Role of Lipid Nanoparticles for Transdermal Drug Delivery Systems

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Abstract:

Non-invasive drug delivery approaches have gained significant momentum as alternatives to conventional parenteral administration. Among them, the transdermal drug delivery system (TDDS) stands out due to its high patient compliance, ease of use, reduced dosing frequency, and ability to bypass first-pass metabolism. TDDS is increasingly applied not only in pharmaceuticals but also in dermatology and cosmeceuticals, where controlled and localized delivery is essential. By enabling drug administration directly across the skin barrier, TDDS minimizes systemic exposure, reduces adverse effects, and prevents undesired accumulation of drugs in non-target tissues.

In recent years, nanoparticle-based carriers—particularly solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC)—have received growing attention for their remarkable potential in enhancing dermal and transdermal drug transport. These lipid-based systems offer advantages such as biocompatibility, controlled drug release, improved stability of labile compounds, and the ability to modulate skin permeation. Their nanoscale size allows closer interaction with the stratum corneum, increased occlusion, and the creation of hydrating effects that facilitate drug penetration. Furthermore, lipid nanoparticles can encapsulate both hydrophilic and lipophilic therapeutics, making them versatile delivery platforms.

Despite their promise, the precise mechanisms governing nanoparticle–skin interactions, penetration pathways, and transdermal transport behaviour remain incompletely understood. Factors such as particle composition, lipid crystallinity, surface charge, and occlusive properties significantly influence permeation outcomes. A deeper understanding of these mechanisms is essential to fully exploit lipid nanoparticles for advanced transdermal therapies.

Keyword: Lipid nanoparticles, Solid lipid nanoparticles (SLNs), Nanostructured lipid carriers (NLCs) Transdermal drug delivery system (TDDS)

1. Introduction:

TDDS offers better patient compliance due to its self-administrable nature, avoidance of first-pass metabolism, reduced dose requirements, improved dosing regimen, ability to terminate therapy at any time, absence of gastric irritation, and overall enhanced convenience. [1] High patient acceptability of topical and transdermal systems is reflected in market growth, with the skin-delivery sector valued at USD 12.838 billion in 2020 and projected to reach USD 13.457 billion. [2].

1.1 Enhancement of TDDS by equipment: TDDS supplemented by appropriate equipment is termed as active transdermal delivery. [3]

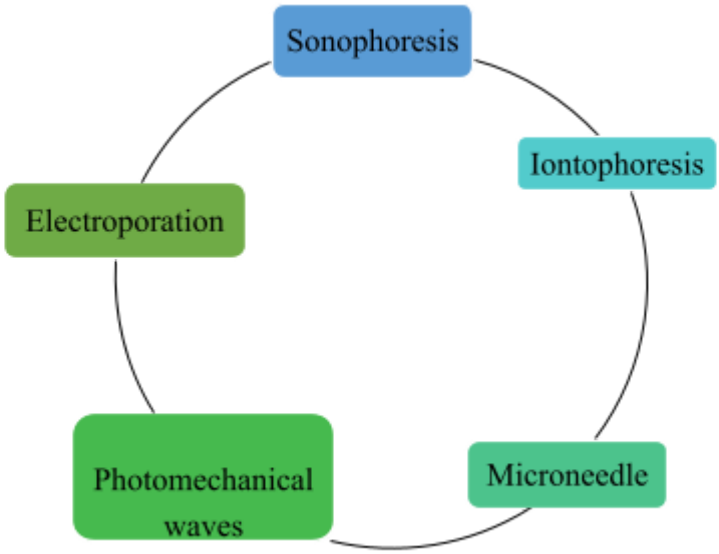

Fig.1 List of equipment enhance TDDS

1.2. TDDS using chemical enhancers: To achieve enhanced transdermal delivery and therapeutic efficacy, drugs should have low MW (less than 1 kDa), an affinity for lipophilic and hydrophilic phases, short half-life, and a lack of skin irritability.[4]

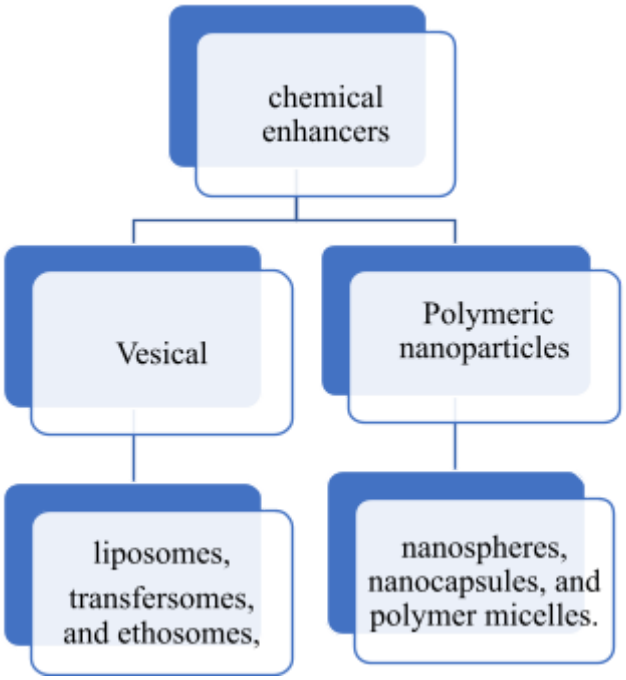

Fig.2 List of chemical enhancers enhance TDDS

2. Lipid nanoparticles

Lipid nanoparticles have gained considerable attention in the last two decades, and have achieved tremendous clinical success since the first clinical approval of Doxil in 1995. [5] Numerous drug delivery systems have been developed for protecting active ingredients, improving drug efficacy and directing site-specific drug delivery. Nanoparticles have been extensively investigated for drug delivery for decades. Lipid-based nanoparticles such as liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) have demonstrated tremendous clinical success in delivering both hydrophobic and hydrophilic therapeutics.[6]

The 1990s marked a turning point for pharmaceutical nanotechnology, when the research groups of Prof. Rainer H. Müller and Prof. Maria Rosa Gasco introduced lipid-based alternatives known as solid lipid nanoparticles (SLN) [5,6].

In recent years, interest in lipid nanoparticles has grown rapidly, reflected by the increasing number of publications on the topic. These systems combine the advantages of other Nano carriers—such as liposomes, nanoemulsions, and polymeric nanoparticles—while reducing many of their drawbacks. Solid lipid nanoparticles (SLN), the first generation of lipid nanoparticles, originated from replacing the liquid oil phase of nanoemulsions with a solid lipid.

SLN offer key benefits including high biocompatibility, good stability, controlled drug release, cost-effective raw materials, and ease of large-scale production. However, they also present limitations such as drug expulsion, low particle concentration in dispersions (1–30%), and restricted drug loading due to limited drug solubility in solid lipids. [7-8].To address these limitations, a second generation of lipid nanoparticles—nanostructured lipid carriers (NLC)—was developed. By incorporating a liquid lipid into the solid matrix, NLC create an imperfect crystal structure that reduces drug expulsion and improves loading capacity. [9].

NLC lipid matrix, obtained from a blend of a solid lipid with a liquid lipid, is characterized by imperfections providing space to locate a high amount of actives. 1.1 Main ingredients and techniques for the production of lipid nanoparticles SLN are composed of solid lipid (0.1-- 30% w/w) dispersed in an aqueous medium, stabilized with 0.5--5% (w/w) of surfactant, while NLC are generally produced using blends of solid and liquid lipids mixed in a ratio of 70:30 up to a ratio of 99.9:0.1 [10]. The surfactants are chosen depending on the administration route and are often used in association in order to prevent particle agglomeration more efficiently. The parenteral route of administration limits the number of surfactants to be used, while the topical application offers a wider choice of use. The production of lipid nanoparticles can be realized by different techniques like formation of a precursor oil-in-water 'nanoemulsion' followed by subsequent solidification of the dispersed lipid phase. Nanoemulsion preparation became the critical step when the aim is to prepare lipid nanoparticles with a very small particle size and a narrow polydispersity index, for instance, SLN for parenteral administration. To overcome the polydispersity and larger than desired droplet sizes, researchers often subject the precursor emulsions to large mechanical forces such as high shear homogenization, high pressure homogenization and ultrasonication. High shear homogenization (HSH) and ultrasound (US) are 'cheap and fast' dispersing techniques even if both methods show some drawbacks. Very often, for instance, the dispersion quality obtained by HSH technique is compromised by the presence of micro particles, while US technique can be affected by metal contamination. Since these problems are often due to long processing times (for both HSH and US techniques), a possible way to minimize these drawbacks is the association of two short cycles of HSH and US during the preparation [11]. High-pressure homogenization (HPH) is the primary method for producing lipid nanoparticles and includes hot and cold techniques. Hot homogenization is most commonly used and can be suitable for temperature-sensitive compounds due to brief heat exposure. Its main limitation is the poor incorporation of hydrophilic drugs, which may partition into the aqueous phase during processing. [13]. The cold homogenization is recommended for preparing lipid nanoparticles containing either highly temperature-sensitive compounds or hydrophilic compounds. Other valid methods of preparation are the microemulsion technique and the emulsification-solvent evaporation or solvent diffusion methods. The first method is based on the evidence that the addition of a microemulsion to water leads to precipitation of the lipid phase forming fine particles [7]. Instead the emulsification solvent evaporation or solvent diffusion methods belong to the solvent-based approaches [14]. In these techniques, the lipophilic material is dissolved in a water-immiscible organic solvent that is emulsified in an aqueous phase. After the sol vent evaporation, a nanoparticle dispersion is formed by precipitation of the lipid in the aqueous medium. The advantage of these methods is the avoidance of any thermal stress while the main problem is the complete removal of the solvent used during the preparation [14].

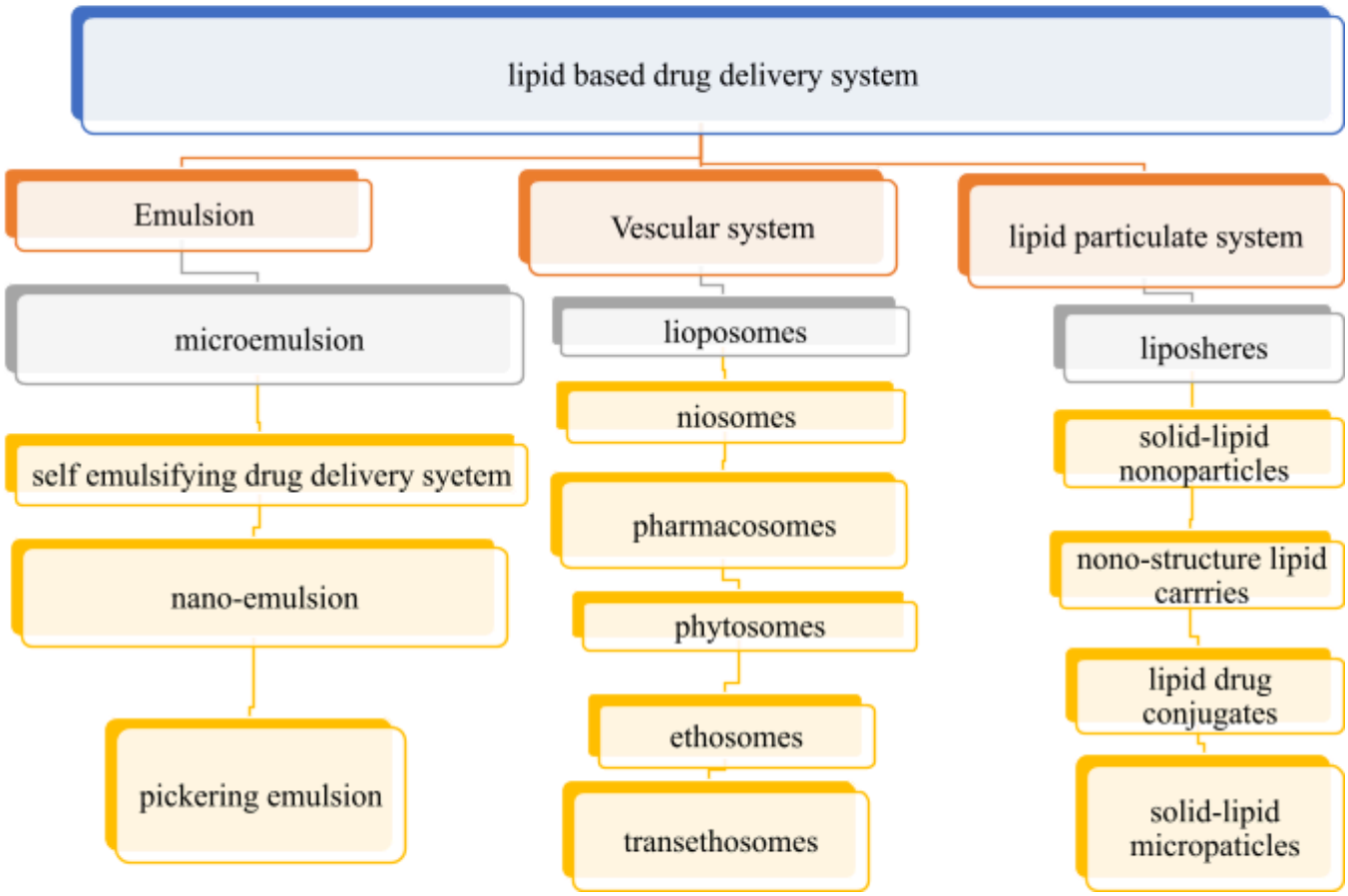

Fig.3 Different types of Lipid-Based Nanoparticles

Among various classes of lipid-based nanoparticles for drug delivery, four typical classes include liposomes, SLNs, NLCs, and hybrid lipid-polymeric nanoparticles.

2.1 Liposomes

Liposomes, first identified in 1965, are spherical vesicles composed of an amphipathic phospholipid bilayer surrounding an aqueous core, enabling encapsulation of both hydrophilic and hydrophobic drugs. Hydrophobic molecules partition into the lipid bilayer, while hydrophilic agents localize in the aqueous core. In formulations such as liposomal doxorubicin (Doxil), DOX is loaded into the core as crystalline $(DOX)_2SO_4$ via a transmembrane ammonium gradient. Liposomes can be prepared using various techniques, including thin-film hydration, microfluidic approaches, and electroporation-based methods. [16]

2.2 Niosomes

Niosomes are vesicles formed by the hydration of non-ionic surfactants, often with cholesterol or other lipids. Depending on the environment, they can take on spherical, multilamellar, or polyhedral shapes. Various surfactants like spans, tweens, brij, and others are used to create them. Like liposomes, niosomes can carry both hydrophilic and lipophilic drugs and range in size from 10 to 1000 nm. They are preferred in many cases due to their better chemical stability and lower production cost compared to liposomes. [17]

2.3Ethosomes

Ethosomes are advanced drug delivery vesicles mainly used for skin and transdermal applications. They are composed of phospholipids, water, and a high amount of ethanol. Ethanol plays a key role by enhancing the vesicles' ability to penetrate deep into the skin. Ethosomes improve drug delivery by interacting with skin lipids, allowing them to merge with the skin and deliver active ingredients more effectively. [18]

2.4Transethosomes

Transethosomes are lipid-based vesicles used for drug delivery through the skin. They are made of phospholipids, ethanol, an edge activator, and water. Phospholipids help carry the drug into the skin, with their structure containing both water-attracting (hydrophilic) heads and water-repelling (hydrophobic) tails. The edge activator softens the vesicle's bilayer, improving its flexibility and permeability. Ethanol adds fluidity to the vesicles, allowing them to pass through tiny gaps in the skin's outer layer (stratum corneum). Together, ethanol and the edge activator make the vesicles more deformable, helping them reach deeper skin layers more effectively. [18]

2.5 solid-lipid nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs), composed of fully crystallized lipids and emulsifiers, were first developed in the mid-1990s using high-melting lipids such as triglycerides, fatty acids, and waxes. SLNs offer improved stability, drug protection, and controlled release, with unable properties based on lipid composition. Depending on drug distribution, three SLN models exist: solid solution, drug-enriched shell, and drug-enriched core. However, they are limited by low drug loading and poor long-term drug retention. During the storage, the lipid matrix underdoes polymorphic transition from high energy state to low energy state, leading to the formation of a more-organized crystalline lattice and the gradual expulsion of the encapsulated drugs. Thus, drug loading capacity is significantly limited by the polymorphism, especially for highly purified lipids. Therefore, liquid lipid or solubilizers were introduced to improve the stability. Consequently, NLCs were developed with the solid lipid partially substituted with liquid lipids. Effectively, NLCs provide enhanced storage stability and drug loading capacity due to the impaired formation of crystallite. [19]

3. Formulations of Lipid nanoparticles for TDDS

3.1 microneedles:

Their nanoscale size and hydrophobic properties, resembling those of the stratum corneum, enable them to achieve deeper skin permeation. Nevertheless, drug concentration that reaches systemic

circulation following transdermal application of lipid nanoparticles is relatively limited. Hence, microneedles can be combined with lipid nanoparticles to enhance skin permeation by forming microchannels in the stratum corneum, thereby improving the penetration of lipid nanoparticles into the deeper skin layers. To date, three types of microneedles have been combined with lipid nanoparticles which are solid, hollow, and dissolving microneedles. The integration between lipid nanoparticles and microneedles has demonstrated significantly higher skin permeation, transdermal bioavailability, and therapeutic efficacy, with sustained release properties, compared to lipid nanoparticles alone via transdermal delivery. [19].

3.2 Hydrogel:

Aqueous dispersions of lipid nanoparticles flurbiprofen solid lipid nanoparticles (FLUSLN) and flurbiprofen nanostructured lipid carriers (FLUNLC) by hot homogenization followed by sonication technique and then incorporated into the freshly prepared hydrogels for transdermal delivery.[20]

3.3 Transdermal patch

Simvastatin NLC preparation was prepared by optimized hot homogenization technique. In-vivo pharmacokinetic studies in NLC loaded transdermal patch show an increase in $AUC_{0-\alpha}$ in mg/ml when compared to marketed oral dosage form.[21]

References:

1) Kumar, V., Praveen, N., Kewlani, P., Arvind, Singh, A., Gautam, A. K., & Mahalingam Rajamanickam, V. (2023). Transdermal drug delivery systems. In *Advanced Drug Delivery: Methods and Applications* (pp. 333-362). Singapore: Springer Nature Singapore.

2) Akombaetwa, N., Ilangala, A. B., Thom, L., Memvanga, P. B., Witika, B. A., & Buya, A. B. (2023). Current advances in lipid nanosystems intended for topical and transdermal drug delivery applications. Pharmaceutics, 15(2), 656.

3) Jeong, W. Y., Kwon, M., Choi, H. E., & Kim, K. S. (2021). Recent advances in transdermal drug delivery systems: A review. *Biomaterials research*, *25*(1), 24.

4) Wang, Y., Zeng, L., Song, W., & Liu, J. (2021). Influencing factors and drug application of iontophoresis in transdermal drug delivery: An overview of recent progress. *Drug Delivery and Translational Research, 12*(1), 15–26.

5) Stanekzai, A., Sudhakar, C. K., Zhakfar, A. M., & Karan, V. S. (2019). Recent approaches in transdermal drug delivery system. Research Journal of Pharmacy and Technology, 12(9), 4550–4558.

6) Mitchell, M. J., Billingsley, M. M., Haley, R. M., Wechsler, M. E., Peppas, N. A., & Langer, R. (2021). Nature Reviews Drug Discovery, 20, 101.

7) Lingayat, V. J., Zarekar, N. S., & Shendge, R. S. (2017). Solid lipid nanoparticles: A review. Nanosci. Nanotechnol. Res., 4(2), 67–72.

8)Vauthier, C., & Bouchemal, K. (2009). Methods for the preparation and manufacture of polymeric nanoparticles. Pharmaceutical Research, 26(5), 1025–1058.

9)Vega-Villa, K. R., Takemoto, J. K., Yanez, J. A., Remsberg, C. M., Forrest, M. L., & Davies, N. M. (2008). Clinical toxicities of nanocarrier systems. Advanced Drug Delivery Reviews, 60(8), 929–938.

10)Müller, R. H., Mehnert, W., Lucks, J. S., Schwarz, C., zur Mühlen, A., Weyhers, H., Freitas, C., & Rühl, D. (1995). Solid lipid nanoparticles (SLN): An alternative colloidal carrier system for controlled drug delivery. European Journal of Pharmaceutics and Biopharmaceutics, 41, 62–69.

11)Gasco, M. R. (1993). Method for producing solid lipid microspheres having a narrow size distribution (US Patent No. 5188837).

12)Schwarz, C., Mehnert, W., Lucks, J. S., & Müller, R. H. (1994). Solid lipid nanoparticles (SLN) for controlled drug delivery: I. Production, characterization and sterilization. Journal of Controlled Release, 30(1), 83–96.

13)Mehnert, W., & Mäder, K. (2001). Solid lipid nanoparticles: Production, characterization and applications. Advanced Drug Delivery Reviews, 47(2–3), 165–196.

14)Bunjes, H., Kühn, K., & Koch, M. H. J. (1996). Crystallization tendency and polymorphic transitions in triglyceride nanoparticles. International Journal of Pharmaceutics, 129(1–2), 159–173.

15)Freitas, C., & Müller, R. H. (1999). Correlation between long-term stability of solid lipid nanoparticles (SLN) and crystallinity of the lipid phase. European Journal of Pharmaceutics and Biopharmaceutics, 47(2), 125–132.

16)Müller, R. H., Radtke, M., & Wissing, S. A. (2002). Nanostructured lipid matrices for improved microencapsulation of drugs. International Journal of Pharmaceutics, 242(1–2), 121–128.

17)Xu, L., Wang, X., Liu, Y., Yang, G., Falconer, R. J., & Zhao, C. X. (2022). Lipid nanoparticles for drug delivery. Advanced NanoBiomed Research, 2(2), 2100109.

18)Akombaetwa, N., Ilangala, A. B., Thom, L., Memvanga, P. B., Witika, B. A., & Buya, A. B. (2023). Current advances in lipid nanosystems intended for topical and transdermal drug delivery applications. Pharmaceutics, 15(2), 656.

19) Gunawan, M., Nadya Bestari, A., Ramadon, D., Efendi, A., & Boonkanokwong, V. (2025). Combination of lipid-based nanoparticles with microneedles as a promising strategy for enhanced transdermal delivery systems: A comprehensive review. Journal of Drug Delivery Science and Technology, 107, 106807.

20) Bhaskar, K., Anbu, J., Ravichandiran, V., Venkateswarlu, V., & Rao, Y. M. (2009). Lipid nanoparticles for transdermal delivery of flurbiprofen: formulation, in vitro, ex vivo and in vivo studies. *Lipids in health and disease*, *8*(1), 6.

21) Brito Raj, S., Chandrasekhar, K. B., & Reddy, K. B. (2019). Formulation, in-vitro and in-vivo pharmacokinetic evaluation of simvastatin nanostructured lipid carrier loaded transdermal drug delivery system. *Future Journal of Pharmaceutical Sciences*, *5*(1), 9.