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The Potency of Polymeric Nanoparticles as New Drug Delivery System: a Narrative Review

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Abstract

Polymeric nanoparticles are particles ranging from 1 to 1,000 nm that can be loaded with active compounds. Polymeric nanoparticles can be classified based on their morphological structure into nano capsules and nanospheres. In addition, polymeric nanoparticles can also be classified based on the compound's origin into natural and synthetic polymer. The nanoparticle production method is adjusted based on the type of drug that will be loaded. The methods commonly used for the production of polymeric nanoparticles are solvent evaporation, solvent emulsification/ diffusion, nanoprecipitation, emulsification/ reverse-salting out, and nanoprecipitation. This review also provides several examples of clinical applications of nanoparticles in the formulation of several drugs/ bioactive including hyperforin, curcumin, and amphotericin.

Keywords: Drugs, Nanocapsules, Nanospheres, Polymeric Nanoparticles.

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Introduction

Nanoparticles have gained significant interest in medicines, both for diagnostics and therapeutics[1]. Nanoparticles are small particles ranging from 10 to 1,000 nm in size that can be made of carbon, metals, metal oxides, or organic materials[2]. Nanoparticles exhibit unique chemical, physical and biological properties at the nanoscale. This phenomenon is caused by a larger surface area relative to volume, an increase in reactivity or stability in chemical processes, as well as an increase in mechanical strength, etc. These huge advantages of nanoparticles support their use for various applications[3].

The use of large materials in drug delivery poses major challenges, for example in vivo instability, poor bioavailability, poor solubility, poor absorption in the body, problems with specific target delivery, drug effectiveness, and side effects. Therefore, using a new drug delivery system for targeting specific tissues or cells may be the right choice in solving this problem[4,5]. Nanoparticles can be used as carriers in drug delivery systems. The nanostructures can last longer in the circulation and allow the release of drugs according to the prescribed dose, thus minimizing plasma fluctuations and reducing side effects. The nano size makes it easier for particles and the drugs they carry to pass through tissues, facilitating efficient drug uptake by cells and ensuring precise targeting. The uptake of nanoparticles by cells is much higher compared to large particles ranging from 1 to 100 μm[6]. Nanoparticles can be classified into several groups such as polymeric nanoparticles, liposomes, dendrimers, micelles and inorganic nanoparticles, based on their synthetic components or structure[7].

Polymeric nanoparticles are the most promising drug carriers compared to liposomes. Polymeric nanoparticles can be made of natural (gelatin, albumin) or synthetic (polylactides, polyalkylcyanoacrylates) materials which are biocompatible and biodegradable. Polymeric nanoparticles can be designed as drug carriers to deliver active molecules to their intended targets. Polymer hydrophobicity, nanoparticle surface area and monomer concentration can affect drug adsorption capacity. During polymerization, drugs can be added and entrapped within the polymeric nanoparticle network. Polymeric nanoparticles can influence drug metabolism at optimal levels for the desired therapeutic effect in target tissues[6]. There are various types of polymers for the synthesis of nanoparticles, which have different physical and chemical properties. Therefore, understanding of polymeric nanoparticles is very important in determining and constructing the right drug carrier according to the desired target. This narrative review discusses about polymeric nanoparticles, including definitions, classifications, production methods, advantages and several examples of their application in drug delivery strategies.

Method

This narrative review was conducted by comprehensively exploring and analyzing existing literature on polymeric nanoparticles and their applications in drug delivery. Sources of information included peer-reviewed articles, review papers, and book chapters from databases such as PubMed, ScienceDirect, and Google Scholar. The search terms used were "polymeric nanoparticles," "drug delivery," "nanocapsules," "nanospheres," "production methods," and "clinical applications."

The inclusion criteria for selecting articles were: (1) studies published in English or Bahasa, (2) studies discussing the development, characterization, and application of polymeric nanoparticles, and (3) original articles

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presenting clinical or preclinical data on drug delivery using polymeric nanoparticles. Articles were excluded if they were (1) not related to drug delivery, (2) not peer-reviewed, or (3) published in languages other than English or Bahasa.

Data were extracted on the types of polymeric nanoparticles, production methods, drug encapsulation efficiency, release kinetics, in vivo and in vitro performance, and clinical outcomes. Information was summarized to highlight key findings and trends in the field. This narrative review aims to provide a thorough understanding of the current state of polymeric nanoparticle research, focusing on their potential advantages and applications in improving drug delivery systems.

Definition and Classification of Polymeric Nanoparticles

Polymeric nanoparticles are particles ranging from 1 to 1,000 nm that can be filled with active compounds. Nanoparticles can be classified based on their morphological structure into nanocapsules and nanospheres. Nanocpasules are composed of an oily core and a polymeric shell. The oily core is where the drug is normally dissolved, while the outer polymeric shell plays a role in controlling the drug release profile. Nanosphere is a matrix particle in which the entire solid mass and molecules can be adsorbed on the spherical surface or encapsulated in the particles[8]. These two types of polymeric nanoparticles are known as reservoir systems (nanocapsules), and matrix systems (nanospheres) which are shown in Figure 1[9]. Furthermore, polymeric nanoparticles can also be classified based on the origin of the compound into natural and synthetic polymers. Natural polymers that are most widely used are alginate, albumin, or chitosan. While synthetic polymers that are widely used are polylactide, polylactide-polyglycolide copolymer, polycaprolactone, and polyacrylate[10].

The Production of Polymeric Nanoparticles

The selection of polymeric nanoparticles production methods are based on the type of drug to be loaded in it[11]. These production strategies employ the dispersion of preformed polymer and the polymerization of monomers[12]. Table 1 lists the methods commonly used for the production of polymeric nanoparticles[13,14]. The method of producing polymeric nanoparticles based on preformed polymer dispersions requires organic solvents in the first step to dissolve the polymer, but these solvents can generate problems related to toxicity and environmental risk[13]. Whereas, the others method namely monomers polymerization can increase efficiency in drug insertion[15].

1. Solvent Evaporation

The principle of solvent evaporation method consists of phase I (aqueous phase) and phase II (organic phase) Figure 2[16]. Firstly, the process of polymer solution emulsification is carried out into phase I. Secondly, the polymer solvent is evaporated, followed by deposition of polymer induction into nanospheres[12].

The whole process of this methods is by preparing phase II which consists of a polar solvent which make dissolve the polymer and active ingredients (e.g., drugs), then followed by dispersion in nanodroplets[12]. Dichloromethane and chloroform have been widely used as organic solvents, but due to their toxicity have been replaced by ethyl acetate[16]. The polymer which precipitates as nanospheres indicates that the drug is finely dispersed in the polymer matrix. Then, the solvents is evaporated by increasing the temperature or by continuous stirring. The advantage of this method is common and easy to use. While, the disadvantage is only used on

fat-soluble drugs and less effective because it requires high energy for homogenization[17,18].

2. Emulsification/Solvent Diffusion (ESD)

The principle of the ESD method consists of internal phase and external phase Figure 3[16]. The whole process of this methods is an internal phase which consists of organic solvent (ethyl acetate or benzyl alcohol) to dissolve polymer, oil, active ingredients (e.g., drugs) and aqueous solution with surfactant. The subsequent was diluted by a large volume of water to induce solvent diffusion from the dispersed droplets into the external phase, resulting in the formation of colloidal particles. In the last steps the solvent are evaporated or filtered. The ESD methods generally used to produce nanospheres, but it can also be used to produce nanocapsules if the ratio of oil is appropriate to polymer. The advantage of the ESD method is efficient in encapsulating (>70%), doesn't require homogenization step, and facilitates to scale up[17,19]. The disadvantage of this method is difficult to remove water during emulsification, it can be affected on encapsulation process. Furthermore, this method is only used effectively for lipophilic drugs[20].

3. Nanoprecipitation

The nanoprecipitation method is known as solvent displacement method. The principle of this method requires two miscible solvents (acetone or acetonitrile) Figure 4[15]. This method is relies on the interfacial deposition of a polymer after the displacement of the organic solvent from a lipophilic solution to the aqueous phase. The whole process of this method is an internal phase which consists of a polymer dissolved in a miscible organic solvent. The solution is added to an aqueous solution under stirring (in a dropwise way) or at a controlled addition rate.. The precipitated polymers form nanospheres or nanocapsules. The disadvantage of this method is only used for lipophilic drugs or drugs with two miscible solvents[18,19].

4. Emulsification/Reverse-Salting Out (ERS)

The principle of this method is based on separation of a hydro-miscible solvent from an aqueous solution, through a salting-out effect formulated from water-miscible polymer solvents such as acetone or ethanol, salts/electrolytes ($MgCl_2$, $CaCl_2$, and $Mg(CH_3COO)_2$), as well as non-electrolytes such as sucrose Figure 5[12,20]. The acetone and water are removed by saturating the aqueous phase, thereby allowing the formation of an o/w emulsion of the other miscible phases. The o/w emulsion is prepared by continuous stirring at room temperature. Then, the emulsion is diluted using an appropriate volume of deionized water or aqueous solution to allow diffusion of the organic solvent to the external phase precipitation of the polymer, and consequently resulting the production of nanospheres. The remaining solvent and salting-out agent are eliminated by cross-flow filtration[18,20].

Polymeric Nanoparticles as Drug Delivery System

Polymer are very stable and are available in a variety of structures, offering considerable design flexibility. These characteristics underlie it's widespread use in a number of therapeutic applications. Polymeric nanoparticles allow loading of a wide variety of bioactive materials, such as small molecules, nucleic acids and other biological materials. Polymeric nanoparticles can also control drug release kinetics. The use of polymeric allows easy modulation of the physicochemical properties (e.g., size, surface charge) of the nanocarrier and the possible chemical functionalization by attaching ligands. Targeting ligands such as antibodies, peptides or small molecules

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can also be conjugated to these encapsulated surfaces to allow specific interactions with tissue components or cellular receptors. Due to these advantages, a number of polymer-based nano-sized oral drug delivery systems have been developed[21].

Among various nanocarriers, polymeric nanoparticles are the most studied to achieve superior therapeutic performance for both oral administration and other routes of administration. There are three main reasons for using polymeric nanoparticles as drug delivery systems. First, the well-formulated polymeric nanoparticles exhibit high stability in the gastrointestinal environment compared to other nanocarriers, such as liposomes or other lipid-based carriers. Based on their stability, polymeric nanoparticles are able to protect the encapsulated drug from various degradation causes (e.g., acidic pH and digestive enzymes). Second, drug release can be predicted and precisely controlled by accurately selecting the polymeric composition with defined release kinetics. The drug release profile and mechanism depend on the nature of the polymeric, and in particular on the rate of degradation, molecular weight and possible interactions with the drug. Finally, because there are a lot of polymeric materials available for the preparation and modification of nanoparticles, it is possible to adapt nanoparticles to the active ingredients they will carry[22].

Targeting. An important focus area in drug delivery is the accurate targeting of the desired cells or tissues. Targeting in a drug delivery system (DDS) refers to the ability of drug carriers to deliver cargo to the right location at the right time. An ideal and efficient nanocarrier should recognize specific target cells or tissues, bind to them and deliver the drug while avoiding unwanted drug-induced side effects to healthy cells and tissues. Polymeric nanoparticles can engineer specificity through surface functionalization and manageable manipulation of their properties, enabling them to deliver higher drug concentrations to the desired sites. DDS follows two main targeting mechanisms: Passive targeting and active targeting. In passive targeting, polymeric nanoparticles reach the target administration site passively, without the need to attach additional ligands to fulfill this goal (Figure 6). An example of passive targeting is the preferential accumulation of chemotherapeutic agents in solid tumors. This occurs as a result of the increased vascular permeability of tumor tissue compared to healthy tissue. Polymeric nanoparticles preferentially accumulate in tumor neoplastic tissue as a result of the phenomenon of enhanced permeability and retention (EPR). This phenomenon occurs as a result of abnormal blood vessels and impaired lymphatic drainage in neoplastic tissue. The size of the polymeric nanoparticles allows them to enter the tumor tissue via the EPR phenomenon. Passive targeting has disadvantages compared to active targeting. Polymeric nanoparticles encounter problem on their way to target sites, i.e. extracellular drug release and uptake by nontarget cells[18,23,24]. On the other hand, active targeting is a term that describes a specific interaction between a drug carrier and a target cell, usually through a specific ligand-receptor interaction. In this targeting mechanism, the surface of the nanoparticles is conjugated with a ligand designed to act as a tracking device by recognizing and binding to specific administration sites. These tracking devices can be small organic molecules, peptides, antibodies, designed proteins and nucleic acid aptamers. For example, specific antibodies can be used as tracking devices for tumor targeting. These antibodies recognize characteristic molecules on the tumor surface and are absent on healthy cells. Since ligand-receptor interactions are highly selective,

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this can allow more effective targeting of the desired site, making active targeting a more attractive route than passive targeting. Advanced specificity due to active targeting also reduces the toxicity and unwanted side effects that occur with nonspecific drug delivery to untargeted cells and tissues (Figure 6)[25,26].

Drug release mechanism. Drug release from polymeric nanoparticles occurs through a combination of diffusion and degradation mechanisms. In nanocapsules, drug release is controlled mainly by the diffusion of the drug through the surrounding polymeric membrane or the aqueous micropore network that penetrates the dense area of the membrane. At the equilibrium point, drug release will be constant over time and largely depends on the diffusion capacity of the drug, its affinity for the membrane, properties, thickness and porosity of the membrane. In nanospheres, the active ingredient is released through the process of diffusion as well, but the rate of release and the concentration gradient at each point of the polymeric matrix varies as a function of time due to a continuous decrease in the amount of drug contained in the system. In addition, polymeric materials may undergo hydrolytic and/or enzymatic degradation due to interactions with biological fluids. This process contributes significantly to drug release, also affecting the rate of diffusion through the matrix or polymeric membrane. Therefore, the chemical composition of the resulting polymer is very decisive in the drug release kinetics so as to allow optimization of its activity profile[28,29].

The Advantages and Limitation of Polymeric Nanoparticles

As previously described, polymeric nanoparticles have many characteristics that make them excellent candidates as drug delivery carriers. These advantages include:

1. **Size:** polymeric nanoparticles are typically 10 to 1,000 nm in size.This size provides an advantage as a drug carrier as it is suitable for intravenous delivery compared to the previously developed micro drug delivery system (DDS). The smallest capillaries in the body have a diameter of 5-6 μm, therefore the size of the particles circulating through the blood stream should be smaller than 5 μm, without forming aggregates, to avoid the formation of emboli caused by the particles themselves[28].
2. **Shape:** Different polymeric nanoparticle structures can be engineered using various methods depending on the nature of the selected polymer and the drug to be loaded. There are two types of polymeric nanoparticles, nanospheres (100-200 nm) and nanocapsules (100-300 nm). The drug can be adsorbed onto the surface or trapped within the nanoparticles themselves (encapsulation), this depends on their structural organization[30].
3. **Biocompatibility and biodegradability:** Natural polymers, in particular polysaccharides and protein-based polymers, show excellent biocompatibility as they can be broken down into polysaccharides and peptides through enzymatic degradation. These biomolecules can then be easily metabolized by the body without any harmful side effects. The biodegradability of polymeric nanoparticles not only contributes to their biocompatibility, but is also a major factor in their drug release ability[28].
4. **Safe, less toxic, non-immunogenic:** The use of polymeric nanoparticles as carriers in the delivery of anticancer drugs has been shown to reduce toxicity, because the polymeric components of the carrier provide protection for the drug and limit its interaction with healthy cells[31].

5. **Specificity:** Polymeric nanoparticles are great choice for intracellular and site-specific drug delivery. This system has the ability to deliver higher drug concentrations to a specific site of administration as it can be specifically modified in terms of size and surface characteristics to reach the specified target cells[32].
6. **Adjustable physical, chemical and biological properties:** The use of polymeric nanoparticles as drug carriers provides the freedom of controlled and long-term release rates, long circulation times and prolonged bioactivity. All these features are very important in the efficiency of drug carrier activity. The addition of polyethylene glycol (PEG) to the polymer was shown to increase the circulation time of the nanocarrier by inhibiting absorption by the reticuloendothelial system (RES). This can be achieved by inhibiting the binding of the protein to the surface of the carrier thereby blocking recognition by RES[28].
7. **Stability:** Polymeric nanoparticles can stabilize volatile drugs, protecting them from the environment until they reach the site of administration[28].
8. **Multiple drug codelivery:** The ability to deliver multiple drugs with synergistic effects. The delivery of multiple drugs in the same polymeric nanoparticles can overcome problems such as multi-drug resistance of tumor cells and achieve synergistic effects between different drugs[31,32].
9. **Fabrication method:** The most suitable fabrication method for synthesizing polymeric nanopolymers depends on the nature of the polymer and properties of the drug to be loaded for delivery (Figure 7)[28].

The primary limitations associated with nanoparticle (NP) production and application stem from several critical factors that can significantly impact their performance and stability. One of the foremost challenges is the tendency for particle aggregation, which can lead to irregular particle sizes and reduce the overall uniformity and dispersibility of the nanoparticles, ultimately affecting their bioavailability and therapeutic potential. Another key limitation lies in the chemical stability of the polymer used to encapsulate or formulate the nanoparticles. Over time, polymers may degrade or undergo chemical modifications, potentially altering the release profile of the active substance or compromising the integrity of the nanoparticles[2].

Furthermore, the quality and properties of the drug or other raw materials utilized during the NP production process play a vital role in determining the success of the final formulation. Variations in the physicochemical characteristics of these materials, such as solubility, molecular weight, and compatibility with the polymer matrix, can introduce inconsistencies and hinder reproducibility[5].

In addition to these factors, the premature release of the active substance poses a significant hurdle. Unintended leakage or burst release of the drug before reaching the target site can not only reduce therapeutic efficacy but may also lead to potential toxicity or side effects. Addressing these limitations is crucial to enhancing the reliability, safety, and effectiveness of nanoparticle-based drug delivery systems[6].

Application of Drugs or Bioactive Compounds Loaded Polymeric Nanoparticles

In recent years, many modern technologies have been developed in the field of pharmaceutical research and development. The field of nanotechnology especially in the use of drug nanoparticles in polymer

form is a universal approach to improve the therapeutic performance of poorly soluble drugs in every route of administration and is also an innovative new drug delivery system. Polymeric nanoparticles from biodegradable and biocompatible polymers are attractive options for controlled drug delivery and for targeted therapy. Nanoparticles can be used therapeutically as adjuvants in vaccines or drug carriers which can contain various drug formulations and bioactive ingredients using several such as active ingredients dissolved, encapsulated, adsorbed or chemically attached. Examples of drugs/ bioactive materials contained in polymeric nanoparticles and their application to certain diseases will be described in (Table 2)[15].

1. Hyperforin as Anti-Inflammatory

Acute inflammation is the initial response to damage to body tissues by noxious stimulation, but if the inflammation becomes excessive and persistent, as in inflammatory arthritis, asthma, cardiovascular disease, Alzheimer's, and autoimmune diseases[33]. Prostaglandins (PGs, such as PGE2) and leukotrienes (LTs) are proinflammatory lipid mediators, resulting from arachidonic acid (AA) involving cyclooxygenase (COX) and 5-lipoxygenase (5-LO) as key enzymes, each of which promotes inflammation and contributes to the classic symptoms of the inflammatory response[34]. Glucocorticoids and nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for the treatment of chronic inflammatory disorders with limited effectiveness and possible side effects[35]. Whereas NSAIDs exert anti-inflammatory properties that essentially block PG biosynthesis through COX inhibition, a new pharmacological strategy targets the concept of inhibition. microsomal double PGE2 synthase-1 and 5-LO, which suppresses pe formation of PGE2 and LTs, however, the problem is that most of the inhibitory enzymes forming PG/LT are hydrophobic with a strong tendency to bind to nonspecific plasma proteins, resulting in poor efficacy[36].

Hyperforin (Figure 8) is a prenylated acylphloroglucinol derived from the plant St. John's Wort (Hypericum perforatum), with numerous pharmacological activities (i.e., antidepressant, anticancer, antiangiogenic, antibacterial, and anti-inflammatory)[37]. Hyperforin has a vinilogous acid moiety (pKa = 3.82) and has four single prenyl residues that give the molecule hydrophobicity. Thus, hyperforin resemble highly lipophilic fatty acid-like molecules with poor water solubility that are potentially susceptible to plasma protein binding. 5-LO is one of the most studied hyperforin binding targets. Hyperforin is able to bind to a unique 5-LO site (that is, a C2-like domain), and 5-LO activity in an in vitro assay was inhibited by hyperforin in the submicromolar range. In vivo inhibition of LT biosynthesis by hyperforin was demonstrated in carrageenan-induced pleurisy in intraperitoneal mice[35]. However, hyperforin failed to inhibit 5-LO activity in blood because it binds strongly to plasma proteins. In this regard, the bioavailability of hydrophobic drugs is a major problem in drug development and pharmacotherapy, so to overcome this detrimental property of hyperforin, the researchers tried to make hyperforin into polymeric nanoparticles and investigated its efficiency in inhibiting 5-LO activity under various conditions[38].

In a previous study of an experimental test on murine, hyperforin was embedded in gold polymeric nanoparticles to increase efficacy in the treatment of autoimmune encephalomyelitis. The encapsulation of hydrophobic drugs into polymeric nanoparticles is a promising approach to overcome the challenges of therapeutic delivery that inhibit drug bioactivity/

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bioavailability[39]. Its main advantage is the presence of ester bonds that cause polymer degradation and release of drug encapsulated into endosomes and also its hydrophobic nature can formulated into polymeric nanoparticles by nanoprecipitation or emulsion techniques[40]. In addition, a commercially available polyester i.e. dextran acetate (AcDex) was developed for the encapsulation of organic/inorganic molecules[41]. Hydrophobic dextran contains acid labile acetals which degrade under acidic conditions in endosomes. The researchers used hyperforin, which has hydrophobic molecular properties, as an anti-inflammatory drug to be encapsulated into AcDex-based polymeric nanoparticles using an emulsion technique. The available data indicate that the encapsulation of hyperforin into polymeric nanoparticles enables a more effective and efficient inhibition of 5-LO activity. In addition, this strategy is also suitable to overcome the binding to albumin, and can increase the efficacy of hyperforin[38].

Comparison of free-hyperforin and encapsulated hyperforin is presented in Figure 9. In the presence of human serum albumin (HSA), free-hyperforin (not encapsulated) (Figure 9A) cannot enter cells to inhibit cellular 5-LO activity which is pro-inflammatory, because it binds to plasma protein (albumin) strongly. However, when hyperforin was encapsulated into polymeric nanoparticles (Figure 9B), which was combined with dextran acetate (AcDex), hyperforin could freely fuse into cells and physiologically perform its function to inhibit 5-LO which is pro-inflammatory. Encapsulated hyperforin has the potential to suppress 5-LO activity on human neutrophils and allows inhibition of 5-LO activity due to effective absorption and no binding to plasma protein (albumin), thereby increasing drug bioavailability and therapeutic efficacy[38].

2. Curcumin (Cur) As Anticancer

Cancer is the second leading cause of death globally. According to the Centers for Disease Control and Prevention more than 14.1 million new cancer cases were identified in 2012 with an estimated increase to 19.3 million by 2025[42]. Cancer is characterized by abnormal cell proliferation and growth that is often associated with gene mutations. Conventional methods for cancer treatment mainly consist of surgery, chemotherapy and radiotherapy. This approach has serious side effects on both cancerous and healthy tissue, in addition to low cure rates and high recurrence rates. Distant metastasis in cancer patients has become a challenging problem in clinical medicine because it is associated with a high mortality rate. During metastasis, various organs such as brain, liver, bones, lungs, etc. are attacked by cancer cells. Chemotherapy, radiotherapy and surgical intervention risk the formation of metastatic lesions resulting from these conventional therapies[43].

Curcumin or 1,7-bis (4-hydroxy-3methoxyphenyl)-1,6-heptadiene-3,5-dione is a diketo structure that tautomerizes between the enol and keto structures under physiological conditions (Figure 10). It is a major constituent of turmeric extract and has many therapeutic uses including anti-inflammatory, anti-oxidant, and anti-cancer activities[44].

The main factor that correlates with the development of all types of cancer is inflammation. Curcumin has been shown to have anti-inflammatory therapeutic effects. In addition, curcumin is a potent anti-cancer agent due to its ability to suppress the growth of various tumor cell lines by targeting multiple pathways involved in carcinogenesis[44].

Curcumin-F108 nanocapsules were prepared using a simple coprecipitation method with

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acetone solvent in which the drug to copolymer ratio was maintained at a 1:1 ratio. The 1:1 ratio is the weight ratio used during the manufacture of nanocapsules. Nanocapsules were formed by self-assembly of F108 in the presence of curcumin in a mixture of acetone and water (Figure 11). Acetone was evaporated during the deposition of the nanocapsules, and the solution was diluted to 10 mL using distilled water. The nanocapsules formed were left for 48 hours to settle. The supernatant solution was discarded, and the nanocapsules were allowed to freeze for two consecutive days. Finally, a lyophilized formulation was obtained and characterized for use in the application[44].

Curcumin is a potent therapeutic agent, but it has limitations, namely its low water solubility. Therefore, many studies have focused on increasing the solubility of curcumin in water to increase its bioavailability. One strategy to improve biological activity and compatibility is by encapsulating curcumin in F108 nanocapsules. Cytotoxicity of nanocapsules, curcumin, and control F108 was assessed using two types of human cancer cells (with or without controlled light irradiation), A549 human lung adenocarcinoma cells and A375 human malignant melanoma. For the A549 and A375, the results show a 34-fold and 32-fold reduction in IC50. This indicates an increase in the anticancer activity of curcumin on encapsulation in F108. IC50 also decreased 3-fold in the presence of light irradiation, indicating an efficient photodynamic therapy. The effect of curcumin and nanocapsules on DNA was further assessed using the comet assay. The results showed DNA damage in A375 cells for curcumin and nanocapsules, which was further increased upon exposure to blue light which was associated with oxidative stress in the cells. These results together illustrate the advantages of encapsulating curcumin in amphiphilic block copolymers for potential drug delivery applications[45].

Block copolymers, known as pluronics, are an example of a water-soluble, non-ionic triblock copolymer. They exhibit amphiphilic properties: a hydrophobic polypropylene oxide (PPO) chain terminated by two hydrophilic polyethylene oxide (PEO) chains, therefore, the general structure is an A–B–A: PEO–PPO–PEO structure (Figure. 12). The chemical differences between the two pluronic blocks make them amphiphilic molecules with surface active properties. The separation in polarity of water-soluble PEO and water-insoluble PPO blocks gives rise to self-assembled micelles in the form of nanostructures[46]. Another important feature of this copolymer is its ability to form solid nanoparticles or nanocapsules upon solvent evaporation and lyophilization. Due to their nanoscopic size, structural diversity and adsorption properties, these structures have proven useful in various applications such as, drug delivery, nanoparticle synthesis, and various emulsion applications. The pluronics nomenclature (e.g., F108) includes a numeric code preceded by a letter denoting the phase. Thus, the letter "L" means liquid, "F" for flake or solid, and "P" for paste. The numerical code defines the PPO and PEO structures of the copolymer[47].

F108 belongs to a class of copolymers that have high hydrophilic character, 80% PEO, and an average molecular weight of 14,600 g mol-1, and can self-assemble into micelles in aqueous solution or can form nanoparticles under certain conditions. The hydrophobic domain provides cargo space for delivering various hydrophobic drugs. In this review, the solubility and bioavailability of curcumin was improved by its encapsulation in poly(ethylene oxide)-block-poly(propylene oxide)-block-poly(ethylene oxide) (F108) nanocapsules. The resulting material was characterized using scanning electron microscopy, Fourier transform infrared spectroscopy, X-ray

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diffraction, thermogravimetric analysis, and emission spectroscopy[44].

Nanocapsules were prepared by adding 10 mg of curcumin to 10 mg of pluronate F108 and dissolved in 2.5 mL of acetone. The solution was stirred continuously for 40 minutes. Meanwhile, 2.5 mL of double distilled water was added dropwise. After that, the acetone was evaporated using a rotary evaporator, and the solution was diluted to 10 mL using distilled water. The nanocapsules formed were left for two nights to settle. Then the supernatant solution was discarded, and the nanocapsules were allowed to freeze-dry for two consecutive days to obtain a lyophilized formulation which was further characterized[48].

3. Amphotericin B (Amp B) for Treatment of Leishmania Infection

Leishmaniasis is a complex disease caused by obligate intracellular protozoa of the genus Leishmania, and usually occurs in tropical and subtropical areas around the world and is mostly caused by sand flies which act as vectors of transmission. It is a major health problem worldwide. Currently, the infected number is 12 million while every year around 1-2 million new cases are reported and can be fatal or self-limiting. The types of leishmaniasis infection are as follows: cutaneous leishmaniasis, mucocutaneous leishmaniasis, visceral leishmaniasis. Cases of cutaneous and visceral leishmaniasis are a major threat worldwide, whereas mucocutaneous leishmaniasis is rarely reported. Parts of the body that are exposed include the skin for cutaneous leishmaniasis, whereas in visceral leishmaniasis, the infection is localized mainly in the spleen, liver macrophages, and lymph nodes. Several wounds/ ulcers due to sand fly bites occur worldwide in skin leishmaniasis[49].

The current treatment for leishmaniasis is using pentavalent antimonials (Pentostam and Glucantime), miltefosine, paromomycin and amphotericin B (AmpB) formulated with deoxycholic acid (Fungizone). Amphotericin B (Amp B) is a second-line leishmaniasis treatment that causes parasite death. Amphotericin B (Amp B) is considered a strong fungicidal drug, especially for treating leishmania infections. Amp B is generally administered intravenously as an anti-leishmanial and antifungal agent which is associated with nephrotoxicity, but its clinical use has limitations and many challenges when administered intravenously or orally, namely its high toxic effect and poor solubility, including the high cost of current drugs. This, as well as the dangers of developing parasite resistance, are also associated with poor absorption of the drug when administered orally[50].

Treatment of leishmaniasis infection requires the development of new drugs, because of the various challenges and problems associated with standard treatment both from preparations that are via the intravenous and oral routes. Considering some of the challenges outlined above, topical application of Amp B is a more appropriate and safe option in many aspects of skin leishmaniasis. Amp B has physicochemical properties, such as low molecular weight, low melting point and adequate lipophilicity, such properties make Amp B suitable for topical drug delivery. Appropriate topical formulations must be able to target the Leishmania parasite in the dermal layer of the skin. Therefore, drug delivery is very decisive in increasing drug penetration into the skin and supporting drug release. Nanocarrier-based topical drug delivery systems can be an option in overcoming various challenges associated with oral and parenteral routes of administration, such as inefficient or low solubility drugs, and optimizing delivery within the desired duration[51].

To achieve the desired goal, polymeric

nanoparticles with nanoprecipitation through high pressure homogenization were developed for the treatment of leishmaniasis. This formulation is desirable to reduce the side effects specifically associated with the oral route of administration. The combination of High-Pressure Homogenization (HPH) and solvent diffusion techniques was used to fabricate the nanoparticles. Smaller particles obtained by HPH technique, which may be very helpful for topical drug delivery[52]. Amp B nanoparticles were formulated and explored in detail using Polycaprolactone (PCL). Polycaprolactone is a biodegradable polymer used for active delivery mainly via routes for topical drug delivery. This approach is able to eliminate the use of materials that are relatively rare and expensive. This method can also provide better drug loading[53].

Polycaprolactone (PCL) nanoparticles loaded with Amp B with nanoprecipitation were developed for topical application in Leishmaniasis infection. Various parameters, such as concentration of PCL and surfactant Poloxamer 407, were varied to optimize nanoparticle formation for Amp B loading using high pressure homogenization and solvent diffusion techniques (Figure. 13). Macrophage targeting via a loaded drug formulation significantly enhanced and enhanced Amp B activity as an anti-leishmanial for intracellular parasite inhibition. The drug formulation loaded for anti-leishmanial activity against infected macrophages showed maximum parasite inhibition. Amp B contained in polymeric nanoparticles formulated with low drug concentrations was able to inhibit intracellular parasite replication[50].

Conclusion

Polymeric nanoparticles are promising drug carriers. Polymeric nanoparticles can be designed as drug carriers for delivering active molecules to their intended targets. The polymeric nanoparticles production methods is adjusted based on the type of drug to be loaded. The hydrophobicity of the polymer, the large surface area of the nanoparticles and the concentration of monomers can affect the adsorption capacity of the drug so that it has the potential as an efficient and effective drug carrier.

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Conflict of Interest

None declared.

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Table 1. The production method of polymeric nanoparticles[2].

Polymeric nanoparticles	Methods of NP Production	Reference
Nanospheres	• Solvent evaporation • Emulsification/solvent diffusion • Nanoprecipitation • Emulsification/reverse-salting out	(2)
Nanocapsules	Nanoprecipitation	(3)

Table 2. Examples of drugs/ bioactive compounds loaded in polymeric nanoparticles[2].

Type of Polymers	Formulated Drug/ Bioactive	Type of Polymeric Nanoparticles/Method	Applications Purpose	Ref
AcDex	Hyperforin	Nanospheres; Hyperforin-loaded AcDex-base NPs formulated via single emulsion /solvent evaporation using ethyl acetate and water	Anti-inflammatory activity	(7–9)
F108: PEG-PPG-PEG	Curcumin (Cur)	Colloidal Nanocapsules; Cur-loaded PEG-PPG-PEG NCs	Anticancer	(3,10)
Biopolymer of PCL	Amphotericin B (Amp.B)	Nanocapsules; PCL-NCs loaded with Amp B, obtained by nanoprecipitation method	Anti-leishmania (Leishmania infection), antifungal	(6)

AcDex—acetalated dextran; F108—poly(ethylene oxide)-block-poly (propylene oxide)-block-poly(ethylene oxide); NPs—nanoparticles NCs—nanocapsules; PCL—poly(ε-caprolactone); PEG—poly(ethylene glycol)

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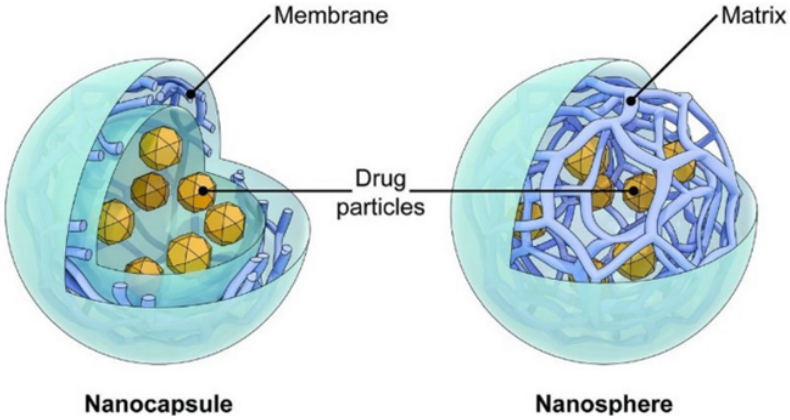

Figure 1. Schematic structure of nanocpasules and nanospheres[1].

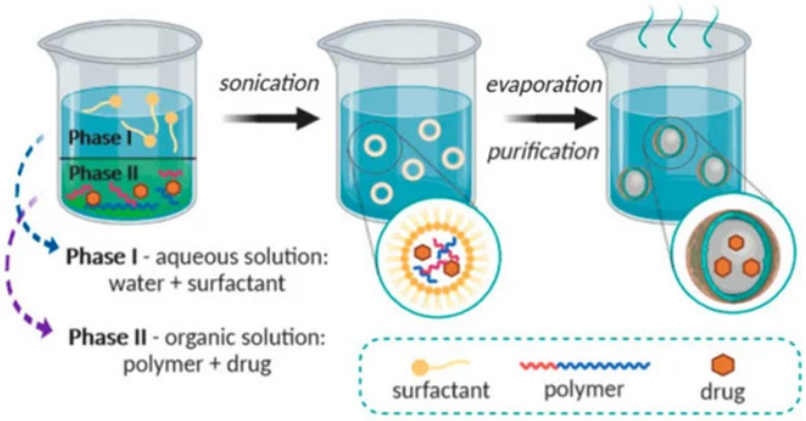

Figure 2. The Method of solvent evaporation[2].

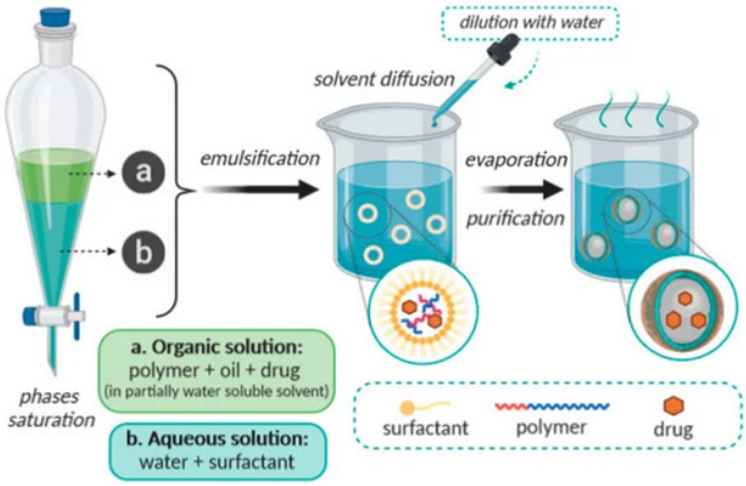

Figure 3. The Method of emulsification/solvent diffusion[2].

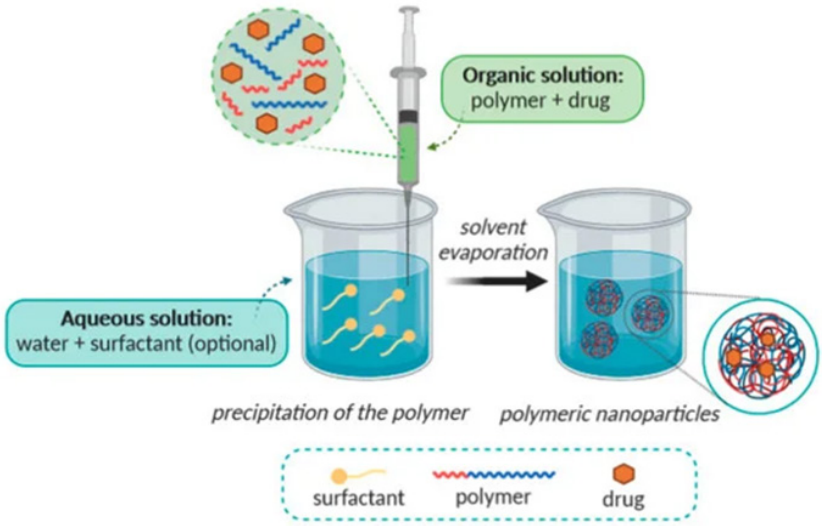

Figure 4. The method of nanoprecipitation[15].

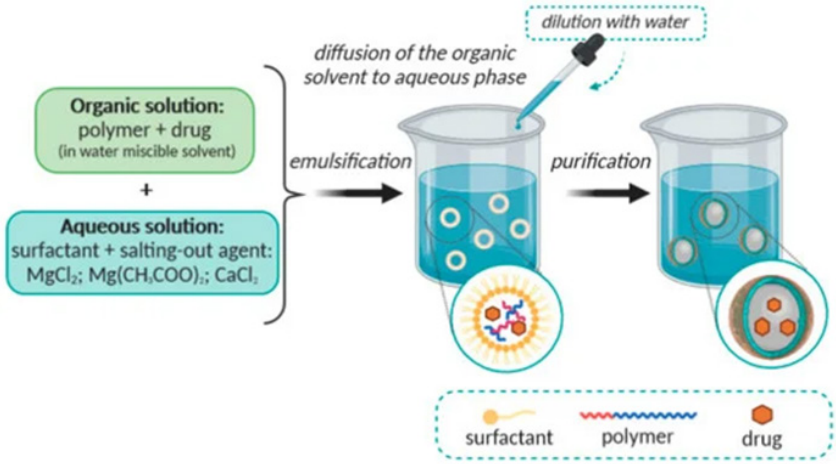

Figure 5. The Method of emulsification/reverse-salting out[15].

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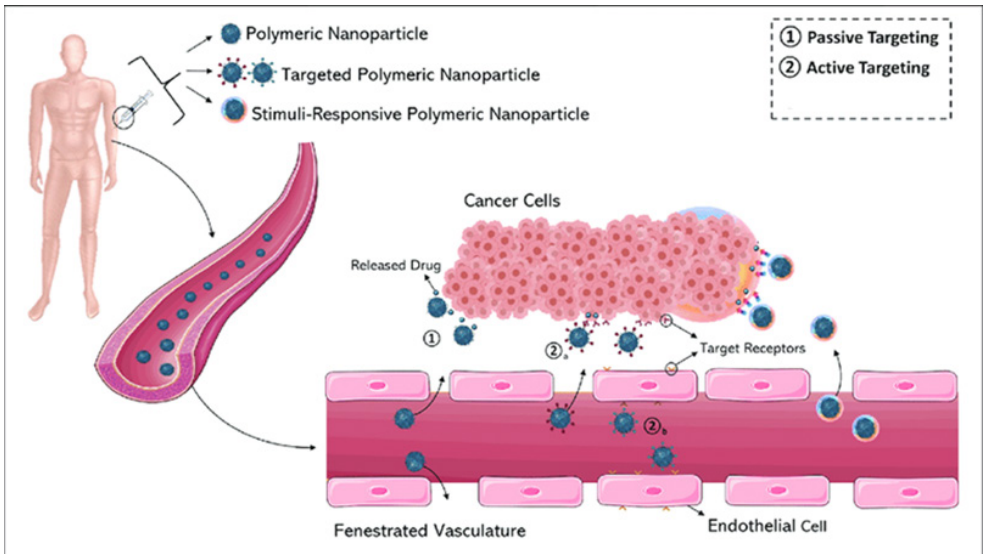

Figure 6. Passive and active targeting of polymeric nanoparticles[4].

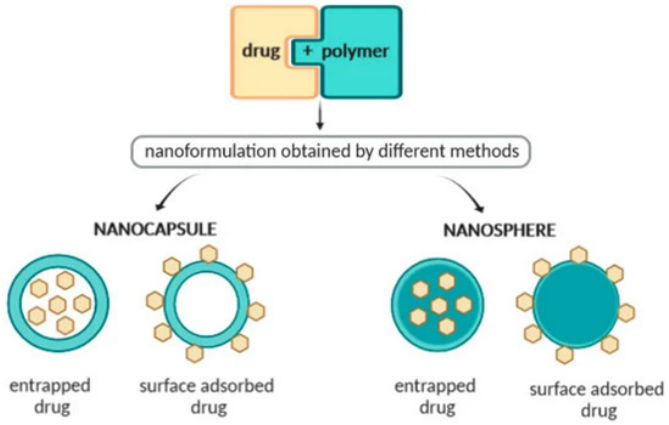

Figure 7. Surface adsorption and encapsulation of drugs on nanocapsules and nanospheres[15].

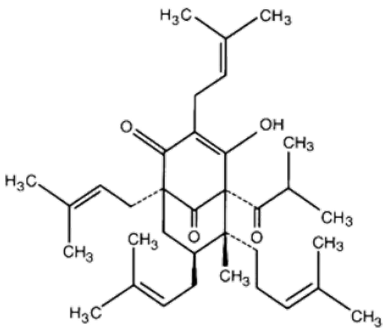

Figure 8. Structure of hyperforin used as the drug[38].

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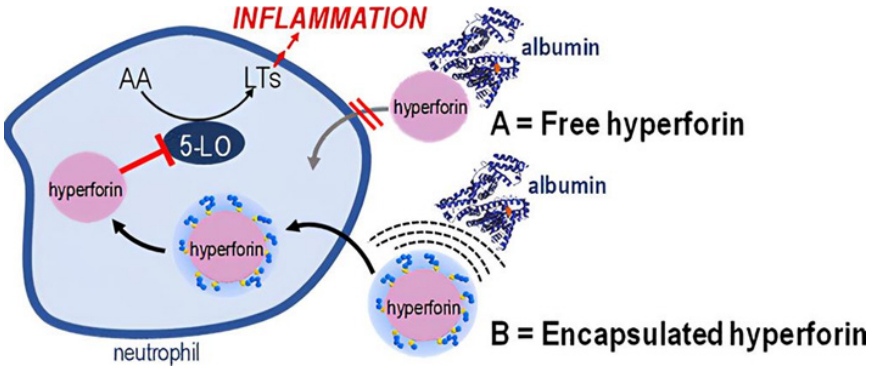

Figure 9. Hyperforin encapsulated polymeric nanoparticles[9].

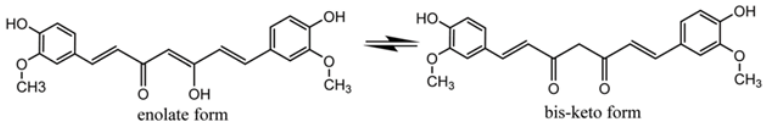

Figure 10. Chemical structures of curcumin tautomers[44].

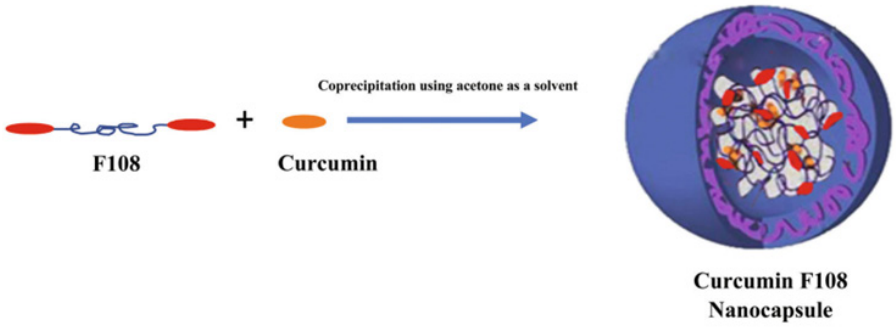

Figure 11. Schematic illustration showing the formation of curcumin-F108 nanocapsules[44].

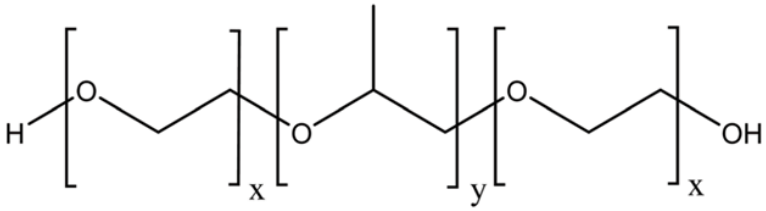

Figure 12. Structure of Triblock Copolymers[44].

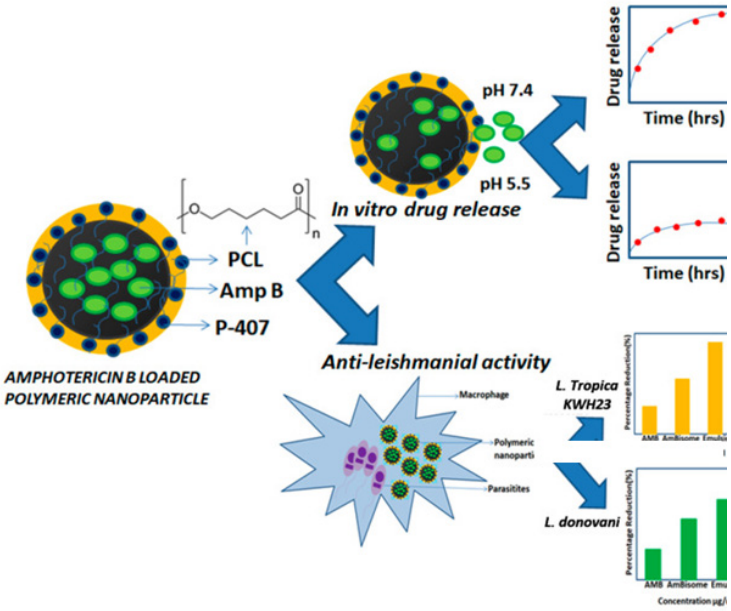

Figure 13. Amphotericin B (Amp B) loaded polymeric nanoparticles preparation to in vitro drug release and anti-leishmanial activity[50].