ISSN: 0975-766X
CODEN: IJPTFI
Review Article

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www.ijptonline.com

NANO FABRICATED DRUG DELIVERY DEVISES

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Received on 29-03-2012 *Accepted on 12-04-2012*

Abstract

This is the second part of a review on Nanotechnology Fabricated Drug Delivery Devises. In the earlier paper (Part 1), deals with the characterization, creation, and utilization of materials. In this paper (Part 2), nanoemulsions as emerging trends for drug delivery. Nano suspensions have emerged as a promising strategy for the efficient delivery of hydrophobic drugs because of their versatile features and unique advantages. Techniques such as media milling and high-pressure homogenization have been used commercially for producing nanosuspensions. Recently, the engineering of nanosuspensions employing emulsions and micro emulsions as templates has been addressed in the literature.

Key words: Nano emulsion, drug delivery, nanotechnology, targeted delivery.

Introduction

Nanotechnology is manipulation of characteristics of materials such as drugs for fabrication of nanoemulsions is able to provide superior drug delivery systems for better management and treatment of diseases. The formulation of poorly water-soluble drugs has always been a challenging problem faced by pharmaceutical scientists and it is expected to increase because approximately 60% or more of the new chemical entities being generated through drug discovery programmes are poorly water-soluble[1]. Nano drugemlusion delivery system can lower systemic drug toxicity, improving treatment absorption rates, and providing protection for drugs against biochemical degradation. Also to fabricate nanoscale core shell particles, by which poor water soluble drugs can be effectively dispersed with rather good stability during storage[2].

The problem is even more intense for drugs such as Abacavir and Efavirenz as they are poorly soluble in both aqueous and organic media. Such drugs often have an erratic absorption profile and highly variable bio-availability because their performance is dissolution-rate limited and is affected by the fed/fasted state of the patient. Efforts in the 1970s and 1980s allowed rational design bearing in mind the proposed use and pathophysiology of the disease target[3]. Study of various methods used to carry the nanoemulsions to the specific targets such as micelles was done by Nishiyama and Kaooka[4]. Similarly Heparin-deoxycholic acid chemical conjugate was used as anticancer drug carrier at nano ranges (180-210 nm) by Kyeongsoon Park et al[5]. Martha Kalkanidis[6] used nanoemulsions based inert (40 nm) solid carrier beads to which antigen was covalently coupled to deliver vaccines. Jun Watanable et al[7] studied about entrapment of compounds into bio compatible nano sized particles and their releasing properties. Although reasonable success has been achieved in formulating water-insoluble drugs using liposomes[8], emulsions[9], microemulsions[10], solid dispersion technology[11]. and inclusion complexes employing cyclodextrins[12] , there is no universal approach applicable to all nanodrug delivery devices. Hence, there is a growing need for a unique strategy that can tackle the formulation-related problems associated with the delivery of hydrophobic drugs in order to improve their clinical efficacy and optimize their therapy with respect to pharmacoeconomics.

Nanosuspensions have revealed their potential to tackle the problems associated with the delivery of poorly water-soluble and poorly water and lipid-soluble drugs, and are unique because of their simplicity and the advantages they confer over other strategies.

Results and Discussions

Different carrier systems are currently being evaluated including, micro emulsions, dendrimers, sol-gel coatings, or other porous inorganic materials. Nano materials and devices can be fabricated using either “bottom-up” or “topdown” fabrication approaches. Controlled drug-delivery strategies have made a dramatic impact in medicine. In general, controlled release micro emulsions systems deliver drugs in optimum dosage for long periods, thus increasing the efficacy of the drug, maximizing patient compliance and enhancing the ability to use highly toxic, poorly soluble or relatively unstable drug. These vehicles can be engineered to recognize biophysical characteristics that are unique to

the target cells and therefore minimizing drug loss and toxicity associated with delivery to non-desired tissues. In general, target micro emulsions comprise the drug, the encapsulating material and the surface coating. The encapsulating material could be made from biodegradable micro emulsions, dendrimes orliposomes. Controlled release of encapsulation material is achieved by the release of encapsulated drugs through surface or bulk erosion, diffusion, or triggered by the external environment, such as change in pH, light, temperature or by the presence of analytes such as glucose14. Controlled release of biodegradable micro emulsions can be syntheized from wide variety of polymers including poly lactic acid, poly glycolic acid, poly lactico-glycolic acid, polyanhydride. Since poly glycolic acid is more susceptible to hydrolysis than poly lactic acid, by changing the ratio of these two components, co-polymers can be synthesized with various degradation rates. We have to look into the areas of improving the properties of the materials such as bio compatibility, degradation rate and control over the size and homogeneity of the resulting micro emulsions.

Method of Fabrication

The method employed for the fabrication of micro emulsions depends on the type and the desired properties of the nanostructure to be produced. Methods of preparing of polymeric nanoparticles have been reviewed[13 & 14] and they include ionic gelation, coacervation, solvent evaporation, spontaneous lsification/ solvent diffusion, salting out/emulsification-diffusion, supercritical fluid technology and polymerization. Depending on the materials utilized, such as phospholipids and glycolipids, the desired liposome structure can be prepared by sonication, electroformation, extrusion from diluted lamellar dispersions, high-shear homogenization, reverse-phase evaporation, gel exclusion chromatography, freeze- lyophilization, calcium-induced fusion, detergent dialysis and racentrifugation62-65.Syntheses of dendrimers include the use of Tomalia's divergent growth approach, convergent growth approach, and orthogonal coupling strategy[15&16] while solid lipid nanoparticles are prepared by high shear homogenization, ultrasound dispersion technique, high pressure homogenization, solvent emulsification/evaporation, microemulsion and solvent diffusion [17 &18] Methods of preparing polymeric micelles include dialysis, solution-casting, direct dissolution, while nanocapsules are prepared by microemulsion,

miniemulsion polymerization and interfacial polymerization. Nanoemulsions are prepared by spontaneous emulsification, high pressure and ultrasonic homogenization. Ceramic nanoparticles are produced by template.

Controllability of Nano-Drug

Nano-drug interactions with nano-carrier and made to be the controlled-release formulations with appropriate methods. When drug-carrier complex enter into the body, the drug is slowly released out of nanoparticles at the constant speed automatically in the scheduled time through the leaching, infiltration and proliferation or dissolution and act on the specific organ, tissue and cell. In addition, the nano-carriers prevent drug be degraded by various enzyme, extends the effective time of drugs. At the same time this controlled-release nano-drug can reduce the peak phenomenon of blood concentration, reduce side effects and improve efficacy. Mainly through diffusion control, chemical control, solvent control and other methods to achieve the purpose of controlled release of drug. Generally speaking, a controlled-release preparation has two or more controlled-release mechanisms.

Diffusion-Controlled Release Drugs or other biologically active substances are combined with carriers; the drug is released in a certain time and at a certain rate to the environment through diffusion. Diffusion controlled is the most common mechanism in the controlled release of drug delivery system, especially the nondegradable polymers carriers; the drug is mainly through this way released. In a biodegradable polymer carriers, where material degradation rate is slower than the diffusion of drug, diffusion of the drug still play a leading role in the release. There are many factors impact the diffusion controlled release, such as geometric designs of system, condition and quality of ambient medium, the character and structure of the host materials, the solubility and loading amount of the drug [19].

Chemical-Controlled Release Through hydrolysis, zymohydrolysis and other chemical reactions, chemical controlled release system control the rate of drug release. According to the role of drug and substrate, mechanism of release, Chemical controlled system can be divided into degradable system and side-chain system. Degradable system: the biological activity drugs is embedded or dispersed in biodegradable polymer, but there is no chemical bonding effects between drug and polymer, the rate of drug release is controlled by the rate of polymer degradation and

erosion. The material of drug carrier is mainly include of biodegradable poly vinegar (such as poly lactic acid, poly caprolactone with vinegar), poly polysaccharide (such as chitosan, gelatin), and so on. These materials is non-toxic, and the ultimate metabolites can be discharged in vitro or absorbed by organism, through regulating the rate of polymer degradation or dissolution to controll the release of drug on a specific location within regular hour. In these systems, the rate of polymer degradation or dissolution mainly influence the rate of drug's release, but the speed of degradation or dissolution also has an important relationship with the quality of the polymer (such as polymer molecular weight, crystallinity, the hydrophilic property and hydrophobicity,etc.), many researchers controlled and regulated the rate of degradation or dissolution material with chemical or physical methods such as reshaping, modification, blending to the polymer, further regulate the speed of drug release. But the nature of drug is also an important factor of the drug's release[20] . The side-chain system of drug carrier may be degradable type or nondegradable type. Through the chemical bond that can be hydrolyzed or enzymolied, drugs in the side-chain system can be connected to the primary chain or side chain (side chain can be used to change the drug's release rate) of polymer. The release of drug is controlled through hydrolysis or enzymolysis. Qing[21] used bovine serum albumin (BSA) as the model drug, at first, the nanoparticles containing proteins were obtained by absorbing BSA from the solution onto the surface of nano scale SiO2, then, PLGA micro sphere loading the solid nanoparticles were fabricated with the solid-in-oil-in-water emulsion method. Study found with the increasing of the mass fraction of BSA in the product of adsorption, the rate of solvent controlled release of BSA is faster. The main mechanism of drug release is the diffusion of drugs and the degradation of the polymer. In the release process, the BSA that was on the surface of micro spheres was first diffused and formed pores. It was conducive to the diffusion of the BSA in the inner layer. Water also could go into the microspheres and resulted in the degradation of microspheres. Microspheres that loaded more drugs diffused more BSA in the early period and also the pores that formed were more and larger, the degradation of the microspheres is faster in the late period, so release of BSA was faster. Yang[22] prepared microspheres that containing antiphthisic drug Rifampin was prepared from poly lactic glycolic acid (PLGA) as carrier by emulsion and solvent evaporation method. In vitro experiment of release, investigated the performance of PLGA

microspheres that was as a carrier of drug delivery. The release time of rifampicin in the PLGA microspheres was more than 30 days, and there was no obvious phenomenon of sudden release. But the release of the mass fraction of rifampicin without microspheroidization was up to 96% in 10 minutes. At the same time, they found PLGA molecular weight and the LLA / GA mass ratio had significant impact on the time of the release[23 & 24]. Because the rate of degradation of low molecular weight PLGA was significantly higher than that of high molecular weight and in the PLGA copolymer, with the GA mass increasing, hydrophilicity of PLGA enhanced, the degradation significantly speed up. While the rate of the drug's release was mainly controlled by the degradable rate, so with the reducing of PLGA molecular weight and LLA/GA mass ratio, the release of rifampicin speed up. The drug release was simultaneously controlled by drug-diffusion and degradation of carrier material, but in this system, degradation played a decisive role in the mechanism of control. Observed the surface morphology of the degradation rifampicin-PLGA microspheres, they found the surface and inside of microspheres appeared large holes, spherical shape almost disappeared, the red faded and turned to white. These result showed that in early period the drug's release was out of carrier materials only through the drug's diffusion and dissolution, with the drug release time prolonging, the mass fraction of the unit of drugs in microspheres reduced, lead to the release rate of drug that diffusion and degradation decrease, however, with the carrier material degrading and the rate of degradation speeding up, the primarily release of drug was degradation of materials, and made up the rate of diffusion and dissolution release reducing, eventually led to the drug in microsphere carrier was release in a constant velocity. Solvent-control include of infiltration and swelling mechanisms. 1) The release of solvent infiltration controlled. It accord to the penetration principle of semi-permeable membrane. Soluble drug is wrapped in polymer, when it is added in environmental media, the external solvent go into polymer matrix by infiltration and forms saturated solution and then under the action of osmotic pressure between saturated solution and environmental media to release drugs outside. 2) Matrix sol-vent control, the more common mechanism is swelling. The controlled-release mechanism is using solvent penetration to makes polymer swelling and achieve the purpose of release. At the beginning, solvent penetrate into polymer matrix and cause to swelling, the polymer glass transition temperature to the environment, and chemical chain get slack, so that drugs can be

released. Solvation process often contains the spread process of drugs at the same time. The release of drug is affected by many factors and conditions, including nature of polymer and drugs, temperature of environment, pH value of medium and so on. The change of one factor or condition will affect the controlled mechanism of drug's release. For example, changing the hydrophilicity and hydrophobicity of de-gradable polymer not only affect the rate of degradation of materials, but also affect swelling and permeability of the material, further affect the release of drugs. Wang[25] prepared self assembled nanomicelle of N-acylcholesteryl succinate-O-carboxymethyl chitosan, paclitaxel was used as a model drug. In vitro experiment, they found that release rate of paclitaxel in nano-CCMC micelle was closely related with the pH value. For ex-ample the rate of release is low when the pH value of PBS was equal to 7.2, but when pH value was equal to 4.0 or 9.0, the release rate increased. Because CCMC molecules were a new type of polymer ampholyte and containing much free-NH2 and-COOH, the isoelectric point was about 7.14 by the turbidity method detection[26]. In meta-acid or alkaline solution, the free-NH_2 or-COOH in CCMC molecules was ionized to -NH^{+3} or-COO^-. Under the action of charges with the same electrical sign repel each other; the gel network structure of self-assembled nano-micelles (CCMC) fully absorbed water, increased permeability of paclitaxel, accelerated the release rate.

Microemulsions as templates

Microemulsions are thermodynamically stable and isotropically clear dispersions of two immiscible liquids, such as oil and water, stabilized by an interfacial film of surfactant and co-surfactant[27]. Their advantages, such as high drug solubilization, long shelf-life and ease of manufacture, make them an ideal drug delivery vehicle. There are several research papers available that describe the use of microemulsions as drug delivery vehicles[28-32]. Recently, the use of microemulsions as templates for the production of solid lipid nanoparticles[33] and polymeric nanoparticles[34] has been described. Taking advantage of the microemulsion structure, one can use microemulsions even for the production of nano suspensions[35]. Oil-in-water microemulsions are preferred for this purpose. The internal phase of these microemulsions could be either a partially miscible liquid or a suitable organic solvent, as described earlier.

The drug can be either loaded in the internal phase or pre-formed microemulsions can be saturated with the drug by intimate mixing. The suitable dilution of the microemulsion yields the drug nanosuspension by the mechanism described earlier. The influence of the amount and ratio of surfactant to co-surfactant on the uptake of internal phase and on the globule size of the microemulsion should be investigated and optimized in order to achieve the desired drug loading. The nanosuspension thus formed has to be made free of the internal phase and surfactants by means of diultrafiltration in order to make it suitable for administration. However, if all the ingredients that are used for the production of the nanosuspension are present in a concentration acceptable for the desired route of administration, then simple centrifugation or ultracentrifugation is sufficient to separate the nanosuspension. The advantages and disadvantages are the same as for emulsion templates. The only added advantage is the need for less energy input for the production of nanosuspensions by virtue of microemulsions.The production of drug nanosuspensions using micro-emulsions as templates has been successfully applied to the poorly water-soluble and poorly bioavailability anti-fungal drug griseofulvin, where a significant improvement in the dissolution rate of the drug (three-fold increase) as compared to the commercial product was observed. It was found that the nature of the co-surfactant affected the dissolution rate of the drug nanosuspension, as anticipated[35]. However, this technique is still in its infancy and needs more thorough investigation.

Formulation considerations

Stabilizer

Stabilizer plays an important role in the formulation of nanosuspensions. In the absence of an appropriate stabilizer, the high surface energy of nano-sized particles can induce agglomeration or aggregation of the drug crystals. The main functions of a stabilizer are to wet the drug particles thoroughly, and to prevent Ostwald's ripening[36 &37] and agglomeration of nanosuspensions in order to yield a physically stable formulation by providing steric or ionic barriers. The type and amount of stabilizer has a pronounced effect on the physical stability and in-vivo behavior of nanosuspensions. In some cases, a mixture of stabilizers is required to obtain a

stable nanosuspension. The drug-to-stabilizer ratio in the formulation may vary from 1:20 to 20:1 and should be investigated for a specific case. Stabilizers that have been explored so far include cellulosics, poloxamers, polysorbates, lecithins and povidones[38]. Lecithin is the stabilizer of choice if one intends to develop a parenterally acceptable and autoclavable nanosuspension. Organic solvents Organic solvents may be required in the formulation of nanosuspensions if they are to be prepared using an emulsion or microemulsion as a template. As these techniques are still in their infancy, elaborate information on formulation considerations is not available. The accept- ability of the organic solvents in the pharmaceutical arena, their toxicity potential and the ease of their removal from the formulation need to be considered when formulating nanosuspensions using emulsions or microemulsions as templates. The pharmaceutically acceptable and less hazardous water-miscible solvents, such as ethanol and isopropanol, and partially water-miscible solvents, such as ethyl acetate, ethyl formate, butyl lactate, triacetin, propylene carbonate and benzyl alcohol, are preferred in the formulation over the conventional hazardous solvents, such as dichloromethane. Additionally, partially water-miscible organic solvents can be used as the internal phase of the microemulsion when the nanosuspensions are to be produced using a icroemulsion as a template.

Co-surfactants

The choice of co-surfactant is critical when using micro emulsions to formulate nanosuspensions. Since cosurfactants can greatly influence phase behavior, the effect of cosurfactant on uptake of the internal phase for selected microemulsion composition and on drug loading should be investigated. Although the literature describes the use of bile salts and dipotassium glycerrhizinate as cosurfactants, various solubilizers, such as Transcutol, glycofurol, ethanol and isopropanol, can be safely used as cosurfactants in the formulation of microemulsions. Other additives Nanosuspensions may contain additives such as buffers, salts, polyols, osmogent and cryoprotectant, depending on either the route of administration or the properties of the drug moiety.

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Conclusion

Nanosuspensions appear to be a unique and yet commercially viable approach to combating problems such as poor bioavailability that are associated with the delivery of hydrophobic drugs, including those that are poorly soluble in aqueous as well as organic media. Production techniques such as media milling and high-pressure homogenization have been successfully employed for large-scale production of nanosuspensions. The advances in production methodologies using emulsions or microemulsions as templates have provided still simpler approaches for production but with limitations. Further investigation in this regard is still essential. Attractive features, such as increased dissolution velocity, increased saturation solubility, improved bioadhesivity, versatility in surface modification and ease of post-production processing, have widened the applications of nanosuspensions for various outes. The applications of nanosuspensions in parenteral and oral routes have been very well investigated and applications in pulmonary and ocular delivery have been realized. However, their applications in buccal, nasal and topical delivery are still awaiting exploration. The development of stealth nanosuspensions laced with functionalized surface coatings capable of eliciting passive or active targeting as per the requirement can be regarded as the future step in the nanosuspension research.

References

1. Lipinski, C. Poor aqueous solubility -an industry wide problem in drug discovery. Am. Pharm. Rev., 2002, 5 ,82-85
2. Yih TC, Al-Fandi M. Engineered nanoparticles as precise drug delivery systems. J. Cellular Biochemistry, 2006, 97, 1184-1190.
3. Drug delivery systems in Cancer Therapy by Dennis M. Brown, 2004, Humana Press.
4. Bingbing Jiang, Ling Hu, Changyou Gaoand Jiacong Shen, Ibuprofen-loaded nanoparticles prepared by a co-precipitation method and their release properties: International Journal of Pharmaceutics, 2005, 304, 1-2, 220-230.

5. Anya M. Hillery, Andrew W. Lloyd, James Swarbrick., Drug delivery and targeting, 2001, Publisher Taylor and Francis, New York.
6. Martha Kalkanidis, Geoffery A. Pietersz, Sue D. Xiang, Patricia L. Mottram, Blessing Crimeen-Irwin, Katie Ardipradja and Magdalena Plebanski., Methods for nano-particle based vaccine formulation and evaluation of their immunogenicity: Methods, 2006, Volume 40, Issue 1, pp 20-29.
7. Jun Watanabe, Satoshi Iwamoto Entrapment of some componds into biocompatible nano-sized particles and their releasing properties., Colloids and Surfaces B: Biointerfaces ., 2005, 42, 141–146.
8. Schwendener, R. A., Schott, H., Lipophilic 1-beta-D-arabi- nofuranosyl cytosine derivatives in liposomal formulations for oral and parenteral ntileukemic therapy in the murine L1210 leukemia model. J. Cancer Res. Clin. Oncol. .1996, 122, 723-726.
9. Floyd, A. G. Top ten considerations in the development of parenteral emulsions. Pharm. Sci. Technol., . 1999, 4,134-143.
10. Lawrence, M. J., Rees, G. D. (2000) Microemulsion-based media as novel drug delivery systems. Adv. Drug Del. Rev. 45: 89-121
11. Serajuddin, A. T. M. Solid dispersion of poorly water- soluble drugs: early promises, subsequent problems, and recent breakthroughs. J. Pharm. Sci., 1999, 88: 1058-1066
12. Stella, V. J., Rajewski, R. A. Cyclodextrins: their future in drug formulation and delivery. Pharm. Res., 1997, 14: 556-567.
13. Soppimath KS, Aminabhavi TM, Kulkarni AR Rudzinski WE. Biodegradable polymeric nanoparticles as drug delivery devices. J. Controlled Release, 2001, 70. 1-20.
14. Lim HJ, Cho EC, Shim J, Kim D-H, An EJ, Kim J. Polymer-associated liposomes as a novel delivery system for cyclodextrin-bound drugs. J. Colloid and Interface Science, 2008, 320, 460-468.
15. Liu M, Fréchet JMJ Designing dendrimers for drug delivery.Pharmaceutical Sciences and Technology Today, 1999; 10, 393-401.

16. Sadler K, Tam JP. Peptide dendrimers: applications biotechnology, 2002, 90,195-229.
17. Lukyanov AN, Torchilin VP. Micelles from lipid derivatives of water-soluble polymers as delivery systems for poorly soluble drugs. Advanced Drug Delivery Reviews, 2004, 56, 1273-1289.
18. Gaucher G, Dufresne M-H, Sant VP, Kang N, Maysinger D, Leroux J-C. Block copolymer micelles: preparation, characterization and application in drug delivery. J. Controlled Release, 2005, 109, 169-188.
19. Masaro, L. and Zhu, X.X. Physical models of diffusion for polymer solutions, gels and solids. Prog.Polymer Sci., 1999, 24, 731-775.
20. Frank, A., Rath, S.K. and Venkatraman, S.S. Controlled release from ioerodible polylners : effect of drugtype and polymer composition. J. Control. Release, 2005,102, 333-344.
21. Du, Q., Hu, J.L., Han, Y.D., Chen, X.S. and Jing, X.B.,Preparation of controlled-release microspheres loading protein through solid-in-oil-water emulsion method. Chem. J. Chin. U., 2008, 29, l262-1266.
22. Yang, Y.N., Lou, L., Liang, Q.Z., Chen, X.S. and Jing, X.B. Preparation and in vitro release of rifampin microspheres encapsulated in biodegradable polyesters. Chem. J. Chin. U., 2004, 25, 162-165.
23. Jain, R.A. The manufacturing techniques of vari- ous drug loaded iodegradable poly(lactide-co-glycolide) (PLGA) devices. Biomaterials, 2000, 21, 2475-2490.
24. Wang, Y.M., Sato, H. and Horikoshi, I. In vitro and in vivo evaluation of taxol release from poly(lactic-co-glycolic acid) microspheres containing sopropyl myri- state and degradation of the micro-spheres. J. Control. Release, 1997,49, 157-166.
25. Wang, Y.S., Wang, Y.M., Li, R.S., Zhao, J. and Zhang, Q.Q. Chitosan-based self-assembled nanomicelles as a novel carrier for paclitaxel. Chem. J. Chin. U., 2008, 29, 1065- 1069.
26. Li, J.H., Yu, Y.W., Yu, Y.L. and Shen, W. Studies on preparation of carboxymethylchitosan. Chin. J. Bio- chem. Pharmaceutics, 2000,21, 175-177.
27. Eccleston, G. M. Microemulsions. In: Swarbrick, S., Boylan, J. C. (eds) Encyclopedia of pharmaceutical tech- nology. 1992 ,Vol. 9, Marcel Dekker, New York, pp 375-421

28. Constantinides, P. P., Scarlart, J. P., Smith, P. L.,Formulation and intestinal absorption enhancement evalua-tion of water in oil microemulsions incorporating medium-chain triglycerides. Pharm. Res. 1994, 11: 1385-1390

29. Constantinides, P. P., Lancaster, C., Marcello, J., Chiossone, D., Orner, D., Hidalgo, I., Smith, P. L., Sarkahian, A. B., Yiv, S. H.,Owen, A. J.,Enhanced intestinal absorption of a RGD peptide from w/o microemulsion of different composition and particle size. J. Control. Release.., 1995, 34: 109-116.

30. Kim, C. K., Gao Gao, Z., Choia, H. G., Shin, H. J., Park, K. M., Lim, S. J., Hwang, K. J. Physicochemical characteriza- tion and evaluation of a microemulsion system for oral deliv- ery of cyclosporin A. Int. J. Pharm. 1998,161: 75-86.

31. Park, K., Kim, C. K. Preparation and evaluation of flurbiprofen-loaded microemulsion for parenteral delivery.Int. J. Pharm. 1999, 181: 173-179.

32. Kawakami, K., Yoshikawa, T. Microemulsion formulation for enhanced absorption of poorly soluble drugs Prescription design. J. Control. Release.,2002 81: 65-74.

33. Gasco, M. R. Solid lipid nanospheres form warm microemulsions.Pharm. Technol. Eur. 1997, 9: 32-42.

34. Rades, T., Davies N., Watnasirichaikul, S., Tucker, I. Effects of formulation variables on characteristics of poly (ethylcyanoacrylates) nanocapsules prepared from w/o micro- emulsions. Int. J. Pharm. 2002, 235: 237-246.

35. Trotta, M., Gallarate, M., Carlotti, M. E., Morel, S. Preparation of griseofulvin nanoparticles from water-dilutable microemulsions. Int. J. Pharm. 2003,254: 235-242.

36. Rawlins, E. A. Solutions. In: Rawlins, E. A. (ed.) Bentley's textbook of pharmaceutics,1982,8th edn, Bailliere Tindall, London, p 6.

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