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Nanostructured lipid carriers: A platform to lipophilic drug for oral bioavailability enhancement

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ABSTRACT

Lipid based drug delivery system such as Solid lipid nanoparticle (SLN) and Nanostructured lipid carriers (NLC) are among the most promising drug delivery system used in many industries such as food, pharmaceuticals and cosmetics industries. Over the last few years, new constituents of lipids have developed and investigated for enhancement of bioavailability. The present manuscript is an attempt on solving the concerned uncertainty with efficacious peroral administration of hydrophobic drugs through fabricating new lipid formulations, NLC. NLC, the second-generation lipid carrier is usually composed of solid lipids and liquid lipids together in a system. This mixing causes depression in melting point of substrates and converts the mixture into solid form at body temperature and termed as NLC. NLC shows a high drug loading with minimum drug expulsion. The unique advantages of NLC over SLN and Lipid-drug conjugates (LDC) are increased capacity of drug loading, avoidance of drug expulsion. This manuscript gives detailed information on definitions and simple way of production methods, new approaches in formulation of NLC and it also highlights how NLC improves bioavailability of bioactive molecules through peroral route and its future perspective as a pharmaceutical carrier. It also gives idea about the supremacy of NLC over other lipid-based system.

Keywords: Bioavailability; Lipids; Lipophilic drugs; Nanostructured lipid carriers; Solid lipid nanoparticle.

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1 Introduction

The peroral approach of administration is the most preferable approach for administration of drug. The lipophilic drug creates problem in efficient oral delivery due to water solubility issues and first pass metabolism[1].There are many different factors which decrease the degree of absorption of lipophilic drugs. Several lipophilic drugs are candidates for efflux transporters such as P-glycoprotein (P-gp) and are also frequently predisposed to metabolism through cytochrome P450 (CYP) enzymes which leads to their significant first pass elimination and poor *in vivo* prospect. These factors are the chief reasons behind insufficient oral bioavailability of hydrophobic drugs[2].

Over the past decade, remarkable attempts have been made to improve bioavailability of bioactive molecule by fabricating nanotechnology based dosage form[3].Among the various nanoparticles, lipid nanoparticles gained more consideration due to their distinct advantages such as highly stable structure, biodegradability, biocompatibility, efficient drug loading and sustained release properties[4].

Lipid nanoparticles are well-known to enhance oral absorption of drugs due to their distinct constituents. Basically three types of lipid nanoparticles such as Solid lipid nanoparticle (SLN), Nanostructured lipid carrier (NLC) and lipid-drug conjugates (LDC)[5] are available. In this review recent advance in orally administered lipid nanoparticles is discussed[6].

Lipid-drug conjugates suffered from disadvantages such as particle growth, uncertain gelation tendency, abrupt polymeric transitions, inherent low loading rate[7, 8]. To address LDC disadvantage, SLN was developed in 1991. SLN have developed for the oral delivery of cyclosporine and Paclitaxel[9]. SLN was based on lipids which have solid nature at room temperature and generally biocompatible and biodegradable. SLN are small with large surface area[10] but suffered from drawbacks such as limited drug loading, drug expulsion tendency[11].

2 Nanostructured lipid carriers

The second generation lipid carrier uses solid lipids and liquid lipids together. Due to this mixing a melting point depression is noticed, but the mixture obtained is solid at body temperature. NLC shows a high drug loading and minimum drug expulsion as compared to SLN.

2.1 Advantages of SLN/NLC over conventional particulate carriers

- Small size permits site-specific delivery.
- Controlled and sustained release of drug.
- Protection of drug from biochemical degradation.
- High drug payload.
- Hydrophobic and hydrophilic drugs can be incorporated.
- Sterilized by autoclave or by gamma radiation.
- Lyophilizes and spray dried.
- Nontoxic metabolites.
- Cheap and stable.
- Easy for large scale production[12].

2.2 Advantages of nanostructured lipid carrier

- Provide sustained drug release.
- Better physical stability.
- High drug loading.
- Useful for loading hydrophobic and hydrophilic drugs.
- Most of lipids used are biocompatible and biodegradable.
- Water based technology.
- Economic than other polymeric or surfactant based delivery system.
- Uncomplicated to validate and to get regulatory approval.
- Easy for large scale production.

2.3 Disadvantages of nanostuctured lipid carrier

- Cause irritation and sensitizing action by few surfactant.
- Cause cytotoxic effects.
- Lack of sufficient clinical and preclinical studies[13].

3 Types of NLCs:

Type I: Highly imperfect solid matrix: In this mixing of lipids causes highly disordered lipid matrix structure due to variation in structures of the lipids. It gives space for bioactive molecule to accommodate.

Type II: Multiple oil/fat/water carriers: Generally bioactive molecule solubility is more in liquid lipids. Due to high liquid lipid concentrations a miscibility gap of solid lipids and liquid lipid occurs at the time of cooling which leads to phase separation.

Type III: Amorphous Matrix: Solid and liquid lipids are mixed in such a manner that they hinder crystallization. The lipid matrix is in solid state, but in an amorphous form, which avoids crystallization and ultimately drug expulsion[14]. (Figure 1)

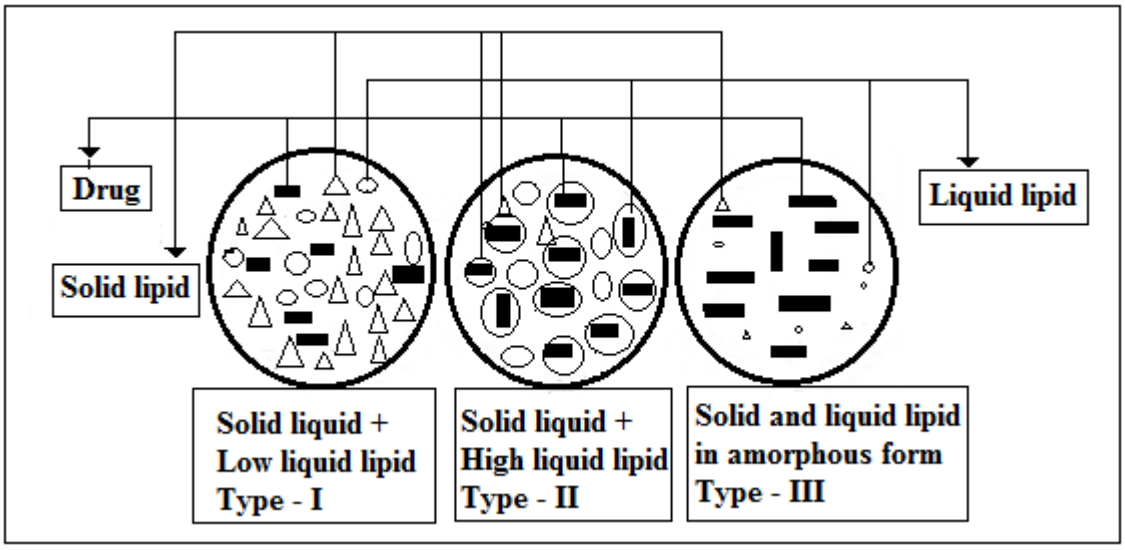

Figure 1: Different Types of NLCs.

4 Composition of NLC:

The NLC consists of solid lipid, liquid lipid, emulsifier and water.

1. **Solid Lipid** (Table 1)

Table 1: Solid lipid for formulation of NLC.

Sr. No.	Solid lipid	Examples	Melting point ^{0}C
1	Hard fats	Stearic acid	67-69
		Behenic acid	80
		Palmitic acid	63
2	Hard fats	Theobroma oil	35-36.5
		Goat fat	40-50
3	Triglycerides	Trilaurin (Dynasan 112)	43-46
		Trimyristin (Dynasan 114)	55-58
		Tristearin (Dynasan 118)	70-73
		Tripalmitin (Dynasan 116)	61-65
		Tribehenate (Dynasan 122)	81-85
		Hydrogenated Palm Oil (Dynasan P 60)	58-62
		Hydrogenated Palm Oil (Softisan 154)	53-58
4	Waxes	Beeswax	62-64
		Cetyl palmitate (Precifac ATO)	51.9-55.9
		Carnauba wax 2442	78-88
		Apifil	59-70
		Elfacos C 26	80
5	Partial glycerides	Glyceryl Monostearate (Imwitor 900)	54-64
		Glyceryl Monostearate (Imwitor 491)	66-77

2. **Liquid lipid for formulation of NLC[15]** (Table 2)

Table 2: Liquid lipid for formulation of NLC.

Sr. No.	Liquid lipid	Monograph name	Viscosity mPa·s 20 ^{0}C
1	CremerCOOR MCT 60/40 EP	Caprylic/Capric/Triglyceride	25 to 32
2	CremerCOOR MCT 70/30 EP	Caprylic/Capric/Triglyceride	26 to 32
3	Miglyol 808	Tricaprylin	~ 23
4	Miglyol 810 N	Caprylic/Capric/Triglyceride	~ 26
5	Miglyol 812 N	Caprylic/Capric/Triglyceride	~ 28
6	Miglyol 818	Caprylic/Capric/Linoleic Triglyceride	~ 33
7	Miglyol 8108	Caprylic/Capric Triglyceride	~ 25
8	Oleic acid	(9Z)-Octadecenoic acid	40
9	Olive oil	-	85
10	Castor oil	-	1-1.5
11	Coconut oil	-	80
12	Soya bean oil,	-	80
13	Palm oil	-	130

3. **Surfactants [14, 15]:** (Table 3)

Table 3: Surfactant for formulation of NLC.

Surfactant	HLB value (hydrophilic-lipophilic balance)
Soy lecithin	4
Egg lecithin	6.6
Polysorbate 80	15
Polysorbate 20	16.7
Solutol HS	15
Poloxamer-188	29
Cremophor EL	12-14

Different mechanisms by which NLC improves bioavailability of lipophilic drug:

Direct uptake:

NLC improves bioavailability of lipophilic drug by intestinal lymphatic transport. Due to utilization of triglycerides, the NLC may trigger the chylomicron formation and causes transcellular absorption. Lipophilic drug takes intestinal lymphatic system route and circumvents first pass effect.

Triglyceride hydrolysis starts in the gastrointestinal tract by lingual lipase and gastric lipase to form triglyceride emulsion. This triglyceride emulsion triggers the production of bile salts, pancreatic juice and biliary lipids. Biliary lipids

adsorbed onto triglyceride emulsion surface and stabilized. With the action of pancreatic lipase triglyceride droplet forms monoglyceride and fatty acid and is absorbed by the enterocyte. These are then processed to form lipid core of chylomicron and stabilized by the addition of phospholipids and apolipoproteins. Then these lipoproteins are secreted into lamina propria and mesenteric lymph node and then to lymphatic circulation[16, 17, 18, 19].

Mucus adhesion: The NLC sticks to the mucus and increases the residence time and so there is increased release of drug from NLC[2, 20].

Mixed micelle formation: The lipid of NLC causes bile secretion in small intestine. The lipid degrades due to enzymes and is mixed with bile to form mixed micelle. This phenomenon gives enhanced solubilization of drug and promotes drug transport[21].

Increased permeability: NLC contains surfactants which causes change in intestinal permeability by different mechanisms. For eg. The surfactant, Poloxamer contorts the cell membrane and opens the tight junction of epithelial cell of intestine promoting paracellular transport[22]. It prohibit P-glycoprotein efflux and increases NLC transport[23].

Inhibits drug degradation: NLC provides protection to hydrophilic and lipophilic drugs by the lipids from chemical and enzymatic degradation and delays in vivo metabolism[24, 25].

6 Methods of Manufacturing of NLC

High Pressure Homogenization Technique (HPH)-

HPH is a most reliable technique for large-scale manufacturing. In HPH method lipids are pushed at very high pressure through a narrow gap. Due to shear stress and cavitations forces, breaking of particle in micron size takes place. HPH has two methods, hot and cold method [26, 27, 28]. In these methods drug is dissolved in the lipid (5-10%) melted at 5-10º C above their melting point.

1. Hot homogenization method-

In this method drug and melted lipid is mixed with aqueous surfactant solution of same temperature by using high shear equipment. The obtained emulsion is stirred by using a piston gap homogenizer and the formed nanoemulsion is cooled at room temperature to form nanoparticles[29].

2. Cold homogenization method-

In this method also drug and melted lipid is mixed with aqueous surfactant solution of same temperature by using high shear equipment. The lipid melt along with drug is cooled quickly by using ice or liquid nitrogen for drug distribution in lipid[30].

Micro-emulsion based method-

The drug is mixed with melted lipid phase and then mixed with surfactant solution prepared in water at same temperature as that of the lipid phase. The microemulsion which is hot is then added to cold water. Reduction in temperature causes formation of nanoemulsion.

Emulsification-Solvent Evaporation Technique-

Lipids along with drug are dissolved in organic solvent like toluene or chloroform. This lipid phase added to that of aqueous surfactant phase. Then evaporate the solvent under reduced pressure. On evaporation of solvent the lipid precipitates causing formation of nanoparticles.

Solvent emulsification-diffusion method-

An o/w emulsion is formed initially consisting of organic phase consisting of solvents such as benzyl alcohol/ ethyl format/ tetrahydrofuran, mutually saturated with water to ensure thermodynamic equilibrium of both liquids to obtain nanoparticle in nanometers size[31].

Phase inversion method-

All formulation ingredients are stirred with magnetic stirrer and subsequently subjected to heating and cooling cycles and is diluted under cooling conditions (85ºC-60ºC-85ºC-60ºC-85ºC). Three cycles of heating and cooling from room temperature was applied at a rate of 4ºC/min. This causes the inversion of the emulsion[32].

Melting dispersion method-

Lipid phase is prepared by adding melted lipids with drug solution which is prepared in an organic solvent. Simultaneously water phase is also heated at the same temperature as that of lipid phase. The oil phase is added to water phase and is stirred at high speed. Then cooled down to room temperature to obtained nanoparticles[33].

High Shear Homogenization or Ultrasonication Technique-

Drug was added to melted solid lipid and liquid lipid. Water phase along with surfactant is also heated at the same temperature as that of lipid phase. The obtained emulsion was ultrasonicated using probe sonicator. In order to prevent recrystalization during the process, the production temperature kept at least 5-10ºC above the lipid melting point. To remove impurities emulsion should pass through 0.45µm membrane[34].

Displacement or Injection method-

Lipid in solvents such as ethanol, acetone or methanol is rapidly injected to an aqueous phase containing surfactant by using magnetic stirrer. An o/w emulsion is formed.

Multiple Emulsion Technique-

Hydrophilic drug was dissolved in aqueous solution and then added to melted lipid. This primary emulsion is stabilized by surfactants. This method applies emulsification followed by solvent evaporation[26, 27].

7 Applications of NLCs

Enhancement in bioavailability and sustained release action are main advantages of NLC after peroral administration[19]. The lipophilic drugs can be entrapped by NLC to solve solubility issues. Repaglinide, a poor water soluble drug has low oral bioavailability[35]. It is most suitable to load into NLC[36]. Qi S et al prepared Repaglinide NLC with Gelucire 50/13 as lipid excipient to dissolve the drug[37]. The result showed significantly greater decrease of the blood glucose level in rats when compared to marketed Repaglinide tablets. Some other examples of drug loaded NLCs are showed in Table 4.

Table 4: Drugs encapsulated in NLC for oral bioavailability improvement.

Drug	Particle size (nm)	Excipient Solid lipid, liquid lipid, surfactant	Outcome	Ref
Valsartan	62±0.494	tristearin, capmul MCM EP, pluronic F68 (hydrophilic surfactant, span 80 (lipophilic surfctant)	Improved solubility and oral bioavailability of valsartan.	38
Lovastatin	235	precirol, squalene, myverol	Enhanced oral bioavailability of lovastatin	39
Indomethacin	311	glyceryl monostearate , oleic acid, tween 80, chitosan, HTCC (coating material)	improved bioavailability of indomethacin by coating of NLC with chitosan and HTCC (chitosan derivative)	40
Lovastatin	23.5±1.6	precirol ATO5, soybean lecithin, Labrasol, cremophor ELP	increased in bioavailability of lovastatin	41
Curcumin and/ or genistein	125	glycerol monostearate, oleic acid, tween 80, lecithin from soy bean,	Developed co-loaded lipid based carriers for curcumin and genistein.	42
Berberine	160	precirol® ATO 5, oleic acid, tween 80	enhanced oral bioavailability and hypoglycemic effect	43
Raloxifene hydrochloride	32.50 ± 5.12	glyceryl monostearate and capmul MCM C8, polyvinyl alcohol	Improved oral bioavailability of poorly soluble Raloxifene hydrochloride.	44
Domperidone	30.45	trimyristin, cetyl recinoleate, tween 80 , soy phosphatidylcholine,	prepared stable and controlled release Domperidone SLN and Domperidone NLC	45
Rosuvastatin	213.26	compritol ATO 888, oleic acid, poloxamer 188	enhanced bioavailability with two folds	46
Ifosfamide	223	Glycerol monooleate , oleic acid, poloxamer 188	Enhanced entrapment efficiency and sustained released property of Ifosfamide.	47
Curcumin	150	cholesterol oleate, glycerol trioleate phosphatidylcholine	enhanced bioavailability	48
Silymarin	78.87	precirol ATO-5, oleic acid, tween-80, Lipoid E 100	improved bioavailability of silymarin	49

8 New approaches in formulation of NLC

Many research papers was published on NLC, many researcher want to improve the performance of NLC in terms of entrapment efficiency of drug, one attempt was made by a researcher Cristina Ott, the researcher evaluated the influence of various kinds of solid lipid matrices on synthesis of effective nanostructured lipid carriers with appropriate average diameters and physical stability. For this purpose two solid lipid mixtures (glyceryl monostearate with carnauba wax and glycerol monostearate with beeswax in combination with natural vegetable oils have been chosen, in order to create high disordered crystal lattice able to accommodate a complex mixture of vegetable extract (e.g. ivy leaves extract)[50].

9 Future perspectives

NLCs are lipid-based system that contains solid lipid and liquid lipid, which causes covering of highly hydrophobic drugs. NLC enables protection of drug and imparts sustained release action of drug. Their composition includes surfactants, lipids that are biocompatible and approved by the FDA for oral administration. NLC formulation methods are simple and can be prepared without an organic solvent. It is easy to scale up the process into large batch sizes. NLC formulation has undergone a continuous betterment in the pharmaceutical and cosmetic field. These amendments played an important role in the application of NLCs. The examples described in this review through oral route clearly illustrate the promise of these NLCs as pharmaceutical carriers. Taking into consideration the increasing number of patented NLC-based formulations and the increasing data of research papers available, one can expect that the number of clinical trials pertaining NLCs will significantly increase in the near future.

10 Conclusions

NLC is known as smarter, latest generation of lipid nanoparticles with efficient drug loading and drug release capacity. NLC as novel systems composed of physiological lipid materials suitable for oral administration. NLC acts as sustained release and site specific drug delivery system and hence attracted wide attention of researchers. NLC is also suitable for large scale production, which will be seen in near future in the pharmaceutical market.

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Conflicts of Interest

The authors report no conflict of interest.

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