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CURRENT ADVANCES IN SUSTAINED-RELEASE INJECTABLE PREPARATIONS

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ABSTRACT

In recent years, there has been a great deal of interests in developing sustained-release systems which can prolong the therapeutic effect, decrease adverse side effects, and reduce administration frequency. Nowadays, the oral sustained-release preparations account for a larger market share comparing to other sustained-release forms, mainly because of its noninvasive pain-free administration. However, the hostile environment of gastrointestinal tract and first-pass effect may lead to low bioavailability of some drugs, such as some proteins, peptides, and hormones. In this paper, the latest research progresses of some new-model sustained-release injectable dosage forms were introduced, including microsphere, microcapsule, liposome, polymeric micelle, and *in situ* forming system.

INTRODUCTION: Since 1960s, sustained-release preparations have been widely studied because of the prominent advantages: less administration frequency, low toxicity, and longer action time enhancement [1]. Recently, many types of sustained-release preparations have been marketed and accepted by most patients; in addition, the oral sustained-release preparations exhibited more superiority in market share compared with other formulations. However, sometimes oral administration cannot achieve a good absorption mainly due to the hostile environment of gastrointestinal tract and first-pass effect [2, 3]. Therefore, more and more researchers focus on the investigations of the sustained-release injectable preparations.

Except for the common advantages of the sustained-release preparations, injectable preparations exhibited some special merits when compared with others. Generally, injectable preparations have a better bioavailability than oral preparations, so are the sustained-release preparations.

The sustained effects of oral sustained-release preparations are restricted by the gastrointestinal tract, so the sustained-release injectable preparations can reach a much longer action time than the oral sustained-release preparations and some sustained-release injectable preparations could attain a consistent drug release for a period of more than one month. However, the more important virtue is that the sustained-release injectable preparations can improve targeting effects and reduce systemic toxicity through local steroid injection. Nowadays, sustained-release injectable preparations have developed rapidly and been widely used in contraception [4], tissue repair [5], oncotherapy [6] and treatment in patients with bipolar disorder [7].

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In the early years, the dosage forms used in sustained-release injectable investigations were limited in some traditional formulations, such as suspension and emulsion. However, the problems such as rheological changes during filling, instability on long-term storage and nonadjustable release rate bring limitations to such systems. Nowadays, as the development of biodegradable materials and the evolution of dosage forms, the sustained-release injectable technique has achieved many advances. In this paper, some new-model sustained-release injectable dosage forms were introduced, including microsphere, microcapsule, liposome, polymeric micelle, and *in situ* forming gel system.

Microsphere: Microspheres are small spherical particles, with diameters in the micrometer range. The methods commonly used in microsphere preparation include emulsion method [8], phase separation method [9], spray drying method [10], ultrasonic atomization method [11], electrospray method [12], and microfluidic method [13]. Among the above-mentioned methods, spray drying method is most widely used in manufacture scale and the emulsion methods are commonly accepted in laboratory level. One of the main advantages is that the microspheres can be suspended into water medium to meet the demand of percutaneous injection. Moreover, the target activity is the significant characteristic differing from traditional dosage forms, leading to higher bioavailability and lower toxicity.

Recently, some natural and chemosynthetic biodegradable materials have been introduced to injectable microsphere technique; for examples, gelatin [14] hemoglobin [15], polycarbonate [16], polyamino acid [17], polylactic acid (PLA) [18], polylactic-*co*-glycolic acid (PLGA) [19], and some segmented copolymers [20, 21]. In above-mentioned materials, PLA and PLGA were approved to use as biomedical material for its biodegradability *in vivo* by FDA and were successfully used in loading tprotein/peptide drugs [22-24].

The sustained-release effects are in relation to the type of polymer, the nature of main drug, the molar ratio of monomers, and the partical size or structure of microspheres.

Various FDA-approved sustained-release injectable microspheres are available in the market (Table 1). The first market product (Decapeptyl®) was developed by Ipsen in 1986. Decapeptyl® is a gonadotropin-releasing hormone agonist, which can decreases pituitary secretion of gonadotropins luteinizing hormone and follicle stimulating hormone.

In following years, nevertheless, the new marketed sustained-release injectable microspheres were merely confined to polypeptides, until Johnson &Johnson launched Risperdal® Consta ® and successfully applied the microsphere technique into the field of low molecular chemistry. Despite there are some widely used market products currently, several problems should not be ignored in design and development process, especially the burst effect in which a large drug volume is quickly released into the body. Therefore, the investigations in sustained-release injectable microsphere are continued, aiming to lower burst effect, improve preparation processes, and enhance the sustained-release property.

TABLE 1: SOME COMMERCIALLY AVAILABLE INJECTABLE SUSTAINED-RELEASE INJECTABLE MICROSPHERES

Trade Name	Main Drug	Types	Manufacturer	Market Time
Bydureon	Exenatide	Polypeptide	Lily, Amylin, and Alkermes	2012
Vivitrol	Naltrexone	Micromolecule	Cephclon	2006
Plenaxis	Abarelix	Polypeptide	Praecis	2004
Risperdal Consta	Risperidone	Micromolecule	Johnson and Johnson	2002
Nutropin	Growth hormone	Protein	Genentech	1998
Sandostatin	Octreotide	Polypeptide	Novartis	1998
Lupron/Enantone	Leuprorelin	Polypeptide	Takeda	1995
Profact	Buserelin	Polypeptide	Aventis	1986
Decapeptyl/Trelstar	Triptorelin	Polypeptide	Ipsen	1986

In recent years, some researchers focused on searching more appropriate biomaterials to combine with PLGA to solve the above problems. Kempen *et al*. [25] developed an ideal biomaterial, propylene fumarate, used for repairing bone defects, which exhibited good mechanical properties, no toxicity, cellular affinity, sustained release behavior, and good biodegradability. This research presented an approach to incorporate PLGA microspheres into an injectable, porous propylene fumarate scaffold. The prepared formulation exhibited a sustained-release release of the main drug for at least 28 days and largely decreased burst release, as compared to drug release from microspheres alone.

Calcium phosphate (CaP) cements have an excellent biocompatibility, a high mechanical strength, and a sustained-release behavior. Habraken *et al*. [26] developed an injectable PLGA microsphere/CaP cement system with sufficient setting/cohesive properties. Results showed that injectability decreased along with the increase in PLGA microsphere content, and all physical parameters were well in range of 10:90 to 20:80 (PLGA microsphere: CaP cements). After 12 weeks the PLGA was totally degraded and a highly porous. This research presented a sign that inorganic materials could also used in preparing sustained-release injectable products.

Nahata *et al*. [27] designed a sustained-release microsphere-based injectable microsphere prepared by solvent evaporation method using PLGA and cholesterol as release rate retardant materials. The prepared formulation could achieve a sustained-release release for 14 days, in an optimum ratio of drug to cholesterol which was screened by D-optimal experimental design. The results have confirmed that the D-optimal experimental design technique can be successfully employed for designing the long acting microsphere dosage form.

Moreover, some researchers focused on the microsphere/hydrogel combination delivery systems to control the release behavior for prolonged time periods. Hydrogels can be used scaffolds for regenerative medicine, and as depots for therapeutic factors or cells [28]. However, hydrogels may release their hydrophilic contents too rapidly causing a large burst effect, and phagocytes may clear microspheres within a short period after administration. Therefore, Lee *et al*., [29] prepared PLGA/alginate gels microspheres to verify that microsphere/hydrogel combination systems can be employed to prepare sustained-release injectable products. The mixing ratio of the components was the primary parameter of sustained effects. After this proof, they loaded a fusion protein (TAT-HSP27) into microsphere/hydrogel combination delivery systems to achieve sustained-release effects [30]. The release behavior of the fusion protein could be controlled by changing the blending ratio of PLGA microspheres to alginate hydrogels. This research provided a novel medication for treating myocardial infarction in a minimally invasive manner.

Microcapsule: Microcapsule is a small sphere encapsulating solid or liquid drugs inside by using natural or chemosynthetic high polymer materials [31]. The formed microcapsules have core-shell structure with diameters between a few micrometers and a few millimeters and the core can be liquid or solid state [32]. The key factor in microencapsulation technique is the physical and chemical properties of the material to be encapsulated. The microcapsule even may have multiple membranes. Many microcapsules have some similarities to these simple spheres, so the materials used for microencapsulation technique are related to microsphere technique [33].

The methods of simple coacervation and complex coacervation are widely used in traditional microencapsulation processes [34, 35]; in addition, simple coacervation is mainly used for encapsulating water-soluble drugs and complex coacervation is appropriate for water-soluble drugs. Besides the above-mentioned methods, there are some other preparation methods such as spray drying [36], also mainly used for large-scale production. The sustained-release effects of micro-capsules depend largely on the particle sizes, the thickness of membranes, and the physicochemical properties of used capsule material.

The investigations of sustained-release injectable microcapsule technique were started in 1970s. Beck *et al.,* [4] described a sustained-release injectable microcapsule system for the sustained-release systemic administration of progesterone, and PLA was used as biodegradable polymer to encapsulate crystalline progesterone.

Results indicated vaginal estrous cycles in rats and cyclic ovarian functions in baboons were both inhibited for 1 month after a single injection of progesterone microcapsules. In the following research, they developed a new sustained-release, injectable contraceptive which provides continuous controlled release of the steroid norethisterone, and the main drug can be slowly released from the microcapsules following intramuscular injection at a rate of 0.90 microgram/day from the polymer matrix. The results indicated ovulation functions was inhibited for 6 months and each one resumed normal ovulation within 1-2 weeks after the norethisterone blood level fell below the limit of detection [37]. However, tests showed burst effects were still remained *in vivo* release and the researches in the following years were still focused on hormone drugs.

Recently, researchers have attempted to apply the sustained-release injectable microcapsule technique to more kinds of drugs. For example, Sigmon *et al.,* [38] developed a sustained-release injectable depot formulation of buprenorphine using microcapsule technique for treating opioid dependence. The data document indicated this depot formulation provides pesticide effect for more than six weeks and the effects persist at approaching undetectable levels. Moreover, Kim *et al.* [39] described the preparation of BSA-FITC-loaded microcapsules as a model protein system for *in vivo* delivery, and the injection of BSA-FITC-loaded microcapsules into rats resulted in a sustained-release behavior of the model protein that maintained the concentrations of BSA-FITC in plasma for up to 2 weeks.

Despite there is a long time for development of sustained-release injectable microcapsule technique, much fewer widely used products was found in market compared to microsphere. The reason may be a lackness of uniform standard in capsule materials and a difficulty of large-scale preparation. Moreover, more and more researchers apply microcapsule technique to many other fields, such as taste masking and oral controlled release [40, 41].

Liposome: There is another major kind of sustained-release injectable formulation, combined with lipids as carriers, such as liposome. A liposome encapsulates a region of aqueous solution inside a hydrophobic membrane; dissolved hydrophilic solutes cannot readily pass through the lipids. Liposomes are used as models for artificial cells and can be made in a particular size range; therefore, they exhibit more cell affinity and target activity [42, 43]. Nowadays, sustained-release injectable liposomes are widely used in medical fields, especially the treatment of malignant tumor [44, 45]. The carrier materials used for liposomes include two categories: phospholipids and cholesterol [46].

Phosphatidylcholine is commonly used in preparing liposomes, and some synthetic phospholipids also have been developed recently [47, 48]. The main methods used for liposome preparation including film dispersion method [49], reverse-phase evaporation method [50], freeze-drying method [51], injection method [52], and proliposome method [53].

The encapsulation by liposomes can lower the excreting and metabolism rates, therefore, delay the release of encapsulated drugs. For an example, the DepoCyt® developed by SkyePharma has been widely used in treating malignant meningitis through intravenous injection.

In 1991, Papahadjopoulos *et al*. [54] discovered that liposome formulations incorporating a synthetic polyethylene glycol-derivatized phospholipid could exhibit more than 5-fold prolongation of liposome circulation time in blood and a marked decrease in uptake by tissues such as liver and spleen. The above-described long-circulating liposome greatly promoted the development of sustained-release injectable liposome formulations. Kajiwara *et al.* [55] developed long-circulating liposome-encapsulated ganciclovir. The prepared PEG-ganciclovir-liposome was 3-fold more effective than ganciclovir solution in inhibiting tumor growth and produced durable complete tumor remissions on day 11 after injection. Moreover, the Caelyx® developed by Sequus in long-circulating liposome technique has been identified as a specific medicine for treating oophoroma.

In recent years, some researchers have focused on improving the sustained-release effect by using some auxiliary materials to modify liposome systems. Bhattarai *et al.* [5] developed an injectable thermo-sensitive hydrogel for sustained release by grafting PEG onto the chitosan backbone and studied the *in*

vitro drug release behavior using bovine serum albumin as a model protein. When more than 40 wt.% of PEG was grafted to chitosan chains via covalent bonding, the resultant copolymer was an injectable liquid at low temperature and transformed to semisolid state at body temperature.

The results indicated that the prolonged quasi-linear release of protein could extend to 40 days and the burst effect was significant reduced. Wu *et al.* [56] described an injectable long-circulating thermosensitive liposome aiming at antitumor therapy by using epirubicin as the model drug.

The pharmacokinetics results in rats suggested a prolonged release behavior of epirubicin, and the concentration *in vivo* was also promoted. Popescu *et al.* [57] explored a novel liposome/hydrogel soft nanocomposite as a controlled drug delivery system and pH-responsive triblock terpolymer was used as an injectable gelator. The control of the calcein release was achieved just by adjusting the gelator concentration and the results showed the *in vitro* drug release period was significantly prolonged from 14 to 32 days.

Moreover, the multivesicular liposomes technology composed of hundreds of polyhedral water-filled compartments separated by lipid bi-layered septa and resembling the architecture of aggregated soap bubbles, allows encapsulating drug with greater efficiency, provides better structural tability and more sustained release effects than lamellar liposomes [58]. Nowadays, some products prepared in this technique have been available, such as DepoCyt®, DepoIGF-I®, and DepoMorphine®.

He *et al.* [59] prepared multivesicular liposomes in a large dose and improved the stability and the sustained release effects by coating PEG. The results confirmed that the PEG coated multivesicular liposomes exhibited a much greater sustained-release effect than normal multivesicular liposomes. Just like the above-mentioned liposome formulations, the future sustained-release injectable products will possess more diverse sustained-release techniques aiming to achieve better effects.

Polymeric micelles: Polymeric micelles are nanoscopic core/shell structures formed by amphiphilic block copolymers with a size around 5-100 nm [60, 61]. The advantages of polymeric micelles include solubilization of poorly soluble molecules, target activity, sustained release, and protection of encapsulated substances from degradation and metabolism [60, 62].

Some preparation methods often used for polymeric micelles include co-solvent evaporation [63], dialysis [22], precipitation [64] and emulsification [65]. Relevant properties discussed in characterization include micellar association, morphology, size and stability [66]. The drug in hydrophilic shell can avoid being absorbed by the reticuloendothelial system, resulting in a prolonged circulation time [60]. Drug release from micelles is governed by the rate of drug diffusion, the partition coefficient, micelle stability and rate of biodegradation of the copolymers.

Other factors include the drug concentration within the micelles, the length of the hydrophobic polymer, the molecular weight, the physicochemical characteristics of the drug, and the localization of the drug within the micelles. Currently, many pharmacy enterprises are aimed at developing polymeric micelles products, for an example, Genexol® has been FDA approved for use in patients with breast cancer.

Recently, some researchers have focus on the investigations of sustained release injectable polymeric micelles. Aliabadi *et al.* [67] investigated micelles of methoxy poly (ethylene oxide)-b-poly (epsilon-caprolactone) (PEO-*b*-PCL) as alternative vehicles prepared in co-solvent evaporation method. The PEO-*b*-PCL micelles exhibited a significant sustained-release behavior in vitro, compared to Cremophor EL micelles. Within 12 h, only 5.8% of the model drug was released from polymeric micelles while Cremophor EL micelles bursted 77% of their drug content.

Zhang *et al.* [68] prepared indomethacin loaded polymeric micelles based on amphiphilic poly-phosphazenes by dialysis procedure. The indomethacin concentration in rats' plasma showed a prolonged release behavior after through topical injection, compared to the group administered with free indomethacin aqueous solution.

The author also hypothesized that this type of amphiphilic copolymers could be applied to more kinds of hydrophobic drugs. Gou *et al.* [69] developed curcumin-loaded biodegradable polymeric micelles for colon cancer therapy. In this work, the curcumin-loaded MPEG-PCL (curcumin /MPEG-PCL) micelles were prepared by encapsulating the curcumin into monomethoxy poly (ethylene glycol)-poly (ε-capro-lactone) (MPEG-PCL) micelles through a single-step nano-precipitation method. The encapsulation of curcumin exhibited a sustained-release and the $T_{1/2}$ and AUC were both improved; in addition, the novel formulation induced a stronger anticancer effect than that of free curcumin. The results indicated the curcumin/MPEG-PCL micelles could be an excellent intravenously injectable aqueous formulation of curcumin.

***In situ* forming formulations:** *In situ* forming formulations are drug delivery systems that are in liquid state with low viscosity before injection, and change to solid or semisolid drug storage once administered [70]. *In situ* forming formulations also designated as implants with less invasive and painful, compared to traditional implants requiring a small surgical intervention to administrate [71]. The phase transformation depends on the physiological conditions *in vivo*, such as temperature [72] and pH values [73], from which the drug gets released in a sustained and controlled manner. Compared to other dosage forms, the phase transformation is a special feature for *in situ* forming formulations. In situ forming formulations include two major categories: in situ forming gel system and in situ forming microparticle system.

***In situ* forming Gel System:** Some *in situ* forming gel systems can achieve accurate positioning administration using fine injection needles, particularly useful for topical administration, and the drug loading capacity can reach ten times of microsphere systems. The preparation technology used for in situ forming gel systems is relatively simple compared to other forms, and the main difficulties are the preparation procedure screening.

The drug pharmacology activity should not be affected by the gelatinization process and the used organic solvent should exhibit good biocompatibility.

Moreover, the most appropriate proportion should be searched in order to achieve proper gelation time and strength; in addition, a slow gelation or a low strength may lead to a burst effect, and a rapid gelation and an excessive strength can be worse painful. Therefore, the gelation time and strength were usually measured as physicochemical characteristics [74].

Recently, some marketed products have been available. The Atrigel® system is a proven sustained-release drug delivery platform that delivers therapeutic levels of a wide spectrum of drugs over a few days to several months with a single injection.

In recent years, some researchers focus on pushing the in situ forming gel system to a broader field. Huynh *et al*. [75] developed a pH and temperature-sensitive hydrogel as a sustained injectable insulin delivery system. The *in vivo* release behavior indicated that insulin was maintained at a constant steady-state level for 15 days through a subcutaneously injection to male Sprague-Dawley rats. The other results suggested that the diabetic rats could be treated for more than 1 week with a single injection, implying the therapeutic potential of this pH- and temperature-sensitive insulin-hydrogel complex system.

Gratieri *et al.* [76] exploited poloxamer/chitosan as vehicles for enhanced corneal permeation and sustained release of fluconazole aiming to improve the therapeutic effect of treating Fungal keratitis. The ex vivo statisitics indicated that the novel preparation exhibited 3.5 fold greater total amount of fluconazole permeated than simple aqueous solutions of model drug.

Kang *et al.* [77] developed a temperature-sensitive hydrogel system containing doxorubicin aiming to improve the therapeutic effect to tumors. The release of doxorubicin from gels was sustained *in vitro* over 20 days, and the *in vivo* experiments showed that a single intratumoral injection inhibited the growth of tumors as effectively as repeated injections of free doxorubicin.

The biodistribution of doxorubicin following a single injection remained at ~13% after 15 days.

***In situ* forming Microparticle Systems:** Compared to in situ forming gel systems, the in situ forming microparticle systems possess some particular advantages: the low viscosity can reduce the levels of pain and the burst effect can be decreased [78]. Emulsion process is usually used in preparing in situ forming microparticle formulations. The water insoluble polymer and drug are dissolved in appropriate organic solvent to form internal phase and the immiscible solvent is used as dispersed phase.

After intramuscular or subcutaneous injection, the dispersed phase outward spread and the moisture in body fluids swarm into internal phase, therefore, solid particles can be formed following the polymer separating out [79].

Kranz *et al.* [80] investigated *in vitro* drug (diltiazem hydrochloride and buserelin acetate) release from different in situ forming biodegradable drug delivery systems. The burst effect from *in situ* forming microparticle systems decreased with increasing polymer concentration and decreasing polymer phase. The type of biocompatible solvent also affected the drug release.

Moreover, the results also indicated that macro-molecular drugs were more easily affected by the dissolution of polymers than small molecule drugs. Despite no products has been marketed, the in situ forming microparticle systems are attractive alternatives for the sustained-release injectable products due to the excellent advantages.

CONCLUSION: Although researchers have made great efforts to develop sustained-release injectable preparations, the amount of new marketed products is far from the expectations. Most of the investigations are limited in laboratory level and there is a long way to large-scale manufacture and real market. The authors attribute this imbalance situation to the following aspects. Firstly, sterile operation is commonly employed in the whole process, including preparation, distribution, and freeze-drying.

The complex preparation procedures may involve more problems and cost when sterile operation is needed.

Secondly, some technical difficulties, such as residual solvents and burst effects, plague almost all the researchers concentrating on the investigation of sustained-release injectable preparations, especially in large-scale manufacture.

Thirdly, the *in vitro* and *in vivo* studies may last to several months for some preparations with excellent sustained-release effect merely in one cycle, which can bring a development cycle with unexpected long time.

Therefore, in the future, researchers should focus on developing novel low-cost biodegradable carrier materials and exploring more simple manufacture methods. Moreover, designing more reasonable and effective accelerated *in vitro* and *in vivo* measuring methods is the main solution to shorten development cycles.

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