ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

REVIEW ARTICLE

Transdermal Drug Delivery System - Simplified Medication Regimen - A Review

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ABSTRACT

A transdermal drug delivery device, which may be of an active or a passive design, is a device which provides an alternative route for administering medication defined as self contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin at controlled rate to the systemic circulation. These devices allow for pharmaceuticals to be delivered across the skin barrier. In theory transdermal patches work very simply. A drug is applied in a relatively high dosage to the inside of a patch, which is worn on the skin for an extended period of time. Through a diffusion process, the drug enters the bloodstream directly through the skin. Since there is high concentration on the patch and low concentration in the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow.
Keywords: Transdermal drug delivery system, diffusion, transdermal patches, Iontophoresis, transdermal permeation.

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ISSN: 0975-8585

INTRODUCTION

Transdermal drug delivery systems are topically administered medicaments in the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate. Transdermal drug delivery systems (TDDSs) facilitate the passage of therapeutic quantities of drug substances through the skin and into the general circulation for their systemic effects [1].

In 1965 Stoughton first conceived of the percutaneous absorption of drug substances. The first commercially available prescription patch was approved by the U.S. Food and Drug Administration in December 1979, which administered scopolamine for motion sickness [2].

Recently there has been a growing recognition that the benefits of intravenous infusion can be closely duplicated without its hazards, by using the intact skin as the port of drug administration to provide continuous drug delivery into the systematic circulation. This is known as the transdermal administration and the drug delivery systems are known as "transdermal therapeutic systems" or popularly as "transdermal patches".

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.

Transdermal therapeutic systems are defined as self contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin at controlled rate to the systemic circulation [2].

Transdermal drug delivery systems are adhesive drug containing devices of defined surface area that deliver a predetermined amount of drug to the surface of intact skin at a programmed rate. These systems provide drug systematically at a predictable rate and maintain the rate for extended period of time thus eliminating numerous problems associated with oral dosing including product stability, bioavailability and the peaks and troughs of pulse dosing.

ADVANTAGES:

- Transdermal medication delivers a steady infusion of a drug over an extended period of time. Adverse effects or therapeutic failures frequently associated with intermittent dosing can also be avoided.
- Transdermal delivery can increase the therapeutic value of many drugs by avoiding specific problems associated with the drug e.g., gastro-intestinal irritation, low absorption, decomposition due to hepatic "first-pass" effect, formation of metabolites that cause side effects, short half-life necessitating frequent dosing etc.
- The simplified medication regimen leads to improved patient compliance and reduced inter & intra – patient variability.

ISSN: 0975-8585

- At times the maintenance of the drug concentration within the biophase is not desired. Application and removal of transdermal patch produce the optimal sequence of pharmacological effect.
- Self administration is possible with these systems.
- The drug input can be terminated at any point of time by removing transdermal patch.

DISADVANTAGES:

- The drug must have some desirable physicochemical properties for penetration through stratum corneum and if the drug dose required for therapeutic value is more than 10mg/day, the transdermal delivery will be very difficult.
- Only relatively potent drugs are suitable candidates for TDDS because of the natural limits of drug entry imposed by the skin's impermeability.
- Some patients develop contact dermatitis at the site of application for one or more of the system components, necessitating discontinuation.
- Clinical need is another area that has to be examined carefully before a decision is made to develop a transdermal product.
- The barrier function of the skin changes from one site to another on the same person, from person to person and with age.

KINEITCS OF TRANSDERMAL PERMEATION [3]:

For a systemically active drug to reach a target tissue, it has to posses some Physico-chemical properties which facilitate the sorption of the drug through the skin, and also the uptake of the drug by the capillary network in the dermal papillary layer. Various events governing percutaneous absorption are shown in Figure.

The rate of permeation, dQ/dt, across various layers of skin tissues can be expressed as

$$\frac{dq}{dt} = Ps(Cd-Cr) \quad \text{..... (1)}$$

Where,

C_d and C_r are respectively, the concentrations of skin penetrant in the donor phase (stratum corneum) and the receptor phase (systemic circulation); and

P_s is the overall permeability coefficient of the skin and is defined by

$$Ps = KsDss/hs \quad \text{……(2)}$$

Where

K_s = Partition coefficient of the penetrant3

D_{ss} = Apparent diffusivity of penetrant

h_s = Thickness of skin

ISSN: 0975-8585

Thus, permeability coeffiefficient (Ps) may be constant since Ks; D_{ss} and h_s terms in equation (2) are constant under the given set of conditions.

A Constant rate of drug permeation achieved, if $C_d > C_r$, then the equation (1) may be reduced to

$$dQ/dt = Ps.\ Cd \qquad \text{.....(3)}$$

And the rate of skin permeation (dQ/dt) becomes a constant, if the C_d value remains fairly constant throughout the course of skin permeation. To maintain the C_d at a constant value, it is critical to make the drug to be released at a rate (R_r) which is always greater than the rate of skin uptake (R_a), i.e., $R_r >> R_a$.

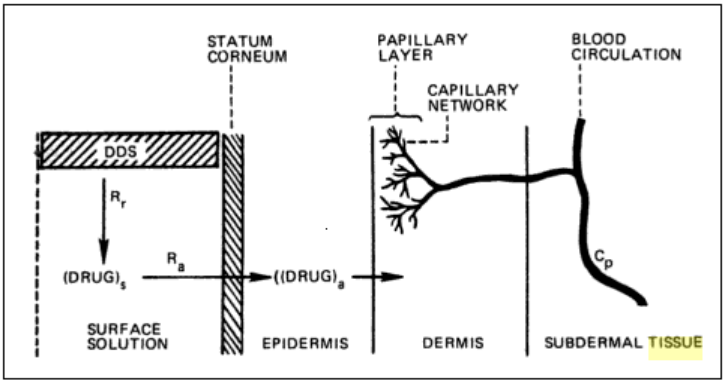

Fig 1: Diagramatic illustration of the relationship between the rate of drug release (R_r) from a Transdermal Drug Delivery

By doing so, the drug concentration on the skin surface (C_d) is maintained at a level which is always greater than the equilibrium (or saturation) solubility of the drug in the stratum corneum (C^e_s), i.e., $C_d >> C^e_s$; and a maximum rate of skin permeation $(dQ/dt)_m$, as expressed by equation (4), is thus reached:

$$(dQ/dt)m = Ps\ C^e_s \qquad \text{.....(4)}$$

Apparently, the magnitude of $(dQ/dt)_m$ is determined by the skin permeability coefficient (Ps) of the drug and its equilibrium solubility in the stratum corneum (C^e_s).

MECHANISM OF ACTION OF TRANSDERMAL PATCHES [4]

The application of the transdermal patch and the flow of the active drug constituent from the patch to the circulatory system via skin occur through various methods.

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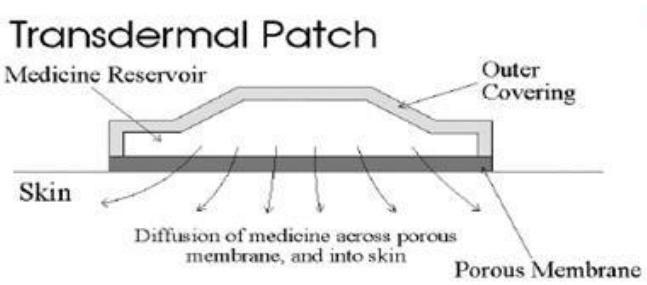

Fig 2: representing mechanism of drug release from transdermal patch

EVALUATION OF TRANSDERMAL FILMS

The evaluation of transdermal patches is done to assess the quality and reproducibility. Various evaluation tests includes

PHYSICO CHEMICAL STUDIES [5]

The physical parameters such as thickness, weight variation, folding endurance, tensile strength, water vapor transmission and drug content were determined.

Microscopic studies: Distribution of drug and polymer in the film can be studied using scanning electron microscope. For this study, the sections of each sample are cut and then mounted onto stubs using double sided adhesive tape. The sections are then coated with gold palladium alloy using fine coat ion sputter to render them electrically conductive. Then the sections are examined under scanning electron microscope [6,7].

Thickness: The thickness of film was measured by using electronic vernier calipers, Screw gauze, and micrometer with a least count of 0.01mm. Thickness was measured at five different points on the film and average of five readings was taken.

Flatness: A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness.

$$\% \text{ constriction} = \frac{I_1 - I_2}{I_1} \times 100$$

I_2 = Final length of each strip

I_1 = Initial length of each strip

Folding endurance: It was determined by repeatedly folding the film at the same place until it breaks. The number of times of film could be folded at the same place without breaking cracking gave the value of folding endurance.

Drug content: Drug content was found out by dissolving patches each of 2 cm x 2 cm in suitable solvent in which drug get dissolved and place it in a shaker device for up to 24 hrs, after that place it in a sonicator and then allow it to filter and the filtrate was analysed spectroscopically.

Content uniformity test: 10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test.

Weight variation: Ten films are weighed and calculate the average weight, and weigh the individual weight .of films. The individual weight of film should not deviate from its mean weight.

Tensile Strength: To determine tensile strength, polymeric films are sandwiched separately by corked linear iron plates. One end of the films is kept fixed with the help of an iron screen and other end is connected to a freely movable thread over a pulley. The weights are added gradually to the pan attached with the hanging end of the thread. A pointer on the thread is used to measure the elongation of the film. The weight just sufficient to break the film is noted. The tensile strength can be calculated using the following equation [8].

$$\textbf{Tensile strength} = F/a.b\ (1+L/l)$$

F is the force required to break; a is width of film; b is thickness of film; L is length of film; l is elongation of film at break point In another study, Tensile strength of the film was determined with the help of texture analyzer. The force and elongation were measured when the films broke.

Moisture content: The prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h [9]. The films are weighed again after a specified interval until they show a constant weight. The percent moisture content is calculated using following formula.

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

ISSN: 0975-8585

Moisture Uptake: Weighed films are kept in a desiccators at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in desiccators until a constant weight is achieved. % moisture uptake is calculated as given below [10].

$$\% \text{ moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Water vapor transmission studies (*WVT)*:.The polymer films were pasted over the brim with the help of adhesive like silicon adhesive grease and the adhesive was allowed to set for 5 minutes. one gram of calcium chloride and placed it in previously dried empty vials having equal diameter Then, the vials were accurately weighed and placed in humidity chamber maintained at 68 % RH. The vials were again weighed at the end of every regular interval of time and an increase in weight was considered as a quantitative measure of moisture transmitted through the patch [11].

In other reported method, desiccators were used to place vials, in which 200 mL of saturated sodium bromide and saturated potassium chloride solution were placed. The desiccators were tightly closed and humidity inside the desiccator was measured by using hygrometer. The weighed vials were then placed in desiccator and procedure was repeated.

$$WVT = W/ST$$

W is the increase in weight in 24 h; S is area of film exposed (cm^2); T is exposure time

ADHESIVE STUDIES [12]*:* The therapeutic efficacy of TDDS can be affected by the contact between the patch and the skin. The adhesion of adhesives capable of bonding to surfaces with the application of light pressure.

Transdermal Product Adhesion

Possible to use criteria outlined in the withdrawn Guidance

- 5-point scale0 = ≥90% adhered (essentially no lift off of skin)
- 1 = ≥75% to < 90% (some edges only lifting off skin)
- 2 = ≥50% to < 75% (less than half of the system lifting off skin)
- 3 = < 50% adhered but not detached (more than half of the system lifting off skin without falling off)
- 4 = patch detached (patch completely off the skin)

The adhesive properties of a TDDS can be characterized by considering the following factors

- Peel adhesion properties
- Tack properties

- Shear strength properties

Peel Adhesion properties: It is the force required to remove adhesive coating from test substrate. It is tested by measuring the force required to pull a single coated tape, applied to substrate at 180° angle. The energy required to detach the dosage form from the substrate material

Fracture energy (G)

$$G = P (1-\cos o)/w = W f (1+k) s$$

Where P is the peel force
w is the peel width
W is the intrinsic work of adhesion and
K is the proportionality constant

Intrinsic work of adhesion is depends on the following

- Peel rate
- Peel angle
- Thickness of adhesive
- Thickness of stripping membrane.

Tack properties: It is the ability of the polymer to adhere to substrate with little contact pressure. Tack is dependent on molecular weight and composition of polymer as well as on the use of tackifying resins in polymer

Thumb tack test: The force required to remove thumb from adhesive is a measure of tack.

Rolling ball test: This test involves measurement of the distance that stainless steel ball travels along an upward facing adhesive. The less tacky the adhesive, the further the ball will travel.
Principle: This tester employs rolling ball method, and tests the primary adhesive properties by testing the bond of measurable strength formed immediately after adhesive specimen and steel ball are brought into contact under low pressure.

Technical Indexes

Adjustable Angle: 0º ~60º
Standard Steel Balls: 1/32~1inch
Dimensions: 320 mm (L) x 140 mm (B) x 180 mm (H)

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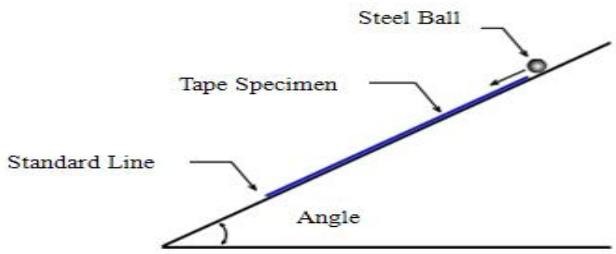

Quick stick (Peel tack) test: The peel force required breaking the bond between an adhesive and substrate is measured by pulling the tape away from the substrate at 90◦ at the speed of 12 inch/min.

Probe tack test: Force required to pull a probe away from an adhesive at a fixed rate is recorded as tack.

Polyken Probe tack Tester: Polyken™ Probe Tack Testers, manufactured by ChemInstruments, Inc., are designed to measure the tack of pressure sensitive adhesives. A precision ground 5.0 mm diameter, flat probe contacts the adhesive, reverses direction and pulls away from the adhesive. The maximum force required to break the adhesive bond is recorded and displayed. These instruments meet the standards set forth in ASTM D2979.

- Probe diameter of 5mm and an annular ring weight that applies 9.79 ± 0.10 kPa of force
- Machine speed is 24" / min. (61 cm/min)
- Automatically designed test cycle produces one second dwell time from beginning of contact to end of contact. PT-1000
- 5 lb (2 Kg) Load Cell permits a wide variety of adhesives to be tested.

Shear strength properties or creep resistance : Shear strength is the measurement of the cohesive strength of an adhesive polymer *i.e.*, device should not slip on application determined by measuring the time it takes to pull an adhesive coated tape off a stainless plate. Minghetti *et al* performed the test with an apparatus which was fabricated according to PSTC-7 (pressure sensitive tape council) specification.

***IN-VITRO* SKIN PERMEATION AND RELEASE KINETICS STUDIES [13]:**

The design and development of transdermal drug delivery systems is greatly aided by in-vitro studies. In-vitro studies can help in investigating the mechanism of skin permeation of drug before it can be developed into a transdermal therapeutic system. The methodology used in the in-vitro study is relatively easy to follow and generally affords the investigator better control over the experimental conditions than is possible in-vitro.

The factors that require consideration when selecting an in vitro system include:

- The rate limiting process: Drug solubilization or diffusion in the vehicle, partitioning from the vehicle, diffusion through the test membrane or partitioning and removal by the receptor phase.
- The intrinsic diffusivity of the permeate and apparent diffusivity.
- The predominating route of diffusion during the experiment and the relative contents of drug binding and metabolism, occurring in the membrane, delivery and receptor phase.
- The predominating route of diffusion during the experimentation and the relative extents of drug binding.
- The intrinsic barrier potential of the membrane and the effects that vehicle components may have on retardative properties. Hydration of the membrane and the presence of penetration enhancers may be important here.

DIFFUSION STUDY:

The kinetics of skin permeation can be more precisely analyzed by studying the time course for the permeation of drug across a freshly excised skin mounted on a diffusion cell, such as the Franz diffusion cell Keshary and Chien have pointed out certain deficiencies in the Franz cell and modified to obtain closer approximation to in-vivo conditions. Some diffusion cells are designed to hold the skin at a vertical position between donor and receptor chambers. A more recent example is the valia-Chien cell, which is superior to similar earlier models in that it does not expose both, the donor and the receptor phases to the same temperature, and does not allow solvent loss from either phase. Moreover, the design overcomes another inadequacy of the Franz cell, namely the susceptibility of its donor phase to the changes in ambient temperature. Finally the donor compartment contents may be stirred which makes the cell suitable for transdermal drug delivery from solution sand suspensions Static diffusion [14].

Diffusion apparatus was classified on the basis of

A. Physical design of diffusion cell

- Horizontal type
- Vertical type
- Flow-through type

B. Method of sampling and measurement

- Continuing system
- Fluid circulation system
- Non circulation system
- Intermittent system : rotating agitation systems

ISSN: 0975-8585

There are several diffusion cells which are being used for in vitro studies some of them are listed below;

- V-C Cell (Horizontal –Small volume)
- G-C Cell (horizontal large volume) or Ghannam – Chein cell
- F-D Cell Franz diffusion cell (Vertical type)
- K-C Cell Modified Franz diffusion cell (Keshary & Chein model)

Differentiation of different diffusion cells

Name of cell	Surface area (Cm^2)	Volume of fluid in compartment (ml)	Stirrer	Speed
V-C Cell	0.165	3.5	Star head magnet	600
G-C Cell	1.39	140-250	Bar shaped magnet	60-100
F-D Cell	1.57-4.71	10-12	Rod shaped	600
K-C Cell	3.14	12	Star shaped	600

V-C Cell (Horizontal –Small volume):

This has been used for studying the skin permeation kinetics of drug using human Cadaver skin or freshly excised skin. The temperature of the both compartments maintained at constant level by circulating water in the jacket surrounding the solution compartment.

G-C Cell (horizontal large volume) or Ghannam – Chein cell:

It contains both donor and acceptor compartments, both the compartments are jacketed and thermostaticated by external circulation bath to maintain temperature.

Franz's diffusion cell:

Franz showed an excellent correlation between in vitro and in vivo studies.Majority of In-vitro experiments are conducted in animal skin i.e. hairless mouse, guinea pig, rabbit etc. Although these exist a number of similarities there is as yet no animal skin that complete mimics the penetration characterization of human skin.

In 1975 Franz developed a static diffusion cell which is now one of the most commonly used in vitro systems in the research of skin penetration. The system has a simple design and is inexpensive to use. Human as well as animal skin can be mounted on the metal grid which divides the donor chamber and the receptor chamber. The skin is set placing the dermis in contact with the receptor fluid below. The skin can be either full-thickness or split-thickness skin. The skin thickness will affect the experimental results as elaborated under Flow-through

system. The receptor chamber of the cell is placed in circulation water in a water bath with a temperature of 37 ºC keeping the temperature at the skin surface at 32° to imitate a real life skin condition as much as possible. The receptor fluid is kept homogenous in concentration and in temperature by a magnetic stirring bar. The fluid in the receptor chamber is manually sampled at predefined time intervals. Any type and any amount of vehicle (that will fit into the donor chamber) may be applied to the skin.

The components of the diffusion cell are showed below

Donor Compartment:

- Easy access to deliver the penetrant to the skin.
- Stirred where possible.
- Temperature controlled ($32^{o}C \pm 1^{o}C$)
- Control of evaporation for vehicles and penetrants.

Membrane:

- For the study of penetration kinetics, only human skin should be used.
- For vehicle/device release studies other barrier may be used.
- The skin sample should contain both stratum corneum and viable epidermis.
- A molecule of known penetration kinetics should used prior to the test molecule, to assess barrier function.
- Where applicable metabolic viability of epidermis may be assessed.

Receptor Compartment:

- Either, flow – through or static.
- Temperature controller ($32^{o}C \pm 1^{o}C$)
- Sufficient volume to maintain infinite sink conditions.
- Stirred without obvious formations of boundary layers.

Receptor Fluid:

- Should not compromise barrier function.
- Should be of favorable partitioning.
- Capable of maintaining epidermal viability where ever necessary.
- Must be contained once collected.

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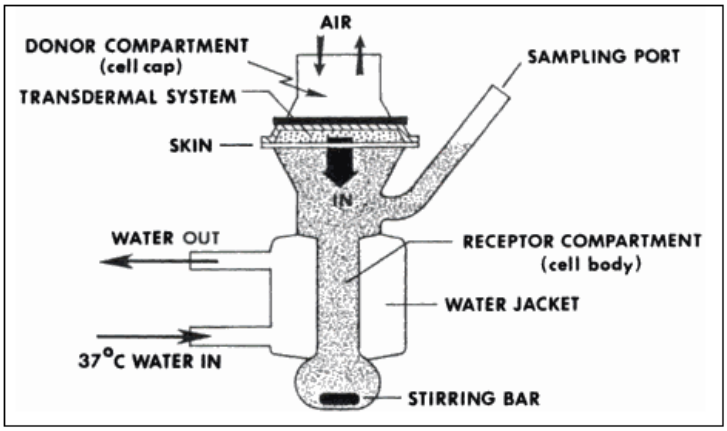

Fig 5: Franz's diffusion apparatus

When testing different substances it is important to be aware of the solubility of the substance. The solubility of a substance influences the sink capacity and is therefore of great importance when it comes to choosing the right sampling frequency and receptor chamber dimension. The size of the receptor chamber determines when the receptor fluid achieves a certain degree of saturation.

The barrier integrity of the skin can be evaluated by capacitance measurement. This value indicates the ability of the skin to separate electrical charge.

Skin samples with a high capacitance are unable to act as capacitors, which mean that the skin is damaged. The measurements are carried out at the beginning and at the end of the study to give an accurate evaluation of the skin barrier.

K-C Cell Modified Franz diffusion cell (Keshary & Chein model):

Franz cell has poor solution dynamics as a result of insufficient mixing. This result in sufficient concentration gradient in diffusion cell and unhomogeneously drug concentration in receptor compartments so this model is to improve efficiency of fluid mixing.

Flow-through system

This is a system consisting of multiple cells. The system is developed by Bronaugh and Stewart in 1985 and is excellent for determining the reservoir effect of the skin. The flow-through cells can - as well as the static cells - be mounted with animal or human full- or split-thickness skin, which will generate skin barriers of different thickness and as in the static cells the skin thickness will affect the experimental results. Prolonged lag-times might be expected in experiments using full-thickness skin. The type of skin preparation generating the most valid data is not obvious and probably one of the reasons why OECD accepts the different experimental approaches in their guidelines (OECD, 2000).

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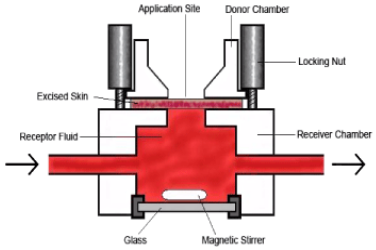


Fig 6: Flow-through cell (Use of picture permitted by Dr. Wilkinson SC, University of Newcastle).

The receptor fluid is in the flow-through cells continuously replaced and collected every hour to imitate an in vivo situation where the blood circulation removes the transdermal penetration substances. This has an additional benefit when dealing with substances with low solubility in the receptor medium and the sink conditions are maximized as the fluid is continually replaced. The donor chamber is, however, very small which gives a small application area, and it is also important to be aware what the system lag-time does to the volume of the receptor chamber and the outlet tubing, which is highly expressed when using a low flow rate. Depending on the amount of cells used in the study, the amount of connecting outlet tubes leading the receptor fluid from the cells to the collecting vials can be quite confusing (see picture below). The mechanical movement, when changing collection vials e.g. every ½ hr., has a tendency to disconnect the tubes.

Advantages/disadvantages

In general the in vitro models have the advantage of avoiding almost all ethical aspect. Since many percutaneous penetration studies would be hazardous to carry out in vivo, e.g. studying chemical warfare agents, the in vitro models meet these risks. The static diffusion cells have some advantages compared to the flow-through system, simply due to the much simpler design in the static system. The static diffusion cells have except from the magnetic stirrer no technical features, and this therefore eliminates many of the technical problems that may occur when using the flow-through system. The costs of the static diffusion cells are lower than those of the flow-through system and the static diffusion cells have a larger area of absorption which makes the absorption indicator better as well as the mass balance assessment. The flow-through system, however, provides an environment similar to real physiological conditions by the continuous replacement of receptor fluid resembling the systemic uptake of the drugs/chemicals in the blood vessels.

Many comparative studies with no difference in skin penetration measurements between the two cell types have been carried out.

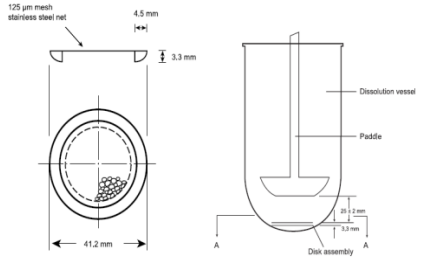
The models are both originally described by OECD guideline 428 (OECD, 2000) for experiments with skin penetration.

ISSN: 0975-8585

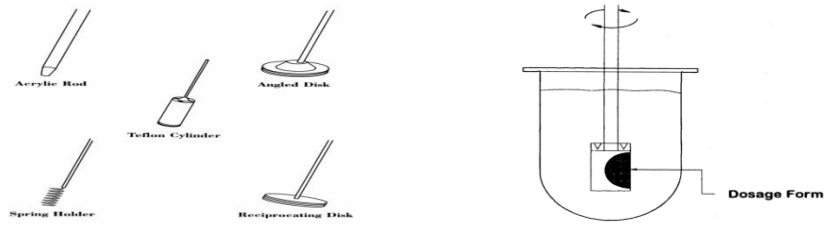
DISSOLUTION STUDIES:

The methodology involved in drug release studies from transdermal films was specified in there are various methods available for determination of drug release rate of TDDS [15].

The Paddle over Disc*: (USP apparatus 5)* This method is identical to the USP paddle dissolution apparatus, except that the transdermal system is attached to a disc or cell resting at the bottom of the vessel which contains medium at 32 ±5°C



The Cylinder modified USP Basket*:* (USP apparatus6*)* this method is similar to the USP basket type dissolution apparatus, except that the system is attached to the surface of a hollow cylinder immersed in medium at 32 ±5°C



The reciprocating disc*:* (USP apparatus 7) in this method patches attached to holders are oscillated in small volumes of medium, allowing the apparatus to be useful for systems delivering low concentration of drug. In addition paddle over extraction cell method may be used.

Primary Skin Irritation Study: Three albino rabbits of either sex weighing 2-2.5 kg were used for the test. The intact skin was used. The skin from the back of each rabbit was depilated 24 hours prior to application of the patch. Two areas of the back of each rabbit, approximately 10 cm apart were designated for the position of the patches. One area was used for application of plain polymeric patch and the other was used for drug patch. The animals were immobilized using rabbit holder during 24 hours exposure. Upon removal of the patches, the resulting reaction was evaluated using weighed scores. Reading was also made after 72 hours and the final scores represent an average of the 24 and 72-hour reading.

Skin irritation studies: White albino rats, mice or white rabbits are used to study any hypersensitivity reaction on the skin. Mutalik and Udupa carried out skin irritation test using mice. The mice were divided into 5 groups, each group containing 6 animals. On the previous day of the experiment, the hair on the backside area of mice were removed. The animals of

group I was served as normal, without any treatment. One group of animals (group II, control) was applied with marketed adhesive tape (official adhesive tape in USP). Transdermal systems (blank and drug loaded) were applied onto nude skin of animals of III and IV groups. A 0.8% v/v aqueous solution of formalin was applied as standard irritant (group V). The animals were applied with new patch/ formalin solution each day up to 7 days and finally the application sites were graded according to a visual scoring scale, always by the same investigator. The erythema was as follows: 0 for none, 1 for slight, 2 for well defined, 3 for moderate and 4 for scar formation. The edema scale used was as follows: 0 for none, 1 for slight, 2 for well defined, 3 for moderate and 4 for severe. After visual evaluation of skin irritation, the animals were sacrificed and skin samples were processed for histological examination. The results of this study showed that the prepared systems (both blank and drug loaded) and USP adhesive tape produced negligible erythema and edema. While standard irritant, formalin produced severe edema and erythema. The histopathologic examination of the skin also indicated that adhesive tape and prepared patches produced mild inflammation and edema.

Stability studies: The stability studies are conducted to investigate the influence of temperature and relative humidity on the drug content in different formulations. The transdermal formulations are subjected to stability studies as per ICH guidelines.

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