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Nanostructure Lipid carrier (NLC) as a Skin Delivery System

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Abstract
Nanoparticles are one part of nanotechnology that is widely developed on Nano medicine and Nanodermatology. Nanomaterial is a system that has sizes ranging from 1-1000 nm (or 10^{-9}-10^{-7} m). Besides being used for drug delivery, nanoparticles are now also widely used in cosmetic preparations to enhance the performance of active ingredients, protect active ingredients from degradation, alert local action, and prevent active ingredients from entering the bloodstream. Nanoparticles used in cosmetic dosage formulations include Nano-emulsion, Nano-crystal, micelles, polymeric Nano-capsules, noisome, liposomes, nanostructured lipid carriers, solid lipid nanoparticles. Nano Lipid Carrier (NLC) which is the second generation of Solid Lipid Nano particle (SLN) delivery system. NLC consists of a certain amount of lipid matrix and liquid lipids, providing enough space to accommodate drug molecules and consequently enhancing drug trapping capacity, preventing drug release, improving drug stability and increasing flexibility to modulate drug release.

Keywords: *Nanoparticle, NLC, Matrix Lipid*

1.0 INTRODUCTION

Current drug development encounters several obstacles such as the degree of solubility of the drug in the low water therefore needs of drug delivery system in a colloidal that is able to maintain the stability of active substances without reducing the effectiveness of the active substance. The nanotechnology delivery system begins with Nano-emulsion but in its journey it finds constraints, i.e. Nano-emulsion is less stable in storage, can form larger droplet sizes.[3,11]The stability of Nano-emulsion is influenced by environmental parameters such as temperature and pH. These parameters may change when the drug is delivered to the patients otherwise nano-emulsion is also unsuitable for a drug with a high melting point. *Nanostructured Lipid Carriers* (NLC) is the latest generation of *Solid Lipid Nanoparticle* (SLN), SLN itself is the first generation in Nano technology system, made using solid lipids, which are dispersed into water as outer phase with surfactant as stabilizer.[3, 9] NLC consists of a certain amount of lipid matrix and liquid lipids. The NLC remains in solid formation by controlling the liquid lipid content added to the formulation, so that the controlled drug release properties for NLC can be achieved.[4,10,12]

2.0 The Advantages of NLC As Delivery System Of Drug Through Skin

Advantages obtained from NLC systems for example, it can be used for controlled drug and targeted drug release, improving pharmaceutical stability, increasing drug loading (when compared with SLN), capable of delivering lipophilic and hydrophilic drugs, most of which are biodegradable, good bio-compatibly, water-based technology (avoiding organic solvents), easy to be *scale-up* and sterilized, more affordable (cheaper than polymer / surfactant-based carrier systems), easy to validate.[1] Some other advantages of NLCs are:***Occlusive effects***: This occlusive effect is influenced by particle size, lipid concentration, and the type of lipid used. Very small particles of lipid particles form high crystals and melting point of lipid becomes low causing increased occlusive properties. In addition, the surface area of NLC particles in contact with the stratum corneum is increased and lipids used are lipids which can make NLC become adhesive to the skin thus increasing penetration of the active ingredient through the stratum corneum and providing an occlusive effect on the skin.[3,1]

2.1 Release of controlled drug: This occurs because the mobility of the drug substances in the lipid becomes lower, causing the drug substance to be released gradually than SLN

2.2 ***Improving the stability of medicinal substances:*** Increasing chemical stability caused by small contacts of medicinal substances with oxygen, light, humidity, ambient temperature and contamination due to drug ingredients trapped in NLCs

2.3 ***Low toxicity:*** In the NLC system, the constituent material comprises of a solid lipid and a liquid lipid having a non-. irritating, biodegradable and safe/*Generally Recognizing As Safe* (GRAS) property so that the preparation with an NLC system has a low toxicity.[3,10]

Improving drug trapping: High carrier capacity so that many drug molecules can be included in the matrix particles, this is due to the decrease of the regularity of the crystalline matrix.[2, 5]

Low viscosity: The NLC dispersion system has a low viscosity so that the molecular mobility of the active ingredient is increased so that there are no barriers in the release of SLN. [2.11]

3.0 NLC COMPONENTS

3.1 Solid Lipid and Liquid Lipid

The term lipid is commonly used for the structure of triglycerides, glycerides, fatty acids, steroids, and waxes. The benefits of using lipids as a drug delivery system for topical routes are well tolerated lipid properties, reduced local irritation risk, and have low toxicity. In the NLC system, a combination of lipid solid (fat) and liquid lipids (oil) is included in the category of Generally Recognized as Safe Status (GRAS) such as tristearin, mono-, di-, and triacylglycerol mixtures (corn oil, soybean oil, olive oil , VCO) fatty acids and cetyl palmitate.7 The presence of oil or liquid lipids in this NLC system provides an advantage of the NLC system in the case of drug trapping because in general the drug is more soluble in oil than in solid lipids and the presence of oil can decrease the lattice order of the lipid matrix crystal due to the differences in the length of the lipid carbon chain on and oil.5,2,8

3.2 Emulsifiers

Some types of emulsifiers that have been widely used to form NLC systems are poloxamers, polysorbates, lecithin, and bile acids. It is known that the emulsifier combination can significantly decrease the particle agglomeration.[2]The emulsifier type can affect the speed of drug release in the NLC system. The NLC system using the soybean phosphatidylcholine (SPC) emulsifier provides a slower release than Myverol, while for trapping effectiveness Myverol provides trapping which is bigger than SPC. The use of Tween 80 and Span 80 as an emulsifier at a concentration of 16% (b/b) can yield an average particle diameter of 100 nanometer and the tendency of particle crystallization increases with increasing saturated hydrophilic chain length from surfactant.5,10,8

4.0 NLC TECHNIQUES PRODUCTION

4.1 High Shear Homogenization and *Ultrasound*

This method is the easiestdispersion techniqueand most commonly used. In this method the fused lipid is dispersed in the aqueous phase at the same temperature as mechanical stirring or sonication.[7]There is the effect of stirring rate, emulsification time, and cooling conditions to particle size and potential zeta value. Increasing stirring rate has more influence on Polydispersity Index (PI) value than in particle size reduction. With this method, the quality of the dispersion is still poor because of micro particles and for the use of ultrasound method there is the possibility of metal contamination.[6]

4.2 High Pressure Homogenization

The High Pressure Homogenization method uses high pressure (100-2000 bar) to push the liquid lipid through a narrow gap. In general, lipid concentration used is 5 to 10%. In this method used shear stress and cavitation as a force that can change the particle into submicron size. There are two approaches in the process of formation of NLC system using HPH method, namely Hot Homogenization Technique and Cold Homogenization Technique. In both of these techniques, the first drug is dissolved or dispersed on a lipid that is melted at 5-10 ºC above its melting point. In the Hot Homogenization Technique, the dispersed active ingredient of the lipid is dispersed in aqueous surfactant solution at the same temperature as stirring using a *high shear device* such as Ultra-Turrax to form a pre-emulsion and homogenized piston gap homogeneously to form a hot o/w Nano-emulsion and cooled at room temperature. At room temperature, the lipids will undergo recrystallization and form nanoparticles. In Cold Homogenization Technique there are different ways of cooling with Hot Homogenization Technique. In Cold Homogenization Technique, melting of lipids containing active ingredients is rapidly cooled using liquid ice or nitrogen. The advantage of this technique is to prevent degradation of the active ingredient by heat, partition of drug into the water phase during homogenization process, and reduce the heat exposure to the sample. [3]

4.3 Micro emulsion Technique

In this method, the lipid mixture is first diluted and then the active ingredient is put into the lipid melting. At the same temperature, prepare a mixture of water, surfactants, and co-surfactants to form a water phase and then a water phase incorporated into a lipid melt with medium stirring. To produce a micro-emulsion, required a precise comparison of each ingredient used. The formed micro-emulsions are then dispersed into the aqueous phase by comparison of the hot micro-emulsion and the water phase (1:25 - 1:50) with moderate stirring rate. [3,9,11]

4.4 Solvent Emulsification-Evaporation Technique **:** In this method, the hydrophobic lipophilic and active ingredients are dissolved in an organic solvent not mixed with water (for instance cyclohexane, dichloromethane, toluene and chloroform) and then the solution is emulsified into a water phase using a *High Speed Homogenizer* to improve emulsification efficiency , the emulsion formed is passed to the micro fluidizer. The final stage is the evaporation of organic solvents by mechanical stirring at room temperature to obtain lipid precipitation nanoparticles.[3,9,11]

4.5 Solvent Emulsification-Diffusion Technique: In this method, the solvent used is a partially mixed solvent with water, for example: benzyl alcohol, butyl lactate, ethyl acetate, etc. Initially, both solvent and water must be saturated to ensure thermodynamic balance of both liquids. The lipid melt is then dissolved in saturated water of organic solvent (organic phase / internal phase) and then emulsified into a water-saturated organic solvent containing emulsifier by stirring using a magnetic stirrer to form an emulsion system o/w, the emulsion is then diluted with water (1: 5-1: 10) for the solvent to diffuse into the water phase and then to aggregate the lipid nanoparticles. This condition is carried out at room temperature or temperature below lipid solubility with constantly stirring constant velocity. The final stage is the process of solvent removal with vacuum distillation or lyophilization.[3,9,11]

4.0 THE TYPES OF NLC

4.1The Imperfect type: This type can accommodate more active ingredients because of its imperfect matrix arrangement. This type can be obtained by mixing solid lipids with a small amount of oil. Due to differences in the length of the chain between fatty acids and the mono-, di-, and triacylglycerol- mixtures, thisNLC cannot form a regular crystal structure. [7.12]

4.2*The Amorphous type:* *This* type is obtained by mixing a special lipid that does not recrystallize after homogenization and cooling such as hydroxyl-octacosanol-hydroxylstearate and isopropyl myristate. These lipids can form amorphous lipid particles that can avoid recrystallization and decrease drug leakage because the lipid matrix maintains the α-polymorphism form. 7.12

4.3*The multiple type:* This type is almost the same as the w/ o/w emulsion which in this type consists of oils in solid lipids in water dispersions where the solid lipid matrix contains thin Nano-compartments of oil. This type can be obtained by mixing solid lipids with high amounts of oil. [7.12] Type NLC can be seen in the picture below:

Nanostructured Lipid Carriers *(NLC)Types*
Type*I(imperfect type);*Type *II(amorphous type);*Type*(multiple type)*[8]

5.0 CONCLUSION

The development of a formula for drug delivery systems encounters several challenges, one of which is the stability of the active ingredient to be used in the formula. Therefore, to overcome the obstacles need to be designed an appropriate delivery system to support the working mechanism of the active ingredient. Another transdermal drug delivery system is the *Nano Lipid Carrier* (NLC) which is the second generation of *Solid Lipid Nano particle* (SLN) delivery system. The NLC consists of a certain amount of lipid matrix and liquid lipids, providing enough space to accommodate drug molecules and consequently enhancing drug trapping capacity, preventing drug release, improving drug stability and increasing flexibility to modulate drug release.

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