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Biodegradable Polymers and Long-Acting Parenteral Formulations: An Overview

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ABSTRACT:

To treat chronic ailments or other serious disorders, patients are frequently required to take daily prescription medications for long periods of time. A frequent and lengthy dose schedule, however, is typically challenging for most patients to follow. Long-acting parenteral formulations (LAPFs) are preferable to traditional ones in management of several ailments. By extending the release time of drug administration, LAPFs may increase patient compliance and, as a result, treatment outcomes. Biodegradable polymer-based long-acting injectable formulations being frequently utilized as drug delivery systems due to their substantial bioavailability, improved encapsulation, controlled release, and lesser toxic characteristics. This review discusses various biodegradable polymers including PLGA, polycaprolactone, hyaluronic acid, and albumin used in Long-acting injectable formulations, and the work reported using that biodegradable polymer for encapsulation of various drugs.

1. Introduction

For many decades, oral drug delivery formulations have been thought of and supported as a practical method of drug delivery. However, these formulations have drawbacks, including unpredictability in gastrointestinal tract absorption and first pass hepatic metabolism resulting into lowering the bioavailability of medications. This problem has led to the development of alternative drug delivery systems, including modified release oral systems including controlled release as well as sustained release dosage forms. The main flaws with these systems, however, are dose dumping and unpredictable retention times.

Rather than administered through the alimentary canal, parenteral preparations are made for administration by injection via the several layers of skin or another tissue of the exterior boundary, allowing active ingredients to be delivered directly into an organ, tissue, lesion, or blood vessel. Consequently, medications can reach the drug's target site swiftly.[1] Additionally, a variety of parenteral delivery methods, including intravenous, intramuscular, subcutaneous, intraperitoneal, intravitreal, intraarticular, intravesical, and intratumoral, are now available for safe and efficient parenteral therapies. Only injectable water or oil solutions were available in conventional parenteral systems; they lacked any long-acting capabilities. [2,3] Although some patients cannot adhere to regular doses, long-acting parenteral formulations were favoured since patients were frequently required to take daily prescriptions of medications for several years to treat the chronic conditions.

The benefits of long-acting parenteral formulations (LAPFs) include decreased toxicity, fewer doses needed to maintain the drug's action for a longer period of time, and decreased body tolerance. It is desirable to create long-acting formulations using biodegradable polymers. Biodegradable polymers are naturally appealing for utilization for development of dosage forms due to two essential properties. First, it might be conceivable to build systems that give nearly continuous release if polymer just erodes through the surface. Second, because it may be assumed that the implanted or injected system will totally dissolve, no treatment will be required to remove it at the ending of the delivery.[4]

Various approaches have been utilised to create long-lasting polymeric formulations, mostly dependent on the application and the kind of medication to be encapsulated. The most popular encapsulation techniques and biodegradable polymers for long-acting

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injectable formulations are covered in the present review, including PLGA (poly-d, l-lactide-co-glycolide), hyaluronic acid, polycaprolactone, polylactic acid, and albumin, as well as their documented efficacy in encapsulating a range of disease-related medications.

2. PLGA Based Long-Acting Injectable Formulations

An FDA-approved biodegradable polymer with a long list of safety characteristics, PLGA is both physically robust as well as extremely biodegradable. Glycolic acid and lactic acid are major biodegradable metabolite monomers that are created in the body when PLGA is hydrolysed.[5] The effect of composition, crystallinity (or Tg), average molecular weight, type of drug, shape and size of matrix, pH, enzymes, and the effect of drug load are only a few of the variables that affect PLGA degradation.[6] However, a number of encapsulating approaches, including solvent extraction, diffusion techniques, and the solvent emulsion-evaporation method, have been described to generate parenteral preparations employing PLGA. Additionally, PLGA/PEG block copolymers are transformed into di-block (PLGA-PEG) or tri-block molecules, including ABA(PLGA-PEG-PLGA) and BAB (PEG-PLGA-PEG).[7] By acting as an obstacle and decreasing interactions to exterior compounds through electrostatic and hydration repulsive force, this layer of PEG enhances shelf stability.[8] PEG, however, decreases the effectiveness of medication and protein encapsulation in the system. PLGA microspheres and nanoparticles successfully trapped and/or absorbed a large number of encapsulators. Following section discusses a few PLGA-based formulations that are successful in treating several common disorders. Table 1 represents the several research on PLGA based long-acting parenteral formulations.

Parathyroid hormone

Since Parathyroid hormone (PTH [1-34]) has widely been utilised in the treatment of osteoporosis, research in humans has shown that intermittent administration of some PTH analogues exhibits an anabolic impact on bones. The last stage of human articular chondrocyte differentiation is inhibited by PTH (1-34). This includes papain-induced osteoarthritis, which can be treated intermittently by injecting a medication into the joints every three days. However, both of these therapies are uncomfortable for the patients. Thus, PTH (1-34) was encapsulated in PLGA microspheres using a twofold emulsion approach to maintain its persistent effect at a therapeutic concentration level. According to the results of the particle size study, more than 90% of the manufactured microspheres fell within the 51–85 μm range. The microspheres did not aggregate or shatter throughout 35 days after release. The drug release from

Table 1: PLGA based long-acting parenteral formulations

Encapsulant	Formulations	Method of preparation	Encapsulation efficiency	References
Parathyroid hormone	Microspheres	Double emulsion technique	62.7%.	[9]
Risperidone	Microsphere	Solvent extraction and diffusion method	96 %	[10]
Alafenamide, elvitegravir, and emtricitabine	Nanoparticle	Emulsion solvent evaporation	50%, 38 % and 46%	[11]
Olanzapine	Microsphere	Solvent extraction/ evaporation technique	100%	[12]
Aceclofenac	Microspheres	Solvent emulsification-evaporation method	91%	[13]

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microspheres prepared with PLGA (65:35) has been sustained over 19 days along with a concentration ranging from 5 to 100 nM at temperature 37 °C and an encapsulation efficiency of 62.7%, according to kinetic data from the publication of a PTH-specific ELISA analysis (1-34). According to an *in vivo* study, the prepared microspheres are an effective way to treat early osteoarthritis.[9]

Risperidone

Atypical antipsychotic medicine risperidone has fewer extra pyramidal side effects (EPS) than traditional antipsychotics. It is widely used for treatment of bipolar illness and schizophrenia. Risperidone is insoluble in water and has a three-hour half-life. It was contained in PLGA and released gradually over a long time (75:25). The solvent extraction and diffusion process has been used to create the parenteral polymeric risperidone-loaded microspheres. Because of their biodegradability, biocompatibility, and capacity to deliver doses over days to months, one of the most effective sophisticated parenteral medication delivery systems on the market today is based on PLGA microspheres. Both drug loading and microsphere entrapment had potencies of 96% and 39%, respectively. More than 85% of the pure medication was transported through the dialysis bag and into the dissolving medium in less than two hours, according to *in vitro* release studies conducted under sink condition.[10]

Antiretroviral drugs

HIV/AIDS was treated with antiretroviral medications including tenofovir alafenamide (TAF), emtricitabine (FTC), and elvitegravir (EVG). These three drugs were encapsulated into a PLGA nano-delivery system using the emulsion solvent evaporation procedure. Antiretroviral medications (ARVs) included in polymeric encapsulation have extended and sustained release along with gradual systemic clearance. The nanoparticles size was 243.2±5.8 nm, and its encapsulation efficiency for TAF, FTC, and EVG, was 50.7±2.6%, 46.4±3.6%, and 38.6±2.9%, respectively. According to the pharmacokinetic study report of nanoparticles on combination antiretroviral drugs (cARV), the cARV concentration had significantly dropped by day 14 after therapy. A considerable rise in target tissue ARVs is also seen after subcutaneous injection of cARV nanoparticles, according to pharmacokinetic studies. Combination antiretroviral medication nanoparticles may therefore represent a novel approach to the treatment of HIV patients because they overcome the drawbacks associated with traditional combination antiretroviral treatments.[11]

Olanzapine

A brand-new antipsychotic medicine called olanzapine is widely utilized for the treatment of bipolar disorder and schizophrenia. This chemical is a thienobenzodiazepine derivative. In reducing the frequency of extra pyramidal symptoms, olanzapine is efficacious towards the adverse symptoms of schizophrenia. It's been demonstrated to attach specifically to central dopamine D2 receptor and serotonin (5-HT2c). The drawback of olanzapine is that it is significantly metabolised in the liver by the cytochrome P450 to nearly 15 metabolites, a few of which seem to be inert and most have a variety of negative effects, including hypotension, tremors, dry mouth, and somnolence. The medication has a reasonable half-life of elimination, allowing it to be taken daily to treat the symptoms of schizophrenia. As a result, an injectable form of olanzapine with an extended half-life was created. It has been incorporated using PLGA with a range of molecular weights and copolymer compositions and released for a very long period. A method of solvent extraction and evaporation was used to prepare the samples. *In vivo* research indicates that higher levels were reached through a 15-day dosage because there was less of an early burst with higher molecular weight, longer-acting PLGA formulations. This showed that the hydrolytic degradation of the lactide and glycoside copolymer decreased the release of PLGA over time.[12]

Aceclofenac

In addition to being a non-selective COX inhibitor, aceclofenac is a medication which is categorised as non-steroidal anti-inflammatory. Through the inhibitory effect on proteoglycan release and metalloprotease synthesis, it operates to induce effects on glycosaminoglycans in the human osteoarthritis cartilage and chondroprotective properties. Clinical studies showed that aceclofenac is preferred and tolerated better than diclofenac. By using the solvent emulsification-evaporation method to manufacture aceclofenac-encapsulated PLGA (75:25) microspheres, a greater encapsulation efficiency of 91% is noted. Studies on the

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in vitro drug release demonstrated that the rate of drug release slowed down as the polymer concentration rose and revealed a prolonged release lasting between 10 and 30 days. The study also noted that a larger quantity of polymer could accommodate a greater quantity of medication, hence improving entrapment efficiency. The medication remained crystalline despite being disseminated throughout the polymer matrix, according to XRD measurements.[13]

3. Polycaprolactone Based Long-Acting Injectable Formulations

Polycaprolactone (PCL), which was developed early in the 1930s by the Carothers group, was one of the first polymers.[14] Having an extremely lower glass transition temperature, it is a semi-crystalline polymer that is hydrophobic, biodegradable, and bioresorbable. The benefits of PCL over PLA and PGAs comprise its higher permeability to tiny medicinal molecules and low propensity to produce an acidic micro-environment through breakdown. In addition, PCL homopolymer degrades relatively slowly, enhancing its suitability for long-term delivery systems lasting longer than a year. With the right blending, the delivery can also be raised or lowered as required.[15,16] A variety of methods can be used to create PCL microspheres, such as o/w emulsification, solvent evaporation/extraction, multiple emulsification solvent evaporation, solution-enhanced dispersion, spray drying, and hot-melt, whereas PCL nanoparticles are typically created through nanoprecipitation, solvent evaporation and solvent displacement.[5,17] The following section includes a few of the compounds that have been effectively added to PCL microspheres and nanoparticles to boost their therapeutic potential. The multiple studies on Polycaprolactone Based Long-Acting Injectable Formulations are shown in Table 2.

Curcumin

Natural ayurvedic compound curcumin has been found to have hepatoprotective effects. In comparison to curcumin, other curcumin analogues, like BDMCA, have been proven to have significant hepatoprotective and antidepressant properties. In this study, microspheres of curcumin analogues of NNdimethyaminocurcumin (NNDMAC) were prepared and evaluated using the emulsification-solvent evaporation process utilising biodegradable polycaprolactone as the polymer. The findings revealed that the average particle size, yield percentage, and entrapment efficiency were 20 μm, 66%, and 22%, respectively. In a pharmacological study, 20 mg of intraperitoneal NNDMAC microspheres dramatically reduced the incidence of liver lesions brought on by CCl_4. The existence of healthy hepatic cords, clearly defined cytoplasm, and a lack of necrosis served as evidence for this. The in-vitro data demonstrated sustained medication release for 10 days and considerable hepatoprotection by microspheres.[18]

Table 2: Polycaprolactone based long-acting parenteral formulations.

Encapsulant	Formulations	Method of preparation	Encapsulation efficiency	References
Curcumin	Microspheres	Emulsion-solvent evaporation method	22%,	[18]
Docetaxel	Nanoparticles	Nanoprecipitation method	86%	[19]
Methotrexate	Microspheres	The single o/w emulsion solvent evaporation	51%	[20]
Paliperidone	Nanoparticles	Nanoprecipitation method	70.6%	[21]
Zopiclone	Microsphere	Emulsion–solvent evaporation method	40%	[22]

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Docetaxel

A semi-synthetic cytotoxic counterpart of paclitaxel is docetaxel. It is a clinically effective chemotherapeutic medication that is effective against a variety of tumours, such as progressed and advanced breast malignancies, cancers of the stomach, prostate, and non-small cell lungs, among others. Docetaxel works by interfering with the formation of the mitotic spindle, which stops the cell cycle. PCL/Pluronic F108 nanoparticles were formulated in this study using the nanoprecipitation technique. With a polydispersity index of 0.156 and a mean size of particles 216±3.4 nm, nanoparticles have surface charge of about -7.37 mV. Additionally, it is discovered that docetaxel has an entrapment efficiency of 86.0±3.9%. Around 30% of the medication was reportedly released in 6 days, according to an *in vitro* release study. The Higuchi paradigm is followed in the kinetics of drug release from the matrix of PCL nanoparticles. *In vitro* cytotoxicity indicated that the formulated nanoparticles preserve the cytotoxicity of free docetaxel. The results of this study point to the possibility that nanoparticles may possibly deliver a sustained release and accumulate passively into the tumour *in vivo*.[19]

Methotrexate

The medication methotrexate (MTX), which has been used in clinical studies for many years, has anticancer, anti-rheumatic, anti-inflammatory, and disease-modulating characteristics. Due to its outstanding efficiency when compared to other medications, it is at present the most often utilised therapy for the management of rheumatoid arthritis and a prominent second-line medication. The drawbacks of MTX in clinical use include poor solubility, a high proportion eliminated through the kidney, a shorter half-life, as well as quick absorption into the bloodstream. Therefore, microencapsulating MTX in a PCL polymer is a practical choice. Methotrexate-charged PCL microspheres were created using the O/W emulsion solvent method. The mean size of the drug-loaded microparticels was 23.88±1.15 μm, and the utmost encapsulation efficiency was found to be 51.68%. The load capacity of the MTX-PCL microparticels was 2.8%. In the process of encapsulation, MTX's crystalline structure was lost, leaving only an amorphous form inside MTX PCL microspheres. The XRD diffractometry examination revealed that PCL retained its semi-crystalline properties all through the creation and characterization of the microspheres. Although the methotrexate was continuously and steadily liberated from the MTX PCL microparticels, only 30% of it was liberated from the microspheres within the first 306 hours.[20]

Paliperidone

Clinically, paliperidone (PP) is used to treat schizophrenia and psychosis. For a long time, long-acting formulations containing paliperidone administered via intramuscular route have attracted significant interest due to its therapeutic potential. Paliperidone-loaded polycaprolactone nanoparticles were created utilising the nanoprecipitation process with a variety of stabilisers, including Tween 80, Pluronic F68 and F127, as well as polyvinyl alcohol. The presence of amine groups within the chitosan molecule caused the zeta potential of formulations coated with chitosan to change from negative to positive, demonstrating the effectiveness of the particle coating. Chitosan coated formulations were associated with a noteworthy increase in particle size ($p<0.05$) in comparison to the corresponding uncoated formulations. The percent yield was in the range of 79.4% (Pluronic) to 32.1% (PVA). The kind of stabiliser employed has little impact on pH. The various formulations' entrapment efficiencies ranged from 51.6±3.3 to 70.6±6.8%. According to release studies, polyvinyl alcohol and chitosan uncoated emitted the greatest explosive effect (almost 45% of drug release), whereas pluronic F127 and chitosan covered emitted the least explosive effect (nearly 28% of drug release).[21]

Zopiclone

A cyclopyrrolone derivative, zopiclone affects the $GABA_BZ$ receptor chloride channel macromolecular complex by interacting with the benzodiazepine receptor complex and attaching to it. Clinical uses for zopiclone include hypnotic, anticonvulsant, anxiolytic, and calming effects. The daily oral administration of zopiclone results in noncompliance from patients and is associated with common side effects such as headaches, dry mouth, and taste alterations. This study used the emulsion solvent evaporation method to create the zopiclone-polycaprolactone sustained release formulation. The improved formulation has a 1:2 drug-polymer ratio based on several evaluation parameters. It

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was found that the yield percentage and entrapment efficiency were 75% and 40%, respectively. According to *in vitro* drug release, the highest drug release was 86.4%, and the drug release was regulated for 10 days. The polycaprolactone-loaded zopiclone microspheres appeared to be more effective than the daily zopiclone solution, according to all of these findings.[22]

4. Polylactic Acid-Based Long-Acting Injectable Formulations

A biocompatible and biodegradable material known as polylactic acid (PLA) polymer serves as a natural intermediary in the metabolism of carbohydrates, splitting within the body into monomers of lactic acid. Solvent displacement, solvent evaporation, solvent diffusion, and salting out have all been used to create PLA nanoparticles.[23,24] Phase separation, non-solvent addition, and solvent partitioning were the main methods used to create PLA microspheres, along with emulsification solvent evaporation as well as double emulsification solvent evaporation. The most fundamental and popular approach, solvent evaporation to an oil-in-water emulsion, has shown a high rate of encapsulation of water-insoluble molecules. The various studies on Polylactic Acid-Based Long-Acting Injectable Formulations are shown in Table 3.

Betamethasone

Betamethasone disodium phosphate nanoparticles were formulated using an o/w emulsification solvent diffusion approach and a mixture of PLA and monomethoxypolyethyleneglycol (PEG)-polylactides block copolymer. PEG functions as a stealth-type (long-circulating) carrier that preferentially accumulates in tumours and inflammatory areas owing to the improved permeability and retention effect. The study's findings suggest that during PLA hydrolysis, betamethasone can be released gradually in cells. Following the administration, the betamethasone content steadily declined and was discovered even 14 days later. At initially, PEG chains on the nanoparticles' surfaces are abundant, but they vanish after a few days. The majority of the betamethasone remains within the nanoparticles during this time and releases steadily over the course of 44 days. According to the stability data, this mixture has a minimum 69-week shelf life when kept at relatively low temperature (below 25 °C).[25]

Table 3: Polylactic acid based long-acting parenteral formulations.

Encapsulant	Formulations	Method of preparation	Encapsulation efficiency	References
Betamethasone	Nanoparticles	Oil-in water solvent diffusion method	13.8 %	[25]
Etoricoxib	Nanoparticles	Emulsion solvent evaporation method	93 %	[26]
Nimesulide	Microspheres	Emulsion solvent-evaporation method	70%	[28]
Hydrochloric thiothixene	In situ gels	-	97%	[29]

Etoricoxib

An anti-inflammatory drug called etoricoxib specifically suppresses COX-2. It is also beneficial in the treatment of inflammatory illnesses like arthritis and osteoarthritis. Etoricoxib oral dosing is associated with serious cardiovascular toxicity issues. Therefore, bioadhesive hybrid nanoparticles loaded with etoricoxib were prepared employing the emulsification solvent evaporation method utilising PLA, Captex 200, chitosan HCl, and different surfactants. PVA with higher molecular weight was capable of creating nanoparticles without aggregations. This might be explained by PVA's

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potent emulsifying abilities. Because Tween 80 was successful in lowering the size of the NPs, it was chosen as a co-surfactant for the manufacture of enhanced PLA nanoparticles, and PVA was chosen as the preferred surfactant for nanoparticle preparation. The *in vitro* study showed that the hybridised NPs (HYB-NPs/3) formulation had the lowest particle size value of 420.30±40.16 nm compared to other formulations due to the highest proportion of Captex200, and the highest release efficiency value of 55.02% and the p-value <0.05 compared to other formulations. The formulation offered could be viewed as an innovative treatment for osteoarthritis.[26]

Trometamol ketone

Acute musculoskeletal pain, dental discomfort, and surgical pain are just a few examples of the moderate to severe pain it is used to treat. The non-narcotic analgesic ketorolac tromethamine is 800 times more potent than aspirin. In patients with intense pain, it is administered intramuscularly every 6 hours to avoid frequent and uncomfortable doses for the patient. Ketorolac of tromethamine was discovered to be appropriate for the parenteral depot system with biodegradable microspheres in this investigation. Various polymers, including polycaprolactone, poly (dl-lactide), and PLA, were used in an emulsion solvent evaporation process to formulate the microspheres loaded with ketorolac tromethamine. In comparison to microspheres made with 1:1 PCL and PLA blends, the topography of the surfaces of PLA and PLA microspheres prepared with PCL was discovered to be smooth and spherical, amid several very small pores on their surface. In comparison to the other polymers, pure PLA likewise showed higher encapsulation (61%), and when it was combined with PCL, it varied from 53-56%. According to *in vitro* testing, the release time of drug can be changed from a few hours to a few days by using PCL in the right amounts and mixing it with different polymers.[27]

Nimesulide

A common NSAID having local effects is nemesulide, a nonsteroidal, antipyretic, and anaesthetic anti-inflammatory medication. Nimesulide's effectiveness when taken orally is constrained by its shorter duration of action and lack of COX-2 selectivity as an inhibitor. To give patients long-lasting and reliable pain relief, however, several repeated injections are required.

Because of potential complications, these approaches are frequently not chosen. A therapeutically important technique to extend Nimesulide's duration of action would be to administer long-acting versions as a single injection. Polylactic acid microspheres were made utilising the emulsification solvent-evaporation technique. The polymer composition primarily affected entrapment effectiveness of Nimesulide-PLA microparticles and was observed about 70%. The Nimesulide-PLA microspheres downloaded and loaded had mean widths of around 42.9 nm and 2.1 nm, correspondingly, according to an analysis of the microparticles system's size. Around 28.67% of the medication was released from the microparticels within 108 hours, according to *in vitro* dissolution experiments. The important insights of the formulation illustrated the possible usage of nimesulide through intramuscular prolonged release system.[28]

Hydrochloric thiothixene

It is a medication that is frequently prescribed for schizophrenia as well as other psychoses like mania, polar disorder, and behavioural problems. Hydrochloric thiothixene (HT) is given intramuscularly in tiny doses of 4 to 8 mg every 8 to 12 hours, or orally in doses of 5 to 15 mg every 8 to 12 hours. Antipsychotic medications were difficult to independently administer under medical orders since psychotics frequently lacked control over their behaviour.

Inadequate treatment efficacy is typically the result of administration errors. In order to treat schizophrenia, Che Xin created a new long-term injectable controlled release in situ gel containing HT based on biodegradable polymer, polylactic acid. The formulation used contains benzyl benzoate, 15% HT, and 45% PLA. The *in vivo* analysis revealed that chosen formulation possessed extended sustained release of drug over a duration of many weeks compared to the control preparation, Hydrochloric thiothixene solution. Furthermore, none of the experimental rats displayed any red swelling or signs of inflammation at the injection location throughout the investigation. *In vivo* sustained releasing period was 28 days, which was a little bit less than *in vitro* sustained release time.[29]

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5. Hyaluronic Acid-Based Long-Acting Injectable Formulations

A naturally existing nonsulfated glycosaminoglycan polymer made up of replicating D-glucuronic acid and (1-b-3) N-acetyl-D-glucosamine disaccharide units is hyaluronic acid (HA), commonly referred to as hyaluronan.[30] HA is an amazing biomaterial that can be used in micro particle preparations to create a matrix. It is a biodegradable, biocompatible, viscoelastic linear polysaccharide with a molecular weight range of 1000 to 10,000,000 Da [31]. In the formulation sector, HA is utilised to create a variety of formations, including intra-articular injectables, nanoparticles, and ocular and nasal gel.[32] A number of studies on Hyaluronic Acid-Based Long-Acting Injectable Formulations are summarized in Table 4.

Table 4: Hyaluronic acid biodegradable polymer for the long-acting parenteral formulation.

Encapsulant	Formulations	Method of preparation	Encapsulation efficiency	References
Triamcinolone	Micelle	Dialysis method	52%	[33]
Donepezil	Hydrogel	-	14 %	[34]
Doxorubicin	Micelle	Solubilization method	31%	[35]

Triamcinolone

Triamcinolone is a member of the corticosteroid class of medications, which are used to treat joint-related conditions like osteoarthritis and rheumatoid arthritis (RA). For prolonged delivery of triamcinolone using the dialysis method, a new HA and 1,2-di-stearoyl phosphatidylethanolamine (DSPE) based polymeric micelle was formulated. Triamcinolone-loaded micelles exhibited 180 nm-sized spherical core-shell particles. According to experiments using differential scanning calorimetry, the crystalline molecules changing into amorphous molecules is what causes freeze-dried triamcinolone-loaded micelle powder to be visible. According to *in vivo* biocompatibility research, HA-DSPE is harmless to cartilage tissue and is biocompatible with it. The micelle was present within the knee joint for a minimum of 3 days following injection before dissipating on day six of the study. Active uptake of HA by particular synovial cells produced better results than the medication alone.[33]

Doxorubicin

By the use of PEG-enabled solubilisation technique with anhydrous dimethyl sulfoxide, the biodegradable and hydrophobic PLGA chains on the backbone of HA were chemically linked, and doxorubicin (DOX) physically enclosed in lipophilic cores. The molecular weights of HA and PLGA in the graft copolymer affected both the size of HA-g-PLGA nanoparticles, which varied from 98.4 to 539.4 nm, and the amount and efficiency of DOX loading, which ranged from 4.8 to 7.2 and 20.2 to 31.0 percent, respectively. The cellular absorption of nanoparticles could be drastically increased on HCT-116 cells overexpressing the HA receptor, and a potent anticancer impact was found.[34]

Donepezil

Acetylcholinesterase (AChE) inhibitors are used orally or as a transdermal patch daily for Alzheimer's disease. However, due to their limited therapeutic index, patients may find it challenging to take them regularly without assistance, which could cause lower efficacy or toxicity from overdosing. The researchers have created a hybrid HA hydrogel including human serum albumin (HSA), microstructured lipid carriers (MLCs), and donepezil (DNP), an AChE inhibitor, for sustained release following subcutaneous injection. Due to the exceptional biocompatibility and rheological relevancy for subcutaneous administration, HA was selected as the biopolymer for preparing hydrogel. The MLC-HSA hybridization enhanced the viscoelastic characteristics of hydrogel of HA, which would give structural stability following injection into the skin, according to rheological investigations. According to

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pharmacokinetics, subcutaneous treatment of hydrogel to rats extended the release of donepezil to 7 days and decreased the basal plasma levels.[35]

6. Albumin-Based Long-Acting Injectable Formulations

Albumin is an exceptionally resilient, soluble, and acidic protein that is capable of tolerating heat up to 60 °C for 10 hours and holds steady within range from pH 4 to 9. It is soluble also in 40% ethanol. It is an excellent choice for drug delivery due to its preferential absorption in tumour and inflammatory tissues, quick availability, degradability, absence of toxic effects, and immunogenicity.[36] Especially in comparison to bovine serum albumin as well as other proteins, human serum albumin is substantially less toxic and immunogenic. Albumin has been claimed to be used in drug delivery for a variety of exciting purposes, together with enhanced blood flow as well as drug targeting. Table 5 provides an overview of several studies on long-acting parenteral formulations based on Albumin.

Table 5: Albumin biodegradable polymer for the long-acting parenteral formulation.

Encapsulant	Formulations	Method of preparation	Encapsulation efficiency	References
Docetaxel	Nanoparticle	Dosio's method	-	[37]
Ketorolac tromethamine	Microspheres	Emulsion cross-linking method	59 %	[38]
Paclitaxel	Nanoparticles	High-pressure homogenizer method	99 %	[39]

Docetaxel

Docetaxel (DTX) is a toxoid that is semi-synthetic and one of the most successful chemotherapy drugs for treating patients with advanced breast cancer. Docetaxel dissolves relatively poorly in water. To prepare nanoparticles of docetaxel succinate was used to bind HSA to docetaxel. The mean diameter of the detected DTX-HSA conjugate ranged from 90-110 nm. According to *in vitro* cell viability study, the conjugated DTX-HSA has higher cytotoxicity or lower cell viability than the medication without DTX. At pH 7.4 20% of DTX in the DTX-HSA compound is released after 24 hours, as per *in vitro* drug release tests. Given that DTX is more powerful than paclitaxel and has a longer *in vivo* circulation life, it may be superior to the paclitaxel-HSA combination for the clinical therapy of cancer.[37]

Indomethacin tromethamine

Ketorolac tromethamine (KT) is a non-steroidal anti-inflammatory drug which is endorsed for temporary treatment of harsh acute pain requiring opioid analgesics. It has various dangers when used in the conventional oral dosage form. Gastrointestinal (GI) problems such as gastrointestinal bleeding or perforations, as well as aphthous ulcers are the most serious side effects. To create and analyse KT-loaded albumin microspheres, the current study slightly modified the emulsion cross-linking process. The largest particle size that was seen was under 40 μm. It is possible that the exterior phase's reduced viscosity, which offers less resistance to the produced spheres, is the cause of the relatively narrow size distribution. About 30% of the medication is released in the first 30 minutes, according to release studies. This can be because the medication is surface-embedded or weakly bound. It is feasible to draw the conclusion that the created albumin microspheres may be helpful for administering ketorolac tromethamine intramuscularly once a day.[38]

Paclitaxel

The three types of tumours that paclitaxel is most commonly used to treat are breast, ovarian, and lung tumours. The biggest drawback of Paclitaxel is how poorly it dissolves in water. Paclitaxel nanoparticles were created using the high-pressure homogenizer technique for suspension for injection. The measured

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particle size was 414 nm. Encapsulation's drug-loading capacity was discovered to be 99% by weight. Before there was a noticeable aggregation, the nanoparticle suspensions remained uniform and stable for 3-5 days.[39]

7. Conclusion

For the biopharmaceutical sector, long-acting injectable formulations based on biodegradable polymer drug delivery methods appear to be a workable and efficient technique. They outperform conventional parenteral medication delivery methods in terms of therapeutic outcomes. They can improve the bioavailability, permeability, and solubility, of a variety of strong medications that might otherwise be challenging to take orally. The frequency of the medicine administration will be reduced while patient compliance is increased with long-acting injectable formulations. Long-acting injectable formulations have the potential to quickly improve the efficacy of many biological medicines with low aqueous solubility, permeability, and bioavailability. Targeted distribution and controlled release are also possible with long-acting injectable formulations based on biodegradable polymeric medicines, making them an innovative treatment.

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