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An Overview of the Usage of Nanostructured Lipid Carriers in the Treatment of Migraines

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ABSTRACT

This Review's objective is to provide a high-level, concise summary of migraine diagnosis, therapy, and management. One common neurological condition that has a major impact on people's lives and healthcare systems is migraine. Low drug solubility, restricted bioavailability, and systemic administration side effects are common problems with conventional migraine treatment methods. A novel drug delivery technology known as nanostructured lipid carriers, or NLCs, has emerged as a viable way to get around these restrictions. The present status of research on the use of NLCs in the treatment of migraines is examined in detail in this thorough review. The review includes an examination of NLCs' special qualities, their potential advantages in drug delivery, and how they can be used to enhance the pharmacokinetics and therapeutic results of migraine treatments. The main points are covered in detail, including enhanced drug solubility, targeted drug delivery, extended- release kinetics, and decreased side effects. The review also points out current road-blocks and potential future paths in the creation of NLC-based migraine therapy formulations. The goal of this synthesis of the available data is to offer insightful guidance to researchers, physicians, and pharmaceutical companies looking for novel approaches to improve the effectiveness of treatments for migraine.

Introduction

The major symptom of migraine is severe throbbing and pulsating pain around the head. Other typical secondary symptoms include nausea, vomiting, and photophobia (1). With an estimated 15% global incidence, migraine is currently the third most frequent condition, mostly affecting people between the ages of 35 and 45. It typically first manifests during puberty. Many delivery methods, including oral, systemic, and nasal, are being investigated for the treatment of migraines. Of them, the nasal route is the most advantageous for quick administration and brain-targeting medication delivery (2). The most popular delivery methods for all kinds of therapies are oral and systemic, but, when it comes to brain drug administration, the blood-brain barrier (BBB) presents a significant challenge because most drugs are unable to pass through it and enter the brain (3). A widely researched strategy to bypass the BBB and administer medication straight to the brain is nasal drug delivery. Due to its non-invasiveness and ease of administration, intranasal delivery also has the benefit of avoiding significant first- pass metabolism, reducing gastrointestinal breakdown, and improving patient compliance. The unique connection made by the trigeminal and/or olfactory nerve systems exists between the brain and the olfactory epithelium, allowing medications to reach the brain without passing through the blood-brain barrier. In recent years, research has demonstrated the benefits of drug delivery systems based on nanoparticles. Intranasal delivery of nanoformulations is being studied intensively for brain targeting because of its high permeability across mucosal epithelium, improved absorption, and high efficacy of drug encapsulation. (4). Additionally, surface treatment of nanoparticles with mucoadhesive polymers improves medicine penetration by enhancing olfactory contact and reducing mucociliary clearance in the nasal cavity (5). Various kinds of nanoparticles, including polymeric, solid lipid, nanoemulsion, and micellar nanocarrier nanoparticles, are being studied for their ability to go from the nose to the brain in migraine treatment. Lipid-based medication delivery systems are becoming more and more popular as a treatment for different types of migraine attacks (6). NLCs, one of the more recent drug delivery methods, provide great drug loading capacity and enhanced stability. With an average size of 10–500 nm, the binary combination of liquid lipid (oil) and solid lipid (solid) that constitutes NLCs acts as a hybrid carrier. The mixture of NLCs is made up of two chains: a short chain of solid and lipid with a ratio of 70:30 and a long chain of liquid and lipid (oil) with a ratio of 99.9:0.1 (7). Nanostructured lipid carriers (NLCs) are a type of lipid nanoparticles that belong to the second generation and have the ability to enhance the drug's mucosal adhesion and retention duration in the nasal cavity (8). They also enhance permeability, entrapment efficiency, and solubilization capacity by avoiding efflux transporters (9).

Migraine Millions of people worldwide suffer from the chronic and recurrent illness known as migraine. Its crippling effects, which include pain, light sensitivity, and other upsetting symptoms, might interfere with day-to-day activities. It is imperative that individuals impacted by this illness seek the appropriate care and assistance (10). The American Migraine Prevalence and Prevention Study found that 43% of women

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and 18% of men reported having migraines (11). But it's thought that more than half of migraineurs go undetected (12). According to a 2007 survey, 71% of migraine sufferers treated their headaches using over-the-counter drugs, while only 8% used preventive medication. Of these, about 53% had never taken preventative medicine (13). A common, crippling neurological condition of the central nervous system, migraine is marked by excruciating headaches that can last anywhere from a few hours to several days (four to seventy-two hours), often with accompanying nausea and vomiting (14). Patients may also have further symptoms, such as, in addition to unilateral or bilateral headaches.

- Photophobia, or light sensitivity
- The sensitivity to sound known as phonophobia
- Visual anomalies
- One-sided paraesthesia
- motor signs and symptoms
- Disturbances in language

Epidemiology: Migraine is a major burden on people and society due to the intensity of the pain and its accompanying symptoms, as well as its high frequency (15). In addition to experiencing significant impairment following an attack (such as decreased work productivity and compromised relationships with family and friends), migraineurs also have a lower quality of life overall (16). Between the ages of 15 and 24, migraine incidence peaks, and between 35 and 45, migraine prevalence reaches its highest point (17). The majority of migraineurs experience one to four episodes of headaches per month and over half of them report being severely impaired or needing bed rest while experiencing an attack (18).

Pathophysiology Pathogenesis incorporates several elements of the peripheral and central nervous systems, however its exact nature is yet unknown. This section provides descriptions of some of the most widely accepted ideas. The earlier vascular theory of migraine states that vasoconstriction causes the aura and vasodilation causes the headache, but this idea is no longer supported (19). According to current theories, migraines are caused by a sequence of intracranial and extracranial alterations resulting from several primary neural abnormalities (20). When neuronal pannexin-1 mega channel opens and caspase-1 is activated, proinflammatory mediators are released, NF-kB (nuclear factor kappa-B) is activated, and this inflammatory signal spreads to trigeminal nerve fibers surrounding pia mater vessels (21). This sets off a chain reaction of meningeal, cortical, and brainstem processes that induce inflammation in the meninges that are sensitive to pain, hence causing headaches via central and peripheral pathways (22). Thus, this pathway can account for both the later, prolonged activation of trigeminal nociception (which causes headache) and the cerebral depression that forms the aura. It is believed that the aura is caused by the cortical spreading depression of Leão, which propagates a wave of neuronal and glial depolarization and starts a cascade. It also activates trigeminal afferents and changes the permeability of the hematoencephalic barrier by activating brain matrix metalloproteinases (23). Cortical depression in migraine without aura is thought to be able to happen in regions like the cerebellum where depolarization is not consciously felt (24). The ophthalmic division of the trigeminal nerve innervates the anterior structures primarily, which may account for the pain in the anterior portion of the head. The anterior to posterior distribution of pain can be explained by the convergence of fibers from the upper cervical roots, which come from trigeminal nerve neurons along with the trigeminal ganglion and the trigeminal nerve at the trigeminal nucleus caudalis. From there, the fibers ascend to the thalamus and the sensory cortex (25). Neurogenic inflammation is a consequence of nociceptor activation, in this case the trigeminal system, as evidenced by vasodilation, edema, and plasma protein extravasation. It is linked to the production of vasoactive neuropeptides released by stimulation of the trigeminal ganglion, including substance P, calcitonin gene-related peptide, and neurokinin (26). Patients with persistent migraines have higher levels of these neuropeptides in their spinal fluid (27). Sensitization, the process by which neurons tend to become more receptive to stimulus, can result from neurogenic inflammation. This may help to explain some of the pain's clinical signs and the shift from episodic to chronic migraines (28).

Phases of Migraine

The main symptom of a group of symptoms linked to migraine, a complex, episodic, and hereditary sensory processing disorder, is headache (29). The four overlapping phases of a migraine episode might last anywhere from four to seventy-two hours (30).

a. Premonitory phase: non-painful signs can show up days or hours before the headache starts. Symptoms include yawning, mood swings, difficulty concentration, stiff neck, fatigue, thirst, and more frequent urination (31).

Aura: About one-third of migraine patients experience a transient, localized neurological symptom known as aura, which is more common in women. It can happen either before or during a headache episode. Visual auras (90%) are the most common type, followed by sensory auras (30–54%) and language auras (31%). Six, because to the atypical nature of the motor, brainstem, and retinal auras, they occur substantially less frequently (32).

Headache: During this stage, the trigeminal sensory pathways responsible for the pounding pain linked to migraines are triggered. Everyday duties are hindered by the headache, which either suddenly occurs or grows greater over time. A headache typically gets worse when you move your head. Nausea and vomiting are usually present along with an allergy to light, sound, smell, and touch (allodynia, photophobia, phonophobia, and osmophobia).

Postdrome: The most typical symptoms during this time include tiredness, drowsiness, difficulty concentrating, and intolerance to noise. The more uncomfortable you are, the worse these symptoms will get and the longer they will last. This stage is sometimes referred to by patients as the "migraine hangover" unofficially (33).

Mechanism of the development of migraine one theory about the initiation of migraine attacks states that primary sensory nerve terminals innervating meningeal blood vessels release vasoactive peptides early in an attack (34). By stimulating perivascular trigeminal neurons, these peptides cause perivascular inflammation, plasma extravasation, and meningeal artery dilatation (35). The pain experienced may be caused by several effects. In the 1990s, selective serotonin 5-HT1B/1D receptor agonists, or triptans, were authorized for the treatment of acute migraines (36).

Pharmacological management and treatment. To reduce the incapacitating and agonizing impacts of migraine-related disability on the patient's quality of life, effective care of migraine headaches is required. While no pharmacological approaches are useful in the long-term effective management of migraine, pharmacotherapy is typically the cornerstone of the treatment strategy (37). The use of pharmaceuticals to treat migraines can be divided into two categories: acute treatment for individual episodes or prophylactic use to stop the headaches from coming again. Patients who suffer from severe migraine headaches regularly probably need both acute and preventive measures (38). When choosing appropriate treatment options, several factors must be taken into account. These factors include comorbid conditions, as well as tolerability and efficacy, or the patient's prior responses to selected agents. In the acute setting, the available pharmacological options can be classified into two categories: agents specifically designed to treat migraines and non-specific drugs that are also used in multiple other settings. The more established ergot alkaloids, the popular and extensively used triptans, several cutting-edge treatments, and on the other hand, non-specific treatment options consist of medications like corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), antiemetics, simple and opioid analgesics, antihistamines, antiepileptic medications, and muscle relaxants (39).

Acute treatment: First-line, second-line, third-line, and adjunct treatments are all categories of acute care that ought to be administered in a phased care manner (40). The selection of medications was based on several factors, including availability, cost, safety, tolerability, and efficacy at each stage.

First-line medication: Acute migraines are treated with over-the-counter analgesics all over the world. Among the medications with proven efficacy are non-steroidal anti-inflammatory medicines (NSAIDs), and the most convincing evidence Encourage the first-line use of ibuprofen, diclofenac potassium, and acetylsalicylic acid (41).

Second-line medication: Patients whose headaches are not adequately eased by over-the- counter drugs should be prescribed triptans. Although the efficacy of all triptans has been well-documented, access to and availability of each differ among nations. When used early in a headache attack, while it's still mild, triptans are most effective. Triptans: These medications include naratriptan, sumatriptan, almotriptan, rizatriptan, zolmitriptan, frovatriptan, and eletriptan. Combined, sumatriptan and naproxen are more effective than either drug alone in treating migraine symptoms (42). Nevertheless, there is no proof to support taking triptans during a migraine attack's aura phase (43). When all other triptans have failed, in patients who experience headaches that become unbearable quickly, or in individuals who are unable to take oral triptans because of vomiting, subcutaneous administration of sumatriptan can be beneficial (44). Relapses occur when a patient has a return of symptoms 48 hours after starting a treatment that seemed to be helping. Relapsed patients have two choices: they can continue taking triptan or combine it with lysine, diclofenac potassium, ibuprofen, or fast-acting naproxen sodium (45).

Third-line medication: If all available triptans prove ineffective after a suitable trial period (no or insufficient therapeutic response in at least three consecutive episodes), or if taking them is not recommended, there are currently limited options. Although they are currently very limited in availability, titans or pants could be used. The only approved triptan for treating acute migraines is Lasmiditan, and the only approved pants are Ubrogepant and Rimegepant. Based on an indirect comparison of data from randomized controlled trials, it appears that triptans and lasmiditan have similar levels of effectiveness (46). However, regular use is probably discouraged by the fact that it is linked to transient driving impairment. After taking lasmiditan, people should refrain from operating machinery for at least eight hours and may not be able to evaluate their driving ability.

Adjunct medication: Metoclopramide and domperidone are examples of prokinetic antiemetics that are useful oral adjuncts for patients experiencing nausea and/or vomiting during migraine attacks.

Prophylactic treatment: There exist multiple potential indicators and signs that warrant initiating migraine prophylaxis. An unbearably high recurrence rate, medication overuse, treatment failure, contraindications, and the potential for developing what are known as "medication overuse" (or rebound) headaches are a few of these (47).

Beta-adrenergic receptor blockers it is generally acknowledged that the most commonly used medications for migraine prophylaxis are beta-adrenergic receptor blockers. In this situation, the following beta-blockers are effective: Propranolol, timolol, metoprolol, nadolol, and atenolol (48).

Antidepressants: Migraine prevention can be achieved with a variety of antidepressant drug types, including tertiary amines, selective serotonin reuptake inhibitors (SSRIs), and tricyclic antidepressants. Serotonin and noradrenaline dual reuptake inhibitors (SNRIs). Despite growing evidence in favour of venlafaxine, only amitriptyline possibly the antidepressant with the most research across the broadest range of indications has been demonstrated to be effective. The latter medication has a far better safety profile than the much older tricyclic antidepressants (49).

Colloidal carriers: The common characteristic of all colloidal carriers is the submicron particle size (50-1000 nm). The composition of nanometric carriers varies, as do their stiffness, stability, releasing characteristics, and capacity to assimilate variously soluble elements. Certain nonmetric carrier systems are more adaptable than others, but there isn't a single nonmetric carrier system that works for all situations. What matters is that the features (size, solubility, charge, etc.) determine which carrier system to utilize (50). Colloidal carrier systems fall into one of three general categories: systems based on polymers, lipids, or surfactants, or a mixture of these. Solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), liposomes, noisomes, nanocapsules, nano sponges, and micro and nanoemulsions are typical examples of carrier systems. Micelles and nanoparticles, which can be made from polymer-surfactant mixes and polymer-lipid conjugates, respectively, are examples of coupled carrier systems. The usage of carcinogenic monomers and toxicologically hazardous reactive cross-linkers in the synthesis of polymeric nanoparticles is one of their drawbacks; it is challenging to fully eliminate these components (51). Additionally, the polymer accumulates due to slow breakdown and may produce hazardous metabolites, which limits the polymer's potential uses as a drug delivery mechanism. Lipid-based colloidal carriers, specifically liposomes, SLNs, and NLCs, have been developed as a solution to the toxicological problems that polymeric Nanoparticulate systems have been displaying. As a result, lipid systems have been the subject of much research over the past few decades. Despite being the standard for lipid-based colloidal carriers for site-specific drug delivery, liposomes have many disadvantages, including issues with storage stability, when a medicine is incorporated into a phospholipid bilayer, it can cause a number of problems, such as burst release of the drug, rapid breakdown by intestinal enzymes, gastrointestinal pH, and bile salts if taken orally, and constraints related to large-scale manufacture (52). For the safe and effective delivery of medications, therefore, alternative methods such as lipid nanoparticles—also referred to as SLNs and NLCs—based on lipid components other than phospholipids offer an option. These lipid nanoparticles are also anticipated to enable more control over the administration of therapies and medication release, as some drugs may not load into liposomes effectively (53).

The lipid-based NLC A type of emulsion known as oil-in-water was the primary source of nanoparticulate systems with a solid matrix. The solid lipid was added to the liquid phase of the emulsion to solidify it at body temperature. Most people agree that the SLN, which was created in the early 1990s from solid lipids, was the first generation of lipid nanoparticles (55). But the NLC, which is made up of one or more blends of liquid and solid lipids, is referred to as a second-generation lipid nanoparticle. Oddly enough, NLC remained firm within the body as well (56). This effect occurs because, without changing the physical state of the core material, the liquid and solid lipid blend tends to lower the melting point of the substance. Additionally, the increased drug loading efficiency in comparison to the SLN and other Nanocarrier systems is explained by the improper organization of solid lipids in the liquid lipids (57). The stability and encapsulation effectiveness of the nanoparticle are improved by the mixed lipid blend with various physicochemical characteristics. NLC has a higher encapsulation effectiveness than SLN because the majority of hydrophobic compounds are more soluble in liquid lipids than in solid lipids (58). Compared to conventional carriers, nanostructured lipid carriers have demonstrated a number of benefits for medication therapy, such as enhanced solubility, improved permeability and bioavailability, decreased side effects, extended half-life, and tissue-

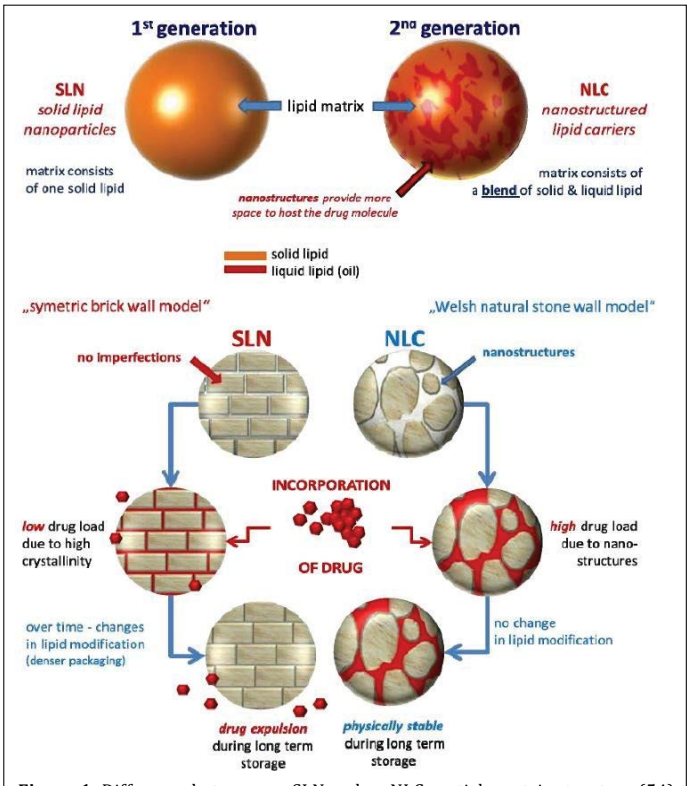

Figure 1: Difference between an SLN and an NLC particle matrix structure (54).

targeted delivery (59). Lipid nanoparticles are thought to be effective therapeutic carriers for nose-to-brain delivery (60).

Compositions of NLC: NLCs composed of an aqueous phase containing a surfactant or combination of surfactants and an unstructured solid lipid matrix composed of a blend of solid and liquid lipids. Solid-liquid lipids are often combined in a 70:30 ratios up to a 99.9:0.1 ratio, with a 1.5%–5% (w/v) surfactant concentration (61). Many combinations of lipids and/or surfactants have been reported in the literature; the majority of these are included in Table 1. The majority of the components listed below are either approved by various regulatory bodies (USA FDA IIG, Generally Recognized as Safe (GRAS), or are commercially available in marketed products.

NLC types: Depending on the lipid blend composition and the different production techniques employed, different types of NLCs are produced. Giving the lipid matrix a particular nanostructure is the basic notion behind improving the payload for active compounds and reducing compound ejection during storage. The three categories of NLCs can be summed up like this:

NLC type I is also called an imperfect crystal.

NLC type II is also called multiple types.

NLC type III is also called an amorphous type (63).

NLC Type I: It is also known as an unfinished kind. An imperfect crystal lattice or matrix is produced when liquid lipid or oil is partially substituted for solid lipid. This effect suggests that pharmaceuticals can fit more comfortably and allows for higher drug loading. Because it inhibits the formation of an exceptionally ordered or structured matrix, which would have driven the drug out of the core, a poorly formed crystal core allows for more drug incorporation.

NLC Type II: Another name for this type is the amorphous/ structureless type. When liquid lipids are combined with solid lipids that retain their polymorph after solidification and storage, an amorphous core is typically formed. Compared to type I NLCs, this is better since the drug stays entrenched in the amorphous matrix and no crystallization happens. Solid lipids with the β polymorph form a matrix with a crystalline structure.

NLC Type III: The idea of w/o/w emulsion gave rise to this multiple type. In essence, it is NLC of the fat-in-water or oil-in-solid variety, which can only be made using the phase separation technique. When a medication shows greater solubility in oil, this technique can be employed to increase drug loading capacity and stability in NLC formulation. A solid lipid matrix is uniformly dotted with small oil droplets, which are subsequently dispersed throughout an aqueous medium (64).

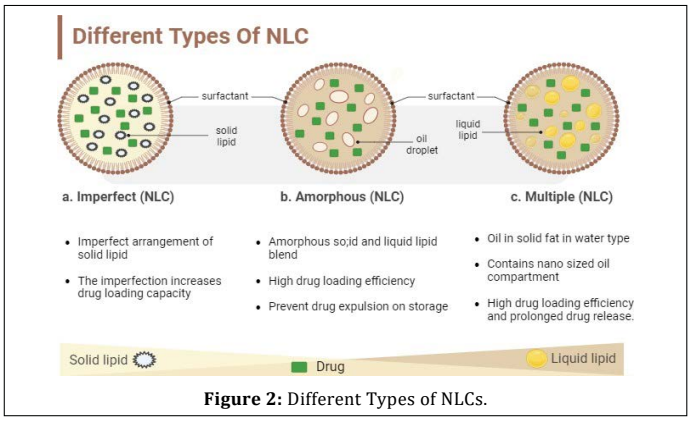

Figure 2: Different Types of NLCs.

Methods for preparation of NLCs the processes used to create lipid nanoparticles, such as SLN and NLC, are quite similar. The only distinction is whether liquid lipids are present in the formulation or not (65).

Commonly used techniques for NLC preparation

- High-pressure homogenization.
- Microemulsion technique.
- Solvent injection method
- Emulsification-solvent evaporation
- Phase inversion
- Emulsification-ultrasonication method
- Solvent diffusion method
- Membrane contractor technique (66).

a) **High-pressure homogenization:** A dependable and well-established technique for preparing lipid nanoparticles is high-pressure homogenization. With HPH's assistance, lipid NP preparation can be scaled up (67). Through this procedure, a stable emulsion including the division of particles into nanosized can be created. In the market, two types of homogenizers are offered a) jet-stream homogenizers and b) piston-gap homogenizers. The following techniques are usually utilized to prepare NLCs high-pressure homogenization (68). Hot homogenization and Cold homogenization (69). The heated homogenization process is done always at a temperature above the melting point of the lipids utilized in the formulation. The solid lipid is crushed into lipid microparticles using the cold homogenization process, which cools the lipid melt (68).

Hot homogenization: To create a drug-dispersed lipid melt, the liquid and solid lipids are combined, heated above the solid lipid's melting point, and medication is added. Separately, the aqueous phase is made by mixing enough surfactant with deionized water. The temperature of this phase is likewise raised to that of the lipid melt. To create pre-emulsion, these two phases are combined and given a brief high-shear homogenization process at a higher temperature. Pre-emulsion is immediately run through HPH for three to five cycles at different pressures. The number of cycles that are repeated typically depends on the target average droplet size of the nano-emulsion. After that, the emulsion is stirred and chilled to room temperature. Here, the solid lipid recrystallizes, causing the droplets to solidify (70). The usage of lipophilic emulsifier in lipid melt. This may be to improve the stability of pre-emulsion during homogenization. This method is suitable for drugs that are not heat-sensitive.

Cold homogenization: One drawback of the well-known hot homogenization procedure is that medications that are hydrophilic and thermolabile may break down due to the high processing temperature. This is avoided by using a straightforward method of quickly chilling the nano- emulsion (71). At a temperature greater than the solid lipid's melting point, both liquid and solid lipids melt. After that, the medication is dissolved or distributed in a heated lipid melt, and hot homogenization is applied. The resulting emulsion is quickly chilled by being exposed to dry ice or liquid nitrogen. To produce microparticles, the resultant solid mass is grounded. To create NLCs, these are distributed in a cold aqueous phase with an appropriate surfactant and then high shear homogenization or ultrasonication is applied (72).

b) Microemulsion: tiny-emulsion with this technique, melted lipids are combined with a hydrophilic aqueous phase that contains a

Ingredients	Material
Solid lipids	Cutina® CP, Imwitor® 900 P, Geleol®, cetyl palmitate, Tristearin, stearic acid, Softisan® 154, and Gelot® 64
Liquid lipids	Miglyol® 812, Transcutol® HP, Lauroglycol® FCC, Capryol® 90, Medium Chain Triglycerides, paraffin oil, 2-octyl dodecanol, Labrafil Lipofile® WL 1349, Labrafac® PG
Hydrophilic emulsifiers	Solutol® HS15, polyglycerol methyl glucose distearate, polyvinyl alcohol Tween 20, Tween 40, Tween 80, Pluronic® F68 (poloxamer 188), Pluronic® F127,
Lipophilic emulsifiers	Span 40, Span 60, Myverol® 18-04K, Span 20
Amphiphilic emulsifiers	Egg lecithin, soya lecithin, phosphatidylcholines, phosphatidylethanolamines, Gelucire® 50/13

Table 1: Excipients used for the preparation of NLCs (62).

co-surfactant and a surfactant, depending on the ratios utilized, to create an emulsion that can be either w/o or o/w. To break the particles down into the micron size range, the emulsion is then thoroughly mixed. Next, a transparent, thermodynamically stable microemulsion is created, and to further reduce particle size and produce NLCs, it is further dispersed in a cold hydrophilic phase. This process produces NLCs without the need for extra energy or equipment, and it is straightforward, affordable, repeatable, and appropriate for medications that are thermolabile. However, the primary drawback of this method is thought to be the substantial surfactant inclusion (73,74).

c) Solvent injection method: The solvent injection method is a straightforward and efficient production procedure that entails dissolving lipids in a water-miscible solvent and swiftly injecting the dissolved surfactants into an aqueous solution using an injection needle (75). The benefits of this approach are low preparatory requirements, avoidance of extreme heat, shear stress, and expensive machinery. However, this method's primary drawbacks are its low particle concentration and usage of organic solvents (76,77).

d) Emulsification-solvent evaporation: This approach involves dissolving medicines and lipids in an organic solvent that is water-immiscible (such as cyclohexane, dichloromethane, toluene, or chloroform), followed by emulsification in an aqueous phase that contains the surfactant before the solvent evaporates. Sonication is applied to the pre- emulsion that has been created. To obtain the aqueous NLC dispersions, the dispersions are then chilled to room temperature (78)**.**

e) Phase inversion: This approach involves gently mixing the drug, lipid, water, and surfactant, then heating the mixture to a temperature higher than the surfactant's phase inversion temperature. The surfactant is dried during the heating process (above the inversion temperature), which alters its hydrophilic-lipophilic balance and, as a result, its affinity for each phase, i.e., the inverted emulsion. Rapid chilling, such as with an ice bath, causes the surfactant to revert to its hydrophilic state, which permits the production of tiny NLC particles (79, 80). This method's low energy input and avoidance of organic solvents are its advantages. However, produced NLCs may have weak stabilities, and multiple temperature cycles may be necessary (81).

f) Emulsification-ultrasonication method*:* In this method Drug, liquid and solid lipids are combined and melted at 5–10 °C temperature above the melting point of solid lipids. The surfactant is heated to the same temperature as the lipid melt after being dissolved in distilled water. After adding the aqueous phase to the lipid phase, the pre-emulsion is homogenized at high shear by applying the necessary rpm for a predetermined amount of time. After a predetermined amount of time spent ultrasonically, this emulsion is added to a predetermined volume of distilled water. To obtain NLCs, this is cooled to room temperature and solidified (82). Contamination of formulation due to metal particles may occur during probe sonication.

g) Solvent diffusion method: The solvent diffusion method requires the use of water- miscible organic solvents such as methanol, ethanol acetone, etc. This technique involves adding the medication and lipids in either a single organic phase or a combination of both. This is kept at a high temperature while being sonicated to produce a distinct lipid phase. An appropriate stabilizer or surfactant is added to the aqueous phase, which is then kept at the same temperature as the lipid phase. At a high temperature, the organic-lipid phase is introduced to the aqueous phase while being mechanically stirred. This dispersion is agitated at room temperature for cooling and evaporation of organic solvent to yield NLCs (83).

h) Membrane contractor method: In this method, pressure is used to encourage the melted lipids to travel through a membrane. The size of the droplets that the lipids create is determined by the membrane's pore size. The generated lipid droplets are eliminated by the tangential flow of the surfactant-containing aqueous phase toward the membrane. After that, the emulsion is cooled to enable the lipids to solidify and create SLNs or NLCs (84).

Characterization of nanostructured lipid carriers

For NLCs, physicochemical characterization is crucial to verify stability and quality control. It is possible to ascertain an NLC's chemical and physical properties. The most frequent parameters for determining NLCs are.

- Particle size
- Polydispersity index
- Zeta potential
- Surface morphology
- X-ray Diffraction
- Drug Encapsulation Efficiency
- Drug- lipid (excipient) interaction
- Stability study
- In-vitro drug release study
- Toxicity study

Particle Size: Size of Particles for regular particle size measurement, photon correlation spectroscopy (PCS) and laser diffraction are the most efficient methods. Another name for PCS is dynamic light scattering. It gauges variations in the intensity of scattered light resulting from particle motion. This method encompasses a specific size range of few nm to 3 μm (85). Laser diffraction can be used to identify the larger size. The diffraction angle's dependency on the particle radius serves as the basis for this calculation. Particle size in NLCs is significantly influenced by the kinds and proportions of lipids and emulsifiers utilized. It is always possible to achieve more thorough emulsification and a more rigid structure by adding more emulsifiers, which reduces the size (86).

Polydispersity Index: The dynamic light scattering method (PCS) can be used to measure product distribution index (PDI), which represents the size distribution of nanocarriers in the product. Formulations that are homogeneous and monodisperse are indicated by lower PDI values (< 0.5). A number greater than 0.5 suggests that the formulation is non-homogeneous or polydisperse. Less PDI will be seen and size distribution fluctuations will be smaller for more uniform particle sizes. Practically speaking, since the colloidal carrier system isn't always monodispersed, a PDI value less than 1 (87).

Zeta Potential: Particle stability in the application is impacted by aggregation and dispersion processes, which are evaluated using surface charge measurement. Because of the electrostatic repulsion, charged particles are generally less prone to aggregate or fuse. Because it binds to the paracellular region of the blood-brain barrier (BBB), which is rich in anionic sites, the positively charged surface of NLCs is effective at passing across the BBB (88). For formulation design, zeta potential determination is useful in determining if the desired cationic surface is attained. In certain cases, stabilizing nanoparticulate systems during storage requires a negative charge on the particle surface.

Surface Morphology: For examining the surface morphology of nanoparticles (NP), transmission electron microscopy (TEM) and scanning electron microscopy (SEM) are often utilized instruments. Whereas TEM offers two-dimensional imagery and information about the interior composition of the particles, SEM offers three-dimensional images of the particles and concentrates on their surface. Electrons that have traveled through the material in the TEM produce the image (89). The resolutions that these methods offer, which vary from 1 to 10 nm for SEM and 0.1 to 0.5 nm for TEM, are likewise distinct (90). The spherical shape and smooth surface of the NLC were observed using SEM examination. The form of the particle was almost spherical and in the nanometer range, according to TEM image analysis (91).

X-**ray Diffraction:** Lipid status can be investigated using X-ray diffraction and DSC, two commonly used techniques. It is well known that lipid molecules with long hydrocarbon chains exhibit polymorphism (92). Wide-angle X-ray diffraction can be used to clarify the crystalline order of NLCs. The X-ray discovered nanoparticles' polymorphism status can be used to validate DSC findings (93). The length of the lipid lattice's long and short spacings can be measured using X-ray scattering.

Drug Encapsulation Efficiency: For NLCs, determining the drug-loading efficiency is crucial since it influences the release properties (94). The medication molecules that are lipophilic have the ability to

either evenly disperse throughout the lipid matrix or enhance the particle shell or core. For hydrophilic medicines, the aqueous and interfacial phases are the preferred sites of loading. Achieving a high loading capacity requires the medicine to be sufficiently soluble in the lipids. Since the solubility drops as the melt cools and may even be lower in the solid lipids, it should be higher than necessary (95). The internal and external phases of the medications are separated to determine the percentage of pharmaceuticals that are encapsulated in NLCs. various methods, including ultrafiltration, ultracentrifugation, Sephadex gel filtration, and dialysis, are frequently employed to separate the dispersions (96). The addition of liquid oil to solid lipids in NLCs causes a significant disruption in crystal order as compared to SLNs. The resultant matrix shows significant lattice imperfections and provides additional room for the medications. This enhances the medicines' loading capacity and trapping efficiency.

Drug-lipid (excipient) interaction: The identification of drug-excipient/lipid interactions is a common application of FTIR. The drug's functional group peaks can be moved or diminished, or there can be peaks in the physical mixture that weren't there to begin with, to demonstrate interaction. Peaks of lipid functional groups are typically seen in NLCs after the medication becomes incorporated into the matrix.

Advantages of NLCs: NLC offers a number of benefits over SLN, the original generation of lipid nanoparticles. The highly pure solid lipid forms an optimally ordered crystal structure that limits the loading capacity of SLN and could potentially cause active material to be expelled during storage. The ideal crystalline structure, on the other hand, may be deformed or amorphous clusters may occur when lipids of different structures are combined. Because of these defects, there are some gaps where active ingredients can fit, which raises the drug loading capacity (97). In addition, by preventing the escape of encapsulated particles, this NLC defect matrix enhances the stability of the nano-carrier system. Below are some more benefits of NLC in addition to these.

- Better physical stability
- Simple preparation and scaling up
- Enhanced dispersibility in a water-based media
- High entrapment of hydrophilic and lipophilic substances
- Efficient particle size management
- A sophisticated and effective transport system, specifically for materials that are lipophilic
- A rise in skin occlusion
- Pharmacological extended-release
- Due to the fact that their lipid components are permitted or utilized as excipients in commercially available topical cosmetic or pharmaceutical preparations, they are one of the preferred transporters for medications applied topically.
- Drug penetration into the mucosa or skin is enhanced by the small size of the lipid particles, which provides close contact with the stratum corneum.
- Increased hydration and flexibility of the skin (98).
- Because of their solid lipid matrices, which are also widely acknowledged as safe or have a regulatory-accepted status, these carriers are extremely effective systems (99).
- Its stability and medication loading capacity is higher (100).
- It is still safe, well-tolerated, and authorized for use in human applications (101).
- It can be produced on an industrial or commercial scale without the need for an organic solvent, which lowers the toxicity and negative effects associated with it (102).
- It has remarkable stability after extended storage, making it appropriate for lyophilization and steam sterilization (103).

Limitations of NLC NLCs have a lot of potential for targeted delivery, yet they have certain drawbacks, such as

- The cytotoxic effects are associated with the concentration and matrix type.
- Certain surfactants have an irritating and sensitizing effect.
- Improved use and efficacy of gene delivery methods and protein and peptide therapies remain imperative. Insufficient preclinical and clinical investigation of these nanoparticles in relation to bone restoration (104).

Role of NLC in different delivery systems

NLCs are employed as biocompatible delivery systems for a variety of medications with medicinal, cosmetic, and biochemical uses. Over the past ten years, a variety of medications or active ingredients, including lipophilic and hydrophilic molecules as well as labile substances like proteins and peptides, have been ensnared in NLC. The fact that they are made with lipids that are physiologically tolerated is their primary characteristic. Because so many different surfactants and co-surfactants may be used to produce these particles, these carriers are excellent choices for a variety of applications, including topical, oral, parenteral, inhalational, and ophthalmic administration (105).

The Blood-Brain Barrier: The blood-brain barrier (BBB) isolates the brain from the body's normal circulation and keeps infections, poisons, and other harmful things out of it. The tightly packed endothelial cells, or BCECs, form a monolayer that makes up this structure of selective permeability (106). About 98% of compounds with small molecular weights and almost all large molecules (> 400 Da) cannot pass through BCEC cells because each one is securely sealed by a tight junction (107). Only tiny, highly lipophilic molecules may pass through this arrangement, which hinders the transport of many nutrients, ions, and neurotherapeutic medicines (108). The BBB is adorned with special transporter molecules and receptors, such as GLUT 1 for glucose and the insulin receptor for insulin, to preserve homeostasis and supply the brain with the necessary nutrients and ions (109). Furthermore, some efflux transporters are also expressed across the blood-brain barrier. One example of these is the P-glycoprotein transporter, which facilitates the release of pharmaceuticals back into the systemic circulation and prevents the absorption of dangerous compounds (110). The basement membrane that connects two distinct types of neurovascular unit cells and preserves the brain's rigidity is another component of the blood-brain barrier structure (111). Furthermore, the barrier function is strengthened by the close association between the astrocytes and pericytes and BCECs (112).

Nose-to-brain drug transport mechanism: The nasal route has drawn a lot of attention as a practical and dependable method for various therapeutics that target the brain. The respiratory and olfactory areas of the nasal cavity are where drugs are directly transported from the nose to the brain. Molecules are mostly absorbed in the respiratory and olfactory epithelia (113). Because olfactory neurons are accessible within the olfactory area, pharmacological substances can be transported directly into the brain by means of these neurons (114). The majority of olfactory mucosal cells are composed of bipolar neurons, basal cells, supporting (sustentacular) cells, and Bowman's glands. The olfactory epithelium contains Bowman's glands, which are responsible for producing the mucous layer (115). Rapid administration of an intranasal medication travels extracellularly via the olfactory nerve pathways, starting in the upper nasal cavity and ending directly in the brain (115). This channel, out of all the nose-to-CNS passages, delivers the most medication to the olfactory bulbs (116). The trigeminal nerve is a different sensory nerve that is surrounded by the olfactory epithelium. The trigeminal nerve (cranial nerve V) is connected to the pons and the cribriform plate by the axons of bipolar neurons. This enables for perivascular transport to the caudal brain areas and the spinal cord. It is believed that extracellular convective bulk flow or perivascular channels are the primary means of transport to other brain regions following entry into the brain (e.g., to the midbrain from the olfactory bulb or the brain stem from the trigeminal nerve) (113). Either transcellular (drugs travel inside the epithelial cell) or paracellular (drugs travel between the epithelial cells) mechanisms carry drugs across the nasal epithelium. Olfactory

sensory neurons (OSN) endocytic uptake to the olfactory bulb is the mechanism by which transcellular transport takes place. Many distinct molecular mechanisms, such as micropinocytosis, clathrinid-mediated, clathrinid-independent, caveolin-mediated, caveolin-independent, and phagocytosis, are involved in the transport of endocytosis (117). Transport through the sustentacular cells to the lamina propria can be extracellular or paracellular. Merely tiny drug molecules can traverse the hydrophilic channels and tight junctional complexes that link the epithelial cells in the paracellular pathway. The tiny size of the nano-formulations makes them attractive formulations for intranasal drug delivery to the brain (118). As a result, they may be utilized as a potential substitute for oral delivery, avoiding issues including poor bioavailability, enzymatic degradation, low solubility in water, and a delayed start of action (119).

Conclusion

The creation of a delivery system with enough adaptability to be used for several administration routes is of importance to the pharmaceutical sector. For the intranasal, intravenous, topical, ophthalmic, oral, cosmetic, chemotherapy, nutraceutical, and food industries, NLCs appear to be appropriate delivery systems. Gene delivery and gene therapy are further potential routes for drug delivery from NLCs. Lipid-based nanoparticles, or NLCs, have an unstructured solid lipid core that allows highly lipophilic medicines to be encapsulated, preventing the medications from degrading and increasing their stability. When compared to current nanoparticulated drug delivery methods, they provide numerous advantages. They are found in commercially accessible products and are composed of lipids and surfactants that have received FDA and/or EMA approval. A major difficulty for the neurologist is always going to be getting drugs into the brain. This is because the brain-brain barrier (BBB) is present, protecting the brain from outside stimuli and preventing drug molecules from entering the brain. Researchers have experimented with various techniques, including intranasal administration to the brain, nanotechnological methods, and innovative drug carrier systems, in their ongoing quest to discover an appropriate means of accessing the brain. Over the past 20 years, nanoparticles have drawn a lot of attention in the biomedical field due to their reduced size and flexible nature. A few nanotechnological systems were approved by the FDA and put on the market as successful treatments for different illnesses. Still untreated are several chronic illnesses, including brain diseases, cancer, myocardial infarction, and many others. The unanticipated reaction of novel medicines in human trials is the main cause of medical science's failure. The majority of nanoparticles are difficult to create on a large scale, disintegrate under physiological settings, and cause toxicity in the biological system when applied for extended periods.

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