MINI REVIEW

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Advanced Pharmaceutical Delivery Systems: Utilizing Emulsification and Nanoprecipitation Techniques for Poly (lactic-co-glycolic acid) Nanoparticles

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Abstract

The pharmaceutical industry extensively uses the adaptable synthetic polymer known as poly (lactic-co-glycolic acid) (PLGA). These benefits have led to its use in drug delivery using nanoparticles (NPs) due to its biocompatibility and biodegradability polymer, which has a wide range of uses as a carrier for creating polymeric nanoparticle drug delivery systems. This article overviews the various PLGA nanoparticles (PNPs) and their preparation techniques, including emulsification-solvent evaporation (Single or Double), emulsification solvent diffusion, emulsification reverse salting out, and nanoprecipitation. A brief overview of PNPs' physicochemical behaviour and morphology, drug loading, particle size and distribution, stability, surface charge, drug release, and cytotoxicity evaluation is provided. A diagram of the significant uses of PNP in various drug delivery systems is presented using the results of this survey in conjunction with surface modifications of PNP. This review discusses the preparation techniques and characteristics of drugs, polymers, and stabilisers used in detail.

Keywords: Nanoparticles, PLGA, pharmaceutical applications of PNPs, Drug, Emulsification solvent evaporation, polymeric nanoparticles.

1. Introduction

Nanotechnology is the general term for designing, producing, characterising, and using materials and technologies with the smallest feasible operation at the nanometer scale (Silva, 2004). Polymeric nanoparticles (NPs) are a great way to monitor and disperse harmful substances in vivo since they are believed to have a longer in vivo circulation and better biological stability (Ibrahim et al., 2019). Polymeric nanoparticles (NPs) are a great way to monitor and disperse harmful substances in vivo

since they are believed to have a longer in vivo circulation and better biological stability. They comprise more than 80% of the therapeutics currently used in clinical settings because of their small particle size, which makes it easier for them to pass through smaller capillaries and then be absorbed by cells. This enables effective drug accumulation at the target sites (Rani et al., 2017). Furthermore, because it is made of biodegradable components, the medication might be released continuously over several days or weeks at the target spot. While natural and synthetic polymers are both valuable biological materials for drug administration, the use of synthetic biodegradable polymers has increased(Michael J. Mitchell et al., 2021). Polylactic acid (PLA) and polyglycolic acid (PGA), particularly PLGA, are thermoplastic aliphatic poly(esters) that have attracted a lot of interest in the synthetic polymer market because of their exceptional biocompatibility, biodegradability, and toxicologically harmless metabolites (Gunatillake & Adhikari, 2003).

PLGA is created by the copolymerisation of lactic and glycolic acids; using different ratios of lactide to glycolide allows the production of different types of polylactic acid (PLGA). A common way to identify these forms is to look at the ratio of the monomers used (PLGA 75:25, for instance, denotes a copolymer that is made up of 25% glycolic acid and 75% lactic acid)(Gentile et al., 2014). PLGA has proven to be one of the most effective biodegradable polymers for the creation of nanomedicine. This is primarily because it can go through hydrolysis within the body, producing biodegradable metabolites like lactic acid and glycolic acid (as shown in Figure I). These metabolites are found in nature and can be efficiently processed by the body through the Krebs cycle, leading to a low level of systemic toxicity. The molar ratio of lactic and glycolic acids in the polymer chain, the polymer's molecular weight, its degree of crystallinity, and its glass transition temperature (Tg) all affect how quickly PLGA degrades (Makadia & Siegel, 2011). The degradation duration of PLGA and, thus, the release profile may be altered by varying the molecular weight and lactide/glycolide ratio (Han et al., 2016). Nanoparticles (NPs) can contain many therapeutic agents, from small lipophilic or hydrophilic drugs to larger molecules like DNA or antisense DNA (Gagliardi et al., 2021). The precise delivery of these nanoparticles to organs like the lymphatic system, brain, arterial walls, lungs, liver, and spleen, as well as their long-term systemic circulation, can be achieved by carefully designing the nanoparticles (Michael J. Mitchell et al., 2021). The active component trapped within the polymeric structure of the nanoparticles is sustained release, either through diffusion or the slow degradation of the polymer matrix. The formulation's therapeutic effectiveness is ultimately increased because of the controlled release mechanism's sustained release properties (Makadia & Siegel, 2011). According to the nature of the therapeutic agent intended to be entrapped within the PLGA nanoparticles and the desired delivery route, the most popular approach for producing polymeric nanoparticles is the single or double emulsion method, the solvent diffusion method, and the nano-precipitation method (Chenthamara et al., 2019). The efficacy of hydrophilic bioactive compounds is lower than that of hydrophobic drug encapsulation. (Rao & Geckeler, 2011; Christine Vauthier & Kawthar Bouchemal, 2009).

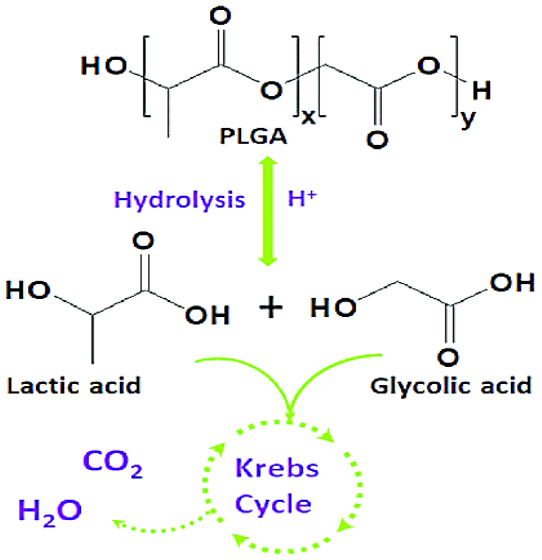

Figure I: Hydrolyzing PLGA yields lactic and glycolic acids. These hydrolysis products are metabolised through endogenous body mechanisms with minimum toxicity(Dodda et al., 2022).

2 .METHOD OF PREPARATION OF PNPs

PNPs has completely recorded in the literature as a bearer framework for different drug delivery frameworks .Various methods are used to prepare polymeric nanoparticles, and the choice of an appropriate method depends upon various factors;

different techniques have been utilised to create PNPs(Krishnamoorthy & Mahalingam, 2015).

As described by numerous researchers, several technologies and devices can produce PLGA nanoparticles via emulsion- or nanoprecipitation-based method (Castro et al., 2022; Qi et al., 2019). The most popular methods are microfluidics, sonication, high shear mixing (HSM), high-pressure homogenisation (HPH), and simple mechanical stirring. Due to their ease of use and simplicity, two commonly used methods include probe sonication and simple mechanical stirring. (Hernández-Giottonini et al., 2020; Huang & Zhang, 2018; Operti et al., 2018). Formulation characteristics may initially modify the physicochemical properties of nanoparticles, as demonstrated by convincing results presented in a recent study by (Hernández-Giottonini et al., 2020). Various methods of preparation are given below:

2.1 .Single Emulsification-solvent Evaporation Method

In this process, an organic phase is produced by dissolving the required amount of PLGA in an organic solvent such as dichloromethane, and later, the drug is given to this organic phase, which leads to dispersion. Then, this dispersion is added to a continually stirred aqueous solution with surfactants like polysorbate 80, forming a stable emulsion. Finally, evaporation removes the organic solvent to get PNPs (Makadia & Siegel, 2011) (Zemljič et al., 2019). This method is schematically shown in Fig.(II).

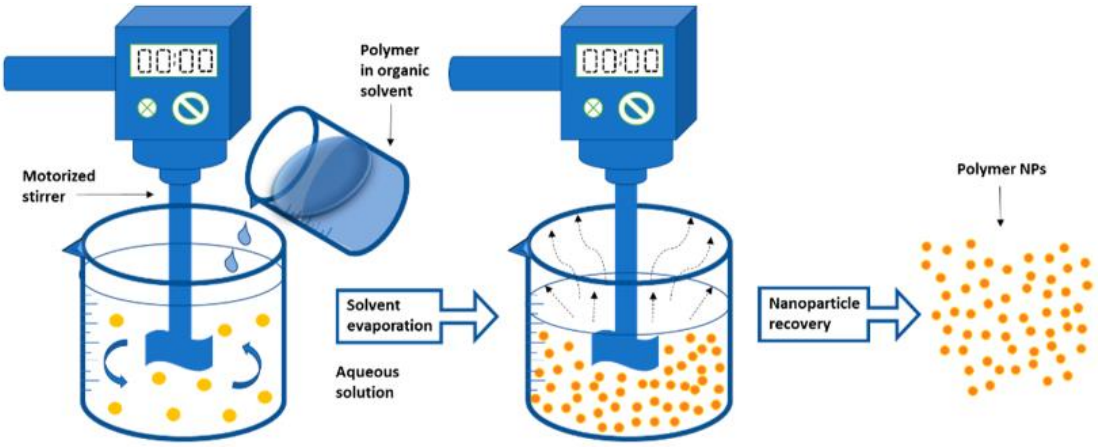

Figure (II). Schematic diagram illustrating the single emulsification solvent evaporation technique (Pulingam et al., 2022)

2.2 .Double Emulsification-solvent Evaporation Method

An appropriate amount of the drug is dissolved in an aqueous phase, followed by an addition of an organic phase, which is developed by dissolving the required amount of PLGA in a volatile organic solvent such as dichloromethane. Further emulsification is accomplished by including the water-in-oil (W/O) emulsion into an aqueous phase followed by simultaneous stirring and afterwards permitting the organic phase to get evaporated, which brings about the development of water-in-oil-in-water (W/O/W) emulsion (Iqbal et al., 2015). This method is schematically shown in Fig. (III).

2.3 .Emulsification Solvent Diffusion Method

In this process, an organic phase is first developed by incorporating the necessary amount of PLGA in a volatile organic solvent such as dichloromethane. After that, the drug is added to this organic phase. Then, the drug-containing organic solution is added to surfactants like polysorbate 80 and polyvinyl alcohol under high-speed homogenisation**.** Finally, water is included in nonstop blending to get PNPs (Kumar et al., 2012; Patil & Patel, 2020). This method is schematically shown in Fig. (IV)

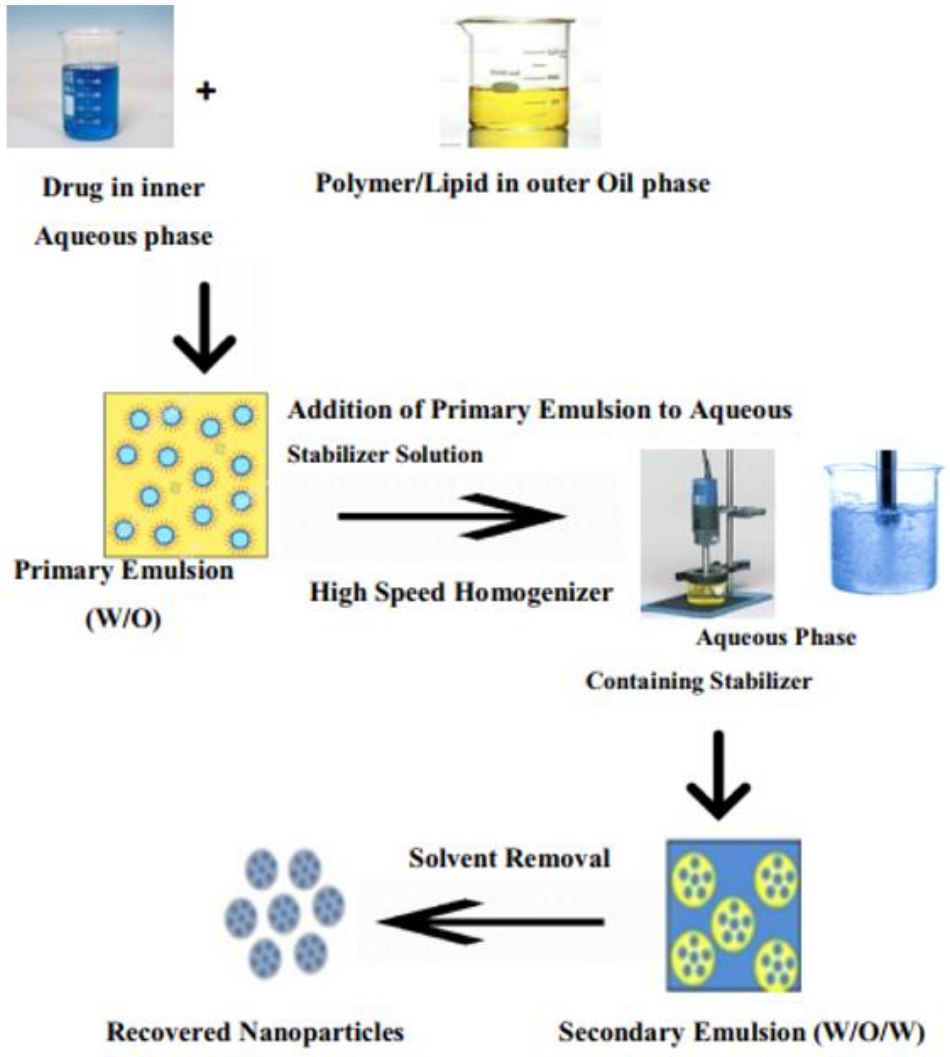

Figure (III). Schematic representation of the method of double emulsion solvent evaporation (Panigrahi et al., 2021)

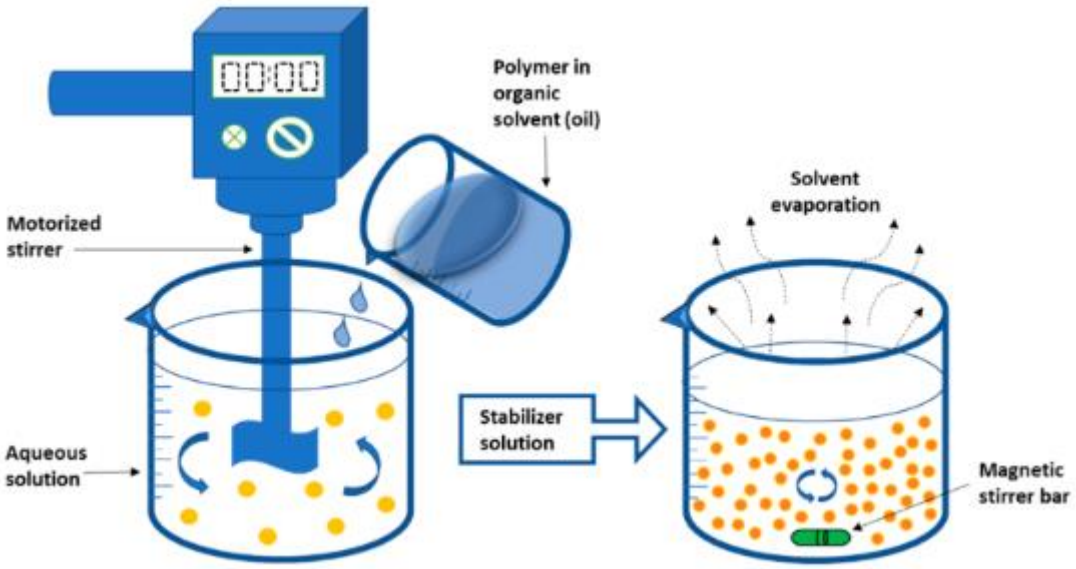

Figure (IV). Schematic diagram illustrating the emulsification solvent diffusion technique (Pulingam et al., 2022).

A modified emulsification solvent diffusion technique was used by (Pereira et al., 2018) to produce PLGA-MET NPs with a mean range of 457.1 nm. PLGA-Cur NPs were successfully introduced into cells, and anti-tumor activity was successfully identified, PLGA-Cur NPs demonstrated better suppression of HL60 and HepG2 cancer cells with lower IC50 values compared to free curcumin. Additionally, confocal microscopy research revealed that curcumin-loaded PLGA NPs increased cancer cell mortality compared to free curcuminv (Pereira et al., 2018).

2.4 .Emulsification Reverse Salting-out Method

In this process, PLGA, and drug are incorporated in a solvent to form an organic phase. After that, an aqueous phase is produced by dissolving salting-out agents such as magnesium chloride with a colloidal stabiliser such as polyvinyl pyrrolidone. Then, magnetic stirring emulsifies the aqueous phase with the organic phase to form oil in water (W/O) emulsion. Finally, PNPs are formed due to the diffusion of the organic solvent into the aqueous solution. Filtration removes the salting-out agents and residual solvent (Vauthier & K. Bouchemal, 2009). This method is schematically shown in Fig. (V).

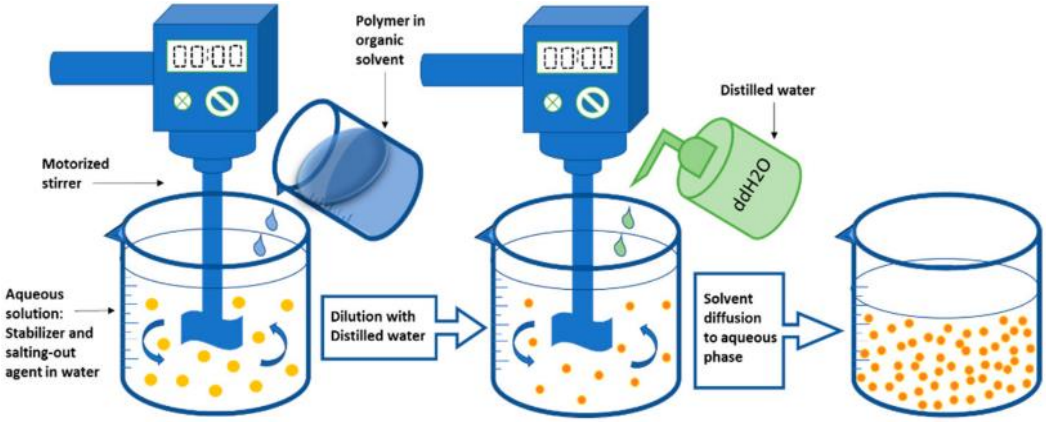

Figure (V). Schematic illustrating the steps for emulsification reverse salting out (Pulingam et al., 2022)

2.5 . Nanoprecipitation

In this technique, PLGA and hydrophobic drugs are first incorporated in a polar solvent such as methanol to form an organic phase. This prepared organic phase is added to an aqueous solution containing emulsifier or surfactant dropwise. The diffusion takes place between solvents that lead to the formation of PNPs (Hernández-Giottonini et al., 2020; Rivas et al., 2017). The method is schematically represented in Fig. (VI).

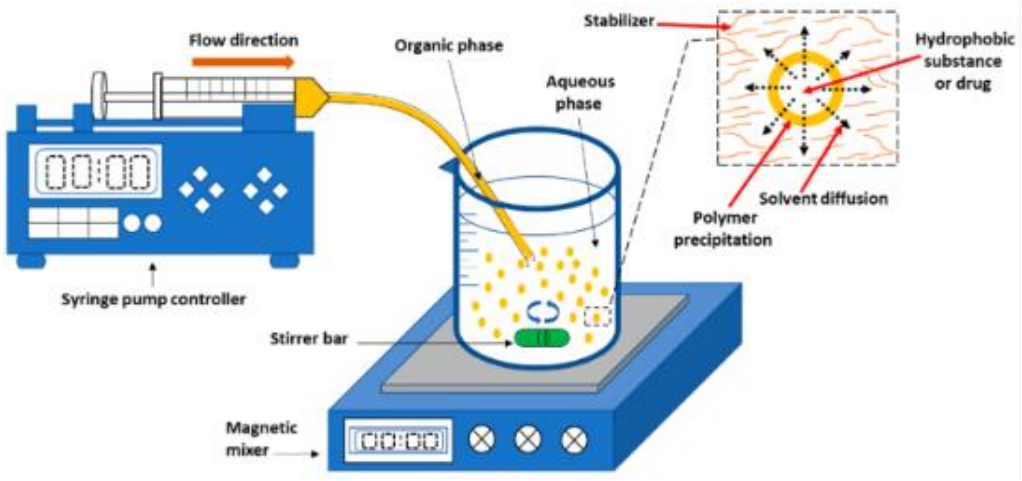

Figure (VI). An illustration of the nanoprecipitation technique (Pulingam et al., 2022)

3 .The physicochemical properties of PNPs

3.1 .Drug Loading/Morphology

Drugs that were loaded into PNPs may be included during PNPs production or after the formation of PNPs by dissolving them in the drug solution. Most PNPs made using the earlier methods have had their morphology examined using TEM, SEM, cryo-TEM, and AFM. SEM is used to determine the shape of the prepared PNPs and their distribution (Basu et al., 2017). TEM is used for the determination of the shape and internal particulars of the prepared PNPs (Jancik Prochazkova et al., 2020; Wang et al., 2014).

3.2 .Particle Size and its Distribution

50 to 600 nm is the recorded mean particle size for most PNPs generated using the previously outlined procedures. Dynamic light scattering is used to determine the particle size and distribution of the prepared PNPs (Huang & Zhang, 2018; McComiskey & Tajber, 2018; Wang et al., 2014). TEM determines the mean particle size of the developed PNPs (Huang & Zhang, 2018).

3.3 . Zeta Potential

Zeta potential is a vital parameter for the determination of the stability of PNPs. Zeta potential affects. The particle stability in suspension. The more favourable or unfavourable zeta potential values are associated with more stable or unstable PNPs due to the reduced particle aggregation, which is the reason for more repulsion between particles (Huang & Zhang, 2018; Yurtdaş Kırımlıoğlu et al., 2016).

3.4. Drug Release

The drug is mainly released from PNPs by diffusion and desorption methods. Numerous parameters impact the medication discharge rate from PNPs, including the type of polymer, the size of PNPs, the biodegradation, dispersion, and solubility of the grid materials (Lee & Yeo, 2015). The equation which is used to release the drug from PNPs is given below:

fraction of drug release at time t, n=pattern of drug release from PNPs, and k = constant, which implies the macromolecular polymer framework properties(Herdiana et al., 2022; Rai et al., 2019).

3.5. Stability

The stability of PNPs is a huge factor in the pharmaceutical field until the loss of therapeutic efficacy (Cheng et al., 2021). Agglomerations of particles, connecting flocculation, and coagulation

are the dominating elements for the physical stability of PNPs (Li et al., 2021). The chemical stability of PNPs relies upon the accompanying conditions like temperature, pH of the medium sort of polymer utilised, and an atomic load of the polymer utilised in detail (Li et al., 2022).

3.6. Cytotoxicity Study & Cellular Uptake

Cytotoxicity of PNPs has been accomplished to determine cell viability. A method known as MTT (3-(4, 5-dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide) has been used to measure cell viability. (Prashant et al., 2010). Efficient cellular uptake is a significant parameter for PNPs. Fluorescence analysis is used to determine the cellular uptake of PNPs (Yu et al., 2019).

4. PHARMACEUTICAL APPLICATION OF PNPs

4.1. Diabetic Drug Delivery

Nanotechnology has opened up new research zones in the drawn-out arrival of medications to decrease the symptoms of the organisation of regular dose structure, particularly for treating diabetes mellitus. Nowadays, PNPs have been extensively used for various anti-diabetic drug deliveries. PNPs have been extensively utilised for anti-diabetic drug delivery, including metformin hydrochloride (Zhao et al., 2020) and insulin (Mansoor et al., 2019; Zhao et al., 2020). In those experiments, PNPs were employed to (i) improve therapeutic effectiveness (M. J. Mitchell et al., 2021), (ii) increase insulin loading capacity in PNPs (M. J. Mitchell et al., 2021), (iii) improve insulin hydrophobicity (Luo et al., 2016), (iv) improve the exemplification proficiency of the peptide and given to diabetic rodents, with decreased BSL, (v) sustaining the release of drug in the GIT (Luo et al., 2016), (v) improving the delivery of insulin(Luo et al., 2016), (vi) facilitating the penetration of NPs in the mucus, (vii) improving the GIT mucoadhesive Ness of PNPs (Amaral et al., 2020), (viii) enhancing GI uptake of insulin, (ix) improving insulin stability

and absorption, (x) increasing drug absorption by lymphatic uptake, (xi) enhancing hypoglycemic effect, (xii) enhancing enzymatic protection and bioavailability of insulin (Luo et al., 2016). Because of poor oral bioavailability and poor drug loading, such as insulin should be restricted until a thorough assessment.

4.2. Cancer Drug Delivery

Cancer treatment delivery is increasing due to the compatibility and biodegradability of polylactic acid (PLGA)(Makadia & Siegel, 2011).PNPs have been widely used for the delivery of anti-cancer drugs, such as taxol (Ma & Mumper, 2013), 9-Nitrocamptothecin (Derakhshandeh et al., 2010), paclitaxel(He et al., 2015), 5-Fluorouracil (Gahtani et al., 2023), docetaxel (Kulhari et al., 2014), thymopentin (Mohanty et al., 2011), xanthones(Tabatabaei Mirakabad et al., 2014), curcumin (Pardeshi et al., 2023; Zhu et al., 2024), endostar (Danhier et al., 2012), hypericin (Dinarvand et al., 2011), rapamycin, doxorubicin, etoposide, cisplatin, and vincristine sulfate & verapamil hydrochloride(Alvi et al., 2022). These PNPs are largely used to slow down drug release, improve anti-tumor efficacy, and control drug release.PNPs were created for the following purposes in the previously mentioned studies:

- ✓ A drug's delayed release over some time up to many days.
- ✓ More effective inhibition of tumour development.
- ✓ Higher antitumor efficacy as compared to free medication.
- ✓ Enhanced NPs display more significant cytotoxicity than free medicine on cancer cells.
- ✓ Greater cell take-up over non-modified particles.
- ✓ Improved adherence of the intestines.
- ✓ Delay drug release for up to four hours.
- ✓ Increasing the bioavailability of curcumin.
- ✓ Indicating sustained release of medication.
- ✓ Inhibiting the development of ovarian tumours.
- ✓ Regulating the growth of cells that cause breast cancer.
- ✓ as an adjuvant therapy for prostate tumours, boosting patient compliance and therapeutic efficacy.
- ✓ Attaining high entrapment efficiency with continuous drug release up to 48 h.
- ✓ Extending the residence time.

4.3. Transdermal Drug Delivery

The transdermal course is commonly considered as “tolerant benevolent” because of the shirking of gastrointestinal reactions, which most need many oral arrangements. NPs increase the efficacy of drug penetration via the skin barrier and the mucous layer. As transdermal drug delivery(Jeong et al., 2019), PNPs were developed for: (i) in transdermal delivery of minoxidil for alopecia treatment (Han et al., 2022), (ii) enhancing transdermal delivery of indomethacin (Zhang et al., 2013), (iii) improving the transdermal delivery of fluefenamic acid (Malinovskaja-Gomez et al., 2016), and (iv) sustaining drug release for 72 hr (Dilawar et al., 2022).

4.4. Protein and Vaccine Delivery

PNPs have been utilised to deliver protein and peptide drugs. PNPs can encapsulate antigenic proteins/peptides into their surface(M. Allahyari & E. Mohit, 2016; Petrizzo et al., 2015). A few things can impact protein discharge rates from PNPs, which inherent highlights of the PLGA can characterise. The accessible PNPs embodying

Antigens of various disorders, for example, hepatitis B antigens, have been considered. Immunostimulants (IS) and antigens co-conveyance with PNPs can prevent the fundamentally detrimental effects of immunopotentiators and stimulate both dendritic cells (DCs) and characteristic executioner (NKs) cells, subsequently improving the restorative viability of antigen-stacked PNPs(M. Allahyari & E. Mohit, 2016; Ma et al., 2012; Rietscher et al., 2016). According to Thomas et al., PNPs containing HBsAg increase secretory IgA, IL-2, and IFN-g levels when

administered with hydrophobic materials (Santos et al., 2012). PNPs layered with Caryota mitis profilin to suppress the eosinophil and Th2 cytokine separation statement (Mojgan Allahyari & Elham Mohit, 2016). Encapsulation of poly (I: C) or CpGODN with OVA antigen in PNPs was developed to induce potent antigen-specific CTL responses(Gutjahr et al., 2016). To improve the RGD in vitro model's transport, modified PNPs carrying OVA antigen were developed. (Silva et al., 2016). Changed PNPs containing HBsAg were created to prompt fundamentally higher mucosal and systemic immune responses as compared to non-targeted NPs (Wang et al., 2020).

PNPs are used as vaccine delivery to convey exogenous antigens that can be cross-introduced through MHCI buildings to CD8+ cells(Gutjahr et al., 2016). PNPs appear to have the exceptional capacity to arrive at the MHCI pathway after their disguise by DCs (Baleeiro et al., 2015; Hewitt, 2003).

CONCLUSION

In the greater part of the case, in vitro examinations convey thankful outcomes. Sadly, these outcomes are regular remote reality in vivo. The money-related perspective must be considered to make them attractive as another pharmaceutical dose structure for patients and the pharmaceutical business everywhere throughout the world. Further advances are required to transform the idea of medication-stacked PNPs innovation into a sensible, down-to-earth application in the up-and-coming age of medication conveyance frameworks.

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