A PROLONGED RELEASE PARENTERAL DRUG DELIVERY SYSTEM – AN OVERVIEW

Hitesh Bari
Bharati vidyapeeth college of pharmacy, morewadi, near chitranagari, kolhapur 416013
Email: barihitesh99@gmail.com

ABSTRACT

The Parenteral administration route is the most common and efficient for delivery of active drug substances with poor oral bioavailability 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 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 options 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 nanoparticles, 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 control the absorption rate of a drug (by modifying dose 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 systems (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

delivery of glycoprotein (GP) IIb/IIIa antagonist, plasmid DNA, Interleukin-. [79,80,81,82] D Q G S U R O L G D V H H Q] \ P H

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 the 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 reduction of drug 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 lipid, 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.

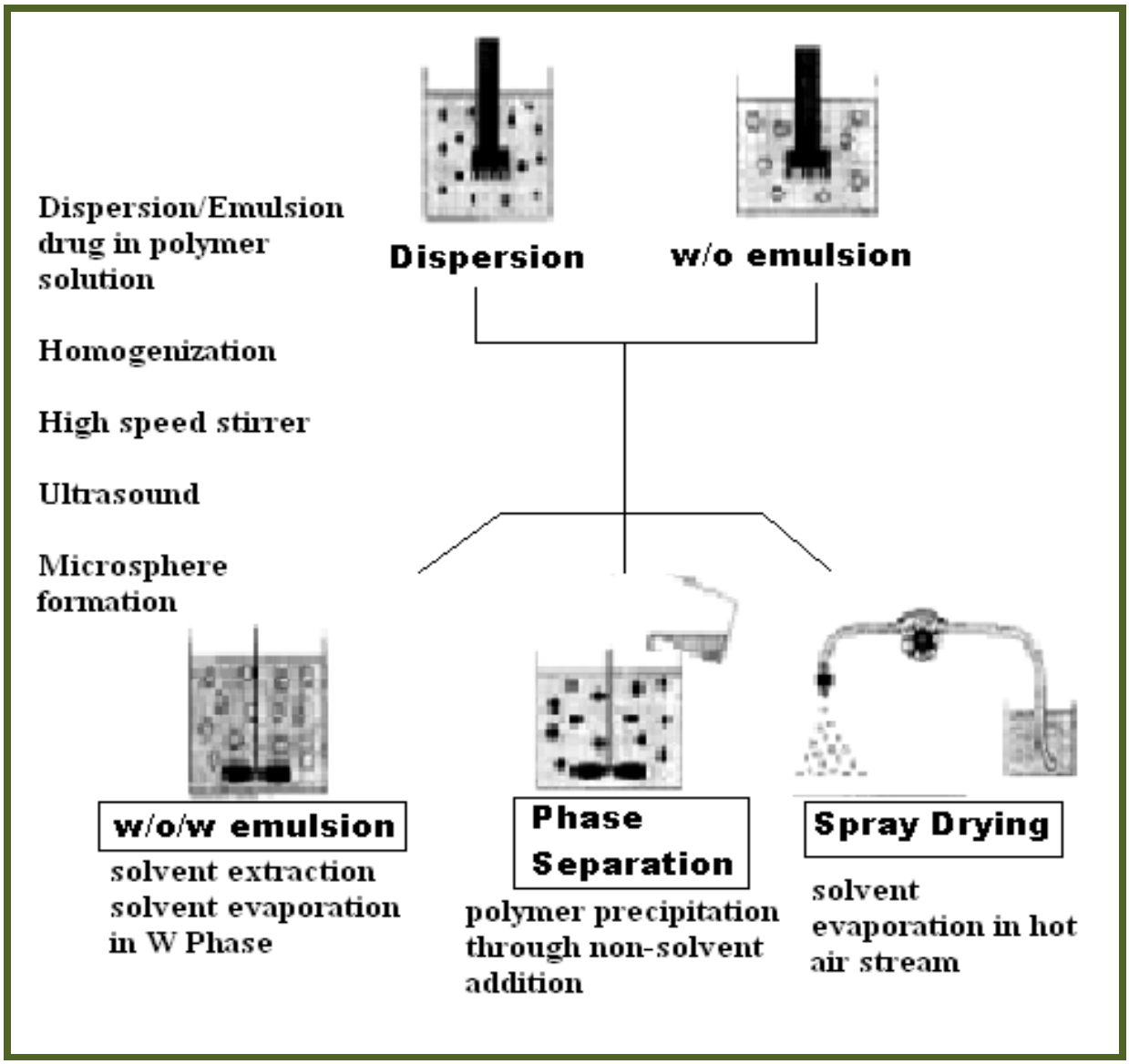

Figure 3: Schematic representation of manufacturing technique for protein containing microsphere

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 10^5 dyn/cm^2, 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[98]. Yamahira et al was developed sustained release oleaginous suspension of spray dried or lyophilized .-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 0.5 – 1.5 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[82] whereas 1% solution (MARCAINE) fails to abate a pain response (tail twitch) after 4hr.

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[85]. 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.

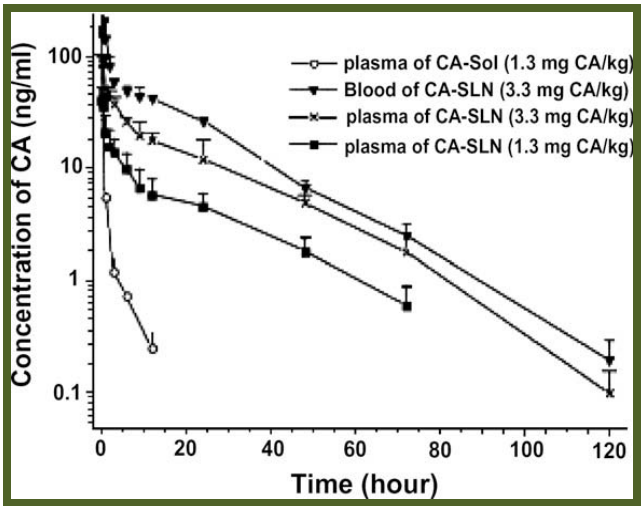

Figure 4: Concentration–time curves of camptothecin after i.v. administration of CA-SLN with doses of 1.3 and 3.3 mg CA/kg in plasma and 3.3 mg CA/kg in blood, and CA-SOL with a dose of 1.3 mg CA/kg in plasma.

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.

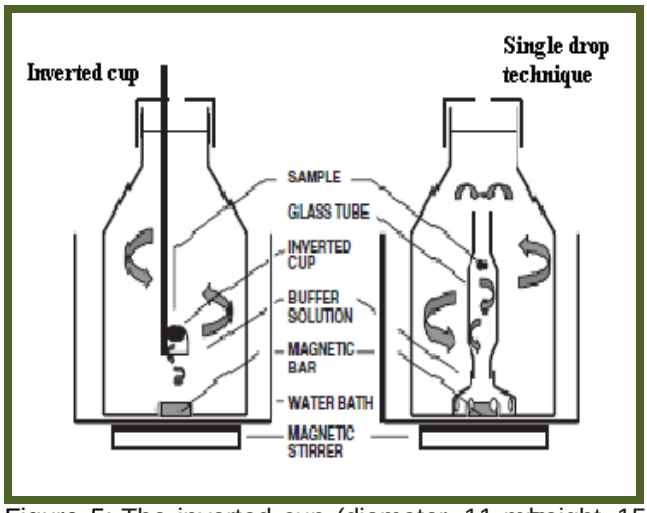

Figure 5: The inverted cup (diameter=11 mm, height=15 mm) is held in place, 60 mm from the bottom of the 1 L bottle (diameter=100 mm, height=230 mm) by a piece of glass tubing attached to the screw cap. Size of magnetic bar is 8×50 mm. The hole in the screw cup (which is used to withdraw buffer solution)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

REFERENCES

1. Naik A, Kalia Y, Guy R, Transdermal drug delivery: overcoming the skin's barrier function, PSTT, 3(9), september 2000
2. Anderson BD, Chu WW, Galinsky RE, Reduction of first-pass metabolism of propranolol after oral administration of ester prodrug, International Journal of Pharmaceutics, 43(3), May 1988, 261-265

3. Shin Hyun, Bae Soo, Lee Myung, Pharmacokinetics of sidenafil after intravenous and oral administration in rats: Hepatic and intestinal first pass effects, International Journal of Pharmaceutics, 320, 2006, 64-70
4. Heller J, Polymers for controlled parenteral delivery of peptides and proteins, Advanced Drug Delivery Review, 10, 1993, 163-204
5. Langer R, New methods of drug delivery, Science, 249, 1990, 1527-1553
6. Tipton AJ, Dunn R, In situ gelling system, in: sustained release injectable product, Senior JH, Radomsky M, Interpharm press, Denver, 2000, 71-102
7. Hollister LE, Sitespecific drug delivery to central nervous system, Neurobiology Aging , 10, 1989, 628-631
8. Levy R J, Vinod L, Strickberger SA, Underwood T, Davis J, Controlled release implant dosage forms for cardiac arrhythmias: review and perspective, Drug delivery, 3, 1996, 137-142
9. Chen L, Apte RN, Cohen S, Characterization of PLGA microsphere for the controlled delivery of IL-1 for tumor immunotherapy, J Control Release, 43, 1997, 261-272
10. Okada H, Docken Y, Ogawa Y, Toguchi H, Sustained suppression of the pituitary-gonadal axis by leuprorelin three month depot microspheres in rats and dogs, Pharm Res, 11, 1994, 1293
11. Sinha V, Trehan A, Biodegradable microspheres for protein delivery, J Control Release, 90, 2003, 261
12. Park TG, Degradation of poly(lactic-co-glycolic acid) microspheres: effect of copolymer composition, Biomaterials, 16, 1995, 1123-1130
13. Allen TM, Hansen CB, Guo L, Subcutaneous administration of liposomes: a comparision with the intravenous and intraperitoneal routes of injection, Biochim. Biophys. Acta 1150, 1993-16
14. Bonetti A, Chatelut E, Kim S, An extended-release formulation of methotrexate for subcutaneous administraton, Cancer Chemotherapy Pharmacology 1994;33:303-306
15. Sharma A, Sharma U, Liposomes in drug delivery: progress and limitations, International Journal of Pharmaceutics. 154, 1997, 123-140
16. Qiang Ye, Asherman J, Stevenson M, Brownson E, Katre N, Depo foam technology: a vehicle for controlled delivery of protein and peptide drug, J Control Release 64, 2000, 155-166
17. Mantripragada S, A lipid based depot (Depot Foam technology) for sustained release drug delivery, Progress in lipid research 41, 2002, 392-406
18. Haglund B, Joshi R, Himmelstein K, An in situ gelling system for parenteral delivery, J Control Release 41, 1996, 229-235
19. Motulsky A, Lafleur M, Hoare D, Boury F, Characterization and biocompatibility of organogels based on L-alanine for parenteral drug delivery implants, Biomaterials 26, 2005, 6246-6253
20. Byeongmoon J, You Han Bae, Sung Wan Kim, Drug release from biodegradable injectable thermosensitive hydrogel of PEG-PLGA-PEG triblock copolymers, J Control Release 63, 2000, 155-163
21. Mingxi Qiao, Dawei Chen, Xichen Ma, Yanjun Liu, Injectable biodegradable temperature-responsive PLGA-PEG-PLGA copolymers: synthesis and effect of copolymer composition on the drug release from the copolymer-based hydrogels, International Journal of Pharmaceutics, 294, 2005, 103-112
22. Kwang-Mi Jin, Yong-Hee Kim, Injectable, thermoreversible and complex coacervate combination gels for protein drug delivery, J Control Release, 127, 2008, 249-256
23. Buckwater FH, Dickison HL, Journal of American Pharmaceutical Association (Sci. Ed.) 47, 1958, 661
24. Chang HC, Li L, C, Marsh KC, Tian Y, Parenteral sustained release dosage forms of butorphanol for dogs, International Journal of Pharmaceuti 176, 1999, 147-156
25. Kranz H, bodmeier R A, novel in situ forming drug delivery system for controlled parenteral drug delivery, International Journal of Pharmaceutics, 332, 2007, 107-114
26. Larsen Claus, On the mechanism of drug release from oil suspensions in vitro using local anesthetics as model drug compounds, Euro. J. of Pharm. Sci., 34, 2008, 37-44
27. Fredholt Karin, Larsen Dorrit, Larsen Clause, Modification of in vitro drug release rate from oily parenteral depots using a formulation approach, Euro. J. of Pharm. Sci., 11, 2000, 231-237
28. Dorrit Bjerg Larsen, Stig Joergensen, Niels Vidiendal Olsen, Clause Larsen, In vitro release of bupivacaine from subcutaneously administered oily solution: comparison with in vitro release, J Control Release, 81, 2002, 145-154
29. Larsen Susan Weng, Jesper Ostergaard, Marit N, Jassen B, Clause Larsen, In vitro assessment of drug release rates from oil depot formulations intended for intra-articular administration, Euro. J. of Pharm. Sci., 29, 2006, 348-354
30. Wissing SA, Kayser O,Muller RH, Solid lipid nanoparticle for parenteral drug delivery, Advanced Drug Delivery Review, 56, 2004, 1257-1272
31. Joshi Medha, Muller Rainer, Lipid nanoparticles for parenteral delivery of actives, Euro. J. of Pharm. and Biopharm., 71, 2009, 161-172
32. Chien YW, Parenteral drug delivery and delivery systems, In: Novel drug delivery system, second Ed, 50, Marcel Dekker, New York, 382-385

33. Avis Kenneth, Sterile poduct, In: The theory and practice of industrial pharmacy, Lachman L, Lieberman H, Kanig J, Varghese publishing house, Bombay, 653-654
34. Bowersock Terry, Martin Stephen, Vaccine delivery to animals, Advanced Drug Delivery Review, 38, 1999, 167-194
35. Bezwada RS, Preparation of liquid copolymers of E caprolactone and lactide, U S Patent 1995, 5:442,033
36. Moreau M, Schneider M, Boisramc B, Gurny R, Controlled delivery of metoclopramide using on injectable semisolid poly(orthoester) for veterinary application, International Journal of Pharmaceutics, 248(1-2), 2002, 31-37
37. Einmahl S, Behar-Cohen F, Tabatabay C, Heinzen FD, Chauvaud D, Heller J, Gurny R, A viscous bioerodible poly(orthoester) as a new biomaterial for intraocular application, Journal Biomed Mater Res, 50, 2000, 566-577
38. Holland SJ, Tighe BJ, Gould PL, Polymers for biodegradable medical devices 1.The potential of polyesters as controlled macromolecular release system, J Control Release, 4, 1986, 155-180
39. Deshpande AA, Heller J, Gurny R, Bioerodible polymer for ocular drug delivery, Crit Rev Ther Drug Carrier Syst, 15(4), 1998, 3-41-20
40. Mali Mahesh, Hajare Ashok, Systems for sustained ocular drug delivery: a review of stimuli-sensitive in situ gel-forming systems, Euro J of parent & Pharm Sci, 14(3), 2009, 7-8-3
41. Zhang X, Jackson JK, Wang W, Min W, Cruz T, Hunter WL, Burt HM, Development of biodegradable polymeric paste formulation for Taxol: an in-vivo and in-vitro study, International Journal of Pharmaceutics, 137, 1996, 199-208
42. Alonso PE, Perula LA, Rioja LF. Pain-temperature relation in the application of local anesthesia, British J Plast Surg, 46(1), 1993, 76-78
43. Dunn RL, English JP, Cowsar DR, Vanderbelt DD, Biodegradable in-situ forming implants and method for producing the same, U S Patent 23Aug 1994, 5:340849
44. Saleem MA, Ahmed SI, Tephrosia purpurea ameliorates benzoyl peroxide-induced cutaneous toxicity in mice: diminution of oxidative stress, Pharm Pharmacol Commun , 5(7), 1999, 455-51
45. Sawhney AS, Pathak CP, Hubell JA, Bioerodible hydrogels based on photopolymeerized poly(ethyleneglycol)-copoly(alpha-hydroxy acid) diacrylate macromers, Macromolecules, 26(4), 1993, 581-587
46. Philbrook M, Lehnert S, Warnock D, Duan S, Enscore D, Tissue adherent depot for prevention of local tumor recurrence, Proceedings 23rd International symposium of Controlled Release of Bioactive Materials, 2000, 510-511
47. West JL, Hubell JA, Localized intravascular protein delivery from photopolymerized hydrogels, Proc Int Symp Control Rel Bioact Mater, 22, 1995, 17-18
48. Chenite A et al, Novel injectable neutral solutions of chitosan form biodegradablegels in situ, Biomaterial, 21(21), 2000, 2155-2161
49. Cohen S, Lobel E, Trevgoda A, Peled Y, A novel, In situ-forming ophthalmic drug delivery system from alginates undergoing gelation in the eye, J Control Rel, 44(2-3), 1997, 201-208
50. Lansdown ABG, Payne MJ, An evaluation of the local reaction and biodegradation of calcium sodium alginate(Kaltostat) following subcutaneous implantation in the rat, J R Coll Surg Edinb, 39, 1994, 284-288
51. Dunn RL, English JP, Cowsar DR, Vanderbilt DP, Biodegradable in-situ forming implans and methods of producing the same, U S Patent 1990, 4,938,763
52. Dunn RL, The atrigel drug delivery system, In: Drugs and the pharmaceutical sciences, 126, Dekker, New York, MA, 2003, 647-655
53. Ravivarapu HB, Moyer KL, Dunn RL, Sustained activity and release of leuprolide acetate from an in situ forming polymeric implant, AAPS Pharm Sci Tech, 1(1), 2000
54. Radomsky ML, Brouwer G, Floy BJ, Loury DJ, Chu F, Tipton AJ, Sanders LM, The controlled release of Ganirelix from the Atrigel injectable implant system, Proc Intern Symp Control Rel Bioact Material, 20, 1993
55. Lambert WJ, Peck KD, Development of an in situ forming biodegradable poly-lactide-co-glycolide system for the con-trolled release of proteins, J Control Release, 33, 1995, 189-195.
56. Shively ML, Bennett AT, Coonts BA, Renner WD, Southard JL, Physico-chemical characterization of polymeric injectable implant delivery system, J Control Release, 33, 1995, 233-243
57. Chandrashekar BL, Zhou M, Jarr EM, Dunn RL, Controlled release liquid delivery compositions with low initial drug burst, US Patent 2000, 6 143 314
58. Brodbeck KJ, Desnoyer JR, Mchugh AJ, Phase inversion dynamics of PLGA solutions related to drug delivery. Part II: The role of solution thermodynamics and bath-side mass transfer, J Control Release, 62(3), 1999, 333-344.
59. Graham PD, Brodbeck KJ, Mchugh AJ, Phase inversion dynamics of PLGA solutions related to drug delivery, J Control Release, 58(2), 1999, 233-245
60. Ismail FA, Napaporn J, Hughes JA, Brazeau GA, In situ gel formulations for gene delivery: release and myotoxdegradable icity studies, Pharm Dev Tech, 5, 2000, 391-397
61. Stile RA, Burghardt WR, Healy KE, Synthesis and characterization of injectable poly(N

isopropylacrylamide) based hydrogels that support tissue formation in vitro, Macromolecules, 32(22), 1999, 7370-7379.
62. Merril EW, Pelakala RW, Hydrogel for blood contact, in: Hydrogels in Medicine and Pharmacy, Peppas NA, Vol. III., CRC Press, 1987
63. Jeong B, Bae YH, Lee DS, Kim SW, Biodegradable block copolymers as injectable drug delivery systems, Nature, 388, 1997, 860-862
64. Bochot A, Fattal E, Gulik A, Couarraze G, Couvreur P, Liposomes dispersed within a thermosensitive gel: a new dosage form for ocular delivery of oligonucleotides, Pharm Res, 15 (9), 1998, 1364-1369
65. Yong CS, Choi JS, Quan QZ, Rhee JD, Kim CK, Lim SJ, Kim KM, Oh PS, Choi HG, Effect of sodium chloride on the gelation temperature, gel strength and bioadhesive force of poloxamer gels containing diclofenac sodium, International Journal of Pharmaceutics, 226(1-2), 2001, 195-205.
66. Joshi A, Ding S, Himmelstrin KJ, Reversible gelling compositions and methods of use, U S Patent 12th October 1993, 5 252 318.
67. Jeong B, Bae YH, Lee DS, Kim SW, Biodegradable block copolymers as injectable drug-delivery systems, Nature, 388(6645), 1997, 860-862
68. Jeong B, Choi YK, Bae YH, Zentner G, Kim SW, New biodegradable polymers for injectable drug delivery systems, J Control Release, 62(1-2), 1999, 109–114.
69. Jeong Byeongamoon, Bae You Han, Kim Sung Wan, Drug release from biodegradable injectable thermosensitive hydrogel of PEG-PLGA-PEG triblock copolymer, J Control Release, 63, 2000, 155-163.
70. Ruel-Gariepy E, Leclair G, Hildgen P, Gupta A, Leroux JC, Thermosensitive chitosan based hydrogel containing liposomes for the delivery of hydrophilic molecules, J Control Release, 82, 2002, 373-383
71. Engstrom S, Engstrom L, Phase behavior of the lidocaine – monoolein – water system, International Journal of Pharmaceutics, 79, 1992, 111-122
72. Bergh Van Den, Gregoriadis G, Water-in-sorbitan monostearate organogels (water-in-oil gels), J Pharm Sci 88, 1999, 611-619
73. Murdan S, Gregoriadis G, Florence AT, Sorbitan monostearate/polysorbate 20 organogels containing neosomes: a delivery vehicle for antigens?, Euro J of Pharm Sci, 8, 1999, 177-186
74. Gao Z, Shukla AJ, Johnson JR, Crowley WR, Controlled release of contraceptive steroids from biodegradable and injectable gel formulations: in vitro evaluation, Pharm Res, 12(6), 1995, 857-864
75. Gao Z, Crowley WR, Shukla AJ, Johnson JR, Reger JF, Controlled release of contraceptive steroids from biodegradable and injectable gel formulations: in vivo evaluation, Pharm Res, 12(6), 1998, 863-868
76. Plourde F, Motulsky A, Couffin-Hoarau AC et al, First report on the efficacy of -alanine based in situ forming impants for the long term parenteral delivery of drugs, J Control Release, 108, 2005, 433-443.
77. Kissel T, Li YX, Volland C, Gsrich S, Koneberg R, Parenteral protein delivery systems using biodegradable polyesters of ABA block structure, containing hydrophobic poly(lactide-co-glycolide) A blocks and hydrophilic poly(ethylene oxide) B blocks, J Control Release, 39, 1996, 315-326
78. Okada Hiroaki, One- and three-month release injectable microspheres of the LH-RH superagonist leuprorelin acetate, Advanced Drug Delivery Reviews, 28, 1997, 43-70
79. Takada Shigeyuki, Kurokawa Tomofumi, Miyazaki Keiko, Iwasa Susumu, Ogawa Yasuaki, Sustained release of a water-soluble GP IIb/IIIa antagonist from copoly (DL-lactic/glycolic) acid microspheres, International Journal of Pharmaceutics, 146, 1997, 147-157
80. Chena L, Apteb Ron, Cohen Smadar, Characterization of PLGA microspheres for the controlled delivery of IL-1a for tumor immunotherapy, J Control Release, 43, 1997, 261-272
81. Genta I, Perugini P, Pavanetto F, Maculotti K, Modena T, Casado B, Lupib A, Iadarolab P, Conti B, Enzyme loaded biodegradable microspheres in vitro vi ex vivo evaluation, J Control Release, 77, 2001, 287-295
82. Diez Sonsoles, Ilarduya Tros de Conchita, Versatility of biodegradable poly(D,L-lactic-co-glycolic acid) microspheres for plasmid DNA delivery, Euro J of Pharm and Biopharm, 63, 2006, 188-197
83. Gabizon A, Barenholz Y, Liposomal anthracyclines from basics to clinical approval of PEGylated liposomal doxorubicin, In: Liposomes: rational design, Janoff AS, Marcel Dekker, New York, 1999; 343-362.
84. Sankaram MB, Commercial sustained-release injectable formulations by encapsulation, In: Sustained-release injectable products, Senior J. and Radomsky M, Interpharm Press, Denver, CO, 2000, 25-39
85. Chiron Corporation, Physicians' Desk Reference, 54, 2000, 935-938
86. Langston Melissa, Ramprasad MP, Kararli TT, Galluppi GR, Katre NV, Modulation of the sustained delivery of myelopoietin (Leridistim) encapsulated in multivesicular liposomes (Depo Foam), J Control Release, 89, 2003, 87-99
87. Tian W, Schulze S, Brandl M, Winter G, Vesicular phospholipid gel-based depot formulations for pharmaceutical proteins: Development and in vitro evaluation, J Control Release, 2009; (article in press)
88. Holger Grohganz, Ingunn Tho, Martin Brandl, Development and in vitro evaluation of a liposome based implant formulation for the decapeptide Cetrorelix, Euro J of Pharm and Biopharm, 59, 2005, 439-448
89. Davis JM, Matalon L, Watanable MD, Blake L, Depot antipsychotic drugs, place in therapy, Drugs, 47, 1994, 741-773
90. Hallas-Moller K, Peterson K, Schlichikrull J, Crystalline and amorphous insulin-zinc compounds with prolonged action, Science, 116, 1952, 394-398
91. Yoshiya Yamahiza, Keiji Fujioka, Sustained-release IFN preparation for parentaral administration, European Patent EP, 1st July 1993, 0138216

92. Kipp JE, The role of solid nanoparticle technology in the parenteral delivery of poorly water-soluble drugs, International Journal of Pharmaceutics, 284, 2004, 109-122
93. Muhlen A, Mehnert W, Drug release and release mechanism of prednisolone loaded solid lipid nanoparticles, PharmaZie , 53, 1998, 552
94. Vgazio E, Cavalli R, Gsaco MR, Incorporation of Cyclosporin A in solid lipid nanoparticles, International Journal of Pharmaceutics, 241, 2002, 341-344
95. Yang SC, Lu LF, Cai Y, Zhu JB, Liang BW, Yang CZ, Body distribution in mice of intravenously injected camptothecin solid lipid nanoparticles and targeting effect on brain, J Control Release, 59, 1999, 299-307
96. Schultz K, Mollgaard B, Frokjaer S, Larsen C, Rotating dialysis cell as in vitro release method for oily parenteral depot solutions, International Journal of Pharmaceutics, 157, 1997, 149-159
97. Soderberg L, Dyhre H, Roth B, Bjorkman S, The "inverted cup"— A novel in vitro release technique for drugs in lipid formulations, J Control Release, 113, 2006, 80-88

****