Transdermal Delivery: A Recent Trend in Treatment of Chronic Diseases

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ABSTRACT

Transdermal drug delivery systems are devices containing drug of defined surface area that delivers a pre-determined amount of drug to the surface of intact skin at a pre-defined rate. The skin as a route for systemic drug administration has become very attractive since the introduction of transdermal therapeutic systems in the form of patches. The discovery of transdermal drug delivery systems (TDDS) is a breakthrough in the field of controlled drug delivery system. Transdermal dosage forms, alternative to the conventional dosage form are becoming very popular because of their unique advantages. Like controlled zero ordered absorption, simple mode of administration and having option to terminate the action in case of adverse effect. So the TDDS makes them desirable for the treatment of chronic diseases where long term treatment is necessary. Scopolamine, clonidine, nitroglycerine, antihypertensive, hypoglycemic, antiischaemic, drug molecules being extensively used in transdermal form. This article is dedicated to the review of transdermal recent research in the area of antiischaemics, antihypertensive, antiemetic, hormones, opioids, anticholinergics and other drug molecules which should be selected for TDDS reported in various pharmaceutical journals.

Key words: Transdermal drug delivery systems, Antihypertensive, Hypoglycemic, Antiischaemic, opioids.

INTRODUCTION:

Transdermal drug delivery systems are devices containing drug of defined surface area that delivers a pre-determined amount of drug to the surface of intact skin at a pre-defined rate.1 The skin as a route for systemic drug administration has become very attractive since the introduction of transdermal therapeutic systems in the form of patches.2 The discovery of transdermal drug delivery systems (TDDS) is a breakthrough in the field of controlled drug delivery systems. The ability of TDDS to deliver drugs for systemic effect through intact skin while bypassing first pass metabolism has accelerated transdermal drug delivery research in the field of pharmaceutics. Over a decade of such extensive research activities, many transdermal patches have been developed and successfully commercialized.3

Most of the transdermal systems are designed to release the actives at a zero order rate for a period of several hours to days following application to the skin. Though several long acting, extended or controlled release formulations are available for the treatment of these conditions with indicated benefits, they have to be taken at least once a day in comparison to transdermal patches that extend drug release for up to seven days.

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herpetic neuralgia indication, its sales grew steadily as it gained additional off-label uses as a local pain treatment option, reaching over $1.1 billion annual sales by the end of 2010. The Exelon® patch, a rivastigmine-containing patch launched in 2007, represents yet another innovative treatment option.

**Advantages of transdermal drug delivery system.**

1. Avoids the risk and inconvenience of intravenous therapy, noninvasive transdermal route
2. Minimizes the variation in the absorption and metabolism associated with oral administration
3. Permits continuous drug administration and use for drugs with short biological half-life.
4. Transdermal delivery can increase the therapeutic value of many drugs via avoiding specific problems associated with the drug. E.g. GI irritation, lower absorption, decomposition due to ‘hepatic first pass’ effect.
5. Treatment can be continued or discontinued whenever necessary.
6. Greater patient compliance due to the reduction of dosing frequency.
7. Easy elimination of drug delivery in case of toxicity.
8. Transdermal medications deliver a steady infusion of a drug over an extended period of time. Adverse effects or therapeutic failure frequently associated with intermittent dosing can also be avoided.
9. Due to above advantage, it is possible that an equivalent therapeutic effect can be elicited via transdermal drug input with a lower daily dose of the drug than is necessary, if e.g. the drug is given orally.
10. Can be applied on any part of skin convenience to patient.
11. The simplified medication regimen leads to improved patient compliance and reduced inter and intra-patient variability.

**Limitations of transdermal drug delivery system.**

1. Skin irritation (contact dermatitis) due to Excipient and absorption enhancers and May increase percutaneous absorption
2. One of the greatest disadvantages to transdermal drug delivery is the possibility that a local irritation will develop at the site of application. Erythema, itching, and local edema can be caused by the drug, the adhesive, or other excipients in the patch formulation. For most patients, site rotation can minimize irritation. However, some patients develop severe allergic reactions to transdermal patches, and, in these cases, therapy must be discontinued.
3. Skin's low permeability limits the number of drugs that can be delivered in this manner because the skin serves protective functions; it inhibits compounds from crossing it. Many drugs with a hydrophilic structure permeate the skin too slowly to be of therapeutic benefit. Drugs with a lipophilic character, however, are better suited for transdermal delivery.
4. Technical development problems due to Batch-to-batch variations and Migration of active during storage
5. Difficulty of permeation due to Highly efficient physical & chemical barrier and due to crystallization

**Preparation of TDDS consists of three basic designs:**

A. Membrane control or reservoir patches (RPs),
B. Matrix or monolithic patches (MPs), and
C. Drug in adhesive patches (DIAPs).

The earliest TDDS were reservoir-type devices that used membranes to control the rate of drug release. Reservoir patches contain the drug in a raised compartment, diffusing it through a polymeric membrane that controls the release rate, usually providing true zero-order kinetics. Matrix patches combine the drug, polymeric membrane, and adhesive into a single layer, the polymeric matrix. Drug is diffused through the polymeric matrix and through the skin. The drug closest to the skin is released first, and drug deeper within the patch travels a longer diffusional path before being released. This pattern departs slightly from zero-order kinetics, but the difference is generally not clinically significant. Matrix patches are smaller and thinner than reservoir patches, features that have increased patch acceptability among patients.

Monolithic matrix systems consist of a polymeric material in which the drug is dispersed or dissolved, acting simultaneously as a combined drug reservoir and skin contact adhesive layer. Today a drug is more commonly dispersed or dissolved in a pressure-sensitive adhesive (PSA) matrix also called as drug in adhesive patches.

In the simplest form, the adhesive matrix or drug-in-adhesive (DIA) design, the drug is directly loaded or dispersed into the PSA polymer. The adhesive matrix provides several functions, including skin adhesion, storage of the drug, and control over drug/enhancer delivery rate, and it also governs their partitioning into the stratum corneum.

Comparison of characteristics of these three, DIAPs and MPs are clearly superior to RPs in terms of patient compliance. It might also be expected, because of their simple structure, that DIAPs and MPs are superior from the commercial viewpoint in terms of the manufacturing process control, quality control and continuous product improvement. Moreover, the thinner construction of MPs and DIAPs may improve wearing comfort for the patient. However, drug formulations for MPs are more challenging to produce, particularly for those patches that incorporate the drug in the adhesive.

**Fig. 1: Matrix type TDDS**

**Fig. 2: Reservoir type TDDS**
The human skin surface is known to contain an average of 40-70 hair follicles and 200-250 sweat ducts on every square centimeter. These skin appendages however, actually occupy grossly only 1% of the total human skin surface. This trans-appendage route of percutaneous absorption provides a very limited contribution to overall kinetic profile of skin permeation. Therefore, the skin permeation of most neutral molecules at steady state can thus be considered primarily a process of passive diffusion through the intact stratum corneum in the interfollicular region. The phenomenon of percutaneous absorption can be visualized as consisting of a series of steps in sequence: sorption of a penetrant molecule onto the surface layer of stratum corneum, diffusion through it and the viable epidermis, and finally, at the papillary layer of the dermis, the molecule is taken up into the microcirculation for subsequent distribution, so diffusion through stratum corneum is often rate limiting step.

The transport of drugs through stratum corneum is shown in Fig. 5. Drug molecules may diffuse through the skin by three different routes: the intact stratum corneum, the hair follicle region and the sweat gland ducts. Despite much investigation carried out on various areas of skin permeation, there is no total agreement on the mechanism responsible for permeation through the intact skin. In initial transient diffusion stage, the drug molecules may penetrate the skin along the intercellular pathway of passive diffusion through the intact stratum corneum in the interfollicular region. The total fluxes of matter (J) across the membrane is the sum of fluxes by each route which is expressed by:

$$J = f_{1p1} + f_{2p2} + \ldots \ldots \ldots + f_{nmp} \Delta C$$  \hspace{1cm} (5)

where,

- $f_{ip}$ - overall permeability co-efficient
- $\Delta C$ - concentration drop

According to equation 3, the rate of drug transport depends not only on its aqueous solubility but is also directly proportional to its oil in water partition coefficient, its concentration in the formulation vehicle and the surface area of the skin to which it is exposed. It is inversely proportional to the thickness of the stratum corneum. An understanding of the transport behavior of drugs is vital for designing an effective topical or transdermal drug delivery system as well as

$$\frac{dq}{dt} = Ps(c_d - c_r)$$  \hspace{1cm} (1)

where,

- $c_d$ - concentration of the permeant in donor phase (stratum corneum)
- $c_r$ - concentration of the permeant in receptor phase (systemic circulation)
- $Ps$ - overall permeability coefficient of the skin and is defined by

$$Ps = \frac{K_s D_{ss}}{h_s}$$  \hspace{1cm} (2)

where, $K_s$ - partition coefficient of penetrant
- $D_{ss}$ - apparent diffusivity of penetrant
- $h_s$ - Skin thickness
- $s$ - Surface area of the skin exposed

Thus permeability coefficient ($P_s$) may be constant if $K_s$, $D_{ss}$ and $h_s$ terms are constant under a given set of conditions. A constant rate of drug permeation is achieved if $c_d > c_r$

Then equation (2) may be reduced to

$$\frac{dq}{dt} = P_s C_d$$  \hspace{1cm} (3)

Molecular penetration through various regions of the skin is limited by the diffusional resistances encountered. The total diffusional resistance ($R_{sio}$) to permeation through the skin has been recruited by Chien as:

$$R_{skin} = R_{sc} + R_e + R_{pd}$$  \hspace{1cm} (4)

where,

- $R$ - diffusional resistance and the subscripts $sc$, $e$ and $pd$ refers to the stratum corneum, epidermis & papillary layer of dermis respectively.

Of these layers, the greatest resistance is put up by the stratum corneum and tends to be the rate-limiting step in percutaneous absorption.

When more than one phase of the membrane is capable of supporting separate diffusional currents through each, the pathways are configured as parallel to one another.
for reasonable predicting and comparing drug behavior in various transdermal formulations.

Several events have to take place during drug transport across the skin after a transdermal patch has been applied to the skin. These events are listed and depicted in factorial fashion in Fig. 3.
1. Drug release from device.
2. Partitioning of the drug on skin surface.
3. Diffusion and binding of drug in stratum corneum.
4. Drug partitioning between stratum corneum / viable epidermis boundaries.
5. Diffusion of drug and bio-conversion in viable epidermis.
6. Drug absorption into blood.

**Fig. 6: Events of drug transport across skin**

In case of transdermal drug delivery systems, percutaneous absorption of drug molecule is important. The rate and extent of absorption of the drug should be adequate to achieve and to maintain uniform systemic and therapeutic levels throughout the duration of use. In general, once the drug molecules cross the stratum corneum barrier, passage into deeper dermal layers and into the systemic circulation occurs relatively quickly and easily.

**Factors effecting transdermal permeability:**

The factors controlling transdermal permeability can be broadly classified as:

**I. Physico-chemical properties of the penetrant molecules:**

1) **Partition coefficient:** Drugs having both lipid and water solubilities are favorably absorbed through the skin. Transdermal permeability coefficient shows a linear dependency on partition coefficient. A lipid/water partition coefficient equal to or more than one is generally required.

2) **pH conditions:** A very high or low pH value can be destructive to the skin. With moderate pH values the flux of ionisable drugs can be affected by changes in pH as these alter the ratio of charged to uncharged species and their transdermal permeability.

3) **Penetrant concentration:** Increasing concentration of dissolved drug causes a proportional increase in flux. At higher concentration, excess solid drug function as reservoir and help to maintain a constant drug concentration for a prolonged period of time.

**II. Physicochemical properties of transdermal drug delivery systems:**

1. **Release characteristics:** Solubility of the drug in the vehicle determines the release rate. The mechanism of drug release depends on the following factors:
   a) Whether the drug molecules are dissolved or suspended in the delivery system,
   b) The interfacial partition coefficient of the drug from the delivery system to skin,
   c) pH of the vehicle.

2. **Enhancement of transdermal permeation:** Majority of drugs will not penetrate the skin at rates sufficiently high for therapeutic efficacy. The permeation can be improved by the addition of permeation enhancer into the system.

**III. Physiological and pathological conditions of skin:**

1. **Reservoir effect of horny layer:** The horny layer especially the deeper layer can sometimes act as a depot and modify the transdermal permeation of drugs. The reservoir effect is due to irreversible binding of a part of the applied drug with the skin.

2. **Lipid film:** The lipid film on the skin surface acts as a protective layer to prevent the removal of moisture from the skin and helps in maintaining the barrier function of stratum corneum.

3. **Skin hydration:** Hydration of stratum corneum can enhance permeability. Skin hydration can be achieved simply by covering or occluding the skin. Increased hydration appears to open up the dense, closely packed cells of the skin and increases its porosity.

4. **Skin temperature:** Raising the skin temperature results in an increase in the rate of skin permeation; this may be due to availability of thermal energy required for diffusivity.

5. **Regional variation:** Difference in nature and thickness of the barrier layer of skin causes variation in permeability.

6. **Pathological injuries to the skin:** Injuries that disrupt the continuity of the stratum corneum increases permeability due to increased vasodilatation caused by removal of the barrier layer.

7. **Cutaneous self metabolism:** Catabolic enzymes present in the epidermis may render the drug inactive by metabolism and influence the topical bioavailability of the drug.

**Product Development**

Because of the uniqueness of this dosage form, the following questions need to be answered to define the final product:

1. Target therapeutic concentration
2. Dose to be delivered
3. Maximum patch size acceptable
4. Preferred site of application
5. Preferred application period (daily, biweekly, weekly, etc)

Once the preferred final product description has been established,
an evaluation of the drug candidate begins. Because of the limitation of loading dose in a patch and a practical patch size, not all drugs can be candidate for transdermal drug delivery.

Table 1: Ideal Properties of a Transdermal Drug Delivery System

<table>
<thead>
<tr>
<th>Properties</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shelf life</td>
<td>Up to 2 years</td>
</tr>
<tr>
<td>Patch size</td>
<td>&lt; 40 cm²</td>
</tr>
<tr>
<td>Dose frequency</td>
<td>Once a daily to once a week</td>
</tr>
<tr>
<td>Aesthetic appeal</td>
<td>Clear, tan or white color</td>
</tr>
<tr>
<td>Packaging</td>
<td>Easy removal of release liner and minimum number of steps required to apply</td>
</tr>
<tr>
<td>Skin reaction</td>
<td>Non irritating and non sensitizing</td>
</tr>
<tr>
<td>Release</td>
<td>Consistent pharmacokinetic and pharmacodynamic profiles over time</td>
</tr>
</tbody>
</table>

The product development of a transdermal formulation generally includes the following stages:

- Selection of drug candidate
- Selection of the appropriate physical form (e.g., acid, base, or salt)
- Selection of the desired design (e.g., reservoir, matrix, etc.)
- Preparation of prototype formulations and testing of their physicochemical properties (tack, shear, peel adhesion, skin adhesion, etc.) Evaluation of in vitro permeation
- Development of analytical methods to quantitate drug in the formulation, skin layers, release medium, and blood (if applicable)
- Evaluation of potential for systemic adverse events (e.g., carcinogenicity, teratogenicity, mutagenicity, etc.)
- Evaluation of skin toxicity (irritation, sensitization, etc.) in animals and humans • Microbial and preservative testing, if necessary
- Phase I, II, and III human clinical trials
- Scale-up activities including development of specifications
- Post approval market surveillance.

Drug selection: ³⁴
The transdermal route cannot be employed for a large number of drugs, only few drug products are currently available via transdermal delivery. In many cases, a drug’s physical properties, including molecular size and polarity, have limited its capacity to be delivered transdermally. Similarly, the biological properties of drug molecules, including dermal irritation and insufficient bioavailability, have been problematic. In the product development the focus must be on the rationality of drug selection based on pharmacokinetic parameters and physicochemical properties of the drug. Physicochemical factors such as solubility, crystallinity, molecular weight <400, polarity, melting point <200, partition coefficient Log P (octanol-water) between -1.0 to 4 must be considered. Biological factor should also be considered such as skin irritation, site of application of the patch e.g. scopolamine patch for motion sickness is applied backside of the ear and Transderm-Nitro is applied on the chest. When a pharmacologically active material has to be presented to the skin, an occlusive or allergic response is significant, limits have to be determined for the acceptability of the undesired effect. The pharmacokinetic information of the drug is a critical factor in deciding its suitability for delivery by the transdermal route as it is suitable only for drugs whose daily dose is in few milligrams. The resulting plasma concentration of active agent depends on the clearance; however, if one assumes a small volume of distribution and relatively long half-life, plasma level in excess of few micrograms per milliliter is very unlikely. Another important factor is the half-life, (e.g., nitroglycerin t 1/2 is 3 min) which provides information on the disposition of a drug in our body other parameters such as effective plasma level; also determine whether a transdermal delivery can be developed or not (Table 2 and Table 3).

Table 2: Factors To Be Considered For Transdermal Dose Calculation

<table>
<thead>
<tr>
<th>Physiochemical</th>
<th>Pharmacokinetic</th>
<th>Biological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solubility</td>
<td>Half life</td>
<td>Skin toxicity</td>
</tr>
<tr>
<td>Crystallinity</td>
<td>Volume of distribution</td>
<td>Site of application</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>Total body clearance</td>
<td>Allergic reactions</td>
</tr>
<tr>
<td>Polarity</td>
<td>Therapeutic plasma concentration</td>
<td>Skin metabolism</td>
</tr>
<tr>
<td>Melting Point</td>
<td>Bioavailable factor</td>
<td>Skin permeability</td>
</tr>
</tbody>
</table>

Table 3: Criteria of Drug Candidate For Transdermal Drug Delivery

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>Should be low</td>
</tr>
<tr>
<td>Half life in hr</td>
<td>10 or less</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>&lt; 400</td>
</tr>
<tr>
<td>Partition coefficient</td>
<td>Log P (octanol-water) between ~1.0 and 4</td>
</tr>
<tr>
<td>Skin permeability coefficient*</td>
<td>&gt; 0.5 x10-3cm/hr</td>
</tr>
<tr>
<td>Skin reaction</td>
<td>Non irritating and non sensitizer</td>
</tr>
<tr>
<td>Oral bioavailability</td>
<td>Low</td>
</tr>
<tr>
<td>Therapeutic index</td>
<td>Low</td>
</tr>
</tbody>
</table>

Drugs for Transdermal research: ³⁴,⁹
Recently Nitroglycerine in the reservoir has been developed to monitor the drug release during emergency or at the volition of the patient. The current research trends give the excitement amongst the transdermal scientist. For developing newer formulation containing other drugs which obeys all the criteria of transdermal delivery system. So for such candidates here showing some drugs which are suitable for transdermal delivery.

A. Antiischaemics:

A1. Isosorbide dinitrate: Bioavailability, when administered by conventional route varies significantly; the drug has a short half life 50 minutes ± 25 minutes. Demanding frequent administration & prescribed dosage regimen is 2.5- 10 mg every 2 to 3 hrs from TDDS route. A flux of 4.01 mg/hr is necessary to achieve the level of clinical efficiency of maintenance therapy.

A2. Verapamil hydrochloride: It is a calcium ion influx inhibitor. It is widely used in the treatment of angina, hypertension, and supraventricular tachyarrhythmia. The plasma half-life of is 2-7 h, which neces-
situates multiple dosing. It is 90% absorbed from the gastrointestinal tract but is subject to considerable 1st pass metabolism and its bioavailability is around 20-30%.

A.3. Nifedipine: a potent drug which is widely used for the treatment of hypertension. Due to extensive first pass metabolism its bioavailability is low. It is preferable for transdermal. Only drug shows less skin permeation but overcome by using penetration enhancers.

B. Antihypertensive:

B.1 Clonidine: is a centrally acting antihypertensive drug having plasma half life of 8-12 h and peak concentration occurs in 2-4 h. It effectively reduces blood pressure in patients with mild-to-moderate hypertension. When transdermal therapy was compared with oral delivery of clonidine, efficacy was similar for the two delivery modalities. However, side effects such as drowsiness and dry mouth occurred less frequently in patients treated with transdermal clonidine.

B.2 Propranolol hydrochloride: a beta blocker which is used in management of hypertension. Due to its short biological half life (3.9 h) it necessitates for controlled delivery.

B.3 Atenolol and metoprolol tartrate: are ß1 blockers that are incompletely absorbed from gastrointestinal tract having half lives of about 6-7 h.

B.4 Timolol maleate: a beta adreno receptor blocking agent used in treatment of cardiovascular diseases like myocardial infarction, angina pectoris and hypertension. It is 8-10 times potent than propranolol. It is rapidly absorbed from gastrointestinal tract with peak plasma concentration of 5-10 ng/mL after 1 h and metabolized up to 80% in liver with a mean half-life of 2.0-2.5 h, thus necessitating frequent administration of doses to maintain therapeutic drug level.

B.5 Nicorandil: belongs to the class of compounds known as potassium channel activators, which exert their action by arteriodilating and venodilating properties, and represents a novel type of compound for use in the treatment of angina pectoris. It has a short half life and the usual oral dosage regimen is 5 to 40 mg taken two to four times a day. Hence, to reduce the frequency of administration and improve patient compliance, once a day TDDS of nicorandil is desirable.

B.6 Nitrendipine: a potent antihypertensive molecule which is a calcium entry blocker and potent peripheral vasodilator, reported to be well absorbed following oral administration, but undergoes extensive first pass metabolism and oral bioavailability in the range from 10% to 20%.

B.7 Diltiazem hydrochloride: a calcium channel blocker used in the treatment of arrhythmia, angina pectoris and hypertension. The literature survey reveals that it undergoes variable and extensive first pass metabolism before entering into systemic circulation and varies with species.

B.8 Carvedilol: a non-selective ß-adrenergic blocker used in hypertension, it is rapidly and extensively absorbed from the gastrointestinal tract. Following oral administration, the apparent mean terminal elimination half life of carvedilol generally ranges from 6 to 10 h, the absolute bioavailability is approximately 25% to 35% due to a significant degree of first pass metabolism.

B.9 Lisinopril dehydrate: (angiotensin converting enzyme inhibitor) is a lysine derivative of enalapril and does not require hydrolysis to exert pharmacological activity. It undergoes extreme hepatic first pass metabolism resulting in bioavailability of 6-60%.

B.10 Amlodipine: a dihydropyridine calcium antagonist that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Elimination from the plasma is biphasic with a terminal elimination half life of about 30-50 h and a bioavailability of 60-65%. It undergoes extensive first pass metabolism.

B.11 Labetolol: is a ß non-selective blocker of adrenergic receptors. It binds competitively with these receptors and inhibits proliferation of cardiovascular symptoms e.g. hypertension. It also undergoes extensive hepatic first pass metabolism (60-75%) leading to poor bioavailability on oral administration.

B.12 Pinacidil: an antihypertensive drug found to be a good candidate for transdermal drug delivery. The oral bioavailability formulations is only 57% due to hepatic first-pass metabolism. The drug has a short biological half-life of 1.6 to 2.9 h, which makes frequent dosing necessary to maintain the drug within the therapeutic blood levels for long periods. The antihypertensive action requires plasma concentration in the range of 100 to 300 µg/L.

B.13 Indapamide: a long-acting hypertensive with both diuretic and vasodilative action and is defined by the 1999 WHO/ISH Hypertension Guidelines and JNC VII as a first line drug for the treatment of hypertension. This antihypertensive action is maximal at a dose of 2.5 mg/day, and the diuretic effect is slight, usually without clinical manifestation. The oral delivery of this drug has certain disadvantages such as frequent administration and adverse drug reactions. Additionally, since indapamide is usually intended to be taken for a long period, patient compliance is also very important.

B.14 Captopril: widely used for the treatment of hypertension and congestive heart failure. The drug is considered a drug of choice in antihypertensive therapy due to its effectiveness and low toxicity. It has a mean half life of 2 to 3 h [18] but action lasts for 6-12 h. Captopril shows 75% bioavailability but presence of food reduces the oral absorption by 30-50%. a captopril disulfide shows poor absorption from the intestine.

B.15 Nicardipine hydrochloride: Nicardipine hydrochloride, a calcium channel blocker is used for the treatment of chronic stable angina and hypertension. The onset of action of the drug is 5-10 min & duration of action is between 15-30 min. The half life of the drug varies between 2-4 h and bioavailability ranges 20-40%.
C. Antidiabetics:

C.1 Glibenclamide: plasma half life 4-6 hrs daily dose 5-15mg
C.2 Glipizide : plasma half life 3-5 hrs daily dose 5-20mg.
C.3 Glimepride: plasma half life 5-7 hrs daily dose 1-6mg.
C.4 repaglinide : plasma half life less than hr daily dose 1.5-8mg.
C.5 Rosiglitazone: plasma half life 4 hrs daily dose 4-8mg.
C.6 Pioglitazone: plasma half life 3-5 hrs daily dose 15-45mg.

A. Opioids:

D.1 Nalazone: Choice for morphine poisoning reversing neonatal asphyxia due to opioids use during labor, plasma half life 1 hr in adult and 3 hrs in neonates daily dose 4-10mg.

D.2 Pentazocine: for postoperative and moderately severe pain in burns, trauma, fracture, cancer etc. plasma half life 3-4 hrs daily dose 30-60mg.

CONCLUSION:
The advance state of research & patent application filed for TDDS clearly indicates the renewed interest of pharmaceutical industry. By knowing different antihypertensive, hypoglycemic, antiischaemic, opioids drugs revealed that transdermal route can improve the bioavailability and patient compliance by many ways. Only demerit is that all the drugs cannot be given by transdermaly due to its physico-chemical properties which should be suited for permeation through skin. Researcher exploring the sophisticated techniques of permeation enhancer like use of electron beam radiation in development of transdermal delivery has opened newer approaches.

There is hope that the drugs which have been poor candidates would be developed in to successful transdermal delivery system in upcoming days.

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