REVIEW ARTICLE

Lipids Selection and Methods of Nanostructured Lipid Carrier for Topical Use

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ABSTRACT

Background: The utilization of nanoparticle systems presents a promising means for enhancing the efficacy of specific therapeutic interventions, particularly in topical applications. One of the nanoparticle systems that possesses several advantages is the nanostructured lipid carrier (NLC). It is comprised of solid and liquid lipids that form a lipid matrix with the addition of a surfactant. The utilization of lipids in NLC could impact various physical characteristics and drug release.

Objective: This study aims to ascertain the considerations involved in selecting solid and liquid lipids.

Method: The research approach to be undertaken is a systematic literature review, which refers to an investigation conducted through the process of identifying, evaluating, and interpreting all pertinent findings related to a study, topic, or phenomenon associated with NLC.

Results: the obtained results reveal that various NLC-related articles indicate that polymorphism, the solubility of active compounds, and the ratio of solid and liquid lipids may exert a significant influence on the physical characteristics and release of active compounds.

Conclusion: Consideration of the choice between solid and liquid lipids can be made to optimize topical therapeutic efficacy.

Keywords: Nanostructured lipid carrier, Liquid lipid, Solid lipid.

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INTRODUCTION

Nanoparticle systems represent a potential therapeutic drug platform that can improve performance and reduce its limitations. Lipid nanoparticles are one of the nanosystems that have been extensively explored and show great potential in the field of medication delivery. Nanostructured lipid carriers (NLC), also known as solid lipid nanocarriers of the second generation, are lipid nanoparticles. NLC is a lipid matrix composed of a mixture of solid and liquid lipids (oil). In comparison to the original solid lipids, the resulting matrix of lipid particles has a lower melting point. However, the matrix persists in a solid state at body temperature.[1] The type and combination of lipids used to make NLC can affect the physical characteristics of NLC.[2] The particle size, polydispersity index, and entrapment effectiveness are influenced by the lipids utilized, both solid and liquid.[3] Furthermore, the proportion of solid lipids and liquid lipids also influences these physical features. Ratio with more liquid lipids can reduce the particle size and polydispersity index.[4] The particle size of the nanocarrier is an important index influencing its drug delivery efficiency.[5]

Solid lipids that are widely used as NLC components include beeswax, stearic acid, tristearin, cholesterol, palmitic acid, compritol 888 ATO, etc, while liquid lipids that are widely used include coconut oil, olive oil, paraffin oil, miglyol 812, oleic acid, castor oil, etc.[6] The choice of lipid for NLC systems may rely on the solubility of the active pharmaceutical ingredients (API) to be incorporated.[7] This was achieved by dissolving API in melted solid lipids and determining the maximum amount of solubilization capacity of each lipid.[8] This method can also be done on the selection of liquid lipids. The selection of liquid lipids to deliver didanosine using the NLC system was based on the solubility of didanosine in a number of liquid lipids such as miglyol, transcutol, lipophilic labrafil, labrafac, lauroglycol

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and capryol. The solubility of didanosine in transcutol results in the highest solubility among the others so that it can be used as a liquid lipid in the constituent components of NLC.

Besides selecting lipids based on the solubility of API, another critical step is lipid blend screening. In a molten state, this ensures that the mixtures of liquid and solid lipids are in the same phase. Also, most importantly, it must be able to form a single phase in the solid state.[9] This review briefly describes the solid and liquid lipids of NLCs, their effects on physical properties, release and penetration, preparation methods and their use in topical application.

Method

The planned research methodology is a systematic literature review characterized by the identification, evaluation, and interpretation of all relevant findings related to a particular study, topic, or phenomena of interest. The data employed in this study comprised articles that were relevant to NLC and were extracted from various online databases, including PubMed, ScienceDirect, and JFIKI. The acquisition of requisite data was conducted through online means during the period of March to April 2023.

RESULTS

Solid Lipid

Solid lipids are lipids that are solid at room and body temperature.[10] Solid lipids can be fatty acids, mono/di/triglycerides or fatty alcohols.[11-13] Use of lipids should increase solubility in molten lipids. Triglyceride lipids have three crystalline forms: the α-form with the hexagonal conformation, the β'-form with the orthorhombic conformation, and the β-form with the triclinic conformation in liquid state.[14] This crystal form difference depends on the activation energy of nucleation. If the activation energy of nucleation is high, the β-form is formed and vice versa. For example, as shown in Figure 1, tristearin can form the hexagonal α-form at low temperatures (50°C), whereas at high temperatures, the crystal configuration changes to triclinic β-form.[15] However, the β-form can form platelet structures and cause crystal growth that requires more surfactant to maintain stability. In addition, this platelet shape allows drug molecules to escape from the lipid nanoparticles to the edge of the surface, stimulating drug release from the system. Moreover, the crystal form may exert an influence on drug release from lipid-based nanoparticles. The α-form of lipids has been shown to significantly enhance drug release compared to the β-form.[15] Therefore, it is preferable to produce and maintain α-form in a lipid nanoparticle system.[16]

The physicochemical properties of solid lipids play an important role in drug entrapment. Drug molecules can be entrapped between fatty acid chains and lipid layers in imperfect crystalline.[16] The high degree of crystallinity can minimize the entrapment of drug molecules.[17] To overcome this, different lipid combinations can be used to create imperfect crystallinity, providing more space to accommodate drug molecules.[18] Additionally, the enthalpy value of solid lipids can affect the forming process of NLC. The melting enthalpy value represents the energy needed for the endothermic process of melting. A melting point test is conducted to verify the formation of the NLC system in the presence of an endothermic lipid component.[19] This may serve as a factor to consider in selecting the melting temperature during the production of lipid nanoparticles.

Cetyl Palmitate

Cetyl Palmitate is an ester formed by the combination of cetyl alcohol and palmitic acid. This substance is a white, crystalline material that has a similar appearance to wax. It has the ability to dissolve in ether and alcohol, but it cannot dissolve in water. It has a molecule weight of 481 with a melting point between 46 to 54°C. Cetyl palmitate is an emollient that also offers body and texture to most cream and lotion formulations. Cetyl palmitate's concentration for semisolid products is between 5 to 10%.[20]

In NLC formulation, cetyl palmitate used as a solid lipid in 8 to 10%.[21,22] NLC containing resveratrol with cetyl palmitate as a solid lipid has small particles (102–311 nm).[21] Additionally, resveratrol's ability to pass through the stratum corneum can be enhanced by NLC combined with cetyl palmitate. Because of lipid nanoparticles, hydrophobic actives can be concentrated more highly in aqueous formulations for potentially greater skin benefits. On the other hand, NLC with cetyl palmitate as a solid lipid with a small concentration can decrease the particle size of NLC.

Glyceryl Palmitostearate

Glyceryl palmitostearate is a combination of mono-, di-, and triglycerides derived from C16 and C18 fatty acids. The product is commonly referred to as Precirol ATO 5 on the market. Glyceryl palmitostearate is a finely ground, white powder with a subtle odor. Glyceryl palmitostearate has a melting point range 52 to 55°C. It is basically insoluble in water, mineral oil, and 95% of ethanol but easily soluble in dichloromethane and chloroform.[23] Sakellari *et al*. found that including Precirol ATO 5 as a solid lipid in NLCs can effectively decrease particle size even at low concentrations (1.7%).[24] Additionally, Precirol ATO 5 alone as solid lipid (without mixed with another solid

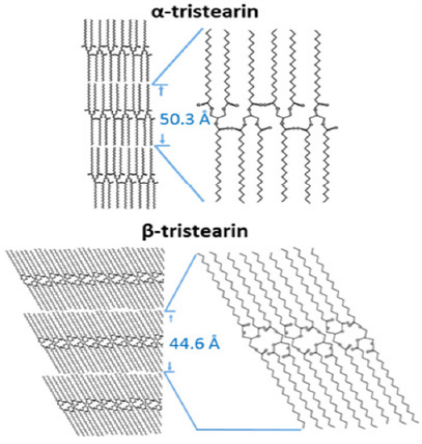

Figure 1: Picture illustrating the structural arrangement of triglyceride molecules in the α and β polymorphs[15]

lipid) can reduce particle size and reduce polydispersity index. The other study showed that precirol ATO 5 improves solubilizing hydrophobic actives. Therefore, NLC with precirol ATO 5 can increase the efficiency of entrapment drugs with hydrophobic characteristics.[25]

Glyceryl Distearate

Glyceryl distearate is needles or plates obtained from the ether, chloroform, and ligroin as solvents. It has a melting point at 79.1ºC and is soluble in ether. Glyceryl distearate as liquid lipid in NLC can form a particle size of 158 nm with encapsulation efficiency up to 94%.[26] It is due to the solubility of drugs in liquid lipids. Active substances with high lipid solubility has relatively high EE, above 80%. In other studies, glycerol distearate as a solid lipid can increase EE up to 80% due to the solubility of hydrophobic drugs with a small particle size of 142 nm.[27]

Glyceryl Monostearate

Glyceryl monostearate is a solid substance with a waxy texture. It is available in the form of beads, flakes, or powder and can be white or cream in color. The texture is reminiscent of wax and it has a little oily scent and flavor. The substance possesses a melting point ranging from 55 to 60°C and exhibits solubility in hot ethanol, ether, chloroform, hot acetone, mineral oil, and fixed oils. While it is highly insoluble in water, it can be effectively dispersed in water by adding a little quantity of soap or other surfactants. NLC using Glyceryl monostearate can form particle size in the range 333 to 610 nm depending lipid ratio.[28]

Stearic Acid

Stearic acid is a waxy substance that ranges in color from white to cream. It has a melting point above 54ºC and is soluble in ethanol, hexane, and ether. Practically not soluble in water. Utilizing stearic acid as a solid lipid and oleic acid as a liquid lipid in nanostructured lipid carriers (NLC) at a ratio of 6:4 has the potential to reduce both particle size and polydispersity. In addition, stearic acid increases the solubilization of lipophilic drugs that improve efficiency entrapment in NLC.[29]

Glyceryl Trimyristate

Glyceryl trimyristate has synonyms include propane-1,2,3 triyl trimyristate and trimyristin. It is known Dynasan in the market. The melting point of glyceryl trimyristate is 56 to 57°C. Glyceryl trimyristate as solid lipid can form NLC with 130 nm in particle size and 0.25 in polydispersity index.[30] In addition, the zeta potential of NLC is in the range -28 to -48 mV. This indicates that liquid lipids in higher concentrations moves to the surface of the particle, increasing the negative charge.

Liquid Lipid

Liquid lipid is lipid with low melting points, which enables it to remain in a liquid state at ambient temperatures.[31] Liquid lipids, including argan oil, coconut oil, black seed oil, oleic acid and others, are employed in the production of NLC.[29-34] Physicochemical characteristics of liquid lipids may influence the properties od NLC, such as chain length, viscosity and concentration ratio. Liquid lipid, such as glyceryl trioleate, glycerol tricaprylate and decyl octadic- 9-enoate possessing longer carbon chains, are capable of producing smaller-sized NLC in comparison with shorter carbon chains. This phenomenon is attributed to the heightened mobility of surfactant molecules at the surface of particles, causing them to move around the interfacial region during polymorphic transformation in order to cover the still- exposed hydrophobic surface.[35] The viscosity of the liquid lipid in which the nanoparticles are produced is recognized to influence the size of the resulting NLC. The high viscosity of liquid lipids might cause a decrease in the size of particles. In addition, the viscosity of the liquid lipid can increase the entrapment efficiency. The concentration ratio of liquid lipids significantly impacts the particle size of NLC. The other study found that the highest liquid-lipid concentration ratio resulted in the lowest particle size when NLC was made with varied solid lipid to liquid lipid ratios (9:1, 8:2, 7:3, 6:4).[36] This may be attributed to the swollen core upon the incorporation of liquid lipids. However, the increase in the quantity of liquid lipids can diminish the surfactant efficiency, resulting in an elevation in surface tension and becoming larger particles. Moreover, as shown in Table 1, the solubility of lipophilic drugs can be influenced by the ratio of solid and liquid lipids. Hence, solubility testing is conducted on several ratios in order to ascertain the highest attainable solubility of the medicine at a specific ratio.[37]

The solubility of hydrophobic drugs in liquid lipids is known to have a significant impact on the efficiency of entrapment. The high drug solubility, whether in liquid and solid lipids, is expected to localize at the core of NLC.[38] Before producing NLC, it's important to find out the drugs can dissolve in a liquid lipid. A study demonstrates that prior to the production of NLC tamoxifen, a solubility test of tamoxifen in various liquid lipids was performed. Liquid lipids used included sesame oil, sunflower oil, corn oil, soybean oil, ethyl oleate, olive oil, isopropyl myristate, oleic acid, maisine, and several forms of Labrafil. Based on the results, it was found that tamoxifen exhibited the highest solubility in Labrafil WL2609BS, thus designating it as the liquid lipid component for the production NLC. Based on the explanations mentioned above, NLC can be illustrated as depicted in Figure 2.

Miglyol 812N

Miglyol 812N is a triglyceride ester composed of saturated caprylid and capric fatty acids obtained from coconut or palm kernel oil, as well as plant glycerol. It is a clear, virtually colorless liquid of neutral odor and taste. Miglyiol 812N used as a liquid lipid, can reduce the particle size of NLC.[39] Miglyol 812N can increase the solubility of hydrophobic drugs in the inner matrix phase space due to the imperfections of the inner phase of the NLC formulation. In that study, showed particle size of NLC was 148.7 nm, which can cause hydrophobic drugs to be deposited in the skin layer.

Oleic Acid

Oleic acid is an omega-nine fatty acid that is found in abundance in nature, making it the most extensively distributed

Table 1: The application of solid and liquid lipids and their respective ratio are employed in the production NLC

Solid lipid	*Liquid lipid*	*Ratio*	*Particle size (nm)*	*EE (%)*	*Reference*
Cetyl palmitate	Miglyol 812N	-	148.7	78.2	[37]
Precirol ATO 5	Oleic acid	9:1	101.2	97.28	[43]
Glyceryl di-stearate	Passion fruit seeds oil	7:3	158	94.91	[25]
Stearic acid	Oleic acid	6:4	351.9	73.85	[27]
Glycerol tri myristate	Isopropyl palmitate	3:1	226.31	94.26	[42]
Stearic acid	Isopropyl palmitate	3:1	201.54	93.73	[42]
Glycerol monostearate	Isopropyl palmitate	3:1	436.30	94.33	[42]
Cetyl palmitate	Isopropyl palmitate	3:1	245.18	94.07	[42]
Glyceryl trilaurate	Isopropyl palmitate	3:1	244.19	90.08	[42]
Glycerol tri-myristate	Propylene glycol dicaprylate/dicaprate	3:1	253.18	93.52	[42]
Stearic acid	Propylene glycol dicaprylate/dicaprate	3:1	241.20	96.88	[42]
Glycerol monostearate	Propylene glycol dicaprylate/dicaprate	3:1	233.41	95.64	[42]
Cetyl palmitate	Propylene glycol dicaprylate/dicaprate	3:1	244.35	94.46	[42]
Glyceryl trilaurate	Propylene glycol dicaprylate/dicaprate	3:1	223.69	94.56	[42]
Glycerol tri-myristate	Glyceryl tributyrate	3:1	245.24	92.68	[42]
Stearic acid	Glyceryl tributyrate	3:1	262.65	93.54	[42]
Glycerol monostearate	Glyceryl tributyrate	3:1	270.45	90.16	[42]
Cetyl palmitate	Glyceryl tributyrate	3:1	257.91	93.34	[42]
Glyceryl trilaurate	Glyceryl tributyrate	3:1	339.64	90.09	[42]

of all-natural fatty acids. Oleic acid is known for its exceptional resistance to oxidation and its ability to boost the effectiveness of antioxidants and anti-polymerization agents[40].

Oleic acid as a liquid lipid can reduce particle size in NLC containing diethylammonium diclofenac as a drug model. Increasing the concentration of oleic acid can reduce the particle size of NLC because Oleic acid can reduce viscosity inside NLC and, as a result, reduce the surface tension to create smaller particles[41].

Isopropyl Palmitate

Isopropyl palmitate is an ester formed by combining palmitic acid and isopropyl alcohol. The product in cosmetics is a transparent, nearly scentless, fluid blend of isopropyl esters that consists of at least 60% isopropyl palmitate and small quantities of isopropyl laurate, myristate, pentadecanoate, heptadecanoate, and stearic acid. Isopropyl palmitate can be employed as a liquid lipid in an NLC. It can produce particles as small as 260 nm.[42]

Propylene Glycol Dicaprylate/Dicaprate

Propylene Glycol Dicaprylate and Dicaprate is a chemical compound consisting of propylene glycol diesters of caprylic and capric acid. It exhibits solubility in alcohols that have a water content of up to 20% and possess a low viscosity. Propylene glycol dicaprylate/dicaprate, when utilized as a liquid lipid, can generate particles as small as 230 nm[43]. On the other study, propylene glycol dicaprylate/dicaprate can reduce particle size up to 86 nm with high entrapment efficiency of up to 86%[44].

Preparation NLC

The production of NLC is facilitated by several methods that employ either low or high energy. Furthermore, there exist techniques that involve the application of organic solvents[45]. High-energy techniques include high shear homogenization, ultrasonication, and high-pressure homogenization (hot and cold), whereas low-energy methods involve microemulsion, double emulsion, phase inversion temperature and membrane contractor, regarding the methods that employ organic solvents such as emulsification solvent diffusion and evaporation, and solvent injection[46].

High Shear Homogenization

In this process, lipids are heated up at 5 to 10°C above their respective melting point. In contrast, the aqueous phase that contains surfactant is generated at an identical temperature as the melted lipids. Afterward, the lipid and aqueous phases are completely blended using a high-shear homogenizer. The formation of NLC is achieved upon cooling the hot emulsion to room temperature. The present method is regarded as simple as it does not entail the utilization of organic solvents that may possibly induce irritation and toxicity upon residual accumulation within the mixture[47].

Ultrasonication

Both lipids were melted at 5 to 10°C over their melting point and blended with surfactant in an aqueous phase at the same heat to produce a preliminary emulsion. The preliminary emulsion is subsequently subjected to sonication for a predetermined period of time at a specific volumetric strength. Subsequently,

the emulsion that is formed is swiftly cooled to room temperature to yield NLC. However, prolonged sonication may lead to the contamination of metal originating from the sonicated probe[48].

Hot High-Pressure Homogenization

The medication was mixed into the lipid melt and liquefied at a temperature 5 to 10°C above its melting point. A biphasic system comprising surfactant-containing air and a lipid phase was subjected to high-speed stirring in order to generate a pre-emulsion. The temperature of the two phases was maintained constant over the process. The pre-emulsion was added to homogenization under high pressure ranging from 100-2000 bar to obtain a nanoemulsion. An inherent limitation of this approach is the generation of heat, which makes it unsuitable for drugs that are sensitive to heat [49].

Cold High-Pressure Homogenization

This method presented offers an alternative to the hot-high-pressure homogenization technique. The lipid and liquid-based drug mixture is subjected to cryogenic cooling using either liquid nitrogen or dry ice. This mixture comprises solid particles, which are subsequently fine-pulverized and dispersed into a surfactant solution. The subsequent step in the course of action involves the process of high-pressure homogenization. Although this method mitigates drug exposure to high temperatures, it inevitably yields larger nanoparticle sizes of NLC[50].

Microemulsion

Drugs are solubilized in a lipid melt and subsequently introduced into an aqueous surfactant solution at an equivalent temperature. Subsequently, the mixture was stirred in order to attain a microemulsion. The microemulsion produced at high temperatures is added to a large amount of cold water, typically ranging from 20 to 50 times the volume of the microemulsion. The significant reduction in the concentration of the microemulsion droplets leads to the formation of NLC through precipitation. However, a large dilution volume can decrease the concentration of active substances, thus necessitating lyophilization as a means of pre-emption[50].

Double Emulsion

The hydrophilic drug was dispersed within a lipid phase consisting of melted lipids, hydrophobic drugs, and hydrophobic surfactants, resulting in the forming of O/W emulsion. Afterward, the oil-containing emulsion was diffused into the aqueous phase containing a hydrophilic surfactant, resulting in the formation of a W/O/W emulsion. The current study explores the use of sonication as a method to evenly mix and blend substances during the emulsification process. The advantage of this method lies in its capability to accommodate hydrophilic drugs[51].

Membrane Contractor

The process of lipid melting was stimulated by the utilization of a membrane with a specific pore diameter, which facilitated the application of pressure onto the lipid. Subsequently, the formed lipid globules were collected into a container containing surfactant in aqueous phase while being stirred at the same heat. This experimental procedure was conducted in an academic fashion. Subsequently, a cooling process was performed in order to obtain NLC. One of the limitations of this method is that the membrane pores may become obstructed.

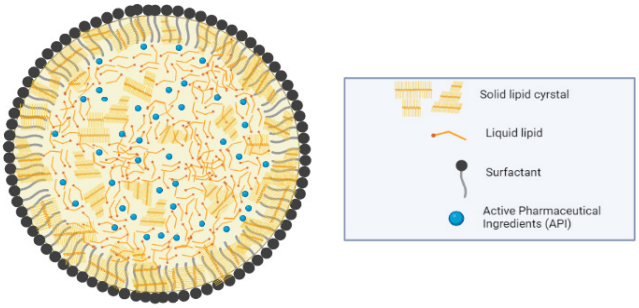

Figure 2: Schematic illustration of nanostructured lipid carrier (NLC)

Emulsification Solvent Diffusion

This method uses organic solvents that are miscible with water, including acetone, ethanol and methanol. Lipids containing API were dissolved in organic solvent, subjected to sonication and subsequently stored at high temperatures. A phase of water-containing surfactants was introduced into a lipid phase through constant agitation at a similar temperature. Subsequently, the formed dispersion was mixed with a decrease in temperature until reaching room temperature to obtain NLC, and the organic solvent can undergo evaporation.

Emulsification Solvent Evaporation

This method bears a striking resemblance to the emulsification solvent diffusion approach, which involves the utilization of a variety of organic solvents. Lipids and drugs are dissolved in organic solvents. The pre-formed emulsion subsequently undergoes sonication or high-pressure homogenization, yielding nanometer-sized particles. Subsequently, the process of cooling accompanied by stirring was conducted until the complete evaporation of the organic solvent[52].

Solvent Injection

The lipid phase containing hydrophobic drugs is injected using a needle into the aqueous phase agitated at a specific velocity. The surfactant-containing aqueous phase is subjected to similar temperature conditions as the oil phase. During the injection process, droplets of oil are formed as they are expelled from the needle. The resulting dispersion is subsequently cooled in order to obtain NLC[52].

NLC Application for Topical Use

Topical therapy targets the epidermis, which is the outermost layer of the skin. During dermal medication delivery, the drug has the ability to penetrate the layers of the skin's dermis. Furthermore, hair follicles can serve as a pathway for both dermal and transdermal delivery, with transdermal delivery potentially reaching systemic circulation[53]. The objective of topical delivery systems for the treatment of cutaneous

diseases is to avoid the necessity of systemic absorption. Topical delivery enables the administration of sufficiently high drug concentrations at the action site while circumventing the first-pass effect. The obstacle faced in delivering hydrophobic chemicals topically is due to the existence of the stratum corneum layer[54]. Due to the hydrophobic nature of most drugs intended for skin diseases, a strategy is required to enhance their penetration, one of which is through the use of nanoparticles. The formation of nanoparticles can be achieved through the utilization of either polymers or lipids. Lipid-based nanoparticles offer distinct advantages compared to polymer-based nanoparticles, including superior entrapment efficiency and drug loading capacity[55]. The lipid-based nanoparticle can be categorized into two types: solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC). Among them, NLC demonstrates many advantages in comparison to SLN, such as superior entrapment efficiency and drug release capabilities. Moreover, there is a direct relationship between the stability of NLC and the amount of pharmaceuticals that are encapsulated within it[56]. The utilization of NLCs intended for topical use are described ahead.

Passos *et al*. developed an NLC incorporating itraconazole for the treatment of sporotrichosis and other fungal infections[57]. NLC were formulated utilizing tricraprylin and Compritol 888 as solid and liquid lipids, with varying ratios of 7:3, 5:5, or 3:7, along with the incorporation of span 80 as a surfactant. The preparation of NLC was realized through sonication for a duration of 20 minutes utilizing a pulse of 50 seconds on followed by 30 seconds off. The resulting NLCs have a size range of 216-340 nm with a high entrapment effectiveness of 97%. The implementation of NLC has demonstrated a decrease in transepidermal water loss, with a range of 23-36%. The NLC has shown the ability to improve the survival rate and health index of *G. mellonella* larvae infected with *S. brasiliensis* yeast and *C. albicans.*

Gajanan S Sanap has developed the formulation of miconazole nitrate into NLC system as an antifungal therapy. The NLC was produced using the hot high-pressure homogenization process, with a rotational speed of 8000 rpm for a length of 4 minutes[57]. The solid lipid in this process was glyceryl tripalmitate, while the liquid lipid was miglyol 812. The resulting particle size was less than 250 nm, with an entrapment efficacy of over 86%. The NLC system has a lower rate of medication release when compared to miconazole gel. The skin layer's resistance to separation during release tests can be attributed to the presence of a substantial deposit[58-59]. The formulation of NLC allopurinol consists of glyceryl distearate as the solid lipid, caprylic/capric triglyceride as the liquid lipid, and tween 80 as the surfactant[60]. The NLC was prepared through the sonication emulsion method, yielding about 193 nm and EE of 52.2%. The NLC form of allopurinol has been observed to exhibit retention within the epidermal and dermal layers. Moreover, NLC allopurinol exhibits the potential to serve as a wound-healing agent.

A study was conducted to construct nanostructured lipid carriers (NLC) loaded with ketoconazole, with the aim of targeting the skin and minimizing negative side effects while prolonging drug release[61]. The NLC was generated utilizing the ultrasonication technique. The resulting NLC exhibits particle size range of 125-295 nm and EE of 69.47-95.49%. The aforementioned NLC is capable of gradually releasing medication over a twelve-hour period. ketoconazole may be deposited in a gel base to avoid systemic absorption.

Furthermore, NLC can be formulated for active compounds derived from natural sources, as demonstrated by the development of NLC ibrutinib with curcumin as therapy for psoriasis. The stated NLC is made up of glyceryl monostearate as the solid lipid and capryol PGMC as the liquid lipid[62]. The NLC products generate nanoparticles with a particle size of 95 nm and an encapsulation efficiency of 86% for ibrutinib and 87% for curcumin. The administration of NLC-based ibutinib supplemented with curcumin has been observed to alleviate symptoms of psoriasis.

The development of NLC for the purpose of minimizing the adverse effects of propranolol when administered orally as a therapeutic agent for infantile hemangioma is discussed[63]. The development of NLC was achieved utilizing liquid lipid from *Rosa rubiginosa* essential oil and solid lipids (stearic acid). The NLCs were prepared via the ultrasonication technique and were developed into two distinct size models, measuring 569 nm and 824 nm, respectively, accompanied by an entrapment efficiency of 99%. The utilization of nanoparticle-based delivery systems, specifically NLC propranolol, has demonstrated the ability to enhance both antiproliferative and antimigratory effects in contrast to conventional propranolol solutions. The administration of NLC propranolol has been shown to effectively inhibit over 50% of the growth of infantile hemangioma within five days of treatment while also limiting the migration of cells by almost 25%. These results suggest that NLC propranolol therapy holds substantial promise as an anti-infantile hemangioma intervention.

A study developed luliconazole in NLC formulation, which exhibits antifungal activity for topical application[64]. The NLC consists of a combination of a solid lipid, specifically Compritol 888 ATO, and a liquid lipid, known as Labrafil M2125CS. The process of creating NLC involves the use of ultrasonication. The NLC generated exhibited a particle size of 86 nm along with an entrapment efficiency of 85%. The NLC formulation of luliconazole has demonstrated $C_{max\ skin}$ that is twice that of the comparator cream and an AUC_{0-24} that is three times that of the comparator cream in both the epidermis and dermis.

The inclusion of minoxidil and latanoprost into the NLC system is conceivable[65]. The NLC was created via the sonication method. The composition of NLC consists of Compritol (a solid lipid), miglyol (a liquid lipid), and surfactants like tween 80 and span 80. Based on the aforementioned method, NLC was produced with a size of 393 nm and high entrapment efficiency for both minoxidil (86.9%) and latanoprost (99.9%). The NLC can be applied to the hair follicle, resulting in improved penetration of both medications compared to the

control (free drug in base), and leading to an approximately 50% improvement in efficacy. NLC can be incorporated into transdermal dosage forms, such as membrane-type patches, to optimize the penetration of drugs. NLC containing diclofenac incorporated into membrane-type patches can increase the flux of dissolution with rat skin as a membrane model[66]. Additionally, NLC can incorporate quercetin as a model of a bioactive compound. Penetration study of quercetin loaded NLC incorporated to membrane-type patch can increase the flux of penetration of quercetin through rat skin as membrane model.[67] Particles of NLC can form a fine layer above the stratum corneum, thus increasing the hydration of the skin. This process allows drugs to penetrate through a passive diffusion mechanism.

CONCLUSION

The process of choosing suitable lipids, which can include both solid and liquid forms, can be accomplished by taking several factors into account. The aforementioned considerations encompass factors such as polymorph form, crystallinity, solubility of the active ingredient, viscosity, and ratios. All of these considerations will subsequently exert an influence on physical characteristics and drug release, thereby influencing the effectiveness of the therapy. The selection of the NLC manufacturing process also considers the stability of its active constituent. The production of NLC can be achieved through various methods, including those that require high-energy input and low-energy input, as well as those that employ organic solvents. Several studies have shown that topical NLCs have a higher level of effectiveness compared to traditional topical bases. Therefore, NLC has the potential to function as a promising method of delivering medication topically.

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