Recent Advances in Cyclodextrin Based Transdermal Drug Delivery

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Abstract- This review addresses case studies incorporating hydro gel, gel patch, micro needles, and liposome micro emulsion to provide a thorough overview of current developments in Cyclodextrins-based transdermal drug delivery. Cyclodextrins have emerged as adaptable excipients with the potential to improve medication transport over the skin as transdermal drug delivery has grown in popularity as a non-invasive and patient-friendly route of administration. The case studies examine how Cyclodextrins are included into each delivery system and look at how they affect the drug's solubility, stability, and permeability. In particular, the addition of cyclodextrin into hydro gel formulations exhibits improved drug penetration and sustained release characteristics, whereas gel patches accomplish controlled drug release and extended skin residence. Drug distribution that is precise and targeted is made possible by integration with micro needles thanks to the development of inclusion complexes. Additionally, better drug encapsulation and release properties are shown by cyclodextrin-stabilized liposome micro emulsions. The paper also discusses production issues and safety concerns, offering insightful information on how cyclodextrin-based transdermal drug delivery systems may revolutionize medication administration for better therapeutic results.

Index Terms- Cyclodextrin, Transdermal Drug Delivery System, Hydrogel, Microneedles, Patch

INTRODUCTION
Despite the challenges, TDD remains an active area of research with significant potential for improving drug delivery and patient outcomes. Continued research and development in this field will undoubtedly lead to further advances and discoveries in TDD. [5]
The review article on Cyclodextrins in transdermal drug administration seeks to give a thorough examination of the function of Cyclodextrins as drug carriers in such systems. The review paper intends to address Cyclodextrins physicochemical characteristics, pharmacological interactions, and utility in improving drug penetration through skin. The goal of the article is to give a general overview of the various cyclodextrin types and how they are used in transdermal medication administration. the capacity of Cyclodextrins to raise TDD's efficiency. Drugs are delivered via the skin using transdermal drug delivery methods for either local or systemic therapeutic effects. There are several transdermal medication delivery methods, such as patches, gels, creams, sprays, and films. [19]

Transdermal delivery of drugs (TDD) is an FDA-approved form of drug delivery that offers several benefits over conventional oral or intravenous routes. The transdermal route is an appealing choice for drug administration since it offers several benefits such as prolong therapeutic effect, controlled and sustained drug release, reduced dosing frequency, bypass first pass metabolism, improve patient compliance and convenience[62]It aids in improving drug bioavailability and decreases drug level fluctuation[63]Transdermal administration also reduces gastrointestinal adverse effects and offers a painless and non-invasive administration strategy.[64] Additionally, it enables the targeted and localized drug delivery for various skin conditions[65] However, it presents unique challenges, such as skin permeability, difficulty in delivering hydrophilic drugs, and maintaining a steady drug release rate.[1] Different obstacles can reduce the efficiency of transdermal drug delivery systems. The stratum corneum is the major barrier, which serves as a protective barrier to stop external substances from entering the skin.[30]Drug penetration is difficult due to its thick structure, which is made up of keratinized cells and lipids.[31] Drug molecular size, molecular weight, hydrophilicity and lipophilicity plays crucial role in transdermal penetration and distribution. Large molecules have more difficulty compared to small molecules in traversing through the stratum corneum, which restricts the sorts of medications that can be delivered transdermally.[32] Drugs that are highly lipophilic may find it difficult to traverse the hydrophilic cellular layers of the skin, while drugs that are overly hydrophilic may have trouble dissolving in the lipid-rich stratum corneum[33]Another obstacle to the administration of transdermal drugs is skin metabolism and enzymatic activity. Drugs can be metabolized and degraded by skin enzymes, especially in the epidermis and dermis, which lowers their bioavailability.[34] Drug penetration can be inhibited by poor drug solubility in the formulation used for transdermal delivery. Low solubility drugs may have slow-release times and decreased efficacy in the selected vehicle.[35] Additionally, individual variation in skin attributed to the age, gender, ethnicity, and skin conditions plays important role in permeability and the overall drug delivery process.[36] Systemic side effects can occur even with transdermal drug delivery systems. Drugs with a narrow therapeutic window may still lead to unintended systemic effects, emphasizing the need for careful dose control [37]

Despite these challenges, there are significant opportunities to develop novel TDD technologies that could provide improved therapeutic outcomes and better patient compliance.[2] Recent research in TDD has focused on various strategies to overcome these challenges, including optimizing the formulation of the drug delivery system, developing novel drug delivery technologies, and exploring new mechanisms to enhance skin permeability. For instance, low frequency sonophoresis is emerging as a viable technology for delivering medications through the skin, and micro needles have been developed as a painless and effective means.
of increasing skin permeability.[3] Other strategy include chemical penetration enhancers, which can help overcome epidermal barriers and facilitate medication administration, and nanoparticles to enhance drug solubility and enable targeted delivery.[4] Iontophoresis uses an electric current to push drug molecules through the skin while they are charged.[38] Skin permeability is temporarily increased by electropermeation using short electric pulses. Permeation enhancers and vesicular systems like liposome and nanoparticles are used in chemical enhancement approaches.[39] Different methods have been used to get over the difficulties of transdermal medication delivery. With the help of these methods, transdermal medication delivery systems will function more effectively and drugs will permeate the skin more readily. To improve drug penetration through the skin and remove obstacles to transdermal drug administration, a variety of approaches are used. These techniques encompass both physical and chemical approaches to improve drug delivery efficiency. Sonophoresis, iontophoresis, electropermeation, and micro needleling are examples of physical enhancement methods. Drug penetration is made easier by micro needles’ temporary development of skin micro channels.[38] Ultrasound waves are used in sonophoresis to disrupt the stratum corneum and improve drug absorption. Permeation enhancers such as fatty acids, surfactants, and terpenes change the characteristics of the epidermal barrier to facilitate drug penetration, whereas Cyclodextrins can improve the aqueous solubility of poorly water soluble drugs to aid in skin permeation.[39] To get over transdermal drug delivery obstacles, nanocarriers such as micro emulsions, polymeric/surfactant nanoparticles, solid lipid nanoparticles, liposome, nano-structured lipid carriers are widely explored. Drug molecules can be entrapped in lipid-based vesicles such as liposomes, which let them penetrate the skin more effectively.[40] Lipid and polymeric nanoparticles specifically allow controlled release of drugs and enhanced skin penetration.[41] The skin penetration of hydrophobic and hydrophilic drugs can be improved by solubilizing them in micro emulsions, which are isotropic, thermodynamically stable systems.[42] Submicron-sized lipid particles known as solid lipid nanoparticles improve drug encapsulation and skin penetration.[43] The therapeutic efficacy of transdermal patches with reservoir or matrix systems is increased by the regulated drug release over an extended period of time.

II. CYCLODEXTRINS

Cyclodextrins have attracted considerable attention in transdermal drug delivery due to their ability to improve drug solubility, stability, and permeability. These cyclic oligosaccharides, composed of multiple glucose units, possess a hydrophobic internal cavity capable of encapsulating drug molecules. The complexation of cyclodextrin and drug molecules can protect the drug from degradation, increase its aqueous solubility, and enhance its penetration through the skin.[6] Cyclodextrins are cyclic oligosaccharides, composed of glucose units connected by alpha-1,4 glycosidic linkages. They are produced from starch by enzymatic conversion, and are typically classified based on their size. Cyclodextrins are well known for their capacity to combine with a variety of guest molecules, such as medications, flavors, and scents, to form inclusion complexes. The inner hydrophobic cavity of the cyclodextrin allows to trap hydrophobic molecules to form inclusion complex, increasing the solubility and stability of the guest molecule.[10]

To improve drug solubility, stability, and bioavailability as well as to address a number of drug delivery issues, modified cyclodextrins have been produced. When compared to their natural counterparts, these modified cyclodextrins have better characteristics, enabling better drug encapsulation and release. Depending on the specific alterations sought, cyclodextrins and modified cyclodextrins can be joined to a variety of functional groups. Functional groups can be added to cyclodextrins to modify their characteristics, solubility, and ability for complexation. Cyclodextrins can be modified by adding common functional groups such as hydroxypropyl, methyl, ethyl, carboxymethyl, and sulfobutyl ether. Enzymatic processes or chemical reactions involving the addition of particular reagents might produce these changes. The desired characteristics and uses of the modified cyclodextrin will determine the functional groups to be used. For example, cyclodextrins like hydroxypropyl-β-cyclodextrin (HP-β-CD) frequently have the hydroxypropyl group attached. This change makes cyclodextrins more water-soluble, which improves the solubility and dissolution of hydrophobic medicines.[44] In sulfobutyl ether-β-cyclodextrin (SBE-β-CD), sulfobutyl ether groups exhibit both hydrophilic and hydrophobic characteristics. This change improves the bioavailability of inclusion complexes created with various drugs by increasing their complexation efficiency and stability.[45]

Azido groups have been added to cyclodextrins to introduce a reactive functional group for subsequent chemical alterations, resulting in mono-6-deoxy-6-azido-α-cyclodextrin which allows the attachment of different moieties, such as polymers or targeting ligands, via click chemistry reactions.[47] This alteration makes it possible to create drug delivery systems based on cyclodextrin that have certain features. Aminoethyl groups can be attached to cyclodextrin, resulting in AE-β-CD.[48][49] Cyclodextrins synthesized using glycol chitosan showed improved mucoadhesion and water solubility.[51] Various modified cyclodextrins such as Succinylated cyclodextrins, PEGylated cyclodextrins and thiolated cyclodextrins to enhance the solubility, stability, and oral bioavailability of hydrophobic drug molecules by improving water solubility and complexation efficiency.[48]

Additionally, it has been demonstrated that adding extra co-formers or co-solvents to the complexation process to generate ternary complexes improves the solubility and stability of drugs. Such co-formers, which work in conjunction with cyclodextrins to enhance drug transport qualities, can be polymers, surfactants, and other excipients. The successful creation of binary and ternary cyclodextrin complexes with a variety of drugs has been reported in several studies, showing increased drug solubility, dissolution rate, and therapeutic efficacy.[52] Studies have examined the ternary complexation of itraconazole with βCD and hydrophilic polymers as well as the binary complexation of curcumin with βCD.[53] The potential of binary and ternary cyclodextrin complexes as effective drug delivery methods is highlighted by these investigations. In pharmaceutical companies, cyclodextrin is frequently used as an excipient to increase the solubility and bioavailability of medicines that are poorly water soluble. They are also used in food and cosmetic industries, as flavor and fragrance carriers, and in the production of encapsulated flavors and fragrances. Cyclodextrins are useful and adaptable compounds with a variety of uses.[11]
Currently used parent cyclodextrins and their derivatives in pharmaceutical product. (Reproduced from [12] with permission from Elsevier).

<table>
<thead>
<tr>
<th>Cyclodextrin</th>
<th>Substitution(s)</th>
<th>Molecular weight</th>
<th>Solubility in water (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Cyclodextrin</td>
<td>–</td>
<td>972</td>
<td>145</td>
</tr>
<tr>
<td>β-Cyclodextrin</td>
<td>–</td>
<td>1135</td>
<td>18.5</td>
</tr>
<tr>
<td>HP-β-cyclodextrin</td>
<td>0.65</td>
<td>1400</td>
<td>&gt;600</td>
</tr>
<tr>
<td>Randomly methylated β-cyclodextrin</td>
<td>1.8</td>
<td>1312</td>
<td>&gt;500</td>
</tr>
<tr>
<td>β-Cyclodextrin SBE sodium salt</td>
<td>0.9</td>
<td>2163</td>
<td>&gt;500</td>
</tr>
<tr>
<td>γ-Cyclodextrin</td>
<td>–</td>
<td>1247</td>
<td>232</td>
</tr>
<tr>
<td>HP-γ-cyclodextrin</td>
<td>0.6</td>
<td>1576</td>
<td>&gt;500</td>
</tr>
</tbody>
</table>

Drug distribution dependent on the aqueous solubility of the drug molecules, and poor aqueous solubility affects the drug distribution of a drug molecule. The hydrophobic internal cavity of cyclodextrins can trap hydrophobic guest molecules, such as drugs, and increase their solubility. This can further improve the bioavailability and efficacy of the drug.[13] Furthermore, cyclodextrins can improve the stability of drugs in transdermal formulations by protecting them from degradation or oxidation. Cyclodextrin complexation also aids in improving stability of drugs by shielding them from environmental elements including light and air imparting improved shelf life. [14] Modified cyclodextrins are widely used for transdermal medication delivery attributed to biocompatibility and generally recognized as safe (GRAS) status. Alpha-cyclodextrin (α-CD), Beta-cyclodextrin (β-CD), Gamma-cyclodextrin (γ-CD), Hydroxypropyl-beta-cyclodextrin (HP-β-CD), Methyl-beta-cyclodextrin (M-β-CD), Sulfobutylether-beta-cyclodextrin (SBE-β-CD) Regulatory authorities have approved their usage after testing. [15] α-cyclodextrin has been used in several transdermal formulations, including lidocaine and ibuprofen patches.[16] β-cyclodextrin has seven glucose units in its structure and a larger hydrophobic cavity than α-cyclodextrin. It is frequently used to increase the solubility and stability of medicines for transdermal drug delivery. β-cyclodextrin has been used in several transdermal formulations, including fentanyl patches.[17] Gamma-cyclodextrin has eight glucose units in its structure and the largest hydrophobic cavity among the cyclodextrins. To make medicines more soluble and stable for transdermal drug delivery, it is frequently used. γ-cyclodextrin has been used in several transdermal formulations, including estradiol patches.[18]

The drug-cyclodextrin complexation process is a dynamic process, where association and dissociation of complexes remain in state of equilibrium. The equilibrium between the drug molecules trapped inside the hydrophobic cavity of cyclodextrins and the surrounding medium explains the mechanism of drug release from cyclodextrin complexes.[54] Different mechanisms, such as inclusion-exclusion complexation, competitive binding, solubilization, and changes in pH or temperature, might cause the release process.[55] The drug molecules are initially complexed and trapped inside the cyclodextrin cavity in inclusion-exclusion complexation, and they progressively diffuse out of the complex into the surrounding media.[56] When other molecules with higher cyclodextrin affinities push the drug out of the complex, competitive binding might result in drug release. Cyclodextrins make hydrophobic pharmaceuticals more soluble, which causes the medication to be released from the complex when it comes into contact with a more soluble media. The stability or structure of the cyclodextrin complex can be changed to cause drug release, as can changes in pH or temperature.[57] To best use cyclodextrin complex-based drug delivery systems, it is essential to comprehend these mechanisms. Non-inclusion complexes are formed when a drug molecule associates with cyclodextrin without the drug being enclosed inside the hydrophobic cavity of the cyclodextrin molecule.[58] Instead, interactions including hydrogen bonding, electrostatic contacts, and hydrophobic interactions are how the drug binds to the cyclodextrin's outer surface to create complexes.[59] When a drug molecule's size or shape is incompatible with the cyclodextrin cavity or when it has functional groups that interact preferentially with the hydroxy groups on the cyclodextrin surface, non-inclusion complexes can develop.[60] These complexes can nevertheless have a significant impact on drug delivery because they affect drug release kinetics and enhance drug solubility, stability, and bioavailability. The development of drug delivery systems based on cyclodextrin requires an understanding of the production and characteristics of non-inclusion complexes.[61]

III CYCLODEXTRIN IN TRANSDERMAL DRUG DELIVERY

Cyclodextrins are well established and widely used in transdermal drug delivery due to several properties such as solubility, stability and biocompatibility that make them useful in this application. Numerous studies have shown that cyclodextrins improve transdermal drug delivery. For instance, a study showed that the complexation of ketoprofen with β- cyclodextrin significantly increased its solubility and skin permeation compared to the free drug.[7] Similarly, it was observed that complexing diclofenac with hydroxypropyl-β-cyclodextrin improved the drug's transdermal distribution.[8] Additionally, cyclodextrins have been used with other strategies to improve transdermal medication delivery. For instance, a study shows that the combination of iontophoresis and cyclodextrin complexation significantly increased the transdermal delivery of lidocaine. [9] Cyclodextrins have proven significant potential for improving transdermal medication delivery, and it is expected that their application in this area will grow over time.

Hydrogel

The oral administration of Duloxetine, widely prescribed medication for depression, is associated with poor solubility, inconsistent absorption, first pass metabolism, and potential gastrointestinal adverse effects. Rajiv kumar et.al investigated complexation with sulfobutylether-β-cyclodextrin to overcome the drawbacks associated with the oral administration of duloxetine. The sulfobutylether-cyclodextrin SBE-duloxetine complex improved the solubility of the drug, and SBE-duloxetine complex loaded
hydrogel showed enhanced skin permeability and metabolic bypass. In comparison with oral administration, transdermal delivery resulted in higher drug absorption in Wistar rats. Additionally, a pharmacokinetic analysis showing improved in vivo absorption shows that the optimized patch has increased $C_{\text{max}}$ (1.82 folds) and AUC0-72 (>2 folds) compared to the commercial formulation. Additionally, compared to the oral route, the transdermal delivery showed improved pharmacological activity in rats over a 24-hour period and sustained drug release. [21]

Cyclodextrin has been widely explored in pharmaceutical formulation development to improve the stability of drug molecules. Resveratrol and curcumin are associated with poor bioavailability due to their limited solubility, poor stability, and significant first-pass metabolism. Curcumin and resveratrol are hydrophobic compounds and undergoes photodegradation, which reduces its stability. R. Pushpalatha et al. developed cyclodextrin nanoparticles loaded hydrogel for transdermal delivery of resveratrol and curcumin. The cyclodextrin nano-sponges improved the in-vitro release of curcumin and resveratrol by 10 and 2.5 folds, respectively, as compared to free curcumin and resveratrol. The photostability of curcumin and resveratrol in cyclodextrin nanosponge Cyclodextrin-based nanosponges (CDNS) hydrogel was increased by approximately 5 and 7 times, respectively, in comparison to hydrogel prepared without CDNS. Ex vivo skin permeation study resulted in 11.5-fold and 2.4-fold permeation enhancement of curcumin and resveratrol respectively. Delivering drugs using a CDNS-hydrogel foundation dramatically improved the penetration of curcumin and resveratrol. [22]

**Nano Carriers**

Paola Mura et al. developed liposomal and microemulsion formulations for transdermal delivery of clonazepam, a poorly water-soluble benzodiazepine drug used for treating anxiety disorders. The study investigated the effect of randomly methylated β-cyclodextrin (RMβCD) on the solubility and permeability of clonazepam in the developed transdermal formulations. Clonazepam’s solubility and skin penetration were both greatly improved by the complexation with RMβCD. The Drug-RMβCD loaded liposomes and microemulsion showed higher flux and lower lag time compared to drug suspension, with or without Me-βCD. Moreover, the formulations showed improved stability and were non-irritant to the skin. The study demonstrated that RMβCD can be used as an effective solubilizer, stabilizer and permeation enhancer in transdermal delivery of clonazepam. Each formulation enhanced drug permeability by a different amount, ranging from 2-fold (liposomes without Me-βCD) to more than 4-fold (microemulsions with Me-βCD).

By combining the strategies of drug-cyclodextrin complex loading into nanocarriers, specifically deformable liposomes or nanostructured lipid carriers (NLC), N.Mennine et al. developed drug-cyclodextrin complex loaded liposomal and NLC for improving the transdermal distribution of the non-steroidal anti-inflammatory medicine Oxaprozin. Study suggested that compared to the drug as ternary complex (3.2 times increase) and the corresponding liposomal or NLC dispersion of plain drug (5.6 and 4.3 times increase, respectively. The combined use of CD with liposomes and NLC significantly increased the drug permeability by 16 and 8 folds, respectively. The study showed that the transdermal distribution of oxaprozin can be considerably improved by combining the cyclodextrin and nanocarriers strategies. [25]

Avobenzone, a UVA absorber frequently found in sunscreens is hydrophilic, susceptible to photodecomposition and has a low transdermal penetration rate. Yang et al. prepared HP-β-CD and avobenzone complex and observed improved solubility, stability and permeability. The photostability studies also demonstrated that HP-β-CD provided protection against UV-induced degradation of avobenzone, which is known to reduce its effectiveness as a sunscreen agent. At higher concentrations of HP- β CD (20% HP- β CD), avobenzone permeated more readily, however, further increase in HP- β CD concentrations (30%) decreased the skin permeability, indicating the formation of avobenzone reservoir. The 30% HP-βCD formulation was discovered to be the most photostable, followed by formulations with 20%, 10%, and 0% photostability. The lowest levels of sunburn cell formation and edema induction were observed in in-vivo experiments, which suggested that the 30% HP-βCD formulation offered the best photoprotection. These results indicated that the addition of HP-β-CD to sunscreen formulations may improve photoprotection by lowering both skin penetration and UV absorber photodecomposition. [24]

<table>
<thead>
<tr>
<th>CLZ formulation</th>
<th>μg/cm² CLZ permeated</th>
<th>$P_{\text{app}}$ (cm/s × 10⁻⁶)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aqueous suspension</td>
<td>3.22 ± 0.15</td>
<td>1.10 ± 0.05</td>
</tr>
<tr>
<td>Aq. suspension + Me-βCD</td>
<td>5.52 ± 0.28</td>
<td>2.21 ± 0.09</td>
</tr>
<tr>
<td>Liposomes</td>
<td>6.90 ± 0.32</td>
<td>2.52 ± 0.10</td>
</tr>
<tr>
<td>Liposomes + Me-βCD</td>
<td>10.24 ± 0.49</td>
<td>3.77 ± 0.12</td>
</tr>
<tr>
<td>Microemulsion</td>
<td>13.24 ± 0.61</td>
<td>4.09 ± 0.13</td>
</tr>
<tr>
<td>Microemulsion + Me-βCD</td>
<td>13.93 ± 0.63</td>
<td>4.25 ± 0.15</td>
</tr>
</tbody>
</table>

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Surapannini Sridevi et al. explored the modified cyclodextrin based transdermal delivery of Ketoprofen to overcome the limited efficacy and adverse side effects associated with oral route. To improve the solubilization and transdermal flux of ketoprofen, the combined use of pH modification and complexation was investigated. Contrary to the well-known pH partition concept, the study investigated how pH and HP-βCD interacted to affect the transdermal distribution of ketoprofen. Study showed that the drug ionized complex was 2.5 times more soluble compared to unionized complex. The flux showed linear increase with increasing HP-βCD.
In order to improve the solubility and compatibility of Polydatin, the study suggests using cyclodextrin (CD) inclusion complexation, specifically with (HP-β-CD). By improving the distribution and therapeutic efficacy of PD, this strategy offers a transdermal administration system that is patient-friendly and offers an effective treatment alternative for the management of acute gout. In a study conducted by Zhiwei Chen et.al polydatin was delivered transdermally for the treatment of acute gout arthritis by dissolving microneedles loaded with polydatin-HP-β-CD inclusion complexes to address the solubility and compatibility issues of drug molecule. A comparative CCK-8 assay conducted using HaCaT cells suggested that polydatin is less toxic compare to the MAP2. Ex vivo studies performed using excised newborn pig skin revealed that MAP1 and MAP2 deposited 141 ±40 μg and 342 ± 34 μg of CAB Na into 0.5 cm2 of skin, respectively after 24h. The in vivo pharmacokinetics of MAP2 over a 28 day period showed pro-therapeutic effects. Preclinical efficacy study suggested that both oral colchicine and PD/HP-β-CD DMNs had significant therapeutic effects.[27]

**Patch**

Fabiana Volpe-Zanutto et al. studied (HP-β-CD) to evaluate its effect on solubility and intradermal distribution of cabotegravir sodium (CAB-Na) via hydrogel-forming microarray patches (HF-MAPs). Two different HF-MAP formulations (MAP1 and MAP2) were developed using tablet reservoirs incorporating CAB-Na and HP-β-CD. Gantrez S97®, poly(ethylene glycol) 10,000, and sodium carbonate made up MAP1, whereas poly(vinyl pyrrolidone), poly(vinyl alcohol), and citric acid made up MAP2. Ex vivo studies performed using excised newborn pig skin revealed that MAP1 and MAP2 deposited 141 ±40 μg and 342 ± 34 μg of CAB-Na into 0.5 cm2 of skin, respectively after 24h. Their in vivo pharmacokinetics of MAP2 over a 28-day period showed prolonged drug release profile for 24 hours, and the highest concentration of CAB-Na that could be measured (Cmax) was 53.4 10.16 μg/mL. This Cmax was higher compared to FDA approved intramuscularly applied CAB-nanosuspension, which had a Cmax of 43.6 ± 5.3 μg/mL. The increase in aqueous solubility, allowed it to pass through the HF-MAP implant polymer matrix, which creates an intradermal drug depot, providing extended-release profile. The improved drug solubility by CD complex allowed administration of therapeutically appropriate amounts of CAB-Na by single application over a 28-day period and the rate-controlled drug delivery.[28]

**Fig. 1**

(A) Concentration of CAB-Na deposited into full-thickness skin after 24h.
(B) Concentration of CAB-Na permeated through the skin after 24h. (Means±S.D, n=6) ND* = drug was not detected.

(Reproduced from [28] with permission from Elsevier.)

The oral administration of bupronolol (BPL) suffers from rapid clearance and significant first-pass metabolism leading to poor bioavailability. Babu et al. chemical altered βCD to produce derivatives with a better water solubility and lower toxicity. The study explored (HP-β-CD) and partly methylated cyclodextrin (PM-β-CD) as a bupronolol (BPL) penetration enhancers. The linear increase of BPL penetration was observed from 1.0-10.0 % w/v of both HP-β-CD and PM-β-CD. At 10% w/v of HP-β-CD and PM-β-CD, both increased the flux of BPL by 3.8 and 4.6 times, respectively. Skin pretreatment with PM-β-CD led to severe disruption of epidermal barrier resulting in 1.7 fold higher flux of BPL, whereas HP-β-CD skin pretreatment showed no visible damage on the skin barrier. [29]
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V. CONCLUSION

The difficulties of delivering medications through the skin have been significantly improved by recent developments in cyclodextrin-based transdermal drug administration. Cyclodextrins have been used to improve medication solubility and penetration due to their capacity to form inclusion complexes with pharmaceuticals. To increase skin permeability and patient-specific medication delivery, novel technologies like those based on nanotechnology, physical techniques like microneedling, and personalised transdermal therapy have been investigated. For localised treatment, targeted distribution to particular locations on the skin has also been researched. To ensure sustained drug release and enhanced patient compliance, novel formulation strategies and non-invasive monitoring approaches are also being developed. With safer and more effective transdermal therapies for a variety of medical diseases, these developments have the potential to revolutionise current drug delivery strategies by providing safer, more effective, and patient-centered treatments for a variety of medical diseases.

IV. FUTURE PERSPECTIVES

Cyclodextrin-based transdermal drug delivery holds great promise for the future of pharmaceutical sciences, especially in terms of research possibilities. Key areas of research include investigating personalised transdermal therapy based on specific patient variables, improving skin permeation technologies with innovative penetration enhancers, and examining targeted delivery for site-specific drugs. To further improve drug distribution and patient outcomes, new biocompatible excipients, efficient formulation methods, and real-time monitoring systems are being developed. The safety, effectiveness, and patient preferences of cyclodextrin-based transdermal drug delivery systems must also be established through extensive pharmacokinetic research and organised clinical trials. Guidelines and standards will be developed in association with regulatory agencies in order to be approved and included into clinical practice. With the advancement of these research areas, cyclodextrin-based transdermal drug administration is poised to revolutionise current drug delivery strategies by providing safer, more effective, and patient-centered treatments for a variety of medical diseases.

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VIII. CONFLICT OF INTEREST
There are no conflicts of interest between the authors.

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