature results in the destabilization of plaques, increasing the risk of thrombosis. These deposits have the potential to rupture, forming blockages in the vasculature, which is a common feature of strokes.

Current treatments for atherosclerosis involve either reducing lipid levels through statins or suppressing immune responses using anticoagulants (Lewis et al., 2011). However, this therapeutic approach for atherosclerosis may lead to muscle-related myopathy and undesirable side effects (Nguyen et al., 2011).

Polymeric nanoparticles have been employed for sustained drug delivery in the long-term treatment of active pharmaceutical ingredients (API). This is achievable due to the flexibility in adjusting size and surface charge parameters, resulting in increased bioavailability. For instance, PLGA (Poly(lactic-co-glycolic acid)) nanoparticles have been utilized to mimic the size and surface charge of high-density lipoproteins, allowing them to target atherosclerotic tissue (Gaytan et al., 2015). The dysfunctional endothelium present in atherosclerosis can facilitate a similar phenomenon known as the enhanced permeation and retention (EPR) effect. EPR enables controlled accumulation of nanoparticles within atherosclerotic plaques. Utilizing this principle, Katsuki et al. (2014) developed PLGA nanoparticles incorporating pitavastatin, which exhibit sustained uptake by macrophages within the plaque. This not only leads to the stabilization of existing plaques but also results in a reduction in plaque size. Additionally, certain characteristics of atherosclerosis, such as

clotting factors and increased expression of cellular adhesive molecules on endothelial cells, can also be harnessed for the delivery of polymer-encapsulated active pharmaceutical ingredients (APIs).

1. **Polymer Nanoparticles for Pulmonary Diseases:** Respiratory diseases continue to be a leading cause of morbidity on a global scale. In comparison to systemic or oral delivery of the same substance, the direct administration of aerosols to the lungs can result in approximately 100 times higher concentrations of the drug at the local site. This leads to increased efficiency in treatment. Intravenously administered nanoparticles bypass first-pass metabolism and can enhance patient compliance by eliminating the need for needles and cold chain storage, as highlighted by Patton et al. in 2007. Despite these advantages, lung administration is favored for most respiratory conditions, and commercial inhaled therapies have primarily been employed for a limited number of small molecule drugs.

   Polymer nanoparticles have gained increasing attention for pulmonary drug delivery, as noted by Mansour et al. in 2009. Large porous polymer particles have demonstrated effectiveness in delivering active pharmaceutical ingredients (APIs) to the lungs by offering unique features like controlled API release. They have succeeded in avoiding macrophage clearance and penetrating lung tissue due to their low density and substantial geometric size, exceeding 20 mm. Biodegradable polymers such as PLGA have paved the way for the development of inhalable insulin with sustained release capabilities in the lungs. The concept of large porous polymer particles has also been adapted for the delivery of polymer nanoparticles, with the large porous polymer particles providing efficient aerosol properties and the polymeric nanoparticles ensuring superior drug release and tissue penetration, as outlined by Tsapis et al. in 2002.

   While traditionally particle sizes between 1 and 5 mm have been considered ideal for pulmonary deposition, recent research indicates that polymeric nanoparticles smaller than 100 nm have demonstrated efficacy in achieving deep lung deposition. Moreover, nanoparticles measuring less than approximately 6 nm in size have shown the ability to diffuse across the epithelium and enter the circulation, as documented by Choi et al. in 2010. By adjusting their size, nanoparticles can be effectively utilized to achieve sustained and controlled release of therapeutic substances for both local and systemic purposes. In summary, polymer nanoparticles have been proven effective in delivering a diverse range of payloads for pulmonary applications, including inhaled vaccines, insulin, antibiotics, and chemotherapeutics.

2. **Polymeric Nanoparticle for Gene Therapy/Genetic Application:** In recent decades, gene therapy has emerged as a novel and effective approach for addressing acquired diseases, including genetic disorders, cancer, cardiovascular conditions, neurological disorders, and diabetes mellitus, as highlighted by Marzbal et al. in 2017. It has evolved into a treatment method for diseases that conventional drug delivery systems often struggle to tackle. An illustrative example is Timothy Ray Brown, the first human immunodeficiency virus (HIV) patient, who successfully recovered from HIV through gene therapy. While conventional methods are generally effective in treating a significant portion of diseases with multiple causative factors, gene therapy proves particularly valuable for combatting diseases resulting solely from the absence or excess of specific proteins.

Scientists recognize the substantial potential of gene therapy in addressing such diseases, especially when considering the diminishing returns associated with the time and financial investments required for conventional drug development in the realm of genetic diseases. Additionally, gene therapy can be applied to the treatment of other conditions such as viral infections and various forms of cancer, as indicated by Sun et al. in 2019. Notably, gene therapy diverges from conventional drug delivery in terms of the properties of the materials that exert therapeutic effects, including considerations like hydrophobicity, as well as the delivery vehicles employed.

Gene therapy involves the transfer of genomic materials, such as small interfering RNA (siRNA) and DNA, utilizing either viral vectors or nonviral vectors. There are two primary gene delivery systems: germline and somatic delivery systems. Somatic delivery is preferred due to ethical concerns associated with germline delivery. The viral vector approach typically employs adenovirus as a carrier for packaging genomic materials, as discussed by Lundstrom et al. in 2018. However, because of concerns related to toxicity, cost, potential replication, and carrying capacity of viral vectors, gene delivery using non-viral vectors has proven to be more advantageous. Non-viral vectors employ polymeric materials as delivery vehicles, as explained by Marzbal et al. in 2017.

Polymeric materials have gained prominence as promising carriers for creating efficient gene delivery systems, thanks to their gene-loading capacity, stability, and customizable properties. The careful selection of polymeric materials is crucial to ensure both the proper release of the gene and the easy removal of the carrier following gene delivery. Typically, biodegradable and biocompatible polymers are preferred over other materials, as highlighted by Ullah et al. in 2017. The choice of polymers for nanoparticle production depends on the desired size and surface characteristics of the particles, as well as the nature of the genes or active ingredients involved. The fabrication process employed for creating matrix-based nanoparticles is contingent upon the physicochemical properties of the selected polymer.

Two types of polymers are commonly used for preparing nanoparticles in gene therapy.
- Natural or bio polymers-these polymers are hydrophilic in nature
- Synthetic polymers- these polymers are hydrophilic in nature

The gene transfection effectiveness of cationic polymers is influenced by factors such as their structure, molecular weight, and surface charge. In the past decade, a range of polymers has found application in gene therapy, including synthetic ones like poly (l-lysine), poly (l-ornithine), linear and branched polyethyleneimine, poly (amidoamine) dendrimers, diethylaminoethyl-dextran, and poly (amidoamine) dendrimers, as discussed in the study by Vangala et al. in 2021. Additionally, natural polymers like dextran, chitosan, gelatin, and pullulan, as well as synthetic counterparts with advanced properties like guanidinylated bio-reducible polymers, have played significant roles in this field.

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. **Polymeric Nanoparticle for Anti diabetic Drugs Application:** Diabetes Mellitus is a collection of metabolic disorders characterized by a complete absence of insulin, a relative shortage of insulin, or the presence of insulin resistance, ultimately leading to hyperglycemia, as detailed by Deopa et al. in 2013. Utilizing polymeric nanoparticles offers numerous advantages as a novel delivery system, making it an effective approach for treating diabetes mellitus. Table 1 provides an overview of various polymeric anti-diabetic drugs and the associated polymers used in their formulation.

Table 1: Polymeric Nanoparticles for diabetic treatment (Gopalasatheeskumaret 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 possess attributes such as bio-adaptability, biocompatibility, and biodegradability. The drug can be either dissolved, entrapped, or encapsulated within the nanoparticle medium. The specific type of nanoparticles, whether they are nano-spheres or nano-capsules, depends on the chosen preparation method. In a nano-capsule system, the drug is confined within a cavity enclosed by a uniform polymer layer, whereas the nano-shell consists of a medium where the drug is physically and evenly dispersed, as described by Ranjit et al. in 2013 and Yadav et al. in 2013. The primary advantages of polymeric nanoparticles include their straightforward preparation

process, targeted drug delivery, reduction of required dosage, and high therapeutic efficiency.

4. **Polymeric Nanoparticle for treatment of Covid – 19:** COVID-19, also known as coronavirus disease, is an infectious illness instigated by the SARS-CoV-2 virus. The outbreak of COVID-19 has evolved into a severe health crisis, posing a potential threat to public health worldwide, with numerous hospitalizations and a substantial death toll. This has prompted global concern and the implementation of extensive precautionary measures. COVID-19 manifests as an acute respiratory infection, characterized by its high transmission rate and global prevalence, resulting in a significant loss of life and considerable economic consequences, as documented by Gennaro et al. in 2020.

Due to their inherent competitive advantages, polymeric-based nanoparticles hold remarkable potential in the battle against the novel coronavirus disease (COVID-19). In order to effectively combat COVID-19 and potential future outbreaks, it is essential to develop robust, reproducible, and cost- and time-efficient vaccines, drug platforms, and prophylactic methods. In response to this urgent need to combat and prevent COVID-19 infection, numerous global initiatives involving nanotechnological approaches have been undertaken, as highlighted by Singh et al. in 2020. The adaptability of polymeric-based nanoparticle engineering offers the following advantages: (i) specificity, (ii) customizable release kinetics, and (iii) the ability to create multimodal drug compositions. This capability has the potential to overcome common limitations encountered during traditional drug development.

The progress made in nanotechnology engineering has significantly influenced various fields of knowledge, including materials, chemistry, tissue engineering, and nanomedicine. These advancements are intimately tied to the nanometer scale of the materials, as pointed out by Chauhan et al. in 2020. In comparison to conventional therapeutic approaches, nanostructured materials have the ability to overcome common limitations associated with target tissue specificity, release rates, biodegradation of bioactive substances, and serve as carriers for both hydrophobic and hydrophilic compounds, all while minimizing side effects. Furthermore, sophisticated strategies to enhance the therapeutic potential of nanomedicines, such as functionalization, passivation, and the incorporation of multiple drugs within a single carrier, can lead to more consistent biological responses compared to traditional methods, as discussed by Zhou et al. in 2020.

Another benefit of employing polymeric nanoparticles lies in their intrinsic colloidal stability and surface properties. These characteristics allow nanomaterials to evade unfavorable interactions with the immune system and prolong their presence in the bloodstream. Alternatively, they can be designed to enhance interactions with the immune system, transforming these materials into valuable tools that can serve as adjuvants and mimic virus-like particles in vaccines, as discussed by Zhou et al. in 2020.

The substantial surface area offered by polymeric nanoparticles makes them highly efficient drug carriers, and their size plays a crucial role in interactions with cell membranes and the traversal of physiological barriers, as elucidated by Kumari et al. in 2010. Furthermore, these nanosystems exhibit distinct physical and chemical characteristics, including (i) prolonged blood circulation time, (ii) reduced adverse

effects, (iii) the ability to safeguard therapeutic agents from degradation, thereby enhancing stability, bioavailability, and drug pharmacokinetics, (iv) ease of chemical modification, (v) controlled drug release, and (vi) improved therapeutic outcomes, as discussed by Gao et al. in 2020, Yang in 2021, and Sun et al. in 2021. Due to these advantages, nanostructured polymers have been explored as valuable tools in the fight against COVID-19, as highlighted by Zhang et al. in 2020.

Among the notable benefits offered by polymeric nanoparticles for combatting the SARS-CoV-2 virus are their high stability, precise control over drug delivery, biocompatibility, adaptability to manipulate physical and chemical properties, compatibility with both hydrophilic and hydrophobic drugs, and suitability for preparation through straightforward and appropriate methods, which encompass factors such as polymer selection, nanoparticle size, administration route, and the specific drug being carried, among others, as emphasized by Bhardwaj et al. in 2020.

5. **Polymeric Nanoparticle for Anti Microbial (or Antibiotic) Therapy (or Application):** Microorganisms play a vital role in human existence, contributing to a wide array of processes such as nitrogen fixation, vitamin synthesis, photosynthesis, and the decomposition of organic matter. However, when the balance between microorganisms and the immune system tilts in favor of microorganisms, it can lead to immune deficiencies, as noted by Chircov et al. in 2019. Infectious diseases, caused by pathogenic microorganisms including bacteria, viruses, fungi, parasites, protozoa, or algae, can be transmitted directly or indirectly (via vectors) from one individual to another, as highlighted by Tripathi et al. in 2019.

Despite significant advancements in the pharmaceutical and medical fields, along with the development of numerous antimicrobial drugs, infectious diseases continue to pose a major health threat, affecting millions of lives daily, as documented by Devrim et al. in 2017. The primary challenges associated with antimicrobial drugs include their limited rate of transportation, low water solubility, oral bioavailability, and stability. Additionally, these drugs often suffer from inefficient drug targeting, significant toxicity, and limited patient compliance. Furthermore, the inefficacy of antimicrobial drugs is exacerbated by the development of antimicrobial resistance among 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 gotsignificant 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 rapid advancement of nanotechnology has led to the creation of numerous nanosystems that have proven effective as antimicrobial agents for treating bacterial and fungal infections. By designing polymeric nanoparticles (PNPs) incorporating conventional antibiotics as therapeutic agents and harnessing the antimicrobial properties of nanosystems themselves, it is possible to overcome the limitations associated with conventional antibiotic therapy. For instance, the treatment of H. pylori using amoxicillin and pectin sulfate-loaded lipid PNPs has demonstrated significant efficacy in eradicating H. pylori in its biofilm form, preventing bacteria from adhering to gastric cells, and reducing the MIC value for amoxicillin. This approach enhances amoxicillin's capacity to inhibit bacterial colonization, even in the face of H. pylori's well-known resistance to antimicrobial treatment, as illustrated by Cai et al. in 2015. Similarly, the potent antimicrobial potential of streptomycin-conjugated magnetic nanoparticles coated with chitosan has shown promise in combating drug-resistant infections, particularly those prevalent in hospital settings, including drug-sensitive S. aureus and its methicillin-resistant counterpart (MRSA), as demonstrated by Hussein-Al-Ali et al. in 2014. More recently, chitosan-coated alginate (CS-ALG) nanoparticles have been proposed as a means to enhance the ocular delivery of daptomycin for treating endophthalmitis caused by MRSA.

6. **Drug Delivery in Ocular Diseases:** The process of delivering drugs to the eye is known to be highly challenging, as the eye can be divided into distinct anterior and posterior segments. The anterior segment includes components such as the conjunctiva, cornea, iris, and lens, while the posterior segment comprises the neural retina, retinal pigment epithelium, vitreous humor, and more. Reaching the posterior segment with drug formulations is particularly challenging due to the presence of various barriers, including the formidable blood-retinal barrier, which significantly restricts drug access. Many of these limitations in ocular therapy drug delivery can be mitigated through the use of nanotechnological systems.

Among the valuable nanocarriers for drug delivery in ocular diseases, dendrimeric nanocarriers have shown significant promise. The pioneering dendritic polymer designed for nanosystems in ocular disease drug delivery is based on polyamidoamines. Yang et al. [52] developed PEGylated polyamidoamine-based dendrimers as nano drug carriers for ocular diseases. These dendrimers were further modified with cyclic arginine−glycine−aspartate hexapeptide (Yang et al., 2019). In a similar vein, Lancina et al. [53] synthesized a polyamidoamine-based dendrimeric core using a timolol analog, a commonly used drug for ocular hypertension (Lancina et al., 2018). Additionally, Tai et al. [54] created a complex utilizing polyamidoamine dendrimers and hyaluronic acid, which was further modified with penetratin and loaded with antisense oligonucleotides for the control and management of ocular diseases. This system was found to significantly enhance eye

permeability. Furthermore, some polylysine (PLL) and phosphorous-based dendrimers have also been developed for use in drug delivery nanosystems for ocular diseases.

Chitosan stands out as one of the frequently employed polymers in the creation of micelles for ocular disease drug delivery. This polymer boasts exceptional penetration properties, rendering it well-suited for drug delivery in the realm of ophthalmology. Imam et al., in 2018, devised micelles using sodium tripolyphosphate (TPP) as a means of delivering drugs for the treatment of ocular infections. The formulation's effectiveness can be enhanced by employing specific media alongside drug-loaded micelles. In a similar vein, Wen et al. [49] modified a gel loaded with nanoparticles to facilitate drug delivery for ocular inflammation (Wen et al., 2018).

Cyclodextrins (CDs) have also been documented for their utility as polymeric nanocarriers. CDs are cyclic oligo- or polysaccharides consisting of six or more glucose units linked by α-1,4 glycosidic bonds. They possess unique structural attributes, featuring an external hydrophilic surface and an internal cavity with hydrophobic properties. Cyclodextrins serve as valuable drug delivery agents, particularly for hydrophobic active ingredients. Rodriguez-Aller et al. crafted a cyclodextrin derivative, propylamino-β-CD, as nanocarriers for latanoprost, a glaucoma treatment (Rodriguez-Aller et al., 2015). This cyclodextrin exhibited enhanced drug stability and availability. Lorenzo-Veiga et al. constructed a library of micelles and poly(pseudo)rotaxanes using soluplus, pluronic P103, and α-cyclodextrin (Lorenzo-Veiga et al., 2019). These entities proved to be highly effective candidates, demonstrating favorable diffusion and sclera permeability coefficients.

PLGA (Poly(lactic-co-glycolic acid)) and CH (chitosan) are commonly employed polymers in the development of nanoformulations for ocular disease drug delivery. Notably, nanoparticles encapsulating the drug everolimus (40-O-(2-hydroxyethyl)-rapamycin) were prepared using Tween-80 and polyoxyethylene stearate as reported in the literature.

7. **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 similarto 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.

8. **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 polymericmicelles 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 play a pivotal role in the delivery of cancer treatments, with hydrogels being crafted from biopolymers and their derivatives. Natural bioactive molecules exert a profound influence on cell signaling pathways, offering potential applications in the management and treatment of cancer. Biopolymers, when engineered into nanoparticles, have proven to be valuable in delivering various types of anticancer drugs across different forms of cancer. A multitude of nanomedicines based on biopolymers are employed in cancer therapy. For instance, the nanoformulation of 3,3'-diindolylmethane has demonstrated substantial reductions in cell viability in pancreatic cancer, as documented by Mousa et al. in 2020.

Biopolymeric formulations serve the dual purpose of safeguarding nanoparticles against degradation and enhancing their stability. The size range of polymeric nanoparticles spans from 1 nm to 1000 nm, with nanocapsules and nanospheres representing the two primary structural forms of these particles. Drug loading is achieved through cross-linked polymers in the case of nanospheres. The polymers employed in nanoparticle preparation are predominantly biodegradable and biocompatible, with chitosan and collagen being recognized for their contributions to polymeric drug delivery systems. Additionally, synthetic polymers like poly(lactide) (PLA) and poly(lactide-co-glycolide) (PLGA) are currently deployed in drug delivery, as highlighted by Zhang et al. in 2022.

The characteristics of polymeric nanoparticles, such as size, shape, zeta potential, and stability, predominantly hinge on the method employed for their synthesis. To facilitate effective drug delivery to vascularized tumors via polymeric nanoparticles, their diameter should ideally hover around 100 nm. The size of the particles plays a crucial role in determining their function and pharmacological properties. These nanoparticles are generated through bottom-up techniques, which involve the polymerization of individual monomer units. Two common methods for forming polymeric nanoparticles are emulsion polymerization and recombination technology.

Furthermore, a range of top-down nanotechnology approaches, including nanoprecipitation, salting out, and the supercritical fluid method, are equally viable for preparing polymeric nanoparticles. Among cancers, breast cancer is prevalent among women, and the role of polymeric nanocarriers in its treatment has been extensively

explored in recent years. For instance, a polymer conjugated with a folate ligand (PFTTQ) has been reported to exhibit inhibitory effects on the positive folate receptors found in tumor cells associated with 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 has been documented to exhibit a potent antiproliferative impact of paclitaxel on specific lung cancer cells. Additionally, inhalable nanocarriers have been designed for the delivery of antineoplastic medications.

IV. ADVANTAGES OF POLYMERIC NANOPARTICLE APPLICATION

Polymeric nanoparticles, owing to their diminutive size, exhibit unique characteristics distinct from the bulk form of the same material. Consequently, they have ushered in numerous innovations across the realms of biosensors, biomedicine, and bio-nanotechnology. The medical domain harnesses nanotechnology for purposes ranging from diagnosis to therapeutic drug delivery and the advancement of treatments for a myriad of diseases and disorders. Here are the advantages of polymeric nanoparticles in various applications, as outlined by Sailaja et al. in 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.

V. TOXICITY OF POLYMERIC NANOPARTICLES

The domain of nanotechnology is steadily expanding and experiencing significant transformations in the realm of drug delivery. Nanotechnology represents an emerging field characterized by the manipulation of materials at the nanoscale. Nanoparticles (NPs) are harnessed as carriers for delivering active agents, and they are considered prime candidates for addressing the issue of poor bioavailability that plagues most drugs, owing to their ability to enhance solubility and permeability across biological membranes. Various nanomaterials, derived from diverse substances like polymers, silicon, lipids, carbon, silica, and metals, find application in drug delivery. Among these options, polymeric nanomaterials are widely favored by researchers due to their well-understood properties. Consequently, polymeric nanoparticles have seen extensive use in drug delivery systems. However, given the associated risks with nanomaterials, there has been a significant uptick in researchers' attention towards the safety considerations concerning polymeric nanoparticles. Particular emphasis is placed on exploring the methodology, design, and morphology, as they provide valuable insights into the intricacies inherent to the approach involving nanomaterials and safety assessment, as indicated by Sharma et al. in 2012. One plausible explanation for this heightened focus might be the insufficient availability of toxicity and safety data pertaining to these nanosystems, which are necessary to meet regulatory requirements. The primary concern regarding the utilization of polymeric nanoparticles in the medical field revolves around their potential toxicity. Polymeric nanoparticles represent a subset of nanomedicines that are continually evolving to enhance drug delivery's precision and effectiveness.

Nanoparticles (NPs) have the potential to serve as a versatile tool for delivering drugs to the brain. This has been a subject of research for over a decade, but unfortunately, successful pharmaceutical developments in this area remain scarce. One contributing factor to this scarcity can be attributed to insufficiently addressed concerns about toxicity. Indeed, in recent years, there has been a growing public apprehension regarding the potential toxic effects of NPs. Consequently, international initiatives have been launched to develop tests for assessing the safety and tolerability of NPs when exposed to biological systems, and some understanding of their mechanisms of action has emerged (De Jong et al., 2008). These efforts have primarily focused on the potential toxicity of NPs following inhalation or

ingestion, primarily investigating lung and gastrointestinal toxicities. However, only a minority of studies have delved into the effects on brain cells. It has been suggested that, unlike chemical toxicity where purity and concentration are the primary factors, the realm of 'nanotoxicity' must also consider particle size, shape, surface properties, and charge. Literature indicates that NPs can induce inflammation, DNA damage, membrane disruption, and the generation of reactive oxygen species. However, specific risks are associated with specific types of particles; for instance, DNA damage and reactive oxygen species production are mainly linked to metal (oxide) NPs, whereas membrane leakage has been observed with the application of polymeric NPs. In-vitro test systems have been widely used to assess nanotoxicity, with the MTT viability test being recommended for this purpose. Nevertheless, relying solely on in-vitro experiments may not suffice as a safety testing strategy for NPs, and there is a notable absence of data correlating in-vitro and in-vivo studies (Dhawan et al., 2010).

Due to their intriguing attributes such as systemic stability, solubility, and targeted localization, nanoparticles (NPs) have brought about a revolution in the field of biomedicine, particularly in drug delivery. Nevertheless, their impact can be both advantageous and potentially harmful, depending on the environmental factors, underscoring the imperative need for conducting nanotoxicology investigations prior to their application in human contexts. Smart drug delivery systems employ polymeric NPs fabricated from either synthetic or natural polymers. Extensive research is underway to explore these materials as carriers for achieving controlled and sustained drug release in drug delivery systems (DDSs). However, the effectiveness of these nanopharmaceuticals is impeded by safety concerns, risks of toxicity, inadequate biocompatibility, and physiological constraints. Drawbacks associated with these NPs encompass potential hazardous degradation, the presence of residual materials, and the potential for monomer aggregation-induced damage.

VI. CHALLENGES OF POLYMERIC NANOPARTICLES

The field of nanomedicine holds the promise of significant advancements in the coming decade, ensuring more effective and safer treatments through a vast array of nanoparticle designs and functionalization options. The potential applications continue to expand to the extent that nanocarriers can now be tailored to precisely accommodate a specific active ingredient, adapt to particular environmental conditions, and deliver the drug to the target site in a controlled manner. However, it is important to acknowledge that NP-based therapies are not without their challenges. First, the selection of polymeric materials available for use as drug delivery systems remains somewhat limited, despite significant progress in research and development over the past decade, transitioning from the micro- to the nanoscale. Achieving the ideal adaptation to delivery requirements, such as site-specific transportation, precise targeting, or the establishment of suitable delivery profiles for various diseases, necessitates the development of new polymers capable of meeting these specific criteria. While selective targeting represents a significant improvement compared to using non-encapsulated drugs, it presents a complex mechanism and, in itself, poses a formidable challenge. Simply having an overexpression of a specific surface protein is insufficient to guarantee selective targeting, as these proteins are typically expressed in normal cells as well. This challenge is particularly critical in cancer treatments, where the drugs administered often exhibit higher toxicity, potentially leading to numerous undesirable side effects compared to drugs used in the treatment of other diseases. Although many assays have demonstrated promising results in small animal models, the translation of these findings from animals to

clinical success has been limited. To gain a comprehensive understanding of the mechanisms of these nanocarriers, more clinical research and data are required. Furthermore, there are limitations related to the uncertain future of pharmaceutical companies, which face substantial expenses associated with clinical trials and decreasing success rates in the development of new entities within the R&D pipeline. Instances of polymeric NPs that do not meet the full spectrum of regulatory prerequisites for clinical assessments have had adverse economic repercussions for pharmaceutical companies, as illustrated by Livatag. Developing novel, cost-effective methods for manufacturing NPs is a pivotal aspect of this challenge, given the limited number of NPs that satisfy the necessary criteria for reaching the intended target and effectively delivering the drug. Additionally, it is imperative for these polymeric NPs to either possess biodegradability or exhibit a high capacity for elimination from the body to prevent accumulation, all while remaining non-toxic and non-immunogenic.

It's worth highlighting the potential role that copolymers could play in fine-tuning interactions with mucosal or blood proteins to control their in vivo fate or stabilize NPs without relying on surfactants. Furthermore, future research in this field could explore stimuli-responsive polymers that confer triggered release properties. While existing methods can readily produce nanospheres and nanocapsules, newer structures like polymerases are awaiting more efficient synthesis techniques to be incorporated into the family of nanoparticulate drug delivery systems.

The pursuit of multifunctional NPs, which possess various capabilities like targeting and image contrast enhancement, necessitates additional synthetic steps, surmounting regulatory hurdles, and incurring higher expenses. While these objectives may seem daunting, there is optimism that a more favorable landscape can be achieved (Begines et al., 2020).

In recent years, there has been a significant worldwide evolution in the realm of nanomedicine. This evolution has fostered a multidisciplinary and cooperative approach that has yielded promising outcomes and achievements. The forthcoming trajectory of collaborations among both theoretical and experimental scientists, the pharmaceutical industry, medical professionals, and regulatory authorities will be pivotal. These collaborations will enable the translation of laboratory findings into clinical practice, thereby paving the way for the emergence of the next generation of clinical therapies.

VII. FUTURE PROSPECT OF POLYMERIC NANOPARTICLES

Polymeric nanoparticles (NPs) represent one of the most extensively investigated organic strategies within the realm of nanomedicine. There is substantial enthusiasm for the potential of polymeric NPs to bring about a profound transformation in modern medicine. While the refinement of regulatory mechanisms for nanomedicines, as well as safety and toxicity assessments, remains a focus for future development, nanomedicine has already ushered in a paradigm shift in how we discover and administer drugs within biological systems. Thanks to the progress in nanomedicine, we have witnessed the actualization of disease diagnosis and the integration of diagnosis with therapeutic interventions (Patra et al., 2018). The fundamental objective of nanoparticles is to optimize the balance between therapeutic benefits and associated risks. Instead of subjecting patients to numerous debilitating side effects in the pursuit of curing a single disease, as is often the case with current cancer treatments, nanoparticles are meticulously engineered to minimize any adverse

effects while effectively treating the same disease. Further research and increased funding are imperative to thoroughly evaluate both the efficacy of nanomedicine and its long-term impact on the human body.

Although lipid-based nanoparticles hold the most promise due to their composition of natural elements and numerous advantages over other nanoparticle types, they are not without imperfections as a drug delivery solution. To propel this technology forward, substantial investments are required in clinical trials, both from governmental and private sectors. Nanomedicine finds application in the treatment of diverse diseases and medical conditions, but it is within the realm of oncology that nanoparticles are most extensively utilized and exhibit the greatest potential. Presently, there are 51 nanopharmaceuticals that have received approval for clinical practice. Furthermore, ongoing clinical trials are investigating more nanoparticle-based treatments for cancer and various other diseases.

VIII. 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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