Expert Opinion

Techniques for efficient entrapment of pharmaceuticals in biodegradable solid micro/nanoparticles

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Importance of the field: Biodegradable solid particles are potential carriers for both hydrophobic and hydrophilic drugs and have been marketed for prolongation of pharmaceutical activity. In developing such particles, it is important to achieve stable encapsulation of the drugs in the particles and a controlled rate of drug release.

Areas covered in this review: In this paper, the principles and techniques for preparing such particles are reviewed.

What the reader will gain: Overall, it remains difficult to identify a general approach for achieving effective entrapment and controlled release, because these qualities are determined by multiple complex factors. The encapsulation efficiency of drugs in particles can be improved through various techniques, including hydrophobic interaction, covalent bonding, ionic interaction and physical isolation. In addition, the release behaviors of drugs are strongly influenced by environmental conditions as well as the physicochemical properties of the polymers and drugs.

Take home message: Solid particles with targeting ability in addition to prolongation of biological activity may have potential for development of a new type of pharmaceutical in the clinical field.

Keywords: biodegradable particles, drug encapsulation, drug release behavior, PLA/PLGA, targeting

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1. Introduction

Recent combinatorial chemistry and high-throughput screening methods have made it relatively easy to identify initial lead candidates for new drugs from numerous chemical libraries and collections [1,2]. The discovered compounds and their analogues can be chemically synthesized and optimized for pharmacokinetic and pharmacodynamic interactions. However, new drug discovery is still a complicated process and generally requires substantial time and monetary investment.

On the other hand, technologies for formulation change provide the benefit of improving pharmaceutical product efficacy and safety, as well as patient convenience [3,4]. These technologies provide a relatively simple approach to creating new pharmaceuticals compared with new drug discovery, because the active compounds used in the formulation have already been approved. Substantial effort has been directed towards the development of carriers (vehicles) for pharmaceutical agents, including liposomes, solid particles, polymeric micelles, synthetic polymers and lipid

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Article highlights.

- Biodegradable solid particles are potential carriers of both hydrophobic and hydrophilic drugs for long-term pharmaceutical activity *in vivo*.
- Several FDA-approved products in the market utilize biodegradable polymers as excipients to achieve sustained release of drugs.
- Although it is certain that hydrophobicity is one of the primary determinants of drug encapsulation in solid particles, other physicochemical properties also influence the encapsulation.
- Direct chemical conjugation of drugs to hydrophobic polymers and ionic interactions between ionizable drugs and polymers also allow formation of particles incorporating drugs.
- Independent of interactions between drugs and polymers, it is possible to encapsulate drugs in solid particles through physical isolation.
- Release behaviors of drugs from solid particles are affected by various parameters such as the physicochemical properties of drugs and particles.
- It is expected that solid particles with multiple functions, for example, targeting ability and long-term pharmaceutical activity, will become a new class of pharmaceuticals in the clinical field.

This box summarizes key points contained in the article.

emulsions, to expand the utility of approved drugs for various clinical applications [5]. Each carrier has its own characteristics, and an appropriate carrier is selected depending on the pharmaceutical agent and target disease. Lipid emulsions [6] and liposomes [7], which have already been used in clinical settings, are easily prepared; however, they generally cannot retain drugs *in vivo* for long periods, because the drugs are entrapped in the vehicles by simple partitioning into the oil phase or physical isolation by lipid membranes, respectively.

Solid particles are promising carriers for stable retention of drugs, because the drug is physically embedded in the solid polymer matrix [8]. In addition, such particles would be expected to have the following advantages in terms of pharmacokinetics and pharmacodynamics. First, stable retention of drugs may physically prevent drug interactions with various biological components *in vivo*, for example, enzymatic degradation or metabolization of drugs. Second, particles formed from biodegradable polymers can achieve a longer-term therapeutic effect through slow release of drugs as the polymers degrade [9,10]. Third, it is possible to control the biodistribution of the drug depending on the properties of the particles [11]. To take advantage of these properties, establishment of a standard method for preparing particles with high drug content and good retention is needed. In this review, entrapment of drugs in solid particulate formulations is focused on, including polymeric micelles, polymeric particles, polymeric capsules composed primarily of biodegradable polymers, and the release behaviors of drugs.

2. Marketed poly(lactic acid)/ poly(lactic-*co*-glycolic acid) formulations for drug delivery

Among the synthetic biodegradable polymers, polyesters such as poly(lactic acid) (PLA) and poly(lactic-*co*-glycolic acid) (PLGA) have long been of great interest in the biomedical field, because they are biocompatible, have low toxicity, are biodegradable, and are immunotolerant [12-14]. These polymers undergo hydrolysis in the presence of water and ultimately decompose into water and carbon dioxide through the citric acid cycle in the body. As the hydrolysis rate of the polymer depends greatly on its composition and molecular mass, various polymer formulations have been used to control the rate of drug release. Several US Food and Drug Administration (FDA)-approved products in the market utilize PLA and PLGA as excipients to achieve sustained release of pharmaceuticals, as shown in **Table 1** [15-17]. It was estimated that the total annual sales for such products exceeded $2.5 billion in 2002 [18]. Formulations of these chemicals can be classified into three primary categories: microparticulate formulations, nanoparticulate formulations and *in situ* forming implants. Most of these products are particulate formulations with micrometer-sized diameters and encapsulate various types of drug, such as low-molecular-mass drugs, peptides and proteins, within the core of the particles. Microparticles have been administered by means of intramuscular, subcutaneous and topical injections and have demonstrated long-term activity through sustained release of drugs from the particles in the body. On the other hand, Genexol-PM, which has been approved for use in South Korea [19], is formed from nanoparticles (polymeric micelles) 20 – 50 nm in diameter [20]. Polyethyleneglycol-polylactide (PEG-PLA) was used in place of Cremophor EL as a solubilizing agent for paclitaxel to avoid side effects, not as a matrix for sustained release of paclitaxel [20]. In addition, *in situ* forming implants have also been developed [21,22]. The products were formed from PLA/PLGA dissolved in water-miscible organic solvent such as *N*-methyl-2-pyrrolidone (NMP), and a drug suspended in this solution. After subcutaneous or topical injection of the formulation into the body, the organic solvent dissipates and water penetrates into the organic phase. This causes precipitation of the polymer forming a depot at the site of injection.

3. Encapsulation of drugs in solid particles

The biopharmaceutics classification system (BCS) is an FDA guideline that determines when a waiver can be obtained for *in vivo* bioavailability and bioequivalence studies, and classifies drug substances based on aqueous solubility and intestinal permeability [23,24]. Using this system, it has been estimated that up to 40% of all new chemical compounds have poor water solubility [25], and the percentage is increasing annually. As low solubility results in low bioavailability, it is preferable to establish methods for solubilizing the drugs efficiently to

Table 1. Formulations containing PLA/PLGA.

Product	Drug	Polymer	Indication	Administration	Marketed by
Microparticle					
Lupron depot	Leuprolide acetate	PLA/PLGA	Prostate cancer, breast cancer, ovarian and endometrial cancer	s.c./i.m.	TAP
Nutropin depot	Human growth hormone	PLGA	Growth deficiencies	s.c./i.m.	Genetech
Trelstar depot	Triptorelin pamoate	PLGA	Prostate cancer	i.m.	Pfizer
Decapeptyl	Triptorelin pamoate	PLGA	Prostate cancer	i.m.	Ferring
Suprecur MP	Buserelin acetate	PLGA	Endometriosis	s.c.	Aventis
Sandostatin LAR	Octreotide acetate	PLGA-Glucose	Acromegaly, symptoms of gastro-entero-pancreatic neuroendocrine tumors	i.m.	Novartis Oncology
Zoladex	Goserelin acetate	PLGA	Prostate cancer, Breast cancer	s.c.	AstraZeneca
Somatuline LA	Lanreotide	PLGA	Acromegaly	i.m.	Ipsen
Risperidal Consta	Risperidone	PLGA	Schizophrenia	i.m.	Johnson & Johnson
Vivitrol	Naltrexone	PLGA	Alcohol dependence	i.m.	Alkermes
Parlodel LAR	Bromocriptine mesylate	PLGA	Parkinson's disease	i.m.	Sandoz (Novartis)
Arestin	Minocycline-HCl	PLGA	Periodontal disease	Subgingival	OraPharma
Nanoparticle					
Genexol-PM*	Paclitaxel	PEG-PLA	Breast cancer	i.v.	Samyang
In situ forming implant					
Atridox	Doxycycline hyclate	PLA	Periodontal disease	Subgingival	Tolmar
Eligard	Leuprolide acetate	PLGA	Prostate cancer	s.c./i.m.	Aventis

*Approved in South Korea.
i.m.: Intramuscular; i.v.: Intravenous; s.c.: Subcutaneous.

expand their utility [26]. On the other hand, progress in genetic engineering has enabled the use of proteins and poly (oligo)nucleotides as pharmaceutical agents for innovative protein and gene therapies. The short half-life and transient activity of these compounds *in vivo* has encouraged the development of solid particulate formulations for encapsulation of these molecules.

Various methods have been proposed for preparing solid particulate formulations encapsulating pharmaceuticals optimized to the drug, polymer and target disease. The primary methods are solvent evaporation, solvent diffusion, spray-drying, salting-out and dialysis, as described in detail in the literature [8,27,28]. Independent of the preparation method, it is generally necessary to prepare particles with high drug content and good retention for clinical use. Several studies have been directed towards functionalizing polymers to enhance the range of drugs that can be incorporated at effective concentrations within the solid polymeric particles. The basic principles for encapsulation of drugs are summarized in **Figure 1** and the following sections.

3.1 Hydrophobic interactions

For micelles made up of low-molecular-mass compounds, it has been reported that the extent of solubilization of drugs in the micelles is influenced by the chemical and physical properties of the solubilizers and the hydrophobicity of the drugs used [29]. Some researchers have noted an increase in solubilization with an increase in the hydrophobicity of the drug [30].

Similarly, it is widely believed that hydrophobic drugs can be easily encapsulated in the hydrophobic loci of solid particles through hydrophobic interactions between the polymers and the drugs. However, it may be difficult to establish a general relationship between any one property of a drug and the extent of drug solubilization, because simple equilibration between drugs and particles may not result in high levels of solubilization [31,32]. In a previous report, a series of corticosteroids were used to evaluate loading in particles consisting of PLA and PEG-PLA block copolymers (**Table 2**) [33]. As can be seen from the octanol-water partition coefficients (log P_{OW}) of the drugs, an indicator of hydrophobicity, there was an increase in encapsulation as the log P_{OW} values increased. This result suggests that the drugs were physically encapsulated in the nanoparticles through hydrophobic interactions with the polymers. However, these properties are not fully correlated, as can be seen from the various encapsulation efficiencies among betamethasone valerate, hydrocortisone butyrate propionate and betamethasone dipropionate, despite their similar log P_{OW} values. Furthermore, four clinically approved drugs, which are non-ionizable, poorly water-soluble and have differing log P_{OW} values, were evaluated for solubilizing/loading in micelles of sodium oleate and/or PEG-PLA [34]. The log P_{OW} values had no apparent correlation with solubilization in the PEG-PLA/sodium oleate system.

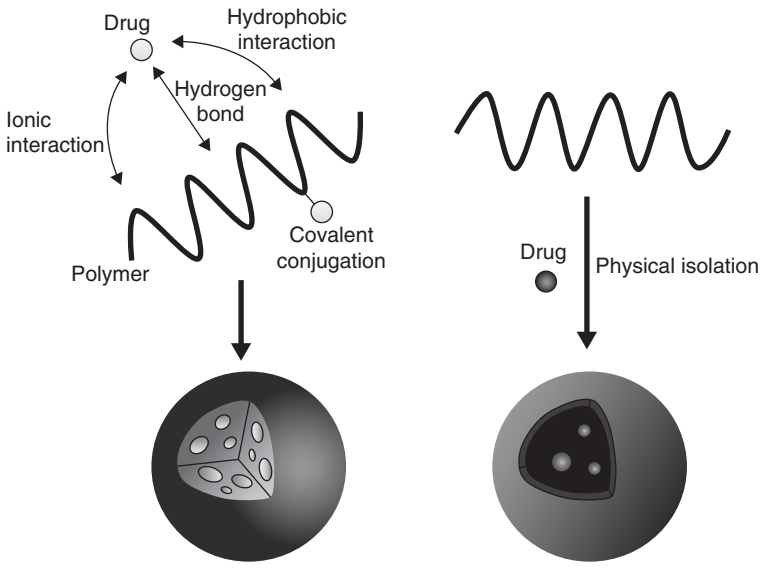

Figure 1. Entrapment of drugs in particulate formulations.

Table 2. Entrapment of corticosteroids in solid nanoparticles.

	Loading efficiency in nanoparticles (wt% ± s.d.)	log P_{ow}
Betamethasone sodium phosphate (BP)	ND	0.7
Hydrocortisone succinate	ND	1.5
Hydrocortisone	ND	2.0
Betamethasone	ND	2.1
Betamethasone acetate	0.07 ± 0.04	2.2
Betamethasone valerate	0.30 ± 0.07	3.4
Hydrocortisone butyrate propionate	0.52 ± 0.18	3.6
Betamethasone dipropionate	1.42 ± 0.47	3.6

Nanoparticles were prepared with PLA, PEG-PLA, and the drugs through the solvent diffusion method.
ND: No drug was detected in the nanoparticles.
Reproduced with permission from [33].

Therefore, it is difficult to predict the encapsulation efficiency of drugs in particulate formulations based on a single indicator of hydrophobicity such as the partitioning coefficient. Although it is certain that hydrophobicity is one of the primary determinants of drug encapsulation in particles, other physicochemical properties such as the molecular mass/volume, conformation, polarity, crystallinity and melting point also influence the encapsulation efficiency [35,36]. In other words, compatibility between the core of the particles and the drugs, which is influenced by multiple properties, may be the dominant factor governing incorporation. Researchers have attempted to clarify what this compatibility entails. Nagarajan *et al.* demonstrated that the Flory-Huggins interaction parameter between the solubilizate and the hydrophobic polymer was correlated with the solubilization capacity in polymeric micelles [37]. Recently, Choi and co-workers reported that molecular dynamics simulation could be applied to identify the molecular mechanisms involved in drug/polymer interactions and the potential influence of these interactions on the level of drug encapsulation [38,39].

In addition, researchers have focused on enhancing the loading capacity of hydrophobic drugs into particles through chemical modification of the polymers with hydrophobic molecules, which allow interaction with the drugs through hydrophobic interactions. Although most polyesters do not have functional groups that could enhance this potential, new polymers have been synthesized on the basis of PLA/PLGA [40,41]. Trimaille *et al.* developed micelles from a new amphiphilic polymer consisting of poly(hexyl-substituted lactides). Incorporation of hydrophobic dye into the micelle core increased with the number of hexyl groups along the PLA chains [41]. In the case of non-polyesters, the introduction of benzyl groups or acyl groups functioning as a hydrophobic source for the polymeric micelle inner core has allowed enhancement of the incorporation efficiency of hydrophobic drugs [35,42]. To enhance encapsulation of aliphatic drugs, fatty acid side chains have been conjugated to poly(aspartic acid) forming the inner core [43]. Micelles made of PEG-lipids or of mixtures of PEG-lipids and lipids provided good solubilization for certain poorly water-soluble drugs owing to an increase in the capacity of the hydrophobic core of the micelles [44,45]. In addition, the introduction of pendant acyl groups on a poly(glycerol adipate) backbone increased the loading efficiency of water-soluble

dexamethasone phosphate through hydrophobic interactions between the steroid nucleus and the acyl groups [46].

Alternatively, the loading capacity of drugs can be enhanced through an increase in the hydrophobicity of the drugs. The formation of salts of some ionizable drugs by adjustment of the pH has resulted in an increase in their incorporation into particles [47,48]. The hydrophilic properties of proteins have prevented the preparation of particles encapsulating proteins to any great extent owing to their low efficiency of incorporation as well as denaturation of proteins during the manufacturing process. The formation of hydrophobic complexes between zinc and proteins such as growth hormones [49,50] and insulin [51] successfully increased incorporation of the proteins into the particles.

3.2 Covalent conjugation

Direct chemical conjugation of drugs to hydrophobic polymers allows the formation of particles incorporating drugs [52]. Doxorubicin [53], paclitaxel [54] and haloperidol [55] have been covalently conjugated to a terminal end group of polymers such as PLGA or PEG-PLA/PLGA, resulting in the formation of particles for sustained release of drugs with hydrolysis of the polymers. In addition, Bae *et al.* synthesized polymer conjugates with doxorubicin using pH-sensitive hydrazone linkers [56] and the polymeric micelles released the drug in response to pH in the surrounding aqueous phase. However, the drugs for which this method can be applied are limited owing to the required chemical synthesis.

3.3 Ionic interactions

Ionizable drugs can be successfully encapsulated into solid particles through ionic interactions with the polymers. It has been reported that, in addition to hydrophobic interactions, ionic interactions between the peptide/protein and the polymer contribute to increasing encapsulation efficiency [9,57,58]. One leading technique is the use of charged hydrophobic polymers. Bioactive oligopeptides with a positive charge have been incorporated through ionic interaction with PLGA having a carboxylic group at one end [9]. Another method is the formation of an electrostatic complex (called 'polyplex') between poly(oligo)nucleotides such as plasmid DNA and siRNA with multiple negative charges and hydrophilic polymers such as polylysine with multiple positive charges [59,60]. Poly(oligo)nucleotides are expected to be used as bioactive molecules for gene therapy. Solid particles consisting of the electrostatic complexes can be obtained by mixing poly(oligo)nucleotides with cationic polymers in an aqueous medium.

3.4 Other interactions

The presence of specialized molecules or groups on polymers can induce further interactions that can improve drug-loading capacity. For example, adriamycin was successfully incorporated into the hydrophobic core of polymeric micelles formed from covalent conjugates between the polymers and adriamycin. In this case, adriamycin was encapsulated into the micelles through π–π interactions as well as hydrophobic interactions [61,62]. In addition, the drug-loading efficiency of papaverine increased substantially using polymeric micelles of PEG-PLA containing a small quantity of carboxylic acid [63]. This increase was attributed to hydrogen bonding between the hydrogen of the carboxylic acid in the copolymer and the unpaired electron of the nitrogen or oxygen atom in papaverine. Increased loading of the tetanus toxoid in PLGA microparticles was also achieved by co-encapsulation of hydroxypropylcyclodextrin [64]. It has been suggested that hydroxypropylcyclodextrin accommodates the amino acid side groups of the toxoid in its cavity and concomitantly interacts with the PLGA through van der Waals and hydrogen-bonding forces. Huh *et al.* developed hydrotropic polymer micelle for delivery of poorly water-soluble drugs such as paclitaxel [65]. The polymer micelles containing hydrotroperich cores showed not only higher loading capacity but also enhanced physical stability. Finally, Yokoyama *et al.* reported that cisplatin, a poorly water-soluble anticancer drug, can be incorporated into polymeric micelles through chelate substitution of the platinum atom of cisplatin [66].

3.5 Physical isolation

Independent of interactions between drugs and polymers, it is possible to encapsulate drugs in solid particles through physical isolation. The classical method is the water-in-oil-in-water or solid-in-oil-in-water solvent evaporation method for incorporation of water-soluble drugs, including proteins and peptides. In addition, Horisawa *et al.* reported that water-soluble drugs with low molecular masses can be loaded into particles using an emulsion solvent diffusion method in oil [67]. Alternatively, the spray-drying method, which produces dry solid particles from an atomized liquid solution of polymers and drugs through rapid evaporation, is available for incorporation [68]. Finally, it is possible to prepare polymer-based capsules [69], such as polymersome [70], that encapsulate drugs in their inner cavities.

4. Drug release from solid particles

It is believed that drugs are released from solid particles by means of various routes: i) desorption of drugs adsorbed onto surfaces; ii) diffusion through the polymer matrix; and iii) physical leakage through porous cavities or surfaces along with biodegradation of the polymer matrix (**Figure 2**) [9,12,71]. The parameters that affect the release behaviors of drugs from solid particles can be classified as follows. First are characteristics of the particles, such as water content, size, shape, viscosity, porosity and rigidity. These characteristics of the particles are determined primarily by the physicochemical properties of the polymers, such as molecular mass, polymer end groups, composition and crystallinity.

The second group is the physicochemical properties of the drugs, such as solubility, log P_{OW}, acid dissociation constant

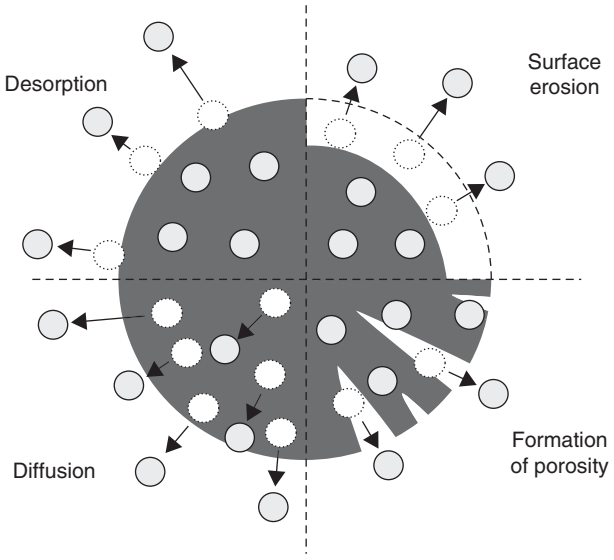

Figure 2. Various routes of drug release from solid particles.

(pK_a), molecular mass/volume, crystallinity and polarity. These characteristics affect both the distribution (loci) of the drug in the particle and the compatibility/affinity between the drug and the particle. Drugs adsorbed onto the surfaces of solid particles are responsible for the initial burst release, drugs embedded in the surface layer are released in the early stages, and drugs localized in the central core are released slowly. Furthermore, it has been reported that drug release from particles is slower for basic drugs compared with acidic or neutral drugs, probably owing to neutralization of the acidic environment of the core matrix, as described below [72,73].

Third, the release rate depends on environmental conditions such as the ionic strength and pH of the surrounding aqueous phase, the temperature, and the presence of biological components such as proteins, lipids and cells. In general, release of drugs from particles has been evaluated in the absence of biological components, but such components may cause drugs to dissociate from particles and disrupt the particle structure. Consequently, the observed results may be misleading with respect to entrapment efficiency, and burst drug release may actually occur *in vivo*. The plasticizing effect of biological components on the matrix of particles has been reported to accelerate the release of drugs from particles *in vivo* [74].

Fourth, drug release is affected by the presence of additives in the particles. It is known that metal salts influence water uptake and the degradation properties of particles. The presence of metal salts such as zinc carbonate and magnesium carbonate has been found to increase water uptake and accelerate degradation [75,76]. On the other hand, some researchers have reported that the degradation rates of polymers are reduced in the presence of metals [77-79]. This decrease in the degradation rate may be due to neutralization by basic salts of protons evolved during hydrolysis, because the polymer degradation rate increases through an autocatalytic process whereby protons that are evolved during ester hydrolysis accelerate the reaction rate through acid catalysis.

Various approaches have been used to improve drug retention and control the rate of drug release, such as physical [80] and chemical [81] crosslinking of polymers in the cores, blending with hydrophobic polymers [82,83] and lipids [84], and use of chemically modified polyesters [85].

5. Particles for sustained drug release and targeting

As shown in **Table 1**, many products containing PLA/PLGA are already being used in the clinical setting. These products have long-term activity *in vivo* through sustained release of active molecules from the products. On the other hand, many nanoparticulate candidates containing PLA/PLGA have also been developed for control of drug biodistribution and specific delivery to target sites, to enhance therapeutic efficacy while reducing side effects. PEG-PLA/PLGA block copolymers and their derivatives have been widely used for the preparation of such nanoparticulate formulations as polymeric micelles and nanoparticles. In general, colloidal particles that are administered systemically are taken up by the mononuclear phagocyte system (MPS), resulting in accumulation in the liver and spleen [11]. On the other hand, pioneering work by Gref *et al.* has shown that polymeric micelles formed from PEG-PLA block copolymers are able to remain in circulation for a prolonged period because the steric barrier of PEG chains on the surface reduces interaction with the opsonins and cells of the MPS [86]. Furthermore, these long-circulating nanoparticles show preferential accumulation in tumors and at inflammation sites

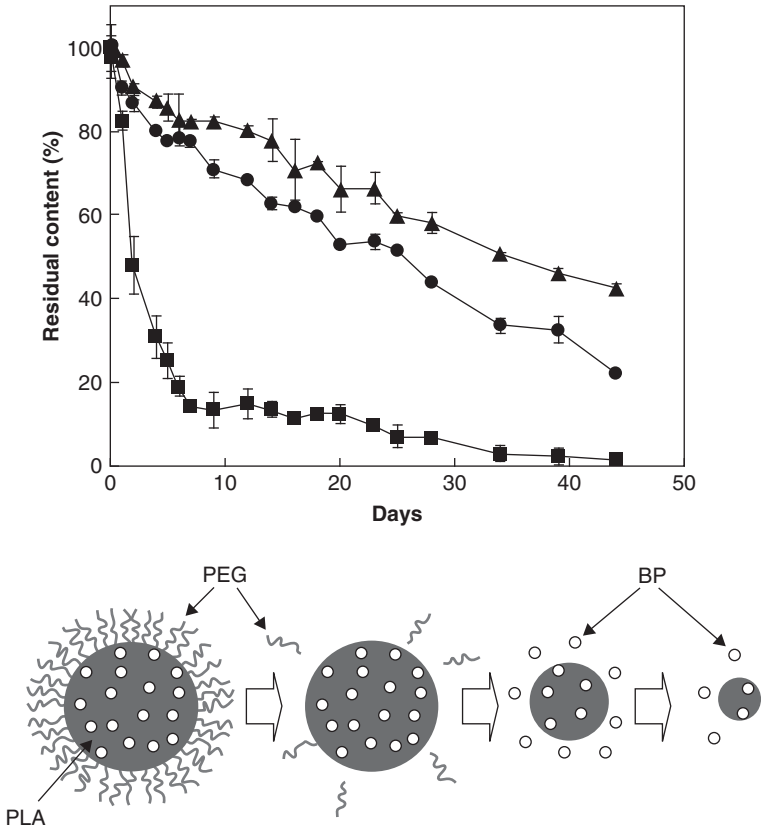

Figure 3. Degradation of nanoparticles during incubation. The remaining amount of BP (circles), PLA (triangles), and PEG (squares) in the nanoparticles was determined during the incubation of nanoparticles in phosphate-buffered saline at 37°C. Each datum point represents the mean ± standard deviation (s.d.) of three independent experiments.
Reproduced with permission from [89].

owing to the enhanced permeability and retention (EPR) effect [87]. This discovery has allowed the preparation of many nanoparticulate vehicles covered with PEG. PEG-PLA has already been used in a clinical setting as a solubilizer of paclitaxel in place of Cremophor EL. However, the drug was excluded from the blood circulation in a relatively short period, probably owing to unstable retention of the drug in the PEG-PLA micelles.

Thus, to take advantage of these properties (targeting and long-term activity), it is necessary to establish a method for preparing nanoparticles with high drug content and good retention. Such nanoparticles with dual functions are expected to show much higher biological activity. In a previous study, nanoparticles were prepared from PLA, PEG-PLA and betamethasone phosphate (BP) in the presence of zinc using the oil-in-water solvent diffusion method [33]. Betamethasone phosphate was more efficiently encapsulated in the nanoparticles than were hydrophobic betamethasone derivatives despite its hydrophilic properties, because zinc was used as an ionic bridge between the carboxyl group of PLA/PLGA and the phosphate group of BP [33]. Ionic interaction through a metal bridge has also been used to encapsulate ionizable prostaglandin E1 in solid nanoparticles [88]. The BP in the nanoparticles was released synchronously with PLA, whereas the PEG molecules were released from the nanoparticles in the initial stage (**Figure 3**), suggesting that BP was released along with surface erosion of the PLA matrix of the nanoparticles, as illustrated in **Figure 3** [89]. Furthermore, the nanoparticles were accumulated in the inflamed lesion *in vivo* [90] and BP was released gradually at the site [89]. High anti-inflammatory activity of nanoparticles has also been shown using an experimental animal model of inflammation [90,91].

6. Conclusions

Biodegradable solid particles are potential carriers of both hydrophobic and hydrophilic drugs for long-term pharmaceutical activity *in vivo*. Although there have been several studies reporting encapsulation of drugs in particles at high concentrations and with controlled release behaviors, it is still difficult to establish general methods for production. As these attributes are determined by multiple complex factors, a formulation consisting of particles and drugs must be tailor-made experimentally. It is expected that solid

particles with multiple functions, for example, targeting ability and long-term pharmaceutical activity, will become a new class of pharmaceuticals in the clinical field.

7. Expert opinion

Biodegradable solid particles encapsulating drugs make possible the gradual release of drugs *in vivo*, prolonging biological activity from a single administration, as verified by a variety of marketed products of this type (**Table 1**). Solid particulate formulations are available for loading of both hydrophobic drugs and hydrophilic drugs, including proteins and poly (oligo)nucleotides; however, encapsulation with high retention and good stability in particles is needed. At present, there is no one overall approach to entrapment of drugs in particles, as described in Section 3.

To establish new drug therapies using solid particles, the target disease of interest must first be determined. Candidate drugs are then selected from the libraries of approved drugs. If a candidate drug is not found, it may be necessary to modify chemically the drug molecules, unless this would lower the activity. Simultaneously, polymers must be obtained or designed that have high compatibility with the corresponding drug. Although it may be possible to predict compatibility to some extent, it remains necessary to screen candidate polymers and to optimize their structures experimentally.

It is expected that more functions of solid particulate formulations beyond prolonged activity will expand the bioavailability of the formulation. It would be particularly significant to add targeting functions to avoid adverse effects in the treatment of many diseases through selective delivery of drugs to specific target tissues or organs. To the authors' knowledge, no product with these two functions is being marketed at present in the clinical field. To add targeting ability to the particles, the surfaces of the particles must be modified in addition to efficient entrapment of the drugs. In addition, nanoparticles of a suitable size for targeting through intravenous administration should be developed. There have been several reports of the preparation of a variety of particles modified at the surface with ligand molecules for active targeting and PEG molecules for passive targeting. However, these particles, which have multiple functions such as stable drug retention, accumulation at the target lesion, sustained release of drugs at the target lesion and further biological activity *in vivo*, have only just begun to be developed. Formation of metal bridges between PLA/PLGA and ionizable drugs may be a suitable technique for preparing such particles, and the authors expect to see these particles used in clinical applications.

On the other hand, other concerns must also be kept in mind, such as the cost of manufacturing, safety of the products, and sterilization methods. Concerning safety, biodegradable polyesters such as PLA, PLGA and PEG-PLA have been confirmed as safe in clinical trials. However, details must be attended to, for example, the amount of remaining organic solvent in the products. Although there are many challenges for the development of new formulations, they may be overcome by the methods described in this paper and by new technologies of the future.

Declaration of interest

The authors state no conflicts of interest and have received no payment in the preparation of this manuscript.

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