Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Short Communication

Influence of process variables on particle size of solid lipid nanoparticles

JS MULLA[1], IM KHAZI[2]

[1]Department of Pharmaceutics, K.L.E.University's College of Pharmacy, Vidyanagar, Hubli-580 031, INDIA

[2] Post Graduate Department of Studies in Chemistry, Karnatak University, Dharwad-580001, INDIA

ARTICLE DETAILS

Article history:
Received on 27 August 2009
Accepted on 6 September 2009

Keywords:
Solid lipid nanoparticles
Microemulsion
Particle size
Glyceryl monostearate
Stearic acid
Trilurin

ABSTRACT

Solid lipid nanoparticles (SLNs) were prepared *via* microemulsion method. SLNs formulation consists of lipid (glyceryl monostearate (GMS), stearic acid (SA) and trilurin (TLN)), stabilizers (soy lecithin and tween 80) and water. Influence of type of lipid, concentration of lipid, individual and in combination of stabilizers and homogenizer speed on particle size were studied intensively. Particle sizes were determined by laser scattering using a Malvern Mastersizer 2000 particle size analyzer. A higher concentration of lipid was found to rapidly increase the size of nanoparticles. In contrast, an increase in stirring rate and concentration of stabilizer agent were found to reduce moderately the size of the nanoparticles.

Solid lipid nanoparticles (SLNs), introduced in 1991, as alternative carrier system to traditional colloidal carriers, such as emulsions, liposomes and polymeric microparticles and nanoparticles [1-3]. It has been claimed that SLNs combine the advantages and avoid disadvantages of other colloidal carriers. Proposed advantages include, possibility of controlled drug release and drug targeting, increased drug stability, high drug payload, incorporation of lipophilic and hydrophilic drugs feasible, no biotoxicity of the carrier, avoidance of organic solvents, no problems with respect to large scale production and sterilization [4]. SLNs formulations for various application routs (parenteral, oral, dermal, ocular, pulmonary, and rectal) have been developed and thoroughly characterized *in vitro* and *in vivo* [5].

Many of pharmaceutical researchers have prepared SLNs as an alternative colloidal therapeutic systems, utilizing different approaches like modified high shear homogenization and ultrasound techniques [1], emulsification-diffusion method [6], solvent injection method [7], solvent diffusion method [8], microemulsion method [9] and hot homogenization technique [10].

The current work endeavors to design optimal SLNs *via* microemulsion method. Different process variables like type of lipid and their concentration, individual and combination of emulsifier/s and their concentration and homogenizers speed on size of particles have studied.

Glycery monostearte and stearic acid are purchased from Loba chemie Pvt Ltd (Mumbai, India), trilaurin and soy lecithin are from Himedia Laboratories Pvt. Ltd. (Mumbai, India), tween 80 by Merck Ltd (Mumbai, India) and Millipore water by Millipore (India) Pvt. Ltd (Bangalore, India). Other chemicals are of analytical grades.

Triluarin based SLNs containing Tmx citrate were prepared according to Gasco and group; developed and optimized a suitable method for the preparation of SLNs *via* microemulsion [11,12]. Briefly, warm microemusion is prepared by stirring, containing molten state of trilaurin, soy lecithin and tween 80. To the molten lipid solution, Tmx citrate was dispersed. The warm microemlsion is then dispersed carefully drop wise using high speed homogenizer (T25 basic Ultra Turrax, IKA, USA) in excess cold water (1:50, 2-3 ^{0}C) using an specially developed thermostated syringe. The excess water is removed by lyophilization in order to increase the particle concentration.

The SLNs were prepared under different processing parameters to study the effect of a number of variables on their particle size. Processing parameters varied as follows; the type lipid used, concentration of lipid varied from 2.5 to 10.0%w/w, soy lecithin surfactant individual and in combination with tween 80 (1-5%w/w) and homogenizers speed (6,500-24,500 rpm).

The size analysis of nanoparticles was performed by laser scattering using a Malvern Mastersizer 2000 particle size analyzer (Malvern Instruments Ltd, Worcestershire, UK). The aqueous nanoparticulate dispersion was added to the sample dispersion unit containing a stirrer and then stirred to minimize the interparticle interactions, and the laser obscuration range was maintained between 10% and 20%. The analysis was performed 3 times, and the average values were taken.

Author for Correspondence:
Email: jameelahmed5@rediffmail.com

It has been found that the average particle size of SLN dispersions is increasing with higher melting lipids (Fig. 1). These results are in agrrement to Siekmann [13] and Ahlin [14] research groups.

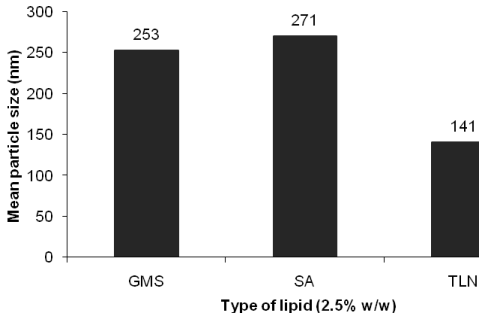

Figure 1: Influence of lipid on particle size
Composition of SLNs: lipid 2.5 % (w/w), soy lecithin 5 % (w/w), speed 6,500 rpm

Increasing the lipid content over 5–10% in most cases results in larger particles and broader particle size distributions (Fig. 2) which agreement with Siekmann *et al* [15].

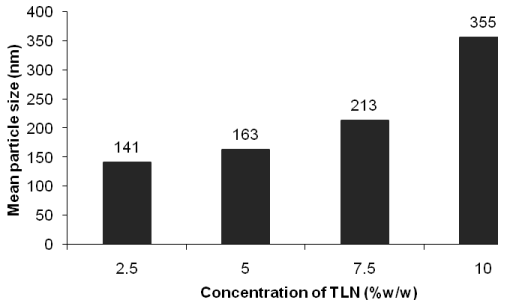

Figure 2: Influence of lipid concentration on particle size
Composition of SLNs: Soy lecithin 5 % (w/w), speed 6,500 rpm

The choice of the emulsifiers and their concentration is of great impact on the quality of the SLN dispersion [16]. Investigating the influence of the emulsifier concentration on the particle size of GMS, authors obtained best results with 5% soy lecithin. Batches produced with lower concentrations of the emulsifier contained higher amounts of bigger particles. Increasing the concentration of soy lecithin to 5%w resulted in XXnm particles with mono dispersion (Fig. 3) which are agreements with Siekmann group [15].

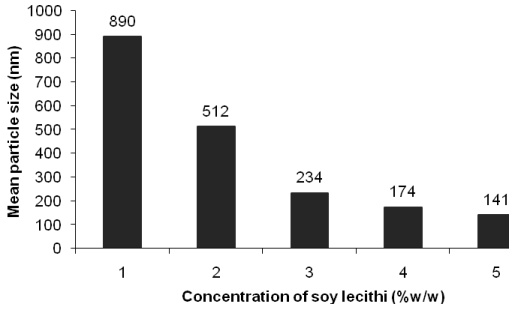

Figure 3: Influence of emulsifier concentration on particle size
Composition of SLNs: TLN 2.5 % (w/w), speed 6,500 rpm

Higher concentrations of emulsifier reduce the surface tension and facilitate the particle partition. The decrease in particle size is connected with a tremendous increase in surface area. The process of primary coverage of the new surface competes with the agglomeration of uncovered lipid surfaces. The primary dispersion contains excessive emulsifier molecules, which might be rapidly covering the new surfaces.

It has been found that SLN stabilized with surfactant mixtures (soy lecithin/tween 80) have lower particle sizes compared to formulations with only one surfactant (Fig. 4).

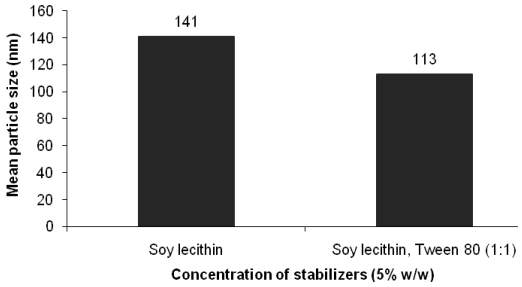

Figure 4: Influence of emulsifier (single, combination) on particle size
Composition of SLNs: TLN 2.5 % (w/w), speed 6,500 rpm

The influence of homogenizer speed on the mean particle size of nanoparticles was also studied. The final size of the nanoparticles in the process depends on the globule size throughout the emulsification process. GMS nanoparticles were prepared using soy lecithin as stabilizer at a constant concentration of 5.0 % (w/w). And homogenization time was fixed at 10 min. The results are shown in Table 5. As expected, a decrease of nanoparticle mean size correlated with an increase of homogenizer speed. But above 13,500 rpm, there was no significant reduction of particle size.

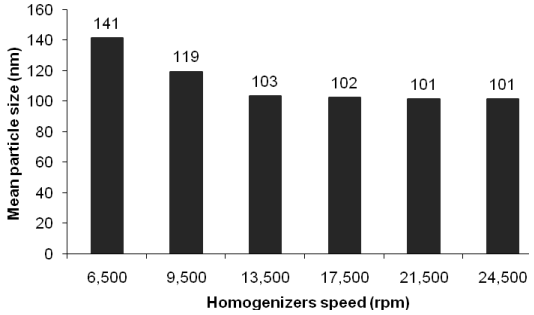

Figure 5: Influence of homogenizer speed on particle size
Composition of SLNs: TLN 2.5 % (w/w), soy lecithin (5% w/w)

SLNs were successfully prepared and optimized for particle size in nano range with monodispersity *via* microemulsion method. The nanoparticle size is influenced by the type and concentration of lipid, individual and in combination of surfactant and their concentration and stirring rate.

REFERENCES:

[1] Hou D, Xie C, Huang K, Zhu C. The production and characteristics of solid lipid nanoparticles (SLNs). Biomaterials. 2003 May;24(10):1781-5.

[2] Müller RH, Mäder K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery - a review of the state of the art. Eur J Pharm Biopharm. 2000 Jul;50(1):161-77.

[3] Müller RH, Radtke M, Wissing SA. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. Adv Drug Deliv Rev. 2002 Nov 1;54 Suppl 1:S131-55.

[4] Mehnert W, Mäder K. Solid lipid nanoparticles: production, characterization and applications. Adv Drug Deliv Rev. 2001 Apr 25;47(2-3):165-96.

[5] Wissing SA, Kayser O, Müller RH. Solid lipid nanoparticles for parenteral drug delivery. Adv Drug Deliv Rev. 2004 May 7;56(9):1257-72.

[6] Quintanar-Guerrero D, Tamayo-Esquivel D, Ganem-Quintanar A, Allémann E, Doelker E. Adaptation and optimization of the emulsification-diffusion technique to prepare lipidic nanospheres. Eur J Pharm Sci. 2005 Oct;26(2):211-8..

[7] Schubert MA, Müller-Goymann CC. Solvent injection as a new approach for manufacturing lipid nanoparticles--evaluation of the method and process parameters. Eur J Pharm Biopharm. 2003 Jan;55(1):125-31.

[8] Hu FQ, Jiang SP, Du YZ, Yuan H, Ye YQ, Zeng S. Preparation and characterization of stearic acid nanostructured lipid carriers by solvent diffusion method in an aqueous system. Colloids Surf B Biointerfaces. 2005 Nov 10;45(3-4):167-73. Epub 2005 Sep 27.

[9] Mei Z, Chen H, Weng T, Yang Y, Yang X. Solid lipid nanoparticle and microemulsion for topical delivery of triptolide. Eur J Pharm Biopharm. 2003 Sep;56(2):189-96.

[10] Venkateswarlu V, Manjunath K. Preparation, characterization and in vitro release kinetics of clozapine solid lipid nanoparticles. J Control Release. 2004 Mar 24;95(3):627-38.

[11] Gasco, M.R. Method for producing solid lipid microspheres having a narrow size distribution. *Uinited State Patent*, 1993, USS 188837.

[12] Marengo E, Cavalli R, Caputo O, Rodriguez L, Gasco MR. Scale-up of the preparation process of solid lipid nanospheres. Part I. Int J Pharm. 2000 Sep 15;205(1-2):3-13.

[13] B. Siekmann, K. Westesen, Submicron-sized parenteral carrier systems based on solid lipids, Pharm. Pharmacol. Lett. 1(1992) 123–126.

[14] P. Ahlin, J. Kristl, J. Smid-Kobar, Optimization of procedure parameters and physical stability of solid lipid nanoparticles in dispersions, Acta Pharm. 48 (1998) 257–267.)

[15] Siekmann B, Westesen K. Melt homogenized solid lipid nanoparticles stabilizd by the nonionic surfactant tyloxapol. I Preparation and particle size determination. Pharm Pharmacol Lett 3 (1994) 194-197

[16] Muller RH, Mehnert W, Lucks JS, Schwarz C, zur Muhlen A, Weyhers H, Freitas C, Ruhl D. Solid lipid nanoparticles (SLN) — An alternative colloidal carrier system for controlled drug delivery. Eur. J. Pharm. Biopharm. 41 (1995) 62–69.