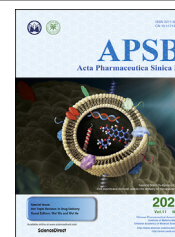




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REVIEW

A review of existing strategies for designing long-acting parenteral formulations: Focus on underlying mechanisms, and future perspectives



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Abstract The need for long-term treatments of chronic diseases has motivated the widespread development of long-acting parenteral formulations (LAPFs) with the aim of improving drug pharmacokinetics and therapeutic efficacy. LAPFs have been proven to extend the half-life of therapeutics, as well as to improve patient adherence; consequently, this enhances the outcome of therapy positively. Over past decades, considerable progress has been made in designing effective LAPFs in both preclinical and clinical settings. Here we review the latest advances of LAPFs in preclinical and clinical stages, focusing on the strategies and underlying mechanisms for achieving long acting. Existing strategies are classified into manipulation of *in vivo* clearance and manipulation of drug release from delivery systems, respectively.

Abbreviations: 2'-F, 2'-fluoro; 2'-OMe, 2'-O-methyl; 2'-O-MOE, 2'-O-(2-methoxyethyl); 3D, three-dimensional; ART, antiretroviral therapy; ASO, antisense oligonucleotide; DDS, drug delivery systems; ECM, extracellular matrix; ENA, ethylene-bridged nucleic acid; ESC, enhanced stabilization chemistry; EVA, ethylene vinyl acetate; FcRn, Fc receptor; GLP-1, glucagon like peptide-1; GS, glycine-serine; HA, hyaluronic acid; HES, hydroxy-ethyl-starch; hGH, human growth hormone; HP, hypoparathyroidism; HSA, human serum albumin; IgG, immunoglobulin G; im, intramuscular; ISFI, *in situ* forming implants; iv, intravenous; LAFs, long-acting formulations; LAPFs, long-acting parenteral formulations; LNA, locked nucleic acid; MNs, microneedles; mPEG, methoxypolyethylene glycol; NDS, nanochannel delivery system; NPs, nanoparticles; OA, osteoarthritis; PCPP-SA, poly(1,3-bis(carboxyphenoxy)propane-co-sebacic-acid); PEG, polyethylene glycol; PM, platelet membrane; PMPC, poly(2-methacryloyloxyethyl phosphor-ylcholine); PNAs, peptide nucleic acids; PS, phase separation; PSA, polysialic acid; PTH, parathyroid hormone; PVA, polyvinyl alcohol; RBCs, red blood cells; RES, reticuloendothelial system; RNAi, RNA interference; SAR, structure-activity relationship; sc, subcutaneous; SCID, severe combined immunodeficiency; SE, solvent extraction; STC, standard template chemistry; TNFR2, tumor necrosis factor receptor 2.

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Implantable systems

And the current challenges and prospects of each strategy are discussed. In addition, we also briefly discuss the design principles of LAPFs and provide future perspectives of the rational design of more effective LAPFs for their further clinical translation.

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1. Introduction

Long-acting formulations (LAFs) are used for pharmacotherapy as sustained-release medications over a period of several days, weeks, or even months. Compared to conventional preparations, LAFs have many distinguished advantages related to its long-lasting curative effect, as well as its reduced toxicity, dosage and frequency of administration. These outstanding features of LAFs have encouraged researchers to pursue their further development to fulfill the unmet need for long-term treatments of chronic diseases or other prevalent diseases that threaten human health.

Patients are often forced to take daily prescriptions of medicine for years to treat chronic diseases or other serious diseases such as HIV/AIDS, psychiatric illnesses, cancer, and diabetes. However, most patients often cannot adhere to a frequent and prolonged dosing schedule. For the treatment of these conditions, long-acting parenteral formulations (LAPFs) are preferred over conventional formulations. The release duration of drug delivery conferred by LAPFs may be able to improve patient adherence and consequently improve treatment outcomes. The replacement of daily oral regimens with antiviral LAPFs could successfully improve HIV/AIDS prevention and treatment. A single subcutaneous (sc) implantation of antiviral LAPFs can provide a protective level of drug concentration for months, a year or even longer¹. Besides AIDS medication, long-acting innovative anti-infective drugs have proven effective to eliminate the hepatitis B virus and chronic hepatitis C virus^{2,3}. Similarly, long-acting antipsychotics formulations can effectively reduce relapse and re-admission to psychiatric institutions and improve long-term prognosis due to their consistent plasma drug concentration^{4,5}. Furthermore, as the prevalence of diabetes is a growing problem worldwide, reaching the target blood glucose level is critical for the vast majority of diabetic patients, as their improper management of glycemia can lead to life-threatening adverse effects⁶. Currently, clinicians have many long-acting basal insulins to select from⁷, but there are still some unmet needs and challenges. Daily variability, low patient compliance and progressive micro and macrovascular risks require further research to formulate novel LAPFs for diabetic patients⁶. In addition to the treatment of above-mentioned diseases, LAPFs also have proven effective for contraception. Long-acting reversible contraceptives are recommended as first-line contraceptives for adolescents and young women⁸. Long-acting hormonal contraceptives with great efficacy and relative ease of use are widely accepted by millions of women with a variety of options^{9–11}. Although great progress has been made in the development of LAPFs to meet clinical needs, it is still far from ideal. All of these indicate that LAPFs are very promising and have market demand.

Presently, small molecules share almost 90% of the global pharmaceutical market and are still a leading in new drug

approvals. However, some small molecular drugs require multiple doses in a day owing to its short biological half-life, which is due to its structure, as well as other characteristics. Therefore, the major issues of these drugs are their large fluctuations in blood concentration and the risk of potential side effects. These factors limit their efficacy and clinical use. So far, many efforts have been made to improve the pharmacokinetics of these drugs and some progress has been made, such as PEGylation of methotrexate¹² or making it into albumin-based nanomedicines^{13,14}, and making vincristine into injectable sulfate loaded dextran microspheres amalgamated with chitosan- β -glycerophosphate gel to achieve long-term effectiveness^{15,16}. Furthermore, combining small molecular drugs with ligands (such as long-chain fatty acids) or albumin prolongs the half-life of the drug. Currently, a greater number of researchers are turning their attention to macromolecular drugs that exert specific therapeutic effects and occupy an increasing market share. However, most of these drugs express poor stability, easy enzymes degradation, and rapid kidney clearance. To achieve therapeutic effects, long-term, frequent, or high-dose administrations are required through injection, which are accompanied by injection-associated pain, discomfort, certain psychological and economic burden. Encouragingly, significant attention and effort have been dedicated to the design and development of LAPFs of macromolecular drugs to keep them active for longer time in the body and improve their pharmacokinetics and therapeutic efficacy^{17,18}.

The principles to produce long-acting therapeutics are based on maintaining the drug activity for longer periods of time and to improve their tolerance in the body. Toward this end, a diverse array of strategies (Fig. 1) has been developed to design LAPFs through endowing the therapeutic drugs with features that include slow and controlled release, delayed clearance, resistance to enzymes, increased stability, extended half-life^{19,20}. By rationally designing, LAPFs are safer and more efficient. Many LAPFs have been clinically approved, which has enabled the reduction of dosing frequency to daily, weekly, biweekly, or even monthly. Along with innovation of popular used approach for designing LAPFs and the emergence of novel strategies, LAPFs candidates have been scaled up to preclinical and clinical studies.

In this study, the recent advances of LAPFs and their corresponding feasible design strategies are discussed. According to their underlying mechanisms, various strategies are classified into two categories: manipulation of drug release from delivery systems and manipulation of *in vivo* clearance. The preclinical and clinical progress of each design strategy together with its current landscape and challenges are discussed respectively. In addition, we also share our perspectives on viable directions for the rational design of LAPFs to improve therapeutic efficacy and further their clinical translation.

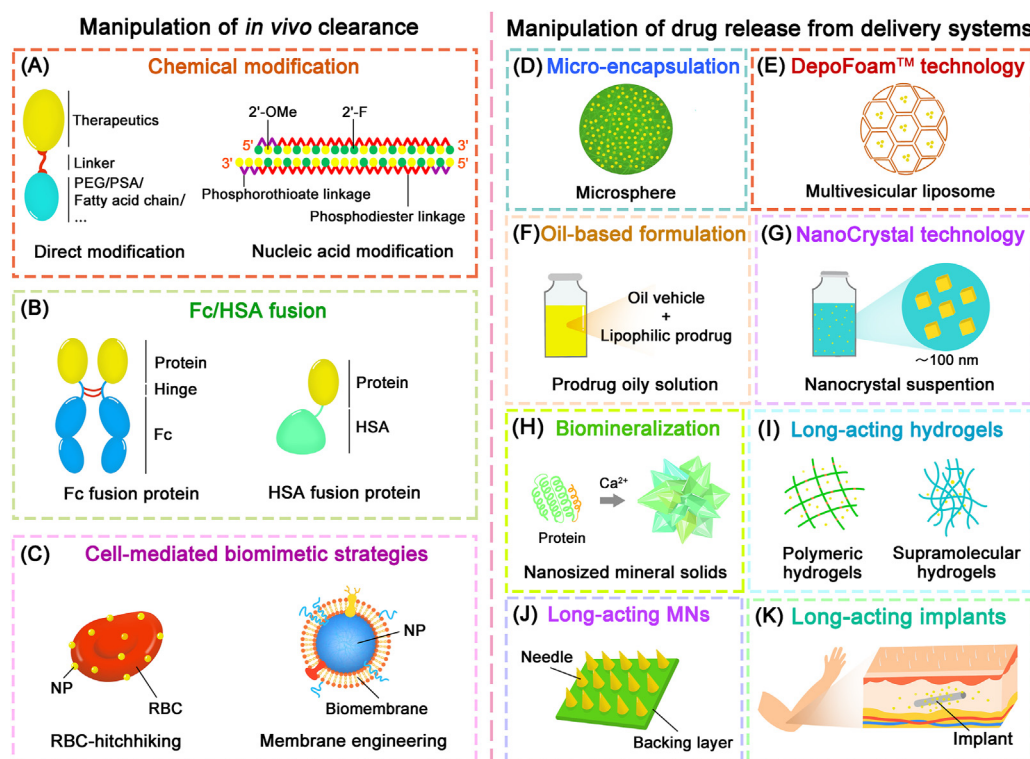


Figure 1 Strategies for long-acting parenteral formulations. (A) Chemical modification. (B) Fc/HSA fusion. (C) Cell-mediated biomimetic strategies. (D) Micro-encapsulation. (E) DepoFoam™ technology. (F) Oil-based formulation. (G) NanoCrystal technology. (H) Biominerallization. (I) Long-acting hydrogels. (J) Long-acting microneedles. (K) Long-acting implantable systems.

2. Existing strategies to manipulate the drug *in vivo* clearance

2.1. Chemical modification

The strategy of chemical modification, such as PEGylation, PSylation and lipidation, etc. has been considered to be one of the most efficient approaches and has been recognized in clinical practice because of its definite structure, lack of impurity, and mature methods²¹. The key of the strategy is to prolong the half-life of drugs with little influence on their bio-activity as much as possible, which requires a comprehensive understanding of the structure–activity relationship (SAR) of drugs, as well as precise site-modification methods.

2.1.1. PEGylation and alternatives to PEGylation

Polyethylene glycol (PEG), a neutral polyether polymer, has become an indispensable part of drug delivery systems (DDS)^{22,23}. The amphiphilic chain of PEG moieties, which is derived from the polymerization of ethylene oxide, increases the size of relatively small therapeutic drugs (*e.g.*, peptides, proteins and nanobodies, etc.) in order to avoid excessive renal clearance and to prolong the residence time in the blood circulation, imparting “stealth” properties²⁴. At the same time, the hydration layer produced by PEG can also play a protective role, thus avoiding enzymatic degradation of bio-macromolecules²⁵. Adagen® (pegademase bovine), the first PEGylated product approved by US Food and Drug Administration (FDA) in 1990, is a modified enzyme used for the treatment of severe combined immunodeficiency (SCID) that is associated with a deficiency of adenosine deaminase. Since then, PEGylation has been considered as a well-tolerated module

for half-life extension and has been utilized for 50 years²⁶. It is worth mentioning that PEGylation can be used not only for the direct modification of drugs, but also for the improvement of DDS.

It is noteworthy that the “PEG dilemma” is brought after the PEGylation, which affects the interaction between carriers/drugs and cells, and limits cell uptake and endosomal escape resulting in the inevitably loss of bioactivity^{27,28}. Therefore, cleavable PEG derivatives, which bonds are easy to break under specific physiological and pathological conditions, are designed to overcome the above limitations^{29,30}. The reported sensitive bonds for cleavable PEG derivatives include peptide bonds, disulfide bonds, vinyl ether bonds, hydrazone bonds, ester bonds, as well as other types of bonds³¹. TransCon™ technology platform (Fig. 2A), developed by Ascendis Pharma, provides a new strategy, which preserves the activity of therapeutic drugs and supports dosing frequency from a daily basis up to a monthly basis by combining the benefits of prodrugs and the sustained release mode³². Several candidate drugs (*e.g.*, TransCon PTH, TransCon hGH, TransCon CNP, etc.), based on TransCon™ technology, have been developed in clinical trial stages³³. For example, TransCon parathyroid hormone (PTH), an inactive prodrug for sc administration, is developed to maintain a sustained release of PTH in the bloodstream, thereby overcoming the limitation about the use of short-acting PTH in the treatment of hypoparathyroidism (HP). As Fig. 2B shows, the PTH is transiently bound to methoxypolyethylene glycol (mPEG) *via* a TransCon linker to form TransCon PTH. The protective carrier has the ability to inactivate and shield PTH, and prolongs the circulation time of hormones due to its reduced renal clearance. Under physiological conditions, active PTH is sustained released

with a half-life of approximately 2.5 days³⁴. Recently, the reported phase I data support TransCon PTH to be a daily replacement therapy for the treatment of HP, providing a physiological level of PTH all day long and advancement into phase II clinical trial³⁵.

It cannot be ignored that PEG is immunogenic and non-degradable^{36–38}. Therefore, developing alternative polymers to PEG have received great attention in the pharmaceutical industry^{39–41}. Poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC), a kind of non-PEG based degradable polymer, was synthesized and coupled to interferon- α -2a to form PMPC-interferon- α -2a, which possesses a longer half-life than PEG modified interferon- α -2a⁴². In addition, naturally degradable polymers including polysialic acid (PSA), hydroxy-ethyl-starch (HES)⁴³ and hyaluronic acid (HA) have also been applied for prolonging half-life as an alternative material to PEG⁴⁴. PolyXenTM technology developed by Xenetic Biosciences, Inc. is an enabling platform for peptide and protein drug delivery. PolyXenTM technology utilizes the proprietary technology to conjugate hydrophilic and biodegradable PSA molecules to specific sites of therapeutic drugs for prolonging their half-life and improving their stability *in vivo*. Both the length and the modification site of the PSA chain can change the apparent hydrodynamic radius of the molecule which influence the properties and biological characteristics of therapeutic¹⁷. In addition, a carbohydrate shield called “glycocalyx” around the therapeutic molecule is formed after PSAylation, protecting the drugs less exposed to the immune system and the clearance systems including renal clearance and serum proteases. Several polysialyated candidates, such as

polysialylated erythropoietin (PSA-EPO) and polysialylated recombinant factor VIII (PSA-FVIII), have been applied in clinical development⁴⁵. The former is currently in phase III of clinical trials and the latter is in phase I.

2.1.2. Lipidation

Human serum albumin (HSA), the most abundant protein in plasma, has a long average half-life of 19 days and possesses the function of transporting exogenous and endogenous compounds^{46,47}. On this basis, conjugating a fatty acid chain to the therapeutic protein can enhance its non-covalent combination with albumin *in vivo*, thus achieving a prolonged half-life. This strategy has been successfully applied in the modification of insulin and glucagon like peptide-1 (GLP-1) for half-life extension. Levemir[®] (insulin detemir), approved by FDA in 2004, is an insulin analog in which the Lys29 is myristoylated at the amino group of the side chain, allowing reversible combination with albumin for longer action time and more stable efficacy⁴⁸. After modification, the long distribution phase of insulin detemir of about 8 h after sc administration is sufficient to achieve a once-daily administration⁴⁹. A similar strategy was utilized to liraglutide which is an insulinotropic GLP-1 analog. The Lys26 of liraglutide is modified with a palmitic acid chain to achieve a half-life of 13 h after sc administration. In addition, the strategy of lipidation is widely applied to optimize drug properties to meet the requirements of various preparations. Although lipidation-based prodrug strategies hold promises for clinical translation of LAPFs, it's essential to note that this strategy is not suitable to all drug molecules to be

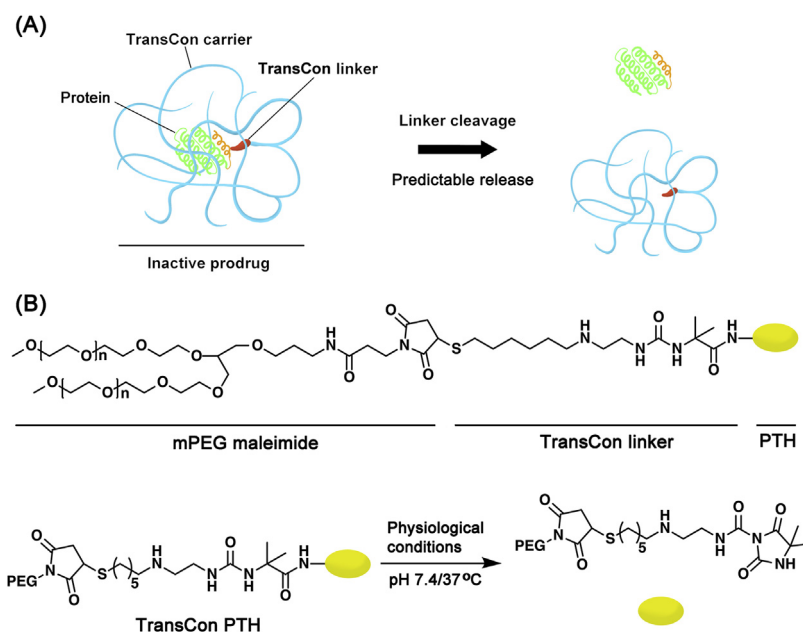


Figure 2 TransConTM technology platform. (A) TransCon molecules consist of three components: a therapeutic drug, a protective carrier and a cleavable linker, which is used to temporarily bind the above two parts. The protective carrier has the ability to inactivate and shield the therapeutic drug and the cleavable linker is designed to achieve the predictable release of active parent drug under a specific physiological environment. (B) The structure of TransCon PTH and the mechanism of drug release. Reproduced with the permission from Ref. 33. Copyright © 2017 Oxford University Press.

modified, especially in case of lack of hydroxyl group and carboxyl group for esterification.

2.1.3. Nucleic acid modification

Gene therapy, based on nucleic acid drugs [e.g., antisense oligonucleotide (ASO), siRNA, miRNA, saRNA, aptamer, etc.], is considered as one of the promising strategies for precision medicine through up-regulation or down-regulation of target genes in specific cells. However, native nucleic acid drugs still have many difficulties to overcome, such as poor stability, rapid degradation by RNase, rapid clearance by the kidneys, immunogenicity and low cell uptake¹⁸. For improving their properties, the structures of nucleic acid drugs can be optimized through chemical synthesis⁵⁰. Fig. 3 shows the structures of common chemical modifications of nucleic acid. In general, backbone modifications [e.g., phosphorothioate (PS), peptide nucleic acids (PNAs), etc.] can enhance nuclease resistance, improve pharmacokinetic characteristics and facilitate cell uptake. Moreover, sugar modifications [e.g., 2'-*O*-methyl (2'-OMe), 2'-*O*-(2-methoxyethyl) (2'-OMOE), 2'-fluoro (2'-F), locked nucleic acid (LNA), 4'-*C*-ethylene-bridged nucleic acid (ENA), etc.] may reduce immunogenicity and toxicity, enhance RNA binding affinity, increase stability and bioavailability^{51,52}. Due to the well development of nucleic acid chemistry, more than ten nucleic acid drugs have been approved on the market. Among them, the recently approved siRNA products, Givlaari[®] (givosiran) and Oxumo[®] (lumasiran) developed by Alnylam Pharmaceuticals, through the combination of the GalNAc conjugation technology and the enhanced stabilization chemistry (ESC) modification technology, represent a surprising long-term effect after initial dosing. At present, dozens of siRNA drugs developed by Alnylam Pharmaceuticals are in clinical trials. Among them, inclisiran (ALN-PCSsc) is utilized in the treatment of hypercholesterolemia and currently in phase III clinical trial. The advantage of treating with inclisiran is that the LDL-C level can be reduced by more than 50% with only two injections per year⁵³. If inclisiran is successful in clinical trials, it will overturn the existing chronic disease treatment model⁵⁴. Recently, Brown et al.⁵⁵ investigated the pharmacodynamic durability of GalNAc-siRNA conjugates, and found that the long-term stability of modified siRNA in acidic intracellular compartments plays a key role for long-term activity. The siRNA can sustainably

escape from these acidic intracellular compartments, which serve as a long-term depot, and subsequently, over time (possibly even weeks), enable RNA interference (RNAi) activity in the cytoplasm after dosing.

Gene therapy holds broad promises for the treatment of multiple human diseases, such as genetic disorders, cancers, virus infection, etc. Nucleic acid chemistry has been approved as an effective way to achieve increased stability, enhanced tissue specificity and reduced toxicity. Although the long-term mechanism of recently approved gene drug has not been clarified, numerous experiences and excellent progresses associated with gene therapy have been achieved in the past 20 years, and its long-term effect may be subversive to the existing treatment model.

2.2. Fc/HSA fusion

The strategy of Fc fusion provides the therapeutic protein a longer half-life by combining them with the Fc domain of an immunoglobulin G (IgG)^{56,57}. Enbrel[®] (etanercept), was the first Fc fusion protein approved by FDA in 1998; it comprises of the extracellular region of tumor necrosis factor receptor 2 (TNFR2) and has been used in the treatment of rheumatoid arthritis^{58,59}. To date, more than ten products, based on Fc fusion proteins, have been approved by the FDA. On the one hand, the binding of Fc-domain makes the size of the therapeutic protein larger than the threshold of kidney filtration resulting in a longer circulation time; on the other hand, the added Fc-domain has the ability to further prolong the circulation time through the neonatal Fc receptor (FcRn) mediated recycling procedure^{60–62}. As shown in Fig. 4A, most Fc-fusion proteins possess the structure of a drug-Fc homo-dimer represented as (drug-Fc)₂. Because of the adjacency of two drug-Fc monomers, the Fc-fusion proteins show physical instability and decreased bioactivity. For solving these issues, the drug-Fc₂ (Fig. 4B) containing a protein linked two Fc domains has been developed and clinically approved. Elocate[®] (recombinant factor VIII Fc fusion protein) and Alprolix[®] (recombinant factor IX Fc fusion protein) based on drug-Fc₂ were both approved by FDA in 2014⁶³. However due to the impurity and low production yields, this technology cannot be utilized for all kinds of protein drugs. Besides, several protease cleavage sites, and the reduction of

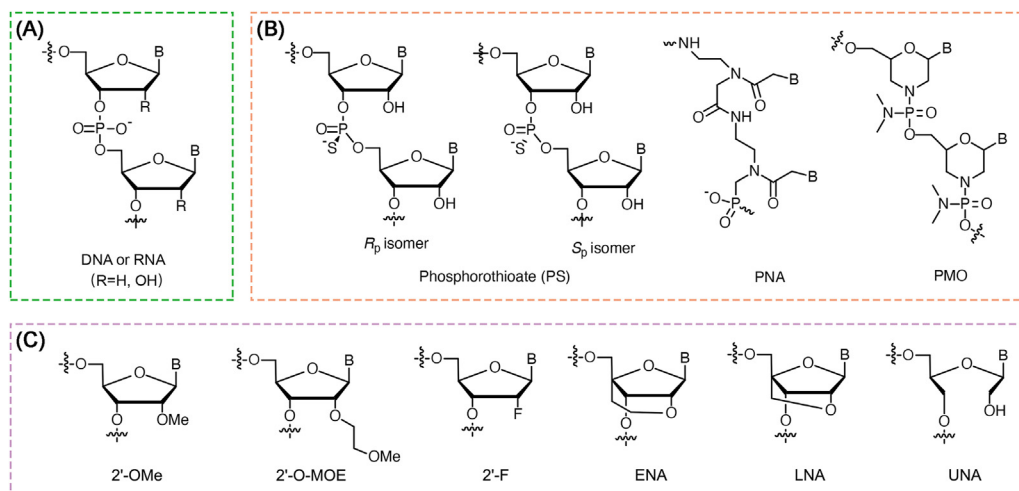


Figure 3 Structures of common chemical modifications of nucleic acid. (A) The structure of natural nucleic acid. (B) The structures of phosphate backbone modifications. (C) The structures of sugar modifications.

disulfide bonds in the hinge region, introduce potential instability of fusion proteins. In order to overcome above limitations, Zhou et al.⁶⁴ developed a novel kind of Fc fusion strategy (Fig. 4C) based on a long and flexible glycine–serine (GS) linker between two Fc chains, and removed the hinge sequence to form a single chain Fc-dimer represented as sc(Fc)₂. In this study, human growth hormone (hGH) was modified by sc(Fc)₂ to create a novel fusion protein, which showed longer half-life and increased bioactivity than traditional Fc fusion-based proteins.

Recently, HSA fusion technology has also been utilized for extending the half-life of therapeutic proteins because of the special kinetic properties of HSA^{65,66}. The mechanism of HSA fusion in prolonging half-life is the same as Fc fusion^{67,68}. Meanwhile, HSA has the features of low immunogenicity and high biocompatibility⁶⁹. Tanzeum® (albiglutide), a GLP-1-HSA fusion protein approved in 2014, is the first product based on HSA fusion for the treatment of type 2 diabetes⁷⁰. The half-life of native GLP-1 is 1–2 min, and the half-life of albiglutide is 4–7 days, which can greatly reduce the frequency of administration in clinic. In 2016, Idelvion® (coagulation factor IX recombinant human), an HSA fusion of coagulation factor IX, was also approved by FDA for the treatment of hemophilia B⁷¹. In addition, Lee et al.⁷² developed a novel drug delivery system through the genetic fusion of an anti-FcRn affibody (AFF) and an albumin binding domain to therapeutic proteins. A synergistic effect on prolonging the plasma residence time can be achieved by the ABD-mediated albumin binding and AFF-mediated FcRn binding. This ABD-AFF fusion strategy is applied to extendin-4 to form EX-ABD-AFF, which revealed a longer half-life and better hypoglycemic effect than control group in mice.

Fc/HSA fusion proteins, as compared to the traditional therapeutic proteins, represent many improved characteristics, and have received extensive attention around the world. With the increasing complexity of fusion proteins, highly analytical and bioanalytical strategies should be established to achieve the comprehensive characterization of fusion proteins. Fusion proteins can not only prolong the circulation half-life of therapeutics, but also achieve superior therapeutic efficacy. Therefore, it has been increasingly recognized as useful and safe therapeutic proteins.

2.3. Cell-mediated biomimetic strategies

To date, a series of nanoparticles (NPs) have been prepared for the treatment of disorders such as malignant tumor, diabetes and

cardiovascular diseases, but few of them have been applied in clinic. These nanomedicines are still recognized as “foreign objects”, resisted out of the physiological barrier or cleared quickly from the body. Biomimetic strategies such as RBC-hitchhiking and membrane engineering endow NPs with new properties in prolonging circulation time, evading host immune response and targeting to specific sites^{73–76}. Different cells have different functions. According to different design requirements to DDS, appropriate cells are selected to modify NPs⁷⁷. Various cells, such as platelets, red blood cells (RBCs), tumor cells, lymphocytes, macrophages, have been modified as “chaperones” for NPs^{78,79}. Among them, RBCs and platelets are often used in the study of long-acting preparations due to their special properties⁸⁰.

RBCs are approximately 7 μm in diameter and possess a long-circulation property (~120 days in humans). Its highly malleable and flexible biconcave shape allow it to squeeze through capillary venules, which ultimately facilitates efficient gaseous exchange. The plasma membrane from an RBC contains more than 300 proteins, among which, CD-47, a surface receptor protein, acts as a “self-recognition” protein that helps the cell to avoid the immune system. Immobilising nanoparticle-based therapeutics on the surface of RBC for transportation, commonly referred to as RBC-hitchhiking (Fig. 5A), is considered to be a promising strategy for increasing the blood circulation lifetime. In 2010, Liu et al.⁸¹ first reported the adsorption of amphiphilic polymers onto the surface of RBCs, and proposed the idea that RBC-hitchhiking can potentially extend circulation time. After that, Anselmo et al.⁸² reported that the noncovalent attachment of NPs to RBCs can significantly increase the circulation time of NPs in the blood and transient accumulation in the lung over a 24 h period, meanwhile decreasing the uptake of NPs by spleen and liver. In this study, RBC-hitchhiking mediated NPs represented a three-fold higher retention in circulation, and a seven-fold increased accumulation in the lung. Moreover, biomembrane engineering is developed to form biomimetic nano-DDS, which retain the functional membrane protein from the origin cells⁸³. In 2011, Hu et al.⁸⁴ first reported a biomimetic delivery system based on RBC membrane-camouflaged polymeric NPs (Fig. 5B). The biomimetic particles in this study revealed significant retention in the blood circulation 72 h following an intravenous (iv) injection. Recently, Gao et al.⁸⁵ reported a strategy that combined HSA binding and RBC membrane engineering. RBC membrane-camouflaged HSA NPs were constructed to delivery antioxidants for relieving Alzheimer’s disease symptoms, providing long-term

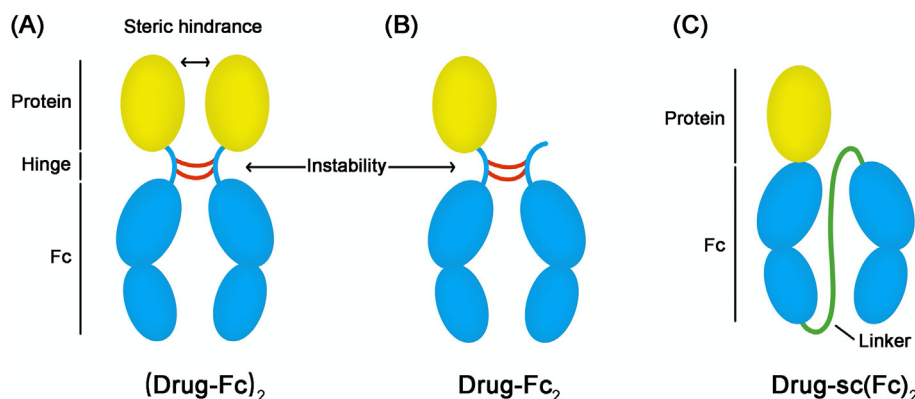


Figure 4 The structures of a series of Fc fusion proteins. (A) The structure of (drug-Fc)₂. (B) The structure of drug-Fc₂. (C) The structure of drug-sc(Fc)₂. Reproduced with the permission from Ref. 64. Copyright © 2017 Elsevier.

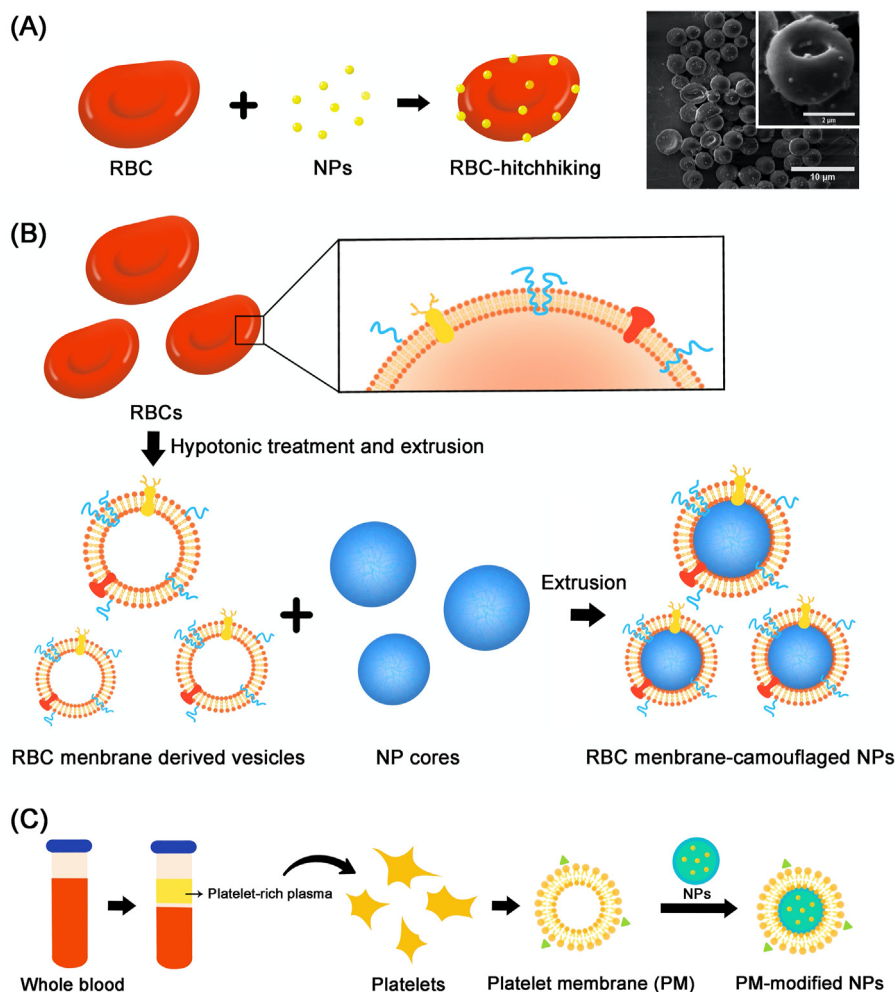


Figure 5 The strategies of RBC-hitchhiking and membrane engineering. (A) The strategy of RBC-hitchhiking. Reproduced with the permission from Ref. 82. Copyright © 2013 American Chemical Society. (B) The membrane of RBCs is used to form camouflaged NPs. Reproduced with the permission from Ref. 84. Copyright © 2011 National Academy of Sciences. (C) The platelet membrane (PM) is extracted from the blood and then used to form PM-modified NPs. Reproduced with the permission from Ref. 88. Copyright © 2015 John Wiley and Sons.

circulation and improved biocompatibility. Similar to RBCs, platelets also have the ability to escape the uptake by macrophage cells and prolong the circulation time *in vivo* due to the “self-recognition” proteins like CD47 on their membranes^{78,86}. Platelet-based biomembrane engineering (Fig. 5C) has been widely used in NPs delivery for long-circulation⁸⁷. Hu et al.⁸⁸ developed a core-shell nano-carrier coated with a platelet membrane (PM) for targeting delivery of anti-tumor drugs. Besides the enhanced anti-tumor efficacy, this kind of nano-vehicle can achieve prolonged blood circulation and effectively eliminate in-circulation tumor cells *in vivo*, which ultimately inhibits the development of tumor metastasis.

The strategy of biomimetic material engineering provides lots of inspiration for the preparation of multifunctional DDS. A large number of long-acting preparations based on bionic strategies have been reported. However, due to the difficulties in obtaining raw materials, complicated preparation process and complex components, biomimetic preparations lack advantages in clinical transformation. Therefore, the design of drug delivery systems involved in biomimetic technologies must keep the principles including scalability and reproducibility in mind for turning scientific advances into clinic.

3. Strategies to manipulate the drug release from delivery systems

3.1. Micro-encapsulation

The process of micro-encapsulation is that solid or liquid drug substances are dispersed or dissolved in polymeric materials to form microspheres, or as a core surrounded by a polymeric shell to form a microcapsule^{89,90}. The first sustained-release injectable microsphere (Lupron Depot[®]) based on biodegradable poly(lactico-glycolic acid) (PLGA) was approved by FDA in 1986 for the treatment of prostatic cancer^{91,92}. The latest approved microsphere-based product (Zilretta[®]) is used for the therapy of osteoarthritis (OA) pain of the knee. This kind of microsphere can slowly release triamcinolone acetonide in the OA joint for over 3 months⁹³. The polymers used to produce microspheres include natural (*e.g.*, gelatin, alginate chitosan, etc.), semisynthetic [*e.g.*, cellulose acetate phthalate (CAP), ethyl cellulose (EC), methyl cellulose (MC), etc.] and synthetic materials [*e.g.*, polylactic acid (PLA), PLGA, etc.]. Among these materials, PLGA is the most popularly used biodegradable material to prepare microspheres, accounting for 46% of all markets. The process of drug release can

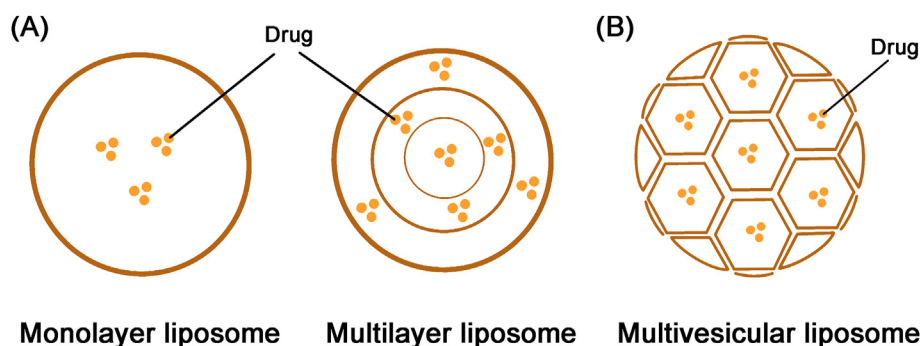


Figure 6 The structures of a series of liposomes. (A) The structure of monolayer and multilayer liposome. (B) The structure of multivesicular liposome. Reproduced with the permission from Ref. 101. Copyright © 2002 Elsevier.

be adjusted by controlling the PLGA molecular weight, the ratio of drug to polymer, the size of microspheres, the ratio of glycolic acid to lactic acid, the end terminus of polymer and the properties of excipients^{94,95}. The major mechanism of drug release from biodegradable microspheres includes diffusion, dissolution as well as polymer erosion and degradation. The possible mechanisms of drug release are following five pathways⁹⁶. The first is initial release from the surface of microspheres; the second is release through the pores in microspheres; the third is diffusion through the intact polymer barrier; the fourth is diffusion through a water swollen barrier; the last is polymer erosion and degradation. All above mechanisms together play a part to achieve sustained drug release^{97,98}. In addition, some polymers such as poly(1,3-bis(carboxyphenoxy)propane-*co*-sebacic-acid) (PCPP-SA), HA, tri(ethylene glycol)-poly(ortho ester) (TEG-POE), etc. are potential alternatives to PLGA, and possess the similar biocompatibility and ability to control drug release over prolonged periods. They are developed for loading drug substances that are incompatible with PLGA. Although many challenges of microspheres including uneven particle size, poor injectability, limited drug loading capacity and poor stability, it is still a promising strategy for preparing long-acting preparations and has been successfully translated in the clinic.

3.2. Multivesicular liposomes

Liposomes are widely used in drug delivery because of its biocompatibility and universality. Different packing modes of lipid vesicles are essential for drug release of liposomes. In general, the packing mode of liposomes is concentric and the lipid membranes are assembled to form monolayer or multilayer structures (Fig. 6A). In this way, the collapse of internal lipid membranes will cause the accumulation of drugs, following the rapid drug release with the breach of external layer⁹⁹. Doxil[®] (doxorubicin liposomal), the first FDA-approved PEGylated liposome, represents increased efficiency and decreased toxicity, but does not have a long-term effect¹⁰⁰. Therefore, sustained release of therapeutics cannot be achieved through packing drugs in traditional liposomes. DepoFoam[™] technology was developed by Pacira Pharmaceuticals, Inc. to produce multivesicular liposomes and has been successfully applied in clinic¹⁰¹. So far, three drugs (Depocyt[®], DepoDur[®] and Exparel[®]) based on DepoFoam[™] technology are approved by FDA and two more DepoFoam drugs including DepoTXA (DepoTranexamic Acid) and DepoMLX (DepoMeloxicam) are under clinical trial stage. Depocyt[®] (liposomal cytarabine), the

first DepoFoam drug approved by FDA in 1999, is a sustained-release formulation for the intrathecal treatment of lymphomatous meningitis with a prolonged drug concentration of cytarabine in cerebrospinal fluid¹⁰². As shown in Fig. 6B, multivesicular liposomes with an average diameter of 3–30 μm are composed of hundreds of non-concentric and polyhedral aqueous compartments, and each compartment is separated by a continuous network of lipid membranes¹⁰³. It achieves sustained drug release through gradual degradation of outermost vesicles. Internal vesicles are protected by outer vesicles to avoid burst drug release and the structure of multivesicular liposomes remains during the rearrangement of internal vesicles¹⁰⁴. Multiple factors such as the properties and composition of lipid phase, interactions between the lipid and the encapsulated drug, composition of the aqueous phase and osmolarity of the aqueous phase contribute to the release rate¹⁰⁴. The preparation of multivesicular liposomes involves a double emulsification process to form a water-in-oil-in-water emulsion. DepoFoam[™] technology is also utilized to tackle pain management before and after surgical procedure. Exparel[®] (bupivacaine liposome), approved by FDA in 2011, is a longer acting form of traditional bupivacaine¹⁰⁵. Day et al.¹⁰⁶ reported that the patients who took Exparel[®] subcutaneously or orally represented extended and better pain control than conventional analgesic regimen in children after pharyngoplasty.

Multivesicular liposomes provide a pragmatic strategy to achieve longer residence time of drug due to its multi-compartment structure. Currently, DepoFoam[™] technology has been applied for the treatment of neurological diseases and cancer, post-surgical pain management as well as reducing surgical bleeding. But the complex manufacturing process of multivesicular liposomes is still a challenge for its clinical translation.

3.3. Oil-based LAFs

Oil-based LAFs can be prepared by covalent attachment of a fatty acid chain and the therapeutics to form prodrugs, which are placed in the oil phase¹⁰⁷. Decanoate, enanthate and caproate are often used to construct an ester bond with the parent drug to increase its solubility in the oil phase and to enhance the partitioning in the fatty tissues¹⁰⁸. Lyogen Depot[®] (fluphenazine decanoate) and Haldol Depot[®] (haloperidol decanoate), two oil-based parenteral formulations, are both typical antipsychotics which have been available in US as LAFs¹⁰⁹. After intramuscular (im) injection, these formulations can form a reservoir, which slowly releases prodrugs into surrounding blood, following the liberation

of active molecules after hydrolysis. The rate of drug release depends not only on the slow release of prodrugs from fatty tissues into the circulation, but also the sustained hydrolysis of ester bonds to release the parent drug. In addition, some parameters such as the drug concentration in the oil phase, the surface area of the oil depot, as well as the partition coefficient between the tissue fluid and the oil depot are essential to control drug release¹¹⁰. Oil-based LAPFs can be used for both systemic and localized drug delivery. Cost-effectiveness and simple manufacturing process are the major advantages of oil-based depot formulations. But this kind of LAPFs is barely employed in recent clinical trials. The cause of the limited number of undergoing clinical trials might be the difficulties in tuning drug release kinetics.

3.4. Nanocrystal suspensions

The strategy of nano-crystallization is widely used to improve the properties of poorly soluble drugs, and the nano-formulation prepared by NanoCrystal technology represents significant long-acting effects, contributing to the treatment of various diseases such as antipsychotic and antiviral therapy^{111,112}. Various technologies such as top-down, bottom-up and combination technologies are developed to prepare these nanocrystals. In this way, the solubility of poorly soluble drugs can be increased by decreasing the particle size of the drug and increasing the surface to volume ratio. Some drugs are modified as hydrophobic prodrugs and then converted into nanocrystals, which are further developed as nanocrystal suspensions. The first monthly injectable atypical antipsychotic Invega Sustenna[®] (paliperidone) based on NanoCrystal technology was approved by the FDA in 2009, which was developed by Janssen Pharmaceuticals, Inc. for the treatment of schizophrenia¹¹³. In 2015, the improvement version Invega Trinza[®] (paliperidone), a three-month injection, was approved by FDA for the treatment of schizophrenia in patients who have been adequately treated with Invega Sustenna[®] for more than four months¹¹⁴. The prescription of nanosuspensions includes poorly water-soluble drug crystals, stabilizers and appropriate buffers. Notably, paliperidone palmitate, the active ingredient of Invega Sustenna[®] and Invega Trinza[®], is an insoluble prodrug synthesized by modification of paliperidone with palmitic acid¹¹⁵. The necessity for liberating the water soluble paliperidone prolongs the release time resulting in a long-acting pharmacological action.

With the successful development of nanosuspension based on nanocrystals of cabotegravir and rilpivirine in phase III clinical trial, long-acting antiretroviral therapy (ART) has the potential to revolutionise current HIV/AIDS treatments¹¹⁶. As shown in Fig. 7, after high-pressure homogenization or wet milling, the nanoscale crystals in range of 50–1000 nm can be obtained, allowing high drug loading capacity, controllable size and long-term storage after lyophilization. It is reported that a drug depot is formed at the injection site after im or sc administration and the drugs are slowly released from the depot. Subsequently, nanocrystals enter the systemic circulation in following possible three pathways. First nanocrystals can be absorbed by blood capillaries, and then directly enter the systemic circulation. Second, after being absorbed by blood capillaries, the nanocrystals are drained into thoracic lymphatic vessels and subsequently released from lymphatic system into systemic circulation. Finally, nanocrystals can also be absorbed by macrophages and then enter lymphatic capillaries to form secondary depot¹¹⁷. In the study of pharmacokinetics of rilpivirine nanosuspension, van't Klooster et al.¹¹⁸

found that the concentration of rilpivirine in the lymph nodes draining the injection site was more than 100-fold higher than plasma concentration of rilpivirine 1 month after im administration in dogs, and decreased to 3- to 6-fold higher than plasma concentration of rilpivirine beyond 3 months. In addition, after direct iv administration, macrophages phagocytize nanocrystals to act as a drug reservoir resulting in sustained drug release in systemic circulation¹¹⁹. The drug dissolution and absorption of nanocrystals are dependent on many factors, such as aqueous solubility, particle size, injection site and depth, phagocytic efficiency of macrophages, degradation rate of prodrugs and the efficiency of lymphatic uptake.

In the past 20 years, drug nanocrystals have been gaining popularity, with the attraction of prolonged release characteristics after im injection. However, there are still challenges which need to be overcome in the future, such as large administration volumes, lower patient compliance, risks from tissue irritation and drug residues and safety requirements. Based on above mentioned, combined with clinical demands, nanosuspensions with sustained release characteristics, high drug loading and reduced administration volume have been developed in order to minimize the administration times and improve the compliance of patients. In the future, more and more intramuscularly administered nanocrystal suspensions will be developed and utilized in clinic for the treatment of different kinds of diseases.

3.5. Biomineralization

Direct use of natural biomaterials is a desirable strategy to bypass the foreign body response and maintain drug activity. Besides cell-mediated biomimetic strategies, the natural biomineralization process has attracted the attention of researchers. Biomineralization is an essential process to form hierarchically structured minerals with unique functions in biological organisms¹²⁰. Interestingly, macromolecule biomineral complexes have the ability to load and release the bioactive molecules in the assembly and disassembly process *in vivo*¹²¹. Inspired by the natural biomineralization, Chen et al.¹²² reported that nanosized mineral solids, based on exendin-4, were formed through the interaction between calcium ions and acidic amino acid residues from the peptide in a supersaturated environment. This biomimetic system responded to physiological supersaturation, following the effective and long-term exendin-4 delivery. The acidic amino acid residues (one aspartic acid residue and five glutamic acid residues per molecule) from exendin-4 provided a “nucleation site” to chelate calcium ions to increase local supersaturation. Under anionic phosphate participation, tiny crystals were formed from calcium phosphate nucleation around the peptides, and further orderly assembled to macromolecule–biomineral complexes. It is worth noting that this strategy presented negligible influence on the bioactivity of the peptide. The mineralized exendin-4 may be dissociated and sustainably released after being spontaneously absorbed by a living body. The long-acting hypoglycemic effect of mineralized exendin-4 has been demonstrated in diabetic mice. Different from others, the strategy based on biomineralization is cost-effective and facile with negligible influence on the activity of proteins. In addition, the biocompatible biomineralized materials can avoid severe foreign body response, and be completely absorbed *in vivo*. Although this kind of biomimetic formulation represents promising application prospects in preclinical study, it's still uncertain whether it can also achieve long-term effect in the human body.

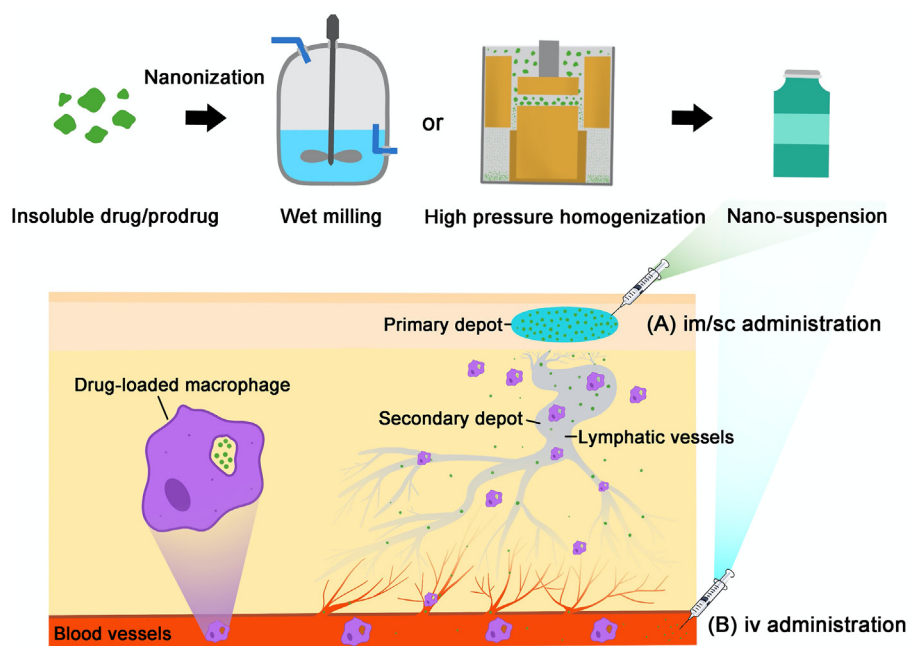


Figure 7 The preparation process and the mechanism of long-acting nanocrystals. This strategy is suitable for drugs/prodrugs with a low solubility in water. The manufacturing of nanocrystals can be achieved by milling or high-pressure homogenization. The long-term effect of the suspension of nanocrystalline is mainly achieved by the following two ways: (A) after im/sc administration, a primary depot of insoluble drugs/prodrugs can be formed in the site of injection, and then the drugs/prodrugs are slowly drained into the thoracic lymphatic vessels to form secondary depot. Subsequently, the active substance is gradually released from the lymphatic system into systemic circulation for long-acting effect; (B) after iv administration, macrophages phagocytize nanocrystals to act as a drug reservoir resulting in sustained drug release in systemic circulation. Reproduced with the permission from Ref. 116. Copyright © 2020 Elsevier.

3.6. Long-acting hydrogels

Hydrogels, which have high water absorbing capacity, are cross-linked hydrophilic three-dimensional (3D) polymer networks¹²³. Due to the close resemblance to extracellular matrix (ECM), hydrogels are considered as biocompatible materials applied to tissue engineering and drug delivery. In addition, the porous structure and aqueous environment of hydrogels are beneficial to drug loading, which makes it a promising candidate for controlled delivery systems for bioactive agents such as gene medicine, chemical drugs and proteins. In general, hydrogels are widely used as long-acting preparations through locally sustained drug release. The mechanism of drug release depends on the swelling of the hydrogels and drug diffusion from the polymer network. However, the phenomenon called “burst release”, which leads to unwanted side effects, limits the clinical application of hydrogels. In addition, the safety of chemical cross-linked hydrogels for long-term use is still unclear because of unidentified biocompatibility, refractory biodegradation and residual trace harmful reagent.

Supramolecular hydrogels are formed by self-assembly of molecular building blocks termed as hydrogelators through non-covalent interactions such as electrostatic interactions, hydrophobic interactions, van der Waals interactions, hydrogen bonding, metal-ligand, π - π stacking and sulfone-sulfone bonding^{124,125}. Although supramolecular hydrogels have similar functions with polymeric hydrogels, the network structures formed by them are different. Supramolecular hydrogels are formed by self-assembly to nanofibers and helices, leading to entangled networks, while polymeric hydrogels are formed

generally through chemical cross-linking^{125,126}. In addition, due to the small molecular weights of hydrogelators, supramolecular hydrogels are easier to be cleaned up *in vivo* than polymeric hydrogels, which have higher molecular weights. Aromatic peptide-based supramolecular hydrogels was successfully employed to co-assemble and slowly release different bioactive factors to respectively enhance the anti-hepatic fibrosis effect of dexamethasone¹²⁷, enhance the anticancer effect of etoposide¹²⁸, overcome organ transplant rejection of tacrolimus¹²⁹, and promote periodontal bone regeneration¹³⁰. Abundant innovative efforts on directed self-assemble hydrogels formed by active small molecules or their derivatives (*e.g.*, rhein¹³¹, raltitrexed¹³², berberine¹³³, a glycyrrhetic acid-modified curcumin¹³⁴, etc.) have been developed from their beneficial high-purity, facile and environmentally friendly nature, void of any chemical synthesis process. For example, Qian et al.¹³² reported that raltitrexed, as a pure anticancer molecular, self-assembled into a hydrogel *via* π - π stacking and hydrogen bond, has the potential to be a long-term auxiliary implement for avoiding postoperative local tumor recurrence.

With the progress of intelligent materials, hydrogels are endowed with various functions in response to environmental stimuli such as temperature, pH, photo, enzyme, ionic concentration and chemical signals^{135,136}. For these stimuli responsive hydrogels or environmentally sensitive hydrogels, as the stimulus appears, the properties of hydrogels such as the structure, swelling behavior, permeability, solubility and mechanical strength can change resulting in the controlled delivery of therapeutics^{137,138}. These changes can be irreversible or reversible. Vong et al.¹³⁹

reported a temperature-sensitive and NO-releasing redox injectable hydrogel (NO-RIG). Under the temperature change after the intracardiac injection to mice, NO-RIG can convert to gel and retain in the myocardial tissue for at least 10 days. Additionally, *situ*-forming hydrogels at the tumor site provide a new strategy for long-term anti-tumor and anti-metastasis. Zheng et al.¹⁴⁰ constructed a *situ*-forming artificial ECM based on fibrinogen and thrombin for selectively cutting-off the tumor metabolic flux. The physical barrier can further inhibit the metastasis of tumor cells. Through the combined application with clinical treatment, this strategy also has the long-term effect of preventing tumor recurrence.

In the past decade, the use of hydrogel preparations as a depot for locally sustained release of drugs has developed quickly especially in the case of contained and localized pathology. Rational hydrogel design can provide stimuli-triggered drug release to impart more precise, long-acting, and potent therapeutic effects. However, there remains challenging issues such as inevitable burst release and the inability to control the release kinetics overtime.

3.7. Long-acting microneedles

Microneedles (MNs), an array of micro-scale needles with a length of 0.2–1.5 mm, provide a painless approach for dermal delivery by overcoming the stratum corneum barrier^{141,142}. Polymeric materials adopted to fabricate long-acting MNs can be divided into three categories including swellable polymers, biodegradable polymers and both. Swellable polymers are often used to form hydrogels through absorbing interstitial fluid from the skin. The diffusion of drug molecules is the main release pattern of swellable polymers based MNs, which its release rate is influenced by the cross-linking density of the polymer, the solubility of the drug and the interaction between the drug and the polymeric materials¹⁴¹. Due to the infusibility to skin tissue, swellable polymers based MNs can be completely removed after application without any safety issues of residual polymers. MNs based on biodegradable polymers, such as PLGA and PLA, control the drug release by the degradation of the polymer matrix rather than drug diffusion^{143,144}. Some polymers derived from natural sources such as silk, fibroin and gelatin, are both biodegradable and swellable. Their respective drug release patterns are complex and rely not only on the rate of swelling but also the rate of degradation of the polymer. In brief, drug release control of MNs can be adjusted through modifying the properties of the polymeric materials.

The design of the drug reservoir is the key of MNs preparation. The needle-based reservoir with separable needles or bioinspired needles is the common design of long-acting MNs. Separable needle-based MNs can regulate the drug containing-needles separate from the backing layer by the following different mechanisms: swelling triggered, bubble-aided¹⁴⁵ and degradation-based separation for drug release¹⁴⁶ (Fig. 8A and B). For example, Li et al.¹⁴⁷ developed a maneuverable and safe microneedle patch, which was able to slowly release the contraceptive hormone for more than 1 month. The separate mechanism of MNs from the patch is triggered by effervescence after contacting with skin's interstitial fluid. However, due to the relatively shallow penetration, MNs fail to tightly contact the skin during long-term use. Bioinspired needles (Fig. 8C) inspired by natural animals are designed to construct a firm adhesion between skin tissue and MNs. MNs with backward-facing barbs are inspired by the stinger

of honeybees¹⁴⁸. Furthermore, the serrated forelegs of praying mantises and the attaching mechanism of endoparasite worms were used to design the shape of MN arrays^{149,150}. A backing layer-based reservoir provides another design of long-acting MNs, which significantly increases the storage capacity to meet the requirement of drug loading for long-term exposure. Dissolvable polymers are used to fabricate the needles at an early stage. Drug diffusion from the backing reservoir is achieved through the micropores created after the needles dissolve completely. However, the micropores formed in this way cannot be retained for a long time. This results in the disruption of drug release. Swellable hydrogel-based needles are applied to overcome the above limitation, which provide a continuous and smooth channel between the drug reservoir and the dermal microcirculation¹⁵¹.

MNs, a promising technology, constructs an ideal drug delivery system because of the convenient and painless dermal route of administration, which translates into high patient compliance¹⁵². Although MNs-based products in clinical trials are currently only used for bolus delivery, long-acting MNs lying on sustained delivery should be available in the near future.

3.8. Long-acting implantable systems

Long-acting implantable systems, which is based on biocompatible materials and intelligent devices, have become a promising strategy for local tissue therapy or systemic delivery. According to different drug release mechanisms, the long-acting implants can be divided into four types including polymer-based implants, implanted pumps, implantable chip and nanochannel based implants¹⁵³. Fig. 9 illustrates the design and mechanism of the above implantable systems, and the following is their introduction in brief.

According to properties of polymeric materials, the polymer-based implants include fully degradable polymeric systems as well as non-degradable polymeric systems¹⁵⁴. The classical degradable implants (*e.g.*, SinoFuan[®], Zoladex[®], Propel[®], etc.), cylindrical solid rods, are prepared by melt extrusion to from biodegradable polymers. The non-degradable implants (*e.g.*, Implanon[®], Nexplanon[®], Vantas[®], etc.) consist of a drug core and a non-degradable film. These implants often employ the polymers such as silicone, ethylene vinyl acetate (EVA) and polyvinyl alcohol (PVA). The rate of drug release is controlled by the properties of polymeric coating, such as molecular weight, coating thickness and polymer configuration, as well as the physicochemical properties of drug, such as molecular weight, particle size and solubility. *In situ* forming implants (ISFI) are liquid or semisolid formulations based on biodegradable polymers, which have the ability to achieve spontaneous gelation/solidification at the site of injection¹⁵⁵. According to the formulation compositions, ISFI can be formed by *in situ* precipitation, *in situ* gelling or cross-linking of the polymer chains. Among them, the solvent extraction (SE)/phase separation (PS) induced *in situ* precipitation has proved to be a successful approach to form long-acting ISFI (*e.g.*, Perseris[®], Eligard[®], Atridox[®], etc.) in clinical practice¹⁵⁶. This kind of ISFI consists of a biodegradable water-insoluble polymer such as PLGA, a water miscible organic solvent such as NMP and DMSO as well as therapeutics dissolved or dispersed in the homogeneous solution¹⁵⁷. Upon sc injection, this polymer-based biodegradable system, which becomes a solid drug depot *in situ* after organic solvent extraction, provides drug release for weeks and even months¹⁵⁸.

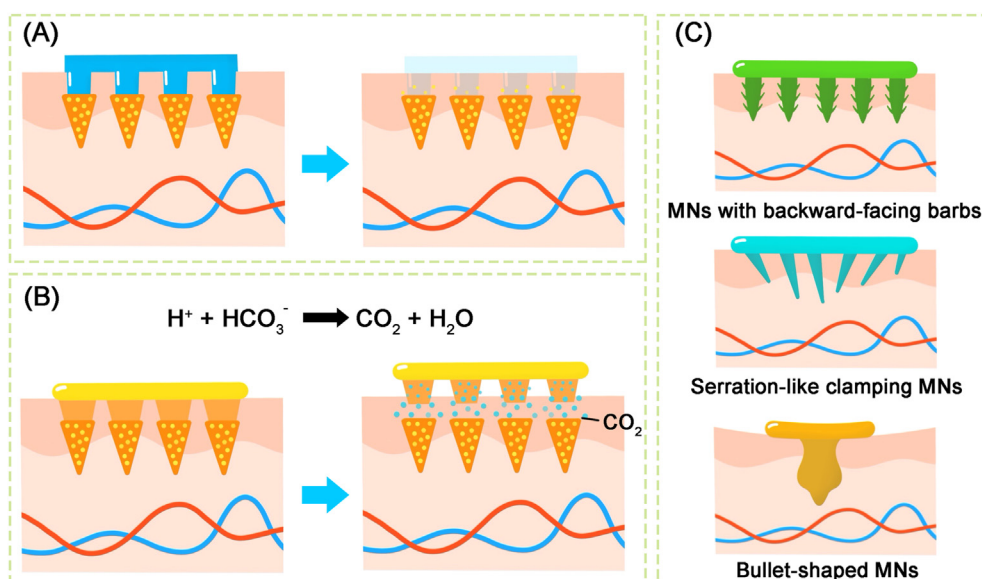


Figure 8 The common designs of microneedles. (A) The needles separate from the backing layer triggered by degradation-based mechanism. (B) The needles separate from the backing layer triggered by bubble-aided mechanism. (C) Bioinspired needles to achieve firm skin adhesion. Reproduced with the permission from Ref. 141. Copyright © 2020 Elsevier.

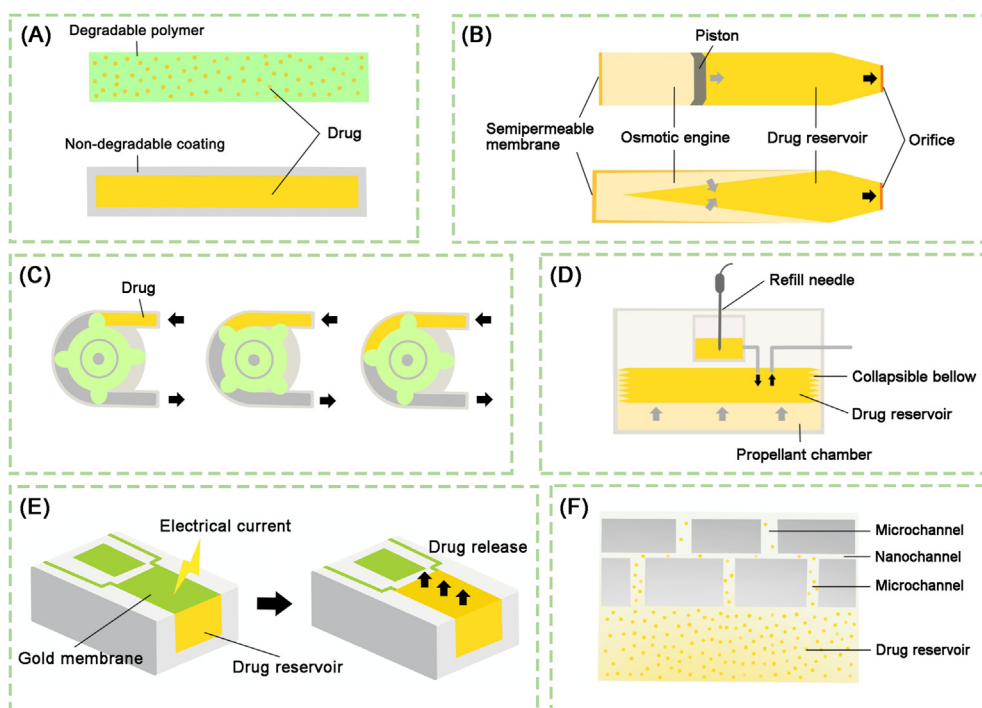


Figure 9 The design of long-acting implantable systems. (A) Polymer-based implants. (B) Osmotic pumps are composed of a drug reservoir, an osmotic engine and a movable piston. A semipermeable membrane is used to separate the osmotic from the outside, and micro-holes are designed to connect the drug reservoir and the outside. The increased hydrostatic pressure in the osmotic engine is the motive force of pumps for drug release. (C) Positive displacement is the motive force of peristaltic pump for transporting the fluid inside the tube. (D) Implantable infusion pumps are divided into three parts including a propellant, a collapsible bellow and drug reservoir. The propellant changes bigger in the volume under body temperature leading to compression of collapsible bellow, following the drug release. (E) The mechanism of implantable chip is that the single reservoir can be opened by applying an electrical potential to the gold membrane resulting in the complete dissolution of the membrane, which subsequently results in the release of the drug. (F) A drug reservoir can be conveniently covered by the nanochannel delivery system (nDS) membrane to achieve zero-order kinetic drug release from the reservoir. Reproduced with the permission from Ref. 153. Copyright © 2019 Springer Nature.

Table 1 List of approved long-acting preparations.

Product name	Therapeutic drug	Strategy	Route of administration	Medical application	Ref.
Adagen [®]	Adenosine deaminase	PEGylation	im	Severe combined immunodeficiency disease	161
Oncaspar [®]	Asparagines	PEGylation	iv/im	Acute lymphoblastic leukemia	161
Peg-Intron [®]	Interferon alpha-2a	PEGylation	sc	Hepatitis C	161
Pegasys [®]	Interferon alpha-2a	PEGylation	sc	Hepatitis C	161
Neulasta [®]	G-CSF	PEGylation	sc	Treat neutropenia during chemotherapy	161
Somavert [®]	HGH antagonist	PEGylation	sc	Acromegaly	161
Macugen [®]	Aptamer	PEGylation	Intravitreal	Age related muscular degeneration	161
Mircera [®]	EPO	PEGylation	iv/sc	Anemia associated with chronic kidney disease	161
Cimzia [®]	PEG-anti-TNF Fab	PEGylation	sc	Rheumatoid arthritis	161
Puricase [®]	Uricase	PEGylation	iv	Gout	162
Sylatron [®]	Interferon alpha-2b	PEGylation	sc	Melanoma	163
Omontys [®]	PEGinesatide	PEGylation	iv/sc	Anemia with chronic kidney diseases	161
Jintrolong [®]	Somatotropin	PEGylation	sc	Growth hormone	164
Plegridy [®]	Interferon beta-1a	PEGylation	sc	Multiple sclerosis	161
Adynovate [®]	Alphapegol	PEGylation	iv	Haemophilia A	165
Rebiny [®]	Coagulation factor IX	PEGylation	iv	Haemophilia A	165
Revcovi [®]	Adenosine deaminase	PEGylation	im	Adenosine deaminase severe combined immunodeficiency	166
Asparlas [®]	Asparagines	PEGylation	iv	Acute lymphoblastic leukemia	167
Ziextenzo [®]	G-CSF	PEGylation	iv	Infection during chemotherapy	168
Esperoct [®]	Coagulation factor IX	PEGylation	iv	Haemophilia A	169
Levemir [®]	Insulin	Lipidation	sc	Diabetes	46
Victoza [®]	liraglutide	Lipidation	sc	Diabetes	170
Givlaari [®]	siALAS1	Nucleic acid modification	sc	Acute hepatic porphyria	171
Oxlumo [®]	siHAO1	Nucleic acid modification	sc	Primary hyperoxaluria type 1	171
Enbrel [®]	Etanercept	Fc fusion	sc	Juvenile idiopathic arthritis	56
Orencia [®]	Abatacept	Fc fusion	iv/sc	Rheumatoid arthritis	56
Arcalyst [®]	Rilonacept	Fc fusion	sc	Cryopyrin-associated periodic syndromes	56
Nplate [®]	Romiplostim	Fc fusion	sc	Chronic immune thrombocytopenic purpura	56
Nulojix [®]	Belatacept	Fc fusion	iv	Prevent transplant rejection in kidney transplant patients	56
Eylea [®]	Ablibercept	Fc fusion	iv	Various eye diseases	56
Zaltrap [®]	Ziv-aflibercept	Fc fusion	im	Metastatic colorectal cancer	56
Elocta [®]	Efmoroctocog α	Fc fusion	Powder and solvent for solution for injection	Haemophilia A (congenital factor VIII deficiency)	56
Alprolix [®]	Eftrenonacog α	Fc fusion	Powder and solvent for solution for injection	Haemophilia B (congenital factor IX deficiency)	56
Strensiq [®]	Asfotase α	Fc fusion	Solution for injection	Paediatric-onset hypophosphatasia	56
Trulicity [®]	Dulaglutide	Fc fusion	Solution for injection	Type 2 diabetes mellitus	56
Reblozyl [®]	Luspatercept	Fc fusion	iv	Beta thalassemia	56
Tanzeum [®]	Albiglutide	HSA fusion	sc	Diabetes	46
Idelvion [®]	Coagulation factor IX	HSA fusion	iv	Hemophilia B	172
Lupron Depot [®]	Leuprolide	Micro-encapsulation	im	Breast and prostatic cancer	20
Sandostatin [®] LAR	Octreotide acetate	Micro-encapsulation	im	Acromegaly, carcinoid tumors	20
Nutropin [®]	Somatotropin	Micro-encapsulation	sc	GH deficiency	20
Suprecur [®] MP	Buserelin acetate	Micro-encapsulation	sc	Endometriosis	20
Signifor [®] LAR	Pasireotide pamoate	Micro-encapsulation	im	Acromegaly	20
Somatuline [®] Depot	Lanreotide	Micro-encapsulation	im	Acromegaly	20
Trelstar [®] Depot	Triptorelin	Micro-encapsulation	im	Prostatic cancer	20
Arestin [®]	Minocycline hydrochloride	Micro-encapsulation	Subgingival	Gum infection	20
Risperdal Consta [®]	Risperidone	Micro-	im	Schizophrenia, psychotic disorders	20

Table 1 (continued)

Product name	Therapeutic drug	Strategy	Route of administration	Medical application	Ref.
Vivitro [®]	Naltrexone	encapsulation Micro-encapsulation	im	Alcohol opioid dependence	20
Bydureon [®]	Exenatide	Micro-encapsulation	sc	Type 2 diabetes mellitus	20
Signifor [®] LAR	Pasireotide pamoate	Micro-encapsulation	im	Acromegaly	20
Zilretta [®]	Triamcinolone acetonide	Micro-encapsulation	Intra-articular	Pain killer	20
Depocyt [®]	Cytarabine	Multivesicular liposomes	iv	Lymphomatous meningitis	103
DepoDur [®]	Morphine sulfate	Multivesicular liposomes	Epidural injection	Post-surgical pain relief	103
Exparel [®]	Bupivacaine	Multivesicular liposomes	Infiltration	Post-surgical pain relief	103
Androcur Depot [®]	Cyproterone acetate	Oil-based formulation	im	Cancer, prostate	20
Clopixol Depot [®]	Zuclopenthixol decanoate	Oil-based formulation	im	Schizophrenia	20
Delatestryl [®]	Testosterone enanthate	Oil-based formulation	im	Breast cancer hypogonadism	20
Lyogen Depot [®]	Fluphenazine decanoate	Oil-based formulation	im	Psychotic disorders	20
Haldol Depot [®]	Haloperidol decanoate	Oil-based formulation	im	Tourette's syndrome, schizophre	20
Fluanxol Depot [®]	Flupenthixol decanoate	Oil-based formulation	im	Schizophrenia	20
Makena [®]	hydroxyprogesterone caproate	Oil-based formulation	im	Preterm Birth	20
Faslodex [®]	Fulvestrant	Oil-based formulation	im	Breast cancer	20
Naldebain ER [®]	Dinalbuphine sebacate	Oil-based formulation	im	Pain management	20
Agofollin Depot [®]	Estradiol benzoate	Nanocrystal suspension	sc	Hypogonadism	20
Aristada [®]	Aripiprazole lauroxil	Nanocrystal suspension	im	Schizophrenia	20
Aristada Initio [™]	Aristada Initio	Nanocrystal suspension	im	Schizophrenia	20
Betason L.A [®]	Betamethasone	Nanocrystal suspension	im, intra-articular, intrabursal or intradermal	Inflammatory & allergic states	20
Bicillin [®] L-A	Penicillin G benzathine	Nanocrystal suspension	im	Syphilis, prophylaxis	20
Depo-Medrol [®]	Methylprednisolone acetate	Nanocrystal suspension	Intra-/peri-articular and intra-bursal	Epicondylitis, others	20
Depo-subQ Provera 104 [®]	Medroxyprogesterone acetate	Nanocrystal suspension	im	Contraception & endometriosis	20
Invega Sustenna [®]	Paliperidone palmitate	Nanocrystal suspension	im	Schizophrenia	20
Invega Trinza [®]	Paliperidone palmitate	Nanocrystal suspension	im	Schizophrenia	20
Kenalog [®]	Triamcinolone acetonide	Nanocrystal suspension	im, intravitreal	Arthritis, inflammatory diseases	20
Zyprexa [®]	Olanzapine pamoate	Nanocrystal suspension	im	Schizophrenia	20
Relprevv [®]	Olanzapine pamoate	Nanocrystal suspension	im	Schizophrenia	20
Atridox [®]	Doxycycline hyclate	Implantable system	Subgingival	Periodontal disease	20
CiproScrew [®]	CiproScrew	Implantable system	Intra-bone insertion	Bone infection in surgery	20
Leuprone HEXAL [®]	Leuprolide acetate	Implantable system	sc	Breast and prostatic cancer	20

(continued on next page)

Table 1 (continued)

Product name	Therapeutic drug	Strategy	Route of administration	Medical application	Ref.
Ozurdex [®]	Dexamethasone	Implantable system	Intravitreal	Macular edema, non-infectious uveitis	20
Suprefact [®] Depot	Buserelin acetate	Implantable system	sc	Prostatic cancer	20
Sinuva [®]	Mometasone furoate	Implantable system	Intra-ethmoidal	Sinusitis	20
SinoFuan [®]	5-Fluorouracil	Implantable system	Intraperitoneal	Cancer	20
Zoladex [®]	Goserelin acetate	Implantable system	sc	Breast and prostatic cancer	20
Perseris [®]	Risperidone	Implantable system	sc	Schizophrenia	20
Eligard [®]	Leuprolide acetate	Implantable system	sc	Prostatic cancer	20
Scenesse [®]	Afamelanotide	Implantable system	sc	Erythropoietic protoporphyria	20

EPO, erythropoietin; G-CSF, granulocyte colony stimulating factor; GH, growth hormone; im, intramuscular; iv, intravenous; sc, subcutaneous.

Implantable pumps are categorized into different classes according to the different motive forces responsible for drug release: osmotic pumps, peristaltic pumps and infusion pumps. They can be suitably chosen depending on disease patterns, the site of implantation and the drug release longevity. The following is an introduction to the different types of aforementioned implantable pumps. TARIS[®] System developed by TARIS Biomedical is based on an osmotic pump, which improves intravesical drug delivery. These intravesical osmotic pumps are currently undergoing clinical trials; its advantages including high loading efficiency, as well as reduced side effects and injection frequency. However, accidental rupture of the implantable pump can lead to drug overdose; moreover, the device might be difficult removed from the body without performing a cystoscopy. SynchroMed[™] II pump developed by Medtronic, Inc. is an implantable FDA-approved peristaltic pump system, which has been used for the delivery of morphine sulfate, treprostinil, ziconotide, etc. This kind of pump can be programmed to control the flow rate, leading to personalizing the drug dose for each patient. Nonetheless, it requires relatively large volumes to accommodate the battery, leading to low loading efficiency of therapeutics. The Codman[®] 3000 pump developed by Codman & Shurtleff Inc. is an approved infusion pump for intrathecal delivery of morphine sulfate as a means of alleviating pain; it is also approved for hepatic arterial infusion of chemotherapy to target sites. Although the pump can achieve a constant rate of drug release under body temperature, and also can be transcutaneously refilled *via* a self-sealing silicone central port, its large size limits the volumetric loading efficiency. Implantable chips utilize the radio-frequency communication between electronic circuitry and the remote-control unit to trigger the procedural dissolution of covered reservoir membranes for controlled drug release. Each micro-chip has an array of drug reservoirs of 300–600 nL, and can be individually opened over time, following a pulsatile delivery profile¹⁵⁹. Chua et al.¹⁶⁰ reported a cylindrical intratumoral device with a nanochannel delivery system (nDS) membrane at one end and a silicone cap on the other end, which is developed to release CD40 and OX40 leading to increased immune cell infiltration. This study highlights the nDS as a potential platform for sustained intratumoral immunotherapeutic delivery.

Long-acting implantable systems could manipulate drug release at specific site for up to years without much plasma concentration fluctuation, and thus have irreplaceable superiority. However, their main problem is that surgical removal is required if the material cannot be completely degraded and causes inflammation, and that the very complex and sophisticated system design of implants increases research difficulty and development costs. In the future, use of smarter and fully biodegradable materials, as well as smaller and gentler implant equipment will contribute to their clinical translation.

4. Future perspectives

While we have highlighted many successful examples of LAPFs (Table 1^{20,46,56,161–172}), challenges still remain in many areas of their application. Improved technologies still need to solve the potential issues of current strategies. As conventional and popular used long-acting strategies, microspheres and nanocrystals are less difficult to industrialize and will continue to be used to innovate formulations and obtain transformed products. Moreover, LAPFs designed through strategies based on endogenous substances have good biocompatibility and *in vivo* safety and will be more developed. With the development of PEGylation, endogenous molecule such as HA, fatty acid, PSAylation, GalNAc conjugation modification technology and fusion protein technology have been derived. Fc/HSA fusion and nucleic acid modification technology have already been widely used to fuse or modify macromolecule therapeutics. With Givlaari[®] and OxLumo[®] being approved in recent years, other drug candidates, designed by nucleic acid modification strategies, have now progressed into preclinical and clinical studies. Endogenous macromolecule, as a modifier with higher safety *in vivo*, has a tendency to gradually replace PEG to modify drugs and manipulate the *in vivo* clearance. These modified strategies are expected to be a hotpot in LAPFs development in the coming years. Furthermore, the use of endogenous polymers represented by HA, dextran and silk protein as soluble microneedle needle construction materials is a trend in the development of long-acting MNs. RBC-hitchhiking and membrane engineering technology, which are both based on endogenous substances, have encountered a series of problems in their transformation due to their individual differences, damage to cells or cell membranes during drug loading, and

preservation problems. With the increase of research in these directions, the above-mentioned problems will be solved one by one, and LAPFs designed by RBC-hitchhiking and membrane engineering strategies will be greatly developed. Besides, with the continuous improvement of functionalized excipients and innovation of drug delivery devices, the long-acting implantable systems integrating medical devices and drugs will be developed. Furthermore, intelligent drug release systems will provide lots of inspirations for designing innovative LAPFs with the development of the electronic technology, precision instrument technology and microchip technology. In these LAPFs, the dynamic release of drugs will respond to changes in human physiological indicators. With the application of more new materials and new formulation technologies, novel LAPFs will be designed to precisely control the dose, manage side effects, and avoid drug-drug interactions. In short, researchers will continue to seek new strategies to develop innovative LAPFs to provide the market with more therapeutic options.

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Author contributions

Yujie Shi, An Lu, Xiangyu Wang and Zakia Belhadj were responsible for original draft and visualization. Jiancheng Wang and Qiang Zhang revised the manuscript. All of the authors have read and approved the final manuscript.

Conflicts of interest

The authors declare no conflicting interests in connection with this article.

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