Recent Advances in Cyclodextrin Based Transdermal Drug Delivery

[1]Neha Chauhan, [2]Sahil Singh, [3]Manpreet Kaur Walia, [4]Pryanka

[1,2]Student, [3,4]Assistant Professor
University School of Pharmaceutical Sciences,
Rayat Bahra University, Mohali, India

***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**

I.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 physiochemical 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 limited 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 electroporation 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, electroporation, and micro needling 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 glyosidic 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 has been added to cyclodextrins to introduce a reactive functional group for subsequent chemical alterations, resulting in mono-6-deoxy-6-azido-α-cyclodextrinwhich 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][50] 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]

Table 1

Currently used parent cyclodextrins and their derivatives in pharmaceutical product. (Reproduced from [12] with permission from Elsevier).

Cyclodextrin	Substitution(s)[a]	Molecular weight[b]	Solubility in water[c] (mg/ml)
α-Cyclodextrin	–	972	145
β-Cyclodextrin	–	1135	18.5
HP-β-cyclodextrin	0.65	1400	>600
Randomly methylated β-cyclodextrin	1.8	1312	>500
β-Cyclodextrin SBE sodium salt	0.9	2163	>500
γ-Cyclodextrin	–	1297	232
HP-γ-cyclodextrin	0.6	1576	>500

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. The 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 hydroxyl 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 $_{Cmax}$ (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).

Table 2

The apparent permeability coefficient and the amount of clonazepam (CLZ) that permeated the synthetic lipophilic membrane per unit area of the different gel formulations at 0.5% drug, whether or not they contained Me-β-CD (25 mg/mL), were measured. (Reproduced from[23] with permission from Elsevier.)

CLZ formulation	μg/cm^2 CLZ permeated	*P* app (cm/s $\times 10^{-6}$)
Aqueous suspension	3.22 ± 0.15	1.10 ± 0.05
Aq. suspension + Me-βCD	5.52 ± 0.28	2.21 ± 0.09
Liposomes	6.90 ± 0.32	2.52 ± 0.10
Liposomes + Me-βCD	10.24 ± 0.49	3.77 ± 0.12
Microemulsion	13.24 ± 0.61	4.09 ± 0.13
Microemulsion + Me-βCD	13.93 ± 0.63	4.25 ± 0.15

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 edoema induction were observed in in-vivo experiments, which suggested that the 30% HP-β-CD 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]

Surapanini 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

concentration, but at pH 6.0, where the drug is primarily in the ionised state, the significantly higher flux was observed. When compared to the intrinsic permeability of the unionised drug, the flux of the ionized drug increased to by 8-fold at a 10% w/v HP-β-CD concentration. The study showed that using co-enhancers, including pH adjustment and HP-β-CD, could be a useful strategy for improving the transdermal distribution of poorly soluble drugs[26]

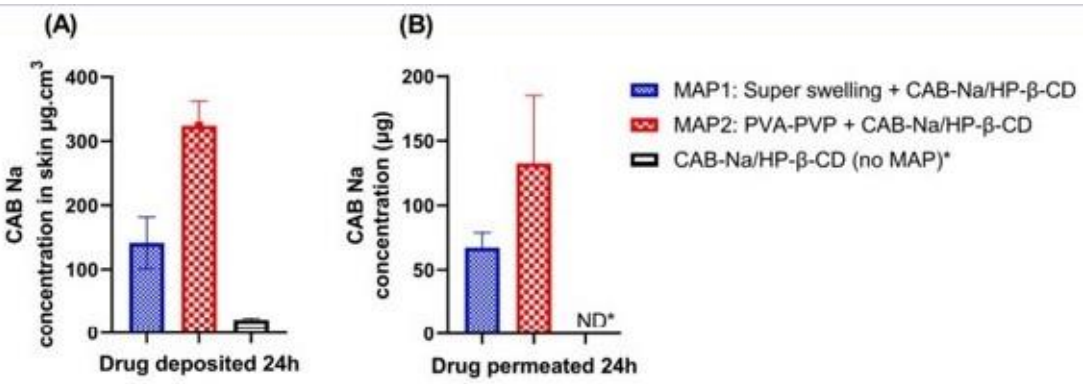
Micro Needles

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 toxicity of polydatin with indomethacin and colchicine, two of the most widely used gout medicines. Further, inclusion complex of polydatin- (HP-β-CD) improved the solubility of polydatin to 124.47 mg/mL .In vitro permeation study suggested that drug-CD complex-loaded dissolving microneedles showed higher permeation compared to absence of complexes .The arthritic mice treated with polydatin-loaded microneedles showed significant increases in body weight during the treatment compared to oral colchicine administration, demonstrating decreased toxicity related to the transdermal delivery of polydatin .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.Thein 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]

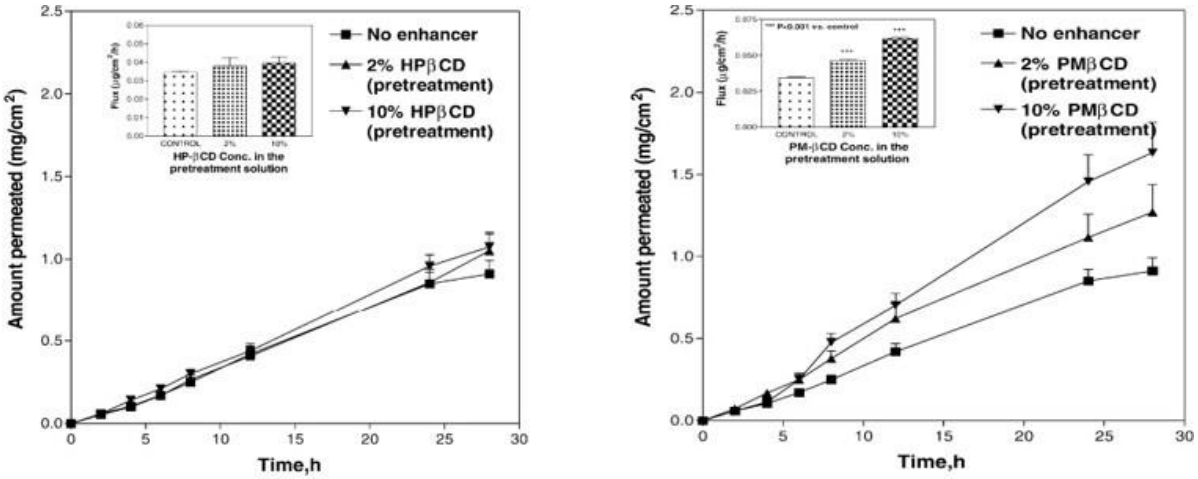
Fig : 1



(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 bupranolol (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]



A) Effect of pretreatment of rat skin with HPβCD on the in vitro permeation of bupranolol.
B) Effect of pretreatment of rat skin with PMβCD on the in vitro permeation of bupranolol. (Reproduced from [29] with permission from Elsevier).

GEL

The poly (pseudo) rotaxanes-based supramolecular transdermal gel was investigated to address the solubility, stability, and transdermal penetrationrelated drawbacks of carvedilol. The gels were prepared by mixing alpha-cyclodextrin (α-CD) and (HP-β-CD) with Soluplus or Solutol.Poly (pseudo)rotaxanes based on solutol formed instantly and had no effect on CAR solubility, whereas Soluplus-based poly(pseudo) rotaxanes were formed in 24-48 h with limited CAR solubility compared to Soluplus micelles. Comparing Solutol poly(pseudo)rotaxanes to Soluplus 20% + α-CD (5-10%), the former showed higher G' and G" but faster CAR release. Spray-dried complexes made of HP-β-CD or CAR-HPβ-CD released drugs morerapidly.With Solutol and Soluplus micelles, CAR solubility was increased, with Soluplus nanomicelles demonstrating more effective CAR encapsulation. As seen in NMR diffusion and STD investigations, both Solutol and Soluplus interacted with α-CD and HPβ-CD, although with different binding relationships. Adding α-CD led to the formation of insoluble poly (pseudo) rotaxanes. [67]

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.

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 medication delivery. The suggested approach for analysing cyclodextrin-based transdermal drug delivery research is crucial because it creates standardised evaluation criteria, systematically gathers knowledge, and identifies knowledge gaps. The framework directs future research, assists in clinical translation decision-making, and promotes breakthroughs in this potential drug delivery strategy by giving a comprehensive grasp of the complexity involved. Its importance is in streamlining efforts to enhance patient care, assisting regulatory decision-making, and developing cyclodextrin-based transdermal drug delivery for safer and more efficient therapies.

VI.FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

VII.ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to S. Gurvinder Singh Bahra, Hon'ble Chancellor and chairman, Rayat Bahra University, Mohali, who gave me a platform for pursuing Masters work in this University. I am greatly indebted to Prof. (Dr.) Parvinder Singh, worthy vice chancellor, for graciously permitting me to carry on the research work.

VIII. CONFLICT OF INTEREST

There are no conflicts of interest between the authors.

REFERENCES:

1. Prausnitz MR, Langer R. Transdermal drug delivery. Nature biotechnology. 2008 Nov;26(11):1261-8.
2. Nagarkar R, Singh M, Nguyen HX, Jonnalagadda S. A review of recent advances in microneedle technology for transdermal drug delivery. Journal of Drug Delivery Science and Technology. 2020 Oct 1;59:101923.
3. Kim YC, Park JH, Prausnitz MR. Microneedles for drug and vaccine delivery. Advanced drug delivery reviews. 2012 Nov 1;64(14):1547-68.
4. Subedi RK, Oh SY, Chun MK, Choi HK. Recent advances in transdermal drug delivery. Archives of Pharmacal Research. 2010 Mar;33:339-51.
5. Benson HA. Transdermal drug delivery: penetration enhancement techniques. Current drug delivery. 2005 Jan 1;2(1):23-33.
6. Loftsson T, Brewster ME. Pharmaceutical applications of cyclodextrins: basic science and product development. Journal of pharmacy and pharmacology. 2010 Nov;62(11):1607-21.
7. Maestrelli F, González-Rodríguez ML, Rabasco AM, Mura P. Effect of preparation technique on the properties of liposomes encapsulating ketoprofen–cyclodextrin complexes aimed for transdermal delivery. International journal of pharmaceutics. 2006 Apr 7;312(1-2):53-60.
8. Scavone C, Bonagura AC, Fiorentino S, Cimmaruta D, Cenami R, Torella M, Fossati T, Rossi F. Efficacy and safety profile of diclofenac/cyclodextrin and progesterone/cyclodextrin formulations: a review of the literature data. Drugs in R&D. 2016 Jun;16:129-40.
9. Benson HA. Transdermal drug delivery: penetration enhancement techniques. Current drug delivery. 2005 Jan 1;2(1):23-33.
10. Cid-Samamed A, Rakmai J, Mejuto JC, Simal-Gandara J, Astray G. Cyclodextrins inclusion complex: Preparation methods, analytical techniques and food industry applications. Food Chemistry. 2022 Feb 16:132467.
11. Paiva-Santos AC, Ferreira L, Peixoto D, Silva F, Soares MJ, Zeinali M, Zafar H, Mascarenhas-Melo F, Raza F, Mazzola PG, Veiga F. Cyclodextrins as an encapsulation molecular strategy for volatile organic compounds–pharmaceutical applications. Colloids and Surfaces B: Biointerfaces. 2022 Aug 5:112758.
12. Jambhekar SS, Breen P. Cyclodextrins in pharmaceutical formulations I: Structure and physicochemical properties, formation of complexes, and types of complex. Drug discovery today. 2016 Feb 1;21(2):356-62.
13. Del Valle EM. Cyclodextrins and their uses: a review. Process biochemistry. 2004 May 31;39(9):1033-46.
14. Yan Y, Xing J, Xu W, Zhao G, Dong K, Zhang L, Wang K. Hydroxypropyl-β-cyclodextrin grafted polyethyleneimine used as transdermal penetration enhancer of diclofenac sodium. International Journal of Pharmaceutics. 2014 Oct 20;474(1-2):182-92.
15. Szejtli J. Cyclodextrin complexed generic drugs are generally not bio-equivalent with the reference products: therefore the increase in number of marketed drug/cyclodextrin formulations is so slow. Journal of inclusion phenomena and macrocyclic chemistry. 2005 Jun;52:1-1.
16. Peptu C, Rotaru R, Ignat L, Cristina Humelnicu A, Harabagiu V, Anisoara Peptu C, Leon MM, Mitu F, Cojocaru E, Boca A, Ionel Tamba B. Nanotechnology approaches for pain therapy through transdermal drug delivery. Current pharmaceutical design. 2015 Dec 1;21(42):6125-39.
17. Benson HA. Transdermal drug delivery: penetration enhancement techniques. Current drug delivery. 2005 Jan 1;2(1):23-33.
18. Karande P, Mitragotri S. Enhancement of transdermal drug delivery via synergistic action of chemicals. Biochimica et Biophysica Acta (BBA)-Biomembranes. 2009 Nov 1;1788(11):2362-73.
19. Patel AV, Shah BN. TRANSDERMAL DRUG DELIVERY SYSTEM: A REVIEW. Pharma Science Monitor. 2018 Jan 1;9(1).
20. Jambhekar SS, Breen P. Cyclodextrins in pharmaceutical formulations I: Structure and physicochemical properties, formation of complexes, and types of complex. Drug discovery today. 2016 Feb 1;21(2):356-62.
21. Kumar R, Sinha VR, Dahiya L, Sarwal A. Transdermal delivery of duloxetine-sulfobutylether-β-cyclodextrin complex for effective management of depression. International journal of pharmaceutics. 2021 Feb 1;594:120129.
22. Pushpalatha R, Selvamuthukumar S, Kilimozhi D. Cyclodextrin nanosponge based hydrogel for the transdermal co-delivery of curcumin and resveratrol: Development, optimization, in vitro and ex vivo evaluation. Journal of Drug Delivery Science and Technology. 2019 Aug 1;52:55-64.
23. Mura P, Bragagni M, Mennini N, Cirri M, Maestrelli F. Development of liposomal and microemulsion formulations for transdermal delivery of clonazepam: Effect of randomly methylated β-cyclodextrin. International journal of pharmaceutics. 2014 Nov 20;475(1-2):306-14.
24. Yang J, Wiley CJ, Godwin DA, Felton LA. Influence of hydroxypropyl-β-cyclodextrin on transdermal penetration and photostability of avobenzone. European Journal of Pharmaceutics and Biopharmaceutics. 2008 Jun 1;69(2):605-12.
25. Mennini N, Cirri M, Maestrelli F, Mura P. Comparison of liposomal and NLC (nanostructured lipid carrier) formulations for improving the transdermal delivery of oxaprozin: Effect of cyclodextrin complexation. International journal of pharmaceutics. 2016 Dec 30;515(1-2):684-91.
26. Sridevi S, Diwan PV. Optimized transdermal delivery of ketoprofen using pH and hydroxypropyl-β-cyclodextrin as co-enhancers. European journal of pharmaceutics and biopharmaceutics. 2002 Sep 1;54(2):151-4.
27. Chen Z, Han B, Liao L, Hu X, Hu Q, Gao Y, Qiu Y. Enhanced transdermal delivery of polydatin via a combination of inclusion complexes and dissolving microneedles for treatment of acute gout arthritis. Journal of Drug Delivery Science and Technology. 2020 Feb 1;55:101487.

28. Volpe-Zanutto F, Vora LK, Tekko IA, McKenna PE, Permana AD, Sabri AH, Anjani QK, McCarthy HO, Paredes AJ, Donnelly RF. Hydrogel-forming microarray patches with cyclodextrin drug reservoirs for long-acting delivery of poorly soluble cabotegravir sodium for HIV Pre-Exposure Prophylaxis. Journal of Controlled Release. 2022 Aug 1;348:771-85.
29. Babu RJ, Pandit JK. Effect of cyclodextrins on the complexation and transdermal delivery of bupranolol through rat skin. International journal of pharmaceutics. 2004 Mar 1;271(1-2):155-65.
30. Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K. Fitzpatrick's Dermatology in General Medicine, 8e. McGrawHill Medical. 2012:2421-9
31. Michaels AS, Chandrasekaran SK, Shaw JE. Drug permeation through human skin: theory and in vitro experimental measurement. AIChE journal. 1975 Sep;21(5):985-96.
32. Barry BW. Novel mechanisms and devices to enable successful transdermal drug delivery. European journal of pharmaceutical sciences. 2001 Sep 1;14(2):101-14.
33. Prausnitz MR, Mitragotri S, Langer R. Current status and future potential of transdermal drug delivery. Nature reviews Drug discovery. 2004 Feb 1;3(2):115-24.
34. Bouwstra JA, Honeywell-Nguyen PL, Gooris GS, Ponec M. Structure of the skin barrier and its modulation by vesicular formulations. Progress in lipid research. 2003 Jan 1;42(1):1-36.
35. Barry BW. Dermatological formulations. Percutaneous Absorptions. 1983:127-233.
36. Lindwall G, Hsieh EA, Misell LM, Chai CM, Turner SM, Hellerstein MK. Heavy water labeling of keratin as a non-invasive biomarker of skin turnover in vivo in rodents and humans. Journal of investigative dermatology. 2006 Apr 1;126(4):841-8.
37. Mitragotri S, Ray D, Farrell J, Tang H, Yu B, Kost J, Blankschtein D, Langer R. Synergistic effect of low-frequency ultrasound and sodium lauryl sulfate on transdermal transport. Journal of pharmaceutical sciences. 2000 Jul;89(7):892-900.
38. Guy RH, Kalia YN, Delgado-Charro MB, Merino V, López A, Marro D. Iontophoresis: electrorepulsion and electroosmosis. Journal of controlled release. 2000 Feb 14;64(1-3):129-32.
39. Williams AC, Barry BW. Penetration enhancers. Advanced drug delivery reviews. 2012 Dec 1;64:128-37.
40. Touitou E, Junginger HE, Weiner ND, Nagai T, Mezei M. Liposomes as carriers for topical and transdermal delivery. Journal of Pharmaceutical Sciences. 1994 Sep 1;83(9):1189-203.
41. Cheng YC, Li TS, Su HL, Lee PC, Wang HM. Transdermal delivery systems of natural products applied to skin therapy and care. Molecules. 2020 Oct 30;25(21):5051.
42. Patel P, Pol A, Kalaria D, Date AA, Kalia Y, Patravale V. Microemulsion-based gel for the transdermal delivery of rasagiline mesylate: In vitro and in vivo assessment for Parkinson's therapy. European Journal of Pharmaceutics and Biopharmaceutics. 2021 Aug 1;165:66-74.
43. Paliwal R, Paliwal SR, Kenwat R, Kurmi BD, Sahu MK. Solid lipid nanoparticles: A review on recent perspectives and patents. Expert opinion on therapeutic patents. 2020 Mar 3;30(3):179-94.
44. Stella VJ, He Q. Cyclodextrins. Toxicologic pathology. 2008 Jan;36(1):30-42
45. Van De Manakker F, Vermonden T, Van Nostrum CF, Hennink WE. Cyclodextrin-based polymeric materials: synthesis, properties, and pharmaceutical/biomedical applications. Biomacromolecules. 2009 Dec 14;10(12):3157-75.
46. Brewster ME, Loftsson T. Cyclodextrins as pharmaceutical solubilizers. Advanced drug delivery reviews. 2007 Jul 30;59(7):645-66.
47. Zhang J, Ma PX. Cyclodextrin-based supramolecular systems for drug delivery: recent progress and future perspective. Advanced drug delivery reviews. 2013 Aug 1;65(9):1215-33.
48. Loftsson T, Brewster ME. Pharmaceutical applications of cyclodextrins: basic science and product development. Journal of pharmacy and pharmacology. 2010 Nov;62(11):1607-21.
49. Van De Manakker F, Vermonden T, Van Nostrum CF, Hennink WE. Cyclodextrin-based polymeric materials: synthesis, properties, and pharmaceutical/biomedical applications. Biomacromolecules. 2009 Dec 14;10(12):3157-75.
50. Sugiuchi H, Uji Y, Okabe H, Irie T, Uekama K, Kayahara N, Miyauchi K. Direct measurement of high-density lipoprotein cholesterol in serum with polyethylene glycol-modified enzymes and sulfated alpha-cyclodextrin. Clinical chemistry. 1995 May 1;41(5):717-23.
51. Rajewski RA, Stella VJ. Pharmaceutical applications of cyclodextrins. 2. In vivo drug delivery. Journal of pharmaceutical sciences. 1996 Nov;85(11):1142-69.
52. Taupitz T, Dressman JB, Buchanan CM, Klein S. Cyclodextrin-water soluble polymer ternary complexes enhance the solubility and dissolution behaviour of poorly soluble drugs. Case example: itraconazole. European Journal of Pharmaceutics and Biopharmaceutics. 2013 Apr 1;83(3):378-87.
53. Yang W, Liang X, Xu L, Deng C, Jin W, Wang X, Kong Y, Duan M, Nei Y, Zeng J, Li B. Structures, fabrication mechanisms, and emulsifying properties of self-assembled and spray-dried ternary complexes based on lactoferrin, oat β-glucan and curcumin: A comparison study. Food Research International. 2020 May 1;131:109048.
54. Szejtli J. Introduction and general overview of cyclodextrin chemistry. Chemical reviews. 1998 Jul 30;98(5):1743-54.
55. Loftsson T, Brewster ME. Pharmaceutical applications of cyclodextrins: basic science and product development. Journal of pharmacy and pharmacology. 2010 Nov;62(11):1607-21.
56. Davis ME, Brewster ME. Cyclodextrin-based pharmaceutics: past, present and future. Nature reviews Drug discovery. 2004 Dec 1;3(12):1023-35.
57. Kang W, Zhang H, Lu Y, Yang H, Zhu T, Zhang X, Chen C, Sarsenbekuly B, Besembaevna OZ. Study on the enhanced viscosity mechanism of the cyclodextrin polymer and betaine-type amphiphilic polymer inclusion complex. Journal of Molecular Liquids. 2019 Dec 15;296:111792.
58. Del Valle EM. Cyclodextrins and their uses: a review. Process biochemistry. 2004 May 31;39(9):1033-46.

59. Simoes SM, Rey-Rico A, Concheiro A, Alvarez-Lorenzo C. Supramolecular cyclodextrin-based drug nanocarriers. Chemical Communications. 2015;51(29):6275-89.
60. Uekama K, Hirayama F, Irie T. Cyclodextrin drug carrier systems. Chemical reviews. 1998 Jul 1;98(5):2045-76.
61. Trotta F, Zanetti M, Cavalli R. Cyclodextrin-based nanosponges as drug carriers. Beilstein journal of organic chemistry. 2012 Nov 29;8(1):2091-9.
62. Prausnitz MR, Langer R. Transdermal drug delivery. Nature biotechnology. 2008 Nov;26(11):1261-8.
63. Williams AC, Barry BW. Penetration enhancers. Advanced drug delivery reviews. 2012 Dec 1;64:128-37.
64. Barry BW. Dermatological formulations. Percutaneous Absorptions. 1983:127-233.
65. Jeong WY, Kwon M, Choi HE, Kim KS. Recent advances in transdermal drug delivery systems: A review. Biomaterials research. 2021 Dec;25:1-5.
66. Sun Y, Du L, Liu Y, Li X, Li M, Jin Y, Qian X. Transdermal delivery of the in situ hydrogels of curcumin and its inclusion complexes of hydroxypropyl-β-cyclodextrin for melanoma treatment. International journal of pharmaceutics. 2014 Jul 20;469(1):31-9.
67. Taveira SF, Varela-Garcia A, dos Santos Souza B, Marreto RN, Martin-Pastor M, Concheiro A, Alvarez-Lorenzo C. Cyclodextrin-based poly (pseudo) rotaxanes for transdermal delivery of carvedilol. Carbohydrate polymers. 2018 Nov 15;200:278-88.