IJPSR (2019), Volume 10, Issue 9 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 18 January 2019; received in revised form, 09 April 2019; accepted, 20 April 2019; published 01 September 2019

A REVIEW ON SOLID LIPID NANOPARTICLES; FOCUS ON EXCIPIENTS AND FORMULATION TECHNIQUES

Ruhi Anjum and P. K. Lakshmi *

G. Pulla Reddy College of Pharmacy, Mehdipatnam, Hyderabad- 500028, Telangana, India.

Keywords:

Solid lipid nanoparticles, Surfactant, Lipid

Correspondence to Author:
Prof. Dr. P. K. Lakshmi

G. Pulla Reddy College of Pharmacy, Mehdipatnam, Hyderabad- 500028, Telangana, India.

E-mail: drlakshmisuresh@gmail.com

ABSTRACT: Nanotechnology has brought about a significant change in the drug delivery system. A plethora of BCS class II drugs are formulated as solid lipid nanoparticles (SLN) due to its poor solubility and bioavailability and has potential applications in drug delivery system. The formulation of SLN involves use of a different type of surfactants and lipids in different concentrations which has shown a greater impact on various physicochemical parameters such as entrapment efficiency, drug release, particle size, zeta potential, storage and stability of the drug. Apart from its unique size-dependent property, merits and demerits, different excipients characterization technique, scale up, storage and stability are reviewed.

INTRODUCTION: Nanotechnology has shown a wide range of applications in drug delivery, diagnostics, prognostics and in treatment of diseases. It is an emerging branch with an enormous scope which makes the drug targeting more specific in the form of different type of nanoparticles [1, 2]. Nanoparticles may be defined as solid particles with a size range of 10-1000 nm in which the drug can be dissolved, encapsulated, entrapped or attached [3, 4]. Solid lipid nanoparticles are prepared from lipids which are solid at room temperature and body temperature [5]. These comprise of lipid which is biocompatible such as compritol 888, Cetyl alcohol, stearic acid, glyceryl monooleate (GMO), tripalmitin/dynasan, tristearin/ dynasan, *etc*. and surfactant for emulsification. These are the nanoparticles which have a small size, large surface area, high drug loading capacity and have a great potential application (intravenous, oral, dermal) [6]. There are different formulation techniques for the preparation of solid lipid nanoparticles (SLNs) which include high-pressure homogenization, solvent injection, ultra-sonification, microemulsion spray drying [5]. This is a potential delivery system for targeted action of cytotoxic drug [7]. As solid lipid nanoparticles are biocompatible and biodegradable, hence these are used as the carrier for formulating the wide variety of poorly water-soluble drugs [8]. Both hydrophilic and lipophilic drugs are feasible to formulate SLN, and it improves the efficacy of the drug and protects the sensitive drugs from external environmental conditions (water, light) [5]. These nanoparticles have good physical stability and low toxicity [9].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.10(9).4090-99

The article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.10(9).4090-99

Lipids: Lipids are the main ingredient of solid lipid nanoparticles. Usually, the lipids used in the preparation are physiological lipids with low toxicity [5]. Before use, the selection of lipid type and the amount is more desirable criteria anyhow there is no specific criteria but based on the solubility of the drug in the lipid. The drug can accommodate in the structural defects of the lipid

due to different crystal lattice as lipid polymorphism influences lipid nanoparticle system. More thermo-dynamically stable form is perfect crystalline lattice however less stable form or metastable forms tend to transform into more stable form. Since the drug molecules are accommodated in the structural defects of the crystal thus this transformation from one form to another pose a problem in the development of the solid lipid nanoparticles this will create an issue of drug loading. Burst release on administration and drug expulsion on storage may result due to drug loading and other factor that influences the selection of lipid is the rate at which transition from metastable to stable from takes place and the tendency to form perfect crystalline lattice [10].

Surfactant: The other critical component of solid lipid nanoparticles is surfactant which is amphipathic with lipophilic moiety and hydrophilic moiety which form head and tail of surfactant. These are used to reduce the interfacial tension between the two phases. Most commonly used surfactants are from the family of Pluronic® and Tween® [8].

Surfactants for the preparation of solid lipid nanoparticles are chosen based on several factors: hydrophilic-lipophilic balance (HLB) scale, intended route of administration, role in *in-vivo* degradation of the lipid, the effect of particle size and lipid modification [10].

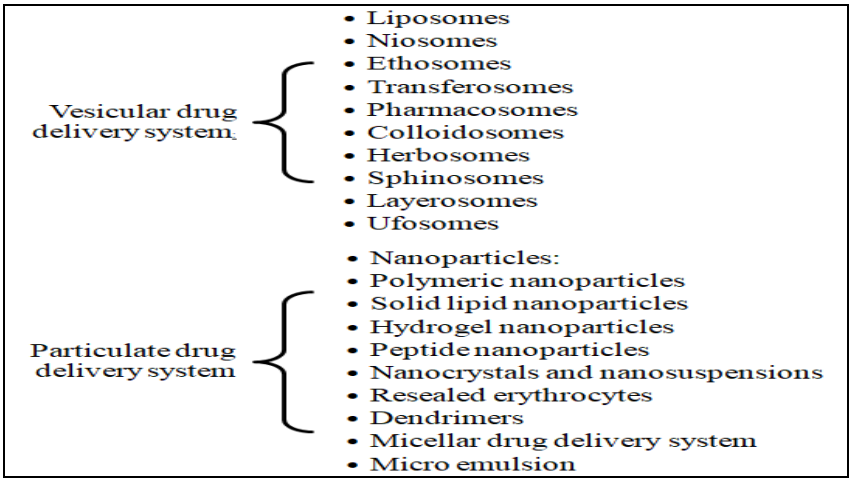

FIG. 1: TYPES OF NANOCARRIER

TABLE 1: DIFFERENT TYPES OF LIPIDS USED IN SOLID LIPID NANOPARTICLES

Lipids	Example	Ref.
Fatty acid	Dodecanoic acid, Myristic acid, Palmitic acid, Stearic acid	11
Monoglyceride	Glyceryl monostearate (GMS), Glyceryl hydroxy stearate, glyceryl behenate	11
Diglycerides	Glyceryl palmitostearate, Glyceryl dibehenate	11,12
Triglycerides	Caprylate triglyceride, Caprate triglyceride, Glyceryl tristearate/tristearate, Glyceryl trilaurate/trilaurate Glyceryl trimyristate/trimyristin, Glyceryl tripalmitate/tripalmitin, Glyceryl tribehenate/tribehenin	11,12
Waxes	Cetyl palmitate, Bees wax	11
Liquid lipids	Soya bean oil, Oleic acid, Medium chain triglycerides (MCT) / caprylic and capric triglycerides, Alpha-tocopherol/vitamin E, Squalene Hydroxy octa-cosanyl, hydroxy stearate Isopropyl myristate	11,12,13
Cationic lipids	Stearyl amine (SA), Benzalkonium chloride, Cetrimide, Cetyl pyridinium chloride, Dimethyl dioctadecyl ammonium bromide (DDAB)	13

TABLE 2: DIFFERENT TYPES OF SURFACTANTS USED IN SOLID LIPID NANOPARTICLES

Surfactant	Example	Ref.
Ionic surfactant	Sodium cholate, sodium taurocholate, sodium taurodeoxycholate, sodium glucocholate, sodium oleate, sodium dodecyl sulphate	13
Non-ionic surfactant	Tween 20, Tween 80, Span 20, Span 85, Tyloxapol, Poloxamer 188, Poloxamer 407, Poloxamer 908, Brij 78, Tego care 450, Solutol HS15	13, 14
Amphoteric surfactant	Egg phosphatidylcholine, soy phosphatidylcholine, Hydrogenated egg Phosphatidylcholine, Hydrogenated soy phosphatidylcholine, Phospholipon 80 H, Phospholipon 90 H	13, 14

TABLE 3: MERITS AND DEMERITS OF SOLID LIPID NANOPARTICLES

Merits	Demerits	Ref.
Biocompatible and biodegradable colloidal carrier	Poor drug loading capacity	11, 12, 16
Prevention of degradation of the drug in body fluid due to encapsulation	Drug expulsion after polymeric transition during storage	11, 12, 16
Increase drug payload	Relatively high-water content of the dispersions (70-99%)	12, 16
The longer half-life of a drug	Particle growth	14, 15, 16
Possibility of sustained release and controlled release of the drug	Unpredictable gelation tendency	12,15, 16
Longer shelf life	Unexpected dynamics of polymeric transitions	15, 16
Drug targeting	Burst release may occur	12, 16
Increased drug dissolution, absorption, and drug bioavailability	Difficulty in manufacturing	11, 15, 16
Feasibility of sterilization and large-scale manufacturing	Appropriate selection of method required	15, 12, 16

TABLE 4: COMMONLY USED FORMULATION TECHNIQUES IN THE PREPARATION OF SOLID LIPID NANOPARTICLES

Formulation technique	Advantages	Drawback	Drugs	Lipids
High-pressure homogenization	Economical and established at lab scale	Energy exhaustive method, biomolecule damage, polydisperse distributions, unconfirmed scalability.	Triamcinolone acetonide acetate, Hydrocortisone, Diazepam, Clotrimazole, Nitrendipine, Isotretinoin, Doxorubicin, Paclitaxel, Vitamin-E, Retinol, Stavudine, Cyclosporine, Oxybenzone, γ-Oryzanol, Vinorelbine-bitartrate	Glyceryl palmitostearate (Precirol®), Glycerol distearate, Glycerol dibehenate, Cetylpalmitate, Glyceryl tripalmitate & (Dynasan® 114), Cetyl palmitate, Glyceryl tripalmitate, Glyceryl tripalmitate, Cetyl palmitate and GMS, Glyceryl palmitostearate, Stearic acid, Tripalmitin, Cetyl palmitate, Tricaprin, Glyceryl behenate and Tribehenate (compritol), Trimyristin (Dynasan 11), Stearic acid, GMS, Cetyl palmitate, Glyceryl behenate, GMS [17-30]
Ultrasonication-high speed homogenization solvent evaporation method	Decrease shear stress, scalable, continuous process, commercially established	Potential metal contamination, extremely energy intensive process, polydisperse distributions	Indomethacin, Vinpocetine, Triptolide, Mifepristone, Oridonin	Glyceryl behenate and Tribehenaten (compritol), GMS, Tristearin glyceride, GMS, Stearic acid, Lecithin [31-35]
The solvent emulsification-diffusion method	Void heat during the production procedure	Biomolecules may get damage	Clobetasol propionate, Gonadorelin Rifampicin, Isoniazid, Pyrazinamide, Doxorubicin	
Supercritical fluid method	Avoid the use of solvents, instead of suspension powder product formed, mild pressure and temperature conditions	Very expensive method	Indomethacin and ketoprofen Bovine serum albumin	Tristearin, tripalmitin and glyceryl behenate (gelucire-50/13), Trimyristin and glyceryl behenate (Gelucire®-50/02) [40-41]
Microemulsion method	Little input of mechanical energy, hypothetical stability	Particularly sensitive to change, labor demanding formulation work, low nanoparticles conc.	Curcuminoids, Podophyllotoxin, Verapamil Tea polyphenol, Cyclosporine A, Insulin, Ketoprofen	Stearic acid and GMS, Stearic acid, Cacao butter, Glyceryl monostearate, Stearic acid, Stearic acid, Beeswax and carnauba wax[42-48]

TABLE 5: SOLID LIPID NANOPARTICLES AS A CARRIER FOR DIFFERENT DRUGS

Drug	BCS class of drug	Therapeutic use	Lipid	Formulation method	Studies
Darunavir	II	Anti-HIV	GMS/Glyceryl Caprylate	High-pressure homogenization	*Ex-vivo* studies using everted rat intestine model [50]
Voriconazole	II	Antifungal	Stearic acid	Ultrasonication/ Microemulsion	Corneal permeation studies (freshly excised from goat) [51]
Gemcitabine	III	Anticancer	Stearic acid	Double emulsification	*In-vivo* drug targeting studies in Wistar rats [7]
Mometasone furoate	II	Treat skin allergies	GMS	Solvent injection	*Ex-vivo* skin permeation studies [52]
Ramipril	II	Antihypertensive	GMO	Hot homogenization	*In-vitro* drug release studies [8]
Vinpocetine	-	Treat Senile dementia	GMS	Ultrasonic solvent emulsification	Oral pharmacokinetic studies in male rats [53]
Paclitaxel	IV	Anti-cancer	Stearic acid, Tripalmitate	Solvent injection	Pharmacokinetic studies in KM mice [54]
Buspirone	I	Anti-anxiety	Cetyl alcohol	Emulsion evaporation	Pharmacokinetic studies in male Wistar rats [55]
Clozapine	II	Antipsychotic	Triglycerides	Hot homogenization	Bioavailability studies in male Wistar rats, tissue distribution studies in Swiss albino rats [56]
Cyclosporine A	II	Immunosuppressant	GMS	Hot homogenization, Microemulsion	Pharmacokinetic studies in young pig [57]
Simvastatin	II	Lipid-lowering medication	Compritol Precirol	Hot melt emulsification method	In-situ intestinal absorption studies, in-vivo studies in rats [58]
Carbamazepine	II	Anticonvulsant	Tristearin	Solvent injection	Maximal electroshock method in male albino Wister rats [59]
Ketoprofen	II	NSAID	Beeswax and Carnauba wax	Microemulsion method	[60]
Diazepam	II	Antianxiety agent	Cetyl palmitate	Hot homogenization	[61]
Clotrimazole	II	Antifungal agent	Glyceryl tripalmitate	Hot homogenization	[62]
Isotretinoin	II	Treat acne	Precirol	Hot homogenization	*In-vitro* skin permeation studies [63]
Doxorubicin	III	Anticancer agent	Glyceryl Caprate (capmul®)	Solvent emulsification-diffusion technique	Cell viability assay [36]
Oridonin	IV	Anticancer agent	Oleic acid, glyceryl monostearate	High-pressure homogenization	Cell culture, cell viability assay [64]
Indomethacin	II	NSAID	Glyceryl behenate and Tribehenate compritol	Homogenization method	*In-vitro* corneal permeation studies [28]
Piroxicam	II	NSAID	compritol	Pre-emulsion probe sonication method	*Ex-vivo* skin permeation studies in rat [65]
Rosuvastatin calcium	II	Treat Primary hyperlipidemia, mixed dyslipidemia, and hypertriglyceridemia.	Stearic acid	Solvent emulsification-diffusion technique	Pharmacokinetics studies in male albino Wistar rat [66]
Candesartan cilexetil	IV	Antihypertensive	Stearic acid	Modified emulsification-ultrasonication method."	Pharmacokinetics studies in male albino Wistar rat [67]

Characterization and Evaluation of SLN:

Particle Size: As per the reported studies, usually a combination of surfactant produces smaller particle size compared to one surfactant alone. For example, tween 80 alone might give higher size nanoparticles when compared to tween 80 and poloxamer 188 in combination. This combination gave smaller size particles because tween 80 and poloxamer 188 rapidly covered the new lipid surfaces generated through the shearing process; thus, reducing aggregation and increasing surface area. Also, surface absorption can be altered by a different combination of emulsifier and their HLB value [68]. Another report had shown that when poloxamer concentration was varied from 0.5% to 1.5% to obtain stable nano-size particles and their effect on particle size was measured, but it was reported that the poloxamer concentration below

1.5% and above 0.5% was effective in producing smaller size SLN.

Larger size SLNs were obtained by increasing the concentration of poloxamer to 1.5%. This report recommends that an optimum concentration of 1% poloxamer was sufficient to give nano-size particles as it covers the surface of nanoparticles effectively and prevent agglomeration during the process. The high concentration of surfactant should be avoided to prevent the reduction in the entrapment efficiency and also toxic effects associated with a high concentration of surfactants [69, 70].

Increasing the lipid content resulted in a subsequent increase in particle size. The viscosity of the samples is one factor to increase the particle size. The use of a low viscosity lipid phase improves size reduction and enhances stability in SLN production. At higher lipid concentrations, the efficiency of homogenization drops due to the higher viscosity of the sample, resulting in larger size particles. Also, high lipid contents increase the chance of particle contact and subsequent aggregation [71, 72].

In addition to lipid concentration, the number of the fatty acid side chain on lipids plays an important role in particle size distribution [73]. In another study of ramipril loaded SLN prepared by using GMS and GMO as a lipid matrix with a different type of surfactant. SLN prepared using GMS has shown large particle size when compared to SLN prepared using GMO. This may be due to the melting point of the lipid; GMS has shown a higher melting point than GMO, which shows slower lipid crystallization from the hot homogenized condition increasing in particle size [8]. In addition to lipid concentration, the number of the fatty acid side chain on lipids play an essential role in particle size distribution [73].

Zeta Potential: Zeta potential is one of the important surface characterization techniques as it indicates a repulsive force between particles, to prevent the aggregation of nanoparticles, helps in determining the possible stability and surface charge of the nanoparticulate system [74]. Usually, large negative or positive zeta potential value is required for formulation stability, as electrostatic repulsion between particles with same charges avoid aggregation of particles. It was noticed in the previous studies that as the amount of surfactant is increased in the formulation, the zeta potential became more negative. A similar result was reported earlier upon increasing tween 80 concentrations from 0.5 to 1%, which was attributed to the formation of a denser surfactant film. Poloxamer 188 being non-ionic surfactant was able to produce the stable SLN formulation.

Although, non-ionic surfactant might not ionize into a charging group like ionic ones, still demonstrated its zeta potential. The reason behind it might be due to molecular polarization and the adsorption of emulsifier molecule on the charge in the water; it gets absorbed to the emulsion layer of the particle/water interface and electric double layer similar to ionic was formed. Poloxamer 188 was one of the most effective non-ionic surfactants to avoid aggregation in the formulation. In addition to electrostatic stabilization poloxamer, 188 can also provide additional steric stabilization to particles. So, the combined effect of both electrostatic and steric stabilization is expected in the SLN formulations [72]. In previous studies, it was found that due to the carboxyl group of stearic acid the formulation which contains stearic acid as the lipid phase has shown negative values of zeta potential[67].

Entrapment Efficiency (EE): Entrapment efficiency is a significant factor for characterizing SLN. In earlier studies by Ekambaram P, Sathali AA reported that all SLN formulations showed high entrapment efficiency using a higher concentration of surfactant irrespective of the type of surfactant. Thus, by increasing surfactant concentration may show a positive effect on EE. This might be due to the enhanced solubility of the drug in the lipid by increasing the concentration of the surfactant. The result was in agreement with the results obtained in previous studies, as the formulation in the studies contain span 20 as a surfactant which has lower HLB value this might be the reason why the formulations containing span 20 showed lower entrapment efficiency. Hence, the entrapment efficiency of various SLNs stabilized by different non-ionic surfactants and increased in the order of span 20 > tween 80 > poloxamer 188. [8]

The data provided by Rawia M. Khalil *et al.,* suggested that all formulations possessed high EE. The results might be related to the structure of the lipid as drug incorporation capacity is dependent on structure of lipid. Drug expulsion might occur in formulation with lipids, which form highly crystalline particles with a perfect lattice (*e.g.,* non-acid triglycerides); a large number of drugs is incorporated by complex lipid forms which have less perfect crystals with several imperfections provide space too. It was found that compritol and precirol SLNs exhibited the highest entrapment of drug compared to geleol SLNs. This can be due to the difference in composition and chain length of these three lipids used.

Due to the long chain, fatty acids attached to the triglycerides, resulting in increased accommodation of lipophilic drug, thus higher drug EE noticed with compritol and precirol. It was also evident that increasing the amount of surfactant at a constant amount of lipid resulted in a significant gradual decrease in the EE of the produced SLNs. This observed decrease in EE could be explained by partition phenomenon. An increase in the partition of the drug from internal to an external phase of the medium may be due to the high surfactant level in the external phase. The increased solubilization of the drug in the external aqueous phase increased the partition so that more drug can disperse and dissolve in it. In case of the formulation containing geleol as lipid, there was no further decrease in EE upon increasing the poloxamer 188 concentrations signifying that an optimum concentration of surfactant was reached enough to cover up the surface of nanoparticles effectively [72]. The higher drug content and entrapment efficiency might be due to the high hydrophobicity due to the long chain fatty acids attached to the triglyceride resulting in high loading of lipophilic drug [75].

Apart from the influence of different lipids and surfactants effect of pH was also found on the EE. The formulations prepared with different fractions of tween 80 and adjusted to different pH values. Indeed, both the fractions of tween 80 in the formulation and the formulation pH had a significant effect on the percentage of drug incorporated within the SLNs. weakly acidic drugs having (pKa of 4.5) demonstrated a pH-dependent EE, consistent with the pH-dependent solubility, which exists predominately in the ionized form above pH 4.5, which will help localize in the aqueous medium. The reported data showed that at all pH values SLNs were stabilized, but with only tween 80, it has shown higher EE. As the fraction of tween 80 in the formulation decreased, a significant decrease in the entrapment of drug in the SLNs was observed at all pH values [76].

***In-vitro* Drug Release Studies:** In recent studies by Ekambaram P, Sathali AA *et al.,* reported that the melting point of lipid, the crystal structure of lipid and HLB value of surfactant affects drug release. Formulations prepared by using GMS as a lipid matrix, with tween 80, poloxamer 188 and span 20 as stabilizers showed a higher drug release. There was an increase in the drug release with the increase in the concentration of the surfactant from the SLN.

But this variation could not be attributed to the formulations prepared by using GMO as a lipid matrix with tween 80, poloxamer 188, and span 20. With an increase in the concentration of surfactant, there was a decrease in the drug release, which could be due to the higher melting point of the GMS than the GMO. The results indicated that formulation with GMS+ poloxamer 188 exhibited a higher drug release and formulation with GMO + span 20 showed a higher decline in the drug release among the three surfactants studied. The reason might be due to the lower HLB value of span 20 (8.6) than the other surfactants used as stabilizers. Thus, the order of the percentage of drug release was span 20 < tween 80 < poloxamer 188 based on the stabilizer. The higher drug release was found for the formulations containing GMS than GMO as a lipid matrix, which showed a more sustained release.

The drug expulsion might occur in GMS when compared to GMO because it has less ordered crystals than GMS and there is less or no drug expulsion from the formulation with GMO because of the imperfect lattice of GMO, leading to the prolonged release of the lipophilic drug. Moreover, GMO has a lower melting point when compared to GMS. The order of the percentage of drug release was GMO < GMS based on the lipid matrix. The drug released was much controlled and slower from

the formulation prepared by using GMO with Span 20. [8]

In the recent studies, it was reported that among all the glycerides used, the formulation with different lipid melting points might show impact release profile, this was in attribution with recent studies with ibuprofen and acylglycerols differing in melting points. The mean diameter of geleol nanoparticles tested was small which suggested the higher amount released from geleol particles. Increase in the lipid concentration resulted in a subsequent decrease in the percentage drug release. However, for geleol and precirol SLNs further increase of the lipid resulted in a significant decrease in the release. This decrease in release profile observed can be attributed to the higher lipid content, the drug encapsulation thus reducing drug partition in the external phase and consequently its release in the receiver media [72].

SLN has the property of initial burst release but later sustained release of drug from SLNs which suggests that drug might have dispersed in the lipid matrix and the adsorption of drug onto the surface of SLNs need not be considered. It generally depends on the preparation procedure. After the organic solvent had been evaporated, the drug gets dissolved in the lipidic Nanoemulsion. The rapid quenching of the nanoemulsion might not have allowed the drug to crystallize, and the drug gets trapped in the solid lipid [77].

Storage and Stability: SLNs have been used in different dosage forms such as oral, topical, etc using various drugs. Some drugs are temperature and light sensitive, and several studies have shown that light and temperature have an impact on the stability of SLN, it may induce particle growth. To keep SLN and dosage form stable it should be stored at 4°C and in dark environment [16, 78]. The way to increase its stability is to convert it into spray dried form another way to increase the stability is by lyophilization. In the case of lyophilization done without cryoprotectants may cause the formation of aggregates in the final product. The commonly used cryoprotectants are trehalose, glucose, maltose, sucrose, and sorbitol. Trehalose was found to be the most effective cryoprotectant for preventing the drug expulsion upon reconstitution [79, 80, 81].

Scale Up of Solid Lipid Nanoparticles: Nanomedicine products are superior to conventional drug delivery system in their therapeutic performance. Hence, they are highly in demand. All the methods described for the production of SLN are either bottom-up methods or top-down methods. Top-down methods are adopted at the industrial level as bottom-up methods require removal of the residual solvents. There are some of the components associated with the scale-up of SLNs from the bench to the market. They are:

- Nature of material.
- Generally regarded as safe (GRAS) status.
- Toxicological features associated with the shape and size of SLN.
- *In-vivo* biodegradability.

For balancing the multi-component system at large scale, one has to be careful before selecting the material, solvent, procedure, cost and the acceptability of finished product by clinician and patients. After the product is optimized, the product has to go through different steps [82].

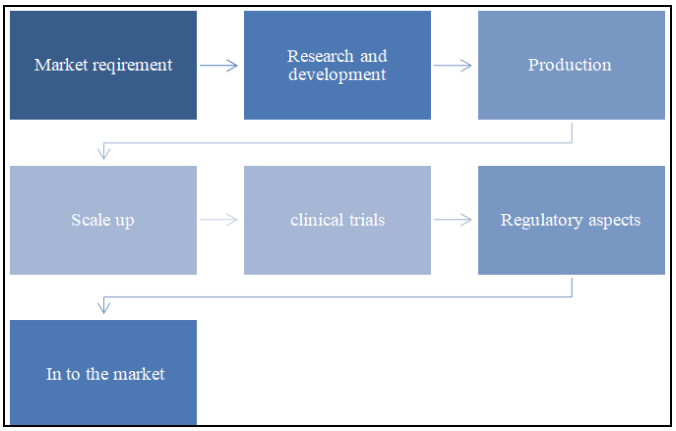

FIG. 2: SCALE-UP OF SOLID LIPID NANOPARTICLES

CONCLUSION: SLN formulations are widely used to deliver lipophilic drugs. This system has shown potential to improve gastrointestinal absorption and oral bioavailability of many oral drug delivery systems apart from its applications in topical drug delivery. This delivery system is used for sustained, controlled and targeted drug delivery systems.

Wide ranges of excipients are available in the market for the formulation of SLN, but these excipients used should be approved by the

regulatory authority. The attractive feature of this formulation system is that it can be easily scaled up. Toxicity studies are required for the excipients with doubtful, unapproved and if used in higher quantities.

ACKNOWLEDGEMENT: Nil

CONFLICT OF INTEREST: Nil

REFERENCES:

1. Martin CR: Welcome to nanomedicine. Nanomedicine 2006; 1: 5-5.
2. Murthy RSR: Vesicular & particulate drug delivery system, nanoparticles, Career Publications, Edition 1st, 2010: 233-63.
3. Buzea C, Pacheco I and Robbie K: Nanomaterials and nanoparticles: sources and toxicity. Biointerphases 2007; 2: 17-71.
4. Mohanraj VJ and Chen Y: Nanoparticles-a review. Trop J Pharm Res 2006; 5.
5. Das S and Chaudhury A: Recent advances in lipid nanoparticles formulation with a solid matrix for oral drug delivery. AAPS Pharm Sci Tech 2011; 12: 62-67.
6. Joshi M, Lata S, Kanwar P and Mishra T: Application of nanostructures in antimicrobial therapy. International Journal of Applied Pharmaceutics 2018; 10: 11-25.
7. Nandini PT, Doijad RC, Shivakumar HN and Dandagi PM: Formulation and evaluation of Gemcitabine -loaded solid lipid nanoparticle. Drug Delivery 2015; 22: 647-51.
8. Ekambaram P and Abdul Hassan Sathali A: Formulation and evaluation of solid lipid nanoparticles of ramipril. J Young Pharmacist 2011; 3: 216-20.
9. Kasar PM, Kale KSR and Phadtare DG: Nanoplex: a review of nanotechnology approach for solubility and dissolution rate enhancement. Int J Curr Pharm Res 2018; 10: 6-10.
10. Madan J, Pandey R, Jain V, Katare O, Chandra R and Katyal A: Poly (ethylene) - glycol conjugated Solid lipid nanoparticles of noscapine biological half-life, brain delivery and efficacy in glioblastoma cells. Nanomed Nanotechnology 2013; 9: 492-03.
11. Yadav N, Khatak S and Sara UVS: Solid lipid nanoparticles-A review. Int J App Pharm 2013; 5: 8-18.
12. Pandey P, Gupta PC and Yadav S: Solid lipid nanoparticle: A potential approach in drug delivery system. European Journal of Pharmaceutical and Medical Research 2018; 5: 225-36.
13. Shah: Lipid Nanoparticles: production, characterization and stability. Springer Briefs in Pharmaceutical Science & Drug Development 2012; 11-22.
14. Sarangi MK and Padhi S: Solid lipid nanoparticles-a review. J Crit Rev 2016; 23: 5-12
15. Rupenagunta A, Somasundaram I, Ravichandiram V, Kausalya J and Senthilnathan B: Solid lipid nanoparticles-A versatile carrier system. J Pharm Res 2011; 4: 2069-75.
16. Ekambaram P, Sathali AH and Priyanka K: Solid lipid nanoparticles: A review. Scientific Review and Chemical Communication 2012; 2: 80-96.
17. Liu W, Hu M, Liu W, Xue C, Xu H and Yang XL: Investigation of the carbopol gel of solid lipid nanoparticles for the transdermal iontophoretic delivery of triamcinolone acetonide acetate. Int J Pharm 2008; 364: 135-41.
18. Jensena LB, Magnusson E, Gunnarsson L, Vermeheren C, Nielsen HM and Petersson K: Corticosteroid solubility and lipid polarity control release from solid lipid nanoparticles. Int J Pharm 2010; 390: 53-60.
19. Sznitowska M, Gajewska M, Janicki S, Radwanska A and Lukoswski G: Bioavailability of diazepam from aqueous-organic solution, submicron emulsion and solid lipid nanoparticles after rectal administration in rabbits. Eur J Pharm Biopharm 2001; 52: 159-63.
20. Souto EB, Wissing SA, Barbossa CM and Muller RH: Development of a controlled released formulation based on SLN and NLC for topical clotrimazole delivery. Int J Pharm 2004; 278: 71-7.
21. Kumar VV, Chandrashekar D, Ramakrishna S, Kishan V, Rao YM and Diwan PV: Development and evaluation of nitrendipine loaded solid lipid nanoparticles: Influence of wax and glyceride lipids on plasma pharmacokinetics. Int J Pharm 2007; 335: 167-75.
22. Liu J, Hu W, Chen H, Ni Q, Xu H and Yang X: Isotretinoin-loaded solid lipid nanoparticles with skin targeting for topical delivery. Int J Phar 2007; 328: 191-5.
23. Miglietta A, Cavalla R, Bocca C, Gabriel L and Gasco MR: cellular uptake and cytotoxicity of solid lipid nanospheres (SLN) incorporating doxorubicin or paclitaxel. Int J Pharm 2000; 210: 61-7.
24. Dingler A, Blum RP, Niehus H, Gohla S and Muller RH: Solid lipid nanoparticles (SLN/Lipopearls)-a pharmaceutical and cosmetic carrier for the application of vitamin E in dermal products. J Microencapsul 1999; 16: 751-67.
25. Jee JP, Lim SJ, Park Js and Kim CK: Stabilization of all-trans retinol by loading lipophilic antioxidants in solid lipid nanoparticles. Eur J Pharm Biophar 2006; 63: 134-9
26. Shegokar R, Singer KK and Muller RH: Production & stability of stavudine solid lipid nanoparticles-From lab to industrial scale. Int J Pharm 2011; 416: 461-70.
27. Muller RH, Runge S, Ravelli V, Mehnert W, Thunemann AF and Souto EB: Oral bioavailability of cyclosporine: solid lipid nanoparticles (SLN) *vs.* drug nanocrystals. Int J Pharm 2006; 317: 82-9.
28. Pandya BJ, Parmar DR, Soniwala MM and Chavda JR: Solid Lipid Nanoparticles: Overview on excipients. Asian Journal of Pharmaceutical Technology & Innovation 2013; 01(03): 01-09.
29. Seetapan N, Bejrapha P, Srinuanchai W and Ruktanonchai UR: Rheological and morphological characterization on the physical stability of gamma-oryzanol-loaded solid lipid nanoparticles (SLNs). Micron 2010; 41: 52-8.
30. You J, Wan F, Cui FD, Sun Y, Du Y and Hu FQ: Preparation and characteristic of vinorelbine bitartrate loaded solid lipid nanoparticles. Int J Pharm 2007; 343: 270-6.
31. Castelli F, Puglia C, Sarpietro MG, Rizza L and Bonina F: Characterization of indomethacin-loaded lipid nanoparticles by differential scanning calorimetry. Int J Pharm 2015; 304: 231-8.
32. Luo YF, Chen DW, Ren LX, Zhao XL and Qin J: Solid lipid nanoparticles enhancing vinpocetine's oral bioavailability. J Control Release 2006; 114: 53-9.
33. Mei Z, Li X,Wu Q, Hu S and Yang X: The research on the anti-inflammatory activity and hepatotoxicity of triptolide-loaded solid lipid nanoparticles. Pha Res 2005; 51: 345-51.
34. Hou DZ, Xie CS, Huang KJ and Zhu CH: The production and characteristics of solid lipid nanoparticles (SLNs). Biomaterials 2003; 24: 1781-5.
35. Zhang D, Tan T and Gao L: Preparation of oridonin-loaded solid lipid nanoparticles and studies of them *in-vitro* and *in-vivo*. Nanotech 2006; 17: 5821-8.

36. HU FQ, Yaun H, Zhang HH and Fang M: Preparation of solid lipid nanoparticles with clobetasol propionate by novel solvent diffusion method in aqueous system and physicochemical characterization. Int J Pharm 2002; 239: 121-8.
37. HU FQ, Yaun H, Zhang HH and Fang M: Preparation of solid lipid nanoparticles containing peptide. Int J Pharm 2004; 273: 29-35.
38. Pandey R, Sharma S and Khuller GK: Oral solid lipid nanoparticle-based anti-tubercular chemotherapy. Tuberculosis 2005; 85: 415-20.
39. Subedi RK, Kanga KW and Choi H: Preparation and characterization of solid lipid nanoparticles loaded with doxorubicin. Eur J Pharm Sciences 2009; 37: 508-13.
40. Chattopadhyay P, Shekunov By, Yim D, Cipolla D, Boyd B and Farr S: Production of solid lipid nanoparticles suspension using supercritical fluid extraction of emulsion (SFEE) for pulmonary delivery using the AERx system. Adv Drug Deliv Rev 2007; 59: 444-53.
41. Santos IRD, Richard J, Pech B, Thies and Benoit JP: Microencapsulation of protein particles within lipid using a novel supercritical fluid process. Int J Pharm 2002; 242: 69-78.
42. Tiyaboonchai W, Tungpradit W and Plianbangchang P: Formulation and characterization of curcuminoids loaded solid lipid nanoparticles. Int J Pharm 2007; 337: 299-306.
43. Xie FM, Zeng K, Li GF, Lin ZF and Sun LD: Preparation of stearic acid solid lipid nanoparticles containing podophyllotoxin. Di Yi Jun Yi Da XueXue Bao 2005; 25: 99-01.
44. Kim BD, Na K and Choi HK: Preparation and characterization of solid lipid nanoparticles (SLN) made of cacao butter and curdlan. Eur J Pharm Sci 2005; 24: 199-05.
45. Ma QH, Xia Q and Lu YY: Preparation of tea polyphenols loaded solid lipid nanoparticles based on the phase behaviours of hot microemulsions. Solid State Phenomena 2007; 121-123: 705-08.
46. Ugazoi E, Cavalli R and Gasco MR: Incorporation of cyclosporin A in solid lipid nanoparticles (SLN). Int J Pharm 2002; 241: 341-4.
47. Zhang N, Ping Q, Huang G, Xu W, Cheng Y and Han X: Lecithin modified solid lipid nanoparticles as carriers for oral administration of insulin. Int J Pharm 2006; 327: 153-9.
48. Kheradmandnia S, Vasheghani-Farahani E, Nosrati M and Atyabi F: Preparation and characterization of ketoprofen-loaded solid lipid nanoparticles made from beeswax and carnauba wax. Nanomedicine 2010; 6: 753-9.
49. Charcosset C, El-Harati A and Fessi H: Preparation of solid lipid nanoparticles using a membrane contactor. J Control Release 2005; 108: 112-20.
50. Bhalekar M, Upadhaya P and Madgulkar A: Formulation and characterization of solid lipid nanoparticles for an anti-retroviral drug darunavir. Appl Nanosci 2017; 7: 47-57.
51. Kare A, Singh I, Pawar P and Grover K: Design and evaluation of voriconazole loaded solid lipid nanoparticles for ophthalmic application. Journal of Drug Delivery 2016; 2016: 1-11.
52. Jyotsana Madan R, Priyanka Khude A and Dua K: Development and evaluation of solid lipid nanoparticles of Mometasone furoate for topical delivery. Int J Pharma Investing 2014; 4: 60-4.
53. Luo YF, Chen D, Ren L, Zhao X and Qin J: Solid lipid nanoparticles for enhancing vinpocetine's oral bioavailability. Journal of Controlled Release 2006; 114: 53-59.
54. Chen DB, Yang TZ, Lu WL and Zhang Q: *In-vitro* and *in-vivo* study of two types of long-circulating solid lipid nanoparticles containing paclitaxel. Chem Pharm Bull 2001; 49: 1444-47.
55. Varshosaz J: Formulation and optimization of solid lipid nanoparticles of buspirone HCl for enhancement of its oral bioavailability. J of Liposome Research 2010; 20: 286-96.
56. Venkateshwarlu V: Preparation, characterization and in vitro release kinetics of clozapine solid lipid nanoparticles. J Control Release 2004; 95: 627-38.
57. Muller RH, Runge S, Ravelli V, Mehnert W, Thunemann AF and Souto EB: Oral bioavailability of cyclosporine: solid lipid nanoparticles (SLN) *vs.* drug nanocrystals. Int J Pharm 2006; 317: 82-9.
58. Padhye SG and Mangal Nagarsenker S: Simvastatin solid lipid nanoparticles for oral delivery: Formulation development and *in-vivo* evaluation. Indian Journal of Pharmaceutical Science 2013; 75: 591-98.
59. Rahul Nair: Formulation and evaluation of chitosan solid lipid nanoparticles of Carbamazepine. Lipid health Dis 2012; 11: 72.
60. Kheradmandnia S, Vasheghani-Farahani E, Nosrati M and Atyabi F: Preparation and characterization of ketoprofen-loaded solid lipid nanoparticles made from beeswax and carnauba wax. Nanomedicine 2010; 6: 753-9.
61. Bary A and Fahmy RH: Diazepam-loaded solid lipid nanoparticles: design and characterization. AAPS Pharma Sci-Tech 2009; 10: 211-9.
62. Madhushri M, Thakur RS, Kiran Jadhav K and Ronak Patel N: Formulation and evaluation of solid lipid nanoparticles containing clotrimazole. Am J Pharm Tech Res 2012; 2: 537-50.
63. Liu J, Hub W, Chena H, Ni Q, Xua H and Yang X: Isotretinoin-loaded solid lipid nanoparticles with skin targeting for topical delivery. International Journal of Pharmaceutics 2007; 32: 191-95.
64. Wang L, Wang S, Chen R, Wang Y, Li H, Wang Y and Chen M: Oridonin loaded solid lipid nanoparticles enhanced anti-tumor activity in MCF-7 cell. Journal of Nanomaterials 2014; Article ID 903646: 1-11.
65. Bhalekar R, Mangesh, Upadhaya P and Madgulkar A: Solid lipid nanoparticles incorporated transdermal patch for improving the permeation of piroxicam. Asian Journal of Pharmaceutics 2016; 10: 45-50.
66. Singh H, Gupta RD and Gautam G: Formulation development, characterization, and *in vitro-in vivo* study of antihyperlipidemic drug rosuvastatin calcium - solid lipid nanoparticles. Asian J Pharm Clin Res 2018; 11: 436-43.
67. Mahajan A and Kaur S: Design, formulation, and characterization of stearic acid-based solid lipid nanoparticles of candesartan cilexetil to augment its oral bioavailability. Asian J Pharm Clin Res 2018; 11: 344-50.
68. Mohtar N, Nurzalin Khan AK and Darwis Y: Solid Lipid nanoparticles of atovaquone based on 24 full-factorial design. Iranian J of Pharm Res 2015; 14: 989-1000.
69. Muller RH, Mader K and Gohla S: Solid lipid nano-particles (SLN) for controlled drug delivery-a review of the state of the art. Eur J Phar Biophar 2000; 50: 161-77.
70. Kumar V, Chandrasekar D, Ramakrishna S, Kishan V, Rao YM and Diwan PV: Development and evaluation of nitrendipine loaded solid lipid nanoparticles: Influence of wax and glyceride lipids on plasma pharmacokinetics. International J of Pharmaceutics, 2007; 335: 167-75.
71. Rahman. Z, Zidan AS and Khan MA: Non-destructive methods of characterization of risperidone solid lipid nanoparticles. European Journal of Pharmaceutics and Biopharmaceutics 2010; 76: 127-37.

72. Rawia Khalil M, El-Bary AA, Mahfoz Kassem A, Mamdouh Ghorab M and Mona Ahmed B: Solid lipid nanoparticles for topical delivery of meloxicam: development and *in-vitro* characterization. 1st Annual Inter Interdisciplinary Conference AIIC 2013; 779-98.
73. Niamprem P, Srinivas SP and Tiyaboonchai W: Development and characterization of indomethacin-loaded mucoadhesive nanostructured lipid carriers for topical ocular delivery. International Journal of Applied Pharmaceutics 2018; 10: 91-96.
74. Diniyanti SN, Werawatganone P and Muangsiri W: Preparation of solid lipid nanoparticles containing mangosteen pericarp extract. Asian Journal of Pharmaceutical and Clinical Research 2018; 11: 81-84.
75. Jenning V and Gohla S: Comparison of wax and glycerides solid lipid nanoparticles. Int J Pha 2000; 196: 219-22.
76. Hippalgaonkar K, Goutham Adelli R, Michael Repka A and Majumdar S: Indomethacin solid lipid nanoparticles for ocular delivery. Journal of Ocular Pharmacology and Therapeutics 2013; 29(2): 216-28.
77. Chen DB, Yang TZ, Lu WL and Zhang Q: *In-vitro* and *in-vivo* study of two types of long-circulating solid lipid nanoparticles containing paclitaxel. Chem Pharm Bull 2001; 49: 1444-47.
78. Sarangi MK and Padhi S: Solid lipid nanoparticles-a review. J Crit Rev 2016; 3: 5-12.
79. Das S and Chaudry A: Recent advances in lipid nanoparticles formulation with a solid matrix for oral drug delivery. AAPS Pharma Sci-Tech 2011; 12: 62-76.
80. Kramer T, Kremer DM, Pikal MJ, Petre WJ, Shalaev EY and Gatlin LA: A procedure to optimize scale-up for the primary drying phase of lyophilization. J Pharm Sci 2009; 98: 307-18.
81. Schwarz C and Mehnert W: Freeze-drying of drug-free and drug-loaded solid lipid nanoparticles (SLN). Int J Pharm 1997; 157: 171-9.
82. Paliwal R, Babu RJ and Palakurthi S: Nanomedicine scale-up technologies: feasibility and challenges. AAPS Pharm Sci Tech 2016; 15: 1527-34.

How to cite this article:
Anjum R and Lakshmi PK: A review on solid lipid nanoparticles; focus on excipients and formulation techniques. Int J Pharm Sci & Res 2019; 10(9): 4090-99. doi: 10.13040/IJPSR.0975-8232.10(9).4090-99.

All © 2013 are reserved by International Journal of Pharmaceutical Sciences and Research. This Journal licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 3.0 Unported License.

This article can be downloaded to **Android OS** based mobile. Scan QR Code using Code/Bar Scanner from your mobile. (Scanners are available on Google Play store)