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Review Article

Basics of Solid Lipid Nanoparticles Formulation

Maryam Hasan Zadeh Navroodi[1], Morteza Marashi[1], Faezeh Talaei[1], Mohaddeseh Argha[1], Soheila Mokari[2], Javad Shokri[2], Shalen Kumar[3,4], Tooba Gholikhani[5,6*]

[1]Faculty of Pharmacy, Islamic Azad University, Ayatollah Amoli Branch, Amol, Iran
[2]Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Research Committee, School of IQ Science, Victoria University of Wellington, Wellington, New Zealand
[4]Ra Biotech ltd, Wellington, Wellington, New Zealand
[5]Department of Pharmaceutics, Faculty of Pharmacy, Islamic Azad University, Ayatollah Amoli branch, Amol, Iran
[6]Nano Ra Pharmaceuticals, Tabriz, Iran

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***Corresponding Author:**
Tooba Gholikhani,
Email: Tooba.souldouz@gmail.com

Abstract
Lipid nanoparticles (LNPs) have captured significant attention in the past few years and are widely used. Nanostructured lipid carriers (NLCs) and solid lipid nanoparticles (SLNs) are two lipid-based NPs with potential applications in research, drug delivery, cosmetics, and other fields. By modifying the size range, they can be used through different routes. Physically stable and targeted SLNs with good release profiles have been designed to overcome the limitations of emulsions and liposomes. NLCs are modified SLNs that enhance loading capacity and stability. Regardless of the preparation method, an initial emulsion is essential. The quality of the initial emulsion can affect the desired size range. This study highlights the critical features required to prepare the initial emulsion wisely and rationally.
Keywords: Preparation method, SLNs, NLCs, Formulation, Size range

Introduction

In recent decades, different carrier systems have been developed for drug delivery to modify the release profiles and improve formation effectiveness for improved outcomes.[1] These novel drug delivery systems have not only facilitated the successful targeting of numerous new pharmaceuticals but have also allowed for the better delivery of existing drugs.[2] Most commonly used drugs exhibit poor biopharmaceutical properties, including rapid metabolism, low solubility, low permeability, rapid elimination, reduced safety, and poor tolerability, making drug delivery a long-term challenging obstacle.[3] The development of a wide range of tailored drug delivery systems using nanoparticles (NPs) is altering the scientific landscape for disease treatment.[4,5] The desired drug is adsorbed, dissolved, attached, encapsulated, or entrapped into or onto a nano-matrix.[6,7] NPs, nanospheres, or nanocapsules can be constructed based on the method of preparation and the different release characteristics and properties to achieve better drug delivery or encapsulation. Colloidal particles known as NPs range in size from 10 to 1000 nm.[8] To reduce toxicity and optimize drug delivery, synthetic or natural polymers are used in their preparation[9]. Recently, they have been considered a promising substitute for liposomes.[10] The ability of NPs to permeate various anatomical barriers and maintain their stability within the target size range is crucial for their successful application in drug administration.[4] However, the widespread clinical application of NPs faces limitations due to the high cost of safe polymers.[11] Lipid nanoparticles (LNPs), due to the availability of biocompatible and non-toxic lipid ingredients, can solve these limitations. LNPs can be categorized into two groups: solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs).[12] These LNPs have a spherical morphology and an average size range of 40 to 1000 nm. They consist of a solid-phase lipid as the dispersion phase and a surfactant as the emulsifier.[13] At room temperature and body temperature, SLNs' dispersed phase remains solid. Glyceride mixtures, extremely purified triglycerides, or even waxes may be utilized. The second generation of SLNs, known as NLCs, modifies the potential drawbacks of SLNs. NLCs enhance stability and capacity loading during storage.[14] Unlike SLNs, the lipidic phase in NLCs comprises both liquid and solid lipids. SLNs and NLCs are advantageous for parenteral, gene transfer, and other medication administrations due to their extensive properties.[15-17] These formulations were created to improve treatment effectiveness while reducing the adverse effects of the potent medications. Several techniques are frequently employed for the preparation of SLNs, including high-pressure homogenization (hot and cold homogenization), evaporation or diffusion, solvent emulsification, ultrasonication or high-speed homogenization, supercritical fluid extraction of emulsions (SFEE), and spray drying[18-21]. Regardless of the preparation method, an initial emulsion is needed. The better the initial emulsion, the more easily the desired size range could be achieved.

However, cumulative decades of research on NLP preparation methods have paved the way for researchers. In this review, we strived to analyze numerous articles to categorize the formulating approach.

Composition of Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

The chemical and physical characteristics of nanomaterials can be altered by size reduction, distinguishing them from their bulk and molecular counterparts. LNP formulations consist of two phases: approximately 0.1–30 (% w/w) of lipids dispersed in an aqueous phase. To improve stability, a combination of surfactants at concentrations ranging from 0.5% to 5% is added.[22] For SLNs, the lipid phase consists solely of solid lipids, while in NLCs, the lipid phase comprises both liquid and solid lipids.[23] "Lipid" is a general term that encompasses triglycerides, steroids, fatty acids, partial glycerides, and waxes.[24] Lipid compounds derived from animal or vegetable sources are biocompatible, safe, and biodegradable.[25]

Different classes of emulsifiers, varying in molecular weight and charge, are used to stabilize lipid dispersions.[26] According to the literature, using multiple emulsifiers more efficiently prevents particle agglomeration.[27] Table 1 lists the lipids that are most frequently utilized. The selection of surfactant or surfactant mixtures at suitable concentrations, considering the route of administration, is crucial for parenteral administrations and helps to maintain SLN stability. Since surfactant changes the surface characteristics of SLN, it has a substantial impact on SLN's quality.[28,29] Proper selection of lipids and surfactants will impact physicochemical properties, particle size, long-term stability during storage, release behavior, and drug loading.[30]

Table 1. The Components Utilized to Make SLN

SLN Preparation Components	
Lipid	**Emulsifiers/Co-emulsifiers**
Triglycerides	
Tricaprin	Poloxamer 182, 188, 407, 908
Trilaurin	Tyloxapol
Tristearin	Polysorbate 20, 60, 80
Trimyristin	Soybean lecithin (Lipoid S75, Lipoid S100)
Tripalmitin	Egg lecithin (lipoid E80)
Hydrogenated coco-glycerides (Softisan 142)	Phosphatidylcholine (Epikuron 170, Epikuron 200)
Hard fat type	
Glyceryl monostearate (Imwitor 900)	Sodium cholate
Glycerol palmitostearate (Precirol ATO5)	Sodium glycocholate
Glyceryl Behenate (Compritol 888 ATO)	Sodium taurodeoxycholate
Palmitic acid	Sodium taurocholate
Decanoic acid	Sodium mono octyl phosphate
Stearic acid	Sodium taurodeoxycholate
Behenic acid	Butyric acid
Acidan N12	Butanol
Witespol W35, H35, H42, E85	Sodium docusate

Note. SLN: Solid lipid nanoparticle.

Formulation Preparation Strategy

Emulsifiers reduce surface tension due to the amphiphilic structure created by the alignment of hydrophobic and hydrophilic groups.[31] Concerning the chosen lipid, the emulsifiers are selected since they need to be quantitatively and qualitatively compatible.[32] To form an emulsion, it is essential to determine the hydrophilic-lipophilic balance (HLB) of the components which relate to their solubility.[33] The required HLB (rHLB) of the desired dispersion can be estimated through calculations based on the HLB of the lipid and the emulsifier(s). The stability of the overall formulation depends on choosing the best chemical emulsifier and estimating the rHLB[34]. The emulsifier mixture must be adjusted to the lipid chains' tail interface to produce oil droplets in an aqueous phase.[35] Emulsifiers can either be adsorbed on the surface directly or loaded into the lipoidal matrix itself.[36]

Concerning the hydrophilic group and its nature (i.e., HLB), emulsifiers are selected.[37] As the name suggests, emulsifiers with a non-ionic nature lack an ionic charge. Polysorbates and Poloxamers dissolve in the aqueous phase of emulsions, and the long polyoxypropylene chains allow aggregation and stabilization.[38-40] Sorbitan fatty acid esters dissolve within melted lipids and are adsorbed onto the surface more effectively.[41] To avoid particle aggregation, an electrostatic charge is needed to improve the zeta potential; as a result, the use of ionic emulsifiers is essential.[42,43] The negative and positive ions in the molecules of the ionic emulsifiers enhance the absorption of particles in the gastrointestinal system.[44] Another subclass of emulsifiers frequently employed is phospholipids.[45-47] The fatty chain makeup of phospholipids derived from soy or egg phosphatidylcholine varies. Due to its amphiphilic qualities, it can also be used to increase permeability for topical administration, reduce particle size, and enhance emulsion stability,[48] as illustrated in Table 2.

Solid Lipid Nanoparticle Preparation Methods

The method used to solubilize the lipid determines whether the production of SLN should use organic solvents or not.[49] The suitable method is chosen based on the drug's characteristics such as thermal stability, molecular weight, and solubility.[50,51] SLN preparation methods are summarized in Box 1.

Among the techniques mentioned above, high-speed homogenization (HPH) is the most practical one (both cold and hot HPH). After melting lipids, the drug is solubilized or distributed[52]. In hot HPH, the mixture of the lipid phase with an aqueous surfactant solution is

Table 2. Common Emulsifiers and Their Characteristics in the Formulation

Type of Emulsifier	System's Structure	Size Range	Class	Example
Ions and small molecules	Nature of dispersed and continuous phase: O/W, W/O	0.1–5 μm	Short-chain fatty acids (e.g., Sodium Oleate), Lecithin	
Non-ionic surfactants	Micelles/ Lamellar structures	size range: 10-100 nm	Polyoxyethylene sorbitan fatty acid esters (Tween®) Sorbitan fatty acid esters (Span®) Polyoxyethylene sorbitol esters (Mirj®) Alkyl aryl polyether alcohols (Tyloxapol) Polyoxypropylene poloxamer, pluronic, or Lutrol® (forming a triblock copolymer) Sugar esters Esters of acids, including lauric, oleic, palmitic, and stearic	
Surfactant mixtures	Micellar emulsions (microemulsions)	5–50 nm. They are thermodynamically stable.	Tween®/ Span® Blends, pluronic-based systems	
Ionic surfactant	Macroemulsions	20–100 nm. Similar to macroemulsions, only having kinetic stability.	Cationic	Stearylamine, cationic lipids, Esterqua
			Anionic	Bile salts, sodium cholate, sodium taurocholate
Other phospholipid	Liposomes/Bilayer structures		Soy or egg, phosphatidylcholine	
Non-ionic polymer	Bilayer droplet	100-1000 nm	Polyethylene Glycol Polymers	
Polyelectrolyte	Double and multiple emulsions	100-5000 nm	Alginate, Chitosan, Polyacrylic Acid	
Mixed polymer and surfactant	Mixed emulsions	variabe	Example: Tween® 80 with Polyvinylpyrrolidone	
Liquid crystalline phase	Hexagonal/Cubic	10-200nm	Examples: Monoolein, Glyceride systems	
Solid particle	Pickered Emulsions	50-500 nm	Examples: Silica, Titanium Oxide, Solid Lipid Nanoparticles (SLN)	

Note. SLN: Solid lipid nanoparticle.

Box 1. Techniques Used in Solid Lipid Nanoparticle Preparation

Different Methods of SLN Preparation
High shear homogenization
• Cold homogenization
• Hot homogenization
Ultrasonication/high-speed homogenization
• Bath ultrasonication
• Probe ultrasonication
Solvent emulsification/evaporation
Micro emulsion
Supercritical fluid
Spray drying
Double emulsion

homogenized by high shear homogenization.[53] To obtain the desired particle size, HPH is used to process the pre-emulsion.[54] Then, the lipid in the obtained nanoemulsion is recrystallized following a temperature decrease, and the SLN is formed.[55]

There are noticeable differences between the cold and hot HPH method[56]. The first is that the mixture of the drug in the melted lipid (solubilized or dispersed) is primarily cooled[57]. To produce a microparticle suspension, the solid lipid mixture is grounded by a mortar in a solution containing aqueous surfactant.[58] HPH is used at room temperature or below to deliver a homogeneous microparticle suspension, forming NPs.[59] In cases when the drug exhibits sensitivity to heat, cold HPH can be used.[60] Distributing drugs in the aqueous phase leads to the production of supercooled melt products during homogenization, and hot HPH results in crystallization. To overcome these drawbacks, cold HPH was developed.[61]

Due to its simplicity in scaling up, hot HPH has become the most frequently used technique, while methods such as high shear homogenization or sonication are less commonly utilized.[62] High shear homogenization or sonication is used to facilitate the emulsification of the aqueous and lipid phases, heated to the same temperature. However, the final dispersion contains microparticles and NPs, which presents a notable disadvantage. The phases are heated above the lipid melting point in the microemulsion technique[63] and subsequently diluted with cooled water to form a nanoemulsion that will be cooled to form the SLN. While stirring, the critical factor is a temperature control that maintains the lipid in its melted condition.[64]

Another technique for SLN synthesis is the double emulsion technique. In this method, a primary water-in-oil (w/o) emulsion is prepared using a high-shear homogenizer by solubilizing the drug in an aqueous phase, which is then added to the lipid phase containing a suitable emulsifier. The resulting mixture is further dispersed in a continuous aqueous surfactant phase to form the final water-in-oil-in-water (w/o/w) emulsion.[65] As a result of the drug being charged in the internal aqueous phase, hydrophilic drugs, proteins, and peptides could avoid chemical and enzymatic degradation.[66] The solvent evaporation technique is used for insoluble lipid drugs. An o/w emulsion is formed from the dispersion of a not water-miscible but lipid-soluble organic solvent in a solution consisting of an aqueous surfactant.[67,68] The

Table 3. Quality Tests for Solid Lipid Nanoparticle

Characteristics	Description	Equipment Used
Mean particle size, electrical charge, and distribution		DLS
Microscopy	Verifying the particle's surface morphology, size distribution, and potential alternative forms that may have developed simultaneously.	SEM, SFM, and TEM
Thermal analysis	Studying polymorphic variations of lipid materials, crystallization, and thermal behavior.	DSC, TGA,TMA, and DTA
Crystallinity and polymorphism	Evaluation of crystallinity	X-ray
Infra-red spectroscopy	Molecular characterization of SLN	FTIR

Note. SLN: Solid lipid nanoparticle; DLS: Dynamic light scattering; SEM: Scanning electron microscopy; SFM: Scanning force microscopy; TEM: Transmission electron microscopy; DSC: Differential scanning calorimetry; TGA: Thermogravimetric analysis; TMA: Thermomechanical analysis; DTA: Differential thermal analysis; FTIR: Fourier-transform infrared spectroscopy.

organic solvent is evaporated during stirring.

The solvent displacement method was originally used to obtain polymeric NPs.[69] Using this method, the lipid phase is dissolved in a water-miscible organic solvent and then added to the aqueous surfactant solution by injection.[70] After diffusion or distillation, the solvent is completely removed, leading to the formation of LNPs by precipitation.

In the emulsification-diffusion process, the lipid is initially dissolved in a semi-polar organic solvent before being mixed with an aqueous surfactant solution to produce a w/o emulsion.[71] Adding an excessive amount of water to the emulsion results in solvent diffusing out from the droplets, leading to SLN formation.[72]

In another method known as phase inversion, the first step is to melt all components and stir using a magnet, then cool down to lower temperatures.[73] Three temperature cycles are employed to achieve the inversion process specified by a temperature range. Then, cold water is added to create an irreversible shock, which leads to the development of stable NPs.[74] In recent years, a novel approach has been developed in which SLN is obtained by controlled coacervation, initiated from fatty acid alkaline salts.[75]

Tests Used for Quality and Structure Characterization of Solid Lipid Nanoparticles

As a drug delivery system, the physicochemical characterization of SLNs is essential for assessing their safety and stability. The most crucial factors investigated in nearly every SLN production-based study include lipid matrix polymorphism behavior, crystallization, and the colloidal stability of SLNs (Table 3).[6] The most commonly used methods are presented in Box 1.

Conclusion

SLNs are complex systems with distinct benefits and drawbacks compared to other colloidal carriers. The issues of drug expulsion and stability in SLNs necessitated the development of NLCs. SLNs and NLCs have exhibited different structural forms depending on their lipid composition and the incorporated drugs. The highly unordered lipid matrix of NLCs enhances drug encapsulation, stability, and release profile. These structures and other lipid NPs can be synthesized both in laboratory settings and on a large scale. Further studies are needed to comprehend the dynamics of LNPs in both in vivo and in vitro phases. Physically and chemically, SLNs provide a safe solid lipid-based delivery system suitable for transporting proteins and medicines with low water solubility. Investigating these characteristics is important as they significantly affect the biopharmaceutical behavior of SLNs. Although knowledge in this field has advanced considerably, it is still crucial to evaluate drug interactions with SLNs to predict their in vitro pharmacological profile. Ultimately, for SLNs to be recognized as a new generation of drug carriers, comprehensive structural studies are required.

Authors' Contributions

Conceptualization: Maryam Hasan Zadeh Navroodi.
Data curation: Morteza Marashi.
Formal analysis: Maryam Hasan zadeh Navroodi, Soheila Mokari.
Funding acquisition: Tooba Gholikhani.
Investigation: Maryam Hasan zadeh Navroodi, Soheila Mokari.
Methodology: Morteza Marashi, Soheila Mokari.
Project administration: Morteza Marashi.
Resources: Faezeh Talaei, Soheila Mokari.
Software: Faezeh Talaei, Soheila Mokari.
Supervision: Tooba Gholikhani.
Validation: Faezeh Talaei, Javad Shokri.
Visualization: Mohaddeseh Argha, Javad Shokri.
Writing–original draft: Mohaddeseh Argha, Javad Shokri.
Writing–review & editing: Soheila Mokari, Shalen Kumar.

Competing Interests

The authors declare no conflict of interests.

Ethical Approval

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References

1. Naseri N, Valizadeh H, Zakeri-Milani P. Solid lipid nanoparticles and nanostructured lipid carriers: structure, preparation and application. Adv Pharm Bull. 2015;5(3):305-13. doi: 10.15171/apb.2015.043.
2. Azhar Shekoufeh Bahari L, Hamishehkar H. The impact of variables on particle size of solid lipid nanoparticles and nanostructured lipid carriers; a comparative literature

review. Adv Pharm Bull. 2016;6(2):143-51. doi: 10.15171/apb.2016.021.
3. Ezzati Nazhad Dolatabadi J, Valizadeh H, Hamishehkar H. Solid lipid nanoparticles as efficient drug and gene delivery systems: recent breakthroughs. Adv Pharm Bull. 2015;5(2):151-9. doi: 10.15171/apb.2015.022.
4. Geszke-Moritz M, Moritz M. Solid lipid nanoparticles as attractive drug vehicles: composition, properties and therapeutic strategies. Mater Sci Eng C Mater Biol Appl. 2016;68:982-94. doi: 10.1016/j.msec.2016.05.119.
5. Mohammadzadeh R, Javadzadeh Y. An overview on oral drug delivery via nano-based formulations. Pharm Biomed Res. 2018;4(1):1-7. doi: 10.18502/pbr.v4i1.139.
6. Mehnert W, Mäder K. Solid lipid nanoparticles: production, characterization and applications. Adv Drug Deliv Rev. 2012;64:83-101. doi: 10.1016/j.addr.2012.09.021.
7. Javadzadeh Y, Azhar Shekoufeh Bahari L. Therapeutic nanostructures for dermal and transdermal drug delivery. In: Grumezescu AM, ed. Nano- and Microscale Drug Delivery Systems. Elsevier; 2017. p. 131-46. doi: 10.1016/b978-0-323-52727-9.00008-x.
8. 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. doi: 10.1016/s0939-6411(00)00087-4.
9. Hou D, Xie C, Huang K, Zhu C. The production and characteristics of solid lipid nanoparticles (SLNs). Biomaterials. 2003;24(10):1781-5. doi: 10.1016/s0142-9612(02)00578-1.
10. Ji P, Yu T, Liu Y, Jiang J, Xu J, Zhao Y, et al. Naringenin-loaded solid lipid nanoparticles: preparation, controlled delivery, cellular uptake, and pulmonary pharmacokinetics. Drug Des Devel Ther. 2016;10:911-25. doi: 10.2147/dddt.S97738.
11. Luo Y, Teng Z, Li Y, Wang Q. Solid lipid nanoparticles for oral drug delivery: chitosan coating improves stability, controlled delivery, mucoadhesion and cellular uptake. Carbohydr Polym. 2015;122:221-9. doi: 10.1016/j.carbpol.2014.12.084.
12. de Oliveira JL, Campos EV, Gonçalves da Silva CM, Pasquoto T, Lima R, Fraceto LF. Solid lipid nanoparticles co-loaded with simazine and atrazine: preparation, characterization, and evaluation of herbicidal activity. J Agric Food Chem. 2015;63(2):422-32. doi: 10.1021/jf5059045.
13. Dal Magro R, Ornaghi F, Cambianica I, Beretta S, Re F, Musicanti C, et al. ApoE-modified solid lipid nanoparticles: a feasible strategy to cross the blood-brain barrier. J Control Release. 2017;249:103-10. doi: 10.1016/j.jconrel.2017.01.039.
14. de Jesus MB, Zuhorn IS. Solid lipid nanoparticles as nucleic acid delivery system: properties and molecular mechanisms. J Control Release. 2015;201:1-13. doi: 10.1016/j.jconrel.2015.01.010.
15. Gaspar DP, Faria V, Gonçalves LM, Taboada P, Remuñán-López C, Almeida AJ. Rifabutin-loaded solid lipid nanoparticles for inhaled antitubercular therapy: physicochemical and in vitro studies. Int J Pharm. 2016;497(1-2):199-209. doi: 10.1016/j.ijpharm.2015.11.050.
16. Cassano R, Ferrarelli T, Mauro MV, Cavalcanti P, Picci N, Trombino S. Preparation, characterization and in vitro activities evaluation of solid lipid nanoparticles based on PEG-40 stearate for antifungal drugs vaginal delivery. Drug Deliv. 2016;23(3):1047-56. doi: 10.3109/10717544.2014.932862.
17. Natarajan J, Baskaran M, Humtsoe LC, Vadivelan R, Justin A. Enhanced brain targeting efficacy of olanzapine through solid lipid nanoparticles. Artif Cells Nanomed Biotechnol. 2017;45(2):364-71. doi: 10.3109/21691401.2016.1160402.
18. Gordillo-Galeano A, Mora-Huertas CE. Solid lipid nanoparticles and nanostructured lipid carriers: a review emphasizing on particle structure and drug release. Eur J Pharm Biopharm. 2018;133:285-308. doi: 10.1016/j.ejpb.2018.10.017.
19. Wang T, Hu Q, Zhou M, Xia Y, Nieh MP, Luo Y. Development of "all natural" layer-by-layer redispersible solid lipid nanoparticles by nano spray drying technology. Eur J Pharm Biopharm. 2016;107:273-85. doi: 10.1016/j.ejpb.2016.07.022.
20. Sánchez-López E, Espina M, Doktorovova S, Souto EB, García ML. Lipid nanoparticles (SLN, NLC): overcoming the anatomical and physiological barriers of the eye - part II - ocular drug-loaded lipid nanoparticles. Eur J Pharm Biopharm. 2017;110:58-69. doi: 10.1016/j.ejpb.2016.10.013.
21. Ezzati Nazhad Dolatabadi J, Hamishehkar H, Valizadeh H. Development of dry powder inhaler formulation loaded with alendronate solid lipid nanoparticles: solid-state characterization and aerosol dispersion performance. Drug Dev Ind Pharm. 2015;41(9):1431-7. doi: 10.3109/03639045.2014.956111.
22. Kaur IP, Bhandari R, Bhandari S, Kakkar V. Potential of solid lipid nanoparticles in brain targeting. J Control Release. 2008;127(2):97-109. doi: 10.1016/j.jconrel.2007.12.018.
23. Das S, Ng WK, Tan RB. 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. doi: 10.1016/j.ejps.2012.05.010.
24. Jawahar N, Meyyanathan SN, Reddy G, Sood S. Solid lipid nanoparticles for oral delivery of poorly soluble drugs. J Pharm Sci Res. 2012;4(7):1848-55.
25. Shit SC, Shah PM. Edible polymers: challenges and opportunities. J Polym. 2014;2014(1):427259. doi: 10.1155/2014/427259.
26. Yadav N, Khatak S, Sara US. Solid lipid nanoparticles-a review. Int J Appl Pharm. 2013;5(2):8-18.
27. Kalaycioglu GD, Aydogan N. Preparation and investigation of solid lipid nanoparticles for drug delivery. Colloids Surf A Physicochem Eng Asp. 2016;510:77-86. doi: 10.1016/j.colsurfa.2016.06.034.
28. Harde H, Das M, Jain S. Solid lipid nanoparticles: an oral bioavailability enhancer vehicle. Expert Opin Drug Deliv. 2011;8(11):1407-24. doi: 10.1517/17425247.2011.604311.
29. Jaiswal P, Gidwani B, Vyas A. Nanostructured lipid carriers and their current application in targeted drug delivery. Artif Cells Nanomed Biotechnol. 2016;44(1):27-40. doi: 10.3109/21691401.2014.909822.
30. Prabhakaran E, Abdul Hasan A, Karunanidhi P. Solid lipid nanoparticles: a review. Sci Revs Chem Commun. 2012;2(1):80-102.
31. Souto EB, Fangueiro JF, Müller RH. Solid lipid nanoparticles (SLN™). In: Uchegbu IF, Schätzlein AG, Cheng WP, Lalatsa A, eds. Fundamentals of Pharmaceutical Nanoscience. New York, NY: Springer; 2013. p. 91-116. doi: 10.1007/978-1-4614-9164-4_5.
32. Westesen K, Siekmann B. Investigation of the gel formation of phospholipid-stabilized solid lipid nanoparticles. Int J Pharm. 1997;151(1):35-45. doi: 10.1016/s0378-5173(97)04890-4.
33. McClements DJ, Gumus CE. Natural emulsifiers - biosurfactants, phospholipids, biopolymers, and colloidal particles: molecular and physicochemical basis of functional performance. Adv Colloid Interface Sci. 2016;234:3-26. doi: 10.1016/j.cis.2016.03.002.
34. Kovacevic A, Savic S, Vuleta G, Müller RH, Keck CM. Polyhydroxy surfactants for the formulation of lipid nanoparticles (SLN and NLC): effects on size, physical stability and particle matrix structure. Int J Pharm. 2011;406(1-2):163-72. doi: 10.1016/j.ijpharm.2010.12.036.
35. Jenning V, Gohla S. Comparison of wax and glyceride solid lipid nanoparticles (SLN). Int J Pharm. 2000;196(2):219-22. doi: 10.1016/s0378-5173(99)00426-3.
36. Sznitowska M, Wolska E, Baranska H, Cal K, Pietkiewicz

J. The effect of a lipid composition and a surfactant on the characteristics of the solid lipid microspheres and nanospheres (SLM and SLN). Eur J Pharm Biopharm. 2017;110:24-30. doi: 10.1016/j.ejpb.2016.10.023.
37. Jannin V, Musakhanian J, Marchaud D. Approaches for the development of solid and semi-solid lipid-based formulations. Adv Drug Deliv Rev. 2008;60(6):734-46. doi: 10.1016/j.addr.2007.09.006.
38. Gullapalli RP, Sheth BB. Influence of an optimized non-ionic emulsifier blend on properties of oil-in-water emulsions. Eur J Pharm Biopharm. 1999;48(3):233-8. doi: 10.1016/s0939-6411(99)00048-x.
39. Boyd J, Parkinson C, Sherman P. Factors affecting emulsion stability, and the HLB concept. J Colloid Interface Sci. 1972;41(2):359-70. doi: 10.1016/0021-9797(72)90122-1.
40. Friberg S, Buraczewska I, Ravey JC. Solubilization by nonionic surfactants in the HLB-temperature range. In: Mittal KL, ed. Micellization, Solubilization, and Microemulsions. Boston, MA: Springer; 1977. p. 901-11. doi: 10.1007/978-1-4613-4157-4_25.
41. Schmidts T, Dobler D, Guldan AC, Paulus N, Runkel F. Multiple W/O/W emulsions—using the required HLB for emulsifier evaluation. Colloids Surf A Physicochem Eng Asp. 2010;372(1-3):48-54. doi: 10.1016/j.colsurfa.2010.09.025.
42. Clumpner JM. Cationic Emulsifier System. Google Patents; 1972.
43. Greth GG, Wilson JE. Use of the HLB system in selecting emulsifiers for emulsion polymerization. J Appl Polym Sci. 1961;5(14):135-48. doi: 10.1002/app.1961.070051402.
44. Meier C, Eisele J, Schnabel M, Schultes K, Grimm S, Petereit HU, et al. Dispersion Comprising a Non-Ionic Emulsifier. Google Patents; 2006.
45. Krog N. Association of emulsifiers in aqueous systems. In: Food Colloids. The Royal Society of Chemistry; 1997. p. 45-54. doi: 10.1533/9781845698263.2.45.
46. Benita S, Friedman D, Weinstock M. Physostigmine emulsion: a new injectable controlled release delivery system. Int J Pharm. 1986;30(1):47-55. doi: 10.1016/0378-5173(86)90134-1.
47. Rydhag L, Wilton I. The function of phospholipids of soybean lecithin in emulsions. J Am Oil Chem Soc. 1981;58(8):830-7. doi: 10.1007/bf02665591.
48. Hu L, Hsieh F, Huff HE. Corn meal extrusion with emulsifier and soybean fiber. LWT Food Sci Technol. 1993;26(6):544-51. doi: 10.1006/fstl.1993.1106.
49. Dingler A, Gohla S. Production of solid lipid nanoparticles (SLN): scaling up feasibilities. J Microencapsul. 2002;19(1):11-6. doi: 10.1080/02652040010018056.
50. Jenning V, Lippacher A, Gohla SH. Medium scale production of solid lipid nanoparticles (SLN) by high pressure homogenization. J Microencapsul. 2002;19(1):1-10. doi: 10.1080/713817583.
51. 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. doi: 10.1016/s0169-409x(02)00118-7.
52. Silva AC, González-Mira E, García ML, Egea MA, Fonseca J, Silva R, et al. Preparation, characterization and biocompatibility studies on risperidone-loaded solid lipid nanoparticles (SLN): high pressure homogenization versus ultrasound. Colloids Surf B Biointerfaces. 2011;86(1):158-65. doi: 10.1016/j.colsurfb.2011.03.035.
53. Das S, Chaudhury A. Recent advances in lipid nanoparticle formulations with solid matrix for oral drug delivery. AAPS PharmSciTech. 2011;12(1):62-76. doi: 10.1208/s12249-010-9563-0.
54. Rahiminejad A, Dinarvand R, Johari B, Jafari Nodooshan S, Rashti A, Rismani E, et al. Preparation and investigation of indirubin-loaded SLN nanoparticles and their anti-cancer effects on human glioblastoma U87MG cells. Cell Biol Int. 2019;43(1):2-11. doi: 10.1002/cbin.11037.
55. Severino P, Santana MH, Souto EB. Optimizing SLN and NLC by 2(2) full factorial design: effect of homogenization technique. Mater Sci Eng C Mater Biol Appl. 2012;32(6):1375-9. doi: 10.1016/j.msec.2012.04.017.
56. Souto EB, Müller RH. Investigation of the factors influencing the incorporation of clotrimazole in SLN and NLC prepared by hot high-pressure homogenization. J Microencapsul. 2006;23(4):377-88. doi: 10.1080/02652040500435295.
57. Souto EB, Wissing SA, Barbosa CM, Müller RH. Evaluation of the physical stability of SLN and NLC before and after incorporation into hydrogel formulations. Eur J Pharm Biopharm. 2004;58(1):83-90. doi: 10.1016/j.ejpb.2004.02.015.
58. Üner M, Wissing SA, Yener G, Müller RH. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) for application of ascorbyl palmitate. Pharmazie. 2005;60(8):577-82.
59. 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. doi: 10.1016/j.ijpharm.2008.10.003.
60. Bhaskar K, Krishna Mohan C, Lingam M, Prabhakar Reddy V, Venkateswarlu V, Madhusudan Rao Y. Development of nitrendipine controlled release formulations based on SLN and NLC for topical delivery: in vitro and ex vivo characterization. Drug Dev Ind Pharm. 2008;34(7):719-25. doi: 10.1080/03639040701842485.
61. Guimarães KL, Ré MI. Lipid nanoparticles as carriers for cosmetic ingredients: the first (SLN) and the second generation (NLC). In: Beck R, Guterres S, Pohlmann A, eds. Nanocosmetics and Nanomedicines: New Approaches for Skin Care. Berlin, Heidelberg: Springer; 2011. p. 101-22. doi: 10.1007/978-3-642-19792-5_5.
62. Fang JY, Fang CL, Liu CH, Su YH. Lipid nanoparticles as vehicles for topical psoralen delivery: solid lipid nanoparticles (SLN) versus nanostructured lipid carriers (NLC). Eur J Pharm Biopharm. 2008;70(2):633-40. doi: 10.1016/j.ejpb.2008.05.008.
63. de Jesus MB, Radaic A, Zuhorn IS, de Paula E. Microemulsion extrusion technique: a new method to produce lipid nanoparticles. J Nanopart Res. 2013;15(10):1960. doi: 10.1007/s11051-013-1960-3.
64. Liedtke S, Wissing S, Müller RH, Mäder K. Influence of high pressure homogenisation equipment on nanodispersions characteristics. Int J Pharm. 2000;196(2):183-5. doi: 10.1016/s0378-5173(99)00417-2.
65. Yang R, Gao R, Li F, He H, Tang X. The influence of lipid characteristics on the formation, in vitro release, and in vivo absorption of protein-loaded SLN prepared by the double emulsion process. Drug Dev Ind Pharm. 2011;37(2):139-48. doi: 10.3109/03639045.2010.497151.
66. Li Z, Yu L, Zheng L, Geng F. Studies on crystallinity state of puerarin loaded solid lipid nanoparticles prepared by double emulsion method. J Therm Anal Calorim. 2010;99(2):689-93. doi: 10.1007/s10973-009-0127-z.
67. Garud A, Singh D, Garud N. Solid lipid nanoparticles (SLN): method, characterization and applications. Int Curr Pharm J. 2012;1(11):384-93.
68. Mukherjee S, Ray S, Thakur RS. Solid lipid nanoparticles: a modern formulation approach in drug delivery system. Indian J Pharm Sci. 2009;71(4):349-58. doi: 10.4103/0250-474x.57282.
69. Noriega-Peláez EK, Mendoza-Muñoz N, Ganem-Quintanar A, Quintanar-Guerrero D. Optimization of the emulsification and solvent displacement method for the preparation of solid lipid nanoparticles. Drug Dev Ind Pharm. 2011;37(2):160-6. doi: 10.3109/03639045.2010.501800.

70. Shahgaldian P, da Silva E, Coleman AW. A first approach to the study of calixarene solid lipid nanoparticle (SLN) toxicity. J Incl Phenom Macrocycl Chem. 2003;46(3):175-7. doi: 10.1023/a:1026301906487.
71. Trotta M, Debernardi F, Caputo O. Preparation of solid lipid nanoparticles by a solvent emulsification-diffusion technique. Int J Pharm. 2003;257(1-2):153-60. doi: 10.1016/s0378-5173(03)00135-2.
72. 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;26(2):211-8. doi: 10.1016/j.ejps.2005.06.001.
73. Heurtault B, Saulnier P, Pech B, Proust JE, Benoit JP. A novel phase inversion-based process for the preparation of lipid nanocarriers. Pharm Res. 2002;19(6):875-80. doi: 10.1023/a:1016121319668.
74. Joshi M, Patravale V. Nanostructured lipid carrier (NLC) based gel of celecoxib. Int J Pharm. 2008;346(1-2):124-32. doi: 10.1016/j.ijpharm.2007.05.060.
75. Battaglia L, Gallarate M, Cavalli R, Trotta M. Solid lipid nanoparticles produced through a coacervation method. J Microencapsul. 2010;27(1):78-85. doi: 10.3109/02652040903031279.