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Nanostructured Lipid Carriers: The Perfectness of Imperfectness

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Short Communication

Nanostructured Lipid Carriers (NLC), developed at the turn of millennium [1] are lipid-based nanoparticles composed of binary mixture of solid lipid and liquid lipid [2]. To obtain the blends for the particles matrix, solid lipids (fats) are mixed with liquid lipids (oils), preferably in the ratio of 70:30 up to a ratio of 99.9:0.1 [3]. This colloidal delivery system is stabilized in an aqueous surfactant solution. They exhibit mean particle size in the submicron range, ranging from approximately 40 nm to 1000 nm [4,5]. The basis of an NLC formulation is to produce particles in which the oil is incorporated into the core of the solid lipid and the drug is solubilized in the oily core. The resulting matrix of lipid particles shows imperfections in the crystal lattice (low crystallinity index [6]), and leaves enough space to accommodate drug molecules (higher encapsulation efficiency [7]), thus leading to improved drug payload [8,9]. The amorphous solid structure results in enhanced physical stability [10]. Moreover, by modulating the amounts of oils added to the formulation, the matrix remains solid at room temperature and body temperature, and as such controlled drug release can be realized [11-14].

The usual methods for preparation of NLC include microemulsion method, solvent evaporation method, solvent diffusion method, emulsion-evaporation and low temperature-solidification technique, film dispersion-ultrasonic method and High Pressure Homogenization (HPH) [15]. Owing to its prominent merits of possibility of large scale production and opportunity to sterilize the preparation, HPH technique is by-and-large utilized. However, the demerits of hot homogeneous technique are that: a) the high heating temperature promotes degradation of heat-labile active compounds, b) instability of NLC induced by reduced emulsifying capacity of low cloud surfactants as a result of their exposure to high temperatures, and c) in the course of homogenization, the hydrophobic drug partially migrates to the aqueous phase resulting in low entrapment efficiency [16]; on the other hand at hot state, lipophilic compound solubility is increased in aqueous phase and thereupon the crystallization of it during cooling, since solid matrix of lipid does not allow return of the bioactive within itself [17].

NLC are promising nanocarriers for lipophilic molecules [18]. This may be due to their potential to increase the solubility of lipophilic drugs [19]. More importantly, since the internalization of lipid nanoparticles into cancerous cells is faster, it has greater potential in cancer therapy [20,21]. These solid lipid nanoparticles of the second generation, which are often used for delivery systems of lipophilic actives offer many benefits. They include: a) low toxicity [22], b) their particulate matrix is easily biodegraded resulting in non-toxic degradation products [23], c) the ability to incorporate lipophilic and hydrophilic drugs [24], d) its ability for drug targeting [25], e) the ability to immobilize the drug in the solid particle matrix yielding in protection of the incorporated drug from degradation [26], f) easy production process and feasibility for large scale production [27], g) provides an opportunity to avoid the use of organic solvents [28] and (h) cheap excipients e.g. lipids and stabilizers.

In recent years, NLC have been intensively investigated for administration of drugs by various pharmaceutical application routes, i.e. peroral [29], dermal [30], parenteral [31], pulmonary [32,33] and ocular [34,35]. However, frequently most studies have been focused on topical application of NLC perhaps for their unique positive features. These features are: a) film formation and subsequent adhesion of nanosized particles to the skin surface which provides an occlusion effect with a reduction in the transdermal water loss [36-38]. It has been postulated that the resulting hydration of the skin's outermost layer (stratum corneum) is attributed to a reduction in corneocyte packing and a widening of the inner-corneocyte gaps, hence facilitating drug penetration into the deeper skin strata [39-41], b) skin mucosa penetration is feasible due to nanosize [42,43] and c) enhanced

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skin bioavailability and chemical stability of the bioadditives as well as physical stability of the lipid nanoparticles as topical formulations [38].

Pulmonary drug delivery route represents a potential route for the local treatment of airway diseases and systemic administration of poorly water-soluble drugs that indicate low bioavailability *via* other administration routes i.e. oral and dermal routes [44-46]. Systemic disorders may be cancer, diabetes and immune deficiencies [5]. This route is most favourable due to benefits such as: a) non-invasive, b) lack of first-pass hepatic metabolism and the lungs are well perfused, with blood flow in the vicinity of 5 L/min which helps in drug absorption and distribution [47], c) large surface area (alveoli; ≈ 100 m^2) for absorption, d) relatively slow degradation due to low enzyme activity [48,49]. However, there are hurdles associated with this route. These include: a) inhalation of certain surfactants which may cause lung inflammation [44] and b) fibrosis may occur due to accumulation of surfactant in the lung tissue over prolonged dosing of NLC which may lead to interstitial lung damage and ultimate loss of its elasticity [50]. According to Jaques and Kim, application of NLC to the lower respiratory tract can be realized with particle size below 500 nm, leading to deposition in all lung regions due to an increased diffusional mobility [51].

In view of parenteral application, NLC ability to increase drug load efficiency and prolong exposure of tumour cells to antineoplastic agent, Enhanced Permeability and Retention (EPR) effect may lead to improved drug concentration in the cancerous tissues after systemic administrations (intravenous and intraperitoneal) and subsequently increased therapeutic effect of the antitumour drug [52-54].

In the context of ophthalmic application, traditional ocular drug delivery systems such as eye drops is very poor because eye is protected by a series of complex defensive mechanisms that make it difficult to achieve an effective drug concentration within target area of the eye [55]. The anatomical and physiological constraints include poor corneal permeability, nasolacrimal drainage effect, and short retention time in the precorneal area [56]. With its unique benefits, NLC colloidal carrier system may be better placed to offer improved drug availability either by facilitating transcorneal penetration or by increasing the precorneal residence time.

With these above elaborated facts, surely, one could unequivocally state that "the perfectness" of the NLC resonates with its "imperfectness" in its crystalline structure. With these superb unique features that NLC system harbours, there is no doubt that someday, they may be fully exploited. It is therefore tempting to say that NLC may be heading to be the most successful lipid delivery system after liposomes.

References

1. 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;54(Suppl 1);S131-55.
2. Müller RH, Radtke M, Wissing SA. Nanostructured lipid matrices for improved microencapsulation of drug. Int J Pharm. 2002;242(1-2):121-8.
3. Pardeike J, Weber S, Haber T, Wagner J, Zarfl HP, Plank H, et al. Development of an Itraconazole-loaded Nanostructured Lipid Carrier (NLC) formulation for pulmonary application. Int J Pharm. 2011;419(1-2):329-38.
4. Pardeike J, Weber S, Matsko N, Zimmer A. Formation of a physical stable delivery system by simply autoclaving Nanostructured Lipid Carriers (NLC). Int J Pharm. 2012;439(1-2):22-7.
5. Weber S, Zimmer A, Pardeike J. Solid Lipid Nanoparticles (SLN) and Nanostructured Lipid Carriers (NLC) for pulmonary application: A review of the state of the art. Eur J Pharm Biopharm. 2014;86:7-22.
6. Varshosaz J, Hassanzadeh F, Sadeghi H, Khadem M. Galactosylated nanostructured lipid carriers for delivery of 5-FU to hepatocellular carcinoma. J Liposome Res. 2012;22(3):224-36.
7. Teeranachaideekul V, Müller RH, Junyaprasert VB. Encapsulation of ascorbyl palmitate in Nanostructured Lipid Carriers (NLC)--Effects of formulation parameters on physicochemical stability. Int J Pharm. 2007;340(1-2):198-206.
8. Jenning V, Thünemann AF, Gohla SH. Characterisation of a novel solid lipid nanoparticle carrier system based on binary mixtures of liquid and solid lipids. Int J Pharm. 2000;199(2):167-77.
9. Souto EB, Wissing SA, Barbosa CM, Müller RH. Development of a controlled release formulation based on SLN and NLC for topical clotrimazole delivery. Int J Pharm. 2004;278(1):71-7.
10. Nnamani P, Hansen S, Windbergs M, Lehr CM. Development of artemether-loaded Nanostructured Lipid Carrier (NLC) formulation for topical application. Int J Pharm. 2014;477(1-2):208-17.
11. 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;50(1):161-77.
12. Doktorovova S, Souto EB, Silva AM. Nanotoxicology applied to solid lipid nanoparticles and nanostructured lipid carriers - A systematic review of *in vitro* data. Eur J Pharm Biopharm. 2014;87(1):1-18.
13. Joshi M, Patravale V. Nanostructured Lipid Carrier (NLC) based gel of celecoxib. Int J Pharm. 2008;346(1-2):124-32.
14. 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;45(3-4):167-73.
15. Luan J, Zhang D, Hao L, Qi L, Liu X, Guo H, et al. Preparation, characterization and pharmacokinetics of Amoitone B-loaded long circulating nanostructured lipid carriers. Colloids Surf B Biointerfaces. 2014;114:255-60.
16. Uner M. Preparation, characterization and physico-chemical properties of Solid Lipid Nanoparticles (SLN) and Nanostructured Lipid Carriers (NLC): Their benefits as colloidal drug carrier systems. Pharmazie. 2006;61(5):375-86.
17. Tamjidi F, Shahedi M, Varshosaz J, Nasirpour A. Nanostructured Lipid Carriers (NLC): A potential delivery system for bioactive food molecules. Innov Food Sci Emerg Technol. 2013;19:29-43.
18. Rane SS, Anderson BD. What determines drug solubility in lipid vehicles: Is it predictable? Adv Drug Deliv Rev. 2008;60(6):638-56.
19. Porter CJH, Pouton CW, Cuine JF, Charman WN. Enhancing intestinal drug solubilisation using lipid-based delivery systems. Adv Drug Deliv Rev. 2008;60(6):673-91.
20. How CW, Rasedee A, Manickam S, Rosli R. Tamoxifen-loaded nanostructured lipid carrier as a drug delivery system: Characterization, stability assessment and cytotoxicity. Colloids Surf B Biointerfaces. 2013;112:393-9.
21. Yuan H, Miao J, Du YZ, You J, Hu FQ, Zeng S. Cellular uptake of solid lipid nanoparticles and cytotoxicity of encapsulated paclitaxel in A549 cancer cells. Int J Pharm. 2008;348(1-2):137-45.
22. Weyhers H, Ehlers S, Hahn H, Souto EB, Müller RH. Solid Lipid Nanoparticles (SLN)-- Effects of lipid composition on *in vitro* degradation and *in vivo* toxicity. Pharmazie. 2006;61(6):539-44.

23. Olbrich C, Müller RH. Enzymatic degradation of SLN-effect of surfactant and surfactant mixtures. Int J Pharm. 1999;180(1);31-9.

24. Müller RH, Radtke M, Wissing SA. Nanostructured lipid matrices for improved microencapsulation of drugs. Int J Pharm. 2002;242(1-2):121-8.

25. Phatak AA, Chandhari PD. Development and evaluation of Nanostructured Lipid Carrier (NLC) based topical delivery of an anti-inflammatory drug. J Pharm Res. 2013;7(8):677-85.

26. Jenning V, Mäder K, Gohla SH. Solid Lipid Nanoparticles (SLN™) based on binary mixtures of liquid and solid lipids: A 1H-NMR study. Int J Pharm. 2000;205(1-2):15-21.

27. Puglia C, Damiani E, Offerta A, Rizza L, Tirendi GG, Tarico MS, et al. Evaluation of Nanostructured Lipid Carriers (NLC) and nanoemulsions as carriers for UV-filters: Characterization, *in vitro* penetration and photostability studies. Eur J Pharm Sci. 2014;51:211-7.

28. Mehnert W, Mäder K. Solid lipid nanoparticles: Production, characterization and applications. Adv Drug Deliv Rev. 2001;47(2-3):165-96.

29. Muchow M, Maincent P, Muller RH. Lipid nanoparticles with a solid matrix (SLN, NLC, LDC) for oral drug delivery. Drug Dev Ind Pharm. 2008;34(12):1394-405.

30. Pardeike J, Hommoss A, Müller RH. Lipid nanoparticles (SLN, NLC) in cosmetic and pharmaceutical dermal products. Int J Pharm. 2009;366(1-2):170-84.

31. Joshi M, Muller R. Lipid nanoparticles for parenteral delivery of actives. Eur J Pharm Biopharm. 2009;71(2):161-72.

32. Hu LD, Jia Y, Ding W. Preparation and characterisation of solid lipid nanoparticles loaded with epirubicin for pulmonary delivery. Pharmazie. 2010;65(8):585-7.

33. Patlolla RR, Chougule M, Patel AR, Jackson T, Tata PNV, Singh M. Formulation, characterization and pulmonary deposition of nebulized celecoxib encapsulated nanostructured lipid carriers. J Control Release. 2010;144(2):233-41.

34. Luo Q, Zhao J, Zhang X, Pan W. Nanostructured Lipid Carrier (NLC) coated with Chitosan Oligosaccharides and its potential use in ocular drug delivery system. Int J Pharm. 2011;403(1-2):185-91.

35. Gonzalez-Mira E, Egea MA, Garcia ML, Souto RB. Design and ocular tolerance of flurbiprofen loaded ultrasound-engineered NLC. Colloids Surf B Biointerfaces. 2010;81(2):412-21.

36. Esposito E, Ravani L, Drechsler M, Mariani P, Contado C, Ruokolainen J, et al. Cannabinoid antagonist in Nanostructured Lipid Carriers (NLCs): Design, characterization and *in vivo* study. Mater Sci Eng C Mater Biol Appl. 2015;48:328-36.

37. Jenning V, Korting MS, Gohla S. Vitamin A-loaded solid lipid nanoparticles for topical use: Drug release properties. J Control Release. 2000;66(2-3):115-26.

38. Müller RH, Petersen RD, Hommoss A, Pardeike J. Nanostructured Lipid Carriers (NLC) in cosmetic dermal products. Adv Drug Deliv Rev. 2007;59(6):522-30.

39. Vitorino C, Almeida J, Gonçalves LM, Almeida AJ, Sousa JJ, Pais AAPC. Co-encapsulating nanostructured lipid carriers for transdermal application: From experimental design to the molecular detail. J Control Release. 2013;167(3):301-14.

40. Puglia C, Bonina F. Lipid nanoparticles as novel delivery systems for cosmetics and dermal pharmaceuticals. Expert Opin Drug Deliv. 2012;9(4):429-41.

41. Sanna V, Caria G, Mariani A. Effect of lipid nanoparticles containing fatty alcohols having different chain length on the *ex vivo* skin permeability of Econazole nitrate. Powder Technol. 2010;201(1):32-6.

42. Das S, Ng WK, Tan RBH. Are Nanostructured Lipid Carriers (NLCs) better than Solid Lipid Nanoparticles (SLNs): Development, characterizations and comparative evaluations of clotrimazole-loaded SLNs and NLCs? Eur J Pharm Sci. 2012;47(1):139-51.

43. Okonogi S, Riangjanapatee P. Physicochemical characterization of lycopene-loaded nanostructured lipid carrier formulations for topical administration. Int J Pharm. 2015;478(2):726-35.

44. Heinemann L, Pfützner A, Heise T. Alternative routes of administration as an approach to improve insulin therapy: Update on dermal, oral, nasal and pulmonary insulin delivery. Curr Pharm Des. 2001;7(14):1327-51.

45. Patton JS, Fishburn CS, Weers JG. The lungs as a portal of entry for systemic drug delivery. Proc Am Thorac Soc. 2004;1(4):338-44.

46. Tronde A, Nordén B, Marchner H, Wendel AK, Lennernäs H, Bengtsson UH. Pulmonary absorption rate and bioavailability of drugs *in vivo* in rats: Structure-absorption relationships and physicochemical profiling of inhaled drugs. J Pharm Sci. 2003;92(6):1216-33.

47. Bosquillon C, Lombry C, Preat V, Vanbever R. Influence of formulation excipients and physical characterstics of inhalation dry powders on their aerosolizaton performace. J Control Release. 2001;70(3):329-39.

48. Pilcer G, Amighi K. Formulation strategy and use of excipients in pulmonary drug delivery. Int J Pharma. 2010;392(1-2):1-19.

49. Bur M, Henning A, Hein S, Schneider M, Lehr CM. Inhalative nanomedicine--opportunities and challenges. Inhal Toxicol. 2009;21(Suupl 1):137-43.

50. Patil-Gadhe A, Kyadarkunte A, Patole M, Pokharkar V. Montelukast-loaded nanostructured lipid carriers: Part II Pulmonary drug delivery and *in vitro-in vivo* aerosol performance. Eur J Pharm Biopharm. 2014;88(1):169-77.

51. Jaques PA, Kim CS. Measurement of total lung deposition of inhaled ultrafine particles in healthy men and women. Inhal Toxicol. 2000;12(8):715-31.

52. Maeda H, Wu J, Sawa T, Matsumura Y, Hori K. Tumor vascular permeability and the EPR effect in macromolecular therapeutics: A review. J Control Release. 2000;65(1-2):271-84.

53. van Vlerken le, Duan Z, Little SR, Seiden MV, Amiji MM. Biodistribution and pharmacokinetic analysis of Paclitaxel and ceramide administered in multifunctional polymer-blend nanoparticles in drug resistant breast cancer model. Mol Pharm. 2008;5(4):516-26.

54. Zhang XY, Qiao H, Ni JM, Shi TB, Qiang Y. Preparation of isoliquiritigenin-loaded nanostructured lipid carrier and the *in vivo* evaluation in tumor-bearing mice. Eur J Pharm Sci. 2013;49(3):411-22.

55. Li X, Nie SF, Kong J, Li N, Ju CY, Pan WS. A controlled-release ocular delivery system for ibuprofen based on nanostructured lipid carriers. Int J Pharm. 2008;363(1-2):177-82.

56. Shen J, Wang Y, Ping Q, Xiao Y, Huang X. Mucoadhesive effect of thiolated PEG stearate and its modified NLC for ocular drug delivery. J Control Release. 2009;137(3):217-23.