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Nanostructure Lipid Carriers: Innovation in Drug Delivery Systems

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Abstract: Nanostructured lipid carriers (NLCs) represent a significant advancement in the field of drug delivery systems, integrating the benefits of both solid lipid nanoparticles and liquid lipid formulations. This review explores the innovations surrounding NLCs, highlighting their unique composition, fabrication techniques, and the mechanisms that enhance drug solubility, stability, and bioavailability. Recent developments in surface modification and targeting strategies are discussed, demonstrating how NLCs can improve the therapeutic efficacy of various drugs, including anticancer agents, anti-inflammatory drugs, and vaccines. Furthermore, the review addresses the challenges and regulatory considerations associated with the clinical translation of NLCs, providing insights into future research directions. By synthesizing current knowledge and emerging trends, this review aims to underscore the transformative potential of NLCs in modern medicine and their role in advancing personalized therapy.

Keywords: Nanostructured Lipid Carriers, Lipid Nanoparticles, Emulsion, Controlled Release.

Introduction:

Lipid-based (Drug Delivery System) DDS is a proven economically feasible method for producing medications in various dosage forms. Lipid compositions such as Nano Lipid Carriers NLCs requires the insoluble Drugs are two major criteria that can be imprved with the formulations such as NLC. Numerous pharmaceutical companies have developed A lipid matrix is present within the freshly created NLCs with a muller produced a particularly unusual nanostructure. This the nanostructure of specific type of NLC also contributes to increasing Bioavailability, drug loading, and the medications solubility in various conditions and environments. There are several approaches, and strategies these kinds of NLCs. Lipid nanoparticles show amazing features that are crucial for their medicinal effectiveness. Nanoparticles [NP] have unique features, including high surface-to-mass ratio. Additional colloidal Particle and their propensity to bind Containing chemicals that make a nanoparticle cleverer to employ medicinal product. Lipid nano formulation produce dispersions of somewhat water-soluble drug and can reduce the distinctive constraints of slow and imperfect Dissolution of fairly water-soluble drug like Biopharmaceutical classification system (BCS) class II and simplify the formulation of solubilized phases, from which drug absorption occurs easily in any vehicle-medicated delivery system, such as an the degree and method of drug release from an emulsion or liposome system play a vital role in mobility of the delivery system in-vivo. Muller constructed a unique nanostructure that includes a lipid matrix within newly created NLCs. The Unique Nanostructure of NLC contributes to increase Bioavailability, drug loading, and the medication solubility in various conditions and environments. There are several approaches, and method by which various kind of NLCs can be prepared. The formulation is similar to high-pressure homogenization. As per the literature there can provide approximate 30-80 percent of product yield. ways after modifying the various conditions and settings. NLCs are a novel type of DDS formulation that improves stability and loading, allowing for concentrated dispersion. Many pharmaceutical firms have developed. Some will-established industrial procedure for the production of large batch of nanostructure lipid carriers, although all major factors, such as lipid section, surfactants, and author necessary excipient and method of preparation vary, leading to change in factors such as particle form, size, phase transition, and solubility. Bioavailability of drugs, etc if process variables such as mixing and stirring (speed and time), melting (temperature),

homogenisation (speed, temperature, pressure) are not followed as per standard guidelines a standard operating procedure. NCLs are a hybrid carrier consisting of solid and liquid lipids, with typical size of 10 to 500 nm.

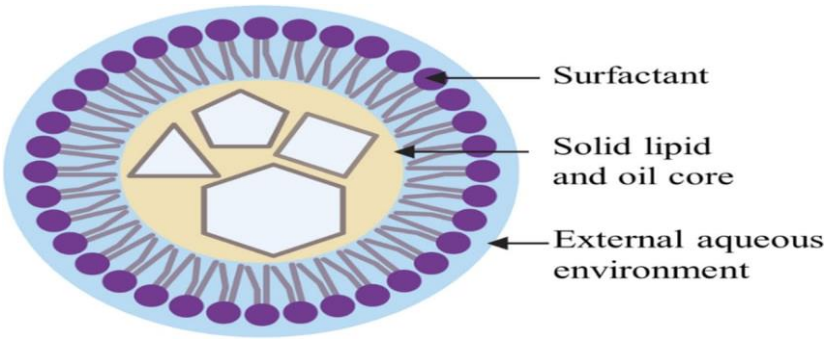

Fig1: Structure of Nanostructured Lipid Carrier

The NLC combination consists of long chain of liquid and lipid (oil). Having a short chain of solid and lipid with ratio of 99.9:0.1 of 70:30. NLCs were first introduced in the 1990s as another carrier system. Solid lipid carrier system is accessible in solid lipid nanoparticle (SLN) in nm range were described as a replacement for liposomes. However, there are several constraints linked with SLN, such as incomplete drug loading capacity and drug expulsion. All of these limits can be reduced or eliminated through storage. Newer solid lipids have DDS property similar to NLCs. There is a new, modified type of NLCs available with a precise nanostructure. These precise nanostructures are accountable and help to improve the stability of the formulation and boost the bioavailability. Drug loading NLCs also minimise the various difficulties that are related with the SLN for many drugs, problems like low payload, drug ejection during storage and SLNs diffusion due to the more water content in it. [1] Topical drug delivery was more effectively retained in the upper layer of the skin when applied topically in NLC formulation compared to emulsion-based formulation. Thus, NLC formulation were claimed to be appropriate for cosmeceuticals that are designed to remain in the skin without penetration, thus limitation the systemic effect. [3] Additionally, NCL might include both hydraulic and hydrophobic medicines. [8] Coarse-grained molecule dynamic simultaneous are utilised to establish the distribution of each component inside the NLC. This allows for interpretation and excrement results. [9]

Recent progress in NLCs:

Recent research examination shows the important role of NLC in the field of medicine. Multifunctional nanocarriers of IR 780 and Coumarin 6 fluorescent dye encapsulated CXCR4- targeted NLCs for breast cancer therapy using photodynamic therapy have been reported. The progress system was show to be extremely effectively blocking cancer cell progressing and metastasis and in parallel permitting imagine. Fabricated an NLC loaded with quantum dot and Paclitaxel that was highly capable of observing and following cancer cell growth and simultaneously inhibiting tumour cell in the murine tumour model of hepatocellular cancer. [4]

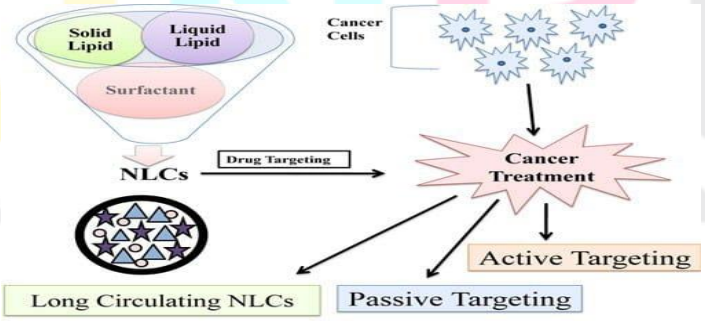

Fig 2: Nanostructured lipid carriers; New insight for cancer therapy

Advantages and limitations:

NLCs improve the chemical stability of active substances by reducing the release of unstable chemicals from the lipid structure and ensuring the physical quality of topical formulations during storage. Because of the less ordered structural arrangement, this improved variant of SLNs has a controlled-release property and is less prone to aggregation when compared to emulsions. Other

advantages include NLCs' potential to lower emulsion water content, ensure transdermal permeation with nanosized particles, prolong half-life, and enable tissue-targeted drug administration. Furthermore, NLCs improve the efficacy and potency of active ingredients and can control drug release while delivering active ingredients with different polarities NLCs improved the chemical stability of active substance by reducing the release of unstable chemical from the lipid structure and ensuring the physical quality and topical formulation during storage. Because of the less ordered structure arrangement, this improve variant of SLNs has a controlled-release property and is less prone to aggregation when compared to emulsions. Other advantages include NLCs potential to lower emulsion water content, ensure transdermal permeation with nanosized particles, prolong half-life, and enable tissue-targeted drug administration. furthermore, NLCs improve the efficacy and potency of active ingredients and can control drug release while delivering active ingredients with different polarities. Despite its potential medication delivery capabilities, NLC technology has significant limitations. These include selecting surfactants with caution to avoid irritation and sensitivity. NLCs applications and efficiency in delivering proteins and peptide medicines, as well as targeted gene delivery, have yet to be completely researched. Furthermore, there are minimal preclinical and clinical investigations on NLCs.[2]The NLC has a higher loading capacity than the SLNs, allowing for more active molecule to be loaded in the imperfections, the particle avoids the early expulsion of the active ingredients. [5]

Types of NLCs:

1) NLC Type I: (Imperfect). There are referred to as imperfect crystal types due to their unstructured matrix, Imperfections create opportunities for medication integration. Has a high trapping efficiency in this scenario, the sum amount of liquid lipid used when compared to solid lipids is lower. Solid lipid and oil are combined and blended to create an oil/water (O/W) nano emulsion that produced lipid particles upon cool to room temperature.[12] Varying the saturation and quantity of carbon atom in lipid can cause distortion. This causes an increase in loading capacity. [7]

2) NCL Type II: (Amorphous/ structureless). Mixings solid liquid with certain liquid that remain polymorphic after solidification results in the formation of Type II NLCs. The use of medium-chain triglycerides, hydroxyocacosanyl, hydroxy stearate,or isopropyl myristate in combination with solid liquid has been shown to produce the required result. This type is often preferred because there is no crystallisation and the medicine is still integrated into the amorphous matrix. This prevents drug release due to crystallisation to β forms during storage. [2] By avoiding recrystallisation during cooling, the drugs undesired release is avoided, and increase its shelf-life [6]

3) NCL Type III: (Multiple)

The oil-in-lipid-in-water types, also Known as the multiple type, is the third form of NLC. Type III NLCs have a higher oil solubility as compared to the solubility of solid lipids. Type III NLCs have a high proportion of oil is combined with solid lipids because the oil molecule may easily diffuse into the liquid matrix at low oil concentration. If adding oil in excess of what is required for its solubility can lead the separation of distinct phases, eventually create little oily nano compartments surrounded by the solid lipid matrix. This kind of formulation allows control medication release and leakage of medication from the lipid matrix.Lipophilic medicines can be made soluble in oil firstly and type III method can be followed with the cooling procedure of a hot homogenization. [13]

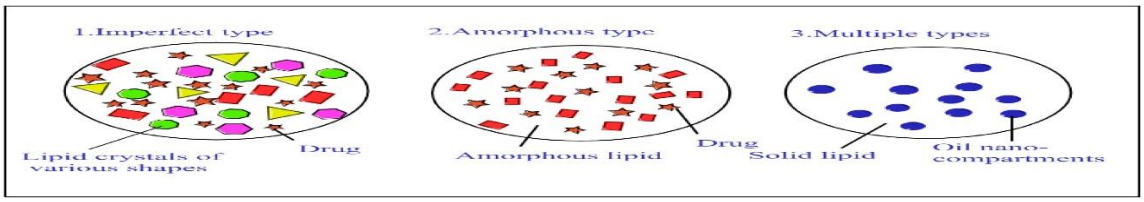

Fig3: Different types of NLC

Excipients used in NLCs:

1) Lipid:

The inner core includes both solid and liquid lipid. solid lipid utilized in NLCs included glyceryl behenate, glyceryl Palmitostearate, fatty acids, triglycerides, steroid, and waxes. At room temperature these lipids exit in solid state. Liquid dissolve at high temperature. And digestible oils derived from natural sources used in NLCs. [14]

2) Phospholipids:

Phospholipids, which contain a phosphate group, are commonly found in biological membranes. Because of their biocompatibility and stability, phospholipids have been widely used to increase the stability of NLCs and drug delivery properties. Phospholipids used include phosphatidylcholine, soy lecithin, and synthetic phospholipids. [2]

3) Fatty acids:

Fatty acid are long chains of carbon atoms, generated from natural sources like Olive, Coconut, and palm oil. Furthermore, fatty acids are commonly employed in the formulation of NLCs to generate a stable lipid matrix for drug delivery. Commonly utilised fatty acids include oleic, stearic, palmitic and arachidic acids. [2]

4) Wax Esters:

Long-chain fatty acids and alcohol combined to form wax esters. This lipid is suited for use as a solid lipid carrier in NLCs, due it to its high melting point and stability. In addition, wax esters stabilised carrier lipid matrix and can be mixed to produce the desired qualities. Palmitate esters, carnauba wax, propolis wax, and beeswax are among the most regularly used wax esters. [2]

5) Surfactants:

Surfactants improve colloidal stability in traditional NLCs production. NLC exhibit varying physical and chemical properties based on surfactant composition and concentrations. Surfactants provide two major functions; they spread the lipid melt in aqueous phase. And after cooling, the lipid nanoparticle in the dispersion become more stable. The key consideration when using surfactants safety and compatibility with various excipients are important consideration when formulating solid lipid nanoparticles. Surfactants can improve epithelial cell permeability and overcome any limitation in medication absorption. Exa; Pluronic F68, polysorbate, polyvinyl alcohol, span*80, and lecithin. [10]

NLC Method Of Preparations: Natural substances can be loaded onto nano liquid carrier to generate enhanced product formulation using a variety of technique and methods. These include high pressure homogenization, high shear homogenization followed by Ultra Sonication, Microemulsion, solvent emulsification/evaporation, membrane contactors, phase inversion and Coacervation. [2]

1) High-pressure homogenization (HPH):

A compartment known as a high-pressure homogenizer (HPH) is used to pass excipient through a micro-size nozzle at high pressure of between 100 and 2000 bar. The excipients are subjected to mechanical and thermodynamic pressure throughout this process, which simultaneously reduce pressure along the Nozzle and Create high shear stress from strong turbulent eddies and cavitation forces. The ability of HPH to degrade the lipid mixture and emulsify natural component into nano-sized droplet make it technical feasible to create NLCs by facilitating production upcasting. But this mechanism primary shortcoming is that it generates sub-micrometers particles, which is main drawback of HPH. [2]

2) High-shear homogenization (HSH) and ultrasonication:

This approach dissolves or disperses a lipophilic drug in a molten mixture of solid and liquid lipids. To prevent recrystallization, use temperature 10C higher than the solid lipid melting point. Pre- microemulsion is formed by combine the aqueous surfactant solution into the liquid phase at the same temperature and swirling it vigorously. Following treatment with probe Sonicator, the pre-emulsions is further homogenised with high shear homogenizers. [16]

3) Microemulsion:

After melting the lipids, the aqueous phase with surfactants is heated to the same temperature. Next, the melted lipids are mixed at the same temperature as the hot aqueous phase is introduced. lipid nanoparticles have solidified, by adding the hot O/W microemulsion in cold water at the temperature of 1:50. [11]

4)Solvent-emulsification/evaporation:

To create lipid nanoparticles through emulsification and solvent evaporation, the lipid mixture is first dissolved in water saturated organic solvent. And then the active material added in this mixture, allowing to dissolved in it completely. The organic phase Is emulsified in an aqueous solution containing an organic solvent and the stabilizing agent. Stirring might be mechanical or ultrasonic,

lastly as the organic solvent evaporates, and nanoparticle precipitate in the aqueous phase. This process is one of the most often used in the preparation of SLN, together with the homogenization under high pressure. [17]

5) Membrane Contactors:

Membrane contactors maintain contact between to phases. A pressurized tanks keep the lipid phase at the temperature above its melting point. It allowed to leak through ceramic membrane perforations under pressure, forming minute droplet. The aqueous phases move tangentially with the membrane module with constant stirring, brushing away the droplet form at the pore outputs. As the mixture cools to ambient temperature, lipid particles are formed. Temperature of aqueous and liquid phase, tangential flow velocity of the aqueous phase, and lipid phase. Pressure and membrane pore size are both process variables that influence the size of lipid nanocarriers. [18]

6) Phase inversion temperature (PIT):

The interconversion of o/w and w/o emulsion caused by thermal change occur at the phase inversion temperature (PIT). Nanoparticles are generated by a variety of methods including spontaneous inversion via freezing-and-heating cycle and lipid crystallisation caused by irreversible thermal shock that ruptured emulsions. [2]

7) Coacervation:

To create lipid nanoparticles, a typical supramolecular stabilisation solution is first created in warm water. A sodium salt of lipidic acid is evenly added into an inventory solution. The polymeric stabilizer produces a transparent solution. This solution is then repeatedly stirred, even when heated far above the sodium salt of the fatty acids, the krafft point. To form a single phase, the drug (hydrolysis ethanol) is added to apparent solution and constantly agitated. This when a coacervating solution is added to the mixture, it creates a supervision it is gradually added. The supervision is then cooled with water bath while being repeatedly agitated; creating drug-laden nanoparticles that are equally distributed. The method for particle formation is decrease in the pH of dilute alkaline solution. Acidity (coacervating solution) causes fatty acid salts to form the use of polymeric coacervation. [20]

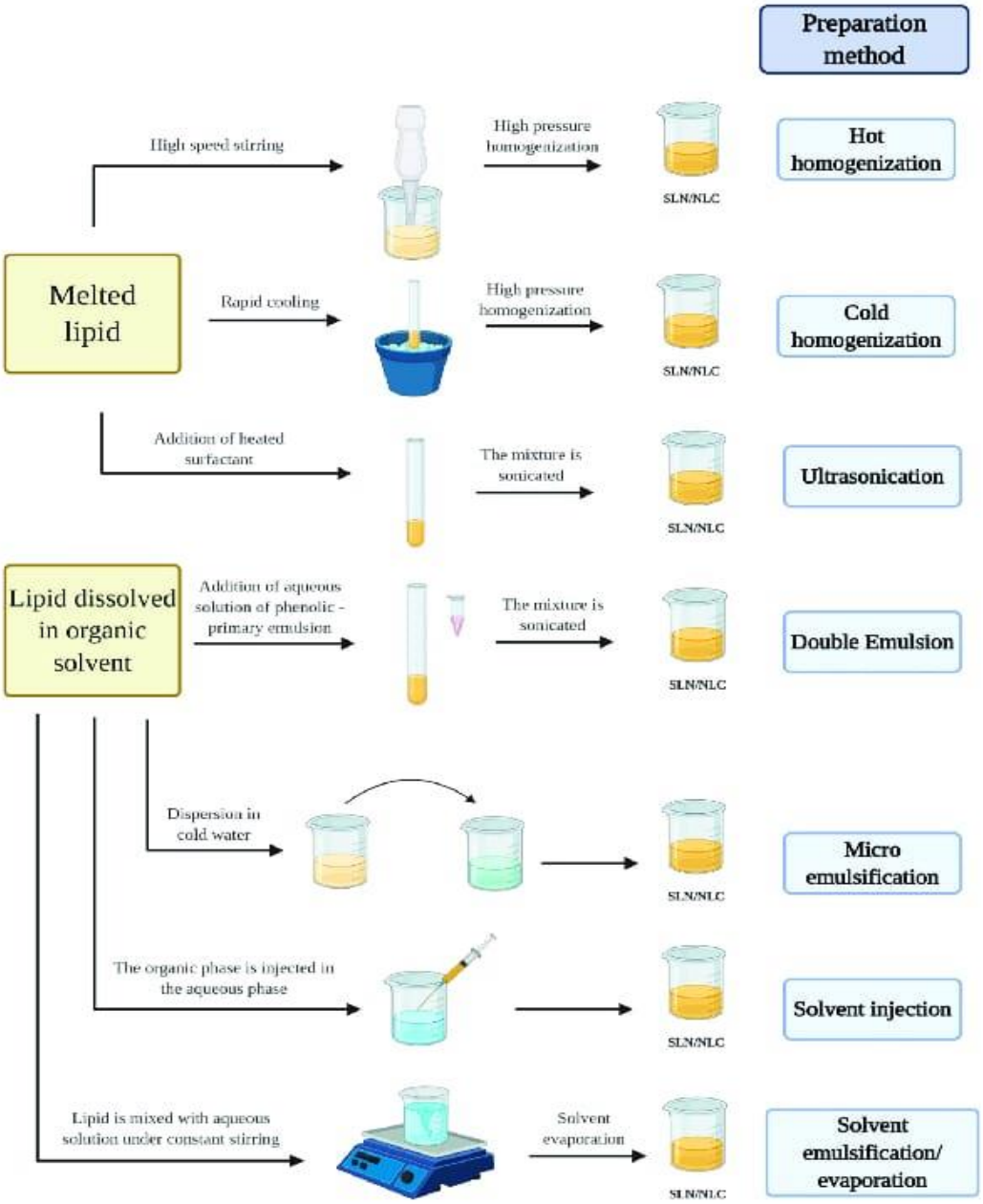

Fig4: Different method of preparations (Nanostructured Lipid Carriers)

NLC characterization:

Physicochemical characterization is essential to control and clarify the quality and stability of NLCs. Furthermore, data on physical and chemical qualities can help designer optimise their design for greater efficacy, stability, and safety. Some typical strategies used to characterize NLCs are listed below.

1) Particle size analysis:

Particle size is a critical characteristic that influence NLC stability, bioavailability, and cellular absorption. Technique like dynamic light scattering (DLS) and nano particle tracking analysis (NTA) can be utilised to determine side distribution. In general, NLCs for cutaneous drug administration typically have submicron particle size ranging from 40 to 1000 nm, depending on lipid composition. [2]

2) Zeta potential analysis:

The zetasizer/pcs analyses, zeta potential. Surface charges assessed to assess particle stability in usage, which is influenced by aggregation and dispersion mechanism. In general, charged particles are less likely to aggregate, or fusion caused by electrostatic opposition. And electrical positive the surface of NLC has a high rate of blood-brain barrier entry (BBB). Because it attached to the blood brain barrier paracellular area, an abundance in anionic site region. The zeta potential can be determined as determined whether the cationic surface is useful for formulation design. To stabilise nano particle system during specific procedures, sometime particle surfaces need to negatively charged during storage. The zeta potential, or particle surface charge, is a measure of how stable

a system during storage. The endurance charge waiting agent were used to stabilize NLC formulation during storage requires a zeta potential of at least 30 mv. [20]

3) Morphology analysis:

Transmission electron microscopy (TEM) offer precise views of the internal structure and shape of NLC on the nanoscale. Scanning electron microscopy (SEM) provides surface pictures of NLCs, exposing their form and surface characteristics. Atomic force microscopy (AFM) it utilized to get three-dimensional surface topography and mechanical features of NLCs. [19]

4) Entrapment efficiency:

Entrapment efficiency (EE) is defined as the proportion of entrapped drug weight to total drug weight added to the dispersion. The quantity of medicine encapsulated per unit weight of NLCs are then determined using an ultrafiltration-centrifugation method. A known NLC dispersion is made and centrifuge in an Ultrafilter-equipped Centrifuge tube following proper dilution, the amount of free drug supernatant is determined using an appropriate analysis method. [2]

5) In vitro release studies:

In vitro release studies assess the kinetic of drug release from NLC under stimulated physiological setting. In this study, NLCs are intended for targeted medication administration, allowing particular drug localization inside the epidermal layers. Furthermore, NLCs enabled prolonged drug release, which is beneficial for long-term theoretical activity. To accomplish this, the lipid matrix is changed to regulate medication release. [2]

6) Crystallinity and polymorphism:

X-Ray Diffraction (XRD) and Differential scanning calorimetry (DSC) are useful method for predicting drug/excipient crystallinity and potential polymorphic forms. The physical shape of the chemical is significant for interpreting the formulation stability and pharmacological action. The XRD pattern contains distinct peak for each component. XRD pattern reveals the nature of the enclosed substance and the extent to which is crystallized. The absence of peak in DSC suggests a reduction in crystallinity or formulation components, which will be responsible for improved solubility. [17]

Conclusion:

In conclusion, this review showed that nano structured lipid carriers are a promising drug delivery system that offers several benefits, including improved bioavailability, targeted and controlled release, and reduced toxicity. NLCs formed by combining solid and liquid lipids, creating a matrix with defect that can accommodate drug molecules, addressing the limitation of solid lipid nanoparticles. Nano structure lipid carrier as a drug delivery system with high loading capacity and sustained release pattern appropriate for treating skin disease. The finding revealed that NLCs had been utilised to delivered antioxidants, which had gained popularity in cosmetics sector due to their potential benefit in terms of skin hydration, occlusion, bioavailability, and skin targeting. This lipid-based systems could also be created using various approaches and characterised by particle size, zeta potential, morphology, and drug encapsulation efficiency evolution.

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