REVIEW ARTICLE

Solid Lipid Nanoparticle; A Potential Lipid-Based Drug Delivery System

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ABSTRACT

The opportunity of delivery of orally administered drugs could be delivered efficiently and smoothly by adopting nanomedicine technology. Solid lipid nanoparticles (SLNs) are featured as a member of a nanomedicine platform and another age of lipid nanoparticles comprising of full lipid matrix as solidify. Oral administration of SLNs exhibits many benefits that exceed ordinary formulations, including well solubility, well-being stability, enhanced membrane permeability, sufficient blood availability, extended half-life, and, finally, lesser side effects.

Keywords: Lipid, Lipid based oral delivery systems, Solid lipid nanoparticles, Surfactant.

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INTRODUCTION

Lipid-Based Drug Delivery

The physiochemical decent variety and biocompatibility of lipids and their capacity to improve oral bioavailability of medications have made lipid nanoparticles take a new dimension with appealing carriers for oral drug delivery. Due to the perception that the oral bioavailability of lipophilic drugs such, troglitazone and atovaquone[1] were significantly enhanced when co-administered with a meal rich in fat, this has led to increasing neoteric usefulness in the formulation of lipophilic drugs in lipids as a promising way to improve sedate solubilization in the Gastrointestinal (GI) tract.[2]

Difficulties of Lipid-Based Conveyance

With the advent of drug design, various molecules with potential for remedial activity have been made. However, most newly revealed substances belong to the biopharmaceutical classification system (BCS)-II, with low aqueous solubility and high membrane permeability. Hence these two features make a frontier the bioavailability of orally administered drugs.[3]

These lipids advance the sub-atomic solubilization potential, porousness, and lymphatic vehicle of the lipophilic medications.[4] Moreover, lipid-based bearers are confirmed to be an appealing possibility for pharmaceuticals readiness, just as diagnostics, antibodies, and nutraceuticals.[5]

The Lipid Formulation Classification System

Lipid-based formulations was first proposed by Colin Pouton in 2000,[6] and modified in 2006;[7] lipid-based formulations differentiate four categories as shown in Table 1.

Type I formulations require desirable digestion in GI tracts aiming to form dispersion as they are oils in features named (triglycerides or mixed mono and diglycerides). While next classified is a type II formulations which ranged within a coarse emulsion (0.25–2µm), and specify as self-emulsifying, like (nonionic surfactants with hydrophilic-lipophilic balance (HLB) values of approximately eleven.

For type III details incorporate water-solvent components, produce exceptionally fine scatterings dispersions (less than100nm), it seems as an optically clear), and further sub-incise into type IIIA and IIIB, and the final one is type IV. it contains no lipid and produces acceptable solutions according to the concentration of surfactant.[8]

The explanations behind the expanding enthusiasm for the lipid-based system are many – overlay include:[9]

- Modified release obtained.
- Pharmaceutical stable platform.

Table 1. Lipid formulation classification system formulation classification system [13]

Excipients in formulations	Content of formulation (%, w/w)				
	Type I	Type II	Type IIIA	Type IIIB	Type IV
Oils: triglycerides or mixed mono and diglycerides	100	40-80	40-80	<20	-
Water-insoluble surfactants (HLB < 12)	-	20-60	-	-	0–20
Water-soluble surfactants (HLB > 12)	-	-	20-40	20-50	30-80
Hydrophilic co-solvents (e.g. polyethylene glycol (PEG), or propylene glycol)	-	-	0-40	20-50	0-50

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- Feasibilities of conveying both lipophilic and hydrophilic drugs.
- Formulation and excipients versatility.
- Availability for immediate commercialization.
- Non-invasive formation of the vesicular system.

Solid lipid as Particulate Drug Carriers

There are generally 2 types of lipid nanoparticles featured with a solid matrix: solid lipid nanoparticle (SLN) and nanostructured lipid carrier (NLC). It could be prepared in non-aqueous liquids, such as Polyethylene glycol 600, followed by liquid dispersion filled into hard or soft capsules. Recent reports also reviewed the utilization of adsorption techniques used to convert SLN or NLC into solid powder. SLN shows a few issues as the expulsion of the typified medicate during stock and generally low medication stacking, leading to the production of NLC that was made of a blend of solid and fluid lipids to create nanoparticles that stay strong at room and internal heat levels.[10,11]

The SLNs and NLCs (in Figure 1), have various focal points, for example, planning without aqueous solvents and development utilizing biocompatible and biodegradable ingredients, diminishing their side effects on the GI tract, sparing delicate medications from the acidic condition, and capacity to exemplify lipophilic drugs all the more without any problem.[12]

Solid Lipid Nanoparticles as a Potential Oral Delivery System

The preventions of chemical and/or enzymatic within the GIT obstruct the verbal transport of various labile medications.

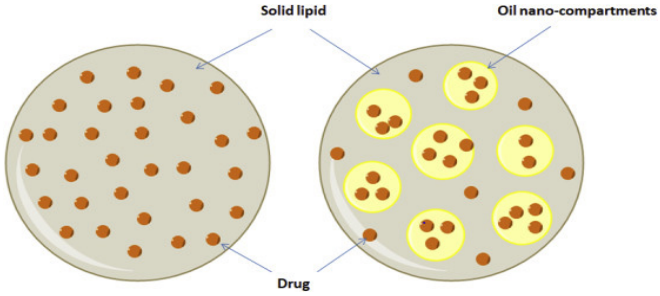

Figure 1: Structures of SLN and NLC

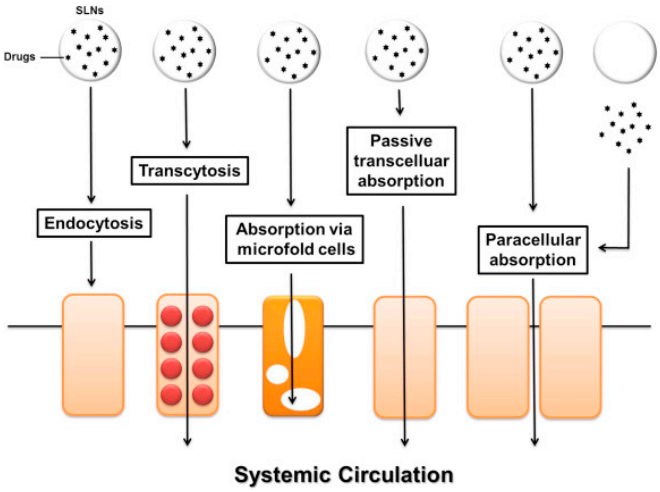

Figure 2: demonstrative display of oral routes of SLNs.

The epithelium additionally adds to destitute penetrability for various medications, bringing about low bioavailability.[13]

Bioavailability improvement of lipophilic drugs that featured by oily solutions, which shuns the need for this GIT.[14]

Figure 2 demonstrates the GIT crossing of nanocarrier strategies.

Solid Lipid Nanoparticles

SLNs are colloidal particles of a lipid matrix that is solid at room temperature and body temperature. They were first introduced by Müller *et al*. in 1993, produced by high-pressure homogenization and in parallel by Gasco by diluting warm microemulsion.[16] SLNs represent a safe and effective alternative compared to conventional nanoparticles derived from physiologically compatible lipids.[17]

SLNs are spherical shaped-colloidal beads (Figure 3) made of bio-degradable physiological solid lipid-core matrix stabilized in aqueous solution by emulsifiers, which make them solid at both room and body temperatures. According to the content differentiation and manufacturing method, they range in size of 50–1000nm.[18]

SLN be worthy, prepared by manipulating the lipid ratio as a liquid feature were replaced by a solid one. SLN contained a solid internal mass that has additional points of interest to a liquid core. The use of solid lipids instead of the latter is an exceptionally appealing thought for accomplishing controlled drug release since tranquilize versatility in a potent lipid ought to be significantly lower contrasted and liquid oil, as well as liposomes, as a rule, appear need of security of typified drugs and medicate discharged.[19]

There are a few points of interest of SLN formulations, such as:

- Biodegradable, biocompatibility and non-toxicity of excipients used in the formulation of SLN[20]
- Chemically labile drug molecules besides photo-moisture[21]
- The ability for incorporation of lipo and hydro-philic drugs and peptides[22]
- Scaling up to industrial production at a high level and sterilization are achievable effortlessly and in a moderately basic manner[23]
- No need for organic solvents in the productions of SLNs[24]
- In the contrary, many limitations are also accompanied with SLNs[25,] such as:

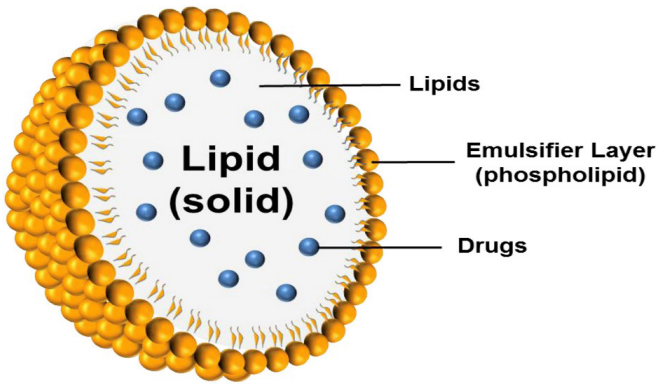

Figure 3: Structures of SLNs

- Low capacities of drug-loading pertain to the crystalline structure of SL

The Fate of SLN following Oral Administration

The oral administration keeps on being a challenging affair as the major appealing pathway to require drugs due to its apparent commercial potential. So, stacking of solutions into lipid nanoparticles sprouts the point of see of updated and less Figure 4 bioavailability and deferred plasma levels. While such frameworks may give the best adaptability in the tweak of the drug release profile inside GIT like peptide drugs.[26]

General Selection Criteria of Excipients

The most common factors that may affect the selection of excipients are solvent capacity, miscibility, cost, toxicity, melting point, self-dispersibility, compatibility, and the fate of digested products.[2]

Lipids

Lipids are the main components of the SLNs. The term lipid is used here a more extensive perspective which encompassed triglycerides (TGs), partial glycerides, fatty acids (FAs), steroids, waxes (e.g., beeswax, carnauba wax, etc.), and phospholipids.[2,27]

Triglycerides (TGs)

TGs are commonly ingested in food, completely processed and assimilated, and subsequently don't present any security issues. The main triglycerides employed for the preparation of SLNs are: Tricaprin, Trilaurin, Trimyristin (Dynasan 114), Tripalmitin (Dynasan 116) and Tristearin (Dynasan 118).[28]

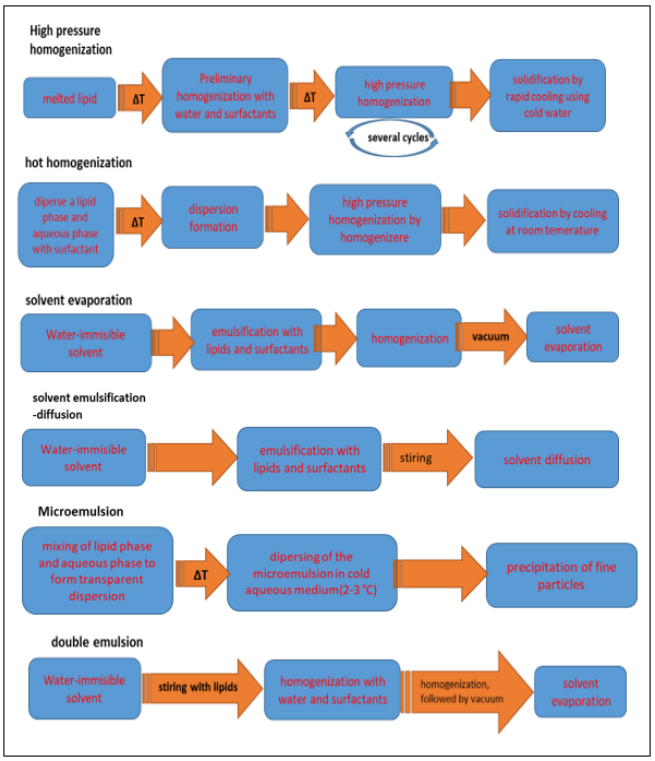

Figure 4: Shows a Schematic diagram of different formulation methods used in preparations of SLNs

Fatty Acids

FAs are aliphatic, the broadest definition includes all chain lengths, but most natural FAs have even chain lengths between C4 and C22, with C18 the most common.[29] Table 2 displayed the names and melting points of some commonly encountered FAs.

Cholesterol

Many pharmaceutical applications represent cholesterol as surfactants, solubilizes, and emulsifiers in colloidal dispersions, and it was reported that the fluidity and permeability of the liposomal bi-layer membrane declined as cholesterol introduced into lipid formulations, posteriorly, it heartens formation of uniformly sized vesicles accompanied with more stable and smaller typed one.[30]

Waxes

Sometimes, waxes might be utilized rather than lipids in the formulation of SLNs. According to the data of recent literature, it was reported that the SLN composed of glycerides show better encapsulation efficiency than waxes, but waxes composed SLNs reveal higher physical stability than glycerides composed SLNs.[31]

Surfactant and Co–surfactant

The surfactant of SLNs is an important excipient. Appropriate excipient selection is vital to successful formulation design. The proper selection of surfactant mainly depends on surfactant properties, namely, charge, molecular weight, and respective HLB values.[32] Table 3 portrays the common surfactants hired in the preparation of SLN.

Preparation Methods of Solid Lipid Nanoparticles

Several methods for the preparation of SLN have been used. These include high-pressure homogenization inclusively like cold, hot homogenization, ultrasonication, injection method, and spray drying. Lyophilization and spray drying are

Table 2: Nomenclature and characteristics of fatty acids

Fatty acid chain length (number of carbons)	Common name	Melting temperature (°C)
8	Caprylic acid	16.5
10	Capric acid	31.6
12	Lauric acid	44.8
14	Myristic acid	54.4
16	Palmitic acid	62.9
18	Stearic acid	70.1
18	Oleic acid	16
18	Linoleic acid	−5.0
18	γ-linolenic acid	−11.0
18	Ricinoleic acid	6
20	Arachidic acid	76.1
22	Behenic acid	80

Table 3: Different types of surfactants used in SLNs

Surfactant	Example	Ref.
Ionic surfactant	Sodium cholate, sodium taurocholate, sodium taurodeoxycholate, sodium glucocholate, sodium oleate, sodium dodecyl sulphate	1
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	6
Amphoteric surfactant	Egg phosphatidylcholine, soy phosphatidylcholine, Hydrogenated egg Phosphatidylcholine, Hydrogenated soy phosphatidylcholine, Phospholipon 80 H, Phospholipon 90 H	59

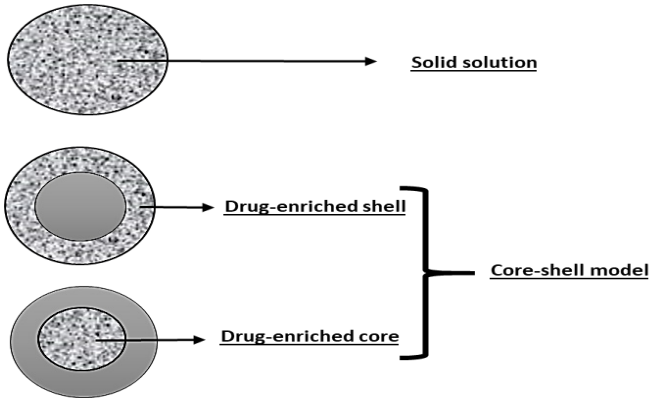

Figure 5: Models of drug incorporation into solid lipid nanoparticles: homogeneous matrix of solid solution (upper), drug free core with drug-enriched shell (middle), drug-enriched core with lipid shell (lower)

finally utilized to feature final solid products from aqueous dispersion.[33] Figure 4 summarizes different methods used in formulations of SLNs.

Drug Incorporation Models

The incorporation of hydrophilic drugs in SLN faces a problem, as their tendency to convey the loaded molecules in the water during the production steps.[34]

There were three drug incorporation models for SLNs, as shown in Figure 5, and these are a homogenous matrix of solid solution, core-shell model (drug-enriched shell), and core-shell model (drug-enriched core).[34]

Characterization of Solid Lipid Nanoparticles

A comprehensive characterization of SLN, including drug incorporation and loading capacity, measurement of particle size and polydispersity index, Fourier transform infrared radiation (FTIR), investigation of crystallinity and polymorphism using X-ray diffraction and differential scanning calorimetry, microscopic studies, thermal analyses, solubility studies, zeta potential, and *in-vitro* dissolution testing and finally *in-vitro* lipolysis models.[35]

CONCLUSIONS AND PERSPECTIVES

Despite hundreds of years of utilization in human well-being history, lipids-based formulations have not yet unwound their maximum capacity as oral pharmaceutical excipients.

As talked about above, SLNs can help the solubilization limit of solid dispersions, permitting higher loading of poorly water-soluble substances to be directed. Correspondingly, SLNs may bless bodily fluid mucus-penetrating properties, in this way advancing the bioavailability of poorly bioavailable APIs, as discussed above, enter in the composition of other delivery systems are used, like sustained, controlled, and targeted drug delivery systems.

REFERENCES

1. Kalepu S, Manthina M, Padavala V. Oral lipid-based drug delivery systems–an overview. Acta Pharmaceutica Sinica B. 2013 Dec 1;3(6):361-372.
2. Pouton CW, Porter CJ. Formulation of lipid-based delivery systems for oral administration: materials, methods and strategies. Advanced drug delivery reviews. 2008 Mar 17;60(6): 625-337.
3. Ali H, Singh SK. Biological voyage of solid lipid nanoparticles: a proficient carrier in nanomedicine. Therapeutic delivery. 2016 Oct;7(10):691-709.
4. Biswas AK, Islam MR, Choudhury ZS, Mostafa A, Kadir MF. Nanotechnology based approaches in cancer therapeutics. Advances in Natural Sciences: Nanoscience and Nanotechnology. 2014 Nov 4;5(4):043001.
5. Poovi G, Damodharan N. Lipid nanoparticles: A challenging approach for oral delivery of BCS Class-II drugs. Future Journal of Pharmaceutical Sciences. 2018 Dec 1;4(2):191-205.
6. Pouton CW. Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and 'self-microemulsifying'drug delivery systems. European journal of pharmaceutical sciences. 2000 Oct 1;11:S93-S98.
7. Pouton CW. Formulation of poorly water-soluble drugs for oral administration: physicochemical and physiological issues and the lipid formulation classification system. European journal of pharmaceutical sciences. 2006 Nov 1;29(3-4):278-287.
8. Mohsin K, Long MA, Pouton CW. Design of lipid-based formulations for oral administration of poorly water-soluble drugs: Precipitation of drug after dispersion of formulations in aqueous solution. Journal of Pharmaceutical Sciences. 2009; 98(10):3582-3595.
9. Geszke-Moritz M, Moritz M. Solid lipid nanoparticles as attractive drug vehicles: Composition, properties and therapeutic strategies. Materials Science and Engineering: C. 2016 Nov 1;68:982-994.
10. HUANG ZR, HUA SC, YANG YL, FANG JY. Development and evaluation of lipid nanoparticles for camptothecin delivery: a comparison of solid lipid nanoparticles, nanostructured lipid carriers, and lipid emulsion. Acta Pharmacologica Sinica. 2008 Sep;29(9):1094-1102.
11. Shidhaye SS, Vaidya R, Sutar S, Patwardhan A, Kadam VJ. Solid lipid nanoparticles and nanostructured lipid carriers-innovative generations of solid lipid carriers. Current drug delivery. 2008 Oct 1;5(4):324-331.
12. Mosallaei N, Mahmoudi A, Ghandehari H, Yellepeddi VK, Jaafari MR, Malaekeh-Nikouei B. Solid lipid nanoparticles containing 7-ethyl-10-hydroxycamptothecin (SN38): Preparation, characterization, in vitro, and in vivo evaluations. European Journal of Pharmaceutics and Biopharmaceutics. 2016 Jul 1;104:42-50.
13. Choonara BF, Choonara YE, Kumar P, Bijukumar D, du Toit LC, Pillay V. A review of advanced oral drug delivery technologies facilitating the protection and absorption of protein and peptide molecules. Biotechnology advances. 2014 Nov 15;32(7):1269-1282.
14. Elgart A, Cherniakov I, Aldouby Y, Domb AJ, Hoffman A. Lipospheres and pro-nano lipospheres for delivery of poorly water soluble compounds. Chemistry and physics of lipids. 2012 May 1;165(4):438-453.
15. Yeap YY, Trevaskis NL, Porter CJ. Lipid absorption triggers drug supersaturation at the intestinal unstirred water layer and promotes drug absorption from mixed micelles. Pharmaceutical research. 2013 Dec;30(12):3045-3058.
16. Gasco MR, inventor; Gasco Maria R, assignee. Method for producing solid lipid microspheres having a narrow size distribution. United States patent US 5,250,236. 1993 Oct 5.
17. Müller RH, Rühl D, Runge S, Schulze-Forster K, Mehnert W. Cytotoxicity of solid lipid nanoparticles as a function of the

lipid matrix and the surfactant. Pharmaceutical research. 1997 Apr;14(4):458-462.
18. Abrishami M, Abrishami M, Mahmoudi A, Mosallaei N, Vakili Ahrari Roodi M, Malaekeh-Nikouei B. Solid lipid nanoparticles improve the diclofenac availability in vitreous after intraocular injection. Journal of drug delivery. 2016;2016.
19. Anjum R, Lakshmi P. A review on solid lipid nanoparticles; focus on excipients and formulation techniques. Int. J. Pharm. Sci. Res. 2019:4090-4099.
20. Kaliamurthi SA, Selvaraj GU. Insight on solid lipid nanoparticles: characterization and application in diabetes mellitus. J Crit Rev. 2016;3(4):11-16.
21. Gambhire MS, Bhalekar MR, Shrivastava B. Investigations in photostability of dithranol incorporated in solid lipid nanoparticles. Pharmaceutical Chemistry Journal. 2012 Jul 1;46(4):256-261.
22. Weiss J, Decker EA, McClements DJ, Kristbergsson K, Helgason T, Awad T. Solid lipid nanoparticles as delivery systems for bioactive food components. Food biophysics. 2008 Jun;3(2):146-154.
23. Rai M, Paralikar P, Jogee P, Agarkar G, Ingle AP, Derita M, Zacchino S. Synergistic antimicrobial potential of essential oils in combination with nanoparticles: Emerging trends and future perspectives. International Journal of Pharmaceutics. 2017 Mar 15;519(1-2):67-78.
24. Park HS, Nam SH, Kim J, Shin HS, Suh YD, Hong KS. Clear-cut observation of clearance of sustainable upconverting nanoparticles from lymphatic system of small living mice. Scientific reports. 2016 Jun 6;6(1):1-7.
25. Choonara BF, Choonara YE, Kumar P, Bijukumar D, du Toit LC, Pillay V. A review of advanced oral drug delivery technologies facilitating the protection and absorption of protein and peptide molecules. Biotechnology advances. 2014 Nov 15;32(7):1269-1282.
26. Su L, Zhou F, Yu M, Ge R, He J, Zhang B, Zhang Y, Fan J. Solid lipid nanoparticles enhance the resistance of oat-derived peptides that inhibit dipeptidyl peptidase IV in simulated gastrointestinal fluids. Journal of Functional Foods. 2020 Feb 1;65:103773.
27. Zhou Y, Liang H, Rodkey T, Ariotti N, Parton RG, Hancock JF. Signal integration by lipid-mediated spatial cross talk between Ras nanoclusters. Molecular and cellular biology. 2014 Mar 1;34(5):862-876.
28. Jannin V, Musakhanian J, Marchaud D. Approaches for the development of solid and semi-solid lipid-based formulations. Advanced drug delivery reviews. 2008 Mar 17;60(6):734-746.
29. Scrimgeour CM, Harwood JL. Fatty acid and lipid structure. InThe lipid handbook with CD-ROM 2007 Mar 13 (pp. 15-50). CRC Press.
30. Cullis PR, Hope MJ. Lipid nanoparticle systems for enabling gene therapies. Molecular Therapy. 2017 Jul 5;25(7):1467-1475.
31. Ekambaram P, Sathali AA. Formulation and evaluation of solid lipid nanoparticles of ramipril. Journal of young pharmacists. 2011 Jul 1;3(3):216-220.
32. Severino P, Pinho SC, Souto EB, Santana MH. Polymorphism, crystallinity and hydrophilic–lipophilic balance of stearic acid and stearic acid–capric/caprylic triglyceride matrices for production of stable nanoparticles. Colloids and Surfaces B: Biointerfaces. 2011 Aug 1;86(1):125-130.
33. Naseri N, Valizadeh H, Zakeri-Milani P. Solid lipid nanoparticles and nanostructured lipid carriers: structure, preparation and application. Advanced pharmaceutical bulletin. 2015 Sep;5(3):305.
34. Truong-Dinh Tran T, Ha-Lien Tran P, Tu Nguyen K, Tran VT. Nano-precipitation: Preparation and application in the field of pharmacy. Current pharmaceutical design. 2016 Jun 1;22(20):2997-3006.
35. Kaukonen AM, Boyd BJ, Porter CJ, Charman WN. Drug solubilization behavior during in vitro digestion of simple triglyceride lipid solution formulations. Pharmaceutical research. 2004 Feb;21(2):245-253.