A REVIEW- POLYMER-BASED NANOPARTICLES AS ORAL ANTICANCER DRUG DELIVERY SYSTEMS

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Abstract-

Breast cancer (BC) becomes the most commonly diagnosed cancer among women around the globe. Oral chemotherapy is preferred in the first place for its convenience and potential to improve patient's quality of life. Non-invasiveness along with improved patient convenience is the biggest ostensible advantage of orally administered drugs. Oral therapy reduces the cost of inpatient and ambulatory patient care services, and ancillary support by healthcare personnel like nurses and technicians. However, oral delivery is restricted by various physicochemical constraints. The significant physicochemical constraints to the efficient oral absorption of anticancer drugs include poor solubility in the aqueous intestinal milieu. In addition, they are either substrates for the biological transporters including P-glycoprotein (P-gp), metabolizing enzyme, cytochrome P450, or both, resulting in a considerable loss owing to their expulsion or first-pass metabolism. Polymer-lipid hybrid nanoparticles (PLHNPs) are an emerging nanocarrier platform made from building blocks of polymers and lipids. PLHNPs integrate the advantages of biomimetic lipid- based nanoparticles (i.e., solid lipid nanoparticles and liposomes) and biocompatible polymeric nanoparticles. The hybrid architecture can provide advantages such as controllable particle size, surface functionality, high drug loading, tunable drug release profile, and improved stability in GIT.

1.0 INTRODUCTION

1.1. CANCER- A brief insight

Cancer is considered one of the hardest health-related threats worldwide. In 2020, World Health Organization (WHO) estimated 19.3 million new cancer cases and 10 million cancer-related deaths (Sung et al., 2020). Cancers are mainly developed due to abnormalities in the inherited material i.e., genes of normal healthy cells owing to exposure to carcinogens like tobacco smoke and chewing, radiation, chemicals, or other infectious factors (Hulvat, 2020). This fatal disease is characterized by the uncontrolled multiplication (cell division) of cancerous cells and can invade adjacent normal healthy tissues/organs. The uncontrolled multiplication of cancerous cells invades and destroys the adjacent normal healthy cells/tissues and becomes a mass. The developed mass is called a solid tumor (Gonzalez-Valdivieso et al., 2021). When solid tumors grow to a certain size (nearly 1–2 mm^3), their uncontrollable growth rate requires a significant increment in the demand for oxygen, nutrients, and growth factors. A high requirement of oxygen, nutrient, and growth factors in the development of tumors result in the formation of their own blood vessel system and this

phenomenon is called angiogenesis (Yezhelyev et al., 2006; Mattheolabakis and Mikelis, 2019). The blood vessels of solid tumors are characterized by a leaky and unorganized vasculature system that can enhance the interstitial fluid pressure that reduces the blood supply to them, which debilitates the chemotherapeutic drug delivery (Chauhan et al., 2012). It affects people at all stages of life with the high risk for most cancer types increasing with age. The most commonly diagnosed cancer worldwide are lung, breast, colorectal, and stomach cancers and contributed to almost 40% of all cases. As per WHO, with almost 12% of all new annual cases, breast cancer become the most common cancer globally in 2021 (WHO, 2021). In India, cancer is the third most common cause of death accounting for 0.5 million deaths per year, and is, therefore, a major concern for public health. The incidence rate has been increasing in most parts of the world, but there is a great difference between developed and developing countries. The incidence rate is higher in developed countries but mortality is relatively higher in developing and poor countries due to short of early detection and treatment facilities (Mathur et al., 2020).

1.2. ORAL CHEMOTHERAPY

To date, most chemotherapeutic drugs are delivered intravenously (i.v) in the management of cancer (O'Neill and Twelves, 2002; Khandelwal et al., 2012). Although there has been a dramatic shift in the administration of chemotherapeutic agents, they are now been given orally differing from the traditional parenteral route (Roop and Wu, 2014; Rizwanullah et al., 2020a). In recent times, oral chemotherapy trends have been observed due to continuous growth in the clinical application of oral cytotoxic drugs, and presently more than 20 oral anti-cancer drugs have been approved for clinical application in the United States and Europe (Weingart et al., 2008; Ruddy et al., 2009; Given et al., 2011). It has mostly been the preference of patients to choose oral therapy relative to i.v. administration simply because of ease of administration and home-based therapy. It is also required that the toxicities associated with oral therapy should not be higher than i.v. therapy and the efficacy should be the same. Improved compliance, tolerance, easy administration, and comparable efficacy of oral therapy relative to i.v. therapy is the major reason behind the choice of oral chemotherapy over i.v. therapy. Compliance is vital for oral chemotherapy because it decides the dose intensity of the therapy and eventually therapeutic efficacy as well as the toxicity of the therapy. A lot of surveys indicate that maximum patients favor oral therapy over i.v. therapy (Liu et al., 1997; Ishitobi et al., 2013; Eek et al., 2016). In a survey, Liu et al. found that 89% of patients favor oral therapy over i.v. therapy. They found that oral chemotherapy was primarily favored due to easy and home-based therapy (57% of patients), thereby avoiding the painful insertion of a catheter in the vein (55% of patients) (Liu et al., 1997). Other reasons were the negative earlier experiences with i.v. therapy and a lesser access rate to the oncology service. The oral administration of cytotoxic agents provides longer drug exposure when compared to i.v. infusion. Drug exposure is dependent on exponential factors which are time and concentration. A drug with a shorter biological half-life achieves better exposure time when given as a nonstop infusion. The exposure time has profound effects on drug toxicities and efficacy. An added advantage of oral chemotherapy is the decrease in the utilization of various resources for inpatient and ambulatory care services. There is also an

improved quality of life with oral chemotherapy. Despite their numerous advantages for convenience and patient compliance, there are however potential challenges with the oral use of chemotherapeutic agents, which clinicians are desired to be aware of and take necessary steps to circumvent or mitigate (Aisner, 2007; Cardoso et al., 2016). Lastly, keeping in mind the rising prices of anticancer therapy, oral therapy of cytotoxic agents is appealing as avoids the requirement of hospitalization, doctors, paramedical staff, and infusion tools. However, most cytotoxic drugs show very limited oral absorption from the GIT due to complex physicochemical characteristics of the drug, instability in the hostile GI environment, and biological barriers present in the GIT (Banna et al., 2010; Mazzaferro et al., 2013). Before systemic absorption, the drug has to go through various biological events including dissolution in GI fluid, passing through the GI epithelial or transmembrane transport in different pH conditions, pre-systemic metabolism, and efflux via para-glycoprotein (P-gp; a multidrug efflux protein) (Koolen et al., 2010; Pridgen et al., 2015). Considering the above challenges that lead to low drug availability, significant efforts have been made in this area for the success of anticancer oral therapy.

1.3. NANOTECNOLOGY

A nano-revolution in polymeric medicine opens the door for safe and effective oral chemotherapy as it shows significant potential to defeat the limitations encountered with conventional oral chemotherapy. In the last three decades, a number of natural as well as synthetic biodegradable polymers have been extensively investigated as biomaterials for chemotherapeutic drug delivery. The unique physicochemical and biopharmaceutical characteristics include excellent biocompatibility, structural variety, controlled degradation in the biological fluids, and non-immunogenicity. Nanoparticles made up of biodegradable polymers are nano-colloidal cargos characterized by a particle size range of 10–1000 nm (Thanki et al., 2013; El-Say and El-Sawy, 2017). As per the current trends, natural polymers such as chitosan, dextran, pectin, and starch as well as synthetic polymers such as poly lactic-co-glycolic acid (PLGA), polylactic acid (PLA), poly(ε-caprolactone) (PCL) are extensively used for therapeutic delivery of a number of cancer chemotherapeutics (Kumari et al., 2010; Banik et al., 2016). In the 21st century, scientists around the world studied extensively and evaluated a number of anticancer drugs for improved oral bioavailability and therapeutic efficacy. The major advantages of these nanoparticles include excellent stability in the harsh GI milieu due to their unique structural characteristics, controlled release of encapsulated drugs, and ability to permeate across intestinal cells. In addition, the ability to encapsulate anticancer drugs in their unique matrix in the amorphous state makes them excellent biomaterials to encapsulate various hydrophilic as well as lipophilic drugs. Furthermore, their favorable physiological characteristics such as biocompatibility and biodegradability further enhance their application in chemotherapeutic drug delivery for oral chemotherapy (Plapied et al., 2011; Thanki et al., 2013; Mishra and Chaurasia, 2017).

For biomedical applications, most of the nanoparticles are prepared from biodegradable as well as biocompatible polymers from natural or synthetic origins that are approved by the US-FDA (Food and Drug Administration) and considered safe for human use (Hrkach et al., 2012; Taghipour-Sabzevar et al., 2019). For long-term treatment and to reduce dosing frequency, polymer-based can be modulated for sustained release of encapsulated anticancer drugs (Ensign et al., 2012). Due to their size in the nanometric range (ideally 10-300 nm), nanocarriers show a large surface area for interaction with epithelial surfaces that results in significantly higher absorption (He et al., 2012; Pridgen et al., 2015). Through the development of polymer-based nanocarriers, many obstacles can be defeated for anticancer drugs for oral chemotherapy. In this regard, polymer lipid hybrid nanoparticles, polymeric nanoparticles, polymeric micelles, and dendrimers are the most common polymer-based nanocarriers that are extensively investigated to deliver anticancer drugs for oral chemotherapy.

1.3.1. Polymeric nanoparticles

Polymeric nanoparticles (PNPs) are the most common among various polymer-based nanocarriers. During the past few decades, the significance of PNPs has increased exponentially in oncology. PNPs represent a large diversity in both structure and physiochemical properties. The main reason for its versatility is the huge variety of monomers that may be used to build up the polymer architectures. The polymers selected for the drug delivery system must full fill a number of requirements including biocompatibility, suitable biodegradation kinetics, and non-immunogenic, can load various chemotherapeutics (Taghipour-Sabzevar et al., 2019). PNPs show the ability to enhance the biopharmaceutical performance of encapsulated drugs such as pharmacokinetic profiles and therapeutic efficacy (Dang and Guan, 2020). Typically, the size of these nanocarriers should be less than 100 nm, but in practice, particles sized up to 300 nm are included in this category. These nanocarriers can differ in terms of their morphology, composition, particle size, zeta potential, and, other physicochemical properties (Guo et al., 2016; Khan et al., 2019). At present, various polymers like chitosan, PLGA, PCL, PLA, etc., that are approved by US-FDA are considered biodegradable, biocompatible, non-immunogenic, and non-toxic for therapeutic drug delivery and are widely used (Taghipour-Sabzevar et al., 2019).

1.3.2. Polymeric micelles

Polymer micelles are typically the self-nano assemblies of macromolecules, which are particularly prepared from the block copolymers by non-covalent bonds. Amphiphilic polymers are characterized by a hydrophobic/lipophilic tail and a hydrophilic head. These nanocarriers are formed by the self-assembly of amphiphilic polymers/block polymers at their critical micelle concentration (CMC) (Ghosh and Biswas, 2021; Perumal et al., 2022). The polymeric micelles that are particularly prepared from block polymers have a core-shell structure. The exceptional physicochemical characteristics of these micelles include low CMC, small size, and spherical shape of the final structure. These physicochemical characteristics are particularly dependent upon the polymer chains in copolymer blocks. Polymer micelles with lower CMC show much better drug loading and colloidal stability (Kotta et al., 2022). The salient features of polymeric micelles like

high loading capacity, excellent stability in physiological conditions, controlled drug release, and easy surface modification makes them an ideal nanocarrier for chemotherapeutic drug delivery for oral chemotherapy (Thanki et al., 2013; Zhang et al., 2014).

1.3.3. Dendrimers

Dendrimers are hyperbranched nanosized spherical polymeric particles characterized by tree-like arms or branches connected from their central core. In dendrimers, the chemotherapeutic drugs can be encapsulated in their central hollow cavity. Further, the drug can also be loaded on the surface/terminals by covalent bonding (Soni et al., 2017; Kim et al., 2018). They have the ability to enhance the specificity and bioavailability of anticancer drugs at the tumor site. Moreover, due to their ultrasmall particle size, the clearance from the systemic circulation via the reticuloendothelial system is also reduced significantly (Singh and Kesharwani, 2021). Easy modulation in their physicochemical characteristics in terms of morphology, size, monodispersity, solubility, and drug loading makes them excellent nanocarriers for chemotherapeutic drug delivery (Abbasi et al., 2014; Kesharwani et al., 2014).

1.3.4. Polymer-lipid hybrid nanoparticles (PLHNPs)

PLHNPs are one of the most advanced nanocarriers for chemotherapeutic drug delivery in oral chemotherapy (Rizwanullah et al., 2020b). PLHNPs are composed of biodegradable and biocompatible lipids and polymers. PLHNPs demonstrate the combined benefits of both lipid as well as polymer-based nanoparticles. The hybrid architecture of PLHNPs provides some potential benefits like small particle size, high encapsulation efficiency, tuneable and sustained drug release, improved aqueous solubility, and stability in the different environments of the GIT (Hallan et al., 2016; Rao and Prestidge, 2016; Date et al., 2018). PLHNPs have the ability to encapsulate more than one lipophilic/hydrophilic chemotherapeutic drug due to the presence of two or more layers of polymer and lipid (Soares et al., 2020).

During the preparation of PLHNPs, the ratio of two different chemotherapeutic drugs can be controlled precisely. Two drugs with different physicochemical properties are co-delivered to tumor cells for combined effect and to avoid multi-drug resistance (MDR) (Garg et al., 2018). Lipophilic drugs can be encapsulated into the polymeric core, while hydrophilic drugs can be encapsulated in the bilayer surface. PLHNPs exhibit significantly higher drug loading ability for lipophilic drugs compared to other nanoparticles, higher storage stability, negligible leakage, and controlled release of drug (Jose et al., 2018). The controlled drug release profile of PLHNPs is because of the slow degradation of polymers present in the core and the diffusional barrier of the lipid shell. The lipid shell of PLHNPs can be decorated as a monolayer or bilayer, depending upon the release characteristics required, and is also based on the drug to be encapsulated in the lipid shell. In addition, targeting ligands can be conjugated to the lipid shell of PLHNPs. By surface decoration with different targeting ligands, PLHNPs can be directly targeted to the tumor site and enhance therapeutic efficacy (Garg et al., 2018).

1.3.5. Classification of PLHNPs

Generally, the PLHNPs are classified on the basis of arrangements in the polymers and lipids within the hybrid system. In the hybrid structures, polymers enhance overall particle stability and modulate the release of encapsulated drugs from the hybrid matrix. However, lipids provide more space for drug encapsulation and biocompatibility of the system. Therefore, the advancement in the LPHNPs exhibits much better and prolonged therapeutic efficacy.

1.3.5.1. Polymer core lipid-shell hybrid nanoparticles

As the name suggested, the polymer core lipid-shell hybrid nanoparticles are composed of a polymer core that is covered by mono/bilayers of a lipoidal shell as depicted in **Figure 1.1A.** The polymeric core significantly enhances the stability of the outer lipoidal shell. The biodegradable polymeric core with a stable outer lipoidal shell makes these PLHNPs an excellent nanocarrier for chemotherapeutic drug delivery in the management of solid tumors (Troutier et al., 2005; Mandal et al., 2013; Garg et al., 2018). The amphiphilicity of biodegradable polymers and lipids promotes the encapsulation of both lipophilic as well as hydrophilic chemotherapeutic drugs within the hybrid system. During the development of these LPHNPs, different physicochemical properties such as size, loading capacity, charge, solubility, release, and colloidal stability can be modulated by modification in the polymer: lipid ratio (Mohanty et al., 2020).

1.3.5.2. Monolithic PLHNPs

Monolithic PLHNPs are the simplest among different PLHNPs and are simply mixed nanosystems of polymer/copolymer and lipids with the help of surfactants. In this system, the lipids are scattered in a polymeric/copolymeric matrix as depicted in **Figure 1.2B** (Shi et al., 2011). The monolithic PLHNPs systems are much similar to colloidal polymeric nanocarriers. In this nanocarrier, phospholipids helped to form a carrier-like structure which is an integral part of the system. In addition, the modification of lipoidal layers with a PEG chain provides flexibility to the nanocarrier. The ratio of the polymer and lipid can easily be adjusted to modulate the physicochemical characteristics of the nanocarrier and can reduce systemic toxicity (Mohanty et al., 2020).

1.3.5.3. Core-shell type hollow PLHNPs

The core-shell type hollow PLHNPs comprises an inner hollow positively charged lipidic core, after that a polymeric layer in the middle, and an outer PEG lipoidal layer as depicted in **Figure 1.1C.** (Zhang et al., 2008). The inner hollow core of the system is filled with water/or buffer. Due to the positive charge, the lipids in the inner core encapsulate the drug more efficiently compared to the PLHNPs with a polymeric core (Pautot et al., 2003). In addition, because of the outer lipid-PEG layer, these nanocarriers escape the uptake by macrophages and enhance the stability in the biological fluids (Shi et al., 2011). During the development of these nanocarriers, the concentration of cationic lipids for the inner core, density of the PEG chain on the outer layer, and molecular weight of the polymers are adjusted to modulate its physicochemical

characteristics (Shi et al., 2011; Sivadasan et al., 2021).

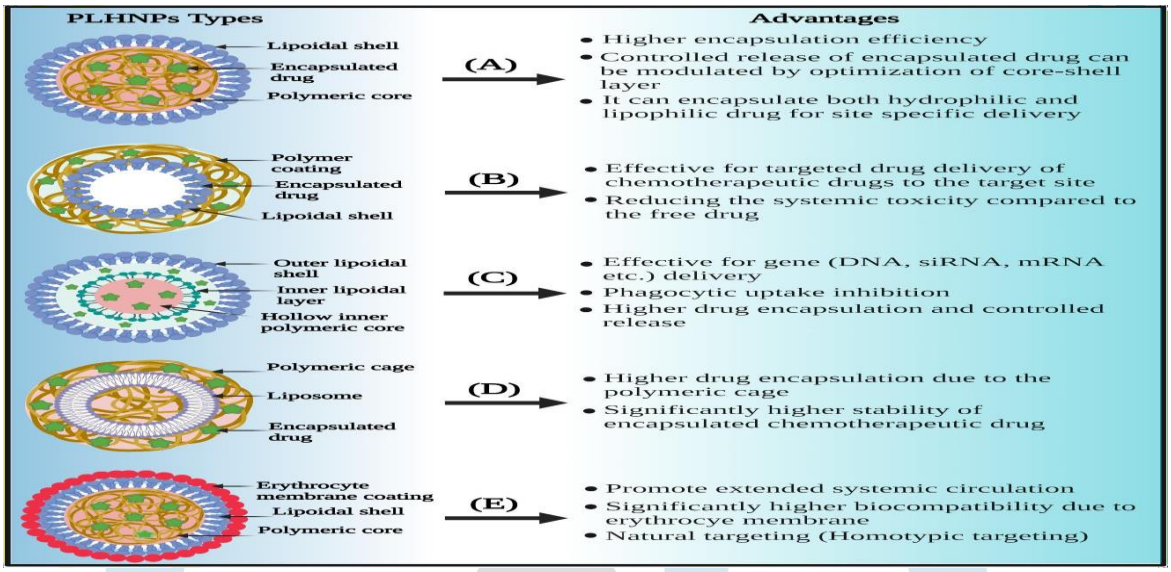

Figure 1.1: Different types of PLHNPs and their advantages: (A) Polymer core lipid shell, (B) Monolithic PLHNPs, (C) Core shell-type hollow PLHNPs, (D) Polymer-caged liposome, and (E) Erythrocyte membrane coated PLHNPs.

1.3.5.4. Polymer-caged liposome

As the name suggests, the structural arrangement of these nanocarriers involves the surface coating of liposomes with biodegradable polymers/copolymers as depicted in **Figure 1.2D.** The surface modification not only imparts surface functionality to the nanocarrier but also enhances its therapeutic efficacy by site-specific targeting and controlled release of the encapsulated drugs. Among all the other PLHNPs, these hybrid nanocarriers show the highest stability in the biological fluids and stimuli-responsive release of encapsulated drugs. In addition, the polymeric cage protects the drug from the external harsh environment and encapsulated drugs can be triggered in specific biological conditions. Further, the polymer coating provides better colloidal stability, sustained drug release, and high loading capacity to the hybrid nanocarriers (Lee et al., 2007).

1.3.5.5. Cell membrane-camouflaged PLHNPs

PLHNPs are coated with cell membranes (e.g., erythrocytes) to develop membrane- camouflaged PLHNPs, as depicted in **Figure 2E.** These hybrid nanocarriers are also called biomimetic hybrid nanocarriers due to their surface chemistry which mimics the natural membranes (Vijayan et al., 2018). The PLHNPs are coated with cell membranes by extrusion technique. The coating of PLHNPs with red blood cells (RBC) becomes the natural vehicle for chemotherapeutic drug delivery, therefore, these nanocarriers can easily escape the uptake by macrophages present in the biological system (Tanaka and Sackmann, 2005). In this system, the drugs are encapsulated in the lipophilic polymeric core, and the lipid density in the outer natural membrane enhances the sustained release of drugs. With the development of these hybrid nanocarriers, the biological barriers in therapeutic drug delivery can be easily defeated. These hybrid nanocarriers show prolonged half-life and stability in the biological system thereby enhancing therapeutic efficacy (Tanaka et al., 2015).

1.3.6. Method of preparation of PLHNPs

Generally, PLHNPs are prepared by two broad methods; (i) two-step method and (ii) one- step method. Both methods can be further subdivided to prepare different PLHNPs. All the methods are discussed in detail in the following section.

1.3.6.1. Two-step method

Initially, the two-step method was adopted for the development of PLHNPs. This method is primarily used to develop the PLHNPs with monolayer, bilayer, or multilayer lipoidal shells. In this technique, vesicles of cationic lipids are combined with anionic polymeric/copolymeric particles by electrostatic interaction to develop PLHNPs. In the first step, the lipoidal shells/nanoparticles are prepared by different techniques such as melt emulsification, solvent emulsification, micro-emulsification, ultrasonication, homogenization, and solvent injection. In the second step, the polymeric cores are prepared by dissolving biodegradable polymers of natural or synthetic origin in organic solvents such as N, N, Dimethylformamide (DMF), chloroform, acetone, methylene chloride, etc., and then the polymeric solution is added in the lipid nanoparticles dispersion (prepared in the first step) and mixed properly by simple vortexing, sonication, or needle extrusion to develop PLHNPs (Hadinoto et al., 2013; Mandal et al., 2013; Dave et al., 2019). The two- step method for the development of PLHNPs is diagrammatically illustrated in **Figure 1. 2.**

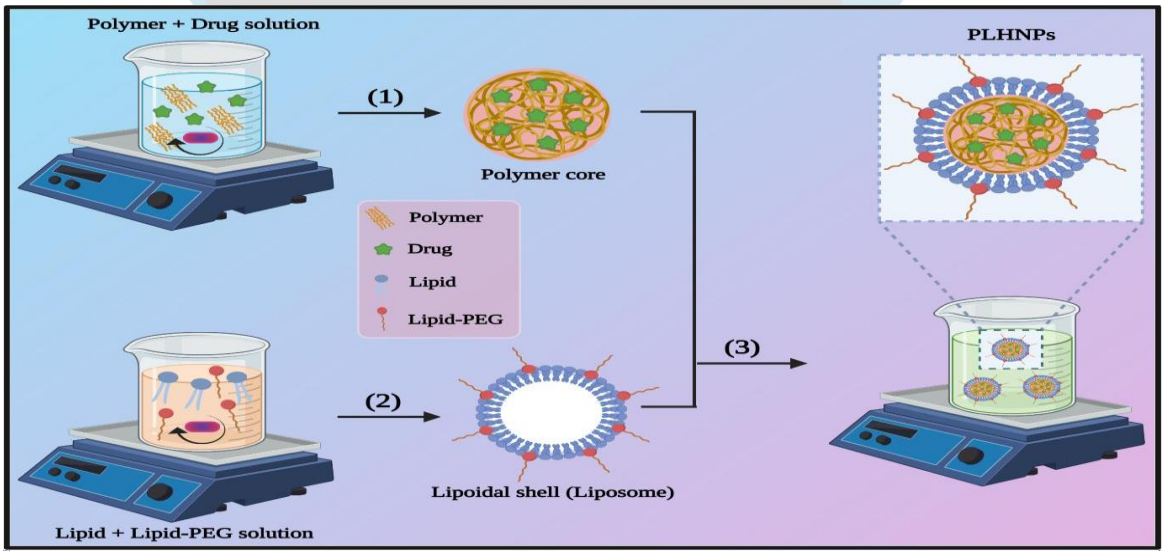

Figure 1.2: The diagram illustrates the development of PLHNPs by the two-step method;
(1) preparation of drug-containing polymer core, (2) preparation of lipidic nanoparticles (liposomes; lipoidal shells) with lipid/lipid-PEG and (3) continuous mixing of polymeric solution and lipoidal shells to develop PLHNPs.

Further, the two-step method is subdivided into two categories; (i) conventional two-step approach and (ii) non-conventional two-step approach.

1.3.6.1.1. Conventional two-step approach

The conventional approach is mainly used for small-scale production of PLHNPs. In the first step, the polymeric nanoparticles are prepared by different techniques such as nanoprecipitation, homogenization, or solvent evaporation. In the second step, a lipoidal shell is prepared by dissolving the cationic lipids in an organic solvent followed by vaporization by using a rotary evaporator. After that, the lipid nanoparticles are poured into the flask bearing a thin film of lipoidal shell and mixed properly. Then, the resulting mixture is taken and subjected to vortexing or ultra-sonication at room temperature to develop PLHNPs. Finally, the resulting solution is centrifuged to separate the final formulation (Hadinoto et al., 2013; Dave et al., 2019).

1.3.6.1.2. Non-conventional two-step approach

The non-conventional approach is primarily used for large-scale production of PLHNPs. In this approach, PLHNPs are prepared by different techniques such as spray drying and soft lithography particle molding. In the spray drying method, biodegradable polymers are used to develop polymeric nanocarriers with small particle sizes. Then, polymeric nanocarriers are dispersed in the organic solvent (chloroform, acetone, dichloromethane, dimethyl sulfoxide, etc.,) containing different lipids. After that, the resulting suspension of lipoidal polymeric nanocarriers is further spray-dried to develop PLHNPs (Wang et al., 2012). The soft lithography molding method also called particle replication in nonwetting templates (PRINT) technique, is mainly used to develop PLHNPs for the delivery of different genetic materials (Hasan et al., 2012). In this technique, firstly, the biodegradable polymers and genetic materials like siRNA, are dissolved in organic solvent at room temperature and then shed into a surfactant i.e., polyvinyl alcohol (PVA) coated polyethylene terephthalate (PET) sheet. After that, the PET sheet is heated while in conformal contact with a PRINT mold and allowing the polymer to pour into the mold. After solidification, heating is stopped and the plate is returned to the ambient temperature to develop polymeric nanocarriers. Then, the polymeric nanocarriers are released from the PVA-coated PET sheet by dissolving the PVA layer with an aqueous solution of lipids. During this procedure, the PLHNPs are formed (Hasan et al., 2012; Dave et al., 2019).

1.3.6.2. One-step method

This conventional method is advantageous over the two-step approach owing to the benefits of low-cost and easy production and being highly scalable. Separate preparation of polymeric as well as the lipoidal shell is costly and time-consuming. Therefore, to overcome the limitations of the two-step method, a one-step method was discovered which involves simple organic solutions bearing lipophilic drugs and excipients in the aqueous solution bearing surfactants and other water-soluble excipients by nanoprecipitation or emulsification solvent evaporation techniques. The one-step method for the development of PLHNPs is diagrammatically illustrated in **Figure 1.3.**

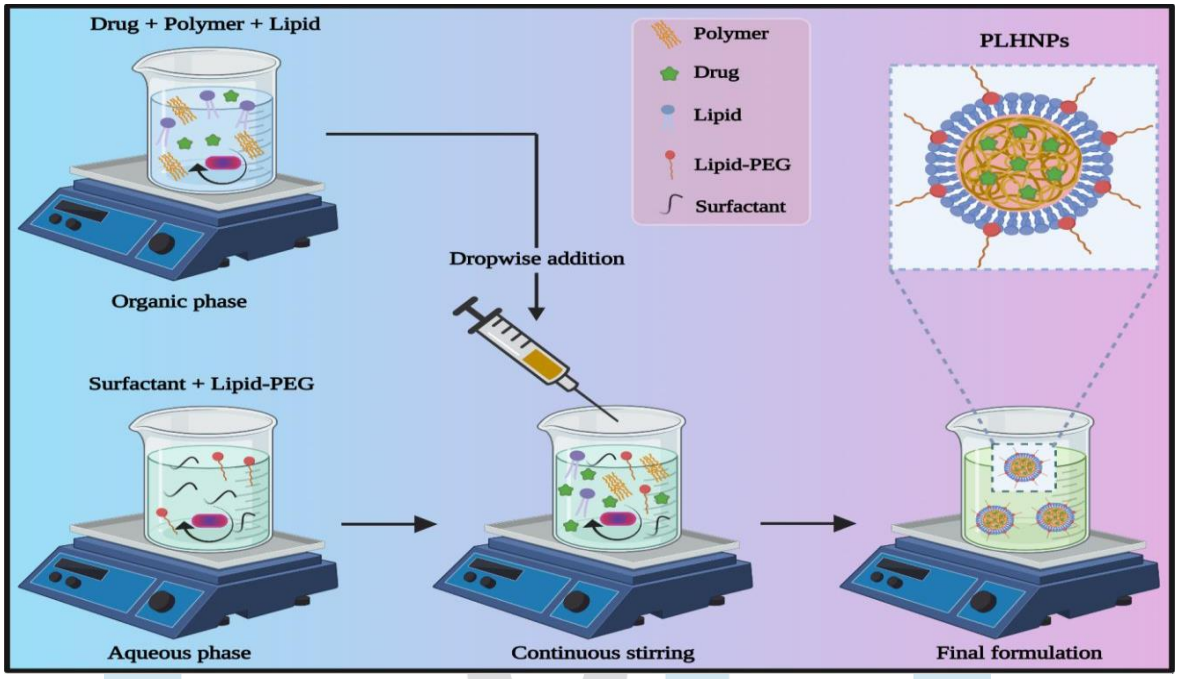

Figure 1.3: The diagram illustrated that the organic and aqueous phases are prepared separately and then the organic solution is added dropwise to the aqueous phase and mixed gently by continuous vortexing.

1.3.6.2.1. Nanoprecipitation method

In this method, PLHNPs are prepared by dissolving the lipophilic polymers and drugs in an organic solvent (organic phase), similarly, the surfactant and other water-soluble excipients are dissolved in water (aqueous phase) to form a homogeneous solution by continuous stirring at room temperature. Then the organic phase is added to the aqueous phase in a dropwise manner to precipitate the polymer, and the lipid molecule self-assembles around the core of the polymer. Afterward, the resulting PLHNPs are subjected to solvent evaporation to remove the organic solvent and then centrifuged to remove extra polymer and lipid (Garg et al., 2015; Rouco et al., 2022). The particle size and size distribution of the developed PLHNPs are highly dependent on the polymer and lipid ratio, solvent volume, and speed as well as the time of mixing of the solution. This method is widely used to develop small-sized PLHNPs (generally <200 nm) with high production yield. The particle size, loading capacity, and dissolution rate can be modulated by adjusting the polymer and lipid ratio (Hadinoto et al., 2013; Sivadasan et al., 2021).

1.3.6.2.2. Emulsification solvent evaporation method

This method is further subdivided into two categories viz (i) single and (ii) double emulsification solvent evaporation method and is briefly discussed as follows.

1.3.6.2.2.1. Single emulsification solvent evaporation method

This method is specially used to develop PLHNPs for the encapsulation of water-insoluble (i.e., lipophilic) drugs. In this method, the lipophilic drug, polymers, and lipids are dissolved in organic solvents to prepare the organic phase and added to the aqueous phase- bearing surfactant dissolved in water to make oil in water emulsion. Afterward, the organic solvent is removed under reduced pressure by using a rotary evaporator.

During the evaporation of the organic solvent, the polymeric core is formed and lipids are self- assembled around the core just like nanoprecipitation and PLHNPs are developed (Ahmed et al., 2022; Ma et al., 2022).

1.3.6.2.2.2. Double emulsification solvent evaporation method

This method is specially used to develop PLHNPs for the encapsulation of water-soluble (i.e., hydrophilic) drugs. In this method, the hydrophilic drug is dissolved in water and mixed with the organic phase (containing polymer and lipid) with continuous stirring to make water in oil (w/o) emulsion. After that, the obtained w/o emulsion is added to the aqueous phase (containing surfactant) with continuous stirring to develop w/o/w emulsion. Then the organic solvent is removed under pressure by using a rotary evaporator which leads to the development of PLHNPs. From this technique, generally, the core shell-type hollow PLHNPs are prepared (Zhao et al., 2012; Hadinoto et al., 2013).

1.4. AROMATASE INHIBITORS

As per the report, almost 75% of breast cancers are hormone receptor (i.e., estrogen and progesterone receptor) positive, and stimulation of hormone receptors plays a significant role in the development of breast cancer (Altundag and Ibrahim, 2006; Yip and Rhodes, 2014). Therefore, the deprivation of estrogenic signaling plays an important role in hormonal therapy for estrogen (ER)-positive and/or progesterone (PgR)-positive breast cancer patients. For the last three decades, tamoxifen (an anti-estrogenic drug) is used clinically as adjuvant hormonal therapy because it blocks the binding of estrogen (Johnston and Dowsett, 2003). However, chemotherapy with tamoxifen boosts the risk of endometrial cancer and thromboembolism by 2 and 2.5 fold respectively (Cuzick et al., 2003). Further, not all breast cancer patients with ER overexpression to tamoxifen, and almost all of those patients who do respond eventually relapse. Therefore, the research has been focused on that agents which block the synthesis of estrogen (Johnston and Dowsett, 2003). The main agents that block the synthesis of estrogen are aromatase inhibitors (AIs). Aromatase is the enzyme that converts the androgens (testosterone and androstenedione) to estrogen (estradiol and estrone). The aromatase enzyme act on the last step of estrogen biosynthesis that converts testosterone to estrogen through the aromatization process. They also significantly decrease the levels of plasma estrogen in postmenopausal women by blocking the aromatase enzyme (Baum et al., 2002; Smith and Dowsett, 2003). The inhibition mechanism of aromatase enzyme by AIs is illustrated in **Figure 1.4.** Clinical data revealed that the AIs represent much better therapeutic efficacy in late-stage breast cancer (Baum et al., 2002; Smith and Dowsett, 2003). Therefore, AIs certainly replace tamoxifen as an agent of choice in adjuvant hormonal therapy for breast cancer patients. Different classes of AIs are summarized in **Table 1.1.**

Table 1.1: Classification of aromatase inhibitors.

Generation	Type 1 (Steroidal inhibitors)	Type 2 (Non-steroidal inhibitors)
First	–	Aminoglutethimide
Second (Currently not in clinical use)	Formestane	Fadrozole Rogletimide
Third (Currently in clinical use)	Exemestane (Aromasin®)	Vorozole Anastrozole (Arimidex®) Letrozole (Femara®)

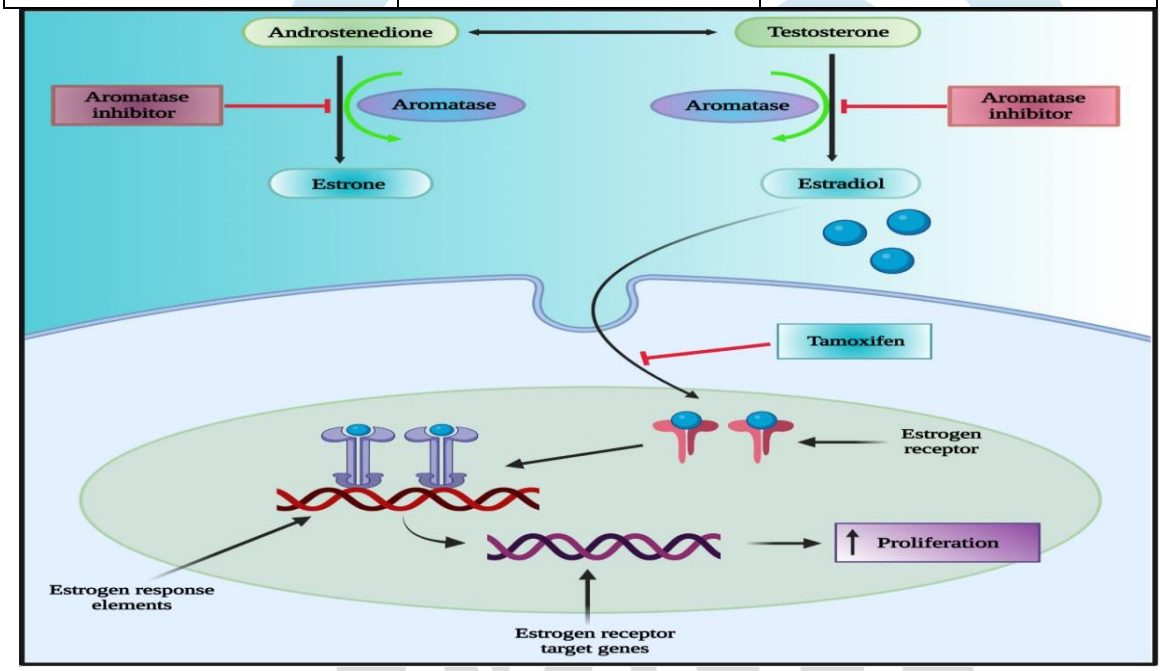

Figure:1.4 The image illustrates the mechanism of action of aromatase inhibitors as well as tamoxifen. Tamoxifen inhibits the binding of estradiol to the ER while AIs inhibit the biosynthesis of estrogen from their androgenic precursors.

2.0 REFERENCE-

- bbasi, E., Aval, S.F., Akbarzadeh, A., Milani, M., Nasrabadi, H.T., Joo, S.W., Hanifehpour, Y., Nejati-Koshki, K., Pashaei-Asl, R., 2014. Dendrimers: synthesis, applications, and properties. Nanoscale Res. Lett. 9(1), 247.
- Agoram, B., Woltosz, W.S., Bolger, M.B., 2001. Predicting the impact of physiological and biochemical processes on oral drug bioavailability. Adv. Drug Deliv. Rev. 50, 41-67.
- Ahmad, J., Kohli, K., Mir, S.R., Amin, S., 2013. Development and validation of RP-HPLC method for analysis of novel self-emulsifying paclitaxel formulation. Res. Rev. J. Pharm. Anal. 2, 17–27.
- Ahmed, M.M., Anwer, M.K., Fatima, F., Aldawsari, M.F., Alalaiwe, A., Alali, A.S., Alharthi, A.I., Kalam, M.A., 2022. Boosting the anticancer activity of sunitinib malate in breast cancer through lipid polymer hybrid nanoparticles approach. Polymers 14(12), 2459.

- Aisner, J., 2007. Overview of the changing paradigm in cancer treatment: oral chemotherapy. Am. J. Health Syst. Pharm. 64(9), 4-7.
- Akhtar, N., Ahad, A., Khar, R.K., Jaggi, M., Aqil, M., Iqbal, Z., Ahmad, F.J., Talegaonkar, S., 2011. The emerging role of P-glycoprotein inhibitors in drug delivery: a patent review. Expert Opin. Ther. Pat. 21(4), 561-576.
- Alam, N., Koul, M., Mintoo, M.J., Khare, V., Gupta, R., Rawat, N., Sharma, P.R., Singh, S.K., Mondhe, D.M., Gupta, P.N., 2017. Development and characterization of hyaluronic acid modified PLGA based nanoparticles for improved efficacy of cisplatin in solid tumor. Biomed. Pharmacother. 95, 856-864.
- Alkhader, E., Roberts, C.J., Rosli, R., Yuen, K.H., Seow, E.K., Lee, Y.Z., Billa, N., 2018. Pharmacokinetic and anti-colon cancer properties of curcumin-containing chitosan-pectinate composite nanoparticles. J. Biomater. Sci. Polym. Ed. 29(18), 2281-2298.
- Alqahtani, M.S., Kazi, M., Alsenaidy, M.A., Ahmad, M.Z., 2021. Advances in oral drug delivery. Front. Pharmacol. 12, 618411.

Altundag, K., Ibrahim, N.K., 2006. Aromatase inhibitors in breast cancer: an overview. Oncologist 11(6), 553-562.

- Ameeduzzafar, El-Bagory, I., Alruwaili, N.K., Imam, S.S., Alomar, F.A., Elkomy, M.H., Ahmad, N., Elmowafy, M., 2020. Quality by design (QbD) based development and validation of bioanalytical RP-HPLC method for dapagliflozin: forced degradation and preclinical pharmacokinetic study. J. Liq. Chromatogr. Relat. Technol. 43(1-2), 53-65.
- Ana, R., Mendes, M., Sousa, J., Pais, A., Falcão, A., Fortuna, A., Vitorino, C., 2019. Rethinking carbamazepine oral delivery using polymer-lipid hybrid nanoparticles. Int. J. Pharm. 554, 352-365.
- Angalaparameswari, S., Thiruvengadarajan, V.S., Kumar, N.A., Kutumbarao, M., Ramkanth, S., Madhusudhanachetty, C., 2012. Analytical method development and validation of exemestane tablet by UV spectrophotometry. J. Chem. 9(4), 2068- 2073.
- Antonio, E., Dos Reis Antunes Junior, O., Marcano, R.G.D.J.V., Diedrich, C., da Silva Santos, J., Machado, C.S., Khalil, N.M., Mainardes, R.M., 2021. Chitosan modified poly (lactic acid) nanoparticles increased the ursolic acid oral bioavailability. Int. J. Biol. Macromol. 172, 133-142.
- Anwer, M.K., Ali, E.A., Iqbal, M., Ahmed, M.M., Aldawsari, M.F., Saqr, A.A., Ansari, M.N., Aboudzadeh, M.A., 2021. Development of sustained release baricitinib loaded lipid-polymer hybrid nanoparticles with improved oral bioavailability. Molecules 27(1), 168.
- Badhani, A., Dabral, P., Rana, V., Upadhyaya, K., 2012. Evaluation of cyclodextrins for enhancing corneal penetration of natamycin eye drops. J. Pharm. Bioallied Sci. 4(1), 29-30.
- Badri, W., Miladi, K., Nazari, Q.A., Fessi, H., Elaissari, A., 2017. Effect of process and formulation parameters on polycaprolactone nanoparticles prepared by solvent displacement Colloid. Surf. A:

Physicochem. Eng. Asp. 516, 238–244.

- Banerjee, P., Geng, T., Mahanty, A., Li, T., Zong, L., Wang, B., 2019. Integrating the drug, disulfiram into the vitamin E-TPGS-modified PEGylated nanostructured lipid carriers to synergize its repurposing for anti-cancer therapy of solid tumors. Int. J Pharm. 557, 374–389.
- Banik, B.L., Fattahi, P., Brown, J.L., 2016. Polymeric nanoparticles: the future of nanomedicine. Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol. 8(2), 271-299.
- Banna, G.L., Collovà, E., Gebbia, V., Lipari, H., Giuffrida, P., Cavallaro, S., Condorelli, R., Buscarino, C., Tralongo, P., Ferraù, F., 2010. Anticancer oral therapy: emerging related issues. Cancer Treat. Rev. 36(8), 595-605.
- Barazzuol, L., Coppes, R.P., van Luijk, P., 2020. Prevention and treatment of radiotherapy-induced side effects. Mol. Oncol. 14, 1538-1554.
- Baum, M., Budzar, A.U., Cuzick, J., Forbes, J., Houghton, J.H., Klijn, J.G., Sahmoud, T., 2002. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. Lancet 359(9324), 2131-2139.
- Bhavsar, D., Gajjar, J., Sawant, K., 2019. Formulation and development of smart pH responsive mesoporous silica nanoparticles for breast cancer targeted delivery of anastrozole: In vitro and in vivo characterizations. Microporous Mesoporous Mater. 279, 107-116.
- Bindu, G.H., Annapurna, M.M., 2018. Development and validation of a new stability indicating ultrafast liquid chromatographic method for the determination of Exemestane tablets. Res. J. Pharm. Tech. 11(10), 4487-4491.
- Biondi, A., Lirosi, M.C., D'Ugo, D., Fico, V., Ricci, R., Santullo, F., Rizzuto, A., Cananzi, F.C., Persiani, R., 2015. Neo-adjuvant chemo(radio)therapy in gastric cancer: Current status and future perspectives. World J. Gastrointest. Oncol. 7, 389– 400.
- Bollenbach, L., Buske, J., Mäder, K., Garidel, P., 2022. Poloxamer 188 as surfactant in biological formulations - An alternative for polysorbate 20/80? Int. J. Pharm. 620, 121706.
- Bose, R.J.C., Ravikumar, R., Karuppagounder, V., Bennet, D., Rangasamy, S., Thandavarayan, R.A., 2017. Lipid-polymer hybrid nanoparticle-mediated therapeutics delivery: advances and challenges. Drug Discov. Today 22(8), 1258- 1265.
- Breda, M., Pianezzola, E., Benedetti, M.S., 1993. Determination of exemestane, a new aromatase inhibitor, in plasma by high-performance liquid chromatography with ultraviolet detection. J. Chromatogr. 620(2), 225-231.
- Breedveld, P., Beijnen, J.H., Schellens, J.H., 2006. Use of P-glycoprotein and BCRP inhibitors to improve oral bioavailability and CNS penetration of anticancer drugs. Trends Pharmacol. Sci. 27(1), 17-24 Brodie, A.M., 1993. Aromatase, its inhibitors and their use in breast cancer treatment.

Pharmacol. Ther. 60(3), 501-515.

- Bu, X., Zhu, T., Ma, Y., Shen, Q., 2015. Co-administration with cell penetrating peptide enhances the oral bioavailability of docetaxel-loaded nanoparticles. Drug Dev. Ind. Pharm. 41(5), 764-771.
- Cardoso, F., Colleoni, M., Di Leo, A., Francia, G., Gennari, A., Gligorov, J., Llombart, A., 2016. Oral chemotherapy in advanced breast cancer: expert perspectives on its role in clinical practice. Cancer Treat. Commun. 6, 1-0.
- Chaturvedi, S., Garg, A., 2022. A comprehensive review on novel delivery approaches for exemestane. J. Drug Deliv. Sci. Tech. 75, 103655.
- Chauhan, V.P., Stylianopoulos, T., Martin, J.D., Popović, Z., Chen, O., Kamoun, W.S., Bawendi, M.G., Fukumura, D., Jain, R.K., 2012. Normalization of tumour blood vessels improves the delivery of nanomedicines in a size-dependent manner. Nat. Nanotechnol. 7(6), 383-388