

Review

Journey to the Market: The Evolution of Biodegradable Drug Delivery Systems

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Abstract: Biodegradable polymers have been used as carriers in drug delivery systems for more than four decades. Early work used crude natural materials for particle fabrication, whereas more recent work has utilized synthetic polymers. Applications include the macroscale, the microscale, and the nanoscale. Since pioneering work in the 1960's, an array of products that use biodegradable polymers to encapsulate the desired drug payload have been approved for human use by international regulatory agencies. The commercial success of these products has led to further research in the field aimed at bringing forward new formulation types for improved delivery of various small molecule and biologic drugs. Here, we review recent advances in the development of these materials and we provide insight on their drug delivery application. We also address payload encapsulation and drug release mechanisms from biodegradable formulations and their application in approved therapeutic products.

Keywords: biodegradable materials; biopolymer; liposome; encapsulation methods; degradation mechanisms; therapeutic products



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1. Introduction

The fabrication of micro- or nano-particle formulations to address challenges in drug delivery has been of interest for decades. Compared with traditional drug delivery systems, microparticle and nanoparticle drug delivery platforms have a number of advantages [1,2], including the ability to: (a) load multiple drugs into the micro- or nano-particles in one step, (b) attach targeting ligands, (c) increase the circulation half-life of the encapsulated drug and/or reduce its non-specific toxicity [3,4].

To successfully design and develop a polymeric drug formulation, there are three main issues that need to be taken into consideration, namely, the physicochemical properties of the drug(s) of interest, the properties of the polymeric carrier, and the drug delivery system [5].

In general, polymeric drug delivery systems may be categorised into one of three types, namely, colloidal carriers [6], implantable networks or hydrogels [7,8], and polymer drug conjugates [9]. Selection of a suitable polymer that is compatible with the encapsulated drug(s) of interest is vitally important for achieving the desired product performance in vivo. In other words, the encapsulated drug candidate's properties including chemistry, hydrophobicity/hydrophilicity and potency, need careful analysis as the drug release profile is influenced by the drug properties, the interaction between the drug and polymer and the release environment [10]. Additionally, the physicochemical characteristics of the polymeric formulation (e.g., particle size and shape, hydrophobicity and hydrophilicity,

surface charge) also affect the in vivo performance and biodistribution of the polymeric formulation [11].

In the following sections of this review, we discuss the evolution of biodegradable polymeric drug delivery systems, methods used for encapsulation of drugs with biodegradable polymers, drug release mechanisms from polymeric formulations, and successful commercial products on the market.

2. The Evolution of Biodegradable Polymeric Drug Delivery Systems

Over the past 60 years, there have been four eras in the evolution of polymeric drug delivery systems. Apart from the maturing of nanotechnology and synthetic polymer chemistry, the size of the delivery apparatus has become progressively smaller, from macroscale to microscale and nanoscale, as summarized in Figure 1.

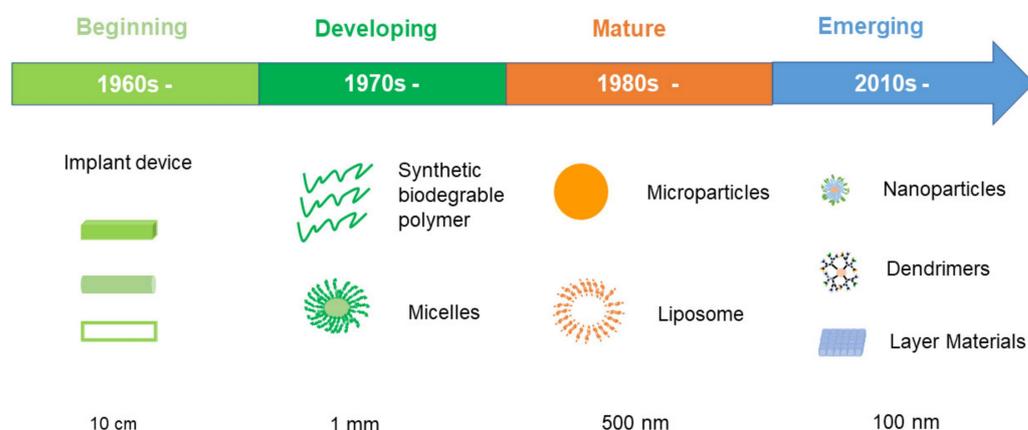


Figure 1. Schematic diagram summarizing the evolution of polymeric drug delivery systems (modified from Kamaly et al., 2016 [10]).

Research on drug incorporation into solid polymers for medical applications began in the mid-1960's [12]. Because the field of nanotechnology was not mature at that time, drug delivery using this approach could only be applied on the macroscale. An example is use of a local drug depot device to achieve spatiotemporal control of drug delivery [10]. In these early applications, only readily accessible natural materials were used and some of them were non-biodegradable polymers. Hence, drug release was mainly driven by diffusion of the drug from the depot due to lack of degradation of the polymer matrix [13], and the implanted device needed to be removed after drug release was complete. Along with the development of synthetic polymer chemistry, more and more biodegradable polymers were utilized to evolve the macroscale devices to new versions to minimize side effects. One successful example approved by the United States (USA) Food and Drug Administration (FDA) in the 1990's was Gliadel[®], an implanted copolymer disk (proliferospin 20) with the cytotoxic drug (carmustine) encapsulated for the treatment of glioblastoma multiforme [14,15].

2.1. Polyesters

Since the pioneering work of Langer and Folkman in the 1970's, biodegradable polymers have been developed and become widely accepted as a mature system to deliver encapsulated drugs in a controlled manner [16]. Synthetic biodegradable polymers such as polyesters are widely used due to their biodegradability, biocompatibility, and their ease of processing [17,18]. They have glass transition temperatures or melting points above 37 °C, which enable them to retain a solid form in the in vivo environment. Among them, poly(lactide-co-glycolide) (PLGA) is the most popular polymer carrier used in microparticle systems. PLGA polymers degrade by random hydrolysis of ester bonds with encapsulated drug released by bulk erosion mechanisms. Their degradation periods vary from days to years according to their molecular weight and lactic acid to glycolide residue ratios [19].

Generally, a higher proportion of lactide units, high molecular weight, and increasing crystalline content leads to a longer degradation time [20]. This means that various polymeric carriers can be used to design and fabricate particles to achieve a range of different release durations and so produce the desired therapeutic drug concentration profile.

2.2. Poly(ortho esters)

Poly(ortho ester) polymeric formulations are designed to achieve steady drug release subsequent to hydrolysis of polymer chains on the surface of the polymer. Poly(ortho ester) biopolymers were developed in the early 1970's and their main applications were in surgical repair materials and sutures [21]. In this decade, their applications in drug delivery systems for delivery of analgesics, DNA vaccines, and antiproliferative drugs have been studied widely [22].

The first generation of poly(ortho esters) were fabricated by the addition of DETOSU (3,9-bis(ethylidene-2,4,8,10-tetraoxaspiro [5.5]undecane) to a diol to form a DETOSU-based poly(ortho ester). Ester hydrolysis takes place within the aqueous environment and the hydrolysis rate can be adjusted by inclusion of acidic or basic units into the polymer matrix. For example, acid-catalysed hydrolysis increased microparticle degradation rate and a zero-order release of 5-fluorouracil over a 15-day period was achieved [23]. In another case, basic excipients stabilized the matrix bulk and facilitated surface-only erosion. By this approach, controlled release of tetracycline over a period of weeks was achieved for the treatment of periodontal disease [24].

Diffusion of acidic excipients out of the polymer matrix leads to unpredictable release kinetics. To address this issue, a new biopolymer structure containing the glycolide sequence was designed and self-catalysed hydrolysis without excipients was achieved [25]. Modification of a diol group by conjugation with an N-methyldiethanolamine can render the polymers pH sensitive in acidic environments [26]. Furthermore, because the poly(ortho ester) is highly hydrophobic, very limited water can penetrate into the matrix, which leads to a relatively low hydrolysis rate. By using poly(ethylene glycol) as the diol, polymer hydrophilicity was increased, which led to increased erosion rates [21].

2.3. Polyanhydrides

Polyanhydride biopolymers were introduced and developed with the motivation of achieving more stable degradation rates compared with other biopolymers. The anhydride bond linkages on the surface are very water sensitive but the polymer matrix is hydrophobic, preventing water penetration into the bulk, and so the predominant effect is surface erosion with a stable rate achieved [27]. In brief, the structure of the poly(anhydride) is comprised of two main components, an aliphatic segment, normally based on sebacic acid (SA) and an aromatic part, typically based on p-(carboxyphenoxy)-propane (CPP) and p-(carboxyphenoxy) hexane (CPH). The aliphatic poly(anhydride) degrades within days, whereas the aromatic poly(anhydride) degrades within years [28], and hence the degradation rate can be adjusted by varying the ratio of polymer units in the material.

The degradation product of polyanhydrides is a non-toxic diacid that can be readily metabolized and/or eliminated from the body, and therefore polyanhydrides demonstrate excellent biocompatibility [29]. This led to development of a polyanhydride controlled release product containing the chemotherapeutic agent, carmustine (Gliadel[®]), which was approved by the FDA for the treatment of brain cancer in 1996 [30]. Additionally, a polyanhydride implant loaded with gentamicin sulphate (Septacin[®]) [31] was developed for sustained local delivery for the treatment of osteomyelitis [14].

Apart from the classic CPP-SA or CPH-SA polyanhydrides, alternatives of CPP and/or CPH anhydrides with poly fatty acid dimers have been developed. As the fatty acid dimers deposit onto the surface of poly matrices in parallel with the degradation process, they can impede the diffusion of small molecule drugs and achieve a longer release period [32]. Furthermore, modification of the anhydride group by linking with imines and/or esters is potentially beneficial [33].

2.4. Polyamides, Polydopamine, and Polyphenol

Polyamides were introduced for prolonged delivery of drug cargos, with amide acid derived polymers being the most widely used [34]. Although they display biocompatibility in animals and produce relatively non-toxic products after metabolism [35,36], applications are restricted due to the intrinsic hydrolytic stability of the amide bond and cleavage rates rely highly on the presence of amidase enzymes. However, by modifying the amide acid group and conjugating the drug via a carboxylate bond [37], polymer–drug conjugates can be designed as insoluble particles [38], which can penetrate into cells and release the drug payload by enzymatic degradation over a long period [39,40]. In this decade, there has been interest in the application of materials such as polydopamine (PDA) and polyphenol. PDA is a nature inspired polymeric pigment that exhibits excellent photo-responsive properties and it has active surface functionality for drug loading [41,42]. Polyphenols are widely used in tissue engineering and drug loading based on their unique polyphenolic structures and inherent biocompatible, bioadhesive, antioxidant, and antibacterial properties [43].

2.5. Phosphorous-Containing Polymers

In contrast to other biodegradable polymers, phosphorous-containing polymers are distinct due to their degradation kinetics determined by the structural modification of the side-chain rather than the polymer backbone [44]. Use of phosphorus-based materials (polyphosphates, polyphosphonates, polyphosphazenes, polyphosphoesters, phosphonated poly(meth)acrylates, etc.) in biomedical applications is increasing due to their good biodegradability and biocompatibility [45,46]. Crommen et al. reported that control of the degradation rate may be achieved by the selection of various amine groups in the side chain [47]. As the degradation products such as phosphate, ammonia, and ethanol are non-toxic, phosphorous-containing polymers are employed as the carrier for controlled delivery of multiple drugs and peptides [48]. For example, a polyphosphazene-based polymeric formulation loaded with naproxen produced sustained release over a 4-week period [49].

2.6. Liposomes

The earliest nanoscale research began with liposome and polymer–drug conjugates. First generation liposomes were introduced in the early 1980s and the aim was to reduce cardiac uptake whilst preserving the anti-tumour activity of adriamycin [50]. However, due to its relatively rapid uptake into the bloodstream, this pioneering formulation type achieved only a limited therapeutic benefit, thereby impeding more widespread application [51–53]. The second generation of liposomes was developed as a means to enhance the stability and circulation time in the bloodstream. As poly(ethylene glycol) (PEG) was introduced into the structure to form sterically-stabilized liposomes, they are normally named PEGylated liposomes [54]. The PEG chain connected on the surface of the liposome establishes a steric barrier preventing opsonisation, leading to a longer half-life [52] as well as reduced drug-related side effects [55–57]. However, the general drawback of PEGylated liposomes is that they impair the approaching ability and interaction with target membranes [58]. To address this problem, a large variety of liposomal structures that shed their PEG coat have been designed such as attaching PEG to short acyl chains or co-administration with uncoated vesicles to act as a sink [59]. Promising ligand-targeted liposomes have emerged in this decade aimed at delivering drugs selectively to designated cell types or organs in vivo that express or over-express specific ligands at the site of the disease [60,61]. Generally, liposomes are phospholipid vesicles comprised of a discrete aqueous phase core enclosed by one or more concentric lipid bilayers (Figure 2).

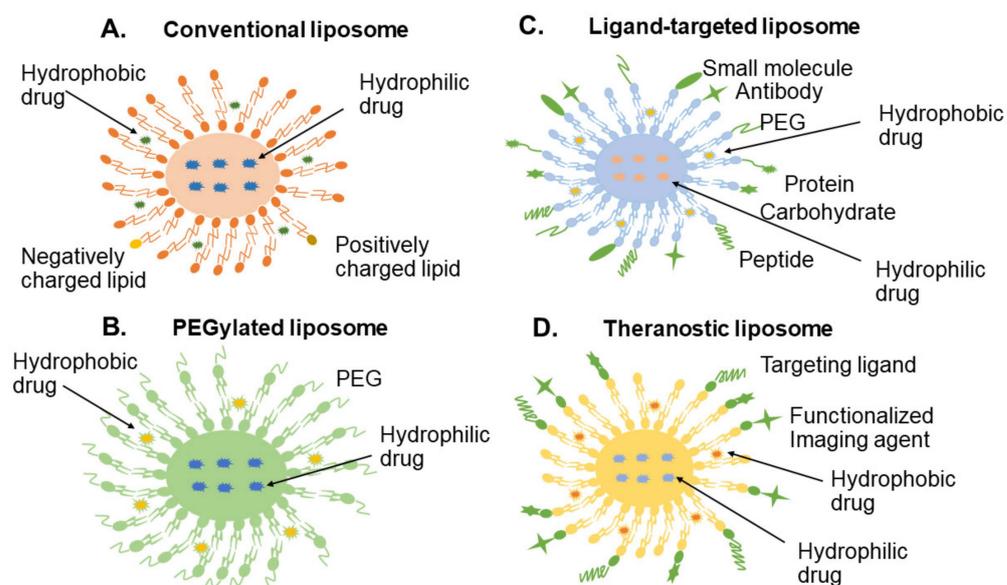


Figure 2. Schematic illustration of different types of liposomal drug delivery systems: (A) Conventional liposome, (B) PEGylated liposome, (C) Ligand-targeted liposome, (D) Theranostic liposome (adapted from Sercombe, L., et al. *Frontiers in Pharmacology*, 2015 [54]).

Many types of ligands are possible including peptide, protein, antibody, small molecule, and carbohydrate. Although the application of ligand-targeted liposomes is potentially broad, limitations on the performance of immunoliposomes have been reported [62,63]. To overcome the limitations of currently available site-specific liposomal carriers, a new generation of liposomal platforms has been designed and introduced [64]. The key strategy integrates advantages of different types of liposomes and establishing a hybrid structure. For instance, adding PEG chains to immunoliposomes can sterically stabilize and improve their pharmacokinetics [65–67].

Compared to conventional formulations, liposome formulations should demonstrate better efficacy and/or reduced side effects compared with their conventional counterparts or existing therapies in clinical trials before successfully entering the market. Apart from products currently marketed (Table 1), there are a number of liposomal formulations currently in clinical trials, and these are also summarized in Table 1. Although there are still some challenges to be overcome, liposomal formulations have a promising future.

Table 1. Liposome based products on the market and in clinical trials.

Encapsulated Drug	Regulatory Approval Year	Product Name	Treatment	Annual Sales	Delivery System	References
Small interfering ribonucleic acid	2018	Onpattro®	Peripheral nerve disease	166.4 million (2019)	Liposomal injection	[68]
Daunorubicin and cytarabine	2017	Vyxeos®	Therapy-Related Acute Myeloid Leukemia (t-AML)	~100 million (2018)	Liposomal injection	[69]
Irinotecan	2015	Onivyde®	Metastatic pancreatic adenocarcinoma (mPAC)	~40 million (2016)	Liposomal injectable suspension	[70]
Doxorubicin	2013	Lipo-Dox®	Some types of cancers	~800 million (2015)	Liposome injection	[71]

Table 1. Cont.

Encapsulated Drug	Regulatory Approval Year	Product Name	Treatment	Annual Sales	Delivery System	References
Bupivacaine	2011	Experal®	Pain management	331 million (2018)	Liposomal injectable suspension	[72]
Cytarabine	2007	DepoCyt®	Anti-neoplastic	7.2 million (2016)	Liposome injection	[73]
Morphine Sulfate	2004	DepoDur®	Pain-management	1.1 million (2005)	Liposome injection	[73]
Inactivated hemagglutinine	1997	Inflexal V®	Influenza		Liposome injection	[73]
Daunorubicin	1996	DaunoXome®	Cancer	4.4 million (1997)	Liposome injection	[74,75]
Amphotericin B	1996	Amphotec®	Fungal	27 million (1997)	Lyophilized powder (Lipid complex)	[76,77]
Doxorubicin	1995	Doxil®	Cancer	82.4 (2000)	Liposome injection	[78]
Amphotericin B	1995	Abelcet®	Fungal	~69 million (2001)	Lipid complex injection	[79]
Prostaglandin E-1 Cisplatin and its analogue L-NDDP Topotecan	Phase II Phase II Phase II Phase I	Liprostin SPI-077 Aroplatin Brakiva	Cardiovascular diseases Lung, head and neck cancers Chemotherapeutic Relapsed solid tumor	Target release Target release Target release Target release	Liposome injection [80] Liposome injection [81] Liposome injection [82] Liposome injection [83]	NCT00053716 NCT00004083 NCT00081549 NCT00054444
Vinorelbine	Phase II	LipoVNB	Advanced Malignancy	Target release	Liposome injection [84]	NCT02925000
Doxorubicin	Phase III	ThermoDox	Hepatocellular Carcinoma	Target release	Lyso-Thermosensitive liposomal [85]	NCT02112656
Paclitaxel	Phase III	EndoTAG-1	Pancreatic cancer Triple negative breast cancer	Target release	Liposome injection [86,87]	NCT03126435
MUC1 peptide	Phase III	Stimuvax	Non-small cell lung cancer	Target release	Liposomal injectable suspension [73]	NCT00409188
Amikacin	Phase III	Arikayce	Lung infection	High efficacy target release	Liposomal inhalation nebulizer [88]	NCT01315678

Source from clinicaltrials.gov (accessed on 25 November 2021).

2.7. Dendrimers

Dendrimers are a class of well-defined highly-branched macromolecules in contrast to linear polymers. Their architecture is comprised of a common core and discrete dendritic branches radiating out in layers around a central core until a spherical structure is established [89–91]. In these unique structures (Figure 3), drugs of interest can be contained within the void space of the interior and/or connected onto the surface by chemical modification. Dendrimers have been employed in biomedical applications, including as

drug carriers by encapsulation and/or conjugation [92–94], as well as being utilized as a part of a formulation or as complexing agents [95–97]. Furthermore, dendrimers as contrast/imaging agents carrying magnetic resonance imaging (MRI) agents and fluorophores have attracted strong interest in research and development [98–100].

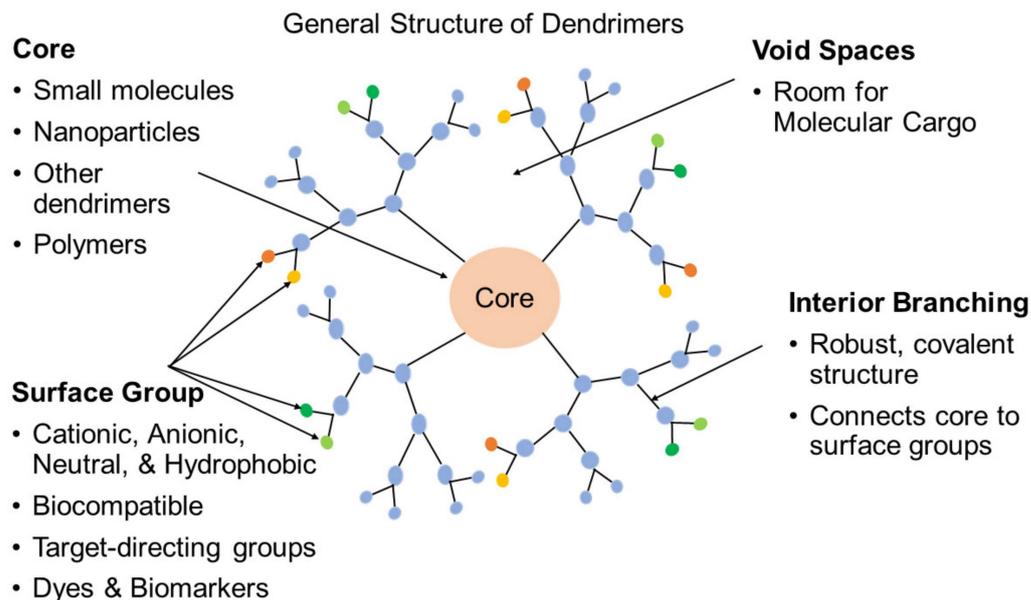


Figure 3. Schematic diagram of the general structure of dendrimers. The architecture is comprised of core and interior branching radiating out in layers. The drug of interest can be filled into the void space and/or connected onto the surface (adapted from *Pharmaceutical Technology*, 2008 [101]).

Compared with traditional linear polymer carriers, there are many advantages for dendrimer carriers. Firstly, by controlled synthesis and their monodisperse nature, an exact number of drugs can be loaded into the carriers and subsequently delivered [102]. Secondly, as dendrimer carriers can undergo two encapsulation processes, physically absorbed and chemically attached, their drug loading abilities are enhanced [91]. Finally, their physicochemical properties are highly correlated with their structures and determine their pharmacokinetics [103,104]. Thus, a predictable and repeatable release profile can be achieved with appropriate modification and optimization of their structure.

However, there are some challenges in translation of dendrimer platforms from the research laboratory to the marketplace. The dendrimer platforms are complex systems with multiple components such as dendritic branches, linkers, and encapsulated drugs, and so the design and synthesis processes are complex. For example, with the same components, linking via an ester bond or via an amide bond of the same drug with two possible sites, these dendrimers display totally different activities in vivo [105,106]. Furthermore, the cytotoxicity and permeability profile are correlated with concentration and surface charge, which means evaluation is challenging and it needs to be conducted on a case-by-case basis.

In summary, dendrimer carriers have considerable potential in biomedical applications. Notably, most of the first generation of dendrimer-based products are used as imaging agents or as diagnostic devices [107,108]. The first dendrimer-based product in the therapeutics field (Vivagel[®]) [109] has antiviral and antibacterial properties and is approved for clinical use in Australia and New Zealand. The phase 3 clinical trial results for both the treatment of bacterial vaginosis (BV) (2012) and the prevention of recurrent BV (2017) strongly supported their marketing applications. The New Drug Application (NDA) for VivaGel[®] BV was submitted to the FDA in 2019 under the Fast Track designation.

2.8. Layered Double Hydroxy Carriers

Layered Double Hydroxides (LDHs) belong to the group of layered materials, also known as anionic clays [110]. Compared with other members in the layered materials group, they are lamellar solids with inorganic components [111,112]. The first generation of LDHs comprised natural material, identified, and reported in Sweden in 1842 [113]. After that, a wide range of layered materials was developed and introduced. Generally, they are constructed by brucite-like hydroxide sheets expanding the two-dimensional layers and the exchangeable anions between the layers (Figure 4), which form a three-dimensional structure altogether [114]. The brucite-like layers are typically composed of divalent or trivalent cations with positive charge, whereas the interlayer galleries are made up of anions and water molecules compensating the charge via electrostatic interaction [115].

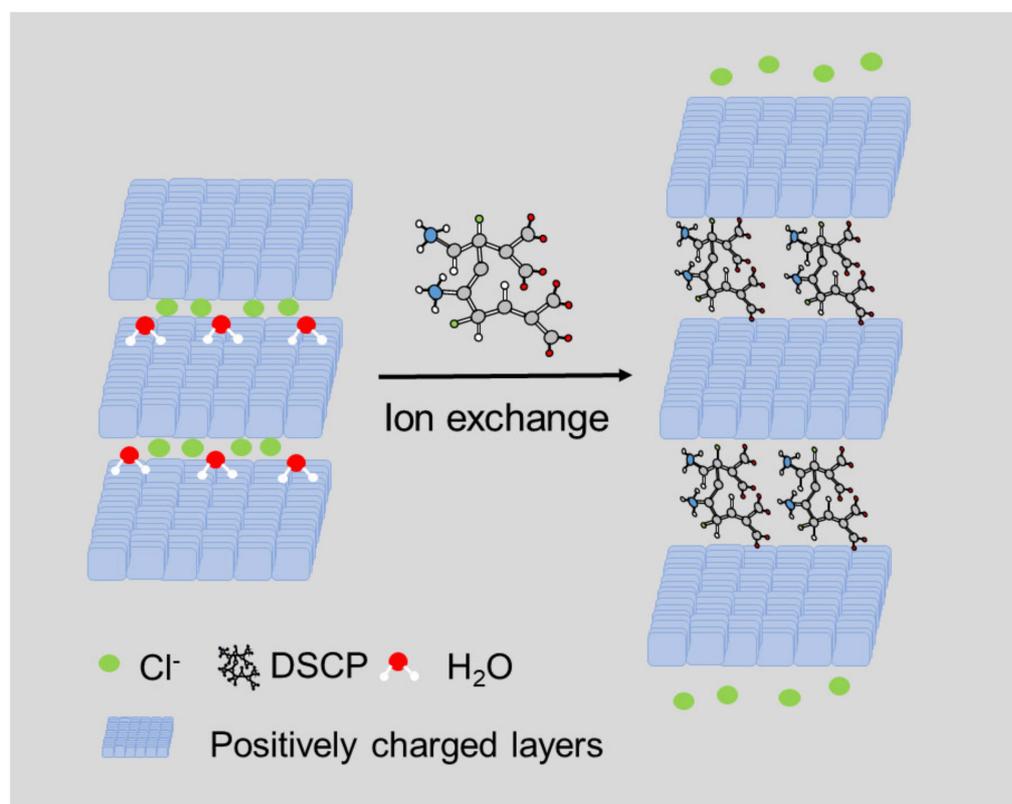


Figure 4. Schematic illustration of loading the cisplatin prodrug, disuccinatocisplatin (DSCP), into Layered Double Hydroxides through ion exchange (adapted from Ma, R., et al. *Journal of Materials Chemistry B*, 2014 [116]).

A large number of divalent or trivalent cations can be used to build the layers (Mg^{2+} , Zn^{2+} , Ni^{2+} , Al^{3+} , Ga^{3+} , Fe^{3+} , or Mn^{2+} , etc.), whereas the compositions of the interlayer gallery can be selected from simple or complex anions (CO_3^{2-} , NO_3^- , Cl^- , SO_4^{2-} , or RCO_2^- , etc.), anionic coordination compounds, and even polyoxo materials [117–121]. The LDH hybrid matrix demonstrates a tunable structure and morphology [111], and with modification of the ordering of cations and charge density of the layers, the physicochemical properties of the interlayer gallery can be consequently adjusted, leading to better biocompatibility [122], which is vitally important for incorporating drug(s) of interest and designing the drug delivery system.

Employed as carriers in drug delivery systems, a wide range of molecules can be intercalated with LDHs such as amino acids, peptides, ATP (adenosine triphosphate), vitamins, and even polysaccharides [114,123]. Because of their unique structures built by cation layers and anion interlayers, drug molecules can be loaded into the interlayer gallery by anion exchange. By adjustment of surface charge, their chemical stability can be adjusted

to various environments [124], leading to controlled release in both rate and site. For instance, in 2004, Choy et al. reported the use of LDHs as a reservoir for folate derivatives facilitating a significant increase in drug delivery efficiency [125]. In another example, a significant decrease in release rate was achieved with a fluvastatin–LDH hybrid [126]. The underpinning rationale was that hydrophobic LDH hybrids have slower release compared with hydrophilic hybrids driven by fast anion exchange and intraparticle drug diffusion. It is important to note that size and morphology can be precisely controlled with LDH hybrids [127,128] and targeted delivery of drugs to tumour tissue with sustained drug release has been achieved [129–131].

Since 2000, the use of LDHs as carriers in drug delivery systems has become increasingly attractive [132]. Most therapeutic agents intercalated as guests can be categorized as targeting diseases, such as anti-cancer, anti-inflammatory, and cardiovascular therapy, and so on. Chemotherapy drug–LDH hybrids have been designed and utilized in the past decade [133]. Examples include methotrexate (MTX), 5-fluorouracil, folinic acid, camptothecin (CPT), and podophyllotoxin (PPT) [133,134]. In a series of papers by Choy et al., MTX–LDH hybrids demonstrated a significantly higher penetration rate through the cell membrane [135] and lower cytotoxicity for certain cells [136]. Additionally, the *in vitro* study of MTX–LDH by Oh et al. showed that the MTX–LDH could achieve the same drug efficacy as MTX alone in spite of the 5000-fold lower concentration in the two osteosarcoma cell lines [137]. In other work by Chakraborty et al. the MTX released from MgAl–MTX–LDH hybrids showed relatively low release best described by first order kinetics with total release completed within 8 days via diffusion and crystal dissolution mechanisms [138]. 5-Fluorouracil (5-Fu) is a neutral weak acid and an anti-metabolite chemotherapeutic drug. The first 5-Fu associated LDH hybrid was reported in 2005 by Wang et al. [139], which was followed in 2008 by Choy et al. [140]. In their work, the drug–LDH hybrids inhibited cancer cell proliferation more effectively than the parent drug [140]. Moreover, the release profile of 5-Fu–LDH hybrids was pH sensitive such that at the same temperature, there was a higher amount of 5-Fu released at pH 7.2 compared with pH 4.8 [141].

Camptothecin (CPT) and podophyllotoxin (PPT) are cancer therapeutics that inhibit the enzyme, topoisomerase [142]. However, their utility is limited by poor water solubility and low bioavailability, fast metabolic inactivation, and drug resistance [114]. To address these issues, LDH-hybrids were formed. For example, the poor dispersion of CPT was improved by its incorporation into MgAl–LDH with the net result being a marked reduction in survival time of glioma cells *in vitro* [143]. Moreover, CPT–LDH hybrids prepared by a reconstruction method (intercalation of CPT into a layered gallery by reconstruction) showed enhanced solubility and increased release time *in vitro* [144]. For PPT–LDH hybrids, they strongly inhibited tumour cell growth compared with bare PPT due to increased circulation time as well as superior tumour cell killing [145,146]. Non-steroidal anti-inflammatory drugs (NSAIDs) are aromatic organic compounds. Generally, they have readily ionisable carboxylic acid groups, which allow them to intercalate into the layer gallery of an LDH host via ion-exchange [147,148]. NSAID–LDH hybrids significantly improve drug solubility in an aqueous environment as well as their absorption rate in living organisms [111,149]. A wide range of NSAIDs, including ibuprofen, fenbufen, naproxen, diclofenac, and indomethacin have been successfully intercalated into LDH hosts through precipitation, ion exchange, and reconstruction methods [133,150–153].

Apart from hosting anti-cancer and anti-inflammatory drugs, cardiovascular drugs employed as guests with LDHs have been well investigated [154]. For instance, captopril intercalated with LDH hybrids showed sustained release over 140 min under various pH conditions *in vitro* (pH 4.60 and pH 7.45, respectively). Notably, release at pH 7.45 was devoid of an initial burst, which is vitally important in controlled delivery [155]. Moreover, the LDHs can be used as carriers for DNA vaccines to enhance *in vivo* antibody responses [156]. In tumour-bearing mice, DNA/LDH hybrids markedly inhibited tumour growth and prolonged mean survival time [157]. Furthermore, for dental treatment, zero

initial burst and remarkably long steady release (up to one year) was achieved by fluoride-LDH hybrids [158,159].

In summary, the unique structure of LDHs means that multiple drug classes can be accommodated in their interlayer gallery or attached to their surface [160]. Drug-LDH hybrids not only successfully deliver the drug(s) of interest to specific cells with an enhanced penetration rate *in vitro*, but they may also demonstrate steady release without side-effects *in vivo* [160], both of which are essential for practical applications in drug delivery. However, there are hurdles still to be overcome and improved with regard to drug-LDH hybrid products. For instance, due to the restricted interlayer space [161], only small molecule drugs can be loaded whereas large molecules can only be attached to the surface, which limits the drug-loading rate. Designing and synthesizing LDH-hybrids is challenging as the structures are complex, and there are potential problems with rapid aggregation [162] and decomposition [163].

2.9. Metal–Organic Framework Carriers

Metal–organic frameworks (MOFs) are hybrid inorganic–organic materials that have emerged in the past decade, whereby the structure (Figure 5) is formed by self-assembled metals and organic linkers under mild conditions [164]. Generally, the metal containing nodes are made of a single-metal, transition metal, or a group of metals while the organic linkers are made of polycarboxylates, phosphonates, sulphonates, imidazonates, and phenolates, etc. [165,166]. Multi-dentate linkers such as di-carboxylates or tri-carboxylates allow the aggregation of metal ions into their cluster. After metal ions are locked into their position in the network vertex by carboxylates, rigid frameworks are established [167]. Their distinct physiochemical properties such as high pore volumes, tuneable pore size, and large surface areas enable them to encapsulate a wide range of drug agents, especially for large molecule drugs [168], leading to potential applications in drug delivery [169–172].

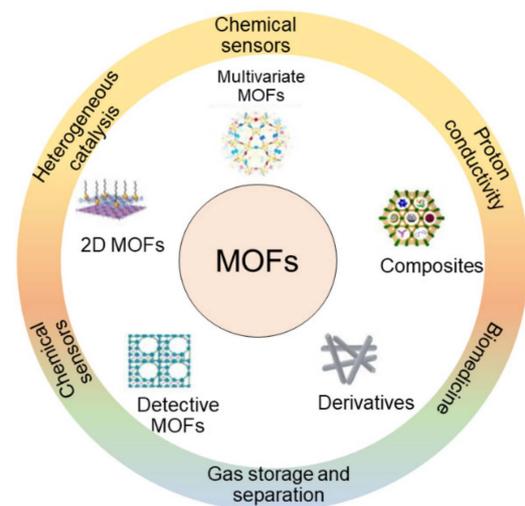


Figure 5. Schematic illustration of MOFs structure and functional applications (adapted from Jiao et al., 2019 [173]).

Generally, there are two main methods for encapsulating drugs into MOFs, namely, non-covalent and covalent [174]. The non-covalent method is the traditional method that is used widely and involves impregnating the porous MOFs into a solution of drug molecules and trapping the drug [175]. The advantage is that the method can be applied to a variety of drugs, regardless of their hydrophilic or hydrophobic physicochemical properties. However, as drug encapsulation is an inherently reversible process, premature release of the drug(s) of interest may be observed [176]. To overcome this problem, covalent methods have been developed [177], whereby the drug molecule is entrapped by tethering it to the MOF surface via a covalent bond [178]. For example, loading of cisplatin into an

amino-functionalized MIL-101 (Fe) using a covalent method and covered with a silica layer, achieved relatively high loading (12.8%) and a prolonged release time (up to 14 h) [179]. For use of this method, the MOF surface should have specific functional groups [180] that interact with the functional group(s) of the drug(s) of interest to facilitate covalent attachment [181,182]. Additionally, the chemical bond should be cleavable from the MOFs under specific biological conditions [164,183,184]. Typically, the release of encapsulated drug is via diffusion through the pores on the surface as well as degradation of the matrix [185–187]. There are three factors that significantly affect the release profile: (i) the interaction between the drug and the matrix surface; (ii) the size of pores on the surface; and (iii) the kinetics of matrix degradation [188]. Thus, controlled release may be achieved, by controlling interactions between encapsulated drugs and MOFs, modulation of the pore size and surface area as well as regulation of degradation rate [189–191].

There are several advantages distinguishing the MOFs from other materials. Firstly, their physicochemical properties can be adjusted along with the modification of the metal and organic linker components [192,193], which means that the pore size and surface morphology are highly tunable [194]. Secondly, as the surface area is large compared with other materials, the potential drug loading capacity is relatively high [195]. Furthermore, the pore size on the surface is large (up to 6 nm), enabling them to accommodate large molecule drugs [196]. However, for practical drug delivery applications, non-toxic or low toxicity MOFs with good biocompatibility properties need be developed. Moreover, systematic assessment of stability and a comprehensive understanding of the release mechanisms of drug–MOF hybrids *in vitro* and *in vivo* are essential for development of clinical applications [183].

Typically, for drug delivery applications, MOFs are categorized as individual MOF carriers or stimuli-responsive MOF carriers [183]. The first example of a drug loaded MOF hybrid was reported in 2006 [197]. Ibuprofen was successfully loaded into MIL-100(Cr) and MIL-101(Cr) and their drug loading and release profiles were investigated. MIL-101(Cr) demonstrated extremely high drug loading (up to 60%) and sustained release for up to 6 days [197]. Since the MIL-101(Cr) is toxic due to the chromium ions, biomedical applications are not feasible. Subsequently, a less-toxic MOF material, MIL-53(Fe) was developed. Following loading with ibuprofen, the release profiles *in vitro* displayed slow sustained release for up to 3 weeks [198]. Based on these findings, a wide range of anticancer and antiviral drugs were investigated with relatively high loading achieved [199], namely, 24% for azidothymidine triphosphate [200] and 16.1% for cidofovir [197,201]. As zinc ions have low-toxicity, Zn-based MOFs have also been investigated. For instance, 5-fluorouracil loaded Zn-MOFs demonstrated high loading (up to 34%) as well as prolonged release for up to a week [202]. Apart from neutral drugs, loading of cationic drugs such as procainamide HCl, which has a short half-life *in vivo*, into Zn-MOFs, resulted in prolonged release ranging from 20 h to 72 h [203]. Furthermore, based on zirconium-based MOFs, co-delivery of cisplatin and multidrug resistance (MDR) gene-silencing siRNAs demonstrated enhanced chemotherapeutic activity compared with bare cisplatin *in vitro* [204].

Stimuli-responsive MOFs are also promising for achieving controllable release in response to specific stimuli, such as pH, ions, temperature, magnetic field, light, and pressure [183]. Among them, pH-responsive MOFs are well investigated, especially for cancer therapy [205,206]. Based upon the low pH of the tumour microenvironment, the release of drug–MOF hybrids could be triggered within this acidic microenvironment, showing enhanced anticancer efficacy as well as being non-toxic to healthy cells [207,208]. For instance, doxorubicin (DOX) loaded gadolinium-based MOFs demonstrate pH-sensitive release at 44% within 5 days at pH 5.4, whereas only 22% was released after 5 days at pH 7 [209].

In the past decade, multifunctionalized MOFs with a core-shell structure have been widely investigated. Coated with a thin silica layer, drug MOF hybrids showed controlled release. This along with adjustment of the silica shell thickness and increased cellular uptake, led to enhanced anticancer efficacy [210]. Moreover, for stabilizing and slowing

down the release rate, novel lipid layers based on cholesterol or 1, 2-distearoyl-sn-glycero-3-phosphoethanolamine-Poly(ethylene glycol) (DSPE-PEG) have been developed. With lipid or lipid-PEG layers, the initial burst release is reduced [211].

In summary, due to their tunable structure and high loading capacity, MOFs are a promising platform for drug delivery systems [181]. However, for practical applications and potential marketable products, they are in their relative infancy.

3. Drug Encapsulation Methods and Mechanisms Underpinning Degradation of Biodegradable Polymeric Based Formulations

To achieve highly efficient and tunable biodegradable polymeric formulations, multiple techniques have been developed and investigated in drug delivery systems. However, to effectively deploy these systems to produce therapeutic products, there are a number of challenges remaining to be addressed including relatively low drug loading, undesirable release profile in vivo, and control of particle size [212]. These topics are addressed below.

3.1. Emulsion Method

Solvent emulsion extraction/evaporation is one of the most common methods used to produce polymeric microspheric particles [213] and it is widely used due to advantages in terms of simplicity, non-temperature sensitive, and good performance in particle size control [212]. Since reports of the first generation of oil-in-water (*o/w*) methods decades ago, there have been a large number of improvements aimed at encapsulating substances with a diverse range of physicochemical properties (e.g., hydrophobic, hydrophilic, large/small molecular weight). Generally, a single emulsion (*o/w*) can be applied to hydrophobic drugs while double emulsions (*w/o/w*) can be applied to hydrophilic drugs. In brief, for the single emulsion method, the drug for encapsulation is dissolved in the solvent phase to which is added the anti-solvent phase with stirring and homogenisation to form the polymeric microspheric particles loaded with drug [214,215]. For most hydrophobic drugs, the procedures usually comprise three steps: (a) the polymer is dispersed and emulsified into an aqueous phase with emulsifier; (b) the solvent of the emulsion droplets is diffused into the aqueous phase; and (c) the solvent is removed by evaporation and the particles are solidified in the aqueous phase [216]. The type and concentration of emulsifier added into the aqueous phase and/or organic solution, plays a crucial role in determining the polymeric formulation properties in terms of quality, actual drug loading, encapsulation efficiency, drug release, pharmacokinetics, and cellular uptake/interaction, etc. [217–219]. The typical surfactants (stabilizers) commonly used are poly(vinyl alcohol) (PVA), PEG, PEG-lipid, proteins, and carbohydrates [220–222]. Furthermore, the stirring speed and evaporation time of the organic solvent used has a significant impact on the size distribution of the particles formed [223], which potentially can affect product injection ability (for parenteral formulations), biodistribution, side-effects, and the release profile of the encapsulated drug [224,225].

In some cases, the drug candidates are hydrophilic and/or are in the form of water-soluble salts. Hence, a water-in-oil-in-water method (*w1/o1/w2*) can be used to encapsulate hydrophilic drugs within biopolymeric particles. Unfortunately, in most cases, the encapsulation efficiency (EE) is poor for hydrophilic small molecules at approximately 20–30% [226,227]. To address this issue, non-ionic surfactants may be added [222] or the hydrophilic salt form of the drugs of interest can be converted to the corresponding free base forms for weakly basic drugs or to the free acid forms for weakly acidic drugs [228], with the EE increasing to 90% and 56%, respectively. Another variant of the emulsion method is the water-in oil-in-oil method (*w1/o1/o2*) where the *w2* water phase is replaced by an organic solvent that is immiscible with the first organic phase and acts as an anti-solvent to the polymer and the drug [229]. For the drug of interest (e.g., methotrexate), the EE was moderately increased from 44% to 51%, but a major drawback was the large amount of the *o2* phase used, such as paraffin, which brings in problems such as solvent residues in the microspheres and problems in recycling and un-friendly environmental issues [229].

3.2. Nano-/Micro-Precipitation Method

The nano-/micro-precipitation method, also called the solvent displacement [230] or dialysis method [231], is widely employed to produce polymeric particles as drug carriers [72]. The main difference between this method and the emulsion method is that the particle formulation process is not under high energy/shear, but is driven by spontaneous diffusion of the organic solvent into the anti-solvent, normally water. In brief, particle production can be described by the following steps: (i) choosing a water miscible solvent as the polymer/drug dissolving phase; (ii) mixing the polymer/drug phase with water and the droplets or particles are formed through the process called the “Ouzo” effect [232]; and (iii) removing the organic solvent by evaporation, extraction, or a combination of both [233–236].

Because the solvents selected for dissolving the polymer/drug should be easily removable and water miscible, the commonly preferred solvents are acetone, acetonitrile (ACN), dimethylformamide (DMF), dimethylsulphoxide (DMSO), and tetrahydrofuran (THF) [235]. The mixing process can also be categorized into three types: (a) pouring anti-solvent (water) into the organic solution in one-shot, (b) adding the water into the organic solution dropwise, or vice versa, and (c) slow dialysis of the organic solution with water. For producing nanoparticles, the concept of the “Ouzo” region (Figure 6) has been proposed [237]. Within the “Ouzo” region, nanoparticles are more prone to be produced rather than microparticles [238,239], and vice versa, which is a vital strategy in fabricating particles with a desirable size range.

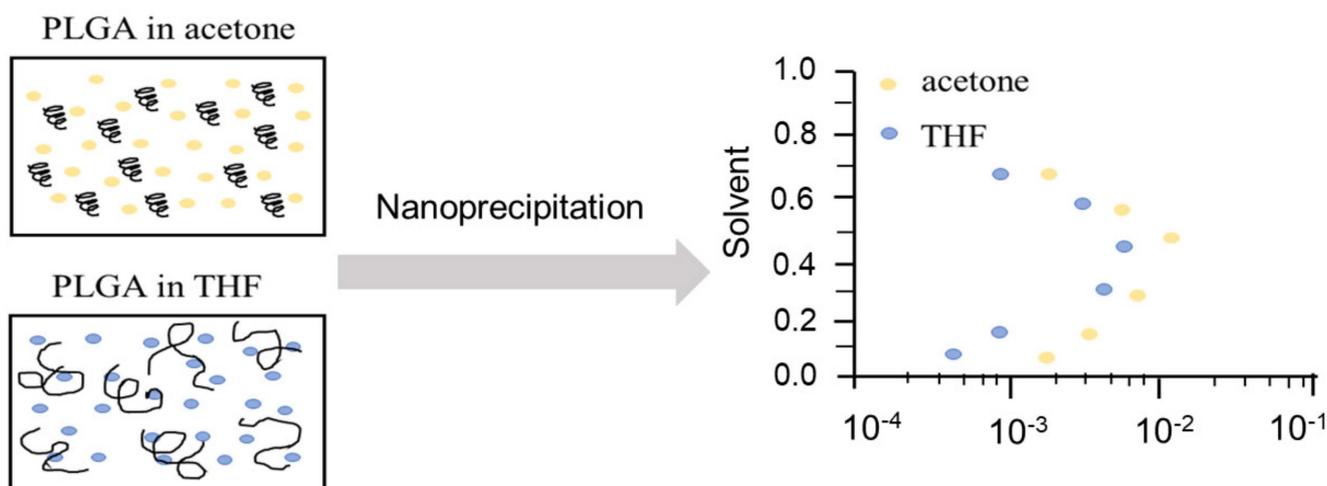


Figure 6. “Ouzo” region of PLGA in two different solvents (adapted from Beck-Broichsitter et al., 2016 [237]).

Overall, the nano-/micro-precipitation method is to some extent, an alternative or modification of the classic emulsion method. Additionally, as this technique is straightforward, fast, and easy to duplicate in practice, commercially available equipment is available for large scale production, making it a preferred and recommended method [240].

3.3. Dissolvable Hydrogel Template Method

The hydrogel template method was developed by Acharya et al. in the last decade [241]. Although it is not widely used as yet, the method demonstrates advantages in terms of high drug loading and a sustained release profile [241]. Because the size and shape of the wells on the master template can be precisely controlled, the microparticles produced with this method display a narrow size distribution and morphology in every dimension [242,243]. Generally, the method is summarized as shown in Figure 7.

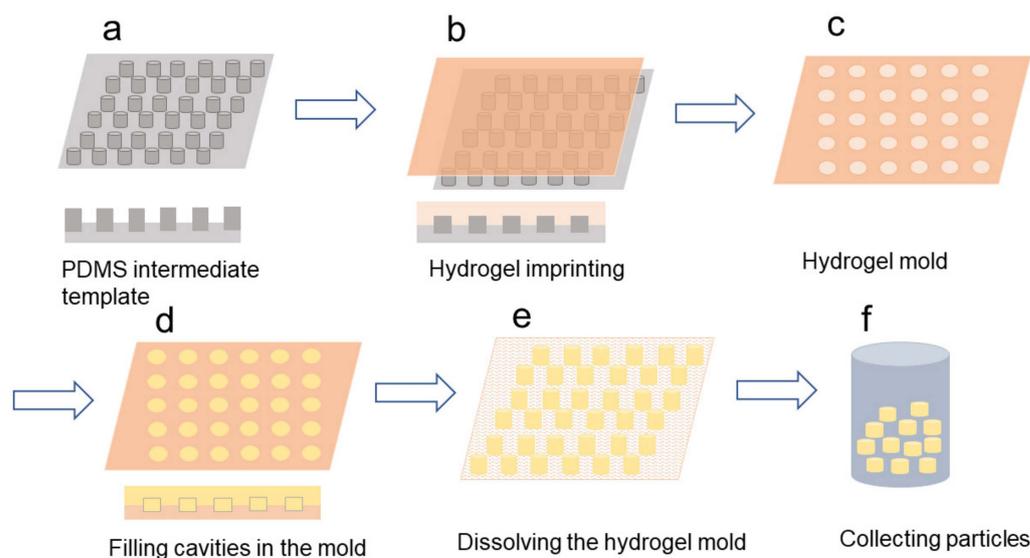


Figure 7. Schematic diagram of the hydrogel template fabrication process for producing drug-loaded microparticles: Steps (a–e): (a) PDMS intermediate template with 20 μm diameter vertical posts was formed using a designed silicon wafer master template with patterns of 20 μm diameter wells; (b) casting hydrogel solution on the surface of the PDMS template; (c) hydrogel template with 20 μm diameter wells; (d) casting drug/polymer solution into the wells of the hydrogel template; (e) dissolution of the hydrogel template; and (f) collection of the microparticles (adapted from Zhu. et al., 2019 [244]).

Firstly, a silicon wafer is produced as the master template with wells precisely controlled in size and shape. These can be fabricated by photolithography or electron beam lithography [241]. Water-soluble materials, normally poly(vinyl alcohol) (PVA) or gelatin can be employed as the hydrogel mould through an imprinting process. After that, a solution of polymer and drug is evenly spread onto the surface of the hydrogel mould to fill the cavities. This is then left at room temperature for a couple of minutes to remove solvent and solidify the particles. After solidification, the hydrogel template can be dissolved in water and particles can be collected by centrifugation and freeze-drying [241].

As an emerging technique, the hydrogel template method has some drawbacks in terms of unstable process control. It is unsuitable for large scale production and restricted to hydrophobic drugs or the corresponding base/acid form of small molecules only [242]. However, the advantages of high drug EE and sustained release profile are notable [241,242]. Recently, an instrument called a SpinSwiper has been developed to manufacture microparticles with more consistency and improving batch to batch reproducibility. With these improvements, the hydrogel template method could be applied to a large number of drug candidates and it potentially has broad applications in the future [245].

3.4. Microfluidics Method

The microfluidics method, similar to the hydrogel template method, was developed in recent years along with availability of microfluidics devices. Apart from the precise control of particle size range and morphology, this method demonstrates significant advantages in building structures and fabricating microencapsulated particles with multiple components in a one-step emulsification by the microfluidic device [246,247]. Additionally, the particles already formed can be re-encapsulated in the same device to cover them with a double layer with core-shell structures [248]. Recently, based on this ability in fabricating multiple layered structures, particles with a PLGA (poly(lactide-co-glycolide)) surface and a PCL (polycaprolactone) core have been reported [249]. Due to their distinct behaviours in degradation, a potentially superior release profile could be achieved [250]. Generally, the method is summarized in Figure 8.

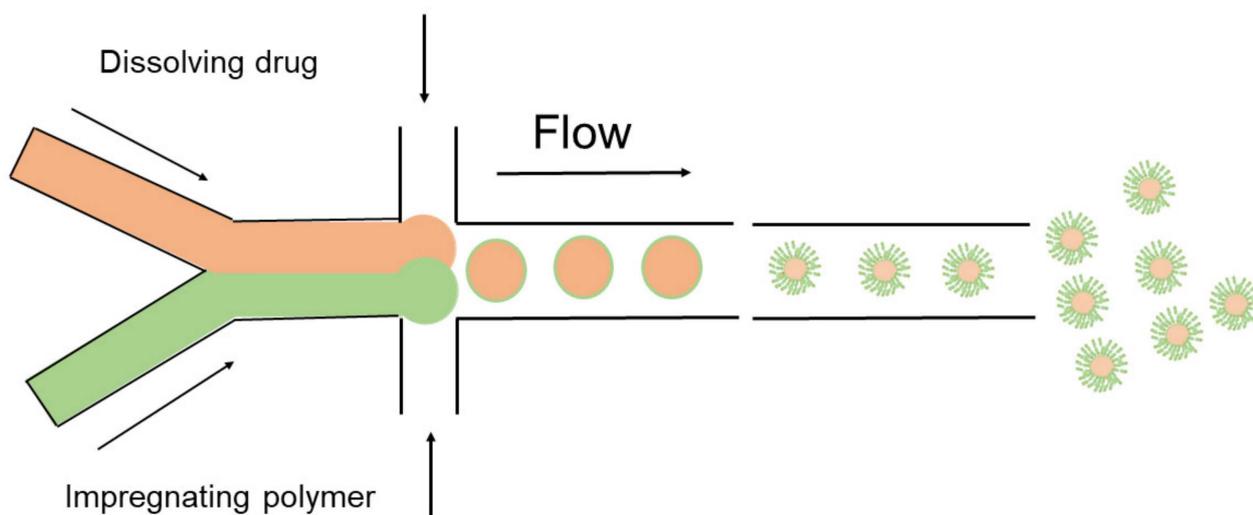


Figure 8. Schematic illustration of the microfluidics method. Nanoparticles are formed in the central channels of the microchips where the continuous phase meets the dispersed phase (adapted from Han. et al., 2016 [212]).

Normally, the microfluidics system is comprised of two main parts, the syringe pump used to precisely control the flow rate of various solvent inputs, and the microchips with multiple channels, in which the continuous phase and the dispersed phase meet and generate particles. For traditional microchips, they are made of PDMS (polydimethylsiloxane), which is less tolerant to high pressure and so vulnerable to breaking [251]. Recently, a glass–PDMS system has been introduced that has broad applications for a wider range of drugs with improved efficiency and higher quality [251,252].

Notably, the droplets size can be precisely controlled in the range 20–100 μm [253] and 100–300 nm [246] along with controlling the flow rates and the concentration of drug and the polymer solution. Particle aggregation in the fabrication and collection process is potentially a serious problem. Aggregation of particles in the microchips could block the channels and even cause breakages. Aggregation of particles in the collection process will affect the size range and generate undesirable particles [254]. The efficiency of particle production is always the main problem with this technique as only one droplet can be generated at a time [212,255]. Recently, a reliable and versatile system called the Droplet Parallel has been introduced to the market (Dolomite Microfluidics, Royston, UK). With the connection of several microchips, up to 30,000 droplets can be generated per second, which greatly boosts method efficiency and the possibility of large-scale production in a broad range of real applications [256,257].

3.5. Supercritical CO_2 Method

Supercritical CO_2 (scCO_2) is a fluid state only formed when it is at/above its critical temperature and pressure [258,259]. Due to the desirable properties of scCO_2 in terms of it being chemically inert, non-toxic, and non-flammable, it is the most widely used supercritical fluid and has been applied in a broad range of industries, such as food, natural oil, and drug manufacture [260,261]. Recently, in the biomedical field, scCO_2 -assisted drug microencapsulation has been used to produce drug-eluting implants and drug particles for oral dosing [262,263]. Generally, the supercritical CO_2 method is summarized in Figure 9.

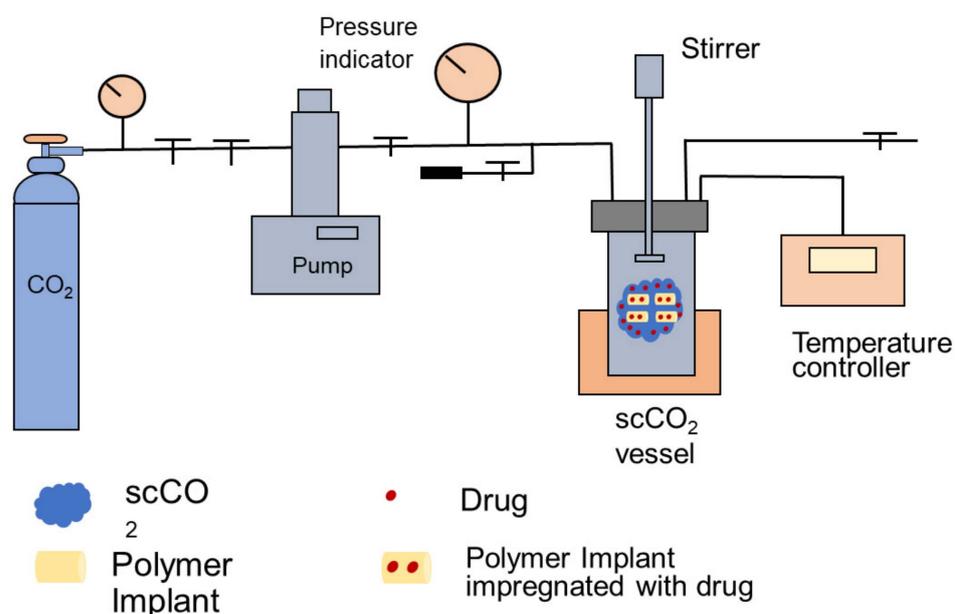


Figure 9. Schematic illustration of the supercritical CO₂ method. The drug of interest is dissolved in scCO₂ and impregnated into the polymer, and the non-impregnated drug is removed with CO₂ through depressurization. (Adapted from Xu., et al. *Drug Delivery and Translation Research*, 2021 [264].)

The supercritical CO₂ process involves three steps: (i) dissolving the drug candidate in scCO₂; (ii) CO₂ sorption and impregnation of the drug into the polymer; and (iii) removing the CO₂ and non-impregnated drug through depressurization. For drug loading, there are several influences due to the interaction and relationship between drug/polymer, polymer/scCO₂ and scCO₂/drug. For example, the drug solubility in scCO₂ affects the percent loading [265,266]; the polymer can interact with CO₂ and has good chain mobility therein [262]; and the interaction strength between the drug and polymer such as via H-bonding and solubility [267]. Furthermore, the effect of temperature and pressure, contact time and diffusive process, and depressurization rate all affect the percent drug loading [268]. The supercritical CO₂ method is an eco-friendly and cost-efficient technique [269]. Compared with traditional polymeric particle formulation methods, use of toxic organic solvents and elevated temperatures are avoided in the formulation process, which broadens the application to temperature sensitive drug candidates [270,271], and so it has a bright future.

3.6. Other Emerging Methods

In the past decade, there are a number of other emerging methods with promise for improving drug delivery systems, all of which have pros and cons. For example, the spray-drying method shows advantages in a wide array of applications for both hydrophilic and hydrophobic drugs [272], but it is not suitable for temperature sensitive drugs [273]. Another method involves use of suitable polymer additives to form polymer-drug conjugates [274] as a means to improve biodistribution and pharmacokinetics of the encapsulated drug [255]. Furthermore, nanoparticles-in-microparticles [275–277], and polymer-brush products [278–280] are exciting approaches for future research.

4. Drug Release Mechanisms from Biodegradable Polymeric Formulations

Control of drug release kinetics is mainly aimed at achieving a steady drug concentration in the circulating bloodstream with concentrations within the therapeutic range, i.e., between the minimum effective concentration (MEC) and minimum toxic concentration (MTC) [281]. Within this range, steady drug release per unit time from carriers is both effective and well-tolerated, and is called zero-order release kinetics [10]. The drug release profile is affected by several factors including the properties and ratio of compo-

sitions for drug, polymer, and their additives, the physical and/or chemical interactions among the multiple components, and even the formulation methods [282]. According to the drug release mechanism, they can be categorized in terms of diffusion-controlled release, degradation-controlled release, and solvent-controlled release [283]. In a classic drug release process, the drug molecule moves from within the polymer matrix to the outside of the particle and finally it reaches the surrounding environment [284]. In the early stage of drug release, the drug molecule is released via diffusion through water-filled pores in the particle [285], mainly driven by the chemical potential gradient or osmotic pressure [286]. However, once polymer degradation commences, polymer erosion may occur on the polymer matrix surface (surface erosion) or within the matrix after water penetrates into the polymer bulk (bulk erosion) [287,288]. Although there are some examples of drug release associated with diffusion-controlled release only [289–291], most examples of drug release from biodegradable polymers involve the combination of diffusion and degradation/erosion simultaneously [287,292].

While zero-order drug release from polymeric particles is preferable to give the desired drug release profile [293,294], the actual drug release from biodegradable polymers is usually bi-phasic or even tri-phasic [287]. In a typical tri-phasic release process, there is an initial burst release whereby the non-encapsulated drug or drug encapsulated near the polymer surface is rapidly released by hydration [295]. The second phase and the third phase could be a slow/rapid process, driven by polymer degradation and erosion [296]. Notably, the first phase of burst release is not always a necessity [297] and in some circumstances, the release speeds of the second and third phases are interchanged. This is shown schematically in Figure 10.

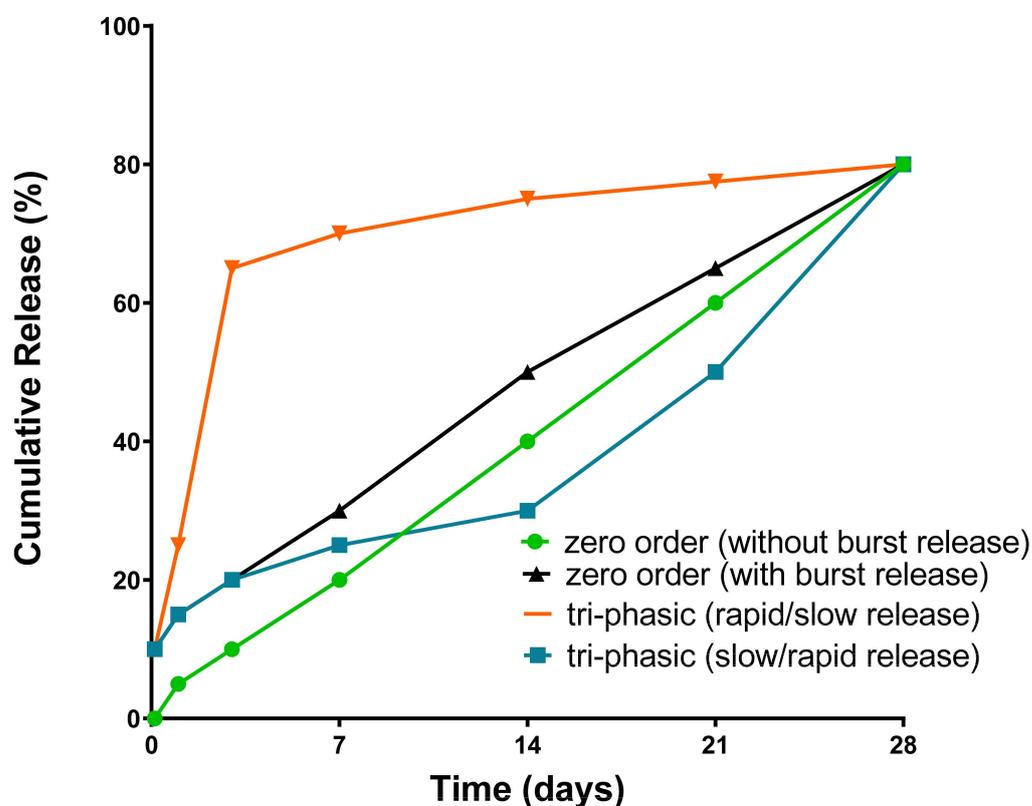


Figure 10. Schematic diagram showing typical drug release profiles over a 28-day period. The green and black lines show zero order drug release with and without initial burst release respectively. The orange line shows rapid phase 2 and slow phase 3 release, whereas the blue line shows slow phase 2 release followed by rapid phase 3 release (modified from Fredenberg., et al., 2011 [287]).

In drug delivery system applications, biodegradable polymers with hydrolysable bonds such as ester-, amide-, and anhydrides are widely studied [298–300]. Following hydrolytic and/or enzymatic breakdown of bonds in the polymer backbone, polymer degradation begins and initiates the onset of release of their encapsulated drugs [301]. Notably, in the realm of degradable polymers, people occasionally confuse the term ‘degradation’ with ‘erosion’. For the term, degradation, it specifically refers to bond cleavage, whereas the term, erosion, commonly refers to depletion of material [302]. In other words, the degradation is a chemical process while the erosion is a physical phenomenon, which is mostly dominated by dissolution and diffusion processes at the polymer surface [33]. In general, biodegradable polymers can be classified as bulk erosion polymers and surface erosion polymers [303]. They have distinct erosion processes in the release environment that affect the drug release profile [302]. In some circumstances, the erosion mechanism for a particular biodegradable polymer may change from one to the other [304]. Typically, most poly(esters), for example, PLGA (poly(lactide-co-glycolide)) and PLA (poly(lactic acid)), undergo degradation by a bulk erosion process, which means the simultaneous degradation of entire matrices [305]. For some poly(ortho esters) [306] and poly(anhydrides) [14], they undergo surface erosion by a mild process from the surface into the core [21], which lead to a relatively slow degradation and water diffusion process [307].

5. Successful Commercial Products Based on Biodegradable Polymers

Compared with non-biodegradable polymers, the main advantage of biodegradable polymers are that they are metabolized and removed from the body via normal endogenous metabolic pathways and so accumulation in the body is avoided [308–310]. Biodegradable polymers are widely used to encapsulate active pharmaceutical ingredients [311] and for other biomedical applications [312], as well as in products for the cosmetics and personal care market [313,314]. Although the original concept for development of controlled release drug formulations was first introduced in 1952 [315], it was three decades before the first generation of drug delivery systems gained regulatory approval for human use [316,317] (Table 2). In 1986, sustained-release triptorelin (Decapeptyl[®] SR) comprising injectable PLGA microspheres was approved for the treatment of prostate cancer [318,319] (Table 2). This was followed in 1989 by approval of a prolonged-release formulation of leuprolide (Lupron Depot[®]) by the United States (US) Food and Drug Administration (FDA) for the palliative treatment of advanced prostate cancer [320] (Table 2). In 2018, annual sales of Lupron[®] were estimated at USD892 million [321] (Table 2). Since the first generation, more than 20 products based upon biodegradable polymers have been approved for human use by the US FDA and the European Medicines Agency (EMA) and eleven of them were approved in this decade (Table 2). For example, an extended-release PLGA microsphere injectable suspension formulation of the corticosteroid, triamcinolone acetate (Zilretta[®]) was approved by the FDA in 2017 for the management of osteoarthritis knee pain for 3 months [322] (Table 2). Two years later in 2019, annual total sales were USD70 million. Triptorelin pamoate (Triptodur[®]) is also an extended-release injectable suspension formulation approved by the FDA in 2017 for the treatment of central precocious puberty (CPP) in paediatric patients aged 2 years and older [323]. It is the first gonadotropin-releasing hormone agonist administered by intramuscular injection at six-monthly intervals, which provides great convenience to patients. Other prolonged-release products comprising drugs encapsulated in biodegradable polymers and that have regulatory approval are summarised in Table 2.

Table 2. Prolonged-release products involving drugs encapsulated in biopolymer formulations and that have received regulatory approval.

Encapsulated Drug	Regulatory Approval Year	Product Name	Therapeutic Indication	Duration of Action	Annual Sales	Prolonged Release Formulation	Reference
Cabotegravir, Rilpivirine	2020	Cabenuva	Human Immunodeficiency Virus (HIV)	2 months		Injectable suspension	[324]
Buprenorphine	2018 2017 2017	Buvidal® Sublocade™ Sublocade®	Opioid use disorder	1 week/month 1 month 1 month	~70 million (2019)	Subcutaneous injection	[325] [326] [327]
Triamcinolone acetonide	2017	Zilretta®	Osteoarthritis knee pain	3 months	~73 million (2018)	Injectable microparticles	[322]
Triptorelin	2017	Triptodur®	Central precocious puberty	6 months		Intramuscular	[323]
Exenatide	2017	Bydureon Bcise®	Type 2 diabetes	1 week	584 million (2018)	Injectable microparticles	[328]
Paliperidone palmitate	2015	Invega Trinza®	Schizophrenia	1 month	604 million (2018)	Injectable nanocrystalline	[329,330]
	2009	Invega Sustenna®	Schizophrenia	1 month	424 million (2010)	Injectable nanocrystalline	[331–333]
Aripiprazole lauroxil	2015 2013	Aristada® Abilify Maintena®	Schizophrenia	4–8 weeks	17.3 million (2016) 2.3 billion (2018)	Injectable nanocrystalline	[334] [335,336]
Lanreotide	2014	Somatuline® Autogel	Acromegaly	2 weeks	1.1 billion (2019)	Depot, Microparticles	[337,338]
Pasireotide pamoate	2014	Signifor® LAR	Acromegaly	4 weeks	72 million (2018)	Injectable microparticles	[339]
Exenatide synthetic	2012	Bydureon®	Type 2 diabetes	1 week	151 million (2013)	Injectable microparticles	[340,341]
Bupivacaine	2011	Exparel®	Local anaesthetic	3 days	76.2 million (2013)	Injectable liposome suspension	[342]
Olanzapine pamoate	2009	Zyprexa Relprevv®	Schizophrenia	2–4 weeks	5.03 billion (2010)	Injectable microcrystalline	[332,343]
Naltrexone	2006	Vivitrol®	Alcohol dependence	4 weeks	7 million (2007)	Injectable microsphere	[344]
Risperidone	2003	Risperdal Consta®	Schizophrenia	2 weeks	737 million (2018)	Injectable microsphere	[345]
Leuprolide acetate	2002	Eligard®	Advanced prostate cancer	1, 3, 6 months	~30 million (2003)	Injectable suspension	[322,346]
Minocycline	2001	Arestin®	Periodontitis	3 weeks	~120 million (2018)	Microparticles	[320,322,347]
Triptorelin pamoate	2000	Trelstar®	Advanced prostate cancer	1 and 3 months	~400 million (2018)	Injectable suspension	[348]
Cytarabine	1999	Depocyt®	Lymphomatous	2 and 4 weeks	~5 million (2002)	Injectable liposome suspension	[73,349–351]
Octreotide	1997	Sandonstatin® LAR	Some types of cancers	4 weeks	~1.6 billion (2019)	Injectable microparticles	[322,352]
Risperidone	1993	Risperdal®	Schizophrenia	2 Weeks	172 million (1994)	Injectable microparticles	[335,353]

Table 2. Cont.

Encapsulated Drug	Regulatory Approval Year	Product Name	Therapeutic Indication	Duration of Action	Annual Sales	Prolonged Release Formulation	Reference
Bromocriptine	1991	Parlodel® LAR	Prolactin-secreting tumour	4 weeks	~800 million	Injectable microparticles	[354,355]
Leuprolide acetate	1989	Lupron Depot®	Peptide prostate cancer	1, 3, 4 months	~800 million (2017)	Injectable microparticles	[347,356]
Goserelin acetate	1989	Zoladex®	Prostate cancer	4 weeks	~900 million (2018)	Injectable microparticle	[345,357]
Triptorelin	1986	Decapeptyl® SR	Prostate cancer	1, 3, 6 months	~400 million (2018)	Injectable microparticles	[354,355]

6. Conclusions

Biodegradable polymers have been used to develop an array of controlled-release therapeutic products. However, many challenges remain to be addressed including low drug payload, unsatisfactory release rate, narrow range of drugs suitable for encapsulation, and translation from laboratory to industrial scale. Nevertheless, the commercial success of approved products along with emerging research in nanomaterials are promising for producing novel controlled-release therapeutic products. Investigation on newer strategies to simplify the manufacturing process is ongoing.

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