A review on formulation of transdermal patch for controlled release action.

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ABSTRACT

The main aim of this study is to review the formulation of transdermal patches using different polymers and permeation enhancers in different ratios to see the release of drug in controlled action and also to check whether the bioavailability is enhanced by the use of permeation enhancers. These transdermal patches were prepared as Matrix diffusion-controlled system. Drug reservoir of homogenous dispersion of drug with hydrophilic or lipophilic polymer is prepared with one of the following methods. Homogenous dispersion of finely ground drug particles with liquid polymer or highly viscous base polymer followed by cross linking of polymer chains OR Homogenous mixing of drug solid with rubbery polymer at an elevated temperature. The main advantage of transdermal patches is that the first pass metabolism is avoided and this also leads to enhancement in the bioavailability. Many drugs are administrated orally, but due to the first pass metabolism in increases the dose and decreases the effects of drug. So, transdermal drug delivery system is design to improve the efficiency and bioavailability of the drug and decreases the number of doses. Transdermal drug delivery system is administrated by skin and drug is delivered directly into systemic circulation maintaining continuous efficacy. These systems provide drug systemically at a predictable rate and maintain the rate for extended period of time thus eliminating numerous problems associated with oral products such as reduced bioavailability, enhanced first pass hepatic metabolism, relatively short residence time, dose dumping and dosing inflexibility Physicochemical point of view, an ideal transdermal drug candidate has to meet a number of requirements such as drug is highly lipophilic in nature, melting point of the drug is above 150, molecular weight is above 500 Dalton, log p values 1-5, no local toxicity and irritation to skin.

Keywords: Lipophilic, Adhesive, Baking membrane, Matrix-diffusion, Controlled release.

1. **Introduction:** Transdermal drug delivery system can be termed as Topical method for administration of medicaments in the form of gels, patches to deliver the drugs into the systemic circulation. The drug is delivered at a predetermined rate for controlled release. This method is widely considered nowadays as it is non-invasive method for delivery of medicament directly into the systemic circulation.(1) TDDS are widely accepted also because they can avoid gastrointestinal problems associated with drugs and low absorption.(2) The drugs that are used in TDDS mostly penetrate through the skin through intercellular micro route and that is why the role of permeation enhancers plays a vital role as they reduce the barrier resistance of stratum corneum reversibly without damaging viable cells. Nicotine patches were the first transdermal drugs that successfully raised the market value of TDDS in medicine to newer heights. Estradiol, fentanyl, testosterone, lidocain, and some other drug combinations are available in the form of TDDS in the present pharma market.(3) Oral drug delivery system of administration was considered the most common and convenient method for administration of any medicaments because of its good patient compliance, cost friendly, also it is easy in production and in predetermining its dose. But some limitations were still with these oral drug delivery systems, i.e. sometimes the drugs are incompletely absorbed due to some change in gastrointestinal behavior. Also the other route i.e. the parenteral route was commonly preferred for administration of any medicament especially because it has the advantage of fast onset of action. But even this method of drug administration found to have certain limitations. As it is invasive method and also painful. And self-administration is also not possible in case of parenteral administration. So over all these limitation in other drug delivery system TDDS is found to be more convenient as it is non-invasive, Self-administration is also possible, does not require any well qualified person for administration and also change in GIT behavior will not affect its activity.(4) Transdermal Patches were introduced in late 1970s , starting with a three day Patch to treat motion sickness and after that the market for transdermal patches has slowly increased.(5)

1.1. Why to choose transdermal drug delivery system?

- Change in the activity of the drug due to change in Gastrointestinal behavior can be reduced
- First pass metabolism is avoided
- Self -administration can be done
- It is non-invasive method so more patient friendly
- No need of water, or well trained professional for administration
- Controlled action of drugs can be obtained without any fluctuation
- Frequent administration is not needed

1.2. Some limitations of TDDS:

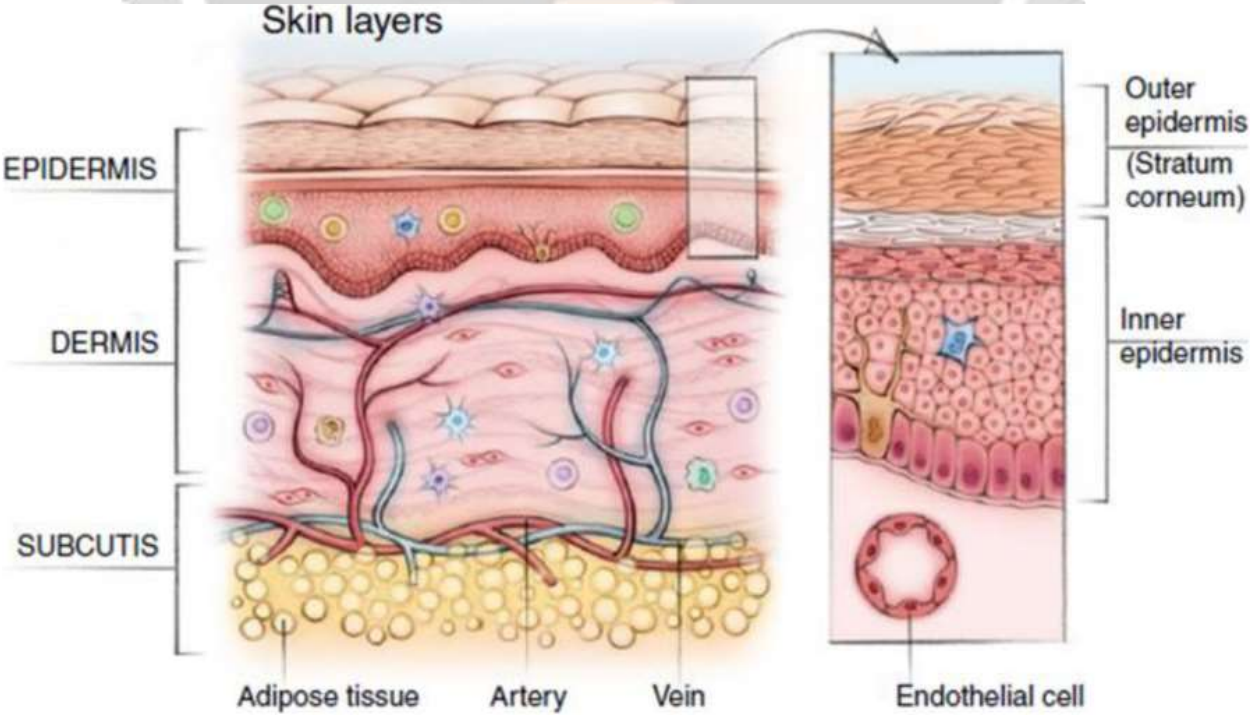
- It may sometimes cause irritation on the local area of application
- Sometimes the skin condition may affect the absorption and penetration of the drug through the skin
- Only those drugs which are lipophilic in nature are considered suitable for TDDS
- Only 5mg or less dose can be administered.(6)

2.0. Parameters to be considered while selection of suitable drug candidate for TDDS:

- The dose of less than 20mg is the effective concentration for its activity
- The molecular weight of the drug should be less than 1000 Dalton
- A drug with short biological half- life is considered as the suitable candidate for TDDS
- The melting point of a suitable candidate should be less than 200°C
- The drug having extensive pre-systemic metabolism are also considered as a suitable candidate.
- The drug should not lead to any toxicity or immunogenic reaction on the skin.

3.0. Anatomy of the skin:

As in case of TDDS the drug is delivered via skin, the drug penetrates through the skin and shows the action. Hence, it is important to know the anatomy of the Skin.



As we know that skin is the largest organ of human body having surface area of about 1.7 m^2 and it covers 16% of the human body mass.(7) Skin plays a very important role for human body as it acts as a protective layer for the body from the external environmental factor. (8)

The skin is divided into three major parts:

1. Epidermis (the outermost layers)
2. Dermis (the middle layer)
3. Hypodermis (the innermost layer).(9,10)

Epidermis

Non-viable epidermis and viable epidermis combined together to form epidermis. (11) Stratum corneum is the non-viable epidermis and the layer below the stratum corneum is the viable epidermis. The viable epidermis constitute of various sub layers of epidermis which is collectively 50-100 µm thick. Blood capillaries and nerve fibers reach the epidermis by passing through the dermis and subcutaneous fat layer. (12) There are different layers of epidermis of which the stratum corneum is the outermost layer which is responsible for several important functions.

Stratum corneum:

The outermost layer of the skin, the stratum corneum, is responsible for the barrier function of the skin. (13) It is also known as non-viable epidermis. (14) The stratum corneum thickness ranges from 10-15 µm and it is composed of dead flattened corneocytes.(15)The main route of permeation is around the corneocytes and thus, the larger the size of corneocytes the longer will be the route for the permeation. Corneocyte size differs according to the site on the body e.g. the size of corneocyte is smaller in the skin of the face as compared to the arm. (16)

Dermis

Once the drug molecule is passed through the stratum corneum, it might pass into the deeper epidermal tissues and enter into the dermis. It is composed of fibrous tissues and is 1-2 mm thick. The dermis is highly vascular because of a rich supply of blood vessels from where the drug gets absorbed into the systemic circulation. Sebaceous glands, sweat glands, and hair follicles rises to the surface of the skin from dermis. (17)

Hypodermis

Histologically, hypodermis is the third layer of the skin found beneath the dermis. Also called as the subcutaneous layer andis an elastic layer and it contains a large amount of fat cells that work as a shock absorber for blood vessels and nerve endings. The average thickness of this layer is 4 to 9 mm.

4.0. Formulation of Transdermal patch: The formulation of TDDS can be discussed under two parts TDDS

1. **Materials used to prepare**
2. **Method of preparation**

4.1. Materials that are used to prepare TDDS: The materials required for the preparation of transdermal patches are:

1. API
2. Excipients

4.1.1. API: The active pharmaceutical ingredients that are combined with excipients to form a dose so that it can be administered conveniently by the patient and show its therapeutic activity.

The API should be chosen very carefully for TDDS. So the ideal drug should be:

1. The molecular size of the drug should be less than 500 dalton.
2. The drug should have both water and lipid solubility with partition coefficient log k ^1-3
3. Unionized drugs show better permeation through the skin.

4.1.2. Excipients: These are the extra additives which are used to either increase the bulk, enhance the flavor, mask the unpleasant taste, as a carrier and for several other role.

The excipients that are used in the formulation of TDDS are:

4.1.2.1. Polymer membrane: Polymers are considered as the most important part of the TDDS. The release pattern of the drug is controlled by these polymers. The polymers used for the formulation of TDDS should be compatible with the drug and other excipients and also should be able to maintain the stability. The drug is

dispersed in the polymer base to prepare the polymer matrix. Some examples of polymer used mostly in preparation of TDDS are: 1. Natural polymers: gelatin, gums etc

2. Synthetics: Polyvinyl alcohols, polyacrylates

4.1.2.2. Permeation enhancers: Those substances that are used to increase the permeability of the drug through the stratum corneum are called permeation enhancers. These substances do their work by interacting with the structural components of the skin.
Examples: Propylene glycol, Dimethyl sulfoxide.

4.1.2.3. Adhesives: To adhere the patch on the surface of the skin several type of adhesives are used and these adhesives must follow some ideal criteria:
1. Should be non irritating
2. It should easily get adhered to the skin and easy to remove
3. Should not leave stickiness that is not washable after removing it.
4. Should be stable and compatible and not affecting the activity of drug penetration.

4.1.2.4. Baking membrane: These are mostly used to prevent the drug loss from the top. These are mainly impermeable layer. These should be compatible with the preparation.
Examples: metallic plastic laminate with the matrix diffusion method.

4.2. Method of preparation: There are several method for preparation of transdermal patches but matrix diffusion method is widely used for controlled released system.

4.2.1. Matrix-diffusion method: In this method the drug is homogeneously dispersed in a lipophilic/hydrophilic polymer to form the drug reservoir. This medicated polymer is then fixed onto an occlusive base plate in a compartment which is fabricated with a impermeable backing layer.
The rate of drug diffusion in this type of system is calculated by:

$$dq/dt = (\frac{ACpDp}{2t})^{1/2}$$

5.1. Conclusion: This study brings us to a conclusion that transdermal route can be the most preferable route as it is noninvasive and painless. This type of drug delivery system will be very beneficial for the patients who feel difficult in swallowing oral medications and also it prevents frequent dosing so is more convienient for the patents to use. Specially the patients with depression are not always stable to take medications time to time at a certain interval and sometimes it is very difficult to manage their breakouts. So, such transdermal systems will be very helpful for these types of patients also.

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