



## Recent Advances in Solid Lipid Nanoparticle Preparation: Methods, Ingredients, and Routes of Administration

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### Abstract

**Objective:** To identify the importance of Solid lipid nanoparticles (SLNs), their most recent methods of preparation and the drugs, lipid(s) and surfactant(s) most recently used for carrier development. **Methods:** Original articles were identified through searches of MEDLINE/PubMed for within the last 5 years (2020–February 2025), with the following search terms; solid lipid nanoparticles. The main aim was to find original articles/research, this led to another search but excluded evaluation. **Study Selection and exclusion criteria:** Articles that discussed active pharmaceutical “drugs” were selected for this study and exclusion criteria of “NOT review NOT mRNA NOT DNA NOT RNA” to narrow down the articles. **Data Synthesis:** More than 500 articles were identified and further reviewed in the literature and were categorized according to the method in which the SLN were prepared; homogenization and/or high-pressure homogenization, ultrasonication, solvent injection and/or solvent evaporation phase inversion, microemulsion/emulsification, nano spray drying and/or others and combination methods. **Conclusion:** As more specific drug targeting and drug delivery systems become more of an interest in the drug development field, solid lipid nanoparticles will be of continuance importance for a strategic role in nanoparticle formulations.

**Keywords:** Solid lipid nanoparticles (SLNs), Homogenization, Ultrasonication, Solvent injection

## Introduction

Solid lipid nanoparticles (SLNs) most recently have been of high interest in the pharmaceutical industrial fields. The original/initial methods of preparation of SLNs have been patented by professor Gasco since 1991[1]. However, more recently these methods have been tweaked and modified accordingly to the needs of each researcher for the development of drug incorporated into the solid lipids of nano size.

SLNs are typically made up of a solid lipid, a surfactant, an active pharmaceutical ingredient and aqueous medium such as water. Some solid lipids commonly used, although there is no specific guideline, include stearic acid, glycerol monostearate, and cetyl alcohol [2–4]. Surfactant choice and concentration is important not only to decrease the particle size to nano range but also to ensure stability of the lipid particles produced and prevent aggregation. Too high surfactant concentration may also lead to micelle formation and depending on type of surfactant chosen may lead to toxicity [5]. Surfactants of many types have been successfully used for the preparation of solid lipid nanoparticles; they vary according to their hydrophilicity-lipophilicity balance (HLB). Although majority of surfactants chosen within

previous research were selected based upon popularity and trial and error method, the most commonly include; polysorbates, lecithin's and sorbitan esters [5–7]. SLNs should not be confused with nano lipid carriers which in addition to the compositions of SLNs also include a liquid lipid such as oleic acid, glyceryl tricaprylate, isopropyl myristate and glyceryl dioleate [8,9].

In this review, we aim to identify the importance of SLNs and their methods of preparation, the recent advances and development of different drugs within the nanosized solid lipid core, and finally the advancement in recent research in the formulation of SLNs and the methods in which they were prepared.

## Advantages of SLNs

Solid lipid nanoparticles, are particles of submicron size below 1000 micrometer. Depending on their route of administration they have found to implicate numerous advantages. The use of SLNs have been widely employed to increase solubility of poorly aqueous soluble drugs.

Majority of drugs are delivered via oral route, as it is the most convenient and less invasive method. Research has shown that drug delivery via solid lipid nanoparticles formulations have led to improve bioavailability, reduce

variation in oral absorption, modulate controlled drug release and have shorter onset of action with longer duration times [10-13].

Advantages of SLNs formulations via ocular route drug delivery systems have found to improve therapeutic efficiency and increase; ocular permeation, drug precorneal retention time, ocular bioavailability and distribution, and drug corneal permeability [14-18]. In addition, SLNs have found to prevent ocular toxicity while maintaining sufficient amount of drug in aqueous humor, vitreous humor and retina [14,19].

Transdermal and topical drug delivery systems have numerous biological barriers which limit the use of therapeutic agents. However, the use of nano lipid carriers such as SLNs have been proven to overcome these biological barriers because their nano size can easily allow permeation through the skin. In addition, to the overall modified and controlled drug release, they

promote skin hydration leading to occlusive effects that also aid in drug permeation through the skin. Moreover, the simple components that can be used to formulate SLNs have deemed to be safe on inflamed skin due to their nonirritant and nontoxic nature [20-22].

Nano particles have played an important role in delivery of biological induced drug therapy such as vaccines. They have been widely sought out due to the ability of ease for scaling up manufacturing process. SLNs for parenteral drug delivery have improved bioavailability and like other routes can modify and control drug release. In addition, they have improved stability and have overall reduced clearance and volume of distribution. Due to their nano size researchers have seen enhanced permeability within tumors with increasing retention times leading to a good and promising approach to anticancer targeting drug delivery systems [23-27].

**Table 1: Summary of advantages of SLN according to the route of administration**

| Route of Administration | Advantage(s)  | Ref     |
|-------------------------|---|---------|
| Oral                    | Improve bioavailability<br>Decrease variation in absorption<br>Modulate controlled drug release<br>Shorter onset of action and longer duration of action  | [10-13] |
| Ocular                  | Improve therapeutic efficiency<br>Increase ocular permeation<br>Increase drug precorneal retention time<br>Increase ocular bioavailability and distribution<br>Increase drug corneal permeability<br>Prevent/reduce ocular toxicity<br>Maintain sufficient amount of drug in aqueous humor, vitreous humor and retina | [14-19] |
| Transdermal             | Increase permeation through the skin<br>Safe, nonirritant and nontoxic<br>Modified and controlled drug release  | [20-22] |
| Parenteral              | Most widely used for biologic delivery as vaccines<br>Improved bioavailability<br>Increase stability<br>Reduce in clearance and volume of distribution<br>Promising approach for anticancer therapy   | [23-26] |

### Challenges and disadvantages of SLNs

Although the formulation of drugs via solid lipid nanoparticles have been proven to be advantageous, there are still many challenges the researcher may face during the production, storage and administration

process. Overall similar disadvantages and challenges the researcher may face are that since SLNs are lipid in nature, there is a limited loading capacity for hydrophilic drugs, drug expulsion during storage and instability of the lipid sized particles may lead to aggregation during storage leading to particle size growth [10,28-30].

## Methods

An initial search on MEDLINE/PubMed of solid lipid nanoparticles within the last five years was conducted in February 2025. This led to 1554 results, in order to narrow the scope of literature available this led to a search of "Solid lipid nanoparticles NOT review NOT mRNA NOT DNA NOT RNA". As a result, 923 articles were available for analysis. The main aim was to find original articles/ research designed to determine the different active ingredients, methods of preparations and lipids and surfactants used. This led to another search but excluded evaluation. Finally, 523 articles were subjected for analysis and were carefully read through to determine researches of interest according to criteria.

## Results and Discussion

Accordingly, literature available on PubMed was screened through and summarized according to the method of preparation, active pharmaceutical ingredient, lipid(s) used and surfactant(s) used. These results were summarized and categorized according to the method of which the solid lipid nanoparticles were prepared.

### Methods of preparation of SLNs

Recent literature and investigations have sought out multiple innovative methods of preparing solid lipid nanoparticles. These include; high pressure homogenization, solvent injection/solvent evaporation, phase inversion, microemulsion, ultrasonication and others.

#### High pressure/shear homogenization

The high-pressure homogenization technique is a highly sought out technique due to its simplicity and lack of organic solvent required during processing. This technique requires the preparation of an emulsion consisting of the solid lipid and drug melted to a temperature above the melting point of the lipid followed by addition to the aqueous phase containing the surfactant heated to the same temperature of the lipid solution. This emulsion is then subjected to a high-speed homogenizer with or without pressure as seen by the formation of SLNs of clotrimazole [31]. The presence of pressure is called the high-pressure homogenization method. In the absence of pressure using homogenizer up to 20,000 RPM is known as high shear homogenization method. The homogenizer usually consists of a rotator of high input energy. The emulsion subjected to high speed allows the reduction of particles to a nano size, this emulsion is then allowed to cool for the crystallization of the solid lipid nanoparticles followed by another round of homogenization. Parameters that affect the formation of solid lipid nanoparticles, not only include the formulation design (types and ratios of surfactant and lipid(s) used), but also the rotation speed of the homogenizer, pressure input, time of homogenization and temperature. The main challenge of high-pressure homogenization is the lack of a high energy input homogenizer in small scale laboratories. In addition, the high energy input always leads to increase of temperature of the formulation, thus during the second round of homogenization it is important to keep the system cool as increase in temperature may lead to the coalescence of the particles leading to an increase in size [32].

**Table 2: Recently developed Solid lipid nano particles using homogenization and/or high-pressure homogenization method.**

| Method of preparation        | Drug(s)                         | Lipid(s)                                       | Surfactant (s)      | Ref  |
|------------------------------|---------------------------------|--|---------------------|------|
| Homogenization               | Gemcitabine                     | Cholesterol                                    | Tween 80            | [33] |
|                              | And oxaliplatin                 | Oleic acid                                     | Phosphatidylcholine |      |
| Homogenization               | Paroxetine                      | Glycerol monostearate                          | Tween 80            | [34] |
| High pressure homogenization | Curcumin                        | Hydrogenated soybean phospholipids             | Poloxamer 188       | [35] |
| High shear homogenization    | Combined Rhein and Methotrexate | Glycerol palmitostearate                       | Poloxamer 188       | [36] |
| High pressure homogenization | Beta carotene                   | Glycerol stearate<br>Medium chain triglyceride | Tween 80            | [37] |
| High pressure homogenization | Abiraterone acetate             | Precirol 5 ATO                                 | Kolliphor 188       | [38] |
| High pressure homogenization | Curcumin                        | Stearic acid                                   | Poloxamer 188       | [39] |
| High pressure homogenization | Cannabidiol                     | Compritol 888 ATO                              | Poloxamer 188       | [40] |
| High pressure homogenization | Beta carotene                   | Hydrogenated sunflower oil                     | Soy lecithin        | [41] |
| High pressure homogenization | Irenotecan                      | Tricaprin                                      | Tween 80            | [42] |

|                              |  |                       |                         |      |
|------------------------------|--|-----------------------|-------------------------|------|
|                              |  | Triethanolamine       | Span 20                 |      |
| High shear homogenization    | Sulconazole  | Glycerol monostearate | Tween 20                | [43] |
|                              |  |                       | Phospholipon 90H        |      |
| Homogenization               | Fexofenadine   | Cetyl palmitate       | Tween 20                | [44] |
| Homogenization               | Rapamycin  | Compritol 888 ATO     | Tween 80                | [45] |
| Homogenization               | P-methoxycinnamic  | Cetyl alcohol         | Tween 80                | [46] |
| High pressure homogenization | Apixaban   | Glycerol monostearate | Polyethylene glycol 200 | [47] |
| High pressure homogenization | Streptomycin sulphate                                    | Precirol 5 ATO        | Tween 80                | [48] |
|                              |  |                       | PEG 600                 |      |
|                              |  |                       | Phospholipon 90G        |      |
| Homogenization               | Tetrahydro curcumin                                      | Compritol 888 ATO     | Tween 80                | [49] |
|                              |  |                       | Phospholipon 90G        |      |
| Homogenization               | Revaprazan   | Precirol 5 ATO        | Tween 80                | [50] |
| Homogenization               | Pazopanib  | Compritol 888 ATO     | Tween 80                | [51] |
|                              |  | Precirol ATO 5        |                         |      |
| Homogenization               | Lawson   | Precirol 5 ATO        | Tween 80                | [52] |
|                              |  |                       | Poloxamer 407           |      |
| High pressure homogenization | Simvastatin  | Precirol ATO 5        | Poloxamer 407           | [53] |
| High pressure homogenization | Docetaxel  | Compritol 888 ATO     | Pluronic F127           | [54] |
|                              |  |                       | Span 80                 |      |
| High pressure homogenization | Combination of Paclitaxel and Curcumin                   | Compritol ATO 888     | Tween 80                | [55] |
|                              |  | Stearic acid          |                         |      |
| Homogenization               | Valsartan  | Precirol 5 ATO        | Gelucire 50/13          | [56] |
|                              |  |                       | Pluronic 188            |      |
| High pressure homogenization | Monoterpenes (alpha-pinene, citral geraniol or limonene) | Imwitor 900K          | Poloxamer 188           | [57] |
| Homogenization               | Vancomycin   | Lineolic acid         | Tween 80                | [58] |
| High pressure homogenization | S-adenosyl-Lmethionine                                   | Tristearin            | Tween 80                | [59] |
| High pressure homogenization | Zataria multiflora                                       | Stearic acid          | Span 60                 | [60] |
|                              |  |                       | Tween 80                |      |
| Homogenization               | Combination of Donepezil and rhodamine B                 | Dynasan 116           | Tween 80                | [61] |
| Homogenization               | Ferulic acid   | Compritol ATO 888     | Tween 80                | [62] |
| Homogenization               | Simvastatin  | Compritol ATO 888     | Poloxamer 407           | [63] |
|                              |  | Precirol 5 ATO        | Tween 80                |      |
|                              |  | Geleol                |                         |      |
| Homogenization               | Fucoxanthin  | Coconut oil           | Tween 80                | [64] |
|                              |  | Glyceryl monostearate | Soy lecithin            |      |

|                              |             |                       |                    |      |
|------------------------------|-------------|-----------------------|--------------------|------|
| Homogenization               | Bedaquiline | Lecithin              | Tween 80           | [65] |
| Homogenization               | Myricetin   | Gelucire              | Poloxamer 407      | [66] |
|                              |             | Compritol 888 ATO     |                    |      |
| High pressure homogenization | Curcumin    | Compritol 888 ATO     | Tween 80           | [67] |
|                              |             | Glyceryl monostearate | Phospholipon 90G   |      |
| Homogenization               | Melatonin   | Compritol ATO 888     | Poly vinyl alcohol | [68] |

### Ultrasonication

Ultrasonication method involves the use of a probe or bath sonicator which allows the breakdown of the formed particles into smaller nano sizes. This method highly depends upon the time of sonication and temperature applied. In addition, sonication of samples

for long periods of time may lead to overheating, thus intermittent sonication has been employed to overcome this problem [69]. Particles developed using ultrasonication method may not be as small as high-pressure homogenization however, combination use with other methods have found successful preparations of solid lipid nanoparticles as can be seen in table 3.

**Table 3: Recently developed Solid lipid nano particles using ultrasonication technique.**

| Method     | Drug                        | Lipid(s)                             | Surfactant(s)                   | Ref  |
|------------|-----------------------------|--------------------------------------|---------------------------------|------|
| Sonication | Lacinin 3147                | Softisan 601                         | Kolliphor RH40                  | [70] |
|            |                             |                                      | Transcutol P                    |      |
|            |                             |                                      | DMSO                            |      |
| Sonication | Nisin Z peptide             | Softisan 601                         | Kolliphor RH40                  | [71] |
|            |                             |                                      | Transcutol P                    |      |
|            |                             |                                      | DMSO                            |      |
| Sonication | Vitamin A                   | Stearic acid                         | Tween 80                        | [72] |
| Sonication | Ibuprofen or hydrocortisone | Witepsol                             | Sodium cholate                  | [73] |
|            |                             |                                      | Cremophor A25                   |      |
| Sonication | Curcumin                    | Cetyl palmitate                      | Tween 60                        | [74] |
| Sonication | Triamcinolone acetonide     | Stearic acid                         | Soy PC                          | [75] |
|            |                             |                                      | Tween 80                        |      |
| Sonication | Pterostilbene               | Compritol 888 ATO                    | Poloxamer 188 and poloxamer 407 | [76] |
| Sonication | Rifampicin                  | Cetyl palmitate                      | Tween 80                        | [77] |
| Sonication | Vitamin A                   | Beeswax                              | Tween 80                        | [78] |
|            |                             |                                      | Span 80                         |      |
| Sonication | Gliclazide                  | Compritol 888 ATO                    | Poloxamer 188                   | [79] |
| Sonication | Clozapine                   | Glyceryl behenate                    | Tween 80                        | [80] |
|            |                             |                                      | Poloxamer 188                   |      |
| Sonication | Mitoxantrone                | Cetyl palmitate                      | Tween 80                        | [81] |
| Sonication | Ascorbyl palmitate          | Glyceryl monostearate                | Pluronic F-68                   | [82] |
| Sonication | Mitoxantrone                | Compritol ATO 888<br>Octadecyl amine | Tween 80                        | [83] |
|            |                             |                                      |                                 |      |
| Sonication | Sulforaphene                | Glyceryl monostearate                | Sodium caseinate                | [84] |
| Sonication | Simvastatin                 | Compritol 888 ATO                    | Gelucire 40/14                  | [85] |

| Poloxamer 407 |   |                              |                                      |      |
|---------------|---|------------------------------|--------------------------------------|------|
| Sonication    | Dimethyl fumarate                                       | Glyceryl monostearate        | Poloxamer 188                        | [86] |
|               |   |                              | Hydrogenated soy phosphatidylcholine |      |
| Sonication    | Combination of Paclitaxel and photothermal agent IR-780 | Tricaprin<br>Cetyl palmitate | Pluronic F-68                        | [87] |
| Sonication    | Cyclosporine A  | Softisan 649                 | Tween 80                             | [88] |
| Sonication    | Griseofulvin  | Stearic acid                 | Chitosan                             | [89] |

Abbreviation: DMSO, Dimethyl sulfoxide

#### Solvent injection/Solvent evaporation

The lack of a sophisticated piece of equipment such as high-pressure homogenizer makes the solvent injection/evaporation technique more popular within small scale laboratories. This method involves the addition of the lipid phase solution to the aqueous phase solution heated to the same temperatures by the use of a syringe. The aqueous phase should be maintained at a controlled temperature with constant stirring or agitation usually accomplished by the use of magnetic stirrer. However, the use of an organic solvent usually; ethanol or methanol is required. Suitable methods or time is required until complete evaporation of the solvent [90]. One study done for the development of adapalene SLNs, injected the lipid solution at a constant flow rate [91] which is similar to the methods employed for the development of antifungal miconazole SLNs [92]. In contrast, in another study mometasone lipid phase was rapidly injected into the aqueous phase [93]. These different addition techniques and different stirring speeds and times allows modifications in preparation of the SLNs. Despite the initial stage of solvent injection, the use of sonication is usually used in combination to ensure stable nano sized particle production.

**Table 4: Recently developed solid lipid nanoparticles using solvent injection and/or solvent evaporation technique.**

| Method of preparation | Drug(s)              | Lipid(s)                         | Surfactant (s)                  | Ref   |
|-----------------------|----------------------|----------------------------------|---------------------------------|-------|
| Solvent-evaporation   | Cryptolepine         | Stearic acid                     | Poloxamer 188                   | [94]  |
| Solvent evaporation   | Tacrolimus           | Stearic acid                     | Tween 80<br>Sorbitan monooleate | [95]  |
| Solvent evaporation   | Microalgae omega 3   | Softisan 649                     | Tween 80<br>Soy lecithin        | [96]  |
| Solvent injection     | Prednisolone acetate | Compritol 888 ATO                | Tween 80<br>Pluronic            | [97]  |
| Solvent evaporation   | Cryptolepine         | Stearic acid                     | Poloxamer 188                   | [98]  |
| Solvent injection     | Rhynchophylline      | Glycerol monostearate            | Tween 80<br>Solutol HS 15       | [99]  |
| Solvent evaporation   | Naloxone             | Glycerol monostearate            | Pluronic 127<br>Tween 80        | [100] |
| Solvent evaporation   | Doxorubicin          | Stearic acid<br>Soy lecithin     | Poloxamer 188                   | [101] |
| Solvent evaporation   | Rapamycin            | Compritol ATO 888                | Tween 80                        | [102] |
| Solvent injection     | Naringenin           | Glyceryl tristearate<br>Lecithin | Tween 80<br>Poloxamer 407       | [103] |

### Phase inversion

The phase-inversion temperature method is a low-energy approach for determining the solubility of polyethoxylated nonionic surfactants when temperatures vary. At high temperatures, the surfactant transitions from hydrophilic to hydrophobic, resulting in negative curvatures and water-swollen reverse micelles. At a certain temperature (the PIT temperature), the

surfactant has an affinity for both the oil and water phases, resulting in no spontaneous curvature and exceptionally low interfacial tension values. When the temperature falls below PIT, hydrated nonionic surfactants have high water solubility and produce fine droplets. The preparation of SLNs using phase inversion temperature technique is very limited within the literature with very few having successful outcomes [104].

**Table 5: Recently developed solid lipid nanoparticles using phase inversion method**

| Method of preparation                   | Drug(s)                    | Lipid(s)   | Surfactant (s)                                 | Ref   |
|---|----------------------------|--|--|-------|
| Phase inversion temperature             | Loratadine                 | Beeswax  | Tween 80                                       | [105] |
| Phase inversion Temperature             | Querectin                  | Triplamitin and/or<br>Glycerol monostearate and/or<br>Stearic acid | CRH 40<br>Kolliphor EL<br>Tween 60<br>Tween 80 | [104] |
| Phase inversion temperature/ sonication | benzo[k,l]xanthene lignans | Precirol ATO 5   | Tween 80                                       | [106] |

### Microemulsion

The microemulsion or emulsification method was first introduced by Gasco in 1993 [107]. Recent literature have used similar methods with various modifications. The production of oil in water emulsion is produced by melting lipid phase separately and heating aqueous phase with surfactant separately. The heated aqueous phase is then added to the lipid phase with continuous

stirring usually on a magnetic stirrer to produce an o/w emulsion. This emulsion is then added to cold water to produce a dispersion of SLN. The ratio of emulsion to cold water varies in literature and may range from a 1:10 ratio to 1:50 ratio, emulsion: water [108,109]. However, due to the low input of energy particles produced may not be as small as those compared to high pressure homogenization and other techniques.

**Table 6: Recently developed solid lipid nanoparticles using Microemulsion/emulsification methods**

| Method of preparation  | Drug(s)                                | Lipid(s)                                     | Surfactant (s)               | Ref   |
|------------------------|--|--|------------------------------|-------|
| Solvent emulsion       | Querectin                              | Glyceryl stearate<br>Cholesterol<br>lecithin | Tween 80                     | [110] |
| Microemulsion          | Orobol                                 | Capmul                                       | Transcutol<br>Labrasol       | [111] |
| o/w Emulsion           | Purpurin-18-N-propylimide methyl ester | Palmitic acid or<br>Glycerol monostearate    | Tween 20 or poloxamer 188    | [112] |
| Emulsification         | Dopamine                               | Glycerol tripalmitin                         | Tween 80                     | [113] |
| Microemulsion          | Hydroquinone                           | Stearic acid                                 | Tween 20                     | [114] |
| Microemulsion          | Trans-ferulic acid                     | Compritol 888 ATO                            | Kolliphor EL<br>Transcutol P | [115] |
| Double emulsion        | Albendazole                            | Beeswax                                      | Poloxamer 407                | [116] |
| Solvent emulsification | Flurbiprofen                           | Stearic acid                                 | Tween 80                     | [117] |
| Emulsification         | Dopamine                               | Gelucire 50/13                               | Tween 85                     | [118] |

|                       |   |   |   |       |
|-----------------------|---|---|---|-------|
| Microemulsion         | Isoniazid<br>Pyrazinamide<br>Rifampicin         | Stearic acid<br>Compritol 888 ATO                             | Poloxamer 188<br>Sodium taurocholate          | [119] |
| Microemulsion         | Lacticin 3147                                   | Softisan 601  | Kolliphor HS15<br>Kolliphor RH40              | [120] |
| Microemulsion         | Leflunomide                                     | Compritol 888 ATO   | Tween 80<br>Phospholipon 90G                  | [121] |
| Microemulsion         | Chondroitin sulfate                             | Stearic acid<br>Octadecylamine                                | Poloxamer 188                                 | [122] |
| Emulsification        | Resveratrol                                     | Stearic acid<br>Lecithin                                      | Myrj 52                                       | [123] |
| Emulsification        | Nintedanib                                      | Glyceryl monostearate<br>Stearic acid<br>Palmitic acid        | Tween 80<br>Poloxamer 188                     | [124] |
| Microemulsion         | Topotecan                                       | Tricaprin   | Tween 80<br>Span 20                           | [125] |
| Microemulsion         | Amorolfine HCL                                  | Stearic acid<br>Monostearin                                   | Sodium taurocholate<br>Sodium tauroglycholate | [126] |
| Double emulsification | Tanespimycin                                    | Precirol ATO 5<br>Glycerol<br>Sorbitan monostearate           | B-cyclodextrin<br>Tween 80                    | [127] |
| Double emulsification | Combination streptomycin and hydroxychloroquine | Stearic acid<br>Lecithin                                      | Poloxamer                                     | [128] |
| Double emulsification | Hydroxyzine HCL                                 | Compritol 888 ATO   | Soy lecithin<br>Tween 80                      | [129] |
| Microemulsion         | Chlorophyll                                     | Trilaurin   | Epikuron 200<br>Cremophor RH                  | [130] |
| Microemulsion         | Econazole                                       | Tripalmitic glyceride<br>Glycerol                             | Tween 80                                      | [131] |
| Emulsification        | Resveratrol                                     | Stearic acid<br>Lecithin                                      | Myrj 52                                       | [132] |
| Double emulsion       | Pralidoxime                                     | Dynasan 114<br>Lipoid S75                                     | Tween 80                                      | [133] |
| Emulsification        | Palmitoylethanolamide                           | Stearic acid<br>Cholesteryl stearate                          | Span 85<br>Pluronic F68                       | [134] |
| Microemulsion         | Docetaxel palmitate                             | Palmitic acid OR<br>Stearic acid OR<br>GMS OR Cetyl palmitate | Tween 80                                      | [135] |
| Emulsification        | Ambrisentan                                     | Glyceryl monostearate   | Tween 80                                      | [136] |

Abbreviation: HCL, hydrochloride

### Nano Spray Drying/ Others

Spray drying technique has been explored as a method to increase the stability of nanoparticles due to the aggregation of particles during storage in a dispersed solution, especially drugs that are highly susceptible to high temperatures and light. This method has been suggested to be a one step process, leading to reduction of costs during the processing steps. Major limitations to this technique include the tendency of the spray dried lipids to stick to surfaces leading to difficulties in recovering of the particles, coalescence and solid-state

transition of irregular lipid crystals produced by spray dry method. Although, reduction of particles to nano size may be achievable by spray drying method it is important to also consider the reconstitution properties of the dried nanoparticles. They should be able to be reconstituted with selected aqueous medium to the same nano sized particles without rapid agglomeration. Therefore, there are many factors that need to be considered before the optimum formulation is selected as final product. Factors as drying time, drying temperature, type and amount of lipid used and type and amount of surfactant used [137-139].

**Table 7: Preparation of Solid lipid nanoparticles using methods that are not as frequent**

| Method   | Drug                    | Lipid(s)              | Surfactant(s)                           | Ref   |
|--|-------------------------|-----------------------|---|-------|
| Nano template engineering using micro syringe filter | Melatonin               | Palmityl alcohol      | Span 40<br>Tween 80<br>Myrj 52          | [140] |
| Hot melt extrusion/ sonication                       | Tilmicosin              | Carnauba wax          | PVA or PVP or Poloxamer 188             | [141] |
| Hot melt extrusion                                   | Docetaxel               | Glycerol monostearate | PEG 2000                                | [142] |
| Effervescent dispersion                              | Felodipine              | Glyceryl behenate     | Tween 80<br>Poloxamer 188               | [143] |
| Supercritical  | Hesperidin              | Stearic acid          | Tween 80                                | [144] |
| Microfluidic preparation                             | Trypsin or testosterone | Cetyl palmitate       | Tween 80<br>Pluronic 68<br>Soy lecithin | [145] |
| Solvent diffusion                                    | Rifampicin              | Glyceryl monostearate |   | [146] |
| Solvent diffusion                                    | B-carotene              | Palmitic acid         | Poloxamer 407                           | [147] |
| Thin film sonication                                 | Curcumin                | HSPC                  | PVP K15                                 | [148] |
| Nano spray drying                                    | 5-Fluorouracil          | Palmitic acid         | PVA                                     | [149] |

Abbreviations: PVA, polyvinyl alcohol; PVP, poly vinyl pyrrolidine

### Combination methods

To overcome coalesces and increase the stability of nano emulsions, an innovative method by Glaubitt, introduced combination of a standard method of preparation of nanoparticles and spray drying. By combining ultrasound-assisted or high shear homogenization with spray drying it was assumed to increase the stability of the otherwise unstable long-term emulsions while

keeping the nano sized particles (preventing irregular crystals) [137].

Table 8 gives an indication of recent development of SLNs using combination of techniques. This proves that the use of more than one method is beneficial to overcome problems during the formulation of SLNs, whether the issue being stability, coalesces, preventing degradation and also to achieve desired nano particle size that may not have been achieved if prepared using a single method.

**Table 8: Recently developed solid lipid nanoparticles using a variety/ combination of methods**

| Method   | Drug  | Lipid(s)  | Surfactant(s)                        | Ref   |
|--|---|---|--------------------------------------|-------|
| Combination of double emulsion and melt dispersion   | Ferrous sulfate                                       | Monolaurin<br>Stearic acid                                    | Tween 80                             | [150] |
| Single emulsification and Double emulsification      | Sodium aescinate                                      | Glycerol monostearate<br>Egg yolk lecithin                    | Poloxamer 188                        | [151] |
| Combination hot homogenization and sonication        | Querctine   | Cetyl palmitate   | Tween 80                             | [152] |
| Solvent evaporation/ emulsification                  | Mangiferin  | Cholesterol egg phosphatidylcholine                           | Poloxamer 407                        | [153] |
| Solvent injection and homogenizer and sonication     | Nystatin or fluconazole                               | Glycerol monostearate   | Tween 80<br>Soy lecithin             | [154] |
| Solvent evaporation/ sonication                      | Bimatoprost   | Glycerol monostearate   | Poloxamer 407                        | [155] |
| Emulsification/ evaporation                          | Morin hydrate   | Glycerol monostearate   | Tween 80<br>Soy lecithin             | [156] |
| Emulsification/ sonication                           | Tolfenamic acid                                       | Stearic acid  | PVA                                  | [157] |
| Emulsification/ homogenization and then Spray drying | Levofloxacin  | Stearic acid  | Tween 80<br>PEG 4000                 | [158] |
| Sonication/ homogenization                           | Paclitaxel  | Stearic acid  | Kolliphor 188                        | [159] |
| Emulsification/ sonication                           | Curcumin  | Softisan 100  | Emulmetik 900<br>Solutol HS 15       | [160] |
| Emulsification/ sonication                           | Curcumin  | Medium and long chain diacylglycerol or glycerol tripalmitate | Tween 20 or Quillaja saponin         | [161] |
| Emulsification/ sonication                           | Beta hydroxybutyric acid, carmustine and temozolomide | Cetyl palmitate   | Tween 80                             | [162] |
| Homogenization/ sonication                           | RVG-29 or Quercetin                                   | Cetyl palmitate   | Tween 80                             | [163] |
| Solvent emulsification/ sonication                   | Morin   | Compritol 888 ATO   | Tween 80<br>Phospholipon 80H         | [164] |
| Microemulsion/ sonication                            | Mannose-6-Phosphate-Human serum albumin-matrine       | Glycerol monostearate   | Poloxamer 188                        | [165] |
| Emulsification/ sonication                           | Tetrahydrocurcumin                                    | Glycerol monostearate   | Tween 80<br>Soy lecithin             | [166] |
| Solvent injection/ sonication                        | Paclitaxel or Sorafenib                               | Cetyl palmitate   | Pluronic F68<br>Poly ethylene glycol | [167] |
| Homogenization/ sonication                           | Hesperidin  | Precirol 5 ATO  | Poloxamer 188<br>Span 80             | [168] |
| Emulsification/ solvent evaporation                  | Gellan gum, Alginate and Nisin                        | Stearic acid  | Poly vinyl alcohol                   | [169] |
| Homogenization/ sonication                           | Loteprednol   | Precirol ATO 5  | Tween 80                             | [170] |

|  |                             |  |  |       |
|--|-----------------------------|--|--|-------|
| Emulsification/ solvent evaporation          | Estradiol                   | Compritol 888 ATO<br>Precirol ATO 5                                      | Pluronic F127<br>Tween 80                          | [171] |
| Hot melt extrusion/ homogenization           | Alprazolam                  | Compritol 888 ATO  | Tween 20   | [172] |
| Emulsification/ high pressure homogenization | Vitamin D                   | Precirol 5 ATO   | Tween 80   | [173] |
| Emulsification/ sonication                   | Budesonide                  | Compritol 888 ATO  | Sodium cellulose sulphate                          | [174] |
| Emulsification/ solvent evaporation          | Phytol                      | 1,3-distearyl-2-oleyl glycerol   | Poly vinyl alcohol                                 | [175] |
| Double emulsion/ solvent evaporation         | Gemcitabine                 | Glycerol monostearate  | Soy lecithin<br>Pluronic F127                      | [176] |
| Homogenization/ emulsification               | Retinol and Pentapeptide-18 | Glyceryl monostearate, hexadecyltrimethylammonium, L-phosphatidylcholine | Tween 80<br>Sodium cholate                         | [177] |
| Homogenization/ sonication                   | Cannabidiol                 | Glyceryl mono stearate   | Tween 80   | [178] |
| Homogenization/ sonication                   | 8-Methoxypсорален           | Compritol 888 ATO  | Poloxamer 188<br>Transcutol P                      | [179] |
| High pressure homogenization/ sonication     | Verapamil                   | Stearic acid   | Poloxamer 188                                      | [180] |
| Homogenization/ sonication                   | Amiodarone                  | Witepsol W 35<br>Glyceryl monostearate                                   | Poloxamer<br>Sodium lauryl sulfate<br>Soy lecithin | [181] |
| Double emulsification/ sonication            | Vildagliptin                | Stearic acid   | Tween 80<br>Span 80                                | [182] |
| Homogenization/ sonication                   | Atorvastatin calcium        | Compritol 888 ATO<br>Lipoid S100   | Gelucire 50/13                                     | [183] |
| Homogenization/ sonication                   | Metformin                   | Glyceryl monostearate  | Span 60<br>Tween 80                                | [184] |
| Emulsification/ evaporation/ sonication      | Sunitinib                   | Glyceryl monostearate  | Tween 80<br>Span 80                                | [185] |
| Emulsification/sonication                    | Gefitinib                   | Stearic acid   | Pluronic F-68                                      | [186] |
| Homogenization/ sonication                   | Kojic acid                  | Glyceryl monostearate<br>Cholesterol                                     | Span 60<br>Tween 20                                | [187] |
| Solvent injection/ sonication                | Atorvastatin                | Glyceryl monostearate  | Tween 40<br>Span 80                                | [188] |
| Emulsification/ evaporation                  | Valsartan                   | Glyceryl monostearate<br>Egg lecithin                                    | Poloxamer 407                                      | [189] |
| Emulsification/ sonication                   | Mirabegron                  | Glyceryl monostearate  | Tween 80   | [190] |
| Homogenization/ sonication                   | Caffeic acid                | Compritol 888 ATO  | Tween 80<br>Pluronic F127                          | [191] |

|  |  |  |   |       |
|--|--|--|---|-------|
| Emulsification/ solvent evaporation      | Combination Amphotericin B and paromomycin | Glyceryl monostearate<br>Soy lecithin  | Tween 80<br>Soy lecithin                  | [192] |
| Double emulsification/ sonication        | Insulin                                    | phosphatidylcholine  | Poloxamer 188                             | [193] |
| Sonication/ film dispersion              | Combination curcumin and paclitaxel        | Hydrogenated soybean phospholipids   | Polyvinyl pyrrolidone k15                 | [194] |
| Microemulsion/ homogenization            | Bedaquiline                                | Capmul MCM C10   | Phospholipon 90G<br>Poloxamer 188         | [195] |
| Homogenization/ sonication               | Acyclovir                                  | Compritol ATO 888  | Tween 80                                  | [196] |
| Solvent evaporation/ homogenization      | Metronidazole                              | Precirol ATO 5   | Tween 80                                  | [197] |
| Homogenization/ sonication               | Foeniculum vulgare                         | Stearic acid   | Phosphatidylcholine<br>Tween 80           | [198] |
| Emulsification/ homogenization           | Naringenin                                 | Glyceryl monooleate  | Tocopheryl polyethylene glycol succinate  | [199] |
| Homogenization/ sonication               | Rifampicin                                 | Glycerol tripalmitate  | Tween 80                                  | [200] |
| Emulsification/ sonication               | Alpha-asarone                              | Precirol 5 ATO<br>Palmitic acid  | Gelucire 53/13<br>Tween 80                | [201] |
| Emulsification/ solvent evaporation      | Perphenazine                               | Glyceryl monostearate<br>Lecithin  | Tween 80                                  | [202] |
| Homogenization/ sonication               | Combination of Docetaxel and erlotinib     | Precirol 5 ATO   | Tween 20                                  | [203] |
| Solvent injection/ homogenization        | Oxiconazole nitrate                        | Tyloxapol<br>Stearic acid  | Tween 80<br>Poloxamer 407                 |       |
| Homogenization/ sonication               | Paclitaxel                                 | Precirol 5 ATO<br>Stearic acid   | Tween 20<br>Poloxamer 407<br>Soy lecithin | [204] |
| Solvent injection/ sonication            | Acyclovir                                  | Stearic acid   | Tween 80                                  | [205] |
| Emulsification/ solvent evaporation      | Curcumin                                   | Stearic acid   | Myrj 52<br>Soy lecithin                   | [206] |
| High Pressure homogenization/ sonication | Capsaicin                                  | Compritol ATO 888 OR<br>Glyceryl monostearate<br>AND Cetyl alcohol OR<br>Stearyl alcohol | Span 80<br>Tween 80                       | [207] |
| Emulsification/ sonication               | Brigatinib                                 | Stearic acid   | Soy lecithin                              | [208] |
| Homogenization/ sonication               | Gabapentin                                 | Cholesterol OR Stearic acid  | Tween 80 OR<br>Pluronic F-68              | [209] |
| Homogenization/ solvent evaporation      | Beta sitosterol                            | Compritol ATO 888  | Phospholipon 90G<br>Tween 80              | [210] |
| Emulsification/ solvent evaporation      | Letrozole                                  | Tripalmitin glyceride<br>Octadecylamine  | Tween 80                                  | [211] |

|                                     |                                     |                   |                         |       |
|-------------------------------------|-------------------------------------|-------------------|-------------------------|-------|
| Emulsification/ sonication          | Insulin                             | Compritol ATO 888 | Soy lecithin            | [212] |
|                                     |                                     |                   | Poloxamer 407           |       |
| High pressure homogenization        | Bromelain                           | Stearic acid      | Tween 80                | [213] |
|                                     |                                     | Tristearin        | Span 80                 |       |
| Emulsification/ solvent evaporation | Curcumin                            | Stearic acid      | Myrij 52                | [214] |
|                                     |                                     |                   | Soy lecithin            |       |
| Homogenization/ sonication          | Lavender oil                        | Cholesterol       | Tween 80                | [215] |
|                                     |                                     | Lecithin          |                         |       |
| Emulsification/ solvent evaporation | Delafloxacin                        | Stearic acid      | Pluronic F-127          | [216] |
| Emulsification/ solvent evaporation | Cilnidipine                         | Compritol ATO 888 | Poloxamer 188           | [217] |
| Homogenization/ sonication          | Penicillin                          | Compritol ATO 888 | Lutrol F68              | [218] |
| Homogenization/ sonication          | Paclitaxel                          | Precirol 5 ATO    | Tween 20                | [219] |
|                                     |                                     | Stearic acid      | Poloxamer 407           |       |
|                                     |                                     | Lecithin          |                         |       |
| Emulsification/ homogenization      | Cannabidiol                         | Compritol ATO 888 | Tween 80                | [220] |
|                                     |                                     | Witepsol E85      | Poloxamer 188           |       |
| Emulsification/ sonication          | Combination of curcumin and Lawsone | Cetyl palmitate   | Polyethylene glycol 400 | [221] |
| Emulsification/ sonication          | Abemaciclib                         | Precirol 5 ATO    | Brij 58                 | [222] |
| Emulsification/ sonication          | Acalabrutinib                       | Compritol ATO 888 | Tween 80                | [223] |
|                                     |                                     | Stearyl palmitate | Poloxamer 188           |       |
| Homogenization/ sonication          | Vancomycin                          | Compritol 888 ATO | Lurol F68               | [224] |

Abbreviation: PVA, poly vinyl alcohol

## Conclusion

Development of drugs incorporated with SLNs have been widely explored within recent years. They have been used for specific drug delivery/targeting. Many methods with modifications of each method have been explored depending on specific needs and requirements of the final SLN. The nano size of SLN have found to have advantages within literature but further exploration is required, in addition although SLN have been described within literature very few have been patented and available within the market. Although there have been some formulations described, investigations within preclinical and clinical trials make the use of drug incorporated within SLN a promising future in drug delivery.

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