

POLYMERIC NANOPARTICLES PREPARATION, CHARACTERIZATION, APPLICATIONS, AND FUTURE PERSPECTIVES

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ABSTRACT: This work examines the fabrication, characterization, application, and potential future advancements of polymeric nanoparticles, a complex and adaptable nanocarrier. Polymeric nanoparticles are synthesized using salting-out, polymerization, emulsion-solvent evaporation, and nanoprecipitation methods. These methods enable precise control over drug-loading efficiency, particle dimensions, and morphology. Dynamic light scattering, electron microscopy, zeta potential analysis, and spectroscopy must be employed to evaluate their performance, stability, and physicochemical properties. Polymeric nanoparticles may deliver medications, DNA, and other compounds at different rates, and they possess biocompatibility and biodegradability. They capture images, cultivate crops, modify genes, diagnose diseases, provide medications, and purify the environment. Despite advancements, challenges remain regarding large-scale manufacturing, long-term safety, regulatory approval, and cost-effectiveness. Future studies indicate that surface-functionalized nanoparticles, intelligent polymers, and stimuli-responsive systems will improve the translation, therapeutic efficacy, and targeting of polymeric nanoparticles in biomedical and industrial applications.

Keywords: *Polymeric nanoparticles; Nanoparticle preparation; Characterization techniques; Drug delivery systems; Biocompatibility; Controlled release.*

1. INTRODUCTION

Nanotechnology is a rapidly evolving and captivating field of biological and pharmaceutical research. Due to their biocompatibility, pharmacological potency, and versatility, polymeric nanoparticles (PNPs) are highly sought-after nanocarriers. Pharmaceuticals are chemically bonded, encapsulated, confined, or dissolved in colloidal polymeric nanoparticles. They are biodegradable polymers that are 10–1000 nanometers in length. This facilitates the safe and efficient distribution of drugs.

Nanospheres and nanocapsules are examples of polymeric nanoparticles. This is contingent upon the structure and assembly. Pharmaceuticals are distributed uniformly throughout the polymer matrix by nanospheres. A hollow core is enclosed by a polymeric exterior in nanocapsule drug reservoirs. Structural change is essential for drug transport, stability, and targeting. Medication delivery systems are facilitated by the capacity of PNPs to modify their internal structure.

Polymeric nanoparticles are employed in biotechnology, medicine, environmental science, and diagnostics. Pharmaceutical distribution is the subject that has been the subject of the most research. PNPs enhance solubility, safeguard unstable compounds, and improve bioavailability, thereby rendering drug delivery systems more appealing, secure, and regulated. Polymeric nanoparticles facilitate the transportation of medications to organs, cells, and tissues. This mitigates systemic damage and optimizes treatment.

Proteins, peptides, nucleic acids (DNA and RNA), and small-molecule medications can be transported intracellularly by polymer-based nanoparticles. Due to their diminutive size, they are capable of traversing cell membranes and remaining in the bloodstream. The treatment of chronic disorders, such as cancer, is significantly improved by the prolonged retention of medication at the intended site.

The significance of nanoparticle polymers is that they alter the appearance and functionality of the system. They facilitate the construction of molecular structures and the modification of surfaces to achieve precise forms, sizes, surface charges, and drug release patterns. Due to their adaptability, distinctive nanoparticles may be created for diagnostic and medical applications. Functionalized polymeric nanoparticles can target specific regions by incorporating ligands. This facilitates the distribution of drugs within the local area.

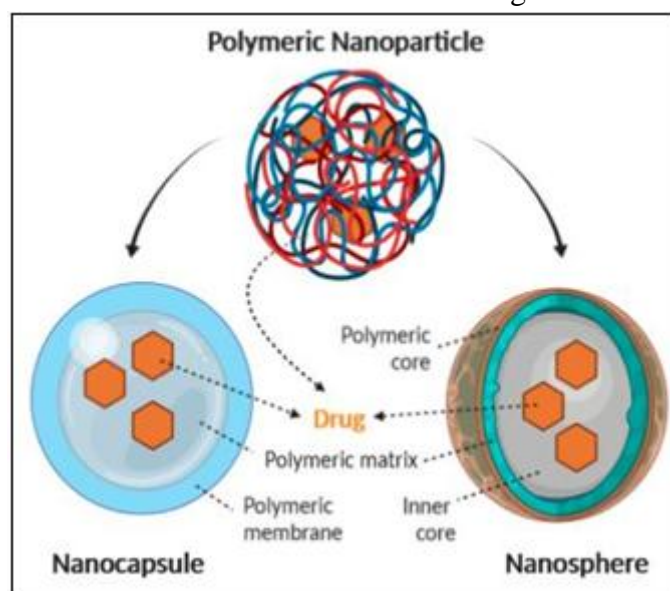


Fig 1: Structure of A Nanocapsule and a Nanosphere

2. METHODS OF PREPARATION OF POLYMERIC NANOPARTICLES

Depending on their purpose, polymeric nanoparticles (PNPs) can be produced in a variety of ways. The properties of the medication, polymer, and nanoparticle will determine your approach. The majority of drug delivery entails either delivering readymade polymers or polymerizing monomers.

The precise control of nanoparticle size, shape, and surface properties is made possible via polymerization. When selecting a polymer and production process, take into account the polymer's composition, hydrophobicity or hydrophilicity, surface charge, swelling or contraction, pH sensitivity, and drug release.

Methods for the Preparation of Nanoparticles from the Dispersion of Preformed Polymers

Solvent Evaporation Method: This method creates an emulsion by dissolving the polymer in an organic solvent and then combining it with water. Solvent evaporation produces nanoparticles.

Nanoprecipitation Method: The polymer precipitates when water is introduced to an organic solvent containing polymers.

Emulsification–Solvent Diffusion Method: To create nanoparticles, the polymer is dissolved in a water-soluble solvent and then dispersed throughout the aqueous phase.

Salting-Out Method: In order to create nanoparticles, salting-out agents separate polymer solvent from the aqueous phase without using heat.

Dialysis Method: This preserves the polymer solutions found in dialysis membranes. The solvent is eventually removed by diffusion to produce nanoparticles.

Supercritical Fluid Technology (SCF): This novel method reduces the consumption of organic solvents while creating nanoparticles utilizing supercritical fluids (such as supercritical CO₂).

Methods for the Preparation of Nanoparticles by Polymerization of Monomers

Emulsion Polymerization

In water, monomer molecules stabilized by surfactants polymerize.

Mini-Emulsion Polymerization: Compared to emulsion polymerization, this method yields more stable, smaller nanoparticles with more uniform diameters.

Micro-Emulsion Polymerization: The process of polymerization turns thermodynamically stable micro-emulsions into nanoparticles.

Interfacial Polymerization: Through polymerization, two immiscible phases combine to create nanoparticles or nanocapsules.

Controlled/Living Radical Polymerization (C/LRP): This method meticulously controls the molecular weight, polymer structure, and functional groups to create precise polymeric nanoparticles.

3. IONIC GELATION OR COACERVATION OF HYDROPHILIC POLYMERS

Solvent Evaporation: Solvent evaporation was used to transform a previously manufactured polymer into nanoparticles. The initial stage in making nanospheres is to make an oil-in-water (o/w) emulsion. The initial step in dissolving the polymer and integrating the active ingredient (such a drug) is to create an organic phase using a polar organic solvent. Chloroform and dichloromethane are still in use, albeit less frequently. Ethyl acetate has taken their position because of its superior biological properties and less toxicity.

An aqueous phase is also produced using a surfactant, such as polyvinyl acetate. The organic solution is homogenized or ultrasonically agitated after being emulsified with a surfactant in water. Nanodroplets spread as a result. When the polymer solvent dissipates and combines with the continuous phase of the emulsion, the nanoparticle suspension is created.

Dichloromethane and chloroform either evaporate at low pressure or magnetically swirl at room temperature. slightly polar to non-polar. Nanoparticles can be cleaned, centrifuged, and freeze-dried for storage once the solvent has evaporated.

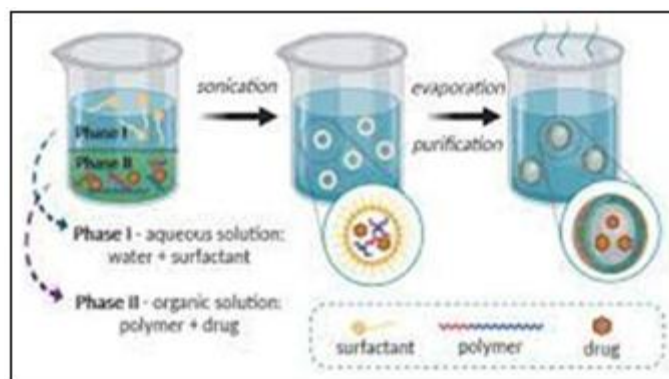


Fig. 2: Schematic Representation of the Solvent Evaporation Method

Nanoprecipitation: Two miscible liquids are used in the solvent displacement procedure. A polymer that dissolves in acetone or acetonitrile and interacts with other substances. They can be swiftly eliminated by evaporation because they don't interact with water. This method works by adding a polymer to the interface between the aqueous phase and the lipophilic solution. Water-miscible solvents with intermediate polarity break down polymers. Then, while stirring, this solution is gradually added to an aqueous solution. Nanoparticles are created when the polymer solution migrates quickly and independently into the aqueous phase. When the solvent separates from the nanodroplets, the polymer forms nanospheres or nanocapsules. Although adding the organic phase to the aqueous phase is common, this can be done the other way around without influencing the creation of nanoparticles. In spite of their presence

Surfactants are necessary for maintaining colloidal suspensions, however they are not required for the formation of nanoparticles. Unlike emulsification solvent evaporation, this method yields nanoparticles with distinct dimensions and a restricted size distribution.

Nanoprecipitation is one of the most dependable laboratory techniques for drug encapsulation. The medication and polymer are dissolved by the foundation's solvent, while it can join with it without dissolving thanks to its non-solvent. The polymer-drug solution diffuses toward the non-solvent when two solutions come into contact. API encapsulation and polymer precipitation take place at the same time. A common method for creating nanoparticles with a low polydispersity index and sizes between 100 and 300 nm is nanoprecipitation. Water is a non-solvent whether stabilized or not. Ethanol, acetone, and tetrahydrofuran are the most widely used solvents. The solvent type, polymer concentration, solvent-to-non-solvent ratio, non-solvent addition flow rate, and agitation rate are typically assessed in order to optimize the process. One common method for producing PLGA nanoparticles is nanoprecipitation. Despite effectiveness in the lab, scaling up is complicated by the effect of the mixture and precipitation. The procedure has been facilitated by microreactors, which can control precipitation variables and generate medium-scale formulations.

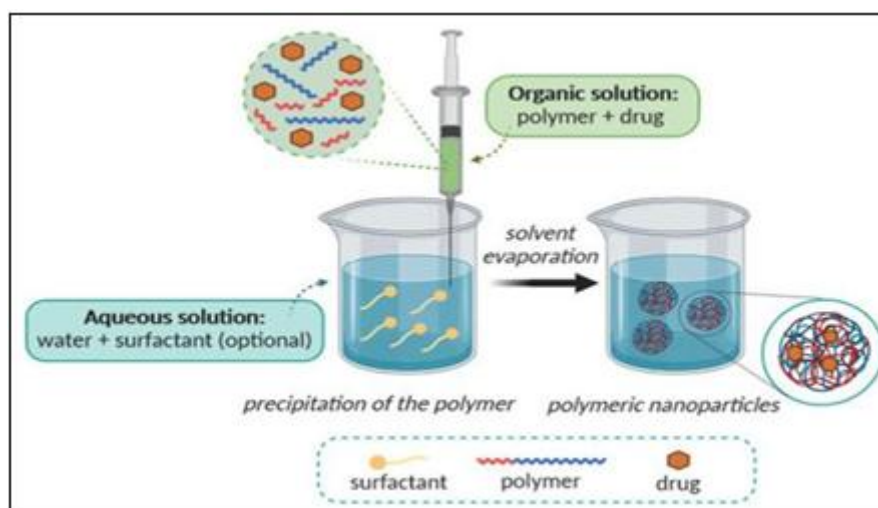


Fig. 3: Schematic Representation of the Nanoprecipitation Method

Emulsification/Solvent Diffusion: To do this, a polymer, water-miscible surfactant, solvent, and a therapeutic ingredient are combined. An organic solvent that is water-saturated and moderately hydro-miscible, such as benzyl alcohol or ethyl acetate, makes up the internal phase of this emulsion. At room temperature, the two phases achieve thermodynamic equilibrium.

When the solvent is highly diluted with water, it moves from the droplets to the outer phase, forming colloidal particles. Like nanospheres, nanocapsules can be created by mixing triglycerides C6, C8, C10, and C12 with a little amount of oil.

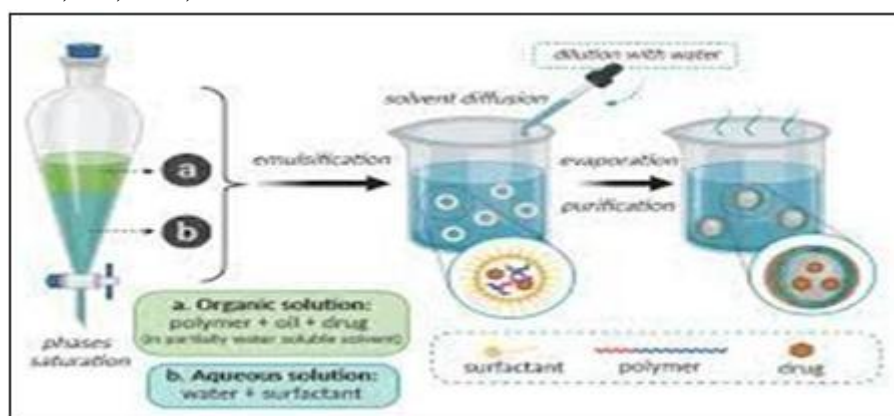


Fig. 4: Schematic Representation of the Emulsification/Solvent Diffusion Method

Salting out: Salting-out occurs when water-soluble solvents separate from aqueous solutions. The salting out technique is a variation of emulsification and solvent diffusion. The polymer and drug are dissolved in acetone and combined with a colloidal stabilizer and a salting-out agent (electrolytes such as sucrose or non-electrolytes like calcium chloride, magnesium chloride, and magnesium acetate). Nanospheres are produced by diluting the oil/water emulsion with water or an aqueous solution. Acetone thus has a greater ability to penetrate the aqueous phase.

The effectiveness of pharmaceutical encapsulation can be significantly impacted by the salting-out agent, therefore cautious selection is required. Solvent and salting-out agent are eliminated by cross-flow filtration. The synthesis of PLA nanospheres is scalable and effective. Salting out reduces stress on protein encapsulants. Since salting out does not raise the operating temperature, it is advantageous when processing materials that are sensitive to

heat. The primary disadvantages of nanoparticles are their lipophilic drug exclusivity and high cleaning requirements.

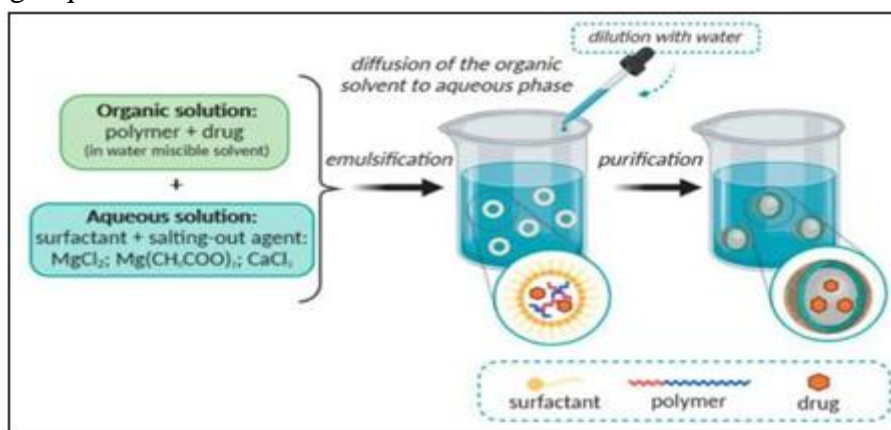


Fig. 5: Schematic Representation of the Salting-Out Method

Dialysis: Dialysis resulted from research into a structure of nanoparticles devoid of surfactants. Dialysis is a widely used method due to its ease of use and ability to manufacture polymeric nanoparticles with a consistent size distribution. Dialysis easily and effectively creates little, uniform products.

PNPs 13 have no surfactants. In the dialysis vessel, a polymer with a specific molecular weight cut-off is dissolved by an organic solvent. Vanguard polymer accumulation and homogenous suspensions result from the decrease in nanoparticle solubility caused by the removal of the solvent from the film. Nanoparticle size and form are influenced by polymer solvents.

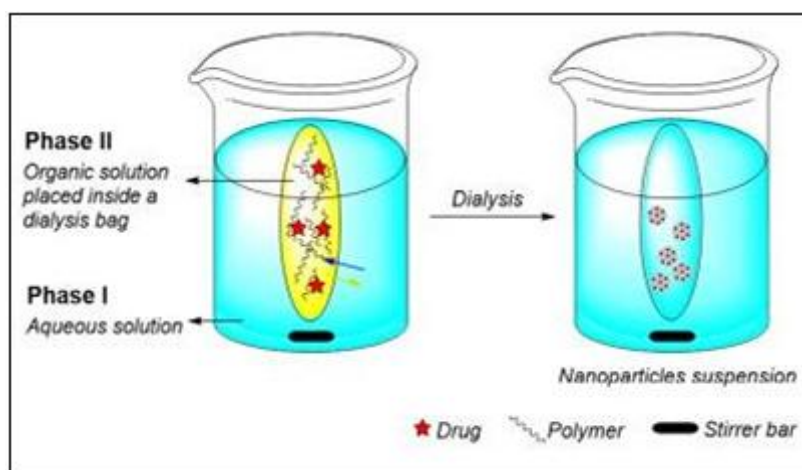


Fig. 6: Schematic Representation of the Dialysis Method

Supercritical Fluid Technology (SCF): The earlier methods make use of organic solvents and surfactants, which can be hazardous to both people and the environment. Understanding this is essential. Drug-loaded PNPs may become toxic and the medication within the polymer matrix may degrade if the original solvent contaminants persist.

Creating precise, flexible, and rapidly scaled nanomedicine production techniques is another difficulty. Researchers have developed ecologically sustainable PNP manufacture techniques to get over these obstacles. Over their critical temperature (T_c) and pressure, supercritical fluids (SCFs) undergo heating and compression. This material possesses both gaseous and liquid-like physicochemical characteristics. Though gaseous, this unusual substance has a liquid-like consistency. The most prevalent supercritical fluid is $ScCO_2$. It is inexpensive, widely available, low-critical, non-toxic, non-flammable, and environmentally benign.

4. PREPARATION OF NANOPARTICLES FROM THE POLYMERIZATION OF MONOMERS:

Emulsion Polymerization: Emulsion polymerization is a highly effective method for the production of polymeric nanoparticles. A continuous phase that is either organic or water-based may be implemented. Energy-generating radicals scatter monomer particles. Through the interaction between monomers and these radicals, polymer chains and particles are produced. The inherent hazard of surfactants necessitates their reduction in use to prevent particle adhesion.

Mini-emulsion Polymerization: Monomers, initiators, water, surfactants, and organic solvents are employed in the mini-emulsion polymerization process. Ultrasonication is one of the highly energetic methods used to manufacture stable monomer nanodroplets. The homogeneity of nanoparticles' droplets renders them more stable than conventional emulsions, owing to their size range of 50–500 nm.

Micro-emulsion Technique: High surfactant concentrations generate thermodynamically stable micro-emulsions. Polymerization does not necessitate ultrasonication. This method generates nanoparticles of diverse shapes and sizes, which typically range from 5 to 50 nanometers.

Interfacial Polymerization: Interfacial polymerization is the consequence of the presence of reactive monomers in two non-mixing liquid phases. Interface polymerization is the process by which nanocapsules, nanofibers, and thin coatings are produced. Conductive polypyrrole and polyaniline nanoparticles are frequently synthesized using this approach.

Controlled/Living Radical Polymerization: One of the most advanced methods for determining the size, weight, and dispersion of nanoparticles is controlled or live radical polymerization. The generation of free radicals reduces chain termination. This method produces nanoparticles that are uniformly sized and well-formed.

Ionic Gelation / Coacervation: Chitosan, gelatin, and sodium alginate are hydrophilic polymers that are biodegradable and are utilized in this method. Polymers with opposing charges generate nanoparticles. Ionic gelation is effective for drug-carrying nanoparticles at ambient temperature and does not require extreme conditions.

Characterization of Morphology: Researchers utilize SEM, TEM, and AFM to examine the morphology of polymeric nanoparticles. These methods reveal the size, shape, surface structure, and interior structure of particles. AFM is capable of exhibiting minute surface details, whereas TEM is capable of distinguishing between nanospheres and nanocapsules.

Particle Size Distribution: Polymeric nanoparticles are typically between 100 and 300 nm in size, although they may be smaller. The optimal size distribution is narrow and unimodal. Scientists utilize DLS, SLS, TEM, and SEM to evaluate particle size and aggregation.

Chemical Composition and Crystal Structure: Atomic absorption spectroscopy and TOF-MS are employed to analyze the chemical composition of nanoparticles. The crystal structure can be determined through the use of electron or particle X-ray diffraction. The crystalline or amorphous nature of nanoparticles is determined by their composition.

Molar Mass Distribution: The molar mass distribution serves as a visual representation of the polymer synthesis and decomposition. Size-exclusion chromatography is employed to determine the molecular weight of polymers. Investigate light scattering through the use of static light scattering.

Surface Area and Chemistry: The high surface-to-volume ratio of nanoparticles induces reactions with other compounds. Surface area estimation frequently involves gas adsorption. Surface chemistry influences the binding and stability of medications. This is examined through the use of XPS and secondary ion mass spectrometry.

Zeta Potential: The stability of the colloid is denoted by the zeta potential, which displays the surface charge of the nanoparticle. Values exceeding ± 30 mV, which indicate satisfactory stability, are indicative of electrostatic repulsion. Additionally, it offers an explanation of surface modification and pharmaceutical loading.

pH of Suspension: The pH of nanoparticles is monitored over time to ascertain their stability. A low pH may suggest surface group ionization or polymer disintegration. pH fluctuations may affect the storage and expiration of medications.

Stability of Polymeric Nanoparticles: Stability is influenced by the substance content, particle size, zeta potential, and pH. Long-term storage may result in the disintegration or clustering of items. The durability and stability of materials are improved through the processes of lyophilization and spray drying.

Drug Association: To determine drug connections, we can utilize ultracentrifugation or ultrafiltration to distinguish unbound drugs from nanoparticle-associated drugs. Nanoparticles are responsible for the distinction between total and unbound substances.

In-vitro Drug Release: Nanospheres demonstrate first-order kinetics as a consequence of polymer degradation or diffusion, according to drug release studies. The zero-order release of pharmaceuticals is typically attributed to the polymer shell of nanocapsules.

Applications of Nanoparticulate Delivery Systems: By transporting pharmaceuticals, polymeric nanoparticles improve their bioavailability, toxicity, and spatial targeting. Gene delivery, cancer treatment, brain targeting, gastrointestinal administration, respiratory delivery, and MRI and optical imaging are all applications that utilize them.

Future Perspectives: The most significant obstacles include size, stability, safety, price control, and large-scale manufacturing. Emulsion-based methodologies are frequently employed; nevertheless, they are susceptible to limitations. Nanoprecipitation is transitioning into a more straightforward and secure alternative.

5. CONCLUSION

Due to their capacity to transport proteins, peptides, vaccines, hormones, and genomes, polymeric nanoparticles (NPs) are promising for the diagnosis and treatment of diseases. Solubility, cellular biodistribution, bioavailability, permeability, targeting, stability, absorption, and localization are all improved by nanoparticles. Patients can also be helped in adhering to the formulation by increasing its accessibility. The principles of the most frequently employed preparation methods in the literature, as well as natural and synthetic polymers, for polymeric nanoparticles. NP materials and technique have the potential to influence drug delivery, release, surface charge, size distribution, and particle size, as demonstrated. When developing NPs, it is imperative to take into account all of these factors. In recent decades, innovation has been focused on the refinement of existing methods and the development of new ones to enable the production of a large quantity of repeatable particles. This has facilitated the commercialization of these formulations. Polymeric nanoparticles are expected to improve the detection and treatment of maladies, as well as satisfy the needs of medication delivery systems.

REFERENCES:

1. Wu S, Neto E, Matos AP, Jafari A, Kozempel J, Silva YJ, Larrea C, Alves Junior S, E. Junior, F. Alexis and R. Oliveira: Radioactive polymeric nanoparticles for biomedical application. *Drug Deliv* 2020; 27: 1544–1561.
2. Ahmad MZ, Mohammed AA, Algahtani MS, Mishra A and Ahmad J: Nanoscale topical pharmacotherapy in the management of psoriasis: Contemporary research and scope. *J Funct Biomate* 2023; 14: 1–19.
3. B. Mukherjee, B. Paul, A. Hoque, R. Sen, S. Chakraborty, A. Chakraborty, Polymeric nanoparticles as tumor targeting theranostic platform, *Design Appli.* (2023) 217.
4. S.R. Pasika, R. Bulusu, B.V. Rao, N. Kommineni, P.K. Bolla, S.G. Kala, C. Godugu, Nanotechnology for biomedical applications, *Nanomaterials* (2023) 297–327.
5. E. Rostami, Recent achievements in sodium alginate-based nanoparticles for targeted drug delivery, *Polym. Bullet.* 9 (2022) 6885–6904.
6. Z. Cheng, M. Li, R. Dey, Y. Chen, Nanomaterials for cancer therapy: Current progress and perspectives, *J Hematol. Oncol.* 14 (2021) 1–27.
7. G. Amoabediny, F. Haghirsadat, S. Naderinezhad, M.N. Helder, E. Kharanaghi, J. Arough, B. Doulabi, Overview of preparation methods of polymeric and lipid-based (niosome, solid lipid, liposome) nanoparticles, *Int. J. Polym. Mate Polymeric Biomat.* 6 (2018) 383–400.
8. R.R. Wakaskar, Role of nanoparticles in drug delivery encompassing cancer therapeutics, *Int. J. Drug Dev. Res.* 3 (2017) 1–17.
9. C.R. Oliveira, D. Almeida, F.F. Padilha, R.R. Souza, R.L. Uniar, Polymeric nanoparticles for the treatment of prostate cancer-technological prospecting and critical analysis, *Recent Patents Nanotechnol.* 17 (2023) 8–14.
10. B. Begines, T. Ortiz, M. Aranda, G. Martínez, M. Merinero, F. Arias, A. Alcudia, Polymeric nanoparticles for drug delivery: recent developments and prospects, *Nanomaterials* 10 (2020) 1403.
11. F. Din, W. Aman, I. Ullah, O.S. Qureshi, O. Mustapha, S. Shafique, A. Zeb, Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors, *Int. J. Nanomed.* 12 (2017) 7291.
12. D.B. Viana, M. Gaedke, N.M. Leao, A. Boker, D.C. Soares, U. Glebe, M.L. Tebaldi, Hybrid protein-polymer nanoparticles based on P (NVCL-co-DMAEMA) loaded with cisplatin as a potential anti-cancer agent, *J. Drug Deliv Sci. Technol.* 79 (2023), 103995.
13. E.A. Madawi, A.R. Jayoush, M. Qalaji M, H.E. Thu, S. Khan, M. Sohail, A. Mahmood, Z. Hussain, Polymeric nanoparticles as tunable nanocarriers for targeted delivery of drugs to skin tissues for treatment of topical skin diseases, *Pharmaceut* 15 (2023) 657.
14. D. Bennet, S. Kim, Polymer nanoparticles for smart drug delivery, *Appl. Nanotechnol. Drug Delivery.* 25 (2014) 8.
15. H. Amani, H. Arzaghi, M. Bayandori, A.S. Dezfuli, H. Toroudi, A. Shafiee, L. Moradi, Controlling cell behavior through the design of biomaterial surfaces: a focus on surface modification techniques, *Adv. Mat. Int.* 13 (2019) 1900572.
16. M.S. Bami, M.A. Estabragh, P. Khazaeli, M. Ohadi, G. Dehghannoudeh, pH-responsive drug delivery systems as intelligent carriers for targeted drug therapy: Brief history,

- properties, synthesis, mechanism, and application, *J. Drug Deliv. Sci. Technol.* 19 (2021), 102987.
17. J. Kleynhans, M. Sathekge, T. Ebenhan, Obstacles and recommendations for clinical translation of nanoparticle system-based targeted alpha-particle therapy, *Materials* 17 (2021) 4784.
 18. S. Kumaresan, S. Vaiyapuri, J.H. Kang, N. Dubey, G. Manivasagam, K.D. Yun, S. W. Park, Additive manufactured zirconia- bio-ceramics for biomedical applications.
 19. E. Avcu, F.E. Bastan, M. Guney, Y.Y. Avcu, M.A. Rehman, A.R. Boccaccini, Biodegradable polymer matrix composites containing graphene-related materials for antibacterial applications, *Acta Biomater.* (2022) 31.
 20. E.R. Radu, S.I. Voicu, T.V.K. Hakur, Polymeric membranes for biomedical applications, *Polymers* 15 (2023) 619.
 21. V.A. Spirescu, C. Chircov, A.M. Grumezescu, E. Andronescu, Polymeric nanoparticles for antimicrobial therapies: an up-to-date overview, *Polymers* 5 (2021) 724.
 22. A. Arun, P. Malrautu, A. Laha, H. Luo, S. Ramakrishna, Collagen nanoparticles in drug delivery systems and tissue engineering, *Appl. Sci.* 23 (2021) 11369.
 23. P.K. Sehgal, A. Srinivasan, Collagen-coated microparticles in drug delivery, *Expert Opin. Drug Deliv.* 7 (2009) 687695.
 24. R. Sarvari, M. Nouri, S. Agbolaghi, L. Roshangar, A. Sadrhaghghi, A.M. Seifalian, P. Keyhanvar, A summary on non-viral systems for gene delivery based on natural and synthetic polymers, *Int. J. Polym. Mat. Polym. Biomat.* 4 (2022) 246–265.
 25. B.E. Abdelmalek, J. Estaca, A. Sila, O. Alvarez, M.C. Guillen, S. Ellouz, M. A. Ayadi, A. Bougatef, Characteristics and functional properties of gelatin extracted from squid (*Loligo vulgaris*) skin, *Food Sci. Technol.* 65 (2016) 924–931.