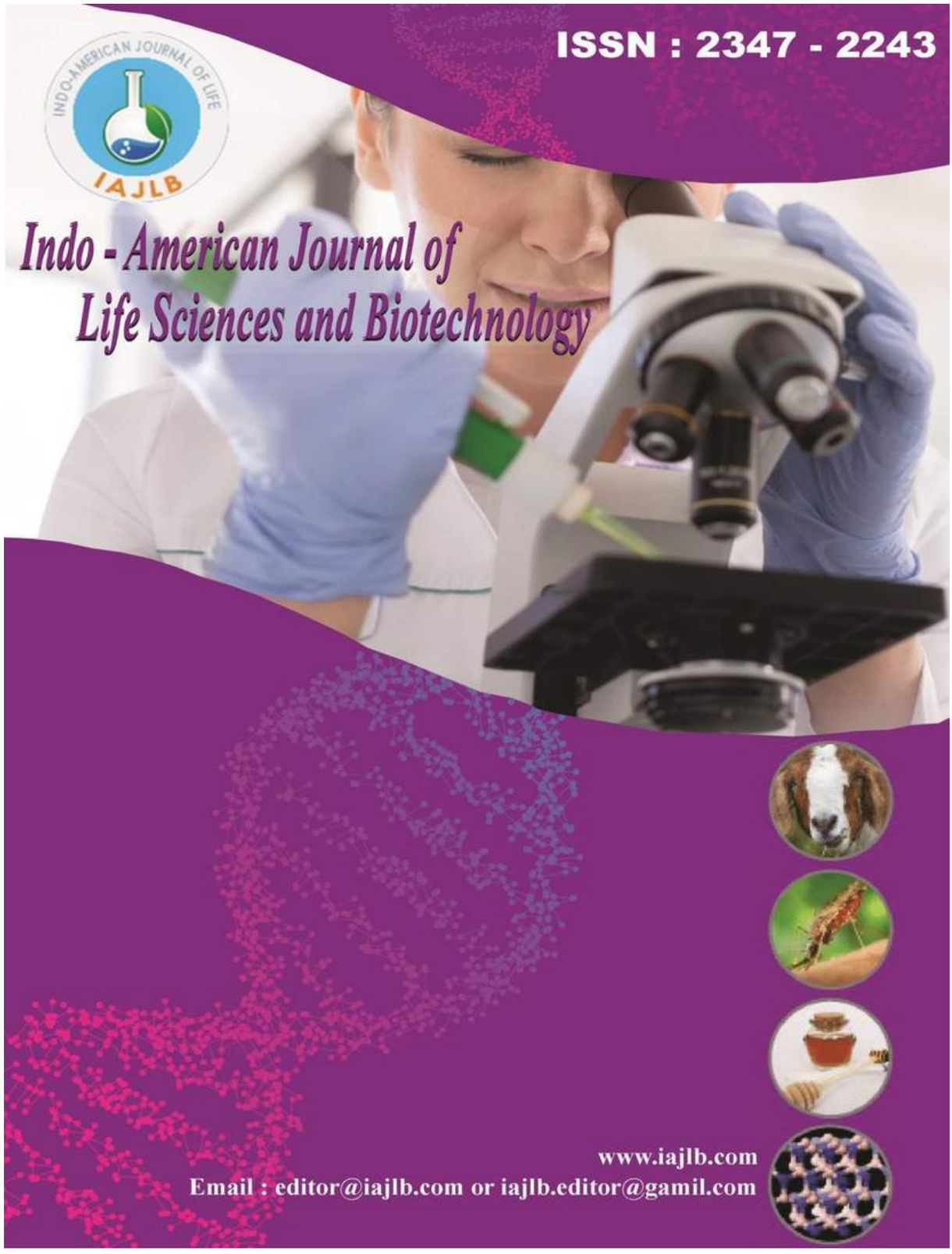
Received: October 21, 2024 | **Accepted:** February 13, 2025 | **Published:** July 4, 2025

DOI: https://doi.org/10.62644/iajlb.2025.v22.i3.pp1-26 Indo-Am. J. of Life Sc & Bt | Vol. 22, Issue 3, 2025 | pp 1-26



Received: October 21, 2024 | **Accepted:** February 13, 2025 | **Published:** July 4, 2025

DOI: https://doi.org/10.62644/iajlb.2025.v22.i3.pp1-26 Indo-Am. J. of Life Sc & Bt | Vol. 22, Issue 3, 2025 | pp 1-26

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ISSN 2347-2243
www.iajlb.com
Indo-Am. J. of LifeSc & Bt.,2025 *Vol.22 Issue.3, Aug 2025*

Indo-American Journal of Life Sciences and Biotechnology

Materials for Pharmaceutical Dosage Forms: Aspects of Controlled Release Drug Delivery and Molecular Pharmaceutics

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Abstract: Compared to immediate release distribution, controlled release delivery has several benefits (such as microparticles and nanoparticles) and is accessible for a variety of administration methods. These benefits include less frequent dosing, improved therapeutic control, and fewer adverse effects; as a result, patients are more receptive to these dose forms. Numerous commercialized controlled release products have been made possible by advancements in polymer material science, particle engineering design, manufacturing, and nanotechnology. Several more are now in pre-clinical and clinical research.

Keywords: pharmaceutical dosage forms, copolymers, biomaterials, biodegradable, microparticles, nanoparticles, particle engineering design, and manufacturing.

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1. Introduction

Better treatment and disease state management for patients via controlled release medication delivery, especially as microparticles and nanoparticles, has been made possible by biodegradable and biocompatible materials for pharmaceutical dosage forms. Compared to immediate release delivery, controlled release distribution has several benefits and is accessible for a variety of administration routes. The types and classes of pharmaceutical polymers that are biocompatible and biodegradable, the kinds of pharmaceuticals that are encased in pharmaceutical polymers, controlled drug delivery using microparticles or nanoparticles, and particle engineering are all covered in this study.
create technology and produce authorized controlled release medication items, as well as controlled release microparticles and nanoparticles.

2. Controlled Drug Release Technology of Drugs

The concentration of released medications from polymeric matrices must fall within the therapeutic window and have little variation in blood levels over extended periods of time at the site of action in order to effectively treat illness [1–3]. Diffusion, erosion, osmotic-mediated processes, or combinations of these mechanisms may regulate drug release [4,5]. A triphasic release pattern is typically seen, with an initial burst [4], which is mainly ascribed to drug precipitates at the particle surface and polymer surface pores, as well as osmotic forces in highly water-soluble peptide formulations [6]. This is followed by a lag period that is contingent upon the molecular weight and polymer end-capping [5], and finally erosion-accelerated

ISSN 2347-2243
www.iajlb.com
Indo-Am. J. of LifeSc & Bt.,2025 Vol.22 Issue.3, Aug 2025
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release [6].

A reduction in particle size (i.e., an increase in the specific surface area) leads to increased release when release rate control is taken into consideration as a crucial component [6]. Additionally, a bigger inner surface caused by increased particle porosity may boost the release medium's influx into the particles, which will speed up the drug's diffusion rate [7]. Furthermore, the drug release rate will be greatly impacted by the particular characteristics of the polymer matrix, such as the chain length, flexibility and swelling behavior, and possible interactions between the polymer and drug [8,9]. The diffusion and drug release rate will thus change if a different molecular weight or an end group capped polymer is used, as well as if block copolymers are used [10,11].

3. A mix of fast- and slow-releasing particles or the usage of copolymers are potential alternative advanced ways to achieve zero-order release kinetics suggestive of uniform release with respect to time, which is sought for the majority of applications [12,13]. Co-injecting zero-order releasing microspheres as a maintenance dosage with a bolus of soluble medication as a loading dose may result in a one-time only dose.

4. Types and Classes of Biodegradable and Biocompatible Pharmaceutical Polymers

A polymer's biodegradability and biocompatibility are two of its most crucial characteristics for use in pharmaceutical applications. The two general steps of biodegradation are as follows: (1) water enters the polymeric matrix and attacks the chemical bonds by hydrolyzing them, which shortens the length of the polymer chain and causes a decrease in molecular weight, fragment metabolism, and bulk erosion; and (2) surface erosion of the polymer happens when the rate at which the water molecules enter the matrix is slower than the rate at which the polymer is converted into water-soluble materials. The term "biocompatibility" describes a material's particular qualities that prevent harmful or toxic effects on biological systems. Irreversible tissue damage, including necrosis, severe fibrosis, dystrophic calcification, and permanent tissue loss, may be brought on by non-biocompatible materials.

It should be remembered, nonetheless, that high biocompatibility does not guarantee high biodegradability. Thermoresponsive hydrogels are made of poly(N-isopropyl acrylamide) (NIPAAM), which is non-toxic and biocompatible but not hydrolyzable. Examining the biodegradability and biocompatibility of produced copolymers is crucial [15,16].

4.1. Polyester-Based Synthetic Polymers

Over the last several decades, biodegradable aliphatic polyester-based drug delivery technologies have made significant advancements. The FDA has approved common polymers like poly (ε-caprolactone) (PCL), poly (lactide acid) (PLA), and poly (lactic-co-glycolic acid) (PLGA) for use as matrices in controlled release drug delivery systems because of their non-toxic, biodegradable, and biocompatible qualities (Figure 1 and Table 1). One of the most researched diblock copolymer biomaterials for drug encapsulation is poly (lactic-co-glycolic acid) (PLGA), which is found in a number of pharmaceutical products that are sold commercially. Over the last 20 years, poly (lactide acid) (PLA) homopolymer has lost its widespread application due to its sluggish rates of breakdown and drug release. Whereas PLA

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Indo-Am. J. of LifeSc & Bt.,2025 Vol.22 Issue.3, Aug 2025
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distributes medications over months, PLGA heteropolymer breaks down comparatively more quickly and may meet release parameters in as little as two to six weeks [7].

PLGA's molecular weight, distribution, lactide/glycolide ratio, polymer end-group, micro/nano particle size, pH, and release medium temperature are all factors that affect how quickly it degrades. In general, PLGA with a low molecular weight breaks down more quickly, which results in a greater initial burst and quicker drug release [17]. The lactide:glycolide ratio determines PLGA's hydrophilicity, which influences the release rate in a formulation of micro/nanoparticles. The medication release rate falls when the lactide/glycolide ratio rises [18]. The primary function of PLGA's carboxyl end groups is to interact with drugs. An ionic interaction between the peptide's amino group and the PLGA's terminal carboxyl group causes the first burst release when a peptide adsorbs to hydrophilic PLGA [10,11]. Additionally, free carboxyl groups' hydrophilic and acidic qualities promote quicker water absorption and ester bond hydrolysis, which increases the number of acidic groups produced by the autocatalytic cycle [19]. Particle preparation techniques and drug-polymer interactions are crucial factors in polymer breakdown for particulate drug delivery systems. Higher emulsification rates [20] and ultrasonic treatment [6] may decrease particle size, increasing the surface area per unit volume and causing the particles to degrade more quickly when exposed to the release media.

Unlike PLGA, Poly (ε-caprolactone) (PCL) has a slow rate of degradation and good permeability to tiny drug molecules, making it appropriate for long-term, prolonged administration over a period of more than a year. The ability to avoid acidic conditions has emerged as one of the main benefits for using PCL as a drug carrier, even though PLGA creates an acidic environment during breakdown that may cause peptide/protein instability [21].

Poly(ethylene glycol) (PEG), often referred to as polyethylene oxide (PEO), is a polymer that is widely used for its "stealth" qualities and improved chemical and physical stability of medications. The technique for the covalent attachment of mPEG to proteins, known as PEGylation, was first reported by Abuchowski, Davis, and others in 1977 [22]. PEG is an amphiphilic polymer that dissolves in both organic solvents and water. It is made up of repeated ethylene oxide subunits. Generally speaking, PEG's characteristics that are especially important for pharmaceutical applications are: (1) longer circulation time because it avoids renal or cellular clearance mechanisms; (2) increased solubility and stability; (3) decreased antigenicity and escape from phagocytosis and proteolysis; and (4) lower dosage frequency with less toxicity [10,23,24]. PEG's rate of degradation is influenced by both its molecular weight and concentration. The mechanism of deterioration is accounted for by PEG's high hydrophilia and the hydrogen-bonding interaction with water [23].

There are some parallels with polyvinyl alcohol (PVA), a homopolymer with detectable surface activity

with PEG in that it consists of a hydrophilic repeating monomer unit, as seen in Figure 1. PVA serves a number of purposes in controlled release delivery systems, such as serving as a particle matrix [25], hydrogel [26], and a surfactant in emulsion systems when micro/nanoparticle formulation is being done [27–29]. A polymeric substrate chain may be used to graft PVA [30, 31]. For instance, sulfobutyl or amine moieties can be added to the PVA backbone of PVA-grafted PLGA polymer to create negatively or positively charged properties. This increases the polymer's hydrophilicity, which is advantageous when transporting delicate biomolecules like proteins, peptides, and DNA [30].

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Indo-Am. J. of LifeSc & Bt.,2025 Vol.22 Issue.3, Aug 2025
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Poly(N-vinylpyrrolidone) (PVP) has been widely employed in controlled release drug delivery because of its good aqueous solubility, chemical stability, and biocompatibility, as seen in Figure 1 and Table 1 [24,32]. Furthermore, PVP in combination with a polymer matrix has been shown to decrease nonspecific protein adsorption [33]. Commercially accessible and often used in pharmaceutical dosage forms, Kollidon®SR is a compressible polymeric mix made of polyvinyl acetate (PVAc) and povidone (PVP) [34]. Kollidon®SR has special qualities due to the amorphous form of PVAc and its low glass temperature (Tg) of 28–31 °C. The matrix forms drug release routes by the slow leaching of water-soluble PVP [35]. Owing to their exceptional solubility, Kollidon®'s soluble grades typically don't slow down the dissolution of medications. They can be used as a hydrophilic component in dosage forms that contain controlled-release excipients, like cellulose derivatives, cetyl alcohol, alginate, polyactic acid, polyvinyl alcohol, ceresine wax, stearic acid, or methacylate copolymers, as binders, or occasionally as plasticizers [34].

4.2. Natural Origin Polymers Used as Pharmaceutical Excipients

Because they resemble the extracellular matrix in the human body and have advantageous specific properties that can be used for "smart" systems, like stimuli-responsiveness, naturally derived polymers—with a focus on polysaccharides and proteins—have gained popularity in biological applications of controlled release systems. One or two alternating monosaccharides make up the class of biopolymers known as polysaccharides. These biopolymers vary in the kinds of connecting units, the degree of branching, and the length of the chain of monosaccharides [36]. The FDA-approved natural origin polymers and their delivery methods are listed in Table 1.

The physical characteristics of starch, which is made up of amylose and amylopectin, are often altered by adding plasticizers such glycerol and water. This increases the starch's flexibility, which is advantageous in pharmaceutical applications [37, 38]. Furthermore, by making up for the weaknesses of plasticized starch, which exhibit poor tensile strength, Young's modulus, and moisture sensitivity, cross-linking procedures may result in sophisticated drug delivery systems [39]. Starch's high hydrophilicity gives it bioadhesive qualities [8], which are advantageous for the distribution of ophthalmologic drugs (such as flurbiprofen and timolol) [40].

N-deacetylation of chitin produces chitosan, a polyaminosaccharide. Because hydroxyl and amino groups form a strong intramolecular hydrogen bond, chitosan is thermostable. Because of its vast number of amino groups, chitosan exhibits reversible pH-sensitive behavior, making it a weak poly-base that may be used in hydrogel smart delivery systems. Because the amino groups are protonated, chitosan is soluble in water and organic acids including citric, tartaric, acetic, and formic at low pH

Because it can be stored and sterilized, alginate, a polysaccharide produced from marine sources, is a readily accessible option for controlled release systems [43]. Composed of β-D-mannuronic acid (M) and α-L-guluronic acid (G), alginate is an anionic block copolymer.

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Indo-Am. J. of LifeSc & Bt.,2025 Vol.22 Issue.3, Aug 2025
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Table 1. Polymeric inactive ingredients for FDA-approved drug products.

	Polymeric inactive ingredients for FDA-approved drug products
Polyester-based synthetic polymers	PLGA (for IM, SC uses) Poloxamer (for oral, topical, IV opthalmic, SC uses) Polyvinylpyrrolidone ethylcellulose (for oral use) Sodium pyrrolidone carboxylate (for topical use) Povidone (for oral, intra-articular, IM, Intrauterine, topical, SC, respiratory, opthalmic uses) PLA (for IM use) PEG (for oral, respiratory, topical, IM, IV, opthalmic uses) PVA (for auricular, IM, intraocular, topical uses) KOLLIDON VA 64 (for oral use)
Natural-origin polymers	Starch (for oral, IV, IM, topical) Hyaluronate (for intra-articular, IM, intravitreal, topical uses), Human albumin (for IV, SC, Oral uses) Gelatin (for IM, SC, IV, oral topical uses) Alginic acid (for opthalmic and oral uses) Collagen (for topical use)

There are two ways that alginate might generate a stimuli-responsive hydrogel. Based on the pKa values for the carboxyl acid groups in M (pKa 3.38) and G (pKa 3.65), the first method is via hydrogen bonding at pH values lower than 2. Ionic interactions with divalent metal ions are the alternative method. Ca2+-responsive hydrogel systems may be created because chelating agents like EDTA or phosphate buffer can readily remove Ca2+ ions [44].

A significant carbohydrate component of the extracellular matrix present in cartilage surfaces and synovial fluids is hyaluronic acid [45]. Because it prevents chondrocytic chondrolysis, hyaluronic acid, a great lubricant and shock absorber, improves surface lubrication and lessens joint discomfort in osteoarthritis [46]. Due to its non-immunological properties, hyaluronic acid has been extensively researched for medication administration, notably for transplantation, injection, and gene transfer [45]. When hyaluronic acid is employed as a carrier, its matrix is cross-linked with glurataldehyde [37], carbodiimide [37], or polyethyleneglycol diglycidylether (PEGDG) [46] to prevent fast breakdown and removal.

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The globular protein known as bovine serum albumin (BSA) is a naturally biodegradable, nontoxic, and non-antigenic biopolymer that may be used for regulated medication administration. BSA particles are usually cross-linked using glutaraldehyde and manufactured in moderate circumstances using coacervation or a desolvation procedure [47, 48]. To counteract glutaraldehyde's possible toxicity, polyethyleneimine (PEI) has been proposed [49].

The main protein found in the extracellular matrix is collagen. Although there are now 27 different forms of collagen, type I collagen is the one being studied the most for use in pharmaceuticals [37]. Collagenase, gelatinase, and other non-specific proteinases may break down collagen, and cell penetration-induced structural contraction is one of the elements that affects collagen's degradability [50]. Due to its many uses, such as its high mechanical strength, strong biocompatibility, low antigenicity, and water absorption capabilities, collagen is one of the most beneficial biomaterials for tissue engineering. Collagen sponge [51] and collagen gel [52] are two examples of these tissues.

Collagen is processed alkalinely and acidically to produce gelatin, a denatured protein [37]. Gelatin may be produced in a range of isoelectric values; the most common types are basic gelatin, which has an isoelectic point of 9.0, and acidic gelatin, which has an isoelectric point of 5.0. Basic gelatin with an isoelectric point of 9.0 is better as a matrix if the biomolecule to be released is acidic, and vice versa. Water does not dissolve any of the gelatins. In order to create a hydrogel by cross-liking, gelatin hydrogels that form polyion complexes with proteins will help release proteins that are physiologically active [53].

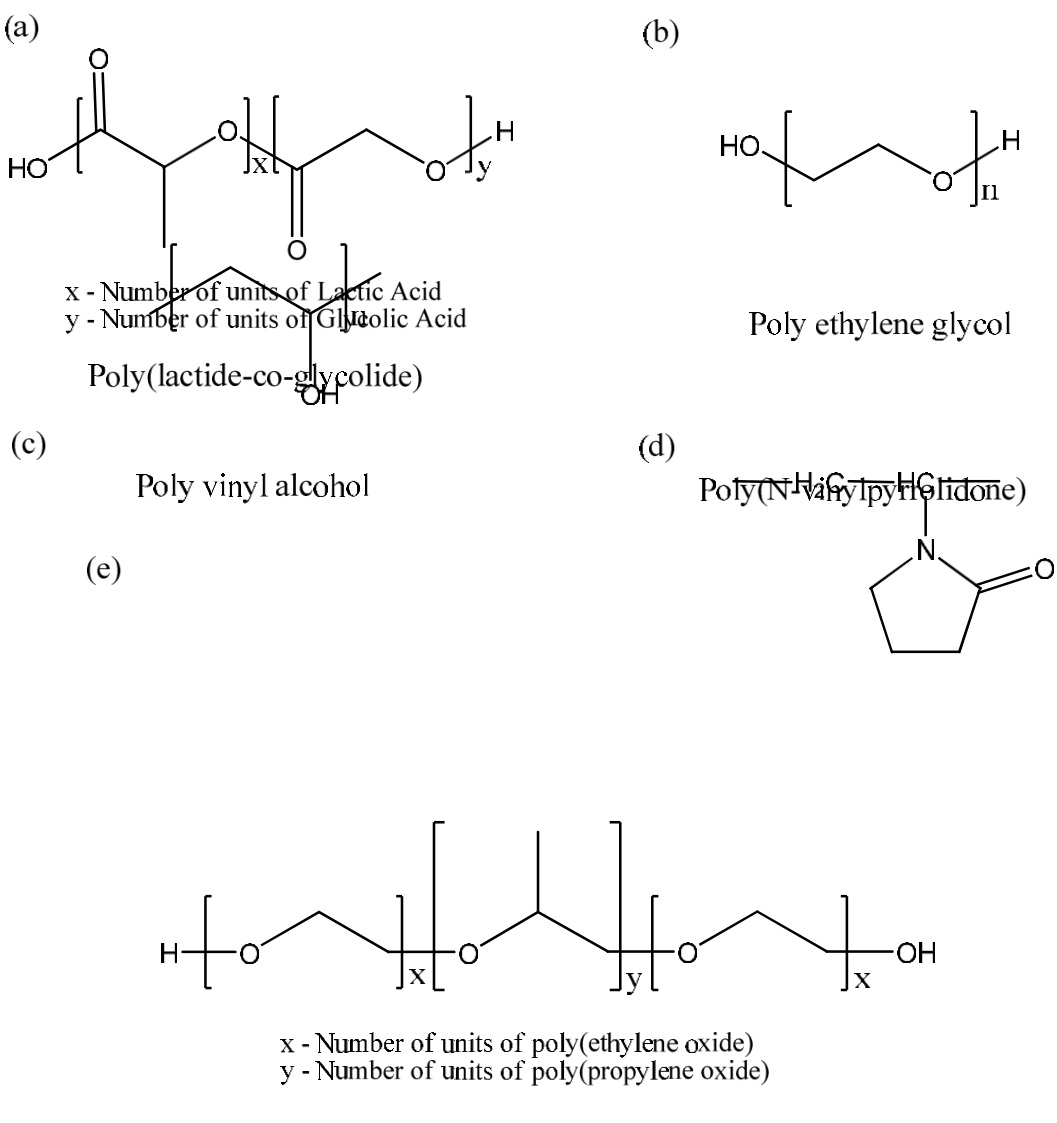
4.3. Homo vs. Diblock Copolymer vs. Triblock Copolymers

Efforts have been undertaken to increase the hydrophilicity, biodegradation rate, and drug stability of polymers in order to improve their desired qualities as a matrix for a controlled drug delivery system. Poly (ethylene oxide)/poly (ethylene glycol), or PEO/PEG, is the most often utilized hydrophilic block for polymeric drug delivery systems. PEO's low toxicity and biocompatibility have earned it FDA approval for parenteral administration [10]. The PEO moiety's ability to effectively prevent protein adsorption to hydrophobic surfaces is one of its main benefits. The length of the PEO blocks in polymeric micelles influences their circulation duration and phagocyte absorption; longer chains result in longer circulation times and lower phagocytosis [54]. PEG (Figure 1), a shell-forming substance for polymeric micelles, gives the micelle a "stealth character" in the blood compartment when combined with PEO, resulting in extended circulation [55]. Because tethered PEG strands have steric repulsion properties, PEG grafted onto the surfaces of nanospheres has been shown to decrease thrombogenicity and improve dispersion stability in aqueous media [56]. In type 2 diabetic rats, glucagon-like peptide-1 (GLP-1) is administered for two weeks using PLGA-PEG-PLGA (ReGel) as a controlled release formulation [16]. To hasten the healing of diabetic wounds, PEG-PLGA-PEG triblock copolymers containing TGF-β1 have been developed [57]. PVA-graft-PLGA, a first-generation PVA-based branching graft polyester carrying PLGA block, exhibits regulated release profiles and reduced burst effects depending on the copolymer's structure and molecular weight [58]. As a second generation, branching poly[sulfobutyl-poly(vinyl alcohol)-g-(lactide-co-glycolide)] (SB-PVA-g-PLGA) was described, where the sulfobutyl groups are covalently attached to the PVA backbone to generate a negatively charged polymer [59,60]. By adding different amino groups to the positively charged PVA backbone, amine-PVA-g-PLGA, the third generation, was created [61].

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The nonionic triblock copolymers known as poloxamers, or Pluronics, are made up of hydrophilic poly(ethylene oxide) (PEO) and hydrophobic poly(propylene oxide) (PPO) blocks, which are referred to as PEO-PPO-PEO [62]. Poloxamer's amphiphilic nature allows it to self-assemble into micelles above the critical micelle concentration (CMC) in aqueous solutions while also exhibiting surfactant capabilities. Furthermore, it has been shown that these copolymers are strong biological response modifiers that may improve drug transport across cellular barriers, including the brain endothelium, and overcome drug resistance in cancer [63,64].

Figure 1. Structures of biodegradable and biocompatible polymers.



5. Therapeutic Agents Encapsulated in Polymeric Particles

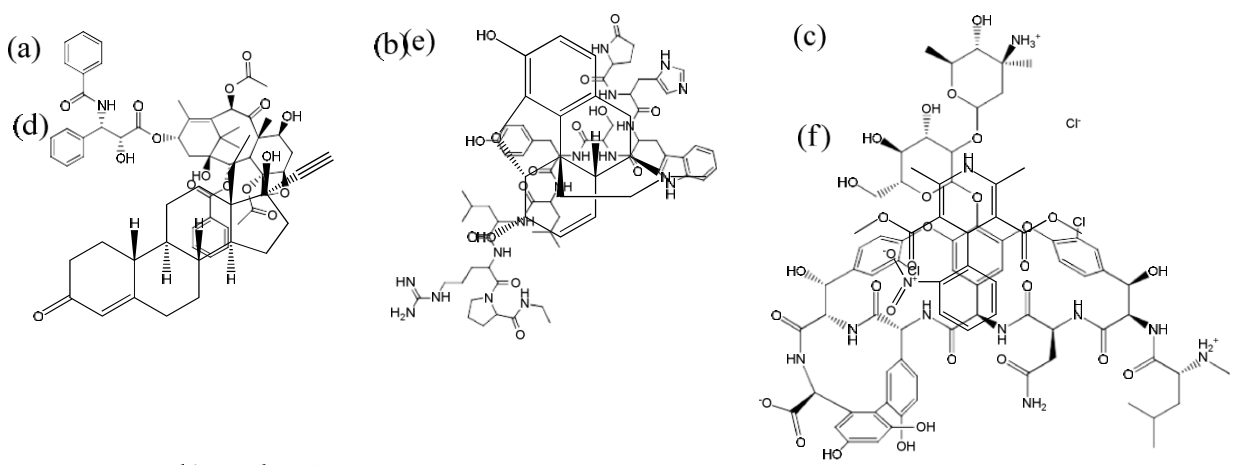
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In order to achieve full drug absorption in the systemic circulation and regulate drug release over a predefined time span ranging from days to weeks to months, the administration of a variety of medications from various therapeutic classes encapsulated in polymeric particles (Figure 2), especially through the parenteral route, has been thoroughly studied.

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Paclitaxel Morphine

Figure 2. Various therapeutic agents from different therapeutic classes that have been encapsulated in polymeric particles.



Levonorgestrel(Norplant®) Leupolide (Lupron®) Vancomycin Nifedipine (Procardia XL®)

Because low tumor cell drug-burden will result in poor cell apoptosis and early drug resistance development, achieving appropriate drug levels at the tumor cell is the most important problem in chemotherapy [65]. Polymeric particulate delivery systems have been successfully used to formulate chemotherapeutic agents (Figure 2), including paclitaxel [66–68], docetaxel [69], vascular endothelial growth factor siRNA [70,71], 5-fluorourasil [72,73], doxorubicin [74,75], adriamycin [76], gancyclovir [77], celecoxib [78,79], bleomycin [80,81], and tamoxifen [29].

Opioids (Figure 2) are essential for managing severe and persistent pain linked to cancer and several chronic illnesses. In order to enhance patient compliance and, therefore, the quality of life for patients with chronic pain, a number of medications have been created to achieve sustained drug release, including morphine [82,83], nalbuphine [84], tramadol [85], buprenorphine [86,87], fentanyl [88,89], and hydromorphone [90]. Additionally, encapsulated medication microspheres have been created for non-steroidal anti-inflammatory medicines (NSAIDs), including celecoxib [93,94], diclofenac [95,96], indomethacin [97,98], flubiprofen [91], ibuprofen [92], and celecoxib [93,94]. Opioids have also been linked to a number of local anesthetics [90,99]. Drug-encapsulated polymeric particulate systems including lidocaine [100], tetracaine [101], bupivacaine [90], and ropivacaine [102] were investigated.

By reducing the bacterial burden at the infection site, antibiotic medication distribution will reduce systemic, liver, and renal toxicities. The use of controlled drug release systems has the benefit of lowering systemic toxicity and drug resistance while preserving a highly site-specific medication concentration for a longer amount of time. Controlled release methods that include antibiotics (Figure 2) include

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Vancomycin [104], amphotericin B [105], gentamicin [106,107], doxycycline [108–110], and chlorhexidine [103].

For formulations with continuous release, growth hormones and birth control hormones (Figure 2) have received the greatest attention. One common method to extend the effects of growth hormone is to encapsulate it in biodegradable PLGA microspheres. By keeping in vivo drug levels within the therapeutic range, human growth hormone, a somatotropic hormone used to treat growth hormone deficiency (GHD), chronic renal insufficiency, Turner's syndrome, and cachexia secondary to AIDS, can lessen the need for frequent administrations [28,111,112]. However, octreotide, a synthetic anti-somatotropic drug used to treat endocrine tumors and acromegaly, has been made in PLGA microspheres and is sold monthly under the brand name Sandostatin® LAR® depot (Novartis Pharma, Basel, Switzerland) [113]. Over time, birth control hormone delivery using polymers has changed. Six levonorgestrel contraceptive implants were used in the initial system, Norplant®, for a period of five years. It was possible to release the same amount of contraceptive steroid delivered by six capsules through two rods by substituting the original model of silastic capsules containing steroid crystals with a solid mixture of the steroid and a polymer (rods) covered by a release-regulating silastic membrane. This is known as the Jadelle® second generation implant system [114]. These goods, however, are silicone-based devices that have significant long-term toxicities and are not biodegradable. As a result, the devices must be taken out after the medicine has run out. Levonorgestrel has been investigated for PLGA microsphere implantation under the skin without the need for specialized surgery in order to address this issue [115–118].

Because of the nature of the illness, problematic side effects, and recurrent symptoms, patient compliance rates with antipsychotic drugs are famously low. In the administration of antipsychotics, sustained and controlled release methods unquestionably provide several benefits, including decreased dosage frequency and improved drug bioavailability [119]. Long-acting particulate formulations of haloperidol [120], risperidone [121,122], clozapine [123], and olanzapine [124] have been and are being researched.

For certain oral dose formulations, the primary release mechanism is osmotic pumping. Osmotic pressure serves as the driving force in this mechanism, causing consistent and predictable medication release. The osmotic pump is made up of a solid core that contains a medicine, either by itself or in combination with an osmotic agent, and is encased in a semi-permeable membrane with a delivery hole. A volume of saturated medication solution is forced through the delivery orifice in a predetermined way when this device is submerged in water because the water is osmotically absorbed into the core [125,126]. Osmotic pump controlled release formulations of propranolol [127], nifedipine [128], allopurinol [129], ferulate [130], diclofenac [131], and pseudoephedrine [132] have been developed.

6. Types of Polymeric Pharmaceutical/Drug Delivery Particles

6.1. Microparticles for Controlled Release Delivery

Current protein and peptide delivery formulations on the market have decreased administration from once a month to every three months as a result of the development of particle drug delivery systems. Microparticles are particles that range in size from 0.1 to 100 µm. Singh and Kang examined the

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Indo-Am. J. of LifeSc & Bt.,2025 Vol.22 Issue.3, Aug 2025
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impact of additives on the in vitro release and physicochemical properties of bovine serum albumin (BSA), a model protein [133]. BSA is further released from PLGA microspheres by the addition of hydrophobic tricaprin additives with low molecular weight PEG-100. The surface morphology of the control and additive-containing microspheres has a direct impact on the differences in their release patterns.

In addition to using stabilizer, Blanco and Alonso examined the size impact of preparation technique, w/o/w solvent extraction against o/o solvent evaporation, and encapsulation efficiency [134]. The inherent viscosity of the polymer solution determined the size of the microspheres produced using the two distinct techniques. While microspheres made by o/o solvent evaporation grew in size with low viscosity polymers, microspheres made by the w/o/w solvent extraction technique grew in size as the inherent viscosity of the polymer solution rose. BSA was released more slowly and with reduced loading efficiency when a stabilizer, such as poloxamer 188 or 331, was co-encapsulated. In the absence of a stabilizer, the pace at which polymers erode and create water-filled channels primarily affect protein release.

Using the phase inversion approach, the impact of protein molecular weight (MW) on release kinetics from polymeric microspheres was investigated. For microspheres with low loading (0.5–1.6%), the release mechanism seems to be reliant on protein MW, whereas for microspheres with high loading (4.8–6.9%), it is independent. While smaller MW proteins seemed to rely on diffusion through pores initially and on degradation subsequently, the release of larger MW proteins at low loading was reliant on diffusion through pores over the course of the research [135].

7. Recent studies on medication delivery to bone tissue have been intriguing and have focused on tissue engineering in the setting of controlled release drug administration. For regulated medication administration in bone tissue, 3D scaffolds have included polymer microspheres as drug delivery vehicles [136–138]. Furthermore, polymeric devices and PLGA microspheres for regulated medication delivery to bone have been developed to include protein and small molecule therapies to support bone formation [139–143].

7.1. Nanoparticles for Controlled Release Delivery

Pulmonary nanomedicine delivery is one of the many administration routes for which the field of nanoparticle drug delivery has attracted a lot of interest recently [144]. Barichello et al. used the nanoprecipitation solvent displacement approach to create surface-bound peptides in order to increase the bioavailability of PLGA nanoparticles [145]. The quantity of insulin encapsulated into the nanoparticles was correlated with the pH and content of the buffer solution; the ideal pH was around the isoelectric point of insulin. Insulin was predominantly surface bound to the PLGA nanoparticles.

Using Pluronic F68 as a stabilizer, w/o/w and s/o/w encapsulation techniques were used to create insulin-loaded PLGA nanoparticles. The batches made using the w/o/w approach with stabilizers had a greater insulin release rate than the nanoparticles made using the s/o/w method. Additionally, stabilizers caused a prolonged release of insulin, which in turn caused the blood glucose level in diabetic rats to drop over time [146].

Drug delivery to specific locations, such cancers, and the development of in vivo imaging are two applications for magnetically manipulated nanoparticles. Magnetic nanospheres may also be used as non-

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targeted contrast agents (MRI) and as drug carriers that are triggered by an external magnet [147]. This magnetic force was used in a different investigation to increase the effectiveness of oral

8. administered protein treatments. The transit time of magnetic particles decreased when an external magnetic field was supplied to the gut; as a result, the oral particles' resident time in the small intestine was prolonged, and protein absorption increased [148].

9. Manufacturing/Particle Engineering Design of Polymeric Microparticles and Nanoparticles

9.1. Double-Emulsion Evaporation Methods

Many hydrophobic medications are weakly soluble in water and soluble in a variety of organic solvents that are water-immiscible. The medication and biodegradable polymer are first dissolved in a solvent, often methylene chloride, using the emulsion/solvent evaporation process. O/W emulsion is created by emulsifying the resultant organic oil phase in an aqueous phase. Evaporation may be used to extract volatile solvents from this emulsion [7]. However, butyl acetate, ethyl acetate, ethyl formate, or methylene ketone may be used in lieu of methylene chloride for medications that do not have a high solubility in it [7]. As an alternative, methylene chloride may be mixed with a cosolvent. To create a w/o or w/o/w emulsion system, hydrophilic proteins or peptides are either treated in an aqueous solution of water-in-oil (w/o) emulsion or dispersed in an organic solution of polymer [149]. However, because of a flow of pharmaceuticals from the dispersed phase to the greater volume of the continuous phase during the production process, it is anticipated that o/w or w/o/w techniques would result in poor encapsulation efficiencies [7]. Furthermore, proteins that have been encapsulated into particles using w/o or w/o/w methods are prone to denaturation, which may lead to a loss of biological activity, aggregation, oxidation, and cleavage, particularly at the interface between the aqueous phase and the solvent [149]. During the initial emulsion phase, stabilizers and surfactants are recommended to enhance protein integrity.

9.2. Supercritical Fluid (SCF) Technology

When a substance is elevated over its critical point, it transforms into a supercritical fluid (SCF), which has the dissolving characteristics of a liquid and the flow characteristics of a gas. Pressure, temperature, and density all have an impact on their solvent power. There are several high-quality evaluations available on this state-of-the-art particle engineering design method, which has shown growing potential in innovative delivery systems for a variety of administration routes, including non-invasive pulmonary delivery by pharmaceutical inhalation aerosols [150–153].

Both the rapid expansion from supercritical solution (RESS) and the gas-saturated solution (PGSS) procedures are viable ways for the drug and matrix polymer to dissolve or melt in the SCF and then form particles. Two phases make up the RESS process, which produces tiny particles utilizing a supercritical fluid as a good solvent: (1) dissolving the solute in a supercritical fluid; and (2) fast supersaturation, which forms the solute as a microparticle [154]. Because it is plentiful, affordable, non-toxic, and has a reasonably accessible critical point (Tc = 304.2 K and Pc = 7.37 MPa), CO2 is a desirable solvent for a range of chemical and industrial processes [154–156]. The dense gas or supercritical fluid is used as a solute in the PGSS process. Proteins and other polar or high molecular weight materials are challenging to dissolve in CO2, which is polarity-free. However, the creation of composite particles in the PGSS process is made possible by CO2's capacity to permeate into organic molecules. The majority of the organic molecules will be polymers, and CO2 reduces the

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melting point and, when a compound's concentration rises, reduces its viscosity. Consequently, the compounds melt in a compressed gas, and as pressure builds up, the concentration of a gas in a molten solute rises, creating a saturated solution. The escape of gas from the condensed phase during the fast depressurization of this solution via a nozzle may result in the formation of composite microcapsules [154].

9.3. Supercritical Antisolvent Method

Because of its availability, low toxicity, and reasonably accessible critical point, CO2 is the most often employed supercritical fluid in medicinal applications [150,155]. The antisolvent approach uses CO2 as an antisolvent for particle production in addition to RESS and PGSS. Utilizing the high miscibility of supercritical fluids with organic solvents, which have a high dissolving power for the chemical, is a benefit of antisolvent approaches [155]. The methods include the aerosol solvent extraction system (ASES), the solution-enhanced dispersion by supercritical fluids (SEDS) processes, the precipitation with compressed supercritical fluid (PCA), and the supercritical antisolvent (GAS/SAS). The supercritical antisolvent method's (GAS/SAS) basic idea is that adding a second fluid as an antisolvent causes a solvent's solubilization power to rapidly drop. The organic solution swells when the antisolvent is added, dissolving the solute and causing the solution to become supersaturated. To get rid of any leftover solvent, the precipitated particles are cleaned with the antisolvent [154]. A number of variables, including composition, temperature, and pressure, may control particle size [154]. The PCA process involves a two-way mass transfer of CO2 into the organic phase, as opposed to the GAS process's one-way mass transfer. The CO2 diffuses into the organic phase, while the organic solvent diffuses into the CO2. The ASES technique creates solid microparticles by dissolving or dispersing the medicine and polymer in an organic solvent, which is typically soluble in supercritical CO2. The solvent is then sprayed into a supercritical CO2 and extracted [157,158]. The mass transfer of the supercritical fluid into the sprayed droplet and the rate of solvent transfer into the supercritical phase are responsible for the particle creation in the SEDS process. Interestingly, there is less agglomeration and a narrower particle size distribution with a strong mass transfer [159].

9.4. Spray Drying Particle Engineering Design

The effective design and manufacture of food and pharmaceutical particles, particularly those intended for use in medicinal inhalation aerosols, has made extensive use of spray drying [151,160]. The process of spray drying [151] involves four steps: The feed solution is atomized into small droplets in a spray; the spray-air interface involves close flow and mixing; the sprayed droplets are dried at high temperatures; and the dried particles are separated from the air [160]. The spray drying process's operational parameters, including atomization pressure, feed rate, airflow, inlet and outlet temperatures, and nozzle orifice size, must all be regulated in order to regulate the different particle properties [161]. Larger particle sizes are typically produced by a low feed concentration, a smaller nozzle aperture, and quicker atomization airflow [162,163]. The kind of input solvent [164] or the output drying temperature [165] may be adjusted to change the particle shape. Particles with rougher surfaces may be produced by mixing lactose and Tween 20 into the feed solution [165].

The process of spray-freeze drying involves atomizing an aqueous drug solution using an ultrasonic nozzle or a two-fluid into a spray chamber that is filled with either halocarbon refrigerant, such as hydrofluorocarbon or chlorofluorocarbon, or a cryogenic liquid, such as liquid nitrogen [166]. The fast heat-transfer rate causes the liquid droplets to solidify rapidly once they come into contact with the

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cryogenic medium. Following the completion of the spraying procedure, the collected contents are lyophilized, and either vacuum or air freeze-drying is used to remove the frozen solvent [167]. The mass flow ratio of atomized nitrogen to liquid feed, which has the most impact on particle size, should be raised in order to achieve a lower particle size [168]. Small microparticles and nanoparticles may be produced by using spray freeze-drying [169,170].

Marketed Controlled Release Polymeric Pharmaceutical Products and Clinical Trials

Numerous medications encapsulated in polymeric particles have been administered; this approach has been thoroughly studied and has been shown to maximize therapeutic effects and improve patient compliance by allowing for full drug absorption in the systemic circulation and controlled drug release over a specified time period, such as days, weeks, or months. For the treatment of endometriosis and prostate cancer, Lupron® Depot is a microsphere formulation of leuprolide that uses PLA or PLGA and lasts for one, three, or four months. For two weeks or a month, Nutropin®, a commercial PLGA microsphere formulation of human growth hormone, is utilized. Octreotide encapsulated in PLGA microspheres, marketed as Sandostatin® LAR®, is a synthetic anti-somatotropic drug that is used monthly to treat endocrine tumors and acromegaly. Additionally, parenteral microsphere formulation products such as Trelstar® Depot for triptorelin, Suprecur MP® for buserelin, Somatuline LA® for lanreotide, Arestin® for minocycline, and Risperdal Consta® for risperidone have been on the market for a long time [171–176]. Clinical studies are underway for micellar nanoparticles containing cisplatin or paclitaxel [177]. Procardia XL® for nifedipine (Figure 2) and Glucotrl XL® for glipizide are two examples of marketed oral dose formulation products for which osmotic pressure is the primary driving factor in the release mechanism [47,48,178].

Conclusions

Pharmaceuticals have advanced thanks to biodegradable and biocompatible materials for dosage forms, which provide patients improved treatment and illness state management via controlled release. Compared to immediate release delivery, controlled release distribution has several benefits and is accessible for a variety of administration routes. These benefits include less frequent dosing, improved therapeutic control, and fewer adverse effects; as a result, patients are more receptive to these dose forms. Numerous marketed controlled release products containing polypeptide and protein drugs that maintain their therapeutic activity over pharmaceutical timescales after being encapsulated in biodegradable materials have been made possible by advancements in polymer material science, particle engineering design, manufacturing, and nanotechnology.

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