A PROLONGED RELEASE PARENTERAL DRUG DELIVERY SYSTEM – AN OVERVIEW

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ABSTRACT

The Parenteral administration route is the most common and efficient for delivery of active drug substances with poor bio-availability and the drugs with a narrow therapeutic index. But parenteral route offers rapid onset of action with rapid declines of systemic drug level. For the sake of effective treatment it is often desirable to maintain systemic drug levels within the therapeutically effective concentration range for as long as treatment calls for. It requires frequent injection, which ultimately leads to patient discomfort. For this reason, drug delivery system which can reduce total number of injection throughout the effective treatment, improve patient compliance as well as pharmacoeconomic. These biodegradable injectable drug delivery system offer attractive opportunities for protein delivery and could possibly extend patent life of protein drugs. This article explores various prolonged release parenteral drug delivery system and their strategies of preparation, their potential benefits/drawbacks and in-vitro testing methods.

Keywords: In situ forming implant, Microspheres, Liposomes, Suspension, Solid lipid nanoparticle, In-vitro testing devices

INTRODUCTION

As in the case of mucosal and transdermal drug delivery, where systemic bioavailability of a drug is always limited by its permeability across a permeation barrier (epithelial membrane or stratum corneum)[1] and oral drug delivery in which the systemic bioavailability of a drug is often subjected to variable gastrointestinal transit time and biotransformation in the liver by "first pass metabolism"[2,3]. Parenteral drug delivery with intravenous, subcutaneous or intramuscular injection can gain easy access to systemic circulation with rapid drug absorption. This rapid drug absorption is unfortunately also accompanied by a rapid decline in the drug levels in the systemic circulation. In the case of chronic conditions, daily or multiple weekly injections for years or even lifetime have resulted in poor patient compliance. For tissue regeneration therapy on the other hand, the in vivo life of some cytokines are limited to hours or even minutes after injection, far from sufficient to exert biological functions in vivo. For the sake of effective treatment it is often desirable to maintain systemic drug levels within the therapeutically effective concentration range for as long as treatment calls for. To achieve constant drug level in the systemic circulation, two strategies can be employed: 1) To control the rate of absorption of a drug or 2) To control the rate of excretion of a drug. In that controlling the absorption rate of a drug (by modifying dosage forms) is easier than controlling the excretion rate (by modifying physiology of body) of a drug. Continuous intravenous infusion has been recognized to maintain a constant and sustained drug level within a therapeutic concentration range for as long as required effective treatment. But it entails certain health hazards and therefore necessitates continuous hospitalization and close medical supervision. The development of new injectable drug delivery system (parenteral depot formulation) has received considerable attention over the past few years[4-6]. The scientists are leaned towards depot formulations because of the advantages these delivery system possess which include ease of application, localized delivery for a site-specific action in the body, e.g. in local anaesthesia/analgesia[7,8], reduced dosing frequency without compromising the effectiveness of the treatment (carter et al 1988), increased dosing compliance, pharmacoeconomic and patent and commercially attractive reason. Examples of applications for prolonged release parenteral delivery include: fertility treatment, hormone therapy, protein therapy, infection treatments (antibiotics and antifungals), cancer therapy, orthopedic surgery and postoperative pain treatment, chronic pain treatment, vaccination/ immunization, treatment of CNS disorders, and immunosupression. Modified release (MR) parenteral drug products are available in several dosage forms, including microspheres[9-12], liposomes[13-17], gels[18-22], suspensions[23-26], in situ forming implants[19,21], lipophilic solutions[27-29], solid lipid nanoparticles (SLN)[30,31] and drug eluting stents.

TYPES OF DEPOT FORMULATION

On the basis of different mechanism, depot formulation categories into four types 1) Dissolution controlled depot formulation 2) Adsorption type depot formulation 3) Encapsulation type depot formulation 4) Esterification type depot formulation[32,33]

Dissolution-controlled depot formulations:

In this depot formulation the rate limiting step of drug absorption is the dissolution of drug particles in the formulation or in the tissue fluid surrounding the drug formulation. So drug absorption can control by slow dissolution of drug particle. The rate of drug dissolution (Q/t)d under sink conditions is defined by

$$(Q/t)d = Sa\ Ds\ Cs/hd \qquad (I)$$

Where Sa is the surface area of the drug particles in contact with the medium; Ds is the diffusion coefficient of drug molecules in the medium; Cs is the saturation solubility of drug in the medium; and hd is the thickness of

the hydrodynamic diffusion layer surrounding each of the drug particle.

Basically, two approaches can be utilized to control the dissolution of drug particle to prolong the absorption and hence the therapeutic activity of the drug.

i) Formation of salt or complexes with low aqueous solubility. Typical examples are preparations of penicillin G procaine (Cs = 4 mg/ml) and penicillin G benzathine (Cs = 0.2 mg/ml) from the highly water-soluble alkali salts of penicillin G and preparations of naloxone pamoate and naltrexone-Zn-tannate from the water-soluble hydrochloride salts of naloxone and naltrexone, respectively.

ii) Suspension of Macrocrystals. Macrocrystals (large crystals) are known to dissolve more slowly than Microrystals (small crystals). This is called the macrocrystal principle (from equation-I, surface area of drug particle is directly proportional to dissolution) and can be applied to control the rate of drug dissolution. Typical example is the aqueous suspension of testosterone isobutyrate for intramuscular administration.

Adsorption-type depot preparation:

This depot preparation is formed by the binding of drug molecules to adsorbents. In this case only the unbound, free species of the drug is available for absorption. As soon as the unbound drug molecules are absorbed a fraction of the bound drug molecules is released to maintain equilibrium. This depot preparation is exemplified by vaccine preparations in which the antigens are bound to highly dispersed aluminum hydroxide gel to sustain their release and hence prolong the duration of stimulation of antibody formation [34].

Encapsulation-type depot preparations:

This depot preparation is prepared by encapsulating drug solids within a permeation barrier or dispersing drug particles in a diffusion matrix. The release of drug molecule is controlled by the rate of permeation across the permeation barrier and the rate of biodegradation of the barrier macromolecules. Both permeation barrier and diffusion matrix are fabricated from biodegradable or bioabsorbable macromolecules, such as gelatin, dextran, polylacticacid, lactide-glycolide copolymers, phospholipids, and long-chain fatty acids and glycerides. Typical examples are naltrexone pamoate-releasing biodegradable microcapsule, liposomes, and norethindrone-releasing biodegradable lactide-glycolide copolymer beads.

Esterification-type depot preparations:

This depot preparation is produced by esterifying a drug to form a bioconvertible Prodrug-type ester and then formulating it in an Injectable formulation. This chemical approach depends upon number of enzyme (esterase) present at the injection site. This formulation forms a drug reservoir at the site of Injection. The rate of drug absorption is controlled by the interfacial partitioning of drug esters from the reservoir to the tissue fluid and the rate of bioconversion of drug esters to regenerate active drug molecules. It is exemplified by the fluphenazine enanthate, nandrolone decanoate in oleaginous solution.

INJECTABLE DRUG DELIVERY SYSTEM

In situ forming drug delivery systems (ISFD):

Injectable in situ forming implants are classified into five categories, according to their mechanism of depot formation: i) Thermoplastic pastes ii) In situ cross linked systems iii) In situ polymer precipitation iv) Thermally induced gelling system v) In situ solidifying organogels.

i) Thermoplastic pastes (TP):

Thermoplastic pastes are semisolid polymers, which injected as a melt and form a depot upon cooling to body temperature. They are characterized as having a low melting point or T_g (glass transition temperature) in the range of 25-65˚C and an intrinsic viscosity in the range of 0.05-0.8 dl/g[35,36]. Below the viscosity of 0.05 dl/g, no delayed release could be observed, where as above 0.8 dl/g the ISFD was no longer injectable using a needle. At injection temperature above 37˚C but below 65˚C these polymers behave like viscous fluids which solidify to highly viscous depots. Drugs are incorporated into the molten polymer by mixing without the application of solvents. Bioerodible thermoplastic pastes could be prepared from monomers such as D,L-lactide, glycolide, E-caprolactone, dioxanone and orthoesters[35-37]. Polymers and copolymers of these monomer have been extensively used in surgical sutures[38], ocular implants[39,40], soft tissue repair[40]etc.

Zhang et al developed a thermoplastic ABA triblock polymer system composed of poly (D,L-lactide)-poly(ethylene glycol)-poly(D,L-lactide) and blend of ABA triblock copolymer and polycaprolactone (PCL) delivery of Taxol within tumor resection sites[41]. Both give release of Taxol for more than 60d but the rate of release was very slow. Another disadvantage associated with this polymeric system was the high melting temperature of thermoplastic pastes requiring injection temperature at least 60˚C. This led to very painful injections and necrosis at the injection site resulting in the encapsulation of the depot by scar tissue, which again inhibited paclitaxel diffusion[42]. Poly(orthoesters), POE have well suited properties for TP due to their good biocompatibility, relatively low softening temperatures in the range of 35-45˚C and degradation by surface erosion[36,37].

ii) In situ cross linked polymer systems:

The formation of a cross-linked polymer network is advantageous, to control the diffusion of the hydrophilic macromolecules. Cross-linked polymer network can be found in situ by free radical reactions initiated by heat (thermosets) or absorption of photon or ionic interactions between small cation and polymer anions.

Dunn et al, used biodegradable copolymers of D, L-lactide or L-lactide with E-caprolactone to prepare a thermosetting system for prosthetic implants and slow release drug delivery systems[43]. It requires free radical producing agents such as benzoyl peroxide into the body which may induce tumor promotion[44]. Hibbell et al.

described a photopolymerizable biodegradable hydrogel as a tissue contacting material and controlled release carrier. This system consisted of a macromer, PEG(polyethylene glycol)-oligo-glycol-acrylate, using a photo initiator, such as eosin and visible light[45,46]. The controlled release of protein was observed over a period of several days. These hydrogel are restricted to surgical sites accessible to a light source as they form with difficulty after injection into the body. The delivery of various proteins from a photopolymerized PEG-PLA (polylactic acid) hydrogel is illustrated in figure.1[47].

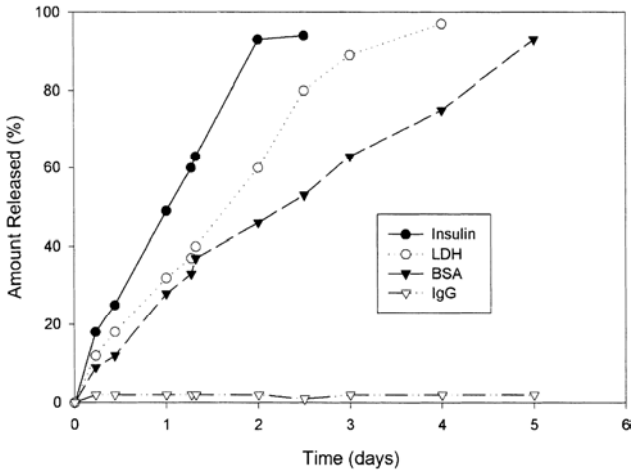

Figure 1: Protein release from photocrosslinked biodegradable hydrogel. Reproduced from Ref.47

Ion-mediated gelation has been reported for a number of polymers, e.g. alginates/calcium ions or chitosan/phosphate ions[48,49]. The concentrations of the counter ion available under physiological conditions are usually insufficient for cross-linking of the above mentioned polymers. Only the calcium concentration in the eye led to in situ formation of alginate formulations[49]. Despite these applications, there are two important factors which limit the use of calcium-alginate. The first factor is their potential immunogenicity and the second is longer time in vivo degradability[50].

iii) In situ polymer precipitation:

The concept ISFD based on polymer precipitation was first developed by Dunn and coworkers in 1990[51]. A water-insoluble and biodegradable polymer is dissolved in a biocompatible organic solvent to which a drug is added forming a solution or suspension after mixing. When this formulation is injected into the body, the water miscible organic solvent dissipates and water penetrates into the organic phase. This leads to phase separation and precipitation of the polymer forming the depot at the site of injection. This method has been designed as Atrigel™ technology, which used as a drug carrier for Eligard™, contains the leuteinizing hormone releasing hormone (LHRH) agonist leuprolide acetate (7.5, 22.5 or 30mg) and poly(lactide-co-glycolic acid)(PLGA) 75/25 dissolved in N-methyl-2-pyrrolidone (NMP) in a 45:55 (m/m) polymer:NMP ratio[52,53]. This system led to suppression of testosterone levels in dogs for approximately 91d. One of the problem with these system is the possibility of a burst in drug release especially during the first few hours after injection into the body. In order to control the burst effect, four factors have been examined, the concentration of polymer in the solvent[54], the molecular weight of the polymer[55], the solvent used[55,56] and the addition of surfactant[57]. Also the drug burst is directly related to the dynamics of the phase inversion.

Brodbeck et al demonstrated that protein release kinetic from ISFD was influenced by solution thermodynamics, e.g. solvent strength and water miscibility[58,59]. They studied NMP, triacetin and ethyl benzoate ternary phase systems with PLGA and water. NMP shows rapid phase inversion associated with a high drug burst where as triacetin and ethylbenzoate yielded low phase inversion rates, resulting in a slow gelation which reduced the drug burst of protein significantly. Himmelstein and joshi studied that polymer complex of PEG, polymethacrylic acid(PMA), and polyacrylic acid(PAA) is stable below pH≤5.7, the complex is insoluble in water but dissolves in a hydroalcoholic solvent to yield a clear viscous solution. After injection the diffusion of ethanol from the liquid transforms the system into a gel upon contact with physiological condition. The gel disappears from the site with time due to complex dissociation into water soluble and low molecular weight component, which can be eliminated by glomerular filtration [18].

Carbopol is a pH dependent polymer, which forms a low viscosity gel in alkaline environment (e.g. pH-7.4) and stays in solution in acidic pH. The addition of HPMC, a viscosity inducing agent, to carbopol reduces the carbopol concentration and hence the solution acidity while preserving the viscosity of the in situ gelling system. This system gels upon an increase in pH when injected[60].

iv) Thermally induced gelling system:

Many polymers undergo abrupt changes in solubility as a function of environmental temperature. The thermosensitive polymer, poly(N-isopropylacrylamide) [poly(NIPAAM)] exhibit sharp lower critical solution temperature, LCST at about 32˚C[61], which can be shifted to body temperature by formulating poly NIPAAM based gels with salt and surfactant. Unfortunately, poly NIPAAM is not suitable for biomedical applications due to its well known cytotoxicity (activation of platelets)[62] and non-biodegradability[63].

Triblock poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) copolymer, PEO-PPO-PEO (pluronics or poloxamers), have shown gelation at body temperature when highly concentrated polymer solution >15% w/w were injected[64,65]. These polymer concentration shown disadvantage of changing the osmolarity of the formulation, kinetics of the gelation, and causes discomfort in ophthalmic applications due to vision blurring and crusting[66]. Macromed produced thermosensitive biodegradable polymers based on ABA and BAB triblock copolymers. Where A is hydrophobic polyester block and B denotes the hydrophilic PEG block. The aqueous polymer solution of PEG-PLA-PEG is loaded with drug at 45˚C after injected into animal form a gel at body temperature, which continuously releasing

hydrophilic model substances fluorescein isothiocyanate dextran (FITC-dextran), over 10-20d[67,68].

An aqueous solution of low molecular weight PEG-PLGA-PEG (550-2810-550) triblock copolymers becomes gel at body temperature. Two model drugs, Ketoprofen (hydrophilic drug) and spirinolactone (hydrophobic drug) were released from the PEG-PLGA-PEG triblock copolymer hydrogel over 2 weeks with first order release profile and over 2 months with an s-shaped release profile, respectively. The higher the initial polymer solution concentration, the slower was the drug release rate observed, as shown in fig.2, due to tighter polymer-polymer contacts among the gel at higher concentrations of the polymer[69]. Thermosensitive Chitosan-β-glycerophosphate (C-GP) formulation containing liposomes demonstrated in vitro controlled delivery of carboxyfluorescein over at least 2 weeks. The release rate strongly depended on the liposome size and composition (i.e. addition of cholesterol), and on the presence of phospholipase in the release medium[70].

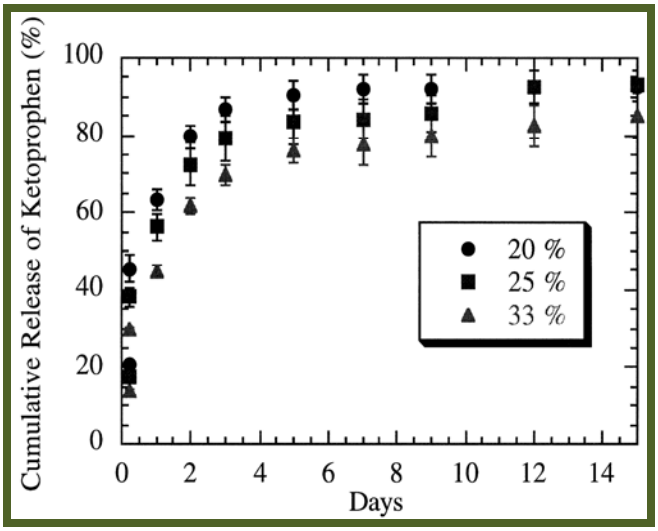

Figure 2a) Ketoprofen (1%w/w) release from PEG-PLGA-PEG triblock copolymer hydrogel in PBS

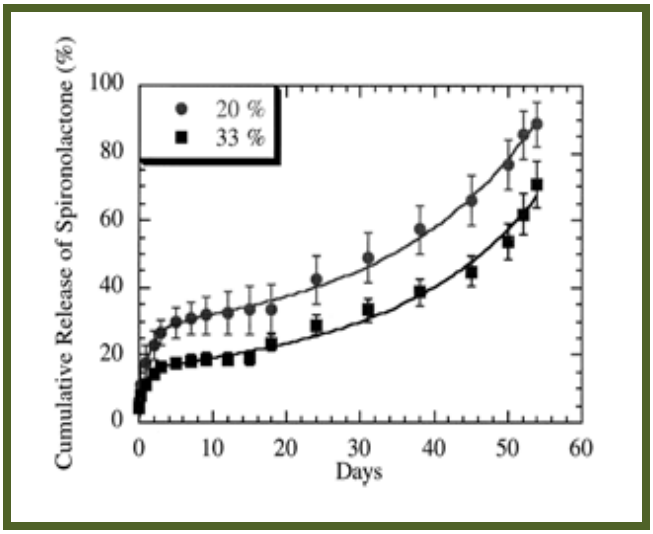

Figure 2b) Spirinolactone(0.25%w/w) release from PEG-PLGA-PEG triblock copolymer hydrogel in PBS. Reproduced from reference[69].

V) In situ solidifying organogel:

Organogels are composed of water insoluble amphiphilic lipids, which swell in water and forms various types of lyotropic liquid crystals. The amphiphilic lipids examined for drug delivery are glycerol monooleate, glycerol monopalmitostearate, glycerol monolinoleate, sorbitan monostearate (SMS) and different gelation modifiers (polysorbates 20 and 80) in various organic solvents and oils. These compound forms a cubic liquid crystal phase upon injection into an aqueous medium which is gel like and highly viscous[71].

SMS organogels containing either w/o or vesicular in water in oil (v/w/o) emulsion were investigated in vivo as delivery vesicles for vaccines using albumin (BSA) and haemagglutin (HA) as model anigens[72,73]. Intramuscular administration of the v/w/o gel yielded the long lasting depot effect (48hr). Controlled releases of contraceptive steroids levonorgestrel and ethinyl estradiol were achieved by Gao et al. In these work biodegradable organogel formulations prepared from glycerol palmitostearate (precirol) in derivatized vegetable oil, show in vitro release of levonorgestrel up to 14d[74], while subcutaneous injection into rabbits demonstrated an estrus blockage for up to 40d[75]. Subcutaneously injected in situ forming organogels prepared from L-alanine derivatives in safflower oil were used in the long term delivery of leuprolide, a LHRH agonist used in prostate cancer[76]. The gels were shown to slowly degrade and release the therapeutic peptide for a period of 14 to 25d.

MICROSPHERES

Numerous biodegradable polymers have been investigated for preparation of microspheres as depot formulation. The application of biodegradable microspheres to deliver small molecules, proteins, and macromolecules using multiple routes of administration has been widely investigated and several products have been brought to market in the last 10–20 years. A list of marketed injectable products is shown in Table 1. For peptide or protein containing microspheres mainly three processes were studied more intensively, namely the w/o/w –technique phase separation methods and to some extent spray drying. Fig.3 summarized schematic representation of all three techniques.

ABA (PLGA-PEO-PLGA) block copolymer was investigated over PLG polymer by using macromolecular model compound, such as FITC-dextrans (molecular mass 4-500 kDa). The in vitro release pattern of macromolecules from ABA microspheres was influenced by the molecular mass of the solute and showed continuous release profiles above threshold level of Ca 20 kDa where as PLG microspheres yielded biphasic release profile independent of the molecular mass of the solute[77].

Lupron Depot®, microsphere containing the LHRH superagonist leuprorelin (leuprolide) acetate with PLGA (75/25)-14000 and PLA-15000, prepared by w/o/w emulsion-solvent evaporation method. The microsphere release drug in a zero order fashion over 1 to 3 months after intramuscular or subcutaneous injection into animals[78]. PLGA microsphere had been also used for

delivery of glycoprotein (GP) IIb/IIIa antagonist, plasmid DNA, Interleukin-1α and prolidase enzyme[79,80,81,82].

LIPOSOMES

In the area of injectable drug delivery system, research into liposomes played a major role in the past few decades. Lipid complex (Abelcet®, Amphotec®) and three liposomal formulation, Ambisome®, Daunosome®, and a stealth liposome (Doxil®) had got approval for human use by regulatory agencies[83,84]. These products have been developed for intravascular administration, for enhancement of circulation times and reducing toxicity by lipid encapsulation. Nowadays, encapsulation of drug into multivesicular liposomes (Depo Foam®) offers a novel approach to sustained release drug delivery. Drug into unilamellar and multilamellar liposomes, and complexation of drug with lipids, resulted in products with better performance over period of lasting several hours to a few days after intravascular administration where as Depo Foam® encapsulation has been result in sustained release lasting over several days to weeks.

A sustained release depot product (Depocyt®) utilizing Depo Foam® technology[85] consist of novel multivesicular liposomes characterized by their unique structure of multiple non-concentric aqueous chamber surrounded by a network of lipid membranes. The route of administration most viable for delivery of drugs via Depo Foam® formulations include intrathecal, epidural, subcutaneous, intramuscular, intra-articular and intraocular. Depo Foam formulatons of a protein such as insulin, myelopoietin (Leridistim)[86] and peptide such as leuprolide, enkephalin, octreotide have been developed and characterized[17]. The data show that these formulations have high drug loading, high encapsulation efficiency, low content of free drug in the suspension, little chemical change in the drug caused by the formulation process, narrow particle size distribution and spherical morphology. Semisolid phospholipid dispersion of vesicular morphology, so called vesicular phospholipid gels (VPGs) is another approach in liposomal technology. A protein such as erythropoietin[87] and peptide such as Cetrorelix[88] were developed and in vitro evaluated by vesicular phospholipid gels.

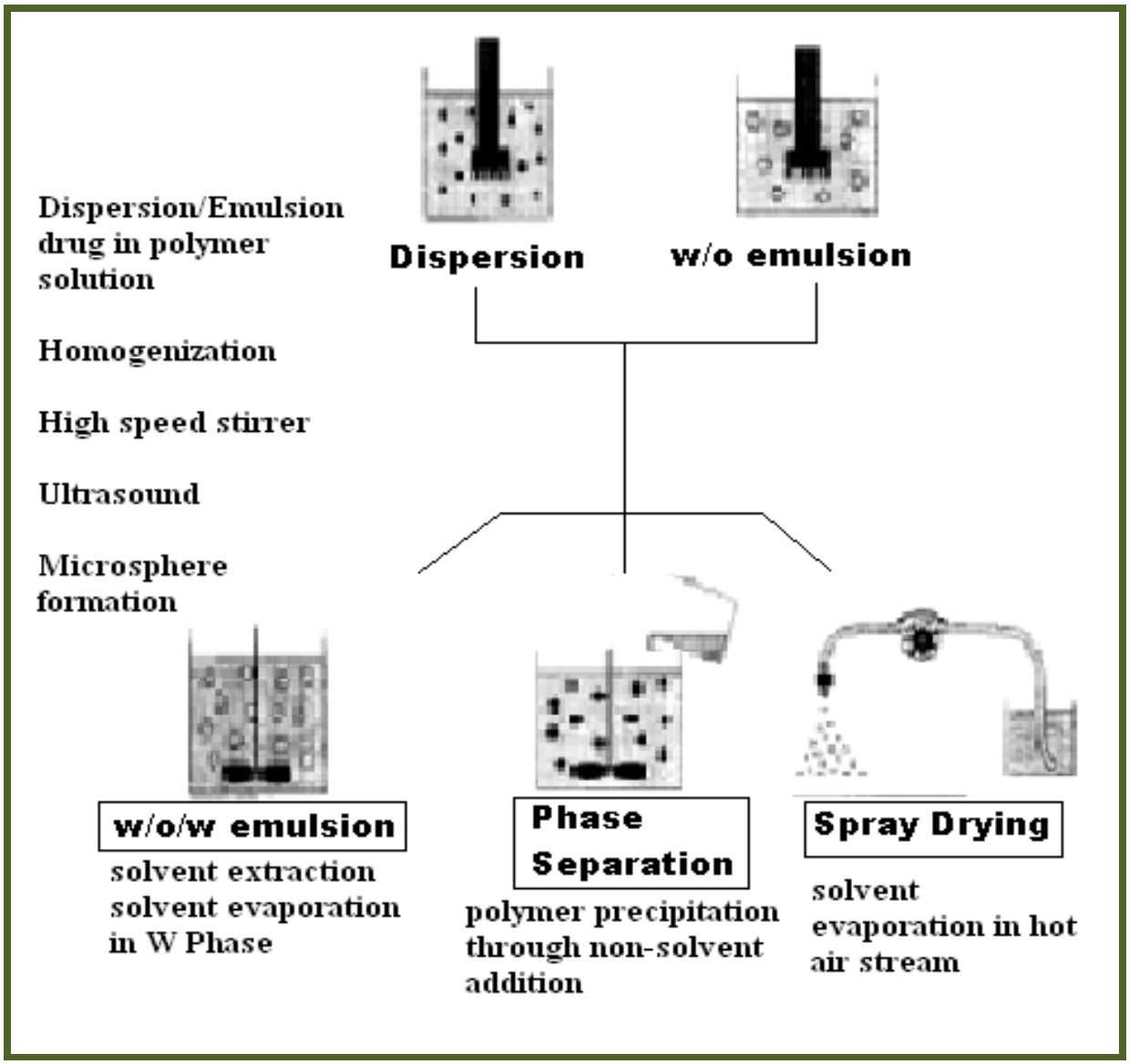

Figure 3: Schematic representation of manufacturing technique for protein containing microsphere

Table 1: List of marketed microsphere drug product

Drug	Commercial name	Company
Risperidone	RISPERDAL® CONSTA®	Janseen®/Alkermes, Inc
Naltrexone	Vivitrol®	Alkermes
Leuprolide	Lupron Depot®	TAP
	Enantone Depot®	Takeda
	Trenantone®	Takeda
	Enantone Gyn	Takeda
Octreotide	Sandostatin®LAR	Novartis
Somatropin	Nutropin®Depot	Genentech/Alkermes
Triptorelin	Trelstar™ Depot	Pfizer
	Decapeptyl® SR	Ferring
Buserelin	Suprecur® MP	Sanofi-Aventis
Lanreotide	Somatuline® LA	Ipsen-Beafour
Bromocriptine	Parlodel LAR ™	Novartis
Minocycline	Arestin®	Orapharma

SUSPENSIONS

A suspension is a widely used pharmaceutical dosage form which offers a potential use as a parenteral sustained release system. Subcutaneous administration of a drug as an aqueous or oil suspension results in the formation of a depot at the injection site (Davis et al)[89]. The depot act as a drug reservoir, slowly releasing the drug continuously at a rate dependent upon both the intrinsic aqueous solubility of the drug and the dissolution of the drug particles into tissue fluid surrounding the drug particle in the subcutaneous tissue. Oleaginous suspension of micronized crystal of penicillin procaine in vegetable oil, such as peanut or sesame oil, gelled with 2% aluminum monostearate was reported to produce therapeutic blood level of penicillin in both animal and human for 162hr[32]. Scientist at Abbott laboratories developed aqueous thixotropic suspension of penicillin procaine (40-70%w/w), such as Duracillin (Lilly), Crystacillin (Squibb) which on intramuscular injection tends to form compact and cohesive depot, leading to the slow release of penicillin procaine. This thixotropic suspension must possess structural breakdown point of at least 105 dyn^{-cm}, so it have syringeability and form depot at the site of injection.

Insulin has long been formulated with zinc as a suspension for subcutaneous delivery (for example, HUMULIN, ILETIN, LENTE and NOVOLIN, developed and manufactured by Lilly) to produce action upto 36hr[90]. Yamahira et al was developed sustained release oleaginous suspension of spray-dried or lyophilized α-interferon[91]. Chang et al formulated aqueous suspension of butorphanol free base and oil suspension of tartarate salt and evaluated in dogs. The in vivo result indicate a sustained drug release profile, with the plasma drug concentration maintained within the desirable therapeutic range of 5-100 ng/ml over a 24hr period[24].

Recently nanosuspension had gain access in parenteral depot system. Intradermal delivery of bupivacaine nanosuspension (10%), prepared above pKa (8.2) as a bolus prolongs local anesthesia in a rat for at least 48hr whereas 1% solution (MARCAINE) fails to abate a pain response (tail twitch) after 4hr[92].

SOLID LIPID NANOPARTICLE (SLN)

SLN are colloidal particles composed of a biocompatible/biodegradable lipid matrix that is solid at body temperature and exhibit size range in between 100 and 400 nm. Upon parenteral administration SLN shows excellent physical stability, protection of incorporated labile drugs from degradation, controlled drug release (fast or sustained) depending on the incorporation of model, good tolerability and site specific targeting. Techniques utilized for preparation of SLN are high pressure homogenization (HPH), microemulsion, solvent emulsification-evaporation or diffusion, w/o/w double emulsion method and high speed stirring and/or ultrasonication[30].

SLN loaded with prednisolone by HPH, released the drug in vitro (i.e. in absence of enzyme) over a period of more than 5 weeks[93]. For stearic acid SLN containing cyclosporine A, cavalla et al determined an in vitro release of <4% after 2hr compared to >60% from solution[94]. Yang et al was performed first in vivo studies of encapsulating anticancer agent camptothecin with stearic acid SLN in the year 1999[95]. They prepared SLN loaded camptothecin by HPH (average particle size 197 nm) and administered intravenously to mice. The concentration of camptothecin at different time intervals after IV administration of camptothecin SLN (CA-SLN) in comparison to camptothecin solution (CA-sol) in mice is depicted in fig.4. These SLN demonstrated higher AUC and MRT (18 fold enhancement) compared to camptothecin solution.

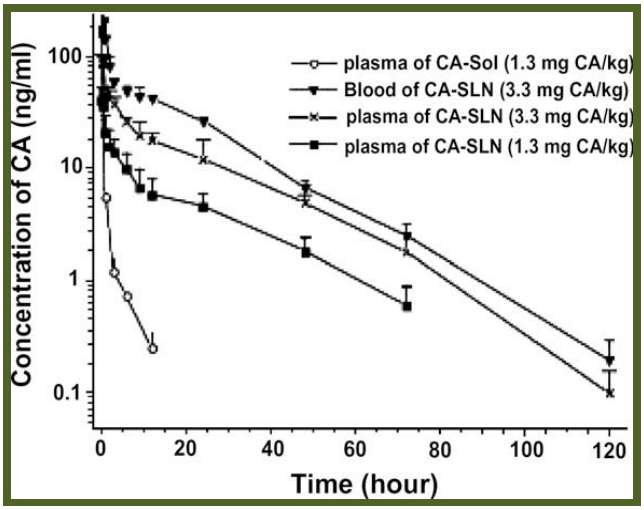

Figure 4: Concentration–time curves of camptothecin after i.v. administration of CA-SLN with doses of 1.3 and 3.3 mg CA/kg in plasma and 3.3 mg CA/kg in blood, and CA-SOL with a dose of 1.3 mg CA/kg in plasma.

IN-VITRO TESTING OF PARENTERAL DEPOT FORMULATION

Modified release dosage forms are typically designed to release their contents over periods of weeks, months or even years, it becomes impractical to wait for a real-time test for batch release of product. Therefore, accelerated methods are often developed to assist in batch release of product. Accelerated tests, by their nature, (e.g. elevated temperature or use of solvents) can change not only the rate of drug release but also the mechanism of release. Consequently care needs to be taken in selecting an accelerated release method. However, the development of an additional real-time test will still be needed if the intent is to develop an in vitro test that is predictive of in vivo product performance. Success has been reported with the use of a modified rotating paddle for suspensions, Franz cell diffusion system for gels, flow-through cell for implants, and floatable dialysis bag for microspheres or nanoparticles. Important factor to be consider while selecting apparatus are its agitation characteristics, flow rate and choice of medium (the medium should mimic the physiological conditions of target animal).

Schultz et al was investigated an in vitro release method based on rotating dialysis cell for parenteral oil depot formulations using different model conditions and test formulations. They found release rate were depend upon total amount of drug available for the release process and to follow first order kinetics[96]. The rotating dialysis cell model offers the advantages of reproducible results and fast distribution and dissolution processes. Commercially available Float A Lyzer® dialysis tubes can also be used as an alternative in vitro model operating at much less intensive stirring conditions to assess drug release from oil solutions and suspensions as well as from biodegradable microspheres. Lars soderberg developed membrane free in vitro release method named “inverted cup” for drugs in lipid formulation. Thirteen formulation containing bupivacaine, lidocaine and/or prilocaine in lipid vehicle of different physical properties were examined and compared with in vivo data, from nerve block and pharmacokinetics study in rats as well as in vitro release profile obtained from “single drop” technique. It showed good agreement between both in vitro release profile and good in-vitro-in-vivo correlations[97]. Design of both inverted cup and single drop technique were shown in fig.5.

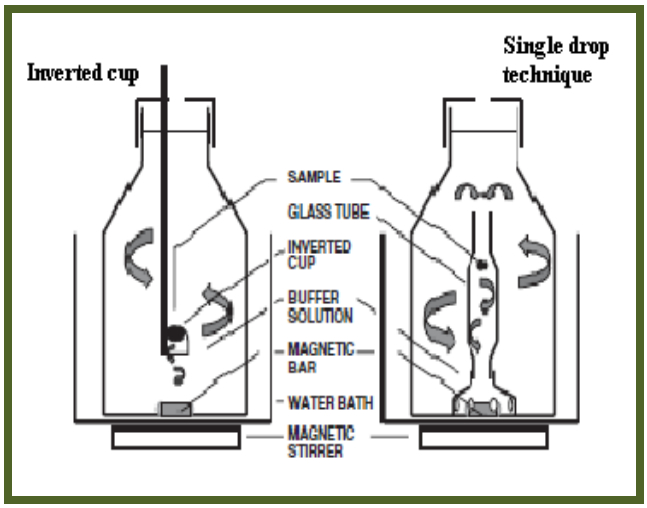

Figure 5: The inverted cup (diameter=11 mm, height=15 mm) is held in place, 60 mm from the bottom of the 1 L bottle (diameter=100 mm, height=230 mm) by a piece of glass tubing attached to the screw cap. Size of magnetic bar is 8×50 mm. The hole in the screw cup (which is used to withdraw buffer solution) has a diameter of 8 mm. Reproduced from reference 97.

CONCLUSION

Extended release parenteral products are complex dosage forms, requiring careful development of test methods and acceptance criteria for the specifications. In particular, the in vitro release test method and acceptance criteria require rigorous scientific consideration and should be developed with an eye toward understanding the mechanisms of drug release. The final specifications need to ensure the safety, identity, strength, performance, and quality of the drug product at release and during storage through the end of its shelf-life. Major progresses in the development of parenteral sustained-release systems have been made in recent years as evidenced by the regulatory approval and market launch of several new products. Both the availability of novel carrier materials and the advances in method of fabrication have contributed to these commercial successes. With the formulation challenges associated with biologics, new delivery systems have also been evolved specifically to address the unmet needs in the parenteral sustained release of proteins.

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