Solvent Injection for SLNs/NLCs Preparation

Subjects: Pharmacology & Pharmacy

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A number of studies have used the solvent injection method to produce solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), and various drugs have been loaded into these carriers for different applications. Here, we present major SLNs and NLCs systems and details of applications that use this method in 2006-2020. Furthermore, we discuss the effects of various parameters of solvent injection method on SLNs and NLCs production and propose some suggestions regarding future developments and applications.

Lipid Nanoparticles | Nanostructured Lipid Carriers | Drug Delivery | Aqueous phase | Organic phase | Emulsifier

1. Introduction

SLNs and NLCs have been produced using numerous methods, such as high-pressure homogenization, emulsion/solvent evaporation, phase inversion, and microemulsion [1][2][3][4][5]. The solvent injection is an alternative method for preparing SLNs and NLCs. It was first used in 1973 and has been one of the effective approaches to prepare liposomes [6]. Many studies have been performed on liposome preparation using this method. In 2003, Schubert et al. first used solvent injection to prepare SLNs and NLCs [7]. The advantages of this method include a fast production process and easiness of handling [8]. In addition, it can be easily performed in laboratories as no complicated instruments, such as high-pressure homogenizers or high-speed stirrers are required [9]. Some studies have investigated the solvent injection method for the production of SLNs and NLCs for different applications [10]. Others have investigated the effects of solvent injection process parameters on the physicochemical properties of SLNs and NLCs [11][12]. In this entry, we summarize important developments made up until now using this method, discuss the effects of various parameters of solvent injection method on SLNs and NLCs production, and propose some suggestions regarding future developments and applications.

2. Solvent Injection Method (2006-2020)

Table 1 summarizes the major features of studies that utilized the solvent injection method, including the lipids used, drugs incorporated, and primary outcomes. References can be found in the original article [13].

Table 1. Overview of lipids, emulsifiers, drugs, and solvents used to prepare SLNs and NLCs by solvent injection method and their significant outcomes.

Lipid(s)/Emulsifier(s)	Drug or Active Ingredient	Solvent	Outcomes	Year
Lipoid®S 100/sucrose fatty acid ester	Paclitaxel	Acetone	PS: 188 nm, PDI: 0.396, and EE: 92.2%SLNs showed sustained-release for 14 days (in vitro)	2006
Palmitic or stearic acid/phosphatidylcholine	Idebenone	Ethanol	PS: 170–183 nm, PDI: 0.113–0.134, and EE: 83–86% SLNs showed sustained-release for 7 days (in vitro) SLNs increased drug protecting activity against free radical-induced oxidative damage of astrocyte cells	2006
Stearic acid, soya lecithin/poloxamer 188	Paclitaxel	Diethyl ether	Drug amount and emulsifier concentration were varied to get the optimized SLNs (PS: 113 nm, PDI: 0.156, and EE: 89.0%) SLNs had lower toxicity on HepG2 cell than free drug SLNs was stable for 90 days	2009
Tristearin, soya lecithin/polysorbate 80	Miconazole nitrate	Ethanol	Parameters were varied to obtain optimized NLCs (PS: 206 nm, PDI: 0.21, and EE: 90.9%) NLCs-based hydrogels increased skin retention 10-fold as compared with miconazole suspension and miconazole hydrogel	2010
Tristearin/polysorbate 80	Hepatitis B surface antigen (HBsAg)	Acetone	HBsAg was loaded onto SLNs surface Mannosylated SLNs (PS: 96.6 nm, PDI: 0.05, and EE: 64.5%) SLNs showed better cellular uptake, lesser toxicity, and greater immune response Subcutaneous administration of SLNs was potential for vaccine delivery against hepatitis B	2010
Monostearin/poloxamer 407	Simvastatin	Isopropanol	A 2^3 factorial design was performed to optimize SLNs (PS: 259 nm, EE: 75.8%)	2010

Lipid(s)/Emulsifier(s)	Drug or Active Ingredient	Solvent	Outcomes	Year
			SLNs showed sustained-release for 55 h (in vitro)	
Tristearin, soya lecithin/polysorbate 80	Doxorubicin hydrochloride	Acetone + ethanol	Mannosylated SLNs (PS: 360 nm, PDI: 0.135, and EE: 70.3%) Mannosylated SLNs showed sustained-release in mice. They delivered a higher dug concentration to the tumor mass.	2010
Glycerol monostearate, oleic acid/poloxamer 407	Simvastatin	Isopropanol	A 2^3 factorial design was performed to optimize NLCs (PS: 212 nm, PDI: 0.344, and EE: 84%) NLCs showed a higher bioavailability than drug suspension and drug-loaded SLNs	2011
Monostearin, soya lecithin/poloxamer 188	Puerarin	Methanol + ethanol	SLNs enhanced oral bioavailability of the drug 3 times Tissue concentration of the drug increased, particularly the hearts and brain after oral administration of SLNs	2011
Stearylamine, soya lecithin, α-tocopherol/poloxamer 188	Paclitaxel	Diethyl ether	Drug amount and emulsifier concentration were varied to obtain optimized SLNs (PS: 96 nm, PDI: 0.162, EE: 75.4%, and DL: 31.5%) SLNs increased oral bioavailability of the drug 10 times in mice	2011
Monostearin/Lecithin + poloxamer 188	Ondansetron hydrochloride	Ethanol	A 2^3 factorial design was performed to get the optimized SLNs (PS: 320 nm, PDI: 0.296, and EE: 49.7%) The SLNs effectively delivered the drug to the brain by intranasal administration on rabbits	2012
Stearic acid/polysorbate 80	Cytarabine	Isopropanol	Drug and lipid was conjugated prior to SLNs	2012

Lipid(s)/Emulsifier(s)	Drug or Active Ingredient	Solvent	Outcomes	Year
			preparation - PS: 137 nm, PDI: 0.151, and EE: 58.4% SLNs showed drug sustained-release (3 days in vitro) and increased toxicity on leukemic EL-4 cells as compared with drug solution	
Glyceryl behenate (Compritol® 888 ATO)/poloxamer 407	Terbinafine hydrochloride	Isopropanol	A 3^3 factorial design was performed to get the optimized SLNs (PS: 274 nm, PDI: 0.32, and EE: 74.6%) SLN-based gel was more effective than a commercial product when applying in rats (pharmacodynamics studies) - SLNs were stable for 90 days	2013
Monostearin/polysorbate 80 + poloxamer 188	Thymoquinon	Ethanol	Box-Behnken design was used to optimize the SLNs (PS: 166 nm, EE: 71.6%) Oral bioavailability increased 5-fold in rats as compared with drug suspension	2013
Dynasan 114, soya phosphatidylcholine/poloxamer 407	Adefovir dipivoxil	Isopropanol	Different process and formulation parameters were evaluated to optimize SLNs (PS: 267 nm, EE: 73.5%, and DL: 2%) SLNs increased oral bioavailability 2- and 1.5-fold as compared with micro-suspension and nanosuspension, respectively SLNs increased drug accumulation in liver, kidneys, intestine, and stomach.	2013
Cetyl alcohol/polysorbate 80	Andrographolide	Ethanol	PS: 154 nm, PDI: 0.172, EE: 91.4%, and DL: 18.6% SLNs increased oral bioavailability (3.41-fold) and antitumor activity as	2014

Lipid(s)/Emulsifier(s)	Drug or Active Ingredient	Solvent	Outcomes	Year
			compared with the drug suspension	
Tristearin, soya lecithin/polysorbate 80	Adapalene	Acetone + ethanol	PS: 148 nm, PDI: 0.169, and EE: 89.9% SLNs-based gel showed sustained-release in vitro	2014
Tristearin, hydrogenated soya phosphatidylcholine/polysorbate 80	Aceclofenac	Ethanol	SLNs was conjugated with chondroitin sulfate (CS-SLNs) with PS: 154 nm, PDI: 0.403, and EE: 65.4% SLNs and CS-SLNs increased drug amount in the inflammatory knee joint (2- and 10-fold as compared with the drug solution, respectively) after IV administration in rats	2014
Monostearin/polysorbate 80	Halobetasol propionate	Isopropanol	A 3^2 full factorial design was applied to optimize the SLNs (PS: 200 nm and EE: 93%) SLNs-based carbopol gels prolonged drug release up to 12 h on human cadaver skin, reduced systemic uptake, increased drug accumulation in skin, and were nonirritant to rabbit skin	2014
Monostearin or stearic acid/polysorbate 80 or poloxamer 188	Tamoxifen	Methanol	Lipid and emulsifier were varied to obtain optimized SLNs (PS: 130 nm, PDI, 0.231, and EE: 86.1%) SLNs increased oral bioavailability (1.6-fold) following oral administration in rats	2014
Monostearin, Tefose-63/polysorbate 80	Mometasone furoate	Ethanol	SLNs was optimized (PS: 124 nm, and EE: 55.6%) SLNs-based carbopol gel increased skin deposition 2.67- and 20-fold as compared with a marketed cream and drug-loaded gel SLNs-based gel increased skin permeability 15.2-fold as	2014

Lipid(s)/Emulsifier(s)	Drug or Active Ingredient	Solvent	Outcomes	Year
			compared with a marketed cream	
Tristearin, distearoyl-phosphatidyl ethanolamine/polysorbate 80	Paclitaxel	Acetone + ethanol	Mannosylated SLNs (PS: 254 nm, PDI: 0.312) Mannosylated SLNs improved antiproliferative efficacy in lung cancer cells. They delivered a higher drug concentration to alveolar cells after IV injection in rats	2015
Tristearin, soya lecithin, stearylamine/polysorbate 80	Rifampicin	Ethanol	Drug-loaded SLNs was coupled with lactoferrin to enhance SLNS delivery to lung (PS: 271 nm, PDI: 0.124, and EE: 68.4%) In vivo biodistribution study: lactoferrin-coupled SLNs had 47.7% drug uptakes by the lungs (3.05 times higher than uncoupled SLNs) following IV injection in rats	2015
Tripalmitin/polysorbate 80	Sumatriptan	Ethanol	A 2^3 randomized full factorial design was performed to optimize the SLNs (PS: 236 nm, and EE 91.3%) SLNs showed a 4.54-fold increase in brain/blood ratio of drug (2 h after oral administration in rats) SLNs improved anti-migraine potential in behavioral studies	2015
Tristearin, hydrogenated soya phosphatidylcholine/polysorbate 80	Nifedipine	Ethanol	SLNs was further coated with polysorbate 80 (PS: 121 nm, PDI: 0.261, and EE: 71.5%) Coated-SLNs increased bioavailability about 5- and 2-fold as compared with free drug and uncoated SLNs, respectively (IV administration in rats) Coated-SLNs increased drug accumulation in brain	2015
Compritol® 888 ATO, Gelucire® 50/13/polysorbate 80	Resveratrol	Ethanol	Box–Behnken design was applied to optimize SLNs	2016

Lipid(s)/Emulsifier(s)	Drug or Active Ingredient	Solvent	Outcomes	Year
			(PS: 191 nm, PDI: 0.156, and EE: 73.7%) SLNs increased oral bioavailability nearly 5-fold in rats as compared with resveratrol suspension Pharmacodynamic data showed a decrease in the serum biomarker enzymes as compared with control and marketed formulation (against paracetamol-induced liver cirrhosis)	
Monostearin/poloxamer 188	Asiatic acid	Ethanol	A Box–Behnken design was used to optimize the formulations (PS: 237 nm, EE: 64.4%, and DL: 31.9%) SLN increased oral bioavailability 2.5-fold following oral administration in rats	2016
Vitamin B6-stearic acid conjugation/polysorbate 80	Doxorubicin	Ethanol	Vitamin B6 was conjugated with lipid to modify charge of SLNs (PS: 114 nm, PDI: 0.101, and DL: 7.1%) Vitamin B6-modified SLNs had an increased therapeutic efficacy and lower toxicity in tumor-bearing rats as compared with free drug Vitamin B6-modified SLNs prolonged drug circulation in blood and increased drug accumulation to tumor site in rats	2016
Sophorolipid/poloxamer 407 and 188	Rifampicin + dapsone	Ethanol	Five different polymers were used to stabilize SLNs, and poloxamer 407 and 188 were the best options - There was no in vivo study	2018
Tripalmitin, Phosal® 53MCT/polysorbate 80	Ondansetron hydrochloride	Ethanol	Various parameters were investigated to get the optimized NLCs (PS: 185 nm, PDI: 0.214, EE: 93.2%, and DL: 10.43%) NLCs showed sustained-	2019

carriers containing ondansetron hydrochloride by cold high-pressure homogenization method: Preparation, characterization, and pharmacokinetic evaluation. *Journal of Drug Delivery Science and Technology* **2019**, *53*, 101185, 10.1016/j.jddst.2019.101185.

Lipid(s)/Emulsifier(s)	Drug or Active Ingredient	Solvent	Outcomes	Year
			release in vitro and in vivo for up to 4 days following subcutaneous administration in rats	
YSK05, cholesterol, DMG-PEG2K	siRNA	Ethanol	NLCs were subjected to post-treatment using an integrated baffle device (PS: 33 nm and EE: 90%) The siFVII knocked down the plasma coagulation factor VII at mice liver tissue more than 80% (IV injection, mice)	2020
Compritol® 888 ATO, oleic acid/poloxamer 407	Temazepam	Acetone + ethanol	A 4^2 full factorial design was applied to optimize NLCs (PS: 307 nm, PDIL 0.09, and EE: 75.2%) NLCs increase oral bioavailability nearly 3-fold in rats as compared with temazepam suspension NLCs improved brain uptake of ^{99m}Tc-temazepam	2020
Stearic acid, phosphatidylcholine	Alpha-tocopherol	Ethanol	Various parameters were evaluated to optimize SLNs (PS: 175 nm, EE: 90.9%, and DL: 59.4%)No in vivo study was conducted	2020

Particle sizes (PSs), polydispersity indices (PDIs), entrapment efficiencies (EEs), and drug loadings (DLs) are for optimized SLNs and NLCs.

3. Process Parameters

3.1. Aqueous Phase

The pH, temperature, and viscosity of an aqueous phase may critically influence SLNs and NLCs, particularly when drugs exhibit pH-dependent solubility. Details can be found in Figure 2 of the original article [13].

3.2. Organic Phase

The organic phase consists of drug and lipid mixtures dissolved in a water-miscible solvent or solvent mixture. Here, we summarize the influences of solvent type on SLNs and NLCs. For the solvent injection method, diffusion

of organic solvent is a critical factor, and thus, the appropriate solvent selection is important. Details can be found in Figure 2 of the original article [13].

3.3. Ratio of Aqueous Phase to Organic Phase

Overall, the relative ratio of aqueous phase to organic phase (Va/Vo) does not considerably affect PSs or PDIs unless it exceeds a critical value. Details can be found in Figure 3 of the original article [13].

3.4. Dispersion Energy

Sonication is frequently used to supply dispersion energy to produce SLNs and NLCs. Overall, the use of short sonication times (2–4 min) is favored for reducing PS and PDI slightly. Longer sonication times should be carefully evaluated because they may have undesirable effects, such as increased PS and PDI or decreased EE and DL.

4. Formulation Parameters

4.1. Total Lipid Concentration

It is important to use an appropriate concentration of lipid in the organic phase. As long as PS and PDI remain within accepted ranges, this concentration can be maximized. Details can be found in Table 3 of the original article [13].

4.2. Liquid Lipid Level

The incorporation of liquid lipids at appropriate levels is beneficial to NLCs with respect to PS, PDI, EE, and DL. Details can be found in Table 4 of the original article [13].

4.3. Drug Hydrophilicity and Drug Amount

Initial drug amounts critically affect the properties of SLNs and NLCs, particularly EE and DL. There is a range in which increasing the initial drug amount improves EE and DL and does not significantly change PS or PDI. One may select the highest initial drug amounts in this range to incorporate drugs into SLNs and NLCs. Details can be found in Table 5 of the original article [13].

4.4. Emulsifier

Although there are differences in the literature, emulsifiers are considered crucial for the preparation of SLNs and NLCs using the solvent injection method. The use of emulsifiers at high concentrations does not favor SLNs or NLCs formation due to increases in PS and PDI, and in some cases, increases in EE and DL. Thus, emulsifiers should be used in their appropriate ranges, usually 0.1–0.5%, and if possible, at low concentrations. Details can be found in Figure 4 of the original article [13].

5. Summary

This entry presents most of the critical issues concerning the preparation of SLNs and NLCs using the solvent injection method. Studies on SLNs and NLCs are certain to be performed due to their potential applications for drug delivery. The solvent injection method requires further investigation as a means of preparing SLNs and NLCs at commercial levels.

The entry is from 10.3390/molecules25204781.