Advances in the transdermal delivery of antiretroviral drugs

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Abstract

Antiretroviral therapy regimens are successful in stopping the advancement of human immunodeficiency virus infection to acquired immunodeficiency syndrome, and other opportunistic infections. However, they do have significant disadvantages, including long-term treatment, limited oral bioavailability, inaccessibility to organs, non-adherence by patients, and the development of medication resistance. Because of the listed drawbacks of available routes and the availability of curative medicines for human immunodeficiency virus/acquired immunodeficiency syndrome, advanced solutions are required. Antiretroviral therapy transdermal delivery is one of the current strategies that have attracted much attention from many researchers. In this narrative review, various in vitro, in vivo, and ex vivo transdermal antiretroviral therapy delivery strategies were reviewed, such as transdermal patches and films, lipid-based nano-delivery systems, microneedles, chemical penetration enhancers, and iontophoresis, which showed promising results. Although the majority of studies on Antiretroviral transdermal delivery have produced hopeful findings, additional in-depth research on passive and physical enhancement techniques, both existing and new, is necessary to fully understand the potential of this route and to make it accessible to human immunodeficiency virus patients.

Keywords

Acquired immunodeficiency syndrome, antiretroviral drugs, human immunodeficiency virus, transdermal delivery

Introduction

Human immunodeficiency virus (HIV) infection develops as acquired immunodeficiency syndrome (AIDS), which has been defined by clinical signs and symptoms.[1,2] For the treatment of HIV infection, which requires lifelong medication, antiretroviral therapy (ART) employs three or more antiretrovirals (ARV) drugs.[3,4] The patients' lifespans and standard of life were greatly improved because of ART.[5,6] Although ART has shown to be effective in combating serious manifestations like AIDS and various infections that are opportunistic, it has substantial drawbacks including lengthy administration, limited oral bioavailability, and potential for enhancing drug resistance.[5,7,8] For instance, the oral bioavailability of tenofovir disoproxil fumarate (TDF) is 25%, that of efavirenz is limited at 40%–50%, and that of zidovudine (AZT) is comparatively low due to first-pass hepatic metabolism (52%–75%), a brief half-life of 1 h. To increase bioavailability and adherence, it is crucial to provide alternative delivery such as transdermal delivery (TDD) for ART with a longer duration of action.[8]

TDD challenges and strategies

It is challenging for drugs to penetrate the skin in reasonable quantities. The stratum corneum (SC), the skin's exterior layer, serves as its primary barrier. Only compounds that can enter SC diffusion through the living epidermis can reach the circulation and show systemic effects.[9,10] Transdermal drug delivery systems (TDDDS) are topically administered drugs in various forms such as patches and films.[9] The key benefit of the TD method is that the medicine can be administered without the need for skilled individuals, and can bypass first-pass metabolism in the liver.[11,12] Simple liquids and

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ointments to multiphase, aided, and nano-technology products are available for skin applications.[13,14]

Various factors affect TDDDS, such as biological (skin situation, age, size of the skin in different regions, and metabolism), physicochemical (skin moisture, temperature, pH, partition coefficient, molecular size, and shape), and environmental (sunlight, cold season, and air pollution).[13,15] Except for medications that have significant potency, medium lipophilicity, and low molecular weight (LMW), SC restricts the systemic distribution of pharmaceuticals. Small molecules (MW $<$ 750 Da) generally have a higher likelihood of being able to penetrate the skin and enter the bloodstream through passive diffusion. This is because smaller molecules have smaller sizes and are more likely to fit through the pores and channels of the skin. Therefore, compounds with LMW may have an advantage in TDDD because they can pass through skin pores and have high solubility and can dissolve in the solvents used in TD patches.[16] Additionally, low melting point (MP) compounds typically have weaker intermolecular interactions between their molecules, which makes it easier for them to dissolve in solvents as well as in lipids of the skin. They frequently exhibit excellent solubility in a wide range of solvents, including those employed in TDDDS.[17] Nevertheless, improvements in delivery methods have increased the number of medicines supplied using TD methods, including hydrophilic compounds and macromolecules.[15,18]

The passive patch administration methods that depended on the relatively simple diffusion of pharmaceuticals were the focus of the previous TDDDS. Active technology patches that get past the skin barrier have made TDDD adaptable to a wider variety of drugs.[19] The development of methods to increase skin permeability is likely to have a significant impact on how the TD transmission pathway develops.[11–13,19,20] Percutaneous absorption can be improved through physical and chemical means.[21] One technique for TD is the use of chemical penetration enhancers (CPE), such as prodrug salification, that interact with skin constituents to improve drug permeability.[13,22] Prodrug salification is important for TDD because it can improve the solubility and permeability of the drug through the skin. It involves attaching a functional group to the drug molecule, which can increase its solubility and improve its ability to penetrate the skin. Additionally, prodrug salification can also reduce the toxicity and side effects associated with the drug, as it may be metabolized more slowly or eliminated more efficiently from the body. Therefore, prodrug salification is an important strategy for improving the delivery of drugs through the skin.[23] Surfactants are frequently included in formulations to help lipophilic medications dissolve lipids inside the SC.[3,24,25] To solve poor penetration concerns, vesicular delivery techniques such as liposomes, niosomes, ethosomes, transferosomes, and nano- or micro-emulsion technologies have recently been developed. TDDD can also be facilitated by the application of physical enhancement methods such as iontophoresis, microneedle (MN), microdermabrasion, electroporation, sonophoresis, ablative laser microporation, and thermal ablation. By altering the physicochemical and hydration characteristics of SC as well as using a carrier mechanism to alter the structure of lipids and proteins in the intercellular channels, they work through three different methods.[8,21] Recently developed types of TD systems for prolonged release are called film-forming formulations. They are employed on the skin as a liquid or semisolid preparation, and as the volatile solvent evaporates, a solid layer forms on the skin.[26]

TDD of ARV

Most ARV drugs are small molecules, which are more likely to pass through skin barriers and enter the bloodstream via passive diffusion.[27] A detailed understanding of the skin and barrier characteristics of SC is essential when developing TDDD for ARV drugs. Drug diffusion and consequently, its movement through the layer of skin is governed by the physical and chemical properties of the drug and the barrier through which the drug diffuses.[22,28] Therefore, to develop efficient TDDDS, it is crucial to comprehend the connection between a compound's physical characteristics and solubility.[18] The most suitable drugs for passive transport via the skin have minimal MW ($<$500 Da), appropriate MP ($<$250 °C), and intermediate $\log^P$ (1–3).[29] As a result, ARV that satisfy these requirements could be developed as TDDDS. A detailed examination of the physicochemical characteristics of the typical small molecule ARV currently on the market reveals that all medications aside from darunavir, lopinavir, and TDF meet the MW requirements for passive transport. Apart from tenofovir alafenamide (TAF), these medications' MP are all $<$250 °C. TDF and TAF are also partially lipophilic based on $\log^P$ values, whereas most ARV are lipophilic ($\log^P > 3$), and lamivudine (3TC), AZT, and emtricitabine (FTC) are extremely hydrophilic with $\log^P < 1$.[8,18,28]

Transdermal films and patches

TD patches are skin adhesive pharmaceutical systems used for systemic treatments or localized treatment of tissues beneath the skin.[30] TD film is utilized as an alternative to TD formulations, which combine the medication with additives that form a film over the skin. A solid material made of polymers that acts as a matrix for the persistent delivery of the medicine to the skin or a residual liquid film that is quickly absorbed in the SC can both be used as the films' basis.[31] The primary adjuvants for film formation include ethyl cellulose (EC), eudragits, and hydroxypropyl methylcellulose (HPMC). To dissolve the medicine and excipients, solvents such as ethanol, methanol/methylene chloride, methanol/ acetone, and mixtures are frequently employed. In the formulation development phase, produced films of polymers

should be evaluated for their physical characteristics such as in vitro release of drugs, ex vivo permeability, homogeneity, swelling properties, thickness, toxic effects, and moisture content.[32]

With the use of permeation enhancers and different polymers, both natural and synthetic, AZT-TD patches were effectively produced through solvent-casting procedures. For AZT-TD patches without a penetration enhancer, a drug release was seen at about 67.42%; however, for TD patches with t-anethole as a permeation enhancer, a drug release was seen at 93.21% at the end of 8 h. Ex vivo tests demonstrated improved AZT release for 8 h with a flux of $614.05 \, g/cm^2/h$.[33]

A study examined the dorsal skin of Wistar rats to assess the ex vivo penetration of TD film containing 2 mg AZT for 8 h. To evaluate the improvement in medication delivery, an iontophoresis approach was applied with a current density of $0.5 \, mA/cm^2$. The outcomes demonstrated that when iontophoresis was used instead of passive permeation, the cumulative amount of AZT increased three times.[8,33]

Investigation of TD patches developed via casting with solvent using Span-80 (Loba Chemie Pvt Ltd., Mumbai) as a permeability enhancer in various medications revealed favorable physicochemical attributes for the polymer ratios of 1:2.5 for 3TC: HPMC, and 1:5 for 3TC: EC. According to in vivo drug uptake tests, about 79.5% of the medication's absorption occurs after 24 h in the form of extended-release of the medicine into the rat's systemic circulation. As a model drug, AZT was used in the study of cross-linked chitosan films with sodium tripolyphosphate that revealed an increase in permeability from $261 \, g/cm^2$ to $965 \, g/cm^2$ at 5% w/w sufficient to attain the therapeutic dose.[34]

By developing transparency patches with acrylate adhesive, suspension patches with silicone and polyisobutylene adhesives, and patches for use in suspension, the in vitro performance of a TD patch containing TAF was also examined. In vitro, permeation tests were carried out using vertical Franz diffusion cells for 7 days. The acrylate-based patches had a maximum flow of $0.60 \, 0.09 \, g/cm^2/h$ and contained 2% w/w TAF and various chemical enhancers. The silicone-based patch with 15% w/w TAF, however, demonstrated the maximum penetration at $7.24 \, 0.47 \, g/cm^2/h$. The TAF target release and duration profile were effectively met by the optimized silicone-based suspension patch approach, which was also determined to be appropriate for weekly drug administration.[29]

Through the use of hydrogel-forming microarray patches (HF-MAP), an additional investigation was conducted on the use of hydroxypropyl-cyclodextrins (HP-CD) to improve the solubility of cabotegravir sodium (CAB-Na) and its impact on TDD. Two different HFMAP formulations, MAP1 (Gantrez S97 + poly (ethylene glycol) 10,000 + Na_2CO_3) and MAP2 (poly (vinyl pyrrolidone) + poly (vinyl alcohol) + citric acid) were combined with these unique reservoirs to develop fully integrated MAP devices, which were tested in both ex vivo and in vivo environments. After 24 h,

the ex vivo skin absorption results for MAP1 and MAP2 revealed that 141 40 g and 342 34 g of CAB-Na, respectively, had been deposited into $0.5 \, cm^2$ of excised newborn pig skin. In comparison to FDA-approved CAB nanosuspension (NS) provided via intramuscular (IM) administration, MAP2 showed a prolonged drug release profile after 24 h of patch application. The TDD of hydrophobic ARV medicines is therefore thought to be a possibility using this tablet-integrated MAP device.[35]

A novel bilayer MAP with a distinctive pattern has been developed as a possible self-administrated TDDDS substitute for cabotegravir (CAB). The innovative MAP has good mechanical qualities and skin penetration abilities and has a high medicine load (3 mg/$0.5 \, cm^2$ of CAB Injectable Long-Acting or its micronized sodium salt) and fast-dissolving tips (8 min). Significantly, this MAP could insert the drug-loaded points in the skin, generating micro-depots, in preclinical in vivo investigations using Sprague Dawley rats. Following a single treatment, both pharmaceutical formulations are gradually released, retaining human therapeutic amounts in rats for 1 month.[36]

Three animal models; mice, beagle dogs, and merino sheep, were thoroughly compared to assess the pharmacokinetics (PK) of TAF implants. In vitro, in mice and dogs, implants were tested that released TAF at various determined release rates. To examine the mechanism behind implant TAF delivery, a PK model that was previously developed and supported by an intravenous (IV) dosing dog study was modified. With zero-order kinetics, TAF in vitro release in the 0.13–9.8 mg/d range was obtained. TAF was released from implants with comparable manufacturing conditions at rates that were not statistically different in mice or sheep but were three times higher in dogs. A two-week creep to C_{max} was seen in dogs for systemic medicine and concentrations of metabolites when two implants were placed in the same subcutaneous pocket, but not in mice. An apparent TAF bioavailability of 9.6 in the single implant groups (relative to the IV group) was obtained by co-modeling IV and TAF implant PK data in dogs, but only 1.5 when both implants were placed into identical subcutaneous pockets. This result provides a basic, transferrable understanding of long-lasting implants for multispecies TAF administration.[37]

Sesame oil and EC were used to formulate a long-acting injectable of TAF-chitosan nanoparticles (NP) of polymer-filled oleogels for extended drug release. Spray-drying was used to formulate chitosan NP with 49% drug concentration. The drug-loaded chitosan NP have been incorporated into the heat–cool method to produce the EC and sesame oil oleogels. The oleogels demonstrated prolonged drug release (56%) for 16 days. Additionally, due to the medication's extended-release through two barriers, chitosan NP and EC gel matrix, ex vivo permeation experiments of the NP-loaded oleogels showed a roughly 10-fold decrease in the flux and penetration of the drug. The outcome demonstrated the possibility of using the developed TAF-chitosan polymeric NP

loaded with EC oleogels as an extended injectable approach for ART.[38]

Using a low frequency cymbal transducer, the ultrasound-mediated TDD investigation assessed enfuvirtide (T-20), an injectable ARV drug, over one month in a pig model. Saline ultrasound control, T-20 injection control, and T-20 ultrasound treatment, were the three groups that received twice-daily therapy. The following ultrasound settings were used: $90 \, mW/cm^2$, 24–26 kHz, and 15% duty cycle during a 30-min exposure. For either the saline or T-20 groups, there was no apparent difference in TD water loss, an estimate of skin health and function, between ultrasound-treated and control epidermal areas. For ultrasound and injection, the average peak plasma levels of T-20 were 0.6 0.2 and 2.8 0.8 mg/mL, respectively. Prolonged low-frequency ultrasound exposure can be a workable method for TDD of ARV such as T-20, according to studies on tolerability and effectiveness.[39]

Chemical penetration enhancers

CPE improve penetration function by dissolving medicines in the lipophilic barrier layer or by disturbing the lipid matrix packing in the SC to increase the absorption of pharmaceuticals in the skin. Alcohols, glycols, sulphoxides, surfactants, and other substances have all been thoroughly investigated for their capacity to improve skin penetration.[8,40,41] It has also been shown that the formation of polymeric ethylene glycol carbonate using AZT as a prodrug increases its flow through the skin of humans by an amount of 2–4 times.[8,42]

Tenofovir (TNF) was used as a model medication in the study of unsaturated fatty acid (UFA) esters of cholesterol (Chol), oleate, linoleate, and linolenate as TD CPE. All Chol-UFA esters at 1% w/w were discovered to be superior as more efficient enhancers when compared to their corresponding parent fatty acids (FA) and saturated FA counterparts. The performance of cholesteryl linolenate (Chol-LLA) was the most effective, with an enhancement ratio (ER) of 3.71. Chol-LLA's highest ER (5.93) was attained at a concentration of 2% w/w. According to the study, TNF enters the skin through both paracellular and intercellular pathways to reach dermal blood vessels. Chol-LLA is a better permeability enhancer due to attributes such as improved lipophilicity, desirable carbon chain length, and the appropriate amount of double bonds. The possible applications of UFA such as palmitoleic acid (PA), linoleic acid (LA), linolenic acid (LLA) and arachidonic acid (AA), and their newly produced dendritic esters [PA1E, LA1E, LLA1E, and AA1E] have had basic tertiary nitrogen as a branching component as TD enhancers of permeation for the administration of TNF have also been examined. Only PA and LLA among the UFA showed TD enhancement potential through ER of 1.35 and 2.9, respectively. When compared to their parent UFA, all synthetic analogs at 1% w/w showed greater effectiveness as enhancers that with LLA1E being the best (ER = 5.31). Additionally, the level of concentration impact analysis showed that LLA1E had a higher ER (6.11) than its parent (ER = 3.85) at 2% wt.[43]

Lopinavir (LPV) was designed as a convenient metered-dose TD spray using CPE and physical penetration enhancing methods in combination. The film-forming polymer and CPE agents used were Kollidon VA 64 and isopropyl myristate, respectively. As a physical mode, MN roller was employed to penetrate the SC. Through the ex vivo microporated pig ear skin, a considerable high TD flux of $52.5 \, g/cm^2/h$ and permeability ER of 1.77 were observed. Compared to the oral suspensions of commercial tablets, in vivo bioavailability studies revealed a significant three-fold increase in relative bioavailability using the TD route.[44]

Apart from AZT, only a small number of ARV drugs have been investigated for TD delivery using CPE methods. The same permeation enhancers used with AZT were employed to evaluate FTC for TD delivery. The permeability enhancer spheroids efficiently cross the SC. Carbamates have been used as permeation enhancers for 3TC, improving their solubility in water while keeping lipophilicity constant. Similar improvements in permeability to AZT were also seen in polymeric ethylene glycol carbonate, which increased drug flux through the skin by two to four times.[2,18]

Lipid-based nano-delivery systems

The development of ARV TDDS may benefit from the adoption of sophisticated formulation techniques for drug formulation in lipid-based vesicular administration. Liposomes operate as enhancers of penetration by disrupting the lipid matrix of the SC via the lipid fusion process because of their distinct chemical composition.[45,46] Transferosomes can move through the hydrophilic pathways that develop in the skin because of their ultra-conformability and adaptability due to the combination of lipids and biocompatible membrane plasticizers.[47]

Ethosomes are flexible, soft vesicles that can carry hydrophilic and lipophilic medications more effectively than conventional liposomes. In comparison to the drug-only, ethanolic drug, and standard liposomal groups, indinavir-loaded ethosomes showed a 9-, 2-, and 4-fold larger TD flow across human cadaver skin, respectively. Additionally, it has been identified that ethosomal TD preparations comprising 3TC may pass through the rat skin 25 times faster than 3TC solutions.[8]

Microneedles

The SC layer can be efficiently penetrated by MN to deliver medications to the deeper skin layers. To enhance drug transport, they make hydrophilic small channels in the top layers of the skin.[48] Different kinds of MN, including coated,

dissolving, hollow, and solid ones, have been produced and investigated.[49,50] Additionally, they can be produced in lengths ranging from 25 to 2000 μm to achieve a tailored medication administration.[51] When a drug-coated MN is introduced into the skin, the drug coating dissolves in the aqueous layer of the skin. Drug-loaded MN dissolve into the skin as they dissolve and are made of water soluble or biodegradable polymers. Furthermore, liquid formulations are delivered into the skin using hollow MN.[52]

It is interesting that Kollidon VA 64, BASF, Mumbai a film-forming agent, and isopropyl myristate, a penetration enhancer, were used to produce a metered dosage TD spray of LPV. The findings demonstrated that the dermaroller (2 mm long MN) microporated pig ear skin had a substantially greater permeation ER of 1.77 and a steady-state flow of 52.5 g/cm²/h of LPV than untreated skin.[44]

Another study examined the in vitro penetration of 3TC-loaded polymeric NP through both untreated and MN-treated rabbit skin. The NP were made using polylactic co-glycolic acid and bovine serum albumin. Relative to the untreated passive flux, the treated group doubled the steady-state flow of 3TC in the NP group.[53]

Physiologically based pharmacokinetic (PBPK) modeling was used in a study to estimate the PK response to islatravir (ISL) given by MN array patches (MNAP). For orally administered ISL in healthy individuals, a PBPK model explaining the transformation of ISL to ISL-triphosphate (ISL-TP) and its whole-body disposition was produced and validated using actual clinical findings. At 3, 6, and 12 months following injection, ISL MAP dosages ranging from 15 to 80 mg were expected to keep ISL-TP contents over the minimal therapeutic concentration. It was determined that the NP release rate and MNAP bioavailability had a significant influence on whether dosing techniques met the requirements. To attain effective ISL-TP concentrations for up to 3 and 6 months, respectively, minimum dosages of 15 mg and 60 mg with NP release rate of 0.0005/h and bioavailability ranging from 25% to 100% were expected to be necessary. Additionally, 80 mg ISL MNAP was expected to maintain ISL-TP levels above the minimal therapeutic concentration for up to 12 months after delivery when a bioavailability of 100% was simulated. The combined TD PBPK model motivated more research into ISL as a potential MNAP administration candidate by outlining the ideal MNAP dose and NP release rates for effective ISL-TP concentrations up to 12 months.[54]

TAF-loaded dissolving and implantable MNAP were formulated to systemically deliver the medicine. In vitro release tests carried out on dialysis membrane models showed that medicine was always delivered rather quickly. According to Franz cells investigation, after 24 h, dissolving and implantable MNAP deposited 47.87 ± 16.33 g and 1208.04 ± 417.9 g of TAF in the skin. MNAP could therefore be utilized in place of existing oral ART.[55]

The systemic PK of CAB and rilpivirine (RPV) MNAP through the TD route was also simulated using a unique PBPK model. The generated models of PBPK were validated using actual PK results from rats receiving IM and TD doses of extended nano-formulated RPV as well as IM doses of both medications to adults who were healthy. For a 70 kg adult, PBPK models predicted loading and maintenance doses for long-acting formulated CAB of 360 mg and 180 mg per four weeks, respectively, at release rates of 1×10^{-3}–3×10^{-3}/h and 1×10^{-3}–1.5×10^{-3}/h. For a 360 mg dosage of CAB, an estimated patch size of 60 cm² was used. RPV needed a 1080 mg pushing dose and a 540 mg preservation dose for q4-weekly administration, with release rates of 1.5×10^{-3}–2.5×10^{-3}/h and 5×10^{-4}–1×10^{-3}/h, respectively.[56]

A wet medium milling approach was used to produce a new bilayer dissolving MN for TDD of long-acting NS of bictegravir (BIC). The dissolving MN was capable of enabling TD to deliver 31% of the loading of drugs from NS-loaded MN in the manner of pharmaceutical depots, according to the PK profiles of Sprague Dawley rats. Both coarse BIC and BIC NS exhibited prolonged release after a single application, keeping plasma concentrations in rats above the human therapeutic threshold (162 ng/mL) for four weeks. These simple and maybe self-administered MN may offer an attractive framework for the delivery of nano-formulated ARV, which prolongs the time that the medicine is released from the body.[57]

To increase patient adherence, dissolving MN integrated with etravirine NS (ETR NS) was produced via sonoprecipitation. After being applied for 6 h, the dissolving MN filled with ETR NS produced $12.84 \pm 1.33\%$ ETR depositions in ex vivo neonatal pig skin. The C_{max} demonstrated by dissolving MN filled with ETR powder and ETR NS were 158 ± 10 ng/mL and 177 ± 30 ng/mL, respectively, in in vivo rat PK experiments. Compared to IV ETR solutions, dissolving MN groups showed larger $t_{1/2}$, T_{max}, and mean residence times, showing the long-acting potential of ETR-administered TD using dissolving MN.[58]

Iontophoresis

Iontophoresis employs an electrode with the same charge as the drug molecule to drive drug molecules through the skin at a low voltage (10 V) and low current density (0.5 mA/cm²).[20] It enhances permeation into the skin through three mechanisms: electro-osmosis, which causes the entire movement of the solvent itself and introduces ions or neutral species into the solvent stream; the interaction between ions and the electric field, which adds a force to drive ions through the skin; and the flow of electric current that improves permeability via skin.[14,59] The main processes for increasing drug transport across the skin and into the systemic circulation during iontophoresis are electromigration and electro-osmosis (Figure 1).[60]
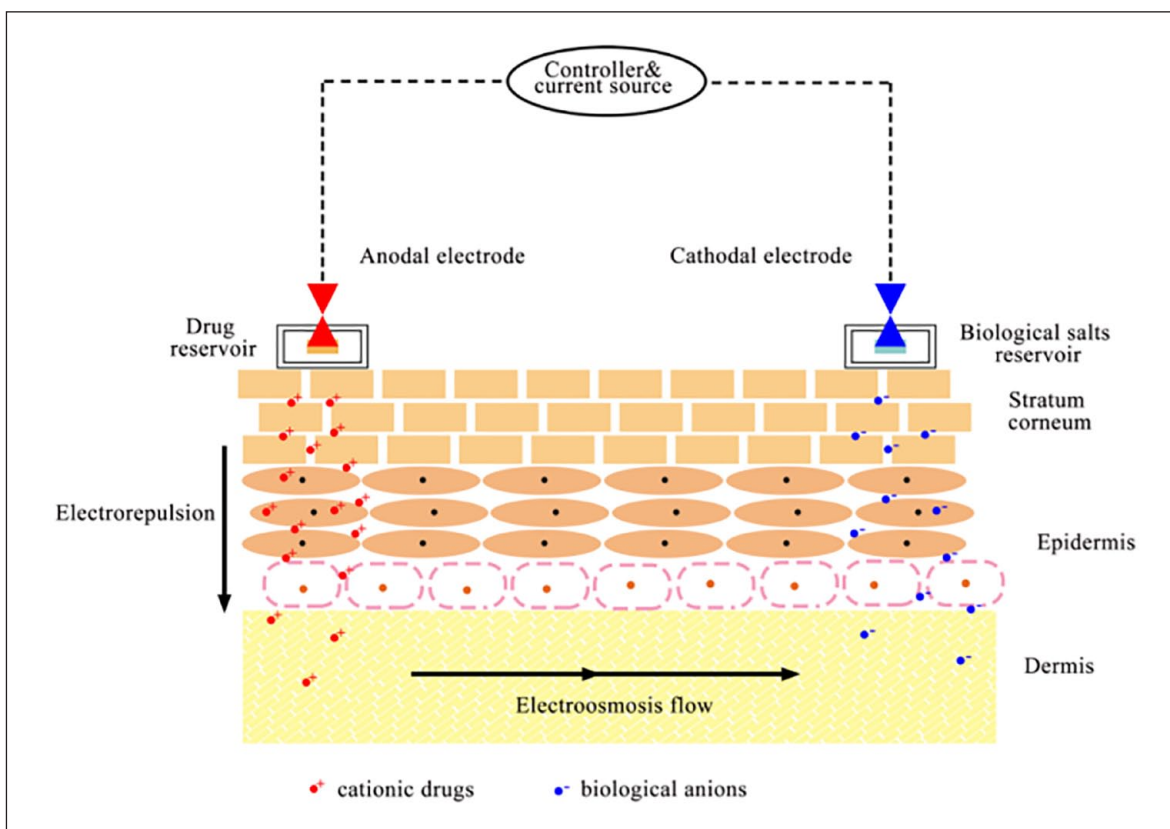
Figure 1. Schematic diagram of the iontophoretic technique.

The electro-osmotic flow, which is always from the anode to the cathode due to the negatively charged nature of human skin, is determined by the direction in which the cations migrate. This makes electro-osmosis anodic release of cations easier while impeding its cathodic release of anions.[33] Iontophoresis is mostly used with hydrophilic medicines because it requires the medications to be water soluble. Water solubility makes FTC, TAF, TDF, AZT, and 3TC suitable candidates for iontophoretic administration. However, by complexing lipophilic medications with anionic cyclodextrins or encapsulating them in charged solid lipid NP or nano-structured lipid carriers, the iontophoretic transport of lipophilic pharmaceuticals could be investigated. In addition to solubility, formulations must have a pH between 4 and 8 to be close to the physiological pH of 7.4 and the pH of the skin surface, which prevents skin irritation.[61]

According to its pKa, the basic medication AZT (pKa: 9.55) is ideal for anodic iontophoresis because it is positively charged at a pH lower than its pKa. However, lowering the pH of the formulation below the pKa of other hydrophilic medications like FTC (pKa: 2.65, basic medicine) and 3TC (pKa: 4.3, basic drug) might irritate the skin. According to its pKa, the basic medication AZT is ideal for anodic iontophoresis because it is positively charged at a pH lower than its

pKa.[11] The amount of AZT that permeated through the skin of rats using monolithic films made with various ratios of Eudragits RL 100 and EC was two to four times greater after anodic iontophoresis ($0.5\,mA/cm^2$ for 3 h) than it was in passive delivery.[8]

Sonophoresis was used to prepare the skin, which greatly enhanced AZT transfer and decreased lag time. The largest overall amount penetrated roughly $624\,g/cm^2$, was obtained when using sonophoresis in continuous mode with 20% amplitude and a 2 min application period. The maximum flux was $27.52\,g/cm^2/h$. The use of MN further increased the flux to $30.41\,g/cm^2/h$, and the total amount permeated to $916\,g/cm^2$ relative to sonophoresis alone.[62]

Limitations

Although this narrative review is of the utmost relevance for scientific audiences to conduct in-depth research on novel ART delivery methods in comparison to conventional delivery to increase their effectiveness and reduce their adverse effects, this review has its limitations. As a narrative review, it lacks a systematic conclusion and a tallied outcome that would allow for the selection of additional research, including clinical trials and the production of the investigated ARV medications. Furthermore, the search

approach was not systematic, and other studies may have been discovered in various databases but were not probably included in this study.

Future perspective

The increasing incidence of multidrug-resistant virus strains, toxicity, drug–drug interactions, challenging treatment regimens, and inadequate bioavailability complicate the traditional delivery of ART. Therefore, there is an urgent requirement for the development of novel ARV delivery methods and treatments. Using various novel TDDDS could be one way of strategy to develop an efficient HIV treatment, which has attracted the attention of many researchers. Many researchers have found various TDDDS using different techniques that increase the permeation of drugs through SC. However, to fully comprehend the potential of this approach, it is necessary to thoroughly evaluate the existing and emerging passive and physical augmentation methods of ARV TDD.

Conclusions

TDD is a method that can provide prolonged ARV drug delivery with simple application and would overcome many problems with the oral route. Utilizing various penetration-enhancing methods, including CPE, iontophoresis, lipid-based nano-delivery systems, MN, TD films, and patches, many TD ARV drug delivery systems have been studied. In this review, various formulation strategies for 3TC, AZT, BIC, CAB, ETR, FTC, IDV, ISL, LPV, T-20, TAF, TDF, and TNF were examined, which were encouraging. It is especially interesting to look at the research on iontophoresis, TD films, and vesicular carriers for AZT TD delivery for HIV treatment because it demonstrated the feasibility of looking at different ARV medications utilizing TDDDS.

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