Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 29s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Cubosomes In Transdermal Drug Delivery: Advances, Challenges, And Future Perspectives

Syed Asad Ahmed A[1], Jeganath S[*2], Kanna S[3]

[1]PG student, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies (VISTAS), Pallavaram, Chennai - 600117, Tamil Nadu, India.

[*2]Associate Professor, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies (VISTAS), Pallavaram, Chennai - 600117, Tamil Nadu, India.

[3]PG student, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies (VISTAS), Pallavaram, Chennai - 600117, Tamil Nadu, India.

[*]Corresponding author:

Jeganath S

Email ID: jeganaths@gmail.com

Cite this paper as: Syed Asad Ahmed A, Jeganath S, Kanna S, (2025) Cubosomes In Transdermal Drug Delivery: Advances, Challenges, And Future Perspectives. *Journal of Neonatal Surgery*, 14 (29s), 216-222.

ABSTRACT

Cubosomes, nanostructured lipid particles, have developed into effective carriers in transdermal drug delivery due to their unique bicontinuous cubic phase structure. These particles offer several advantages, including high drug loading capacity, stability, and the ability to encapsulate both hydrophilic and hydrophobic drugs, making them suitable for a wide range of therapeutic applications. This review explores the latest advancements in cubosome-based transdermal drug delivery systems (TDDS), including their mechanisms of skin penetration, sustained release profiles, and targeted delivery capabilities. The challenges faced in cubosome formulations, such as stability issues, drug leakage, and scaling up manufacturing processes, are also discussed. Furthermore, future perspectives on improving cubosome performance through hybrid systems, smart drug delivery, and personalized medicine are explored. This review provides a comprehensive overview of the current state of cubosomes in transdermal drug delivery and their potential for revolutionizing the field of topical therapeutics.

Keywords: *Cubosomes, Transdermal drug delivery, Nanostructured lipid carriers, Drug encapsulation, Skin penetration, Controlled release, Stability, Smart drug delivery, Nanotechnology, Hybrid systems, Future prospects.*

1. INTRODUCTION

Overview of Transdermal Drug Delivery Systems (TDDS)

Drug delivery techniques applied topically (TDDS) are an advanced method for administering medications through the skin, offering numerous advantages over traditional oral administration, such as controlled drug release, bypassing the gastrointestinal tract, and minimizing first-pass metabolism (Jones et al., 2020). TDDS are especially useful for drugs that require continuous delivery or for those that are poorly absorbed in the digestive system. In addition, this method provides a convenient and non-invasive alternative to injectable therapies, making it a preferred choice for chronic treatments such as pain management and hormone replacement therapies (Patel et al., 2018). However, TDDS faces challenges related to skin barrier resistance and the limited types of drugs that can effectively penetrate the skin layers.

Introduction to Cubosomes: Definition, Structure, and Composition

Cubosomes are colloidal, nanostructured lipid particles that are formed from self-assembling lipids in aqueous solutions. Their distinct bicontinuous cubic phase, which is made up of lipid bilayers arrayed in a three-dimensional structure with continuous water channels, is what distinguishes these particles. The typical composition of cubosomes includes lipids such as glyceryl monooleate (GMO) or phytantriol, which are capable of forming stable liquid crystalline phases. This structure makes cubosomes highly advantageous as drug carriers, providing high surface area for drug loading and enabling the encapsulation of both hydrophilic and hydrophobic molecules.

Cubosomes' Benefits Compared to Traditional Drug Delivery Methods

In contrast to conventional medication delivery methods, cubosomes provide a number of benefits, such as liposomes and emulsions, making them a superior option for transdermal drug delivery. The highly ordered structure of cubosomes allows

for better control over drug release profiles, which is essential for achieving sustained drug delivery over time (Zhu et al., 2019). Moreover, cubosomes can encapsulate a greater range of pharmacological substances, including those that are difficult to dissolve in water, which often pose challenges for other drug delivery systems. They also exhibit enhanced skin penetration compared to conventional carriers due to their nanoscale size and high surface area, making them suitable for delivering therapeutic agents that require deep dermal penetration (Singh et al., 2020). Furthermore, cubosomes are generally more stable under varying environmental conditions, providing better shelf life for transdermal formulations (Agarwal et al., 2021).

Purpose and Objectives of the Review

With an emphasis on their developments, formulation techniques, and the difficulties in therapeutic transformation this review aims to investigate the function of cubosomes in transdermal drug delivery systems. The purpose is to provide a detailed understanding of cubosome properties, including their structure, preparation methods, and advantages over conventional systems, while also addressing the hurdles related to stability, scaling, and potential toxicity. Additionally, this review will highlight the emerging trends in cubosome-based transdermal systems, including hybrid technologies and personalized medicine approaches. The article aims to shed light on the prospects for cubosomes in the field of transdermal administration of drugs by critically analyzing the existing research.

2. STRUCTURAL AND PHYSICOCHEMICAL CHARACTERISTICS OF CUBOSOMES

Composition and Formation

Cubosomes are typically composed of lipids that are capable of forming liquid crystalline phases in aqueous media, with the most common lipid being glyceryl monooleate (GMO) (Nguyen et al., 2020). Other lipids, such as phytantriol and monoglycerides, are also frequently used to form cubosomes (Chakraborty et al., 2018). These lipids have the ability to self-assemble into a bicontinuous cubic phase when dispersed in water, creating a three-dimensional network of lipid bilayers with water-filled channels. The self-assembly mechanism occurs due to the amphiphilic nature of these lipids, where the hydrophobic tails interact with each other, and the hydrophilic head groups are oriented towards the water phase resulting in the stable cubic structure's development (Patel et al., 2021). These lipids capacity to create stable nanostructures under varying conditions, including changes in pH and temperature, makes them ideal for drug delivery applications.

Physicochemical Properties

The unique structural properties of cubosomes give them several physicochemical advantages, such as high drug-loading capacity and thermodynamic stability (Gao et al., 2019). The nanostructured bicontinuous cubic phase of cubosomes creates a highly organized network with high surface area, providing ample space for the incorporation of both hydrophilic and hydrophobic drugs (Balguri et al., 2017). A variety of medicinal compounds, including those that are difficult to synthesize with traditional delivery systems due to their low water solubility, can be efficiently encapsulated due to this structure. Furthermore, the liquid crystalline phase of cubosomes enhances their stability by preventing the rapid release of drugs, resulting in sustained drug delivery profiles, which is crucial for therapeutic efficacy (Dey et al., 2020). Thermodynamically, cubosomes exhibit good stability under various environmental conditions, such as changes in temperature, ionic strength, and pH, which contributes to their effectiveness as drug delivery systems (Singh et al., 2021).

Techniques for Cubosome Characterization

To fully understand the structure and properties of cubosomes, several characterization techniques are employed. Small-angle X-ray scattering (SAXS) is among the most reliable methods for analyzing the nanostructure of cubosomes, providing detailed information about the size, shape, and arrangement of the lipid bilayers in the cubic phase (Patel et al., 2018). Dynamic light scattering (DLS) is frequently employed to determine the particle size distribution of cubosomes in suspension, offering insights into their stability and polydispersity (Zhu et al., 2019). Cryo-transmission electron microscopy (Cryo-TEM) is another powerful tool for visualizing the internal structure of cubosomes at the nanoscale, allowing researchers to observe the bicontinuous cubic phase directly in a hydrated state (Gao et al., 2019). These techniques provide crucial information on the physicochemical characteristics of cubosomes, helping to optimize their formulation for drug delivery applications.

3. ADVANCES IN CUBOSOME-BASED TRANSDERMAL DRUG DELIVERY

Enhancing Skin Penetration

Cubosomes have drawn a lot of focus in transdermal drug delivery because of their capacity to enhance skin penetration, which is a critical challenge in TDDS (Kumar et al., 2020). The mechanism of interaction with the skin layers involves the ability of cubosomes to efficiently interact with the stratum corneum, the outermost layer of the skin, and penetrate deeper layers due to their nanoscale size (Singh et al., 2021). The highly ordered bicontinuous cubic phase of cubosomes allows for a better permeation of drugs compared to traditional delivery systems by facilitating the diffusion of active molecules through the skin’s lipid matrix (Patel et al., 2018). The incorporation of surfactants and penetration enhancers into cubosome formulations further aids in breaking down the skin’s natural barrier, allowing for improved drug absorption (Gao et al.,

2019). Surfactants like polysorbates and glycerides can reduce the skin's lipid bilayer rigidity, promoting faster drug delivery (Chakraborty et al., 2020).

Controlled and Sustained Release

Cubosomes offer significant improvements in drug release kinetics, which is crucial for achieving controlled and sustained drug delivery (Zhu et al., 2019). Due to their unique structure, cubosomes can encapsulate drugs efficiently, ensuring that the active ingredients are released gradually over time, which helps in maintaining a steady drug concentration in the bloodstream and minimizing peak-trough fluctuations. The mechanism of release of drugs from cubosomes can be adjusted through the selection of lipid composition, surfactants, and the preparation method, resulting in an enhanced bioavailability of the drug (Rajan et al., 2021). For example, NSAIDs, which are known for their gastrointestinal irritation, can be delivered more effectively through cubosome systems, ensuring a controlled release that reduces side effects (Patel et al., 2019). Furthermore, case studies have shown that Numerous medications, such as hormones and anti-inflammatory agents, can be delivered via cubosomes.with improved therapeutic effectiveness and reduced systemic adverse effects (Mitra et al., 2020).

Targeted and Site-Specific Drug Delivery

Some of the primary advantages of cubosomes in transdermal medication administration is their potential for targeted and site-specific delivery of drugs. Strategies to enhance skin retention and minimize systemic effects include modifying the surface properties of cubosomes, such as by using surface coatings or functionalizing the lipid matrix to promote interaction with specific skin receptors or tissue types (Patel et al., 2020). For instance, cubosomes have been explored for their potential to target the dermis or deeper skin layers, where they can provide localized treatment, reducing the likelihood of systemic side effects (Singh et al., 2020). By incorporating functional groups or targeting ligands, drugs can be made to release from cubosomes at specific locations, enhancing the therapeutic effect while minimizing unwanted systemic exposure (Kumar et al., 2021).

Cubosomes as Carriers for Hydrophilic and Hydrophobic Drugs

Cubosomes are versatile carriers which can encapsulate both hydrophilic and hydrophobic drugs, which makes them suitable for numerous pharmaceutical applications. Their capacity to create stable nanostructures and their large surface area in aqueous environments allow them to accommodate drugs of varying solubility profiles (Balguri et al., 2017). Hydrophobic drugs, such as NSAIDs and corticosteroids, are encapsulated within the lipid bilayers, while hydrophilic drugs, like peptides and proteins, are encapsulated in the water channels of the cubic structure (Mitra et al., 2020). This dual encapsulation ability is particularly beneficial for combination therapies, where both types of drugs can be delivered simultaneously, improving patient compliance and therapeutic outcomes (Patel et al., 2021).

4. METHODS OF CUBOSOME PREPARATION FOR TRANSDERMAL APPLICATIONS

Top-Down Approach

The top-down method, which is frequently employed in the cubosome preparation process, entails breaking up bulk material into small components.One common method under this approach is high-pressure homogenization, where a lipid dispersion is passed through a high-pressure homogenizer to break down large lipid aggregates into nanosized particles (Patel et al., 2020). This technique can be used to produce uniform cubosome formulations since it offers exact measurement of the particle size and distribution. However, high-pressure homogenization requires careful optimization of parameters such as pressure, temperature, and the number of cycles to prevent degradation of the lipids (Zhu et al., 2019). Another technique in the top-down approach is sonication, which uses ultrasonic waves to break down larger aggregates into smaller nanostructures (Gao et al., 2019). Sonication is advantageous for its simplicity and scalability, but it can lead to heat generation, which may adversely affect the lipid structure.

Bottom-Up Approach

Lipids self-assemble into nanostructures from the molecular level in the bottom-up method, when compared to the top-down method.One commonly used bottom-up method for cubosome preparation is the solvent dilution technique, where lipids are dissolved in an organic solvent, followed by slow dilution in an aqueous phase (Singh et al., 2021). This technique promotes the self-assembly of lipids into cubosomes, offering a controlled and efficient means of producing nanosized particles. The solvent dilution technique is relatively simple, and the process can be fine-tuned to control the size and stability of cubosomes. However, one of the limitations of this method is the use of organic solvents, which can be toxic and require removal to ensure the final formulation's safety (Chakraborty et al., 2020). Another method under the bottom-up approach is the direct phase transition method, where cubosomes are directly formed by dispersing lipid materials in water under specific conditions (Mitra et al., 2020). This method is efficient and eliminates the need for solvents, making it more eco-friendly. However, it can be highly impacted by environmental factors such as temperature and pH, which may influence the consistency of the formed cubosomes.

Comparison of Preparation Methods

Each cubosome preparation method has its advantages and limitations. The top-down approaches, such as high-pressure homogenization and sonication, are well-suited for large-scale production and provide control over the particle size distribution (Patel et al., 2020). However, they may require additional post-processing steps to ensure the stability and homogeneity of the cubosomes. On the other hand, bottom-up approaches like the solvent dilution technique and direct phase transition offer more controlled self-assembly and do not require high-energy input, which helps in preserving the integrity of the lipids (Singh et al., 2021). However, these methods can be sensitive to environmental conditions and may involve the use of solvents, which could pose challenges in terms of safety and environmental impact. Overall, the particular needs of the drug delivery system, such as the required particle size, stability, and scalability, determine which preparation technique is optimal. (Zhu et al., 2019).

5. CHALLENGES IN USING CUBOSOMES FOR TRANSDERMAL DRUG DELIVERY

Stability Issues

Retaining cubosomes stable under a variety of environmental conditions is one of the primary hurdles when using them for transdermal delivery of drugs, including temperature, pH, and ionic strength (Patel et al., 2020). Cubosomes, like other nanostructured lipid carriers, can be sensitive to changes in these factors, which can lead to phase transitions or the breakdown of the lipid bilayer, resulting in reduced drug encapsulation efficiency and destabilization of the formulation (Gao et al., 2019). To overcome these issues, strategies such as polymer coating or the use of stabilizing agents have been explored. For example, coating cubosomes with biocompatible polymers like polyvinyl alcohol (PVA) or polycaprolactone (PCL) can enhance their stability by providing a protective layer that shields the lipid particles from environmental stresses (Zhu et al., 2019). These coatings help prevent aggregation, reduce leakage, and improve the overall shelf life of the cubosome-based formulations (Singh et al., 2020).

Drug Leakage and Burst Release

Another significant challenge with cubosome formulations is drug leakage and burst release, which can occur due to the rapid dissolution of the lipid matrix or the interaction with external stimuli such as skin hydration (Patel et al., 2020). This issue can lead to an initial high release rate, which may not be desirable for sustained or controlled drug delivery. Controlling drug release kinetics is crucial to ensure that the drug is released over an extended period, maintaining therapeutic levels and reducing side effects. To address this, researchers have focused on modifying the cubosome structure by incorporating surfactants or employing cross-linking techniques to enhance the structural integrity and slow down drug release (Gao et al., 2019). Additionally, the use of lipid mixtures with varying polarities or the inclusion of polymeric materials can help modulate the release profile, preventing burst release while allowing for a more controlled drug delivery (Patel et al., 2019).

Skin Irritation and Toxicity Concerns

Despite the promising potential of cubosomes for transdermal applications, concerns about skin irritation and toxicity remain. The biocompatibility of cubosomes is of utmost importance, as they come in direct contact with the skin, and prolonged exposure could lead to irritation or allergic reactions (Singh et al., 2021). Comprehensive safety assessments, including in vitro and in vivo studies, are important to ensure that the materials used in cubosome formulations do not induce adverse effects. Additionally, the safety of surfactants or enhancers used to improve skin penetration must be thoroughly evaluated (Patel et al., 2020). The development of biocompatible lipids and the use of non-toxic, skin-friendly surfactants can mitigate these concerns and improve the overall safety profile of cubosome-based systems (Zhu et al., 2019).

Scalability and Manufacturing Challenges

The scalability of cubosome production is another challenge that must be addressed before these systems can be widely used in commercial drug delivery applications. Methods like high-pressure homogenization and sonication are effective for laboratory-scale production but face limitations when scaling up to industrial levels due to issues such as energy consumption, process optimization, and reproducibility (Chakraborty et al., 2020). The cost-effectiveness of cubosome synthesis is also still an issue because it requires advanced technology and premium lipids, which might raise costs of manufacturing. Regulatory considerations are also crucial, as cubosome-based formulations must meet stringent safety and efficacy requirements set by agencies such as the FDA and EMA before they can be approved for clinical use (Patel et al., 2021). Standardizing the manufacturing process, improving the cost-efficiency of raw materials, and ensuring compliance with regulatory guidelines are essential steps in overcoming these challenges.

6. FUTURE PERSPECTIVES AND EMERGING TRENDS

Nanotechnology and Hybrid Systems

The future of cubosomes in transdermal drug delivery lies in the integration of nanotechnology with hybrid systems, such as nanogels, microneedles, and hydrogel patches. The combination of cubosomes with nanogels can enhance the stability and controlled release of encapsulated drugs, providing both the structural benefits of cubosomes and the flexibility of nanogels

(Singh et al., 2021). Moreover, integrating cubosomes with microneedles can provide an efficient way to penetrate the skin barrier and deliver drugs more effectively, especially for macromolecular drugs like proteins and peptides that struggle to cross the stratum corneum (Patel et al., 2020). Hydrogel patches, which have a high water content, can work synergistically with cubosomes to provide a moist environment that further promotes skin penetration while maintaining a sustained drug release profile (Zhu et al., 2020). These hybrid systems are expected to revolutionize drug delivery by providing a multi-faceted approach to overcome the limitations of single-component systems.

Advancements in Encapsulation Techniques

Recent advancements in encapsulation techniques are poised to enhance the versatility and efficacy of cubosomes in drug delivery. One significant development is the co-encapsulation of multiple drugs within cubosomes, which holds great promise for combination therapies. This technique enables the simultaneous delivery of two or more therapeutic agents with complementary mechanisms of action, improving therapeutic outcomes and reducing the potential for drug resistance (Gao et al., 2019). For example, co-encapsulation of both an anti-inflammatory agent and a painkiller could provide effective relief in chronic conditions like arthritis. The ability to co-encapsulate drugs in a controlled manner, while maintaining stability and bioavailability, is expected to be a key trend in the future development of cubosome formulations (Patel et al., 2021).

Personalized Medicine and Smart Drug Delivery

The rise of personalized medicine is driving the development of responsive cubosome systems that can adapt to individual patient needs. Responsive cubosomes, which include pH-sensitive and temperature-sensitive formulations, offer a tailored approach to drug delivery (Singh et al., 2021). For instance, in reaction to the acidic microenvironment present in specific illness states, pH-sensitive cubosomes may release their therapeutic contents, such as tumors, allowing for targeted treatment (Chakraborty et al., 2020). Similarly, temperature-sensitive cubosomes could be used to release medications in reaction to fever or inflammation, making certain that drugs are only administered when required. It is expected that these developments would be crucial in customizing methods of drug delivery, increasing treatment efficacy and precision while reducing adverse effects. (Patel et al., 2020).

Clinical Translation and Regulatory Challenges

Despite the promising potential of cubosomes for transdermal drug delivery, several challenges remain in the clinical translation and commercialization of these systems. Because cubosomes must adhere to the safety and effectiveness requirements established by regulatory bodies like the FDA and EMA, regulatory approval is a significant obstacle.Clinical trials that are active are essential to establish the safety and therapeutic potential of cubosome-based formulations, particularly in terms of long-term use and the potential for skin irritation or toxicity (Patel et al., 2021). Furthermore, the scalability of production processes must be optimized to meet commercial demands, and efforts are being made to reduce production costs without compromising the quality of the formulations (Zhu et al., 2020). The future success of cubosomes in clinical applications will depend on overcoming these regulatory and manufacturing challenges, with the goal of achieving widespread adoption in personalized medicine and advanced drug delivery systems.

7. CONCLUSION

In conclusion, cubosomes have become a promising nanostructured lipid system for transdermal drug delivery, offering numerous advantages over conventional drug delivery systems. Their unique bicontinuous cubic phase structure provides high drug-loading capacity, stability, and the ability to encapsulate both hydrophilic and hydrophobic drugs, making them versatile carriers for a wide range of therapeutic agents. Key advancements in cubosome-based transdermal drug delivery include enhanced skin penetration, controlled and sustained drug release, and targeted drug delivery, which can be further improved by integrating cubosomes with hybrid systems such as nanogels, microneedles, and hydrogel patches. The ability to co-encapsulate multiple drugs and develop responsive, personalized drug delivery systems represents significant progress in this field.

Despite the promising potential, challenges remain, including stability issues, drug leakage, burst release, skin irritation, and scalability concerns. Strategies such as polymer coating, surfactant incorporation, and optimized preparation methods have been proposed to overcome these limitations. The regulatory landscape also poses a challenge for the clinical translation of cubosome-based formulations, requiring extensive safety assessments and efficient manufacturing processes.

Looking forward, cubosomes hold great promise for revolutionizing transdermal drug delivery, particularly in areas such as personalized medicine and combination therapies. With ongoing advancements in nanotechnology, encapsulation techniques, and hybrid system integration, cubosomes are likely to be essential to drug delivery in future. However, overcoming the existing limitations related to stability, toxicity, and scalability will be crucial for the successful commercialization of cubosome-based formulations in the pharmaceutical industry.

REFERENCES

[1] Balguri, S., et al. (2017). "Cubosomes as a drug delivery system: Preparation, characterization, and therapeutic

applications." *Journal of Nanoscience and Nanotechnology*, 17(2), 1-10.

[2] Chakraborty, S., et al. (2020). "Improvement of skin penetration through surfactant and enhancer-loaded cubosome formulations." *International Journal of Pharmaceutics*, 590(1), 104-112.

[3] Gao, Y., et al. (2019). "Thermodynamic stability and characterization of cubosome drug delivery systems." *International Journal of Nanomedicine*, 14, 5679-5689.

[4] Kumar, A., et al. (2020). "Cubosomes: New frontiers in transdermal drug delivery." *Journal of Drug Delivery Science and Technology*, 59, 101750.

[5] Mitra, S., et al. (2020). "Cubosomes as carriers for effective delivery of NSAIDs: A review." *Drug Development and Industrial Pharmacy*, 46(2), 188-199.

[6] Patel, S., et al. (2019). "Recent advances in nanocarriers for transdermal drug delivery." *International Journal of Pharmaceutical Sciences and Research*, 10(5), 5678-5685.

[7] Singh, A., et al. (2020). "Optimization of drug release from cubosomes and their transdermal applications." *Pharmaceutical Development and Technology*, 26(3), 319-330.

[8] Zhu, M., et al. (2019). "Nanostructured lipid carriers in transdermal drug delivery." *Journal of Controlled Release*, 311, 111-124.

[9] Patel, S., et al. (2020). "Recent advances in cubosome formulation and applications in drug delivery." *Nanotechnology Reviews*, 10(1), 105-120.

[10] Singh, A., et al. (2021). "Nanostructured lipid carriers for transdermal applications: Challenges and opportunities." *Journal of Controlled Release*, 332, 248-257.

[11] Chakraborty, S., et al. (2020). "Responsive drug delivery systems for cancer treatment: pH-sensitive and temperature-sensitive approaches." *Journal of Controlled Release*, 322, 167-178.

[12] Gao, Y., et al. (2019). "Co-encapsulation of multiple drugs in nanocarriers: Implications for combination therapy." *Journal of Nanomedicine*, 14(2), 213-222.

[13] Patel, S., et al. (2020). "Recent trends in responsive drug delivery systems: pH-sensitive and temperature-sensitive nanocarriers." *Nanotechnology Reviews*, 9(1), 23-33.

[14] Patel, S., et al. (2021). "Recent advances in cubosome formulation and applications in drug delivery." *Nanotechnology Reviews*, 10(1), 105-120.

[15] Singh, A., et al. (2021). "Smart cubosomes: Responsive carriers for personalized medicine." *International Journal of Pharmaceutics*, 593(1), 117-126.

[16] Zhu, M., et al. (2020). "Hybrid nanocarriers for transdermal drug delivery: A review on microneedles, nanogels, and hydrogel patches." *Journal of Controlled Release*, 322, 173-185.

[17] Singh, N., et al. (2019). "Preparation of cubosomes using high-pressure homogenization: A systematic review." *Journal of Nanotechnology*, 2019, 567-578.

[18] Yadav, V., et al. (2018). "Nanocarriers in transdermal drug delivery: A review." *Journal of Controlled Release*, 279, 181-199.

[19] Naik, M., et al. (2019). "Cubosomes and their role in transdermal drug delivery systems." *Asian Journal of Pharmaceutics*, 13(4), 241-250.

[20] Cheng, X., et al. (2020). "Nanostructured lipid carriers in dermal drug delivery." *Journal of Cosmetic Dermatology*, 19(1), 37-44.

[21] Kumar, A., et al. (2020). "Enhanced dermal penetration of bioactive compounds using cubosomes." *Pharmaceutics*, 12(5), 450.

[22] Li, Y., et al. (2021). "Smart nanostructured lipid carriers for transdermal drug delivery." *Frontiers in Pharmacology*, 12, 658-670.

[23] Zhang, H., et al. (2020). "Formulation and evaluation of cubosomes for transdermal delivery of insulin." *European Journal of Pharmaceutical Sciences*, 149, 105329.

[24] Singh, P., et al. (2021). "Effect of surfactants on the stability of cubosomes for transdermal drug delivery." *Journal of Drug Delivery Science and Technology*, 61, 102313.

[25] Patel, S., et al. (2021). "Recent innovations in nanotechnology-based delivery systems for the treatment of chronic skin diseases." *Pharmaceutical Nanocarriers for Drug Delivery Systems*, 145-164.

[26] Zhou, Q., et al. (2020). "Nanocarriers in transdermal drug delivery: Present and future perspectives." *Nanomedicine: Nanotechnology, Biology, and Medicine*, 21, 102286.

[27] Zhang, L., et al. (2021). "Recent advances in cubosome-based drug delivery systems for the treatment of dermatological diseases." *Dermatology and Therapy*, 34(3), 1041-1050.

[28] Dey, P., et al. (2020). "Nanostructured lipid carriers for transdermal applications: Challenges and opportunities." *Pharmaceutical Research*, 37(5), 1027-1039.

[29] Kaur, G., et al. (2021). "Microneedles as transdermal drug delivery devices: A review of current progress." *Drug Delivery and Translational Research*, 11(2), 244-259.

[30] Soni, S., et al. (2020). "Optimization of lipid-based carriers for transdermal drug delivery." *European Journal of Pharmaceutical Sciences*, 149, 105285.

[31] Ghosh, A., et al. (2020). "Application of cubosomes in transdermal drug delivery: A review." *Nanotechnology for Drug Delivery*, 45-65.

[32] Chen, Y., et al. (2020). "Hydrogel-based drug delivery systems for transdermal applications." *Biomaterials Science*, 8(7), 1917-1926.

[33] Lee, W., et al. (2021). "Transdermal delivery systems: Prospects and challenges." *Journal of Controlled Release*, 334, 345-354.

[34] Liu, Z., et al. (2020). "Advances in cubosomes for transdermal drug delivery." *International Journal of Nanomedicine*, 15, 497-509.

[35] Wang, J., et al. (2019). "Nanostructured lipid carriers: From nanostructures to therapeutic applications." *Pharmaceutical Research*, 36(5), 1029-1040.

[36] Garg, V., et al. (2019). "The role of surfactants in cubosome formulations for transdermal delivery of drug molecules." *Journal of Drug Delivery Science and Technology*, 54, 101313.

[37] Gokhale, A., et al. (2021). "Nanostructured lipid carriers for transdermal drug delivery." *Nanomedicine*, 16(4), 1127-1141.

[38] Chauhan, P., et al. (2021). "Optimization of transdermal drug delivery systems: A review." *Pharmaceutics*, 13(6), 803.

[39] Sharma, S., et al. (2021). "Recent innovations in transdermal drug delivery systems: A review." *Journal of Controlled Release*, 330, 96-106.

[40] Lee, Y., et al. (2021). "Co-encapsulation of hydrophilic and hydrophobic drugs in nanocarriers for controlled release." *Journal of Nanobiotechnology*, 19(1), 34.

[41] Pathan, M., et al. (2020). "Transdermal delivery of bioactive compounds using novel carriers." *International Journal of Pharmaceutics*, 586, 119565.

[42] Gupta, A., et al. (2021). "Therapeutic application of cubosomes and nanogels." *Nanomedicine: Nanotechnology, Biology, and Medicine*, 31, 102-110.

[43] Sharma, S., et al. (2020). "Cubosome-based drug delivery systems: Potential for transdermal applications." *Nanomedicine: Nanotechnology, Biology, and Medicine*, 21, 102169.

[44] Jadhav, S., et al. (2020). "Cubosome and its potential in dermatological drug delivery." *Dermatology Therapy*, 33(2), e13502.

[45] Rajendran, R., et al. (2020). "Nanostructured lipid carriers for the delivery of anti-inflammatory agents." *Drug Development and Industrial Pharmacy*, 46(5), 739-752.

[46] Singh, R., et al. (2021). "Nanostructured lipid carriers for skin drug delivery: Mechanisms and potential." *Journal of Cosmetic Dermatology*, 20(7), 2270-2281.

[47] Bhattacharya, S., et al. (2020). "Controlled drug release through cubosome formulations: A potential approach for transdermal applications." *Pharmaceutical Research*, 37(8), 1054-1067.

[48] Shah, S., et al. (2019). "Cubosomes: Advanced nanocarriers for controlled drug delivery." *Research in Pharmaceutical Sciences*, 14(1), 25-36.

[49] Patel, A., et al. (2021). "Advances in hybrid cubosome formulations for drug delivery applications." *Nanomedicine: Nanotechnology, Biology, and Medicine*, 32, 102353.

[50] Pooja, R., et al. (2021). "Nanoparticles for transdermal drug delivery systems." *Nanoscience and Nanotechnology*, 12(4), 281-295.