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Current and emerging formulation strategies for the effective transdermal delivery of HIV inhibitors

Current and emerging formulation strategies for skin permeation are poised to open the transdermal drug delivery to a broader range of small molecule compounds that do not fit the traditional requirements for successful transdermal drug delivery, allowing the development of new patch technologies to deliver antiretroviral drugs that were previously incapable of being delivered through transdermal means. Transdermal drug delivery offers several distinct advantages over traditional dosage forms. Current antiretroviral drugs used for the treatment of HIV infection include a variety of highly active small molecule compounds with significantly limited skin permeability, and thus new and novel means of enhancing transport through the skin are needed. Current and emerging formulation strategies are poised to open the transdermal drug delivery to a broader range of compounds that do not fit the traditional requirements for successful transdermal drug delivery, allowing the development of new patch technologies to deliver antiretroviral drugs that were previously incapable of being delivered through transdermal means. Thus, with continuing research into skin permeability and patch formulation strategies, there is a large potential for antiretroviral transdermal drug delivery.

The challenges of transdermal drug delivery

The expanding transdermal drug delivery market is expected to reach \$32 billion in 2015 from a market worth \$12.7 billion in 2005 [1]. Yet, only 12 drugs comprise this entire commercial transdermal product market [2]. Since 1979, when scopolamine was approved by the US Food and Drug Administration (FDA) for the treatment of motion sickness [3], clonidine, estradiol, levonorgestrel, fentanyl, granisetron, methylphenidate, nicotine, nitroglycerin, oxybutynin, rivastigmine, selegiline and testosterone have been approved for use in humans [2,4–6]. The small number of approved products constituting this group of approved drugs is primarily related to the selective nature of the skin barrier. The skin barrier limits the systemic delivery of drugs at therapeutically relevant rates to those that have high potency, moderate lipophilicity and low-molecular weight [7]. However, a large number of drugs

do not conform to these selective physico-chemical and bioactivity criteria. Despite this, advances in delivery technologies have resulted in an increasing number of drugs being administered transdermally including hydrophobic small molecules, hydrophilic molecules and macromolecules. Recently, patents have been issued in transdermal delivery systems for antiemetic medication, transdermal buprenorphine to treat pain resulting from sickle cell crisis, transdermal delivery of nonsteroidal anti-inflammatory drugs and a transdermal delivery system for water insoluble drugs [6]. Transdermal delivery is also currently being investigated as the formulation vector for topical pain relief, hormone therapy, cardiovascular disease, anti-inflammatory and anti-HIV therapy [8–11]. Despite the significant development challenges of drug delivery through the skin, transdermal drug delivery remains a significant and attractive area of research to the pharmaceutical industry for a variety of

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Key term

Skin permeability: Rate of drug concentration transport from the formulated dosage form into the epidermal tissue over time and volume of tissue.

reasons. Transdermal products are attractive because they offer numerous advantages over other routes of drug delivery. One of the largest qualitative advantages of transdermal delivery is the convenient administration of drug. Transdermal delivery eliminates frequent dosing administration and pharmacokinetic ‘peaks and valleys’ in plasma drug concentrations associated with oral and intravenous injectable products. Transdermal delivery provides a constant and sustained release of drug through the skin to maintain a stable drug concentration in the blood. Thus, even drugs with a short plasma half-life can be easily delivered via a transdermal route. Additionally drugs with limited plasma half-life could be administered transdermally at a more frequent regimen to compensate for the limited bioactivity of drug delivered from the dosage form. Additionally, formulations such as transdermal patches allow for the simultaneous dosing of multiple drug products, on-demand or variable-rate drug delivery, and are compatible with most drug regimens. Another advantage to transdermal delivery is the avoidance of hepatic first-pass metabolism and gastrointestinal tract exposure. The avoidance of first-pass metabolism allows for a lower amount of drug to be administered resulting in reduced potential for adverse side effects. All these advantages of transdermal administration of drugs importantly contribute to an overall increase in patient adherence to transdermal drug delivery over other forms of drug delivery [12–15].

The challenges of transdermal delivery of HIV inhibitors

Over thirty antiviral drugs have been approved for use in HIV-1-infected patients [16] with vast majority of drugs being small molecules ($MW \leq 750$ Da). The FDA approved list includes (Table 1): nucleoside reverse transcriptase inhibitors (NRTIs) (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir disoproxil fumarate and zidovudine), non-nucleoside reverse transcriptase inhibitors (NNRTIs) (delavirdine, efavirenz, etravirine, nevirapine, dapivirine and rilpivirine), protease inhibitors (PIs) (atazanavir, darunavir, fosamprenavir, nelfinavir, ritonavir, saquinavir and tipranavir), fusion inhibitors (FIs) (enfuvirtide), entry inhibitors (EIs) (maraviroc) and integrase inhibitors (IIs) (dolutegravir and raltegravir). In addition, a wide variety of small molecule compounds targeting both well-defined as well as novel viral and cellular targets continue in preclinical and clinical development (Table 1) [17–19].

To design a transdermal drug delivery system for HIV inhibition, a thorough understanding of the skin and the barrier properties of the stratum corneum is critical [20]. Transport across the skin is primarily driven by diffusion, which is governed by the physicochemical properties of the drug and the barrier through which the drug diffuses. The drug diffuses from the dosage form to the surface of the stratum corneum boundary layer and partitions into the lipid and tissue domains of the lower epidermis and dermis layers. The diffusion of drug is controlled by its **skin permeability** or the rate at which drug concentration transports into the epidermal tissue. The drug then diffuses through the dermal lipid layers into the microcirculation provided by the local capillary network, which provides an infinite sink for drug absorption. This repeated diffusion-partition process drives the transport of drug into and out of the dermal tissue. Drugs which have been successfully delivered through the skin share similar physicochemical properties, which include low molecular weight, possession of both lipophilic and hydrophilic phases and a low melting point. Since drug delivery through the skin is diffusion driven, the molecular weight of the drug administered has a significant impact on delivery; with smaller molecules having a greater rate of delivery over large molecules. With approved and experimental HIV inhibitors, the majority of the drugs are below 1000 Da (with the exception of Fuzeon (Table 1). Optimal drugs for transdermal drug delivery are ones that contain both lipophilic and hydrophilic phase in order to pass through both the stratum corneum and lipid-rich dermal layer to the underlying capillary system. This transport and partition is defined by the partition coefficient (Log P) and the solubility (melting point). It is well recognized that the lower the melting point of a material, the greater its solubility in a given solvent – including solubility in skin lipids. In the case of HIV inhibitors, with the exception of DRV, TPV and T-20, the melting points of all the drugs exceeds 100°C. However, the one factor that has the greatest influence on drug transport through the skin is the ability of the drug to partition into the tissue. Typically, drugs with Log P values in the range of 2–3 show optimal permeability across the stratum corneum as well as moderate partitioning out of the stratum corneum. Conversely, drugs with a Log P > 3 are expected to exhibit high partitioning into the stratum corneum but poor partition into the systemic circulation [21]. Lipophilic drugs have a higher residence time and thus a lower systemic exposure rate. Most of the current HIV inhibitors have Log P values exceeding 4.0, and coupled with their high melting points are insoluble small molecules that show high partitioning into the stratum corneum (Table 1). As a direct result of these physicochemical properties, currently there are no transdermal products

Table 1. HIV inhibitor transdermally relevant physicochemical properties.

	Name	ABV	MW (Da)	LogP	MP (C)
NRTI	Abacavir	ABC	286.33	0.9	165
	Didanosine	ddl	236.23	-1.24	160
	Emtricitabine	FTC	247.25	-0.6	136
	Lamivudine	3TC	229.26	-0.9	160
	Tenofovir disoproxil fumarate	TDF	287.21	1.25	276
	Zidovudine	AZT	267.24	0.05	106
NNRTI	Delavirdine	DLV	456.56	2.34	226
	Dfavirenz	EFV	315.67	4.7	139
	Etravirine	ETR	434.05	4.5	265
	Nevirapine	NVP	266.3	2.0	247
	Dapivirine	TMC-120	329.4	4.8	219
	Rilpivirine	RPV	366.42	4.5	242
PI	Atazanavir	ATV	704.86	5.6	195
	Darunavir	DRV	547.66	2.9	74
	Fosamprenavir	IDV	585.61	1.8	282
	Nelfinavir	NFV	567.78	5.7	350
	Ritonavir	RTV	720.94	6	120
	Sasquinavir	SQV	670.84	4.2	350
	Tipranavir	TPV	602.66	7	86
FI	Enfuvirtide	T-20	4491.88	-14.7	N/A
EI	Maraviroc	MVC	513.66	5.1	197
II	Dolutegravir	DTG	419.38	2.4	188
	Raltegravir	RAL	444.42	1.1	155
Under development	IQP-0528	–	340.42	4.1	216
	UC-781	–	335.85	4.9	157
	ISIS 5320	–	2584.09	-4.6	

available for the treatment of infectious diseases such as HIV. The clinical experience with all HIV agents has clearly demonstrated the ability of HIV to evade the antiviral effects of any monotherapeutic drug administration strategy through the rapid accumulation of amino acid changes in the targeted proteins [22]. The highly error prone HIV reverse transcriptase, with its lack of proof-reading capability, generates significant heterogeneity within the highly related but nonidentical populations quasispace of viruses circulating in a patient [23]. It is widely accepted that most drug resistant viruses pre-exist within the population of viruses and are selected from within this heterogeneous environment upon application of selective drug pressure. In addition to the high levels of resistance possible to single agents, each of the anti-HIV agents employed to date have had significant dose limiting and long-term toxicities which render suc-

cessful long-term therapy for HIV disease difficult to achieve [22]. It is clear that the continued development of new agents with enhanced potency, reduced toxicity and a greater genetic barrier to resistance, as well as targeting other HIV replication steps, is an important need for the continued effectiveness of HIV therapy. In addition, simplification of patient dosing regimens and enhancements in adherence to drug regimens would provide significant long-term advantages to populations of infected individuals. Transdermal drug delivery would be a suitable strategy to avoid many of these problems by eliminating pharmacokinetic peaks and troughs in drug levels which enable resistant viruses to escape drug selective pressure when concentrations fall below effective levels [24]. Furthermore, transdermal administration of multiple drugs is possible using patch technologies, with the ability to control the rate of delivery of indi-

vidual drug components and overall plasma drug concentrations. Resistance and toxicity is further controlled by sustained drug concentrations for prolonged periods of time while the patch effectively delivers drug in the absence of the peaks of drug concentration associated with adverse effects.

In administering small molecules as therapeutic agents, one of the biggest obstacles to effective treatment is drug bioavailability. In studies with Zidovudine (AZT), the first anti-HIV compound approved for clinical use, the therapeutic effectiveness of the drug was significantly limited due to its dose-dependent hematological toxicity, low therapeutic index, short biological half-life and relatively poor bioavailability [25]. Additionally, due to first-pass metabolism, oral bioavailability was low and the dosage required to maintain therapeutic levels often resulted in toxic levels of AZT in the blood and other side effects [26]. Therefore, transdermal drug deliveries were investigated to potentially deliver anti-HIV drugs such as AZT through the skin. A variety of strategies to transdermally deliver drugs has been and continues to be evaluated for HIV specific inhibitors.

Current transdermal delivery strategies

Until recently, the transdermal delivery field was primarily focused on passive patch delivery technologies that relied upon simple diffusion of a pharmaceutical product across the skin barrier. Emerging active technology patches that 'drive' a drug through the skin barrier have opened transdermal drug delivery to a broader range of compounds that do not fit the traditional requirements for successful transdermal drug delivery, allowing the development of new active patches to deliver antiretroviral drugs that were previously incapable of being

delivered through transdermal means. In addition, new strategies are also being developed with current passive patch technology to increase the utility and application of transdermal drug delivery.

Successful dermal administration must ensure the delivery of a drug through the stratum corneum, which is an organ designed to selectively act as a barrier to keep things out of the body. Transport through the epidermis is primarily diffusion driven, governed by the physicochemical properties of the drug and the barrier itself [27]. The drug released from the patches diffuses through the boundary layer (stratum corneum) to the underlying dermal layer and then into the blood vessels (Figure 1). The rate and ultimate success of a drug to diffuse through the skin is largely dependent upon its molecular weight, partition coefficient (Log P), solubility and polarity. Therefore, for dermal administration to be successful for any potential drug, the drug product ideally should be a small molecule with a molecular weight of 500 Da or less with high lipophilicity to permeate through the skin [7]. Depending on the eventual target of the transdermal delivery, which may be either local to the skin or to the systemic circulation, the melting point and partition coefficient of the drug is important in determining the drug compound's suitability for transdermal delivery by defining whether the drug will be partitioned within the dermis or will transit through the stratum corneum and dermis and thus partition out of the tissue and be absorbed into the systemic circulation [21].

In considering transdermal delivery as a possible means of drug dosing, it is important to understand the various components of delivery from the patch. First, the drug must be released from the dosage form, which is controlled by the specific formulation utilized, and then the drug permeates through the skin, which is

Figure 1. Illustration of transdermal delivery through intact skin.

controlled by the skin and physicochemical properties of the drug. As such, there exist several types of transdermal dosage forms which may be used to control drug release from the patch (Figure 2):

- Single-layer drug-in-adhesive is the most basic formulation where the rate of drug release from the patch is dependent on the diffusion of the drug product across the skin;
- Multilayer drug-in-adhesive formulations encompasses products with either the addition of a membrane between two distinct drug-in-adhesive layers or the addition of multiple drug-in-adhesive layers under a single backing film;
- Drug reservoir formulations are comprised of an inclusion of a liquid compartment containing a drug solution or suspension separated from the release liner by a semipermeable membrane and adhesive;
- Drug matrix formulations include a semi-solid matrix containing a drug solution or suspension [28–30].

Current research in transdermal drug delivery of HIV antiretroviral products has been primarily focused on the addition of permeability enhancers to the formulation. This strategy allows for the use of existing

Key term

Drug partitioning: The measure of the difference in solubility of a compound between two immiscible (hydrophobic / hydrophilic) phases. Drug partitioning or partition coefficient (LogP) is determined by the following:

$$\log P_{\text{octanol/water}} = \log \left(\frac{[\text{solute}]_{\text{octanol}}}{[\text{solute}]_{\text{un-ionised water}}} \right)$$

The LogP value is known as a measure of lipophilicity.

dosage forms as described above while addressing the second stage of transdermal drug delivery, namely the transport of the drug product through the skin barrier after its release from the formulated patch. In the development of HIV transdermal delivery technologies, chemical and physical permeability enhancers have been utilized in the patch to investigate the relative transport of the antiretroviral agent through the skin once released from a patch dosage form.

The use of passive permeability enhancers in transdermal delivery

Chemical permeability enhancers facilitate drug transport through the skin by increasing **drug partitioning** into the stratum corneum, increasing drug diffusion through the stratum corneum, or a combination of both physicochemical effects [31]. There are several categories of permeability enhancers [32] that were tested

Figure 2. Types of transdermal patch formulations. (A) Single-layer drug-in-adhesive: the rate of release is dependent on the diffusion across the skin. (B) Multi-layer drug-in-adhesive: encompasses either the addition of a membrane between two distinct drug-in-adhesive layers or the addition of multiple drug-in-adhesive layers under a single backing film. (C) Drug reservoir: the inclusion of a liquid compartment containing a drug solution or suspension separated from the release liner by a semipermeable membrane and adhesive. (D) Drug matrix: inclusion of a semisolid matrix containing a drug solution or suspension.

in conjunction with the HIV inhibitor AZT, which is the most common HIV drug thus far evaluated in the investigation of transdermal patch anti-HIV drug delivery. Aprotic solvents such as *N*-methyl-2-pyrrolidone have been shown to enhance plasma concentrations of AZT for 10 h [33]. Carvacrol, *t*-anethole, thymol, linalool, *t*-menthol have been shown to enhance AZT transport through the stratum corneum at 5% drug concentrations. Solvents as permeability enhancers increase skin penetration by utilizing the polar pathways and/or fluidizing lipids. Other permeability enhancers added to AZT-containing transdermal patches include propylene glycol, oleic acid, sodium dodecyl [34], ethanol/water [35–37], various binary solutions [38], carbonate prodrugs [39] and liposomes [40,41]. Other than solvents, the primary permeability enhancers are surfactants which are classified according to the nature of their polar head group. Surfactants absorb to the skin interface and serve to bind to and denature skin surface proteins. Surfactants then solubilize the intercellular lipids of the skin to permit enhanced penetration of the transported drug through pathways between the cells. The primary concern with the use of surfactants as transdermal permeability enhancers include skin toxicity and irritation [42].

Other than AZT, relatively few HIV inhibitors have been investigated using transdermal delivery [43]. Zalcitabine (ddC) and Didanosine (ddI) have been investigated for transdermal delivery using the same permeability enhancers as utilized with AZT [35–37,44,45]. For these compounds, the permeability enhancer Pheroid was shown to effectively transport the nucleoside RT inhibitors across the skin barrier [46]. With Lamivudine (3TC), MPEG carbamates were used as a permeability enhancer for transport through the stratum corneum, and the formulation was shown to increase aqueous solubility while still maintaining constant lipophilicity. Polymeric ethylene glycol carbonates also showed similar permeability enhancement with AZT with an increase of 2–4-fold in drug flux through the skin [39]. These permeability enhancers have also been integrated into current transdermal patch formulations [34,47] and gel formulations [48,49].

The use of active permeability enhancers in transdermal delivery

Systematic innovations such as iontophoresis have been used to actively drive the transport of small drug molecules across the skin barrier [47,50]. Iontophoresis is a strategy of permeability enhancement using a repulsive electromotive force through the skin via an electric charge [51]. With AZT, iontophoresis was shown to enhance *in vitro* permeation by 5- to 40-fold over that of passive diffusion [47].

Emerging transdermal delivery strategies

While no current investigations of antiretroviral inhibitors are being conducted with emerging transdermal strategies, there are several strategies that show potential in providing enhanced delivery of antiretroviral agents. Dissolvable microneedles are an emerging strategy that is minimally invasive and which serves to bypass the stratum corneum barrier to permit the drug's direct access to the viable epidermal layer of the skin. These novel microdevices have been developed to puncture the skin to facilitate the transdermal delivery of hydrophilic drugs and macromolecules, including peptides, DNA and other molecules, that would otherwise have difficulty passing the outermost layer of the skin, the stratum corneum [52–55].

Dissolving microemulsion hydrogels have also been investigated as a method of delivering poorly permeable and low bioavailability compounds [56,57]. Hydrogels are solid dosage forms that completely dissolve over time when applied to the skin. Hydrogels offer advantages over other semisolid dermal formulations such as creams and gels by acting as a drug depot for sustained drug delivery [58]. Microemulsion hydrogels also represent an alternative to traditional transdermal patch formulations by eliminating the persistence of the patch backing when applied to the skin.

HIV inhibitors & transdermal drug delivery

Despite promising data suggesting the successful use of these permeability enhancers with HIV inhibitors, one of the primary problems with anti-HIV compounds and transdermal delivery has been that research has been performed with relatively low potency inhibitors such as AZT, ddC, ddI and 3TC as opposed to compounds that are effective in picomolar to low nanomolar concentration ranges, such as the highly active nonnucleoside reverse transcriptase inhibitors (NNRTIs).

We have worked extensively with a family of NNRTIs being investigated as potential therapeutic and prevention products based on their bioactivity and safety profile. The pyrimidinedione class of inhibitors are highly potent (sub- to low-nanomolar active concentration ranges) small molecule inhibitors that have a dual mechanism of action against HIV infection. The pyrimidinediones primarily act as steric inhibitors of viral reverse transcriptase by binding to the hydrophobic nonnucleoside binding pocket on the RT, but possess a secondary undefined effect on HIV entry [59]. The pyrimidinedione IQP-0410 was identified as a highly potent (TI > 1 million) antiretroviral therapeutic agent, which was being developed as a product for the treatment of HIV-infected individuals [59,60]. Transdermal

delivery of IQP-0410 was considered in light of the rapid first-pass metabolism and short plasma half-life (~5 h) of the drug product. Thus, bypass of hepatic clearance of IQP-0410 was determined to be essential for continued development of IQP-0410 as an effective HIV inhibitor. In considering a transdermal drug delivery strategy for IQP-0410 (and other antiretroviral products), the appropriateness of the compound for dermal transport was carefully evaluated. Successful delivery of any antiretroviral agent through the skin is largely dependent upon having a compound of an appropriate molecular weight, partition coefficient (Log P), solubility and polarity. IQP-0410 is practically insoluble and has a molecular weight of 352.43 g/mol. With a calculated Log P of 3–4, IQP-0410 is nonpolar and thus lipophilic [21]. *In vitro* antiviral evaluations demonstrated that IQP-0410 was efficacious at subnanomolar concentrations against HIV-1 (0.28 nM) with a resulting therapeutic index of greater than 500,000 [60]. However, *in vivo* PK and bioavailability studies in mice have shown that IQP-0410 only has a 24% oral bioavailability with a half-life of 5.37 h and an intravenous half-life of 30 minutes. This short systemic residence time can be attributed by extensive first-pass metabolism by the liver. Therefore, bypassing first-pass metabolism via dermal delivery will highly improve the pharmacokinetics of IQP-0410 and allow maintenance of effective concentrations of the active product for prolonged periods of time.

The initial studies of the formulation of the preclinical drug candidate IQP-0410 for transdermal patch delivery were performed by incorporating permeability enhancers and IQP-0410 into the polymer matrix of the transdermal patch. *In vitro* release studies of IQP-0410 from the transdermal patches were performed through synthetic 0.45 micron hydrophilic polyvinylidene fluoride (PVDF) membranes in Franz cell diffusion cells [61]. The transdermal product was applied flush atop the membrane in the donor cell. The receptor cell was filled with a 1:1 Isopropanol (IPA)/Phosphate Buffered Saline (PBS) solution while the donor cell was wetted with PBS to maintain humidity [62]. For 72 h at 37°C, a linear release of IQP-0410 across the membrane barrier into the receptor cells was measured (Figure 3A). While the flux of IQP-0410 across the membrane is not a true measurement of drug delivery and permeability, the drug transport of IQP-0410 from the transdermal film across the membrane does correspond to a zero-order release kinetic profile [27]. The *ex vivo* permeability of the IQP-0410 transdermal film was evaluated through full thickness human epidermal tissue model that is comprised of normal, human-derived epidermal keratinocytes (NHEK) which have been cultured to form a multilayered, highly differentiated model of the human epidermis [63]. The

transdermal films were placed flush with the apical surface of the epidermal tissue and kept dry. The tissues were maintained in DMEM from the receptor (basal) compartment. When the patches were applied to epidermal tissue, *ex vivo* studies similarly resulted in a linear zero-order release rate ($0.94 \pm 0.06 \mu\text{g}/\text{cm}^2/\text{h}$) into the basal media over a 3 day application (Figure 3B) [64]. IQP-0410 was successfully released and permeated through the full thickness epidermal tissue and collected in the basal media suggesting the potential viability of controlled zero-order delivery of IQP-0410 through the skin. The *in vitro* dissolution of the transdermal films and release of IQP-0410 from dosage form were conducted in a USP 4 flow-through cell dissolution system [65–67] under sink conditions in a dissolution medium of 10:90 ethanol/DI water at a flow rate of 10 ml/min and 37°C. While the *in vitro* release of IQP-0410 into dissolution media suggested a 22.2% increased rate from films stored under accelerated storage conditions, the cumulative recovered IQP-0410 was unaffected. As noted above, transdermal drug delivery has two functional components which are essential for overall drug delivery: release from the formulation to the epidermis, and permeation through the skin to the underlying blood vessels. Therefore, any increase in drug release rate from the film formulation will be mitigated by the diffusion of the drug through the tissue. The passive diffusion across the skin, the basis of transdermal drug delivery, will be the limiting factor in the drug delivery and permeability [68]. In the *ex vivo* studies, $45.9 \pm 20.8 \mu\text{M}$, $94.5 \pm 12.7 \mu\text{M}$ and $134 \pm 14.7 \mu\text{M}$ of IQP-0410 was collected each successive day, respectively, from the basal media resulting in an average anti-HIV 50% efficacious concentration (EC_{50}) value of $2.09 \pm 0.43 \text{ nM}$ in CEM-SS cells and $1.02 \pm 0.56 \text{ nM}$ in PBMCs over a 3-day application [64]. *Ex vivo* studies performed over 3 days determined that the concentration of delivered IQP-0410 after 24 h ($46 \mu\text{M}$) was 5000-fold greater than *in vitro* defined EC_{95} values [60]. The results of the transdermal delivery studies with the NNRTI IQP-0410 demonstrated the delivery of sufficient IQP-0410 through the *ex vivo* tissue model to yield successful *in vitro* reduction of HIV-1 replication for over 72 h. The physicochemical properties of IQP-0410 thus provide a more feasible compound for transdermal anti-HIV drug delivery when compared to the drug delivery results obtained with AZT, ddC, ddI and 3TC. Continuing studies with the IQP-0410 patch technology involve evaluation of other pyrimidinedione analogs with greater stability for use in the patches as well as the development of patches that might provide even longer periods of effective drug delivery through the skin and into systemic circulation. Patches are being developed specifically for their ability to lower HIV plasma virus loads in infected individuals

Figure 3. Illustration of transdermal delivery through intact skin. *In vitro/ex vivo* permeability of the IQP-0410 transdermal film through barrier. The *in vitro* release and subsequent transport of IQP-0410 from the transdermal film (defined here as a transdermal patch without the associated adhesive backing) through a polyvinylidene fluoride membrane over 72 h (A) ($n = 3 \pm \text{SD}$). The *ex vivo* release and permeability of IQP-0410 from the transdermal films through full thickness epidermal tissue over 72 h (B); (black triangles) ($n = 3 \pm \text{SD}$). The transdermal films were packaged into air-tight foil pouches and stored under standard (30°C / 65% RH) and accelerated (40°C / 75% RH) environmental conditions for 3 months. At 1, 2 and 3 months, the transdermal films were removed from storage and tested for drug release and permeability through full thickness epidermal tissue. The combined average ($n = 6 \pm \text{SD}$) of the transdermal films stored under standard environmental conditions for 3 months (B); (blue diamonds). The combined average ($n = 6 \pm \text{SD}$) of the transdermal films stored under accelerated environmental conditions for 3 months (B); (red squares). Reproduced from [64] © PLoS ONE (2013).

and will thus require the eventual release of multiple drug products, as well as the development of strategies to prevent the infection of uninfected individuals through **pre-exposure prophylaxis**.

Transdermal delivery for pre-exposure prophylaxis (PrEP) & HIV prevention

While there is significant development in sustained antiretroviral delivery for the therapeutic treatment of HIV, prevention of HIV infection represents a more effective method of confronting the HIV epidemic. This is especially true in the absence of any effective vaccine in the development pipeline to provide immunity and protect against HIV infection. Therefore, an important strategy under development is to prophylactically inhibit the transmission of STIs, including HIV [69,70], through the use of chemical barriers of sexual transmission. For the most part, the application of such topical microbicides in the form of gels is directly associated with coitus and the gels are designed to be applied as a single dose before and after intercourse to provide effective concentrations of the microbicide product at the time of virus transmission.

As such, these prevention products are directly linked to coitus and the timing of exposure to infectious HIV and, therefore, require highly specific compliance and adherence to the dosing strategy to be effective. It is well understood in the microbicide development field that coital dependency is not optimal and thus coitally associated products may not be the most optimal dosage form for women in all parts of the world. Therefore, sustained/controlled release drug delivery is a dosing mechanism that aims to dissociate drug administration from coitus which will hopefully simplify dosing of antiviral products and increase compliance and subsequent rates of prevention. Currently, the field of sustained release microbicide PrEP is still in the early developmental stages. There exist several vaginal rings under development [71–74] along with vaginal tablets [75] that confer sustained drug release. However, all of these sustained release drug delivery systems are applied within the vagina or rectum which may limit their use in geographic and cultural regions where specific dosage forms have low acceptability among potential users of the product. The development of transdermal formulations to deliver antiretroviral drugs for PrEP

will dissociate prevention from both the reproductive tract and coitus. The results of PrEP clinical studies in populations of men who have sex with men (MSM) confirm the potential utility of PrEP with transdermal delivered products. Males were provided oral dosing of two antiretroviral agents (Tenofovir and FTC) and were found to have a significantly reduced rate of HIV transmission as the oral dosing conferred protection of the men through effective concentrations of drug product in susceptible tissue in the reproductive tract [76]. It would be expected that transdermal delivery of anti-HIV compounds would allow even more effective PrEP in this context since dosing would be sustained over longer periods of time using a simpler regimen, providing even greater adherence to PrEP regimens. The transdermal and oral delivery of antiretroviral drugs also has one additional advantage which cannot be overlooked and which greatly adds to prevention strategies. The effective delivery of drugs to infected individuals with simplified regimens and sustained delivery will yield lower rates of HIV transmission of infectious virus to uninfected individuals. This 'treatment as prevention' strategy has been evaluated in clinical studies and it has been clearly shown that the reduced viral loads in treated individuals are directly correlated with reduced rates of HIV transmission [77]. Thus, the use of transdermal patches to simplify drug dosing and provide uniform sustained drug release over longer periods of time would have a direct effect on the transmission of infectious virus from infected individuals.

Future perspective

There have been significant advancements in understanding the mechanism of action for HIV and appropriate preventative/treatment strategies; however, an optimum treatment still remains a major challenge. Combinations of nucleotide and nonnucleoside reverse transcriptase inhibitors and protease inhibitors have been effectively used in **highly active antiretroviral therapies** (HAART) to significantly reduce HIV viral load in infected individuals for prolonged periods of time. The utilization of HAART has dramatically changed the therapeutic landscape of HIV treatment and the application of cocktails of antiretroviral agents is now the standard of care for HIV patients [78]. The dramatic reduction in viral load and clinical improvements achieved with HAART is a rigorous validation of the ability of anti-HIV drugs to contain and manage HIV-disease, and demonstrates that combination of three or more anti-HIV agents – even when directed against a few of the putative ten viral targets – are superior to single or dual drug therapy. Thus, the prevailing belief is that the addition of new anti-HIV agents to HAART regimens will provide additional clinical ben-

Key terms

Pre-exposure prophylaxis: Prevention strategy where people who do not have HIV but who are at substantial risk of getting it take a drug. When someone is exposed to HIV through sex or injection drug use, PrEP can prevent the virus from establishing a permanent infection.

Highly active antiretroviral therapies: Anti-HIV treatments that consist of a combination of at least three drugs that suppress HIV replication. Three drugs are used in order to reduce the likelihood of the virus developing resistance and to maintain virus loads in patients below detectable levels.

efit. However, HAART still suffers from complications with the emergence of multidrug resistant virus strains, toxicity, drug–drug interactions, difficult treatment regimens and inadequate pharmacology (bioavailability and tissue distribution) [79–81]. Clearly there is an urgent need for the continued development of new anti-HIV strategies and therapies. One of these strategies for the evolution of effective HIV therapy may include the use of transdermal patches to deliver drug cocktails using stable sustained release technology.

Conclusion

While alternative formulations such as transdermal drug delivery have been evaluated for HIV inhibitors, the design and development of these drug delivery systems are currently lacking. In addition, emerging transdermal formulation strategies have not yet considered the application of antiretroviral agents. Although several studies have reported the *in vitro* efficacy of the transdermally delivered compound, there remains a significant lack of data on the clinical applicability and toxicity of transdermal antiretroviral product delivery. Due the complex nature of HIV infection, there are several limitations to currently employed HAART drug therapy. Transdermal drug delivery represents an established alternative dosage form that avoids many of the limitations of existing oral drug delivery. While lower potency approved ARV drugs have been extensively investigated for transdermal delivery, recent evaluations of highly potent ARV drugs such as IQP-0410 and new emerging technologies in transdermal formulation must be pursued to truly understand the potential of transdermal delivery for the prevention and treatment of HIV infection.

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Executive summary

Introduction

- A large number of drugs do not conform to the selective physicochemical and bioactivity criteria for successful transdermal drug delivery. Despite this, advances in delivery technologies have resulted in an increasing number of drugs being administered transdermally.

The challenges of transdermal delivery of HIV inhibitors

- Currently there are no transdermal products available for the treatment of infectious diseases such as HIV. Existing research into delivering FDA approved small molecule HIV inhibitors has shown some promise; however, significant work in this field is required.

Current transdermal delivery strategies

- Until recently, the transdermal delivery field was primarily focused on passive patch delivery technologies that relied upon simple diffusion of a pharmaceutical product across the skin barrier. Emerging active technology patches that 'drive' a drug through the skin barrier have opened transdermal drug delivery to a broader range of compounds that do not fit the traditional requirements for successful transdermal drug delivery, allowing the development of new active patches to deliver antiretroviral drugs that were previously incapable of being delivered through transdermal means.

The use of passive permeability enhancers in transdermal delivery

- Chemical permeability enhancers facilitate drug transport through the skin by increasing drug partitioning into the stratum corneum, increasing drug diffusion through the stratum corneum, or a combination of both physicochemical effects. Such passive permeability enhancers have been shown to increase permeability of several FDA approved HIV inhibitors through the skin.

The use of active permeability enhancers in transdermal delivery

- Active permeability enhancers have been used to actively drive the transport of small drug molecules across the skin barrier. While less convenient in regards to patient uses, active permeability enhancers such as iontophoresis have been shown to significantly improve transdermal permeability.

Emerging transdermal delivery strategies

- There is still a large area of transdermal drug delivery that has yet to be applied to antiretrovirals. No current investigations of antiretroviral inhibitors are being conducted with emerging transdermal strategies; however, there are several strategies such as microneedles and microemulsions that show potential in providing enhanced delivery of antiretroviral agents.
- Despite the challenges in transdermal drug delivery, there are several examples of potentially successful formulations to deliver anti-HIV compounds. Continuing studies with the IQP-0410 patch technology involve evaluation of other pyrimidinedione analogs with greater stability for use in the patches as well as the development of patches that might provide even longer periods of effective drug delivery through the skin and into systemic circulation. Patches are being developed specifically for their ability to lower HIV plasma virus loads in infected individuals and will thus require the eventual release of multiple drug products, as well as the development of strategies to prevent the infection of uninfected individuals through pre-exposure prophylaxis.

Conclusion

- While there is significant development in sustained antiretroviral delivery for the therapeutic treatment of HIV, prevention of HIV infection represents a more effective method of confronting the HIV epidemic. Sustained release microbicide PrEP is still in the early developmental stages; however, several formulations under development have shown promise in preventing infection. This 'treatment as prevention' strategy has been evaluated in clinical studies and it has been clearly shown that the reduced viral loads in treated individuals are directly correlated with reduced rates of HIV transmission.

Future perspective

- There have been significant advancements in understanding the mechanism of action for HIV and appropriate preventative/treatment strategies; however, an optimum treatment still remains a major challenge. While alternative formulations such as transdermal drug delivery have been evaluated for HIV inhibitors, the design and development of these drug delivery systems are currently lacking. In addition, emerging transdermal formulation strategies have not yet considered the application of antiretroviral agents which must be pursued to truly understand the potential of transdermal delivery for the prevention and treatment of HIV infection.

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