An Introduction to the Transdermal Delivery of Antiretrovirals

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Abstract

AIDS is a collection of symptoms and infections resulting from the specific damage to the immune system caused by the human immunodeficiency virus (HIV). The late stage of the condition leaves individuals prone to opportunistic infections and tumors. Although treatments for AIDS and HIV exist to slow the virus’s progression, there is no known cure. HIV is transmitted through direct contact of a mucous membrane or the blood stream with a bodily fluid containing HIV, such as blood, semen, vaginal fluid, preseminal fluid and breast milk. Most researchers believe that HIV originated in sub-Saharan Africa during the twentieth century, it is now pandemic, with an estimated 38.6 million people now living with the disease worldwide. As of January 2006, the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) estimate that AIDS has killed more than 25 million people since it was first recognized on June 5, 1981, making it one of the most destructive epidemics in recorded history. In 2005 alone, AIDS claimed an estimated 2.4–3.3 million lives, of which more than 570,000 were children. A third of these deaths are occurring in sub-Saharan Africa, retarding economic growth and destroying human capital. Antiretroviral treatment reduces both the mortality and the morbidity of HIV infection, but routine access to antiretroviral medication is not available in all countries. The absorption of drugs through the transdermal route improves bioavailability of drugs that might otherwise be metabolized by first-pass effect (pre-systemic drug elimination) during their passage through the gastrointestinal tract. Drug absorption from the transdermal route is mainly via passive diffusion through the lipoidal membrane. Thus, transdermal route of drug delivery has attracted the attention worldwide for optimizing the drug delivery.

Keywords: AIDS, Transdermal delivery, Enhancers, Patch etc.
**Introduction**

The human immunodeficiency virus (HIV) and the disease it causes (AIDS) represent a major challenge facing humanity. Nearly thirty years since the first AIDS cases were identified, about 30 million people have died of the disease (1) and 34 million people were thought to be living with HIV in 2010 (2). While new infections have been declining, 2.7 million new infections and 1.8 million deaths occurred in 2010, 1.2 million of those in Sub-Saharan Africa (3). Progress has been made, especially in providing treatment, but the challenge remains.

The Acquired Immunodeficiency Syndrome (AIDS) was first recognised in the United States of America, in the summer of 1981, and has since become a major worldwide pandemic (4). The Human Immunodeficiency Virus (HIV) is known as the primary cause of AIDS. According to 2004 statistics an estimated 42 million people worldwide were living with HIV, the greater portion in resource-poor countries. Of those who could benefit from combination antiretroviral therapy, fewer than 5% were receiving treatment, even though it would have reduced the complications of infection and prolonged life (5). The Center for Disease Control (CDC) defines AIDS as a disease that is at least moderately predictive of an underlying cellular immune deficiency that results in a cellular defect in an individual, with no known resistance to the disease (6). The most common route of transmission of HIV worldwide is through sexual intercourse. It is, however, also spread through infected blood, the common use of contaminated needles and from mothers to their babies during pregnancy or birth (4). HIV is immunosuppressive because it infects cells of the immune system which leads to the destruction or functional impairment of these cells. A diagnosis of AIDS is given to infected HIV-individuals when the CD4+ T-cell count declines below 200 cells/lmm3 of blood. A healthy, uninfected person generally has 800 - 1200 CD4+ T-cells/lmm3 of blood (7, 8). Two major families of HIV exist, namely HIV-1 and HIV-2 (5). HIV-1 is the major cause of AIDS in the world today. This virus infects the cells of the immune and central nervous systems. The T helper lymphocyte is the main cell infected with HIV and plays an important role in the immune system, so that a large decrease in the number of T helper cells can dangerously weaken the immune system (9). The T helper cell is infected with HIV since it has protein CD4 on its surface. HIV uses this protein to attach itself to the cell before entry. The virus then replicates extensively and can infect other healthy cells followed by a severe reduction in the number of T helper cells (9). After only a few days to a few weeks after exposure to HIV, an acute flu-like illness begins to appear in most infected individuals. The most common symptoms to appear are fever, maculopapular rash, oral ulcers, etc. (4). This stage is known as the primary infection stage (9).

**HIV and AIDS:**

Human immunodeficiency virus (HIV) is a lentivirus (a member of the retrovirus family) that causes acquired immunodeficiency syndrome (AIDS), a condition in humans in which the immune system begins to fail, leading to life-threatening opportunistic infections Infection with HIV occurs by the transfer of blood, semen vaginal fluid, pre-ejaculate, or breast milk. Within these bodily fluids, HIV is present as both free virus particles and virus within infected immune cells. The four major routes of transmission are unsafe sex, contaminated needles, breast milk, and transmission from an infected mother to her baby at birth (perinatal transmission). (10)
**Figure 1:** SEM of HIV-1 (in green) budding from cultured lymphocyte.

**Table 1:** Virus classification

<table>
<thead>
<tr>
<th>Group</th>
<th>Family</th>
<th>Genus</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group (ssRNA- RT)</td>
<td>Retrovirida</td>
<td>Lentivirus</td>
<td>HIV 1, HIV 2</td>
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</table>

**Table 2:** Comparison of HIV species

<table>
<thead>
<tr>
<th>Species</th>
<th>Virulence</th>
<th>Infectivity</th>
<th>Prevalence</th>
<th>Inferred origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV 1</td>
<td>High</td>
<td>High</td>
<td>Global</td>
<td>Common Chimpanzee</td>
</tr>
<tr>
<td>HIV 2</td>
<td>Low</td>
<td>Low</td>
<td>West Africa</td>
<td>Sooty Mangabey</td>
</tr>
</tbody>
</table>

**History**

HIV is thought to have originated in non-human primates in sub-Saharan Africa and was transferred to humans late in the 19th or early in the 20th century. The first paper recognizing a pattern of opportunistic infections characteristic of AIDS was published in 1981. Both HIV-1 and HIV-2 are believed to have originated in West-Central Africa and to have jumped species from non-human primates to humans. HIV-1 appears to have originated in southern Cameroon through the evolution of SIV (cpz), a simian immunodeficiency virus (SIV) that infects wild chimpanzees (Pan troglodytes). The closest relative of HIV-2 is SIV (agm), a virus of the sooty mangabey (Cercocetus atys), an Old World monkey of Guinea-Bissau, Gabon and Cameroon. AIDS was first clinically observed between late 1980 and early 1981. Injection drug users and gay men with no known cause of impaired immunity showed symptoms of Pneumocystis carinii pneumonia (PCP), a rare opportunistic infection that was known to present itself in people with very compromised immune systems. Soon after additional gay men developed a previously-rare skin cancer called Kaposi’s sarcoma.
Many more cases of PCP and KS quickly emerged, alerting U.S. Centers for Disease Control and Prevention (CDC). A CDC task force was formed to monitor the outbreak. After recognizing a pattern of anomalous symptoms presenting themselves in patients, the task force named the condition acquired immune deficiency syndrome (AIDS). In 1983, two separate research groups led by Robert Gallo and Luc Montagnier independently declared that a novel retrovirus may have been infecting AIDS patients, and published their findings in the same issue of the journal. (10)

**Stages:**

HIV infection has four basic stages:

1. **Incubation period:**

   The initial incubation period upon infection is asymptomatic and usually lasts between two and four weeks.

2. **Acute HIV infection:**

   During this period (usually 2–4 weeks post-exposure) most individuals (80 to 90%) develop an influenza or mononucleosis-like illness called acute HIV infection, the most common symptoms of which may include fever, lymphadenopathy, pharyngitis, rash, myalgia, malaise, mouth and esophageal sores, and may also include, but less commonly, headache, nausea and vomiting, enlarged liver/spleen, weight loss.

3. **Latency stage:**

   A strong immune defense reduces the number of viral particles in the blood stream, marking the start of the infection's clinical latency stage. Clinical latency can vary between two weeks and 20 years. During this early phase of infection, HIV is active within lymphoid organs, where large amounts of virus become trapped in the follicular dendritic cells (FDC) network. The surrounding tissues that are rich in CD4 + T cells may also become infected, and viral particles accumulate both in infected cells and as free virus. Individuals who are in this phase are still infectious. During this time, CD4 + CD45RO + T cells carry most of the proviral load. (10)

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**Figure 2:** Main symptoms of acute HIV infection
**AIDS:**

When CD4+ T cell numbers decline below a critical level of 200 cells per µL, cell-mediated immunity is lost, and infections with a variety of opportunistic microbes appear. The first symptoms often include moderate and unexplained weight loss, recurring respiratory tract infections such as sinusitis, bronchitis, otitis media, pharyngitis, prostatitis, skin rashes, and oral ulcerations. In the final stages of AIDS, infection with cytomegalovirus (another herpes virus) or Mycobacterium avium complex is more prominent. Not all patients with AIDS get all these infections or tumors, and there are other tumors and infections that are less prominent but still significant. (10)

**Mechanism of infection:**

HIV primarily infects cells with CD4 cell-surface receptor molecules, using them to gain entry. Many cell types share common epitopes with this protein, though CD4 lymphocytes play a crucial role. In macrophages and in some other cells lacking CD4 receptors, such as fibroblasts, an Fc receptor site or complement receptor site may be used instead for entry of HIV. Cells of the mononuclear phagocyte system, principally blood monocytes and tissue macrophages, T lymphocytes, B lymphocytes, natural killer (NK) lymphocytes, dendritic cells (Langerhans cells of epithelia and follicular dendritic cells in lymph nodes), hematopoietic stem cells, endothelial cells, microglial cells in brain, and gastrointestinal epithelial cells are the primary targets of HIV infection.(10)

**Pathology of AIDS:**

Human immunodeficiency virus (HIV) is the causative agent for AIDS. It is a sexually transmitted disease. Infection is aided by Langerhans cells in mucosal epithelial surfaces and by the presence of other sexually transmitted diseases that can produce mucosal ulceration and inflammation. The CD4+ T-lymphocytes have surface receptors to which HIV can attach to promote entry into the cell. The infection extends to lymphoid tissues which contain follicular dendritic cells that can become infected and provide a reservoir for continuing infection of CD4+ T-lymphocytes. HIV can also be spread via blood or blood product. When HIV infects a cell, it must use its reverse transcriptase enzyme to transcribe its RNA to host cell proviral DNA. It is this proviral DNA that directs the cell to produce additional HIV virions which are released. The genome of HIV contains only three major genes: env, gag, and pol. These genes direct the formation of the basic components of HIV. The env gene directs production of an envelope precursor protein gp160 which undergoes proteolytic cleavage to the outer envelope glycoprotein gp120, which is responsible for tropism to CD4+ receptors, and transmembrane glycoprotein gp41, which catalyzes fusion of HIV to the target cell's membrane. The gag gene directs formation of the proteins of the matrix p17, the "core" capsid p24, and the nucleocapsid p7. The pol gene directs synthesis of important enzymes including reverse transcriptase p51 and p66, integrase p32 and protease p11.

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**Figure 3:** Life cycle of HIV
In addition to the CD4 receptor, a coreceptor known as a chemokine is needed for HIV infection. Chemokines are cell surface fusion-mediating molecules. Such coreceptors include CXCR4 and CCR5. Their presence on cells can aid binding of the HIV envelope glycoprotein gp120, promoting infection. Initial binding of HIV to the CD4 receptor is mediated by conformational changes in the gp120 subunit, but such conformational changes are not sufficient of fusion. The chemokine receptors produce a conformational change in the gp41 subunit which allows fusion of HIV. The differences in chemokine coreceptors that are present on a cell also explains how different strains of HIV may infect cells selectively. There are strains of HIV known as T-tropic strains which selectively interact with the CXCR4 chemokine coreceptor to infect lymphocytes. The M-tropic strains of HIV interact with the CCR5 chemokine coreceptor to infect macrophages. Dual tropic HIV strains have been identified. The presence of a CCR5 mutation may explain the phenomenon of resistance to HIV infection in some cases. Over time, mutations in HIV may increase the ability of the virus to infect cells via these routes. Infection with cytomegalovirus may serve to enhance HIV infection via this mechanism, because CMV encodes a chemokine receptor similar to human chemokine receptors. The life cycle of HIV shown with the points at which pharmacologic agents may block viral maturation, including points for inhibition of reverse transcriptase, integrase, TAT transcription, and protease. It is characterized by gradual destruction of cell-mediated (T-cell) immunity; it also affects humoral immunity and autoimmunity because of the central role of the CD4 + T lymphocyte in immune reactions. This highlights the importance of treating AIDS. (11)

Pathophysiology:

Sexual

The majority of HIV infections are acquired through unprotected sexual relations. Sexual transmission can occur when infected sexual secretions of one partner come into contact with the genital, oral, or rectal mucous membranes of another. In high income countries, the risk of female-to-male transmission is 0.04% per act and male- to-female transmission is 0.08% per act. For various reasons, these rates are 4 to 10 times higher in low-income countries. The rate for receptive anal intercourse is much higher, 1.7% per act. The correct and consistent use of latex condoms reduces the risk of sexual transmission of HIV by about 85%. However, spermicide may actually increase the transmission rate.

Blood or blood product

In general, if infected blood comes into contact with any open wound, HIV may be transmitted. This transmission route can account for infections in intravenous drug users, hemophiliacs, and recipients of blood transfusions and blood products. It is also of concern for persons receiving medical care in regions where there is prevalent substandard hygiene in the use of injection equipment. Health care workers such as nurses, laboratory workers, and doctors have also been infected, although this occurs more rarely. Since transmission of HIV by blood became known medical personnel are required to protect themselves from contact with blood by the use of universal precautions. HIV has been found at low concentrations in the saliva, tears and urine of infected individuals, but there are no recorded cases of infection by these secretions and the potential risk of transmission is negligible.

Mother-to-child

The transmission of the virus from the mother to the child can occur in utero (during pregnancy), intrapartum (at childbirth), or via breast feeding. In the absence of treatment, the transmission rate up to birth between the mother and child is around 25%. However, where combination antiretroviral drug treatment and Cesarian section are available, this risk can be reduced to as low as one percent. Postnatal mother-to-child transmission may be largely prevented by complete avoidance of breast feeding; however, this has significant associated morbidity. (10)
**Structure and genome:**

HIV is different in structure from other retroviruses. It is roughly spherical with a diameter of about 120 nm, around 60 times smaller than a red blood cell, yet large for a virus. It is composed of two copies of positive single-stranded RNA that codes for the virus's nine genes enclosed by a conical capsid composed of 2,000 copies of the viral protein p24. The single-stranded RNA is tightly bound to nucleocapsid proteins, p7 and enzymes needed for the development of the virion such as reverse transcriptase, proteases, ribonuclease and integrase. A matrix composed of the viral protein p17 surrounds the capsid ensuring the integrity of the virion particle. (10)

![Diagram of HIV](image)

**Figure 4:** Diagram of HIV

**Replication cycle:**

Viral replication consists of several steps:

1. Adsorption to and penetration into susceptible host cells;
2. Uncrating of viral nucleic acid;
3. Synthesis of early regulatory proteins, e.g., nucleic acid polymerases;
4. Synthesis of RNA or DNA;
5. Synthesis of late, structural proteins;
6. Assembly (maturation) of viral particles; and
7. Release from the cell. (12)

Antiviral agents can potentially target any of these steps (Figure 5).

**India HIV & AIDS Statistics**

India has a population of one billion, around half of whom are adults in the sexually active age group. The first AIDS case in India was detected in 1986 and since then HIV infection has been reported in all states and union territories. The highest HIV prevalence rates are found in Andhra Pradesh, Maharashtra, Tamil Nadu and Karnataka in the south; and Manipur and Nagaland in the north-east. (13, 14)
Estimated number of people living with HIV/AIDS, 2007 (NACO (National AIDS Control Organization))

- People living with HIV/AIDS: 2.31 million.
- Adults (15 years or above) prevalence: 0.34%.

**HIV statistics, 2007:**

Across India HIV prevalence appears to be low among the general population, but disproportionately high among high-risk groups, such as IDUs, female sex workers, men who have sex with men (MSM) and STD clinic attendees, the average HIV prevalence among women attending antenatal clinics in India is 0.48%. Much higher rates are found among people attending STD clinics (3.6%), female sex workers (5.1%), injecting drug users (7.2%) and men who have sex with men (7.4%). As the table below shows, the rates among different groups vary widely between states. (14)

**Table 3: HIV prevalence (2007) of different states of India (13)**

<table>
<thead>
<tr>
<th>State/Union Territory</th>
<th>Antenatal clinic HIV prevalence 2007 (%)</th>
<th>STD clinic HIV prevalence 2007 (%)</th>
<th>IDU HIV prevalence 2007 (%)</th>
<th>MSM HIV prevalence 2007 (%)</th>
<th>Female sex worker HIV prevalence 2007 (%)</th>
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<td>0.80</td>
<td>7.76</td>
<td>5.61</td>
<td>5.92</td>
</tr>
</tbody>
</table>
The National Family Health Survey, which tested more than 100,000 people for HIV, also found prevalence to be higher in urban areas (0.35%) than in rural areas (0.25%). (14)

**AIDS statistics:**

NACO has not produced estimates of the number of people living with AIDS and the number of people who have died from AIDS. Some of the last figures produced were from 2005, which showed that by the end of 2005 the total number of reported AIDS cases in India was 116,905 of which 34,177 were women. (4) Around a third of these were among people younger than 30 years. (14)

**Diagnosis:**

HIV infection is diagnosed by finding antibodies to HIV in plasma using various serological analysis methods such as (15)

- ELISA (Enzyme Linked Immuno Sorbent Assays)
- Orasure western blot
- SUDS (Single Used Diagnostic System)
- Orasure HIV-1

**Commencement of treatment:**

According to the United States Food and Drug Administration and World Health Organization guidelines, the antiretroviral therapy is commenced with these observations (16):

- When patients experience severe symptoms of HIV infection
- Diagnosed with AIDS
- When viral load in the blood sample is found to be 50,000 copies/ml
- When the CD4 cell count is less than 200-350 cells/mm$^4$

**Therapy:**

There is currently no vaccine or cure for HIV or AIDS. Therapy is based on avoiding exposure to the virus or an antiretroviral treatment directly after a highly significant exposure, called post-exposure prophylaxis (PEP). (16)

The major classes of antiretroviral agents are as follows:

- Nucleoside reverse transcriptase inhibitors (NRTI)
- Protease inhibitors
- Non-nucleoside reverse transcriptase inhibitors (NNRTI)
- Integrase inhibitors
- Entry inhibitors (or fusion inhibitors)
- Maturation inhibitors

**Nucleoside reverse transcriptase inhibitors (NRTI):**

These are the first class of antiretrovirals. All compounds of in this class are prodrugs which need to be converted intracellularly in the cytoplasm to their active form before exerting their antiviral activity. The active forms of these drugs are substrates for reverse transcriptase enzyme and they result in termination of DNA chain elongation of the retrovirus. (16)

**Protease inhibitors (PI):**

They act at the end of the HIV life cycle to cause the formation of non-infectious immature virions. These agents represent a major advance in the management of HIV disease and have dramatically altered disease progression to AIDS.
### Table 4: FDA approved NRTI drugs

<table>
<thead>
<tr>
<th>Name</th>
<th>FDA approval date</th>
<th>Dosage forms</th>
</tr>
</thead>
<tbody>
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<td>Zidovudine(AZT)</td>
<td>19th March 1987</td>
<td>Capsule, tablet, syrup, injection</td>
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<td>Didanosine(ddI)</td>
<td>9th October 1991</td>
<td>Tablet, solution</td>
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<td>Zalcitabine(ddC)</td>
<td>19th June 1992</td>
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</tr>
<tr>
<td>Stavudine(d4T)</td>
<td>24th June 1994</td>
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<td>Lamivudine(3TC)</td>
<td>17th November 1995</td>
<td>Tablet, solution</td>
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<tr>
<td>Abacavir</td>
<td>17th Dec. 1998</td>
<td>Film, coated tablet</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>26th Oct 2001</td>
<td>Tablet</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>2nd Oct 2003</td>
<td>Capsule</td>
</tr>
</tbody>
</table>

### Table 5: FDA approved PI drugs

<table>
<thead>
<tr>
<th>Name</th>
<th>FDA approval date</th>
<th>Dosage forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saquinavir</td>
<td>6th Dec 1995</td>
<td>Capsule</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>1st Mar 1996</td>
<td>Capsule, solution</td>
</tr>
<tr>
<td>Indinavir</td>
<td>13th Mar 1996</td>
<td>Capsule</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>14th Mar 1997</td>
<td>Tablet, powder</td>
</tr>
<tr>
<td>Amprenavir</td>
<td>15th Apr 1999</td>
<td>Capsule, solution</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>20th June 2003</td>
<td>Capsule</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>20th Oct 2003</td>
<td>Tablet</td>
</tr>
</tbody>
</table>

### Non-Nucleoside reverse transcriptase inhibitors (NNRTI):

They inactivate the HIV-1 reverse transcriptase enzyme by non-competitively binding directly to the HIV-1 reverse transcriptase structure likely at amino acid positions 100 and 103. These are not active against HIV-2.

### Table 6: FDA approved NNRTI drugs

<table>
<thead>
<tr>
<th>Name</th>
<th>FDA approval date</th>
<th>Dosage forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevirapine</td>
<td>21st June 1996</td>
<td>Tablet</td>
</tr>
<tr>
<td>Delavirdine</td>
<td>4th Apr 1997</td>
<td>Tablet</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>17th Sept 1998</td>
<td>Capsule, film, coated tablet</td>
</tr>
</tbody>
</table>
**Integrase inhibitors:**

They inhibit the enzyme integrase, which is responsible for integration of viral DNA into the DNA of the infected cell. There are several integrase inhibitors currently under clinical trial.

- Ralegravir

**Entry inhibitors (or fusion inhibitors):**

They interfere with binding, fusion and entry of HIV-1 to the host cell by blocking one of several targets.

- Maraviroc
- enfuvirtide

**Maturation inhibitors:**

They inhibit the last step in gag processing in which the viral capsid polyprotein is the mature capsid protein (p24). Because these viral particles have a defective core, cleaved, thereby blocking the conversion of the polyprotein into the virions released consist mainly of non-infectious particles. There are no drugs in this class currently available, though two are under investigation. (10)

- Bevirimat
- Vivecon

**Drawbacks of Conventional Route:**

Currently available anti HIV agents have following drawbacks:

1. Short half life
2. Low bioavailability
3. Poor CNS penetration and retention
4. Hepatic first pass metabolism
5. Undesirable side effects
6. Frequent dosing regimen

So, these drawbacks give researchers tremendous opportunities to design and develop novel drug delivery systems to overcome the transport barriers and inherent elimination and metabolism problems associated with this anti HIV drugs. (16)

The novel drug delivery systems are developed by the application of the concepts and techniques of controlled release drug administration which not only extend the potent life of existing drug but also minimize the scope and expenditure of testing required for FDA approval and which make clinically already established drugs do their therapeutic best. (17)

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and maintain the desired drug concentration. Many novel drug delivery systems have been developed e.g. Transdermal, Intrauterine, Intravaginal, and Implants etc. These drug delivery systems have added a new dimension of optimizing the treatment of several disease conditions by modifying various pharmacokinetics parameters. These drug delivery system releases the drug either by zero order kinetics or by first order kinetics or by both simultaneously.

Transdermal drug application has been well known since ancient times. Several ancient cultures used ointments, pastes, plasters and complex inunctions in the treatment of various symptoms or disease.
TRANSDERMAL DRUG DELIVERY SYSTEM

Transdermal drug delivery system releases the drug by zero (or pseudo zero order) or by first order or both kinetics and which maintain the drug level for prolonged period for desired action. Transdermal delivery of anti HIV agents improve the bioavailability, reduce dosing frequency, avoid side effects and hepatic first pass metabolism which are the most common problems faced with the oral route.

Advantages and Disadvantages of Transdermal Drug Delivery Systems (DDS):

The advantages of transdermal DDS have been well summarized by Cleary (18) and Washington. (19)

- It avoids chemically hostile gastrointestinal (GI) environment containing acid, food and enzymes and variable GI absorption.
- Avoids the risk and inconvenience of intravenous therapy and of the varied conditions of absorption and metabolism associated with oral therapy.
- Continuity of drug administration, permitting the use of drug with short half life.
- Achievement of efficacy with low daily dosage of drug by continuous drug input and by preventing hepatic first pass elimination.
- Less chance of over or under-dosing as the result of prolonged programmed delivery of drug at the required therapeutic rate.
- To reduce frequency of administration with rapid termination of drug input by removal of the system from skin surface.
- Provision of a simplified therapeutic regimen, leading to better patient compliance.
- Ability to easily terminate the medication as needed by simply removing the drug delivery device from the skin surface.
- Patient compliance also well known and it is well accepted as it can provide sustained plasma profile over several days, without severe dips occurring in night.

These delivery systems have some limitations also:

- Drugs may be metabolized by bacteria on the skin surface. (20)
- Enzymatic activity in the epithelium may be different to that in the gastrointestinaltract (GIT), leading to unpredictable routes of break down of drugs. (21) However this may be useful since prodrugs can be administered which are metabolized to active species after adsorption. (22)
- Slow transport of many drugs across the skin due to barrier properties of SC which limits the use of potent drugs which require high plasma concentrations.
- High cost of delivery system.
- Possibility of irritation and hypersensitivity reactions.
- Useful only for low dose drugs.

THE SKIN (23, 24)

The surface of the body is entirely covered by the skin. It is one of the most extensive and readily accessible organs of the human body. The skin of an average adult body covers a surface area of approximately 2 m² and receives about one-third of the blood circulating through the body. The skin functions as a protective barrier that interface with a sometimes-hostile environment. It is also very involved in maintaining the proper temperature for the body to function well, to eliminate wastes and also protect tissues from infection. It gathers sensory information from the environment, and plays an active role in the immune system protecting us from disease. Understanding of how the skin can function in these many ways starts with understanding the structure of the 3 layers of skin - the epidermis, dermis, and subcutaneous tissue (Figure. 6). (19)
The uppermost layer, epidermis, is also known as scurf skin or cuticle. It is thickest in the areas of the palms and soles and becomes thinner over the ventral surface of the trunk. It is a multilayer structure consisting of five thinner layers composed of cellular system. From top to bottom the layers are named stratum corneum (SC), stratum lucidum (clear layer), stratum granulosum (granular layer), stratum spinosum (prickly layer), and stratum basale. The layer that interacts with the environment is the stratum corneum, or horny layer. The stratum corneum is the skin's primary defense against invasion and is a composite of corneocytes, or terminally differentiated keratinocytes, which are surrounded by crystalline lamellar lipid regions. (25) The corneocytes suspended in this lipid matrix, in addition to the lipid envelope surrounding the cells, form a ‘brick-and-mortar’ barrier that permits retention of water within the corneocytes in addition to hampering the penetration of foreign particles. (26, 27) Below the stratum corneum lies the stratum granulosum, which is a granular layer, followed by the stratum spinosum. The stratum spinosum has an abundance of desmosomes that give a spiny appearance to the cells, hence its by name, the prickly layer. The stratum basal, also known as the stratum germinativum, is a single layer of columnar basal cells that are attached to the basement membrane, or basal lamina, via hemidesmosomes. (28) The stratum basal is the regenerative layer composed of undifferentiated keratinocytes and stem cells. (29) Studies have shown that the stratum corneum is replenished about every 2 weeks in a mature adult. (30, 31) The stratum corneum is responsible for the barrier function of the skin. It also behaves as the primary barrier to percutaneous absorption. (32) The thickness of this layer is mainly determined by extent of stimulation of skin surface by abrasion and bearing of weight; hence thick palms and soles are developed. (33) Like stratum corneum the stratum granulosum and stratum lucidum are also physiologically important. Removal of these three upper epidermal layers results in water loss and enhancement of skin permeability. (34)

Major lipid classes within the SC are ceramides, cholesterol, and fatty acids. Examination of skin
scrapings also shows that there are free amino acids among the keratin; these may act as buffers and protect skin from action of acids and alkalis. (30)

Under the epidermis lies the true skin known as dermis or corium. Electron microscopic examination shows that the dermis is made up of robust collagen fibers of fairly uniform thickness. It is approximately 2-3 mm thick and forms the bulk of the skin and is made up primarily of fibroblasts. The dermis is composed of three types of tissues that are present throughout. These are collagen, elastic tissue, and reticular fibers. The two layers of dermis are papillary and reticular layers. Upper, papillary layer contains a thin arrangement of collagen fibers. Lower, reticular layer, is thicker and made of thick collagen fibers that are arranged parallel to the surface of the skin. The dermis contains many specialized cells and structures. The hair follicles are situated here with the erector pili muscle that attaches to each follicle. Sebaceous (oil) glands and apocrine (scent) glands are associated with the follicle. This layer also contains eccrine (sweat) glands, but they are not associated with hair follicles. Blood vessels and nerves course through this layer. The nerves transmit sensations of pain, itch, and temperature. There are also specialized nerve cells called Meissner’s and Vater-Pacinii corpuscles that transmit the sensations of touch and pressure. (30,35)

The last layer, subcutaneous tissue, is a sheet of fat-containing areolar tissue, known as the superficial fascia, attaching the dermis to the underlying structures. This layer is important in the regulation of temperature of the skin itself and the body. The size of this layer varies throughout the body and from person to person.

**Drug Delivery Pathways Across the Skin**

Drug diffusion from transdermal delivery system to blood can be considered as passage through a series of diffusional barriers. Firstly drug has to pass the delivery system then through stratum corneum, epidermis, and then dermis. Each of these layers has different barrier properties due to their differences in the composition of different layers. There are two possible routes of passage of drugs through the stratum corneum, these are hydrophilic keratinized cells and the lipid channels between the cells. The lipoidal nature of the lipid channels favors the passage of hydrophobic molecules and this is the major route of entry. Behl and coworkers (36) showed that hydration increases the penetration of polar molecules than non-polar molecules. Thus hydration of the lipid channels is more important than hydration of keratinized cells.

<table>
<thead>
<tr>
<th>Intercellular</th>
<th>Intracellular</th>
<th>Transfollicular and transductal</th>
</tr>
</thead>
</table>

![Figure 7: Transport of drugs through stratum corneum](image-url)
It is well known that transdermal permeation of drug molecules are occur in two ways: 1) by passively proceeding through the epidermis or 2) by entering a shunt pathway such as a hair follicle or eccrine gland. (37) The figure (Figure 7) depicts these routes with the first arrow representing ingress through a sweat gland, the second, transdermal penetration and the third entrance is through a sebaceous gland. (38)

Figure 8: Routes of transdermal delivery

However, shunt pathways only account for approximately 0.1% of the total skin surface, thus passive diffusion has a higher probability of occurring. Molecules with a high molecular weight such as peptides, antibodies and DNA, however, may require such appendages. (39,40) Additionally, it is believed that the pilo sebacous unit, which includes the hair follicle, hair shaft and sebaceous gland, might be a highly desirable route for transdermal drug delivery as sebaceous gland cells are more permeable than corneocytes. The increased blood flow to the hair follicle could enhance systemic drug delivery as well as delivery to the dermis. (39) For molecules to passively penetrate the epidermis, they can either pass through the corneocytes and lipid matrix in a transcellular route, or by intercellular travel between the corneocytes in the lipid matrix. (37) The latter, lipophilic route is the proposed mechanism for most drugs as it is the pathway of least resistance. (41, 42, 43) Lipophilic molecules are better accepted by the stratum corneum. Ideally, a drug must possess both lipidic and aqueous solubility. If a drug is too hydrophilic, the molecule will be unable to transfer into the stratum corneum, however if it is too lipophilic, the drug will tend to remain in the stratum corneum layers. (44)

Stratum Corneum as the Transdermal Penetration Barrier

Stratum corneum mainly consist of the keratinized dead cells and water content is also less as compared to the other skin components. Once the dosage form is applied topically, the percutaneous absorption or transdermal permeation can be visualized as a composite of a series of steps.

1. Adsorption of a penetrant molecule onto the surface layers of stratum corneum.
2. Diffusion through stratum corneum and through viable epidermis.
3. Finally through the papillary dermis and into the microcirculation. (17)
The viable tissue layers and the capillaries are relatively permeable and the peripheral circulation is sufficiently rapid, so that, for the great majority of substances, diffusion through the stratum corneum is the rate-limiting step. The stratum corneum acts like a passive diffusion medium.

**Percutaneous Absorption (45):**
Percutaneous absorption is defined as penetration of substances into various layers of skin and permeation across the skin into systemic circulations. The percutaneous absorption is a step-wise process and can be divided into three parts;

- **Penetration** is the entry of a substance into a particular layer.
- **Permeation** is the penetration from one layer into another, and is different both functionally and structurally from the first layer.
- **Absorption** is the uptake of a substance into systemic circulation.

The stratum corneum is a wall-like structure with protein bricks and lipid mortar. The lipid matrix (Keratin phospholipids complex) of the stratum corneum plays a significant role in determining the permeability of substances across the skin. This is supported by the evidence from controlled stripping experiments, electron microscopy studies and also from the analysis of penetration and permeation data.

**Factors Affecting Transdermal Permeability (46):**
The principle transport mechanism across mammalian skin is by passive diffusion through primarily the transepidermal route at steady state or through transappendageal route at initially, non steady state. The factors, which affect the permeability of the skin mainly the stratum corneum, are classified into following categories:

- Physicochemical properties of the penetrant.
- Physicochemical properties of the drug delivery system.
- Physicochemical and pathological conditions of the skin.

1) **Physicochemical properties of the penetrant molecule:**

**A. Partition co-efficient:**
Drug possessing both water and lipid solubilities are favourably absorbed through the skin. Transdermal
permeability co-efficient shows a linear dependence on partition co-efficient. Varying the vehicle may also alter a lipid/water partition co-efficient of a drug molecule. The partition co-efficient of a drug molecule may be altered by chemical modification without affecting the pharmacological activity of the drug.

**B. pH condition:**
The effect of pH is mainly on the rates of absorption of acidic and basic drugs, unchanged form of drug has better penetrating capacity. Transport of ionizable species from aqueous solutions shows a strong pH dependence.

**C. Drug concentration:**
Transdermal permeability across mammalian skin is a passive diffusion process and this depends on the concentration of penetrant molecule on the surface layer of the skin.

**2) Physicochemical properties of the drug delivery system:**

**A. The affinity of the vehicle for the drug molecules:**
It can influence the release of the drug molecule from the vehicle. Solubility in the vehicle will determine the release rate of the drug. The mechanism of drug release depends on whether the drug is dissolved or suspended in the delivery system and on the interfacial partition co-efficient of the drug from the delivery system to skin tissue.

**B. Composition of drug delivery system:**
Composition of drug delivery system may affect not only the rate of drug release but also the permeability of the stratum corneum by means of hydration.

**C. Enhancement of transdermal permeation:**
Release of the drug from the dosage form is less due to the dead nature of the stratum corneum. Penetration enhancers cause the physicochemical or physiological changes in stratum corneum and increase the penetration of the drug through the skin. Various chemical substances found to possess drug penetration enhancing property.

**3) Physiological and pathological condition of the skin:**

**A. Skin age:**
Foetal and infant skin appears to be more permeable than adult skin. Percutaneous absorption of topical steroids occurs more rapidly in children than in adults. Water permeation has shown to be same in adults and in children.

**B. Lipid film:**
The lipid film on the skin surface is formed by the excretion of sebaceous glands and cell lipids like sebum and epidermal cell which contain emulsifying agent may provide a protective film to prevent the removal of natural moisturising factor from the skin and help in maintaining the barrier function of the stratum corneum.

**C. Skin hydration:**
Hydration of stratum corneum can enhance transdermal permeability. The rate of penetration of salicylic acid through skin with dry and hydrated corneum was measured when the tissue were hydrated, the rate of penetration of the most water soluble esters increased more than that of the other esters.

**D. Skin temperature:**
Raising skin temperature results in an increase in the rate of skin permeation. Rise in skin temperature may also increase vasodilation of blood vessels, which are in contact with skin leading to an increase in percutaneous absorption.

**E. Cutaneous drug metabolism:**
After crossing the stratum corneum barrier, some of the drug reaches the general circulation in active form and some of this in inactive form or metabolic form, because of the presence of metabolic enzymes present in the skin layers. It was reported that more than 95% of testosterone absorbed was metabolized as it present through the skin.

**F. Species differences:**
Mammalian skin from different species display wide differences in anatomy in such characteristics as the thickness of stratum corneum, number of sweat glands and hair follicles per unit surface area.
G. Pathological injury to the skin:

Injuries to the skin can cause the disturbance in the continuity of stratum corneum and leads to increase in skin permeability.

**PENETRATION ENHANCERS (46)**

The stratum corneum has long been considered a major barrier to penetration of topically applied chemicals. Studies have shown that most compounds have low permeability through skin. There are three major limitations to the topical delivery of the drug (47):

- Most of the drugs permeate poorly across the stratum corneum.
- If the drugs permeate across the stratum corneum, they are not easily retained in the skin for localized therapy.
- Many drugs are too irritating to the skin to deliver topically.

By permeation, one really means flux and one is concerned with problem of increasing flux across membrane. For any region within the membrane the flux, \( J \) can be given by (48)

\[
J = -D \frac{\delta C}{\delta X}
\]

for flow in one dimension. Where,

- \( D \) = diffusion co-efficient (size, shape of permeant)
- \( C \) = permeation co-efficient (thermodynamic origin)
- \( X \) = special co-ordinate

Therefore, enhancement of flux across the membrane depends on:

- Thermodynamics (lattice, energies and distribution co-efficient).
- Molecular size and shape.
- Reducing the energy required to make a molecular hole in the membrane.

There are two kinds of enhancement measurements. The comparison of fluxes of the same molecule from two different vehicles and the comparison of fluxes of two different molecules from the same vehicle. The amount of increasing penetration is simply the ratio, \( R \)

\[
R = \frac{J_1}{J_2}
\]

Where,

- \( J_1 \) = flux from vehicle 1 (molecule 1)
- \( J_2 \) = flux from vehicle 2 (molecule 2)

Often these fluxes will not be at steady state since the membrane barrier properties will be changing with time if enhancement is occurring. For \( R \) to be true measure of the vehicle enhancement, drug should have same thermodynamic activity either by using saturated solutions or equal fractions of saturation. This in turn depends on activities of two drugs, which in turn depends on concentration and solubility. For vehicle (mediated) induced penetration enhancement to occur, the energy for making diffusion holes must be altered. The process can take place if the solvent swells the barrier but in case of skin, proteins and/or lipids must be altered to make it easier for a molecule to diffuse through the media. Surfactants can be used for polar molecule, which alters the proteins of stratum corneum and thus increase penetration. The more hydrophilic surfactant (ionic/zwitterionic) interacts strongly with the keratin and alter transport of less hydrophilic surfactant (long chain alcohol) interact weakly and do not alter the transport of polar molecule. For example urea has been reported to enhance skin permeation penetration and at high concentration denatures skin.

To alter fluid properties of stratum corneum lipids it must be able to swell the lipid

or increase the volume/molecule. The low permeability of the skin, relative to other biological tissues, is well known and it is perhaps this fact that has kept the skin as a minor part of entry of drugs. As compared to the oral or gastric mucosa, the stratum corneum is compact and highly keratinized. The lipid of the proteins of the stratum corneum as explained in ‘Brick and Mortar’ model provides a complex structure that is quite impermeable. To
reduce the resistance of the stratum corneum and its biological variability, penetration enhancers can be defined as a chemical with the unique property in relation to skin that it reversibly reduced the barrier layer of the horny layer without damaging any viable cells. (49) According to Chein et al. (50) penetration enhancers or promoters are agents that have no therapeutic effect of their own but can transport the sorption of drugs from drug delivery systems onto the skin and/or their subsequent transdermal permeation through the skin. The penetration enhancers are the agents that increase the permeability of the skin. The penetration enhancers are the agents that increase the permeability of the skin or substances that reduces the impermeability of the skin.

Katz and Poulsen (49) define a spectrum of properties, which such a material should ideally possess. An expanded list of desirable attributes is as follows (49, 51, 52):

- The enhancer should be pharmacologically inert and should possess no action of it as receptor sites in the skin or in the body in the amount or concentration used.
- The material should not be toxic, irritant or allergic.
- On application, the onset of action should be immediate and the duration of the effect should be predictable and suitable.
- When the enhancer is removed from skin, the exposed tissue should immediately and fully recover its normal barrier properties.
- The barrier function of skin should reduced, so as to promote penetration into skin. Body fluids, electrolytes or other endogenous material should not be lost to the atmosphere.
- The enhancer should have a good enhancement efficacy and be chemically and physically compatible with a wide range of drugs and pharmaceutical adjuvant.
- The enhancer should be an excellent solvent for drugs, so that only minimal quantities of drugs are required.
- The enhancer should spread well on the skin and possess a suitable skin feel.
- The enhancer should be able to formulate readily into lotions, suspensions, ointments, creams, gels, aerosols and skin adhesives.
- The enhancer should be inexpensive, odourless, tasteless and colourless to be cosmetically acceptable.

Based on conceptual diagram, accelerants have been classified according to their organic and inorganic character into three areas. (54)

Area -1: In this enhancers are solvents
Area -2: Enhancers for hydrophilic compounds
Area -3: Enhancers for hydrophobic compounds

**Solvents (55):**

Hydrophilic solvents like Dimethyl sulfoxide (DMSO), N-methyl-2-pyrrolidone (NMP), Dimethyl formamide (DMF), Dimethylacetamide (DMAc), Glycerol, Polyethylene glycol (PEG), can be used to solubilize drugs. These solvents can affect the penetration of the drug through the skin by allowing the stratum corneum to swell and solubilize or partially leaching of the epidermal lipids.

**Azones (55):**

Chemically it is 1-dodecylazacyclocloheptane-2-one. Azone was found to be absorbed in very low amounts. It increases the release rate of drugs like steroids, antibiotics and antifungals from polymer matrix. The use of azone as a penetration enhancer with various concentration is restricted completely as above 10% azone causes skin irritation.

**Alcohol and Glycols (55):**

Of the various alcohol studied as skin penetration enhancers, ethanol is most widely used. It increased the flux of levonorgestrol by six folds and estradiol by 40 folds through the rat skin. Propylene glycol can significantly enhance the permeability of human skin to lipophilic compounds.
Fatty acids (55):

Percutaneous absorption of drugs has been increased by a variety of long chain fatty acids, the most popular of which is oleic acid.

Surfactants (53):

Surfactants permeation promoting activity is due to decrease in the surface tension to improve the wetting of the skin and to enhance the distribution of drugs. Hydrophilic head groups such as in sodium lauryl sulfate are very effective in altering the penetration of polar molecules, but alcohols which have low hydrophilicity are ineffective. The more hydrophilic surfactants interact strongly with the keratin and alter transport and the less hydrophilic surfactants (long chain alcohols) interact weakly and do not alter the transport of polar molecules. Anionic surfactants like sodium lauryl sulfate and cationic surfactants irritate the skin strongly, swells the stratum corneum, however nonionic surfactants are harmless. Enhancing activity is strongly depend on the surfactant structure and concentration.

Phospholipids:

Many studies have employed phospholipids as vesicles to carry drugs into and through human skin. A few studies have used phospholipids in a non-vesicular form as penetration enhancers. For example theophylline (56) was enhanced through mouse skin by 1% phosphatidylcholine in PG. Phospholipids could act as a penetration enhancer by following mechanisms: Firstly, phospholipids may exert a direct influence on permeability characteristics, secondly a phospholipid is incorporated with in the viable cells via intercellular lipids in the stratum corneum and form a lipophilic route for the permeability of drugs, thirdly an exogenous phospholipid disrupts the lamellar structure of the stratum corneum and increases lipid fluidity of stratum corneum.

Pyrrolidones (55):

N-methyl-2-pyrrolidone (NMP) and 2-pyrrolidone (2P) are the most widely studied enhancers of this group. They have been used as permeation promoters for numerous molecules including hydrophilic and lipophilic permeants. In terms of mechanisms of action, the pyrrolidones partition well into human corneum stratum. Within the tissue they may act by altering the solvent nature of the membrane and pyrrolidones have been used to generate ‘reservoirs’within skin membranes for sustained release of permeant.

Essential oils, Terpenes and terpenoids:

Various naturally occurring essential oils like eucalyptus oil, turpentine oil, peppermint oil, oil of ocimum sanctum, or their active constituents like menthol, terpenes, eucalyptol etc. have been reported as penetration enhancer. Panchagnula et.al studied the terpene penetration enhancers in ethanol/water co-solvent system. (57) The permeation studies with DSC and partitioning experiments revealed that increased lipid disruption was probably the mechanism involved in enhancing ability of formulation containing 1,8-cineole, menthone and nerolidone. (55)


<table>
<thead>
<tr>
<th>CLASS</th>
<th>EXAMPLES</th>
<th>MECHANISM OF ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrating substances</td>
<td>Water</td>
<td>Hydrates the SC</td>
</tr>
<tr>
<td></td>
<td>Occlusive preparations</td>
<td></td>
</tr>
<tr>
<td>Keratolytics</td>
<td>Urea</td>
<td>Increase fluidity and hydrates the SC</td>
</tr>
<tr>
<td>Organic solvents</td>
<td>Alcohols</td>
<td>Partially extracts lipids</td>
</tr>
<tr>
<td></td>
<td>Poly ethylene glycol</td>
<td>Replace bound water in the intercellular spaces</td>
</tr>
<tr>
<td></td>
<td>DMSO</td>
<td>Increase lipid fluidity</td>
</tr>
<tr>
<td>Fatty acids</td>
<td>Oleic acid</td>
<td>Increase fluidity of intercellular lipids</td>
</tr>
<tr>
<td>Terpenes</td>
<td>1,8-Cineole , Menthol</td>
<td>Opens up polar pathway</td>
</tr>
<tr>
<td>Surfactants</td>
<td>Polysorbates</td>
<td>Penetrates into skin, micellar solubilisation of SC</td>
</tr>
<tr>
<td></td>
<td>Sodium lauryl sulfate</td>
<td></td>
</tr>
<tr>
<td>Azone</td>
<td>1-Dodecylhexahydro-2HAzepine-2on2</td>
<td>Disrupts the skin lipids in both the head group and tail region</td>
</tr>
</tbody>
</table>

**Liquid-protein-partitioning theory of skin penetration enhancement** (52):

The liquid-protein-partitioning theory of skin penetration enhancement suggests that accelerants usually act by one or more of three main mechanics, they can alter the intracellular lipid or intracellular protein domains of the horny layer and they may also increase partitioning into the skin of the drug, a co-enhancer, water or any combination of this. The penetration enhancers can acts at different sites of intercellular domain of skin, which are shown in Figure 8.

**Molecular interaction for enhancer action within the intercellular domain:**

**Interaction of Site A:**

Many penetration enhancers should react with the polar head groups of the lipid and modify hydrogen bonding and ionic forces. They will disturb the hydrogen spheres of the lipid and the subsequent alterations in head group interactions should upset the packing of the polar plane. This disruption may make the domain more fluid and so promote the diffusion in particular polar penetrants. A second response may be to allow more aqueous fluid to enter the tissue and so increase the water volume between lipid layers. These swallowing should provides a larger functional volume of 'free' water as distinct from structured water and hence increase the cross-sectional area available for polar diffusion (Site B). An important secondary feature is that disruption of interfacial structure will also alter packing of lipid chains. The lipid hydrophobic route thus becomes more disordered and more readily transversed by a lipid-penetrant (Site C).

**Direct action at site B:**

An accelerant may affect the aqueous region in ways additional to those that alter bond interactions and there by increase the water content. Thus, the enhancer may directly change the constitution of domain. For example, when vehicles or transdermal devices deliver high concentration of solvents such as propylene glycol, ethanol, the pyrrolidones or dimethyl-sulphoxide to the skin, the solubility ability of aqueous side may increase.
Then the location may better dissolve molecules such as estradiol and hydrocortisone and the result is that the operational partition co-efficient now favors the development of a high drug concentration in the skin. A complicating feature is that this solubilising effect may decrease the chemical potential of the drug in stratum corneum, temporary decrease in the driving forces for diffusion. When the solvent diffuses out of the stratum corneum into the viable epidermis, the drug follows at a relatively high flux as it diffuses down its new raised chemical potential gradient.

**Action at site C (The lipid domain):**

Many penetration enhancers, because of their structures, should insert between the hydrophobic tails of the bilayer, so upsetting their packing, increasing their fluidity and thus permitting easier diffusion of penetrants. These alterations in lipid packing can reflect back to provide some disorder in the polar head group region and so promote polar route penetration. Those enhancers with large polar head groups may also modify site ‘A’ directly. Alteration at sites A & C will have a combined effect on amphiphilic penetrants. These will insert in a bilayer in a way similar to the lipid molecules and then more easily flex, rotate and in particular, diffuse laterally.

**The intracellular route:**

For some specific penetrants, the intracellular pathway provides a significant route by enhancing interaction with lipid remains in the corneocytes. As regards a polar route, we should need to consider the keratin fibrils and the interactions with enhancers such as the aprotic solvents (e.g. DMSO, DMF and DMAc), the pyrrolidones and surfactants undergo with proteins. These mechanisms include interaction with polar groups, relaxation of binding forces and alterations in the conformation of the vehicles. Extensive interaction may form pore routes through the tissue.

**Polymer Selection for Transdermal Drug Delivery System**

The development of transdermal system requires judicious selection of a polymeric material or a series of polymers whose diffusive characteristics will be such that a desirable permeation rate of a specific drug can be obtained. (58)

Following factors are taken into consideration during the selection of polymer. (48)

- Molecular weight and chemical functionality of polymer must allow proper diffusion and release of specific drugs. Increased polymer weight decrease drug diffusivity in polymers.
- Polymer should not react with the drug.
- The polymer and its degradation products must be non-toxic.
- The polymer should not decompose on storage or during the useful life of device.
The polymer must be easy to manufacture and it should yield itself into desired product and should allow incorporation of large quantities of active component without deteriorating its mechanical properties.

Cost of polymers should not be excessive.

Selection of the Drug for Transdermal Drug Delivery System

Before the development of the transdermal drug delivery system of any drug various physicochemical properties, pharmacokinetics and pharmacodynamic properties are taken under consideration. Typical requirement for transdermal delivery of drug includes (46)

- Low molecular weight ranging from 500 to 1000 Daltons.
- Low melting characters (150-200°F).
- Aqueous solutions neither too acidic nor basic (between 5 and 9 pH units).
- Preferable lipid/water co-efficient i.e. partition co-efficient.
- The most important requirement of the drug to be delivered transdermally is demonstrated by need for controlled delivery, such as short half-life and adverse effects associated with other routes or complex oral route or IV dose regimen.
- Drugs, which get extensively metabolized in the hepatic, first pass effect. (53)

Transdermal Patch

A transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. Often, this promotes healing to an injured area of the body. (59)

Basic Components of TDDS:

- Polymer matrix / Drug reservoir
- Drug
- Permeation enhancers
- Pressure sensitive adhesive (PSA)
- Backing laminates
- Release liner
- Other excipients like plasticizers and solvents

Polymer matrix / Drug reservoir:

Polymers are the backbone of TDDS, which control the release of the drug from the device. (60)

Natural Polymers: e.g. cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan etc.

Synthetic Elastomers: e.g. polybutadiene, hydriin rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, butylrubber etc.

Synthetic Polymers: e.g. polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate etc.

Drug:

The transdermal route is an extremely attractive option for the drugs with appropriate pharmacology and physical chemistry. It is generally accepted that the best drug candidates for passive adhesive transdermal patches must be non ionic, of low molecular weight (less than 500 Daltons), have adequate solubility in oil and water (log P in the range of 1-3), a low melting point (less than 200°C) and are potent (dose in mg per day).

Permeation Enhancers:

These are the chemical compounds that increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug candidate. Penetration enhancers interact with structural components of stratum corneum i.e., proteins or lipids. They alter the protein and lipid packaging of stratum corneum, thus chemically modifying the barrier functions leading to increased permeability. (61)

Pressure sensitive adhesives:

A PSA is a material that helps in maintaining an intimate contact between transdermal system and the skin surface. PSA should be physicochemically
and biologically compatible and should not alter drug release. (62)

**Backing Laminate:**

While designing a backing layer, the consideration of chemical resistance of the material is most important. Excipient compatibility should also be considered because the prolonged contact between the backing layer and the excipients may cause the additives to leach out of the backing layer or may lead to diffusion of excipients, drug or penetration enhancer through the layer.

**Release Liner:**

During storage the patch is covered by a protective liner that is removed and discharged immediately before the application of the patch to skin. It is therefore regarded as a part of the primary packaging material rather than a part of dosage form for delivering the drug. **Other excipients:**

Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir. In addition plasticizers such as dibutylphthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch.

**APPROACHES USED IN THE DEVELOPMENT OF TDDS (63, 64, 65, 66)**

**Membrane permeation controlled systems:**

In this type of system, the drug reservoir is totally encapsulated in a shallow compartment moulded from a drug-impermeable metallic plastic laminate and a rate controlling membrane, which may be micro porous or non-porous. The drug molecules are permitted to release only through the rate-controlling membrane. In the drug reservoir compartment, the drug solids are either dispersed in a solid polymer matrix or suspended in viscous liquid medium such as silicone fluid to form a paste like suspension (Figure 11).

A thin layer of drug compatible, adhesive polymer like silicone or polyacrylate adhesive may be applied to the external surface of the rate controlling membrane to achieve an intimate contact of the transdermal system and skin surface. The rate of drug release from this type of system can be tailored by varying the polymer composition, permeability coefficient and thickness of the rate limiting membrane, and adhesive. The major advantage of membrane permeation controlled transdermal system is the constant release of drug. However, a rare risk also exists when an accidental breakage of the rate controlling membrane can result in dose dumping or a rapid release of the entire drug content.

![Figure 11: Matrix controlled transdermal delivery system](image)

Examples; Nitroglycerin-releasing transdermal system (Transderm-Nitro/Giba, USA) for once a day medication in angina pectoris. Scopolamine-releasing transdermal system (Transderm-Scop/Giba, USA) for 72 hrs prophylaxis of motion sickness.
**Matrix diffusion-controlled systems:**

In this approach, the drug reservoir is prepared by homogenously dispersing drug particles in a hydrophilic or lipophilic polymer matrix. The resultant medicated polymer is then moulded into a medicated disc with a defined surface area and controlled thickness.

The drug reservoir can be formed by dissolving drug and polymer in a common solvent followed by solvent evaporation in a mould at an elevated temperature and/or vacuum. The drug reservoir containing polymer disc is then pasted on to an occlusive base plate in a compartment fabricated from a drug impermeable plastic backing (Figure 12). The adhesive polymer is then spread along the circumference to form a strip of adhesive rim around the medicated disc. The advantage of this system is the absence of dose dumping since polymer cannot rupture.

**Figure 12:** Adhesive Dispersion Type transdermal delivery systems

Example; Nitroglycerin-releasing transdermal therapeutic systems (Nitro-Dur and Nitro-Dur II / Key Pharmaceuticals, USA).

**Adhesive dispersion-type systems:**

This system is a simplified form of the membrane permeation-controlled system. Here the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer eg., poly(isobutylene) or poly (acrylate) adhesive and then spreading the medicated adhesive, by solvent casting or hot melt, on to a flat sheet of drug impermeable metallic plastic backing to form a thin drug reservoir layer. On the top of the drug reservoir layer, thin layers of non-medicated, rate controlling adhesive polymer of a specific permeability and constant thickness are applied to produce an adhesive diffusion controlled delivery system (Figure 13).

**Figure 13:** Matrix controlled transdermal delivery system
Example: Isosorbide dinitrate releasing transdermal therapeutic system (Frandol tape/Yamanouchi, Japan) once-a-day medication of angina pectoris.

**Microreservoir type or microsealed dissolution controlled systems:**

This system is a combination of the reservoir and matrix diffusion type drug delivery systems. The drug reservoir is formed by first suspending the drug solids in an aqueous solution of a water-soluble liquid polymer and then dispersing the drug suspension homogenously in lipophilic polymer viz. silicone elastomers by high-energy dispersion technique to form several discrete microscopic spheres of drug reservoirs. The quick stabilization of this thermodynamically unstable dispersion is accomplished by immediately cross-linking the polymer chains in-situ, which produces a medicated polymer disc with a constant surface area and fixed thickness. Positioning the medicated disc at the center and surrounding it with an adhesive produce a transdermal therapeutic system (Figure 14).

![Figure 14: Microreservoir type transdermal delivery system](image)

Example: Nitroglycerin releasing transdermal therapeutic system (Nitro disc, Searle, USA) for once a day therapy of angina pectoris.

**TYPES OF TRANSDERMAL PATCHES**

**Single layer drug in adhesive:**

In this type the adhesive layer contains the drug. The adhesive layer not only serves to adhere the various layers together and also responsible for the releasing the drug to the skin. The adhesive layer is surrounded by a temporary liner and a backing.

**Multi-layer drug in adhesive:**

This type is also similar to the single layer but it contains a immediate drug release layer and other layer will be a controlled release along with the adhesive layer. The adhesive layer is responsible for the releasing of the drug. This patch also has a temporary liner-layer and a permanent backing.

**Vapour patch:**

In this type of patch the role of adhesive layer not only serves to adhere the various layers together but also serves as release vapour. The vapour patches are new to the market, commonly used for releasing of essential oils in decongestion. Various other types of vapor patches are also available in the market which are used to improve the quality of sleep and reduces the cigarette smoking conditions.

**Reservoir system:**

In this system the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the ratecontrolling membrane, which can be micro porous or non porous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel or dispersed in a solid polymer matrix. Hypoallergenic adhesive polymer
can be applied as outer surface polymeric membrane which is compatible with drug.

Matrix system:

i. Drug-in-adhesive system:

In this type the drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated adhesive polymer by solvent casting or melting (in the case of hot-melt adhesives) on an impervious backing layer. On top of the reservoir, unmediated adhesive polymer layers are applied for protection purpose.

ii. Matrix-dispersion system:

In this type the drug is dispersed homogenously in a hydrophilic or lipophilic polymer matrix. This drug containing polymer disk is fixed on to an occlusive base plate in a compartment fabricated from a drug impermeable backing layer. Instead of applying the adhesive on the face of the drug reservoir, it is spread along with the circumference to form a strip of adhesive rim.

Microreservoir system:

In this type the drug delivery system is a combination of reservoir and matrix-dispersion system. The drug reservoir is formed by first suspending the drug in an aqueous solution of water soluble polymer and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unreachable, microscopic spheres of drug reservoirs. This thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer in situ by using cross linking agents.

Ideal product requirements (67):

- Shelf life up to 2 years
- Small size patch (i.e., less than 40 cm²)
- Convenient dose frequency (i.e., once a day to once a week)
- Cosmetically acceptable (i.e., clear, white color)
- Simple packaging (i.e., minimum number of pouches and steps required to apply the system)
- Easy removal of the release liner (i.e., for children and elderly patients)
- Adequate skin adhesion (i.e., no fall off during the dosing interval and easy removal without skin trauma)
- No residue i.e., “cold flow” around the edge of the patch in storage or after application to skin or beneath the patch after removal
- No unacceptable dermal reactions (i.e., contact dermatitis, skin sensitization, photo toxicity, photosensitization, erythema, itching, stinging, burning, etc.) Consistent biopharmaceutical performance (i.e., precision of the required pharmacokinetic and pharmacodynamic response between individuals and in the same individuals over time.
- Improve bioavailability.
- Decrease the dose to be administered.
- Decrease side or unwanted effects.
- Decrease gastrointestinal side effects.
- Easy to discontinue in case of toxic effects.
- Increase patient compliance.

Why Transdermal Route for Antiretroviral drugs:

Due to following advantages over oral route:

- Avoids hepatic first pass metabolism.
- Maintains constant blood levels for longer period of time.
### Table 8: Characteristics of several drugs delivered transdermally.

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Mol. Wt. (Dalton)</th>
<th>Trade Name(s)</th>
<th>Daily Dose</th>
<th>Frequency Of Application</th>
<th>Type of System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine</td>
<td>230</td>
<td>Catapres-TTS®</td>
<td>0.1-0.3 mg</td>
<td>Weekly</td>
<td>Reservoir</td>
</tr>
<tr>
<td>Estradiol</td>
<td>272</td>
<td>Vivelle®</td>
<td>0.025-0.1 mg</td>
<td>Weekly</td>
<td>Drug in adhesive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vivelle-Dot®</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Esclim®</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Climara®</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>337</td>
<td>Duragesic Transdermal System®</td>
<td>0.6 mg</td>
<td>Once in every three days</td>
<td>Reservoir</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>234</td>
<td>Lidoderm®</td>
<td>Not started</td>
<td>Daily</td>
<td>Drug in adhesive</td>
</tr>
<tr>
<td>Nicotine</td>
<td>162</td>
<td>Nicoderm CQ®</td>
<td>7-21 mg</td>
<td>Daily</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nicotrol®</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>227</td>
<td>Nitro-Dur®</td>
<td>1.4-11.2 mg</td>
<td>Daily</td>
<td>Drug in adhesive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nitrodisc®</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scopolamine</td>
<td>303</td>
<td>Transderm-Scop®</td>
<td>0.33 mg</td>
<td>Once in every three days</td>
<td>Reservoir</td>
</tr>
<tr>
<td>Testosterone</td>
<td>288</td>
<td>Androderm®</td>
<td>2.5-5.0 mg</td>
<td>Daily</td>
<td>Reservoir</td>
</tr>
</tbody>
</table>

The absorption of drugs through the transdermal route improves bioavailability of drugs that might otherwise be metabolized by first-pass effect (pre-systemic drug elimination) during their passage through the gastrointestinal tract. Drug absorption from the transdermal route is mainly via passive diffusion through the lipoidal membrane. Thus, transdermal route of drug delivery has attracted the attention worldwide for optimizing the drug delivery.

**Future of Tdds**

The market is slowly moving from passive patches which were the dominant product earlier. With the introduction of Androgel, the first transdermal testosterone gel for males in the year 2000 and lidocaine using pandermal technology (iontophoretic technology) the transdermal drug delivery holds promise for many therapeutic moieties. Much focus is towards developing transdermal technology that utilizes mechanical and electrical energy to increase the flux through the barrier layer and the intense research is towards developing micropores in the stratum corneum, which is expected to be a painless therapy. Another upcoming technique to enhance the transdermal permeation of the drug is Magnetophoresis which promotes the skin delivery of drugs. It involves the
use of magnetic chip embedded in the skin and the magnetic waves direct the drug into the blood circulation.

**Conclusion**

Treatments for AIDS and HIV with conventional Antiretroviral drugs cause a lot of side effects due to its high dose and first pass metabolism. Due to that it is suitable to give another route like transdermal route that reduces side effects and its dose. The absorption of drugs through the transdermal route improves bioavailability of drugs that might otherwise be metabolized by first-pass effect (pre-systemic drug elimination) during their passage through the gastrointestinal tract. Drug absorption from the transdermal route is mainly via passive diffusion through the lipoidal membrane. Thus, transdermal route of drug delivery has attracted the attention worldwide for optimizing the drug delivery.

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