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## TRANSDERMAL PATCHES: PHYSIOCHEMICAL AND *IN-VITRO* EVALUATION METHODS

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**ABSTRACT:** Various drugs are available these days, which may either require long term administration via multiple doses or may be susceptible to enzymes and first pass-metabolism or all the above. One way to administer such drugs is through the transdermal route. After a transdermal delivery system is designed, it is important to evaluate it for various essential parameters that help us determine how effective it is, i.e. its physiochemical parameters, which describe the physical and some of the chemical properties of the patch and its *in-vitro* parameters, which would mimic how the patch would behave on exposure to real time conditions On the body. This article briefly reviews the ideal characters for choosing this mode of drug delivery, its advantages and provides an in-depth analysis of the techniques used to physio-chemically evaluate the delivery system's important parameters and also the conditions that help understand the systems behavior in a real time scenario.

**INTRODUCTION:** Transdermal systems have evolved a lot over the decade. Maintenance of drug level above minimum effective concentration has always been considered as a superior mode of drug delivery. It is always desirable to bypass first pass metabolism and also to maintain constant, prolonged, and effective drug concentration levels in the plasma. Using transdermal systems has been highly advantageous in mimicking above state<sup>2-6</sup>.

The transdermal systems have various advantages which led to its exploitation As a drug delivery system and vast number of advancements have been observed over time. Various advantages are listed in the flow chart (**Fig**). Listed below are the biopharmaceutical parameters for the selection of an ideal drug for transdermal drug delivery.

Biopharmaceutical Parameters for selection of an ideal drug for transdermal drug delivery<sup>3,4</sup>:

- Dose: Should be low (generally <20mg/day).
- Elimination Half-life of drug (hr.):  $\leq 10$ .
- Molecular weight: < 500-400 Daltons.
- Partition Coefficient: Log P (Octanol-Water) should be in the range of 1 to 3.
- Skin permeability:  $>0.5 \times 10^{-3}$  cm/hr.
- The drug should be non-irritating and non-sensitizing.
- Drug with low oral bioavailability.
- Drug with low therapeutic index.

Transdermal patches are designed to control the drug delivery through the skin, resulting in a prolonged and constant systemic absorption. The rate limiting step for systemic absorption of the drug substance is usually the permeation through the epidermis layer. Formulation and product design influence the permeation of the drug through the skin, which can be characterized by the *in vitro* release of the drug in a dissolution medium and also by the *in vitro* permeation through the human/ animal skin. Physiochemical and biological

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properties of the drug also influence the rate and extent of transdermal delivery. Such properties include molecular weight, partition coefficient, melting point, pKa, solubility and pH effects, as well as solid state characteristics such as particle size and polymorphism.

The solution state and solubility of the drug substance in the drug product should be determined. The risks of precipitation / particle growth / change in crystal habit / changes in thermodynamic activity arising from changes in temperature and on storage should be assessed and appropriate tests included in the stability studies. The drug and the excipients must be compatible with one another to produce a product that is stable. This is very significant if the excipients are new.

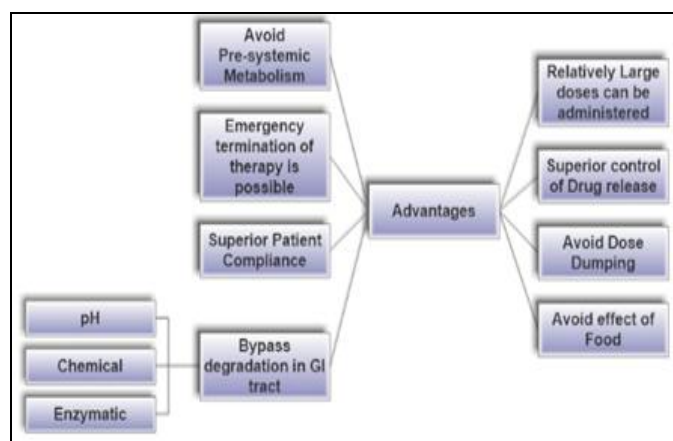


FIG. 1: HIGHLIGHTS OF VARIOUS ADVANTAGES OF TRANSDERMAL DRUG DELIVERY SYSTEM.

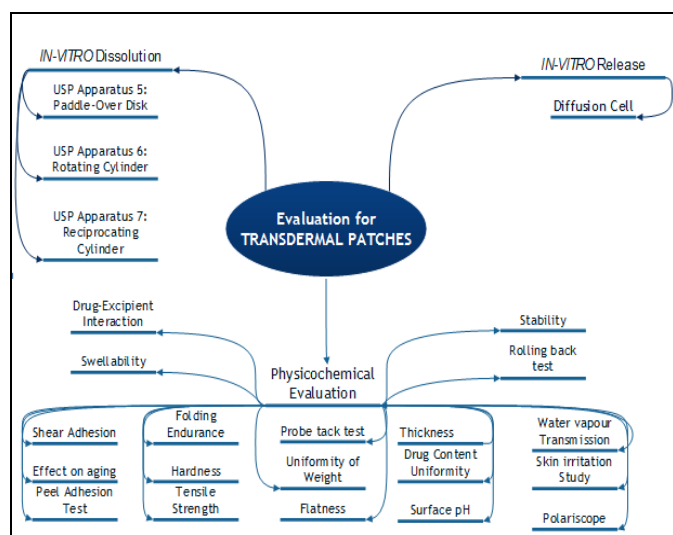


FIG. 2: FLOWCHART DEPICTING ALL THE PHYSICO-CHEMICAL AND *IN VITRO* EVALUATION METHODS.

## Physicochemical Evaluation methods:

Following are the physicochemical evaluation methods performed for a transdermal patch.

### 1. Thickness:

As the uniform thickness of the film is desired, the thickness of the film is measured at three different places using micrometer, and mean values were calculated. High-quality Mitutoyo Digimatic micrometer are widely used for this purpose<sup>7-9</sup>.

### 2. Weight variation:

Weight variation needs to be minimized or removed among the patches of same batch but there are always chances of some weight variation, thus this test gives an idea regarding weight variation in patches if any. Basically, five patches are selected randomly and weighed accurately. The mean was calculated. The individual weight should not deviate significantly from the average weight. The difference in weights of patches gives us an idea regarding weight variation.

### 3. Flatness:

The ideal transdermal patch should possess a smooth surface and should not fold or constrict with the progress of time. The flatness of a patch can be studied by performing the following test: three longitudinal strips are cut from each patch i.e. the patch is cut from the center, left side and right side of the patch thus covering almost the entire part of patch surface. The length of each strip should be measured and minimum deviation is preferred. The variation in length is measured by determining percent constriction<sup>10,11</sup>.

$$\text{Constriction}(\%) = \frac{l_1 - l_2}{l_2} \times 100 \quad (1)$$

Where,  $l_1$  = initial length of each strip,  
 $l_2$  = final length of each strip.

### 4. Tensile strength:

Tensile strength instrument or tensiometer can be used for this purpose. Tensile strength is the maximum stress applied to a point at which the specimen breaks. Tensile strength helps

understand the mechanical properties of the polymeric patches.

The instrument consists of two load cell groups, the lower one is fixed and the upper one is movable. The strips (dimension- 2\*2 cm) are fixed between these two groups. Force is gradually applied till the film breaks and the break force recorded is expressed in kg. Also elongation can be measured with the help of pointer mounted on the assembly.

$$T.S. = \text{break} \frac{\text{force}}{a \times b \times (1 + \Delta L/l)} \quad (2)$$

Where, a- width of strip.

b- Thickness of strip.

l- Length of strip.

$\Delta L$ - Elongation of patch at break point.

### 5. Hardness:

Hardness test is performed on three different patches individually from each batch and tested by fabricated hardness testing instrument and the average is calculated. Hardness is an equally important parameter as it determines the ability of a patch to take up mechanical stress, be it during packaging, transportation or after application.

Hardness apparatus consists of a wooden stand of 8 cm in height and a top area of 8 x 8 cm. A hole of 0.2 cm diameter is made in the center of the wooden top. A small plastic pan is fixed horizontally on one end of a 2 mm thick smooth iron rod. Rod having the pan on its upper end is inserted into the hole of the wooden top and its lower sharp end was placed on a metal plate.

Battery of three-volt is widely used to make an electric circuit. Assembly is set in such way that, the bulb lights up only when the circuit is complete via the contact of the metal plate and the sharp end of the rod.

The patch of interest is placed between the metal plate and the sharp end of the iron rod and the weights were gradually added on to the pan and total weight required to penetrate the

patch is indicated by the lighted bulb which was noted as observations<sup>10,12</sup>.

### 6. Folding Endurance:

Folding endurance is number of folds required to break a polymeric patch. This test not only depicts the strength of the patch prepared using different polymers, but also checks how efficiently the polymer imparts flexibility.

This test involves a simple phenomenon i.e. repeatedly fold the same patch at the same place until it breaks. Thus, the number of times the patch could be folded at the same place without breaking/cracking gives us the value of folding endurance<sup>11,13</sup>.

### 7. Drug Content Uniformity:

The transdermal patch of specified area generally 3.14 cm<sup>2</sup> is dissolved in 100 ml of pH 7.4 phosphate buffer. The above solution is stirred for 2 hours was provided to get a homogeneous solution followed by filtration. A blank is performed using a drug free patch. The drug content in each formulation is determined by measuring the absorbance at a specific wavelength after suitable dilution using a UV-visible spectrophotometer<sup>10,14</sup>.

### 8. Swellability:

This test is to check the swellability of the patch due to presence of polymer. This test requires petri plates and double distilled water, to see how much the patch would swell upon contact with water. The patches of 3.14 cm<sup>2</sup> are weighed and placed in a petri plates containing 10 ml of double distilled water and are allowed to imbibe for specified time. Increase in weight of the patch is then determined at specific time intervals until a constant weight is observed<sup>10,15</sup>.

The degree of swelling (% S) is calculated using the formula

$$S(\%) = \frac{W_t - W_0}{W_0} \times 100 \quad (3)$$

Where, S is percent swelling,

$W_t$  is the weight of patch at time t,

$W_0$  is the weight of patch at time zero.

### 9. Surface pH:

Surface pH of the patches is described by Bottenberg *et al.* The patches are kept in 0.5 ml double distilled water and thus allowed to swell for 1 hour. The surface pH is known by bringing a combined glass electrode near the surface of the patch and allowing it to equilibrate for 1 minute<sup>10, 16</sup>.

### 10. Water vapour transmission:

Quantity of moisture transmitted through a unit area of a patch in unit time is referred as water vapour transmission. This in turn helps us to know the permeation characteristics. Glass vials of equal dimensions are generally used. Desiccant (for example, fused calcium chloride-1gm) is taken in a vial and polymeric patch is fixed using adhesive. These pre weighed vial is stored in a humidity chamber at RH of 80% with the temperature set to 30°C for a period of 24 hours. The weight gain is calculated every hour till a period of 24 hours<sup>10, 17</sup>.

The water vapour transmission was calculated using the equation

$$\text{Rate} = \frac{WL}{S} \quad (4)$$

Where, W is gm of water permeated / 24 hr.

L is thickness of the patch

S is exposed surface area of the patch

### 11. Skin Irritation Study:

The studies need to be performed firstly on animals like Rats or Rabbits (**Table 1**). These tests give us an idea regarding skin sensitization or irritation to the formulation. The patches require direct contact with the skin, hence the rat's back is shaved. Following this it is usually cleaned with distilled water to remove loose hairs and tissue.

The rats are divided into five groups. Animals of group I are used as a blank, without any treatment. The marketed adhesive tape is applied to one group of animals (Group II, control). Transdermal systems (blank and drug loaded) are applied onto the skin of animals of groups III and IV. A 0.8 % v/v aqueous

solution of formalin is applied as a standard irritant (Group V). A new patch is applied to each group each day up to 7 days and finally the application sites are graded according to a scoring scale<sup>18</sup>.

**TABLE 1:DRAIZE SCORING METHOD**<sup>19</sup>

Skin Reaction			
S.No	Erythema and Eschar Formation	Edema formation	Score assigned
1	No Erythema	No edema	0
2	Very slight Erythema	Very slight edema	1
3	Well defined Erythema	slight edema	2
4	Moderate to severe Erythema	Moderate edema	3
5	Severe Erythema	Severe slight edema	4

### 12. Uniformity of dosage:

A patch should consist of the drug amount which is necessary to show the desired activity. The uniformity of dosage in the patches is checked in this test. A specific area of the patch is cut into small pieces and dissolved in a volumetric flask of fixed capacity post which it is sonicated, volume is made up, the solution allowed to settle, following which the supernatant is diluted to a fixed concentration. This on filtering through a 2µm membrane and analysis via HPLC will give drug content per piece. This test is most accurate when done in triplets from different parts, so that we get an average value of content<sup>10</sup>.

### 13. Polariscope:

The uniform distribution of drug throughout the patch is necessary to have optimum activity. The drug accumulation at one site may create problem during absorption. This test is involves examination of the drug crystals in the patch by using a polariscope. A specific surface area of the piece is to be kept on the object slide and is observed for the drugs crystals to distinguish whether the drug is present as crystalline form or amorphous form in the patch. The polymorphic form play important as 2 different forms show different solubility and hence can show different release and permeation rates<sup>10, 12, 21-23</sup>.



**14. Shear Adhesion:**

The test signifies the cohesive strength of an adhesive polymer. A number of factors decide shear adhesion, such as the molecular weight, the degree of crosslinking, the composition of the polymer, its type and the amount of tackifier added. An adhesive coated tape is applied onto a stainless steel plate; a specified weight is hung from the tape, to affect it pulling in a direction parallel to the plate. Shear adhesion strength is determined by measuring the time it takes to pull the tape off the plate. The longer the time take for removal, the greater is the shear strength<sup>18,12,21-23</sup>.

**15. Effect on aging:**

The effect of progressed time span on the nature of the patch is studied in this test. The effect of aging on physical appearance is studied by packing the polymeric films in properly sealed aluminium foil and then storing them in a desiccator at ambient conditions for 30 days. The patch is then thoroughly studied for its physical and physicochemical characterization<sup>18,12,21-23</sup>.

**16. Peel Adhesion test:**

The force required to remove an adhesive coating from a test substrate gives peel adhesion factor. Molecular weight of adhesive polymer, the type and amount of additives are the variables that determine the peel adhesion properties. A single tape is applied to a stainless steel plate or a backing membrane of choice and then the tape is pulled from the substrate at a 180° angle and the force required for tape removed is measured. This gives Peel adhesion rate<sup>6,12,21-23</sup>.

**17. Rolling ball tack test:**

In this, Stainless steel ball of 7/16 inches in diameter is released on an inclined track so that it rolls down and comes into contact with the horizontal, upward facing adhesive. The distance the ball travels along the adhesive provides the measurement of tack, expressed in inch<sup>6,12, 21-23</sup>.

**18. Probe Tack test:** The Force required to pull a probe away from an adhesive at a fixed rate is

recorded as tack. The tip of a clean probe with a defined surface roughness is brought into contact with adhesive and when a bond is formed between probe and adhesive, the subsequent removal of the probe mechanically breaks it. The force required to pull the probe away from the adhesive at fixed rate is recorded as tack and it is expressed in grams<sup>6,12, 21-23</sup>.

**19. Stability and Drug-Polymer Interaction:**

The stability of the drug in the patch is determined by accelerated stability studies as per the protocol for stability studies in ICH guidelines. The stable drug can be quantified using a stability indicating RP-HPLC or other chromatographic methods. The drug-polymer interaction can be studied with the help of differential scanning calorimetry (DSC), X-ray diffraction technique and FT-IR. The individual drug polymer peaks can be compared with that of the mixture. X-ray diffraction technique also confirms the final form of the drug in the patch<sup>20-23</sup>.

**20. Texture analyser:**

The adhesiveness of the patches is critical in the drug delivery mechanism, the texture analyser can be used to quantify the force required to break the probe surface and adhesive side of the patch contact by investigating into the adhesiveness of transdermal delivery patches by probing with a ball probe through a holed plate<sup>11, 24-26</sup>.

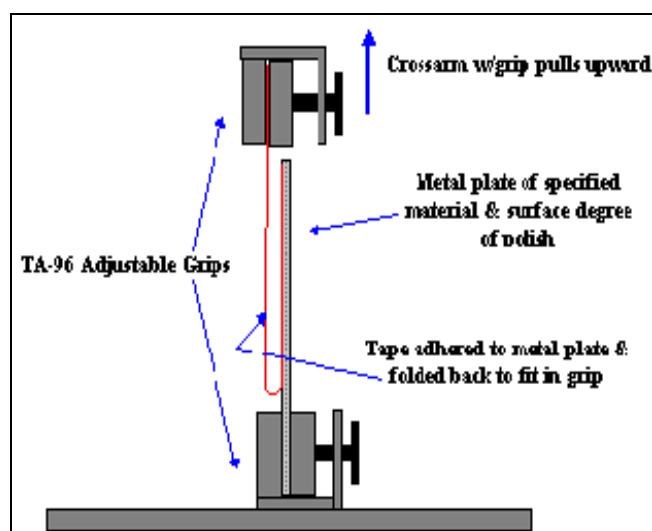


FIG. 3: ILLUSTRATION OF TEXTURE ANALYZER.

**Skin permeation *In - Vitro* Method:****Diffusion Cell permeation test:**

Permeation test involves various skin tissues, whole skin, epidermis or dermis in a specialized cell also known as “diffusion cell” (Fig) <sup>27</sup>. Skin or tissue is mounted sandwiched between the donor and the receptor compartment. Drug formulation is placed in the donor compartment. It is in contact with tissue on one side and the tissue is in contact with the receptor solution. The temperature is controlled throughout the process. The sampling time points are fixed and the receptor solution is assayed for the drug <sup>6, 28, 29</sup>. Since the skin membrane is used in between the compartments, it is essential to find out whether a drug is immobilized or is it permeating through the skin, if so then at what rate. The Franz cell can also be modified by using it directly for drug dissolution wherein, the skin membrane is replaced by the transdermal membrane <sup>23, 28</sup>.

The various factors affecting the testing performance <sup>27</sup>:

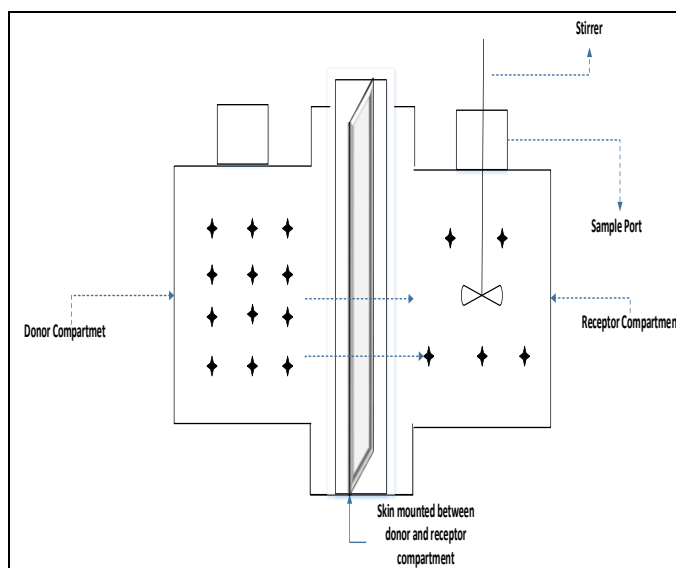
- System Design
- Effect of Temperature
- Effect of Stirring
- Drug Solubility

**1) System design:**

The primary concern is that method must be able to put up the basic system size and type. The arrangement should be planned such that it too must be able to fit the system's theoretical release pattern. In case the system is to provide burst release or loading dose, the time intervals of sampling should be set to specifically, in order to capture the part of release pattern in addition to the controlled-release rate portion.

**2) Effect of temperature:**

The temperature has a significant effect on the diffusion of drug through the polymer and rate control membranes. The target temperature is generally 32/35°C (mimic the temperature on the surface of the skin). Temperature control is required throughout the test within the range  $\pm 0.3^\circ\text{C}$  for accurate and precise measurement of the rate. Temperature effect will be prominent for the controlled portion rather than the burst portion.



**FIG. 4: DIFFUSION CELL.**

**3) Effect of Stirring:**

Diffusion dependent controlled release of the system is directly relative to ‘Apparent concentration’ at the system-receptor solution interface. Poor stirring leads to building up of the concentration gradient at the interface, leading to reduced diffusional drug flow. Too high stirring rates will be futile.

**4) Drug Solubility:**

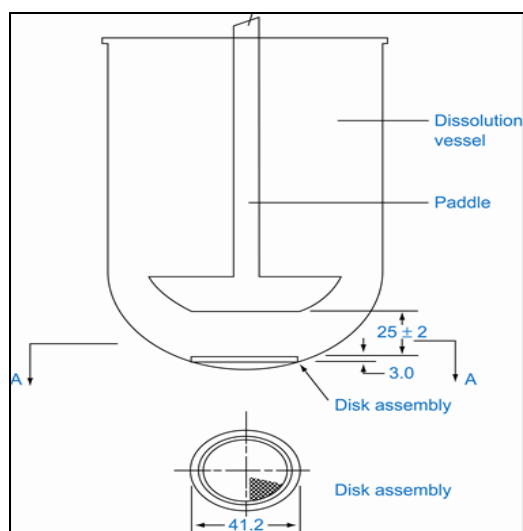
Release of the drug from donor to receptor compartment is affected directly by the drug in the receptor solution in general and at the system-solution interface in particular. The drug release is affected by “percent saturation” (also known as activity) in the system and the receptor solution. The difference in concentration (concentration gradient) is driving force for diffusion. The release mechanism are best predicted when we can limit drug concentration in the solution to less than 10% saturation (sink condition). For hydrophobic drug/drug with low solubility, their solubility can be improved by adding a surfactant or organic solvent to receptor compartment. However, it may cause to increase the release rate or modify diffusion coefficients of the drug in the membranes. Therefore, the easiest way to limit saturation effects is to use larger volumes or shorter collection intervals to maintain sink condition.

***In-Vitro* Dissolution Methods:**

The USP 30 has three official apparatuses (5, 6 and 7). The whole system for dissolution study needs to

have a larger receptor solution volumes that can meet saturation-limit requirements. Therefore, diffusion cells are not the apparatus of choice. Collection format is a characteristic feature. It is either cumulative, flow through or interval.

In the cumulative collection format we collect the released drug in a single container. For example apparatus 5 and 6. Apparatus 5 (**Fig. 5**) is referred to as “paddle over disk” and 6 (**Fig.7**) utilizes a spinning cylinder to stir the system. Drug concentration increases in vessel in a cumulative manner. Apparatus 6 uses the same system as apparatus 1, except the basket is replaced with the “cylinder stirring element”. The transdermal is attached to the circumference of the cylinder with the help of a water-permeable occlusive Cuprophan. Cuprophan is inert porous cellulose material.



**FIG. 5: USP 23 APPARATUS 5<sup>1</sup>.**

Flow through/interval systems (USP apparatus 7) have small “cell volumes” and controlled flow of receptor solution is used through cell to collect the drug. Drug solution can either be measured in flowing solution or from a well-stirred collection vessel. The main advantage of this format is that the fresh receptor solution is constantly in the contact with donor solution. Interval collection involves collecting the drug released in a series of receptor solutions, each indexed at particular intervals, USP apparatus 7<sup>27,30</sup>.

#### **A. Paddle over disc (type 5):**

- ***In - vitro* drug release studies:**

This type of apparatus is used to study the In Vitro drug release kinetics of transdermal patches. It is also known as a USP type V apparatus. The main components of the system are a basket, a paddle and a glass slide which is used to support the prepared film.

The film that is to be studied is taken and a specific portion of it is cut. The dimensions of the cut are fixed and noted as they will be later required during the calculation of drug release. The adhesive part of the patch is attached onto the glass slide which is placed in the basket. This is followed by the addition of the 500mL of the dissolution medium or phosphate buffer at pH 7.4.

The temperature of the medium is set to  $32 \pm 0.5^\circ\text{C}$  and the paddle is placed at a distance of 2.5mm from the surface of the membrane. The paddle is run at 50 rpm. The samples (5mL) can be drawn at fixed time intervals up to 24 hrs. The drawn sample must be replaced with an equal quantity of the dissolution media. Data obtained from this would be more accurate when done in triplicates<sup>31</sup>.

Alternatively, the patch can be compressed between a glass slide and a mesh<sup>32</sup> and used in a type 2 dissolution apparatus, by placing the above “sandwich” at the base of the basket. The sandwich can be held by using either Plastic<sup>33</sup> or binder clips<sup>34</sup>.

- ***In vitro* skin permeation studies:**

This process can be done in one of two ways with reference to the membrane used. It can either be done using the abdominal skin of Male Wistar Rats<sup>31</sup> or using Human abdominal Skin<sup>29</sup>.

In case of Human abdominal skin, first, the adipose tissue is removed via blunt dissection. This is followed by the immersion of the epidermis in water at  $60^\circ\text{C}$  for 1 min, which causes it to separate<sup>35</sup>. This is followed by careful removal of the epidermis and then preserving it by storing it at  $-20^\circ\text{C}$ . Before performing the experiment, the epidermis is defrosted carefully followed by cutting sections of the desired size for use. It is placed in the Franz Diffusion cell after the receptor compartment is filled with the desired media. Once the donor compartment is filled, it is covered by a

backing membrane in order to prevent loss of the reservoir solution or membrane dehydration. In this case it is essential to maintain the receptor compartments temperature at 37°C.

In case of Wistar Rats (weighing 200-250gm), the hair from the abdominal skin must be carefully removed, followed by thorough cleaning of the skin (dermal surface) with distilled water. It is now equilibrated in either the dissolution medium or phosphate buffer of pH 7.4 for one hour. If the fluids are stirred during this process, it helps achieve better equilibration. In this case, the temperature is maintained at  $32 \pm 0.5^\circ\text{C}$  using a thermostatically controlled heater.

Once equilibrated, the Rats skin is placed between the donor and receptor compartments. The remaining procedure is repeated as done with Human abdominal skin. The receptor compartments dissolution media should be replenished after each sample withdrawal. Samples are to be filtered before UV or HPLC analysis.<sup>31, 36</sup>

### B. Apparatus 6 (Rotating Cylinder Method):

This is similar to the above apparatus, except the basket and the shaft/stirrer are replaced with a stainless steel cylinder and shaft. This apparatus is designed as per the specifications in FIG. 5: USP 23 APPARATUS 5. The dosage to be tested is placed in the cylinder and the shaft is arranged at a distance of  $25 \pm 2$  mm during the test. The required volume of dissolution fluid is added and the temperature is maintained at  $32 \pm 0.5^\circ\text{C}$ .

The membranes adhesive surface is applied to a piece of cuprophan, following which it is dried for 1 min. This is followed by attaching the adhesive part of cuprophan base (with the membrane attached to its non-adhesive part) to the cylinder along its outer circumference (FIG. 7). The cylinder can now be placed in the apparatus and is rotated at the desired rate. Samples are withdrawn at the fixed time intervals from the space between the upper rotating portion of the cylinder and the surface of the dissolution fluid but not less than 1cm from the wall<sup>37</sup>.

This system is less preferred over Type 5 since in this, the membrane is in motion (spins on the

cylinder) where as in the actual design, and the membrane is stagnant. Thus, it is not an exact mimic of the actual system. Furthermore, the rotation may cause the membrane to release more drag than it actually would since a larger surface area is in contact with the mobile fluid.

TABLE 2: ACCEPTANCE CRITERIA <sup>1</sup>.

Level	Number Tested	Criteria
L1	6	No individual value lies outside the stated range
L2	6	The average value of the 12 units (L1+L2) lies within the stated range. No individual value is outside the stated range by more than 10% of the average of the stated range
L3	12	The average value of the 24 units (L1+L2+L3) lies within the stated range. Not more than 2 of the 24 units are the stated range by more than 10% of the average of the stated range, and none of the units is outside the stated range by more than 20% of the average of the stated range

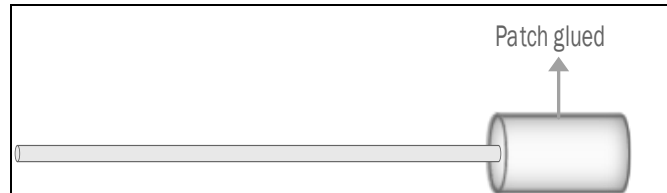


FIG. 6: APPARATUS 6 ROD WITH CYLINDER

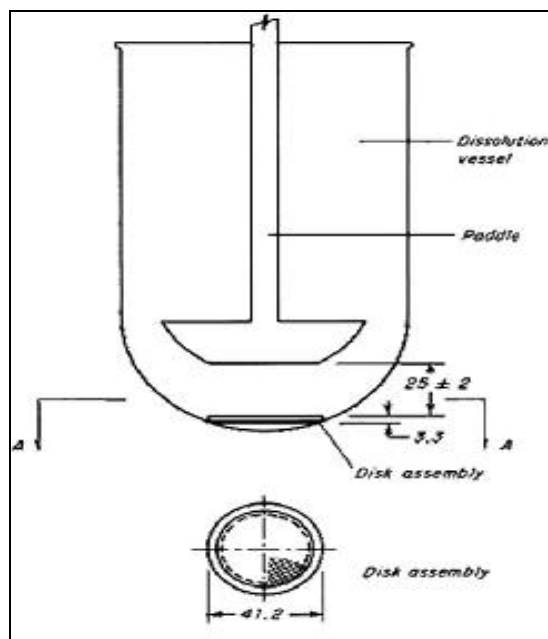


FIG. 7 USP APPARATUS 6 <sup>1</sup>.



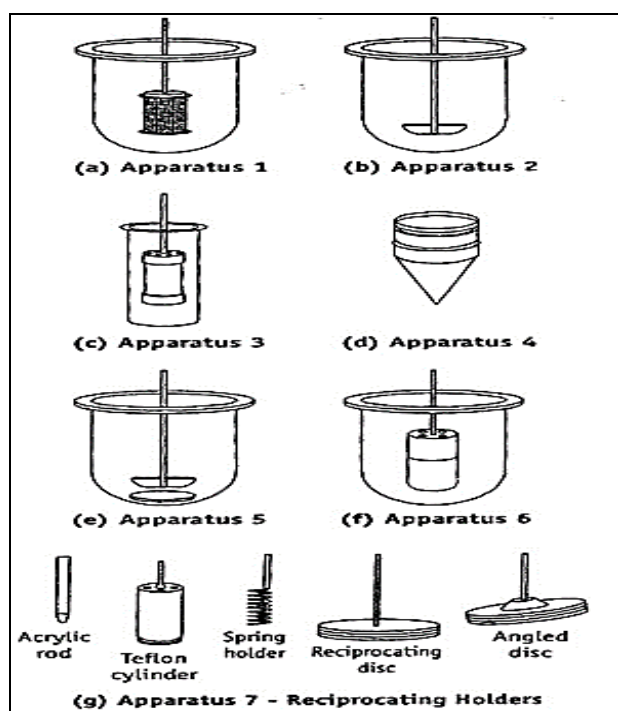


FIG 8: DIFFERENT USP APPARATUS TYPES<sup>38</sup>

### C. USP Type 7:

The vessels (previously calibrated) used in this are either made of glass or any suitable inert material. It also has a motor and drive assembly which helps the machine to automatically reciprocate the system vertically and also allows it to index the system horizontally to a different to a different row of vessels and suitable sample holders.

The containers are partially immersed in a water bath. This apparatus must be operated in a disturbance (physical) free room and on a stable platform. The size container and sample holder are used as specified in the individual monograph.<sup>37</sup>

The sample is attached by cyano-acrylate glue to a sample holder, followed by which the system is pressed onto a dry piece of cuprophan. The cuprophan must be pressed on order to remove entrapped air. This in turn is attached to a sample holder containing an O-ring. Now the back of the sample membrane is attached to the base of the holder and its frontal part is exposed to the solution. This entire arrangement is attached to a suitable sample holder as per the specified monograph.

*In Vitro* Release Criteria— the time points chosen should record drug release at 1 hour of dissolution

and when 50 and 85% of the drug has been released. Refer to **Table 1** for quantities of active ingredients expected to be released, unless specified otherwise.

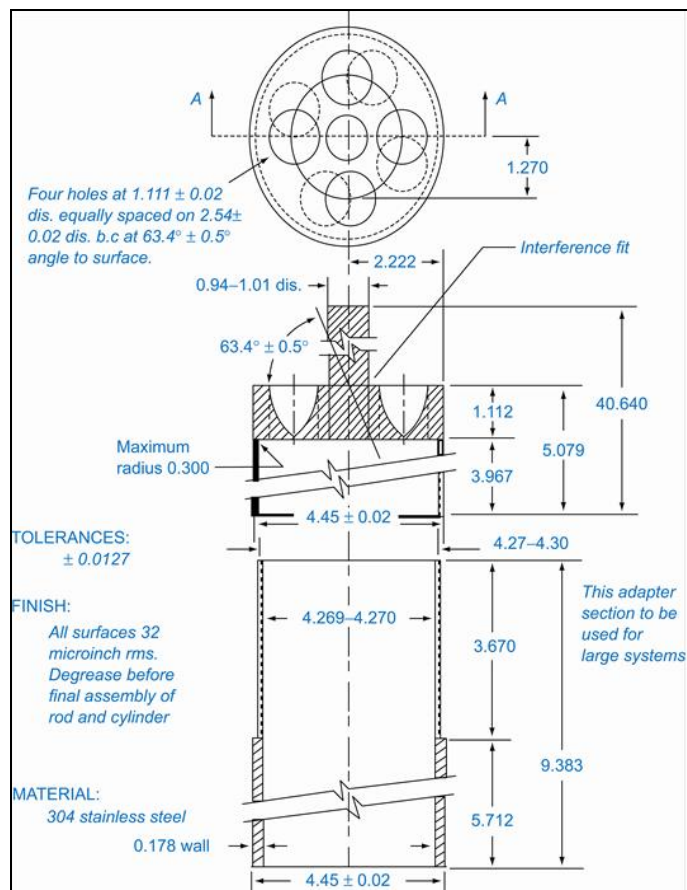


FIG.9: USP TYPE 6<sup>1</sup>

**CONCLUSION:** A number of *In vitro* techniques are available both to analyze the physical and chemical properties of the patch and also to analyze/ mimic its behavior in real time conditions. These tests help us further understand how altering the excipients or any of the physical properties of the patch can affect the drug release from the patch in real time conditions. Further research needs to be focused on a customized platform that can be used as a standard to deliver any drug for transdermal use.

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