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"NANOSTRUCTURED LIPID CARRIERS FOR THE TREATMENT OF MUCOR MYCOSIS: A COMPREHENSIVE REVIEW"

Mr. Shubham Vijay Chavan[1], Dr. Mohamed Zerein Fathima[2]

[1]*(Research Scholar), School of Pharmaceutical Sciences, VISTAS (Vels Institute of Science, VISTAS advanced studies), Pallavaram, Chennai.*

shubchavan808@gmail .com

[2]*(M. Pharm, Ph.D. Assistant Professor), School of Pharmaceutical Sciences, VISTAS (Vels Institute of Science, VISTAS advanced studies), Pallavaram, Chennai.*

zereinfathima@gmail.com

Corresponding author

Dr. Mohamed Zerein Fathima,

M. Pharm, Ph.D, Assistant Professor, School of Pharmaceutical Sciences, VISTAS (Vels Institute of Science, VISTAS advanced studies), Pallavaram, Chennai.

zereinfathima@gmail.com

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Abstract

Nanostructured lipid carriers (NLCs) have provoked the incessant impulsion for the development of safe and valuable drug delivery systems owing to their exceptional physicochemical and then biocompatible characteristics. Lipid nanocarriers are developed as an alternative to

polymeric nanoparticles, liposomes and emulsions. Further, Nanostructured Lipid Nanocarriers are the second generation lipid carriers developed to overcome problems associated with Solid Lipid Nanoparticles and are utilized in various therapeutic approaches. In situ gelling systems becomes one of the most popular and prominent. It had a tremendous potential advantage of delivery systems due to many benefits like easy-to-use simple manufacturing; improve both adherence and patient comfort by minimizing the frequency of drug administration by its unique characteristics feature of sol to gel transition Mucormycosis is an infection caused by a group of filamentous molds within the order Mucorales. Infections may result from ingestion of contaminated food, inhalation of spores into the nares or lungs, or inoculation into disrupted skin or wounds. In developed countries, mucormycosis occurs primarily in severely immunocompromised hosts. This article describes the NLC with respect to structures, methods of preparation, advantages and its application of NLCs over first generation lipid nanoparticles and Mucormycosis with respect to their type of Mucormycosis, scenario, overview, the current treatment of Mucormycosis.

Key-word: Nanostructured lipid carriers (NLCs), Mucormycosis, In situ gel.

INTRODUCTION -

An effective drug delivery system is essential to ensure that pharmaceuticals are delivered safely and efficiently. Various carrier systems are being investigated, but the quest is ongoing for a biocompatible, biodegradable, and stable carrier system capable of targeting specific organs. Such qualities are due to the materials used to manufacture the carrier system *(Nikam Supriya S. et al., 2021).* Lipids provided biocompatibility and biodegradability, which are difficult to obtain using other materials. When these lipid-based systems are used as nanosized carriers, they exhibit features that are difficult to replicate in their bulk counterparts *(Sable et al.,2020).* Nanostructured lipid carriers (NLCs) have emerged as a potential medication delivery mechanism. NLCs as the name suggest are nanosized multi-particulate system in the size range of 50 nm to 500 nm. The particle size distribution of NLC depends on nanoparticles' manufacturing process and composition (*Shadab khan et al., 2022*)

In the 1990s, solid lipid nanoparticles (SLNs) were proposed as an alternative to traditional lipid carriers such emulsions, liposomes, and polymeric nanoparticles due to their low toxicity, large-scale production capability, and availability of excipients. Nanocarriers made from biocompatible polymers, lipids, and oils have emerged as a means of delivering both hydrophilic and hydrophobic pharmaceuticals while also improving their pharmacokinetics and pharmacological characteristics. Lipid nanocarriers made of natural or synthetic lipids offer the advantage of regulating drug release while being biocompatible and biodegradable. (*E. Gomaa et al., 2021*)

NLC has various advantages, including biocompatibility, biodegradability, nonimmunogenicity, high drug loading capacity, improved stability, controlled drug release, and a simple manufacturing technique with scale-up capabilities. These carriers are great for drug delivery due to their numerous advantages. The potential for cytotoxicity and irritation from surfactants are important concerns. (*Mirgane et al., 2022*)

Structure of NLC's

a) NLC Type I: It is also known as imperfect type. An uneven crystal lattice or matrix forms when a portion of the solid lipid is replaced by liquid lipid or oil. This occurrence demonstrates the availability of additional space for drug accommodation and permits increased drug loading. Drug incorporation is allowed greater room when an irregular crystal core forms rather than a highly structured or ordered matrix, which would have forced the drug out of the core. *(Chaudhari et al., 2021)*

b) NLC Type II: This type is also referred to as amorphous or structureless. When combined with liquid lipids, solid lipids that maintain their α polymorph after solidification and storage often create an amorphous core *(Sharma A, Baldi A et.al., 2018).* Since the medication stays entrenched in the amorphous matrix and no crystallization takes place, this is preferable to type I NLCs. The β polymorph of solid lipids forms a matrix with a crystalline structure *(Ana Beloqui et.al., 2016)*

c) NLC Type III: The concept of w/o/w emulsion served as the basis for this multiple type. This type of NLC is essentially oil-in-solid or fat-in-water, and it can only be produced using the phase separation approach. This method can be applied to the formulation of NLCs to increase drug loading capacity and stability when the medication exhibits greater solubility in

oil. Small oil droplets are evenly distributed throughout a solid lipid matrix, which is then distributed throughout an aqueous media. *(Shidhaye et al., 2008)*

ADVANTAGES OF NLCs *(Patil A et.al., 2010 and Dilip et.al., 2013)*

- Higher entrapment efficiency.
- Smaller size and low polymorphic changes.
- Possibility of controlled drug release and drug targeting.
- Increased drug stability.
- High drug payload.
- Feasibility in incorporation of lipophilic and hydrophilic drugs.
- No Biotoxicity of the carrier.
- No problems with large scale production and sterilization.
- Formulation are often avoided the utilization of organic solvent. One of the carriers of selection for locally applied medicine as a result of their super molecule elements have associate degree approved standing or are excipients utilized in commercially on the market topical cosmetic or pharmaceutical preparations.
- Small size of the super molecule particles ensures shut contact to the stratum membrane therefore enhancing drug penetration into the mucous membrane or skin.

LIMITATIONS *(Chaudhari et al., 2021)*

- Despite the great potential of NLCs in targeted delivery, they face certain limitations like: Cytotoxic effects related to the nature of matrix and concentration.

- Irrigative and sensitizing action of some surfactants
- Application and efficiency in case of protein and peptide drugs and gene delivery systems still need to be better exploited,
- Lack of sufficient preclinical and clinical studies with these nanoparticles in case of bone repair**.**

Methods for preparation of NLCs

1. High pressure homogenization:

1.1 Hot HPH: For medications that are thermostable, this technique uses hot, high-pressure homogenization; for pharmaceuticals that are thermosensitive, it uses cold, HPH. Heat homogenization is carried out at temperatures higher than the lipids' melting points *(M. Uner et, al., 2006)* Separate preparation is done for the aqueous phase, which consists of doubledistilled water and hydrophilic emulsifiers, and the lipid phase, which consists of both liquid and solid lipids and lipophilic emulsifiers. Before being combined, the two phases are heated to a high temperature independently. To get a tiny and homogenous size distribution, the mixture can be homogenized using a high-shear homogenizer and then subjected to additional sonication. *(E. Gomaa et al., 2021).*

1.2 Cold HPH: In order to enable the quick recrystallization of the solid lipid particles, cold HPH entails combining the medication with the lipid phase at a temperature that is marginally over the lipid melting point *(Van-An Duong et.al., 2020).* The combination is then rapidly cooled using dry ice or liquid nitrogen. Subsequently, the particles undergo a milling process and are homogenized using a high-pressure homogenizer in a cold aqueous phase, enabling the creation of smaller nanostructures. Large-scale production, the avoidance of organic solvents, and enhanced product stability are just a few benefits of this approach, albeit it may be difficult

to meet the high pressure and temperature requirements. Furthermore, insufficient homogeneity could lead to the emergence of microparticles instead of a consistent size distribution. *(Ana Beloqui et. al., 2017)*

2. Microemulsion

The medication is dissolved in the mixture of melted lipid and hot oil. The surfactant is dissolved in distilled water to create the aqueous phase. A high temperature is maintained and both phases are heated. To create a microemulsion, lipid phase is introduced to the aqueous phase while being mechanically stirred at the same temperature. Stirring, the warm microemulsion is introduced to the cold water (between 2 and 3^0C). Here, the precipitation of microemulsion globules to produce NLCs requires dilution with a considerable volume of cold water. The concentration of actives is reduced by dilution with a significant volume of water. Therefore, additional formulation concentration or lyophilization is needed *(Sharma A, Baldi A 2018)*

3. Solvent diffusion method

Water miscible organic solvents, such as methanol, ethanol, and acetone, are used in the solvent diffusion method. 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. A 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. To obtain NLCs, this dispersion is agitated at room temperature to cool and let the organic solvent to evaporate *(V.R. Salvi and P. Pawar, 2019).*

4. Emulsification-Ultrasonication Method:

This approach and HPH are somewhat comparable. Lipids (drug, liquid, and solid) are combined and melted at a temperature (5–10 °C) over the solid lipid's melting point. 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. In order to obtain NLCs, this is cooled to room temperature and solidified. Probe sonication may introduce metal particle contamination into the formulation *(Cláudia Viegas et. al., 2023).*

5. Solvent emulsification evaporation method

This method involves dissolving the active ingredient and lipids in a solvent that is immiscible with water *(Van-An Duong et.al.,2020).* Aqueous surfactant solution is then used to emulsify the resulting solution. After that, the solvent evaporates while being continuously stirred, forming NLCs. This method works well with heat-sensitive actives because it doesn't involve any heat. The primary drawbacks of this method include diluted NLC particles as a result of the lipids' insufficient solubility in the solvents utilized, and toxicity linked with solvent residue *(M. Elmowafy and M.M. Al-Sanea., 2021).*

6. Hot melt extrusion technology:

In the hot melt extrusion process, raw material is pumped into a barrel and then sonicated to produce NLC. This method involved utilizing a volumetric feeder to inject the medication and

solid lipid combination into an extruder barrel. A peristaltic pump was used to add liquid lipid and aqueous solutions at extrusion temperature. Pre-emulsion was formed by extruding this mixture at component melt temperature. To lower NLC particle size, the resulting hot preemulsion is subjected to further sonication (*Shadab khan et al., 2023*).

Sr. no	Lipid based nanocarriers	Drug	Outcome of the study	Reference
1	**Nanostructured Lipid Carriers (NLCs)**	Voriconazole	Improved permeation (66.45 %), sustained release (11 hours), anti-fungal studies showed 1.5 times higher zone of inhibition as compared to free drug.	*(Waghule Tejashree et. al.,2020)*
		Luliconazole	An ex vivo rat skin diffusion investigation revealed that luliconazole NLC had higher skin deposition (62%) than marketed luliconazole cream (48%). In vitro antifungal efficacy against T. rubrum	*(Baghel et. al.,2020)*

			showed that luliconazole NLC had a larger zone of inhibition (93 mm) than commercial luliconazole cream (83 mm).	
		Miconazole	Ex vivo goat cadaver skin permeation revealed that miconazole NLC gel had higher dermal retention (50-60%) than miconazole solution. When compared to commercial gel, in vitro antifungal activity against T. mentagrophytes demonstrated a 1.7-fold greater zone of inhibition (2 percent miconazole).	*(Singh et. al., 2015)*
		Itraconazole	Ex vivo skin permeation testing found that itraconazole NLC gel has a 2.46-fold greater permeability flux than itraconazole gel. When	*(Ameeduzzafar et. al.,2020)*

			compared to conventional itraconazole loaded gel, itraconazole NLC gel displayed 2.6 and 2.36-fold higher zone of inhibition against Candida albicans and Candida fumigatus, respectively.	
2	**Solid Lipid Carriers (SLNs)**	Miconazole and Econazole	For the manufacturing of SLNs, a microwave-assisted microemulsion technique was adopted. Miconazole-SLN and Econazole-SLN demonstrated promising antifungal efficacy against Candida albicans, with MIC50 values ranging from 2.50-5.00 g/ml.	*(Young-Guk Na et.al., 2019)*

		Clotrimazole and	The surface of the SLN was coated with a cationic lipid, dimethyl dioctadecyl	*(Carbone, C., et.al., 2019)*
		alphalipoic acid (ALA)	ammonium bromide. In vitro antifungal activities demonstrated that coated clotrimazole SLN had a 2-fold lower MIC50 than uncoated clotrimazole SLN.	
		Luliconazole	In vitro antifungal activity demonstrated a 4-fold reduction in MIC50 values for luliconazole SLN dispersion against Candida albicans and a 2-fold reduction in MIC50 values for Candida niger compared to luliconazole suspension.	*(Sharma, M., et.al.,2020)*

		Vorico nazole	In vitro antifungal activity of voriconazole loaded SLN against voriconazole susceptible and resistant strains of A. fumigatus exhibited a remarkable 16fold reduction in MIC50 when compared to voriconazole. The ability of SLN to overcome drug resistance was demonstrated.	*(Waghule, T., et.al., 2019)*
3	**Microemulsion**	Clotri mazole and ketoco nazole	When compared to commercial formulations, Canesten® and Kenazole®, the zone of inhibition against Candida albicans was shown to be 2.5-3 folds higher for microemulsion formulations.	*(Alam et.al., 2017)*

		Sertaconazole	When compared to the marketed formulation (Onabet® cream), the improved microemulsion formulation demonstrated 3fold greater skin retention on the abdomen skin of mice. The zone of inhibition against Candida albicans was greater for microemulsion hydrogel (23.54 0.72 mm) than for Onabet® cream (16.53 0.63 mm).	*(S. Sahoo et. al., 2014)*

		Clotrimazole and Itraconazole	In vitro antifungal activity against Sporothrix brasiliensis revealed a larger zone of inhibition for microemulsion comprising clotrimazole and itraconazole (43.67 mm) than for their individual equivalents, itraconazole microemulsion (33 mm) and clotrimazole microemulsion (33 mm) (41.67 mm).	*(Ferreira, P., et.al., 2019)*
4	**Transfersomes**	Sertaconazole	An ex vivo human cadaver skin diffusion investigation revealed that sertaconazole transfersomes gel had the highest skin deposition (83 percent) when compared to commercialized cream (69%). When compared to commercialized cream,	*(Mandlik, K. S., at.al., 2017)*

			sertaconazole transfersomal gel and sertaconazole gel demonstrated 1.386-fold and 2.14-fold increases in the zone of inhibition against Candida albicans, respectively.	
5	**Nanoemulsion**	Amphotericin B	Excipients with innate antifungal activity against A. fumigatus and Candida albicans were added to an amphotericin B-loaded nanoemulsion. Peceol and Labrasol inhibited the most A. fumigatus and Candida albicans strains. The amphotericin B-loaded nanoemulsion was chosen because of its small particle size (74.8 nm) and high zone of inhibition against A. fumigatus (21.8 mm) and Candida albicans (19.7 mm). Ex vivo skin permeation of	*(Hussain, A., et.al., 2016)*

			optimized nanoemulsion exhibited 3.99-fold greater permeability compared to commercial formulation of amphotericin B (Fungisome® cream) and 7.3-fold improvement compared to plain drug solution. When compared to normal drug solution, the MIC50 for amphotericin B nanoemulsion was 11-fold higher against A. fumigatus and 6.5-fold higher against Candida albicans.	

		Sulconazole	The core composite design was used to optimize the nanoemulsion. Ex vivo skin permeation on rats revealed that the optimized nanoemulsion had 1.7-fold higher permeability than the commercial product (miconazole cream) and 3fold higher permeability than the sulconazole-DMSO solution. When compared to the marketed cream and sulconazole-DMSO solution, the nanoemulsion demonstrated a greater zone of inhibition against C. albicans (23.5 2.4 mm) and T. rubrum (20.4 2.5 mm).	*(Yang et. al.,2019)*

Table No:01 Lipid based nanocarriers for superficial fungal infections associated with the skin.

Application of Nanostructured Lipid Carriers

1. **Oral application:** As oral route of administration is the most favored route owing to its painlessness, accurate dosing, ease of administration and patient compliance, I will begin with application of NLCs in oral route. *(M. A. Iqbal et al., 2012)*

1.1 Enhancement of oral bioavailability:

According to the US Food and Drug Administration (FDA), bioavailability is the rate (how quickly the active ingredient enters the general circulation) and extent (how much of the claimed strength enters the general circulation) with which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. Poor bioavailability is still a concern with orally delivered medicines. However, it is mainly attributed to either physiologically associated issues such as extensive first pass effect, enterocytes' efflux transportation, instability of the dug moiety in gastric fluids, fast gastric emptying and restriction by the intestinal barrier, or physiochemically/formulator associated issues such as poor solubility, improper drug partition coefficient, and high molecular size of the drug. Interestingly, the clever structure of NLCs may overcome the majority of the conditions that contribute to low bioavailability. *(Elmowafy & Al-Sanea, 2021)*

1.2 Treatment of GIT local diseases:

Local gastrointestinal illnesses, such as Crohn's disease and ulcerative colitis, are distinguished by heavily secreted mucus, crypt abnormalities, ulcers, and immune cell infiltration. Inflammatory bowel illnesses are also suggested as targets of orally delivered NLCs because to their improved adherence to and retention in gut wall epithelium.

(Beloqui et al., 2016). Furthermore, especially in relation to such sickness, the physiological features of the intestinal barrier are altered, particularly for intestinal lipids that are lacking in such circumstances *(Beloqui et al., 2014a)*.

1.3 Mitigation of drug associated toxic effects:

In the case of extensively metabolised medicines in the liver, overproduction of highly reactive metabolites is regarded as the primary toxicity predisposing factor. So, bypassing the liver and absorption via the lymphatic system might reduce the synthesis of such metabolites, hence mitigating their harmful effects. Elmowafy and colleagues synthesised carbamazepine in bees wax with NLCs to improve drug solubility, reduce plasmatic fluctuations, and reduce carbamazepine-induced toxicity. In terms of biochemical, histological, and immunohistochemical alterations, NLCs demonstrated the safest formulation when compared to carbamazepine suspension and the market product (Tegretol). *(Elmowafy et al., 2018a)*

2. Cutaneous application:

Shifting the administration to be through the skin is essential if the local cutaneous effect (dermal) is desired as the skin is then the target site of action (in case of local diseases such as acne, dermatitis, and dermal fungal infection) or the systemic effect (transdermal) is desired as the active is subjected to acid degradation or first pass effect followed oral administration *(A. Garcês et. al,.2018).* For both impacts, the outermost layer, stratum corneum (SC), is considered the primary barrier to absorption. SC is a horny layer created by corneocytes owing to keratinocyte death, comprised of ceramides (45-50 percent), cholesterol (25 percent), long chain free fatty acids (22 and 24 carbon atom chain length;

15 percent), and other lipids (5 percent). These lipids form multilamellar bilayers. SC's primary function is to defend against water loss as well as the invasion of harmful compounds and bacteria. The cutaneous medication diffusion may take place via trans epidermal route (across intact epidermis and constitutes the major route) and/or trans appendageal route (through skin appendages such as hair follicles) *(Trommer and Neubert 2006).*

3. Ocular application:

Because of its unique anatomical structure, the eye presents a challenge to drug delivery methods and is a highly protected organ. Ocular bioavailability is hampered by a number of factors, including strong blood-ocular barriers, muco-aqueous barriers, lymphatic tear turnover, the ciliary epithelium's non-pigmented layer, nasolacrimal drainage (which drains more than 75% of solutions), and reflex blinking *(Diebold and Calonge 2010)*. In addition to increasing ocular medication absorption, the objectives of ocular DDS are reducing systemic absorption and, consequently, generalised adverse effects. Numerous drug delivery techniques, including liposomes, nanoparticles, microemulsions, and micelles, were developed to overcome the shortcomings of traditional ocular administration systems. Lipid nanoparticles have been found to enhance the corneal penetration of active ingredients, resulting in effective ocular administration. *(SanchezLopez et al., 2017).* Generally, NLCs can overcome ocular barriers via different mechanisms: *(Ana Beloqui et.al., 2015)*

- Prolongation of drug release and hence residence time of the encapsulated drug.
- Improvement of ocular bioavailability of the encapsulated drug via both transcellular and paracellular mechanisms.

- Conquering blood ocular barriers.
- Fortification of the encapsulated drugs against inactivation by lacrimal enzymes.
- Raising the patient compliance by decreasing the dosing frequency.

4. Brain application:

The blood brain barrier, a diffusion-restricting barrier, keeps dangers from entering the brain (BBB). The BBB can completely stop the transport of most macromolecules and tiny (98 percent). Tight junctions and efflux transporters—most notably Pgps and MRPs—play protective roles that limit the chemicals' ability to diffuse into the brain through paracellular and transcellular routes, respectively *(Baratchi et al., 2009).* That means that receptor-mediated endocytosis is the only method of getting therapeutic concentrations into the brain. Wu and coworkers developed transferrin receptor monoclonal antibody OX26 surface decorated NLCs aiming to deliver salvianolic acid B and baicalin to the brain. Surface decorated NLCs enhanced brain delivery of both drugs when compared to NLCs and solution *(Wu et al. 2019).* Khan and coworkers investigated brain delivery by evaluation of anticonvulsant and anxiolytic effects of carbamazepine loaded NLCs *(Khan et al.,2020)*. Zhao and coworkers designed lactoferrin decorated NLCs to deliver nimodipine (neuroprotective agent) to brain tissue efficiently *(Zhao et.al., 2018).*

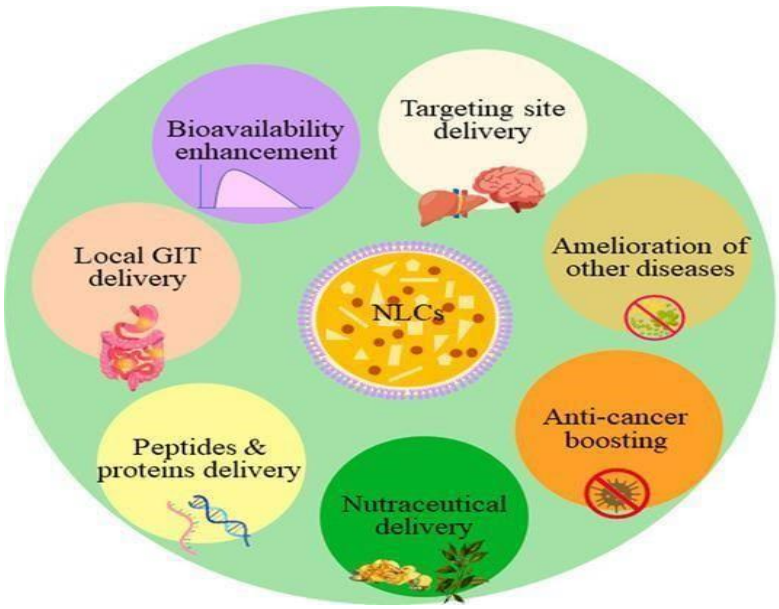

Fig: Application of NLCs

IN SITU GEL

In situ gels are liquids or suspensions that gel upon reaching a specific spot owing to interaction with bodily fluids or physicochemical changes such as pH, temperature, ionic concentration, UV radiation, the presence of certain molecules or ions, external triggers, etc. In situ gel creates a consistent plasma drug profile in the body by delaying the release of a drug, allowing it to be attached and absorbed in gel form, and is known to lengthen the drug's life in the mucosa. As previously stated, drug delivery systems with sol to gel transition capabilities may be widely exploited to construct sustained delivery vehicles for bioactive compounds. *(Padmasri et al., 2020)*

Oral, buccal, subcutaneous, transdermal, intraperitoneal, ophthalmic, nasal, rectal, vaginal, and parenteral routes are possible uses for in situ gels. less complex, which reduces investment and manufacturing costs from a manufacturing perspective. Gel formulations are utilized in

the discovery phase to increase the local and systemic exposure of possible lead compounds, which is perfect for rapidly and economically developing animal models for a range of situations. Despite the enormous diversity of gels, pharmaceutical research over the past few decades has concentrated on one type of gels in particular smart polymer gels. *(Deka et al., 2019)*

When their surroundings change, these clever polymers adapt their physicochemical characteristics. Utilizing the changes in physiological individuality has been feasible with the recent developments in in situ gels. In situ gels, which have been the subject of much research, have proven to be among the most innovative drug delivery methods (NDDS) *(Anna Czajkowska-Ko´snik et. al., 2022)*

In situ gel formulations are liquid solutions that undergo a phase transition to form a gel at the site of application when exposed to specific physiological conditions. These gels are particularly useful for localized drug delivery, improving bioavailability, and prolonging the residence time of the drug at the application site. The formulation of in situ gels involves selecting appropriate polymers, solvents, and other additives to achieve the desired gelation properties. Here's a general overview of the formulation process. The specific formulation process will depend on the characteristics of the drug, the desired gelation mechanism, and the intended application site. It's important to conduct thorough testing and optimization to ensure the stability, efficacy, and safety of the in-situ gel formulation. *(Kurniawansyah et al., 2023)*

Mucormycosis (previously zygomycotic), is an Angio invasive fungal infection caused by fungi of class zygomycetes and order Mucorales. Mucormycosis (phycomycosis or

zygomycosis) is a noninfectious fungal illness caused by various zygomycete genera *(Sanap et. al., 2022).* The name "mucormycosis" is extensively used because the majority of these diseases are caused by Mucoraceae family members. Members of the Mucoraceae family can be found all over the world and are known to cause organic materials to degrade. *(M. Imran et al., 2021).*

Rhizopus arrhizus is the leading cause of mucormycosis in humans. Mucormycosis can also be caused by other fungi such as Mucor sp., Saksenaea sp., Absidia sp., Entomophthora sp., Basidiobolus sp., Conidiobolus sp., Apophysomyces elegans, Cunninghamella bertholletiae, and Rhizomucor pusillus *(Sanap et al., 2022).*

According to the World Health Organization (WHO), Mucormycosis is substantially more widespread in India than elsewhere in the world, with estimated rates ranging from 0.02 to 9.5 cases per 100,000 people. However, a paucity of population-based data makes it difficult to accurately quantify the incidence and prevalence of Mucormycosis in India. In a recent year, a computational model suggested that the number of incidences of Mucormycosis in India is approximately 14 per 100,000 persons. *(Md. Faiyazuddin et al.,2023)*

TYPE OF MUCORMYCOSIS

Gastrointestinal mucormycosis

All organ systems are susceptible to mucormycosis, although the most common sites of involvement are the lung, orbit, brain (rhino-orbital-cerebral), and sinuses in the nose.

Gastroscopic mucormycosis was uncommon for a very long period, particularly in wealthy nations. The symptoms of Gastrointestinal Mucormycosis differ depending on the location of infection *(Kaur et al., 2018).* Symptoms often include stomach discomfort, distention, nausea,

and vomiting. Fever and hematochezia are also potential adverse effects. The patient is usually misdiagnosed with an intraabdominal abscess. To diagnose the condition, an endoscope or a biopsy of the suspected region after surgery may be utilized. An iatrogenic epidemic of gastric mucormycosis developed as a result of infection of wooden applicators used to mix drugs for patients with nasogastric feeding tubes lately. *(Prabhu & Patel, 2004)*

Rhinocerebral Mucormycosis

Rhinocerebral mucormycosis has a 33–50% incidence. The presumed a etiological agent is thought to be Apophysomyces elegans. a sinus illness that starts in the paranasal sinuses, spreads to the nose, eyes, and sometimes the brain when spores are inhaled. Before reaching intracranial structures, its clinical manifestations begin with palate and sinuses necrosis and then spread to the orbit. Fever, blindness, exophthalmos, nosebleeds, facial paralysis, and indications of trigeminal nerve invasion are among the symptoms. Unresolved rhino-sinus mucormycosis will result in cavernous sinus thrombosis. There is also a reddish-black nasal septum and turbinate appearance, as well as a nasal discharge. As the illness spreads to the cerebral vault, patients experience convulsions, blindness, and lethargy before passing away. *(Suganya et al.,2019).*

Pulmonary Mucormycosis

The pathogen's second most common site of invasion is the lungs, where it causes pulmonary mucormycosis. Hemoptysis, pleuritic chest discomfort, and dyspnea were also observed in a few patients, with a nonproductive cough being a prevalent symptom. Immunocompromised individuals accounted for the highest number of instances, which might be due to

hematological diseases or organ transplantation. Diabetes mellitus was shown to be the underlying illness in a large majority of patients *(Kasvala et al., 2021)*

Pulmonary Mucormycosis is less frequent than other lung fungal infections, understanding its radiologic presentation and progression is crucial due to the high rates of morbidity and death experienced by infected individuals. Although the results of the imaging tests may not be specific, there are some radiologic hints that might help with diagnosis. The radiologist can be extremely important in the patient's care since antifungal therapy administered early increases survival rates. Reversing the underlying predisposing factors for infection should be attempted if possible. Treatment options include managing metabolic acidosis, reducing the dosage of immunosuppressive medications, or controlling blood glucose levels *(François Danion et. Al., 2023).*

When it comes to individuals with localized illness, surgery is advised since it produces better results than antifungal medication alone. Patients with unifocal illness often have wedge resection, lobectomy, or pneumonectomy as surgical options. Although surgery for bilateral illness is rare, it has been demonstrated to be successful in source control *(Salwa O. Mekki et.al., 2020)*.

Cutaneous mucormycosis

Cutaneous mucormycosis develops in immunocompetent hosts (43-67 percent) who become infected as a result of skin damage or breach. Depending on the amount of infection, cutaneous mucormycosis can be classified as localized (affecting just the skin) or deep extension (including muscle, bones, or tendons). Cutaneous mucormycosis can progress slowly or rapidly, resulting in gangrene and dispersion (*Anna Skiada et. al 2022).* Necrotic eschar

surrounded by erythema is a common feature of cutaneous mucormycosis, and an insignificantly tiny erythematous macule may become widespread in immunocompromised people. Penetrating trauma is a major issue in cutaneous mucormycosis, whereas lesser problems include intramuscular injection, surgery, open wound trauma, accidents, contaminated dressings, and so on. Visual diagnoses may include the appearance of nodules, blisters, necrotic ulcers, pustules, and so forth. The prevalence of cutaneous mucormycosis in children is around 27%, accounting for roughly 19% of all cases. A meta-analysis revealed that Saksenaea sp. and Apophysomyces sp. are frequently related with cutaneous mucormycosis *(Dogra et. al., 2022).*

Disseminated Mucormycosis

Mucorales are capable of infiltrating blood vessels and so entering hematogenous routes. The most common site of dissemination is the lungs, followed by the CNS, sinuses, and liver. SOT recipients and those with hematological malignancies are more likely to develop disseminated mucormycosis. Individuals with neutropenia, iron overload, or significant immunosuppression, leukemia, and those on deferoxamine are prone to disseminated mucormycosis *(Skiada et al., 2020)* Fatal occurrences of disseminated mucormycosis are linked to the use of self-monitoring blood glucose technology, which reveals a mild presentation of disseminated mucormycosis. Tissue cultures of immunocompromised people offer no unambiguous skin results, which is a serious problem in case of disease transmission *(Hocker et al., 2010).*

Overview of fungal diseases

Fungal illnesses, or mycoses, are infections caused by several forms of fungus. Fungi are common microorganisms that may be found in the environment; while many are innocuous or even useful, others can infect humans, animals, and plants *(Shinde et al 2021).* Fungal infections can affect several regions of the body, including the skin and internal organs. This is an overview of fungal illnesses. *(Voltan et. al.,2016)*

1. Superficial Fungal Infections: *(Kelly et.al.,2012)*

- Dermatophytosis (Ringworm): A category of fungal diseases that attack the skin, hair, and nails. Despite its name, it is caused by dermatophyte fungus, not worms.
- Candidiasis: Candida species cause this infection, which can damage the skin, mucous membranes (such as the mouth and genitals), and internal organs.
- Tinea Versicolor: Malassezia, a yeast, causes discolored areas on the skin.

2. Subcutaneous Fungal Infections: *(Garber, et, al.,2001)*

- Sporotrichosis: Sporothrix schenckii is the fungus that causes the disease, which is generally transmitted by contact with polluted soil or plants.
- Chromoblastomycosis: A persistent fungal infection that affects the skin and subcutaneous tissues, usually caused by traumatic injection with certain fungi.

3. Systemic Fungal Infections: *(Angel León-Buitimea et.al., 2021)*

- Aspergillosis: Caused by Aspergillus species, this infection can be allergic, colonizing the lungs, or invasive, spreading to other organs, especially in immunocompromised individuals.

- Candidemia: Systemic infection caused by Candida species, often affecting individuals with weakened immune systems.
- Cryptococcosis: Caused by Cryptococcus neoformans, primarily affecting the lungs and central nervous system, especially in immunocompromised individuals.
- Histoplasmosis: Caused by Histoplasma capsulatum, this infection is often contracted through inhalation of fungal spores and can affect the lungs and other organs.
- Coccidioidomycosis (Valley Fever): Caused by Coccidioides species, primarily found in arid regions, and can cause respiratory symptoms.

4. Opportunistic Fungal Infections: *(Badiee, P et,al., 2014)*

- Candida auris: An emerging multidrug-resistant yeast causing healthcare-associated infections.
- Pneumocystis pneumonia (PCP): Caused by Pneumocystis jirovecii, often affecting immunocompromised individuals, particularly those with HIV/AIDS.

Fungal infections can range in severity, and risk factors include compromised immune systems, certain medicinal treatments (such as broad-spectrum antibiotics or corticosteroids), and underlying health disorders. Laboratory testing is frequently used to diagnose the condition, and antifungal drugs may be prescribed as therapy. Good cleanliness, avoiding contact with polluted settings, and controlling underlying health issues are all recommended prevention techniques.

Sr. No	**Antifungal drug**	**Chemical class**	**Site of action**	**Target molecules**	**References**

1.	Terbinafine, Naftifine	**Allylamines**	Biosynthesis of Ergesterol	Sqalene epoxidase	*(Waghule, T., et.al., 2019)*
2	Amorolfine	**Morpholines**	Biosynthesis of Ergesterol	Sterol reductase and isomerase	*(annemarie Polak et.al.,1998)*
3	Amphotericin B, Nystatin	**Polyenes**	Biosynthesis of Ergesterol	Membrane barrier function	*(Parente-Rocha et.al., 2017)*
4	Griseofulvin	**Griseofulvin**	Fungal mitotic apparatus	Sliding of microtubules	*(Mirgane et.al.,2022)*
5	Tolnaftate	**Thiocarbamate**	Biosynthesis of Ergesterol	Sqalene epoxidase	*(Mirgane et.al.,2022)*
6	Imidazoles Miconazole, Econazole, Bifonazole, Clotrimazole, Ketoconazole	**Azoles**	Biosynthesis of Ergesterol	Cytochrome P450 14α-Lanosterol demethylase	*(Arnold, Dotson, Sarosi, et. al., 2010)*

7	Fluconazole, Itraconazole, Terconazole, Posaconazole	**Triazoles**	Biosynthesis of Ergesterol	Cytochrome P450 14α-Lanosterol demethylase	*(Arnold, Dotson, Sarosi, et. al., 2010)*

Table no:2 Antifungal Drug Classes and target site

Risk & Challenges of Mucor Mycosis

Mucormycosis, often known as black fungus, is an uncommon but dangerous fungal illness caused by a kind of mould called Mucormycetes. While mucormycosis is not a novel disease, its prevalence has grown in some populations, particularly those who have recovered from COVID-19 and those with weaker immune systems. Here are some hazards and obstacles related to mucormycosis *(Sharma et.al., 2022)*

1. Weakened Immune System:

   Individuals with compromised immune systems, such as those with uncontrolled diabetes, cancer, organ transplant recipients, or those taking immunosuppressive medications, are at higher risk for mucormycosis *(A.K. Singh, R. Singh, S.R. Joshi et al., 2015)*

2. COVID-19 and Mucormycosis:

   There have been reported cases of mucormycosis among individuals recovering from severe cases of COVID-19, particularly those who have been treated with steroids. The use of corticosteroids, especially in high doses, can weaken the immune system and potentially contribute to the development of fungal infections *(A.K. Singh, R. Singh, S.R. Joshi et al. et. al., 2015)*

3. Diabetes:

Uncontrolled diabetes is a significant risk factor for mucormycosis. Elevated blood sugar levels provide an environment conducive to fungal growth *(Reid et. al.,2020)*

4. Environmental Exposure:

   Mucormycetes are ubiquitous in the environment, found in soil, decaying organic matter, and on various surfaces. Exposure to the spores of these molds can occur through inhalation, ingestion, or entry through skin wounds. *(Sharma et.al., 2022)*

5. Surgery and Trauma:

   Individuals who have undergone surgery, especially involving the sinuses or respiratory tract, and those who have experienced trauma or injury with open wounds, are at an increased risk of mucormycosis *(Kevin Brunet & Dr Blandine Rammaert et.al.,2020)*

6. Iron Overload:

   Some medical conditions, such as hemochromatosis (iron overload), can create an environment that is favourable for the growth of mucoromycetes *(Ram Kumar Sahu et.al.,2021)*

7. Challenges in Diagnosis:

   Mucormycosis can be challenging to diagnose, and early detection is crucial for effective treatment. The symptoms can be nonspecific, and the infection may be mistaken for other conditions *(Pandey et.al., 2023).*

8. Limited Treatment Options:

   Treatment typically involves antifungal medications, such as amphotericin B, but these medications can have side effects and may require careful monitoring. Surgical removal of infected tissue may also be necessary. However, the success of treatment depends on early diagnosis and prompt intervention. *(Dr Mrudangsinh Rathod et.al., 2022)*

9. High Mortality Rates:

Mucormycosis can be a rapidly progressing and invasive infection, leading to high mortality rates, especially in cases where diagnosis and treatment are delayed. *(Sharma et.al., 2022)*

10. Post-COVID Complications:

Individuals recovering from severe COVID-19 may have lingering health issues and complications, and the added risk of mucormycosis further complicates the post-recovery period. Controlling underlying medical issues, maintaining proper hygiene, and avoiding areas with high dust and mould concentrations are examples of preventive approaches. For people who are more vulnerable, prompt medical assistance is essential when experiencing symptoms like sinus discomfort, nasal congestion, black discharge from the nose, or facial numbness. *(Prakash, H. et,al., 2021)*

Future perspectives

NLCs are lipid-based nanoparticles containing an unstructured solid lipid core that enables the encapsulation of highly lipophilic drugs, protecting drug from degradation and enhancing their stability. They present many advantages compared to existing nanoparticulated drug delivery systems. They are made of surfactants and lipids that are approved by the FDA and/or EMA and are commercially available in marketed products (Table 1), mainly for oral, dermal and intravenous administration. NLC preparation procedure can be accomplished in the absence of an organic solvent and the process is easily scalable into large batch sizes by high pressure homogenization.

Over the past decade, NLC formulation has undergone a continual improvement in the biomedical field. The ‘why now’ and the ‘how’ can be explained by defeated technological

barriers hindering the formulation process (e.g. lack of non-diffusing lipophilic dyes) and increased knowledge of the underlying mechanisms of transport of NLCs via different administration routes (e.g. oral or ocular). Both amendments played a major role in the application of NLCs and achieving successful outcomes.

Due to their special characteristics, they are crucial to downstream production, which calls for in-depth study. There is a lot of potential in understanding how particle size, synthesis, crystallinity, porosity, and strength affect drug release. Increasing yields, repeatability, and cost-effective production are the newest trends; these will aid in quick mass production.

Despite the simplicity of the current NLCs preparation techniques, a significant shortcoming in the chemical process is the existence of residual liquids or reaction remnants in the finished product, which might very likely result in harmful consequences.

Conclusion

NLCs are made possible by combining nanotechnology with lipids as a structural material. NLC are a versatile platform for drug delivery via various routes. These nanocarriers have drawn the interest of researchers from all over the world. Partially crystallized lipidic nanocarriers have high drug loading and stability than their predecessors such as liposomes, nanoemulsions, and SLNs. These nanocarriers are biodegradable, biocompatible, safe, and effective with high drug loading capacity. These nanocarriers can also be employed for active or passive drug targeting to different organs or tumor cells. NLC has proven its worth in the cosmetics industry, but its potential in the pharmaceutical industry has yet to be fully explored. NLC can be useful in diseases whose management is difficult, such as cancer, infections, neurodegenerative diseases, localized drug delivery as well as genetic diseases which

conventional carrier systems cannot achieve. More research is required in this area to shift these interesting nanocarriers from lab to market. There is a need to evaluate the toxicity profile of such nanocarriers and solve the problems associated with nanomedicines such as complexity in formulation and characterization. Lack of sufficient clinical studies and data results in a slow development of these nanocarriers.

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