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Research Article

FORMULATION AND EVALUATION OF TRANSDERMAL DRUG DELIVERY SYSTEM OF HESPERIDIN

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Abstract:

The present study focuses on the formulation and evaluation of a transdermal drug delivery system (TDDS) of Hesperidin, a natural bioflavonoid known for its antioxidant, anti-inflammatory, and Vaso protective properties. Due to its poor oral bioavailability and extensive first-pass metabolism, the transdermal route was selected to enhance systemic absorption and ensure sustained therapeutic action. Transdermal patches were prepared using various combinations of polymers such as Ethyl Cellulose, HPMC and Eudragit RSPO, along with suitable plasticizers. The formulations were evaluated for physicochemical properties including thickness, weight variation, folding endurance, moisture content, drug content uniformity, and in vitro drug release. The optimized formulation exhibited good mechanical strength, satisfactory drug content, and a sustained drug release profile over 12 hours. The study concludes that Hesperidin-loaded transdermal patches can serve as a promising alternative to conventional dosage forms, potentially improving patient compliance and therapeutic efficacy.

Keywords: Hesperidin, Ethyl Cellulose, HPMC and Eudragit RSPO

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INTRODUCTION:**Controlled drug delivery**

Treatments of acute and chronic diseases have been accomplished by delivery of drugs to patients using various pharmaceutical dosage forms. These dosage forms are known to provide a prompt release of drug. But recently several technical advancements have been done and resulted in new techniques for drug delivery. These techniques are capable of controlling the rate of drug release.

The term controlled release has a meaning that goes beyond scope of sustained release. The release of drug ingredients from a controlled release drug delivery advances at a rate profile that is not only predictable kinetically, but also reproducible from one unit to other¹. The difference between sustained release and controlled release is shown by fig.1.

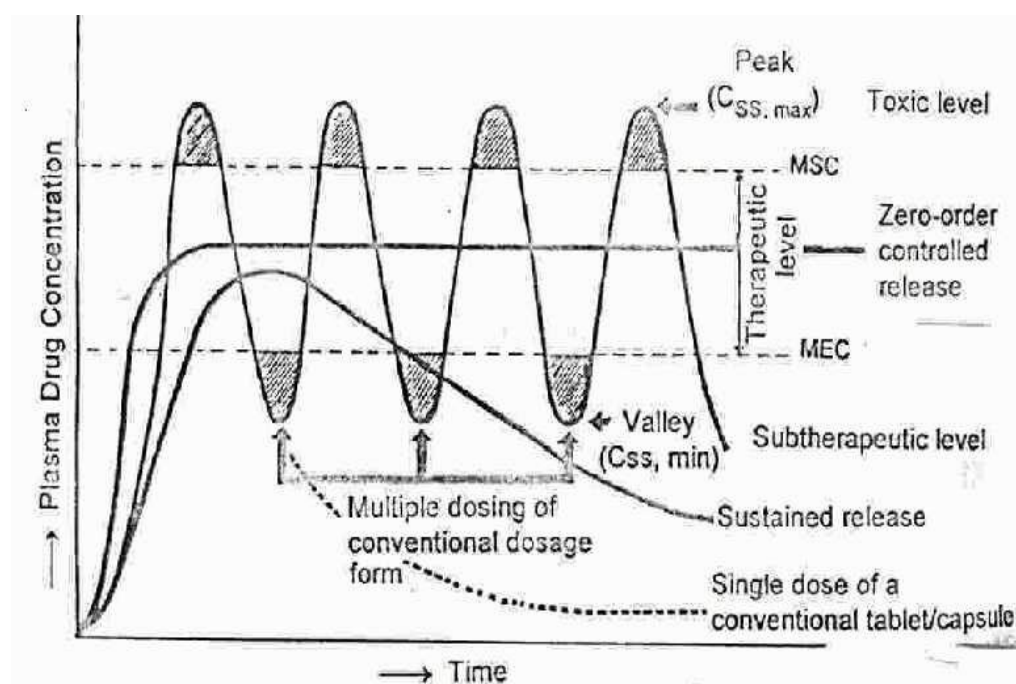


Figure 1. 1: Comparative graphs of conventional, sustained- and controlled release delivery systems.

The classification of controlled drug delivery can be given as follows.

1. Rate-preprogrammed drug delivery systems
2. Activation-modulated drug delivery systems
3. Feedback-regulated drug delivery systems
4. Site-targeting drug delivery systems

Out of these classes first class contains new drug delivery systems as transdermal delivery, intra uterine delivery, ocular inserts, and sub dermal implants. The transdermal drug delivery has advantage to deliver medicines via skin to systemic circulation at a predetermined rate and maintain therapeutic concentration for prolong period of time.

1.1 Transdermal drug delivery: An Introduction

The idea of delivering drugs through skin is old, as the use is reported back in 16th century B.C. Today the transdermal drug delivery is well accepted for delivering drug to systemic circulation.

Until recently, the use of transdermal patches for pharmaceuticals has been limited because only a few drugs have proven effective

delivered through the skin typically cardiac drugs such as nitroglycerin and hormones such as estrogen.

Definition: Transdermal therapeutic systems are defined as self-contained discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at controlled rate to the systemic circulation.

The first Transdermal drug delivery (TDD) system, Transderm-Scop developed in 1980, contained the drug Scopolamine for treatment of motion sickness. The Transdermal device is a membrane-moderated system. The membrane in this system is a microporous polypropylene film. The drug reservoir is a solution of the drug in a mixture of mineral oil and polyisobutylene. This study release is maintained over a one-day period.

Non-medicated patch markets include thermal and cold patches, nutrient patches, skin care patches (a category that consists of two major sub-categories — therapeutic and cosmetic), aroma

patches, and weight loss patches, and patches that measure sunlight exposure. Transdermal drug delivery has many advantages over conventional drug delivery and can be discussed as follows.

Advantages^{2, 3, 4, 5}

1. They can avoid gastrointestinal drug absorption difficulties caused by gastrointestinal pH, enzymatic activity, and drug interactions with food, drink, and other orally administered drugs.
2. They can substitute for oral administration of medication when that route is unsuitable, as with vomiting and diarrhea.
3. They avoid the first-pass effect, that is, the initial pass of a drug substance through the systemic and portal circulation following gastrointestinal absorption, possibly avoiding the deactivation by digestive and liver enzymes.
4. They are noninvasive, avoiding the inconvenience of parenteral therapy.
5. They provide extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration.
6. The activity of a drug having a short half-life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release.
7. Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.
8. They are easily and rapidly identified in emergencies (e.g., unresponsive, unconscious, or

comatose patient) because of their physical presence, features, and identifying markings.

9. They are used for drugs with narrow therapeutic window. At the same time transdermal drug delivery has few disadvantages that are limiting the use of transdermal delivery.

Disadvantages^{3, 4, 6}

1. Only relatively potent drugs are suitable candidates for transdermal delivery because of the natural limits of drug entry imposed by the skin's impermeability.
2. Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.
3. The delivery system cannot be used for drugs requiring high blood levels.
4. The use of transdermal delivery may be uneconomic. For better understanding of transdermal drug delivery, the structure of skin should be briefly discussed along with penetration through skin and permeation pathways.

1.2 Structure of skin

An average adult skin has a surface area of approximately 2 square meters and receives about one third of the blood circulating through the body. It is one of the most readily accessible organs of the human body with a thickness of only a few millimeters (2.97±0.28 mm). Its major roles are to regulate body temperature, protect tissues from infection, prevent fluid loss, and cushion internal structures^{7,8}

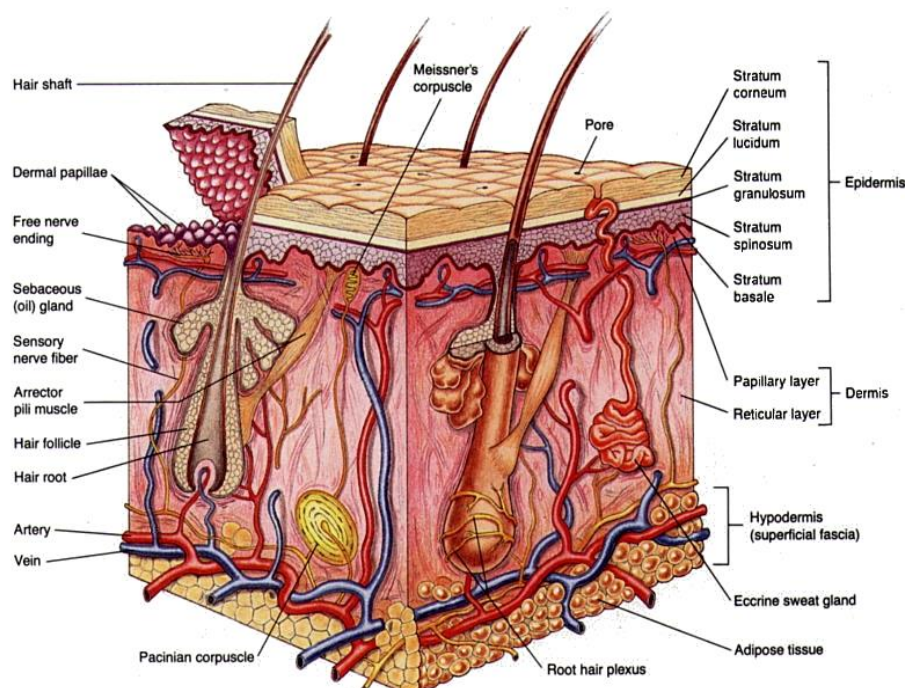


Figure 1.2: Structure of skin

The skin is a multilayered organ composed of many histological layers. It is generally described in terms of three major tissue layers.^{6,9,10.}

☞ **The epidermis** – thin protective outer layer.

☞ **The dermis** – the tough elastic second layer.

☞ **The hypodermis** – layer of fatty and connective tissue.

The Epidermis:

The outer (epidermal) layer of the skin is composed of stratified squamous epithelial cells. The multilayered envelope of the epidermis varies in thickness, depending on cell size and then number of cells and then number of cell layers, ranging from about 0.8mm on the palms and the soles down to 0.66mm on the eyelids. Cells which provide epithelial tissue differ from those of all other organs provide epithelial tissue differ from those of all other organs in that as they change in an ordered fashion from metabolically active and dividing cells to dense, dead, keratinized protein.

Stratum germinativum (basal layer):

The basal cells are nucleated, columnar, and about 6 microns wide, with their long axis at right angles to the dermoepidermal junction; they connect by cytoplasmic intercellular bridges. Mitosis of the basal cells constantly renews the epidermis and this proliferation in healthy skin balances the loss of dead horny cells from the skin surface. The epidermis thus remains constant in thickness. Below the basal cell layer lies the complex dermoepidermal junction, which constitutes an anatomic functional unit. The junction serves three functions of dermal-epidermal adherence, mechanical support for the epidermis, and control of the passage of cells and some large molecules across the junction.

Stratum spinosum (prickle cell layer):

As the cells produced by the basal layer move outward, they alter morphologically and histochemically. The cells flatten and their nuclei shrink. These polygonal cells are called as prickle cells because they interconnect by fine prickles.

Stratum granulosum (granular layer):

As the Keratinocytes approach the surface, they manufacture basic staining particles, the keratohyalin granules. It was suggested that these granules represent an early form of keratin 3, 4. The term transitional zone is convenient region between living cells and dead keratin.

Stratum lucidum:

In the palms and the soles an anatomically distinct, poorly staining hyaline zone forms a thin, translucent layer immediately above layer immediately above the granular layer. This region is the stratum lucidum.

Stratum corneum (horny layer):

As the final stage of differentiation, epidermal cells construct the most the superficial layer of the epidermis, the stratum corneum. On general body areas the membrane provides 10-15 layers of much flattened, keratinized dead cells (corneocytes). Ultimately these cells are sloughed off through desquamation. A keratinocyte's journey from basal layer to horny layer takes about 14 days. The cell travels through the layers of stratum corneum for another 14 days before it is finally shed. So the normal turnover rate of the epidermis is atleast 28 days. The stratum corneum plays a crucial role in controlling the percutaneous absorption of drug molecules.

The barrier nature of stratum corneum depends critically on its unique constituents; 75-80% is protein, 5-15% is lipid with 5-10% unidentified on a dry weight basis. The protein is located primarily within the keratinocytes and is predominantly alpha-keratin (around 70%) with some beta-keratin (approximately 10%) and a proteinaceous cell enveloping (around 5%). Enzymes and other proteins account for approximately 15% of the protein component. The cell envelop protein is highly insoluble and is very resistant to chemical attack. This outer keratinocytes protein has a key role in structuring and ordering the intercellular lipid lamella of the stratum corneum; the keratinocytes is bound to a lipid envelop through glutamate moieties of the protein envelop. The lipid envelop thus provides an anchor to the keratinocytes and links the proteinaceous domains of the keratinocytes to the intercellular lipid domains. Human stratum corneum is a unique mixture of lipids and, for most permeates; the continuous multiply bilayered lipid component of the stratum corneum is key component in regulating drug flux through the tissue. It is clear that the lipid content of the stratum corneum varies between individuals and with body site, but major components of the domain include ceramides, fatty acids, cholesterol, and cholesterol sulfate and sterol/wax esters.

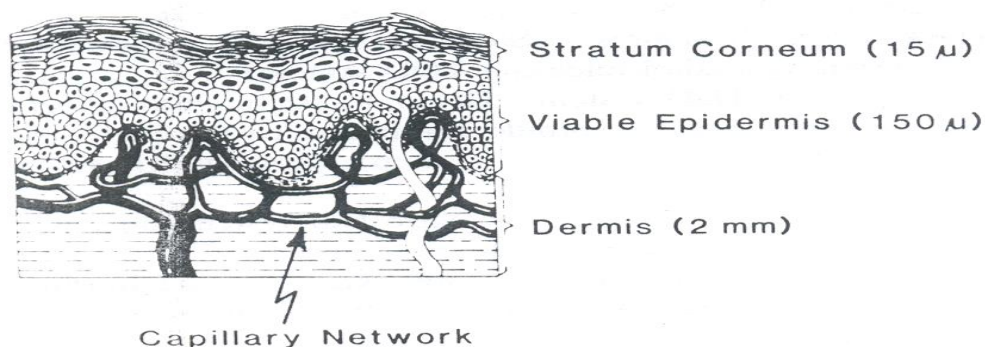


Figure No.1. 3. The structural relationship between stratum corneum, viable epidermis, and the capillary network at the dermoepidermal junction.

The Dermis:

The dermis (cornium) consists essentially of a matrix of connective tissue woven from fibrous proteins which embed in an amorphous ground substance on mucopolysaccharides providing about 20% of the mass. Blood vessels, nerves, and lymphatics cross this matrix and skin appendages (eccrine sweat glands, apocrine glands and pilosebaceous units) penetrate it. In man, the dermis divides into a superficial, thin papillary layer which forms a negative image of the rigid lower surface of the epidermis, and a thick underlying reticular layer which merges with the fat-containing subcutaneous tissue.

The dermis needs a rich blood supply which regulates temperature and pressure, delivers nutrients to the skin and removes waste products, mobilizes defense forces, and contributes to skin color. The blood supply reaches to within 0.2mm of the skin surface, so that it readily absorbs and systemically dilutes most chemicals which penetrate past the stratum corneum and the viable epidermis. The vascular surface available for the exchange of materials between local tissues and

the blood is enormous. Of particular relevance to biopharmaceutical studies is the fact that this generous blood volume usually functions as a "sink" with respect to the diffusing molecules which reach it during the process of percutaneous absorption. This sink condition ensures that the penetrant concentration in the dermis remains near and therefore the concentration gradient across the epidermis is maximal.

The Hypodermis:

This is a sheet of fat-containing areolar tissue known as superficial fascia, attaching the dermis to the underlying structure.

Skin Appendages:

The epidermis and dermis support several appendages: The eccrine, apocrine and sebaceous glands, the hair follicles and the nails. Of these, hair follicles and sweat ducts can act as diffusion shunts, i.e. relatively easy pathways for diffusion through the rate-limiting stratum corneum.



Figure 1. 4. Transepidermal (A) and transappendageal route of transport into the skin. The transappendageal route (B) includes diffusion via the hair follicle and the sweat gland.

Eccrine Sweat glands: Eccrine sweat glands develop over the skin surface but not over mucous membranes. The gland density varies greatly with skin site; for example, the thighs possess about 120 glands per square centimeter and the soles of the feet have about 620 per square centimeter. The composition and the quantity of the sweat varies

greatly with subject, time, environmental conditions, exertion and skin site.

Apocrine Sweat Glands: Apocrine sweat glands are epidermal appendages which develop throughout the skin of the embryo as part of the pilosebaceous follicle. Most of the glands subsequently disappear so that the characteristic

adult distribution is in the axilla, the perianal region and the areola of the breasts.

Hair follicles: Hair follicles developed over the entire skin surface except the palms the soles, the red portion of the lips and the parts of the sex organs. The average fractional surface area of the openings is about 0.1%. Hair contains “hard” keratin, which differs from the “soft” keratin of desquamating tissues in its high sulfur content.

Sebaceous Glands: Sebaceous glands are largest and most numerous on the back. The palms and soles are usually free of them. The flask like sebaceous glands from ducts which usually open into the neck of the hair follicle. Sebum is complex mixture of lipids i.e. glycerides, free fatty acids, wax esters, squalene, cholesterol, esters. Several functions have been attributed to sebum, such as controlling water loss, and protecting the skin from fungal and bacterial infection.

1.3 Skin Pathways For Transdermal Drug Delivery Systems

When drugs are applied on the skin surface, penetration into and through the skin can occur via various routes.

Drugs penetrate either via the stratum corneum (transepidermal) or via the appendages

(transappendageal) (Figure 1.3 and 1.4). During penetration through the stratum corneum, two possible routes can be distinguished,¹¹

- i) Penetration alternating through the corneocytes and the lipid lamellae (transcellular route) and
- ii) Penetration along the tortuous pathway along the lipid lamellae (intercellular route).

Generally it is accepted that the predominant route of penetration through the stratum corneum is the intercellular route. This is mainly caused by the densely cross-linked cornified envelope coating the keratinocytes. However transcellular transport for small hydrophilic molecules such as water cannot completely be excluded. The appendage route or shunt route includes either the duct of the eccrine sweat glands or the follicular duct. The content of the eccrine sweat glands is mainly hydrophilic, while the content of the follicular duct is lipophilic. This is mainly due to the sebum excreted into the opening of the follicular duct. It is generally accepted that due to its large surface area, passive skin permeation mainly occurs through intact stratum corneum.

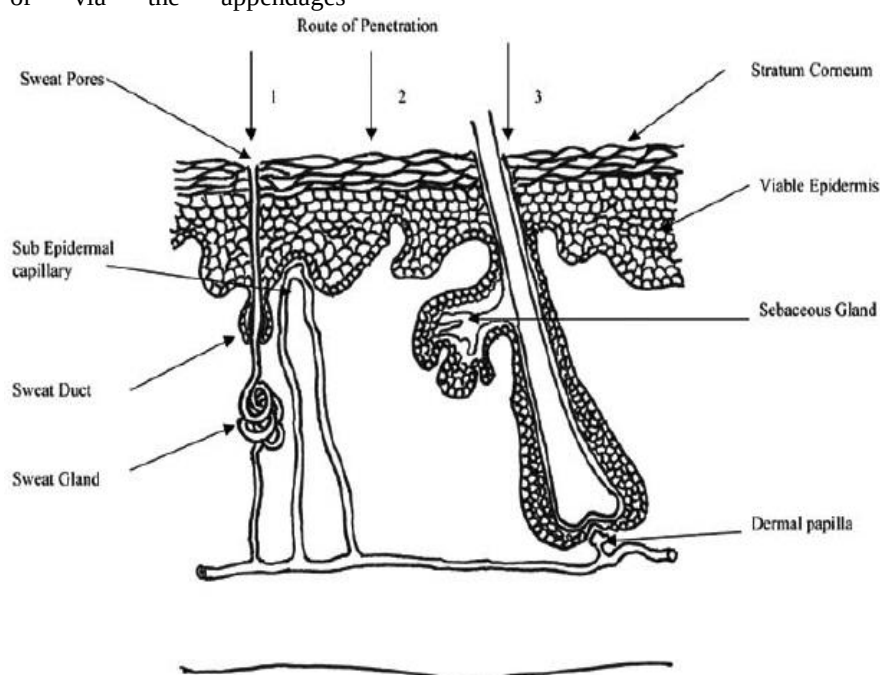


Figure No. 1.5. Simplified Representation of skin showing routes of penetration: 1. Through the Sweat ducts, 2. Directly across the Stratum Corneum, 3. Via the Hair follicles.

1.4 Steps Involved in Drug Transport from TDDS through the Skin:

The various steps involved in transport of drug from patch to systemic circulation are as follows:

- * Diffusion of drug from drug reservoir to the rate controlling membrane.
- * Diffusion of drug from rate limiting membrane to stratum corneum.

- * Sorption by stratum corneum and penetration through viable epidermis: The structure of stratum corneum is often compared with a brick wall, with the corneocytes as the bricks surrounded by

the mortar of the intercellular lipid lamellae.

- * Uptake of drug by capillary network in the dermal papillary layer.
- * Effect on target organ.

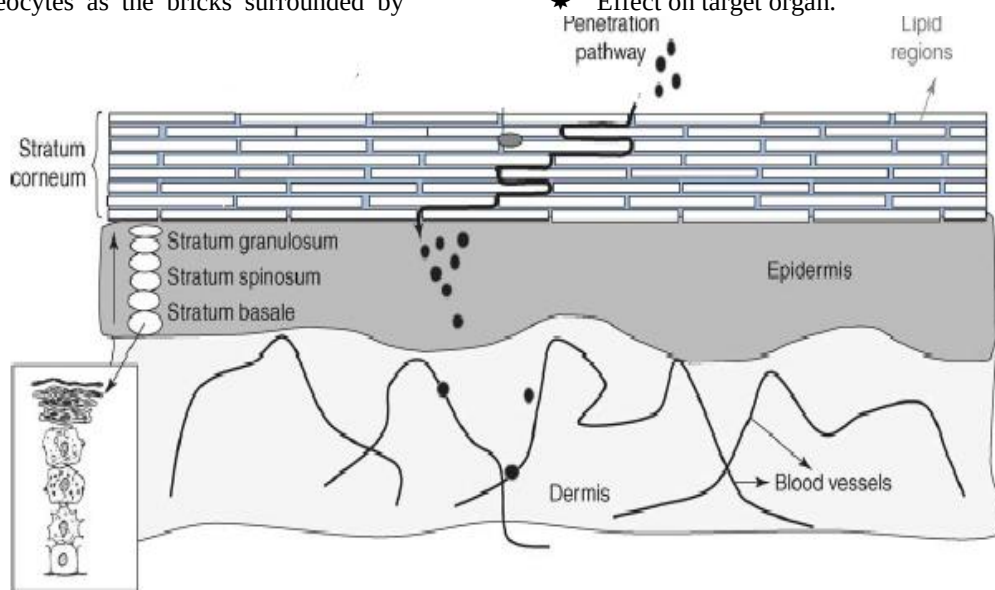


Figure No.1.6. Penetration pathway of drug molecules through the skin¹²

1.4 Basic Components Of Transdermal Drug Delivery Systems^{2,9}

The components of transdermal devices include:

- Polymer matrix or matrices
- The drug
- Permeation enhancers
- Other excipients

a) Polymer matrix:

The Polymer controls the release of the drug from the device. The following criteria should be satisfied for a polymer to be used in a transdermal system.

- Mol.Wt, glass transition temperature and chemical functionality of the polymer should be such that the specific drug diffuses properly and released through it.
- The polymer should be stable, non-reactive with the drug, easily manufactured and fabricated into the desired product and inexpensive.
- The polymer and its degradation products must be non-toxic or non-antagonistic to the host.
- The mechanical properties of the polymer should not deteriorate excessively when large amount of active agent is incorporated into it.

Possible useful polymers for transdermal devices are:

- ♦ **Natural Polymers:** Cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, starch etc.
- ♦ **Synthetic elastomers:** Polybutadiene, Hydrin rubber, Polysiloxane, Silicone rubber, Nitrile, Acrylonitrile, Butyl rubber, Styrenebutadiene rubber, Neoprene etc.
- ♦ **Synthetic Polymers:** Polyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyurea, Polyvinylpyrrolidone, Polymethyl methacrylate, Epoxy etc.

b) The Drug

For successful development of transdermal drug delivery system, the drug should be chosen with great care. The following are some of the desirable properties of a drug for transdermal delivery.

Physicochemical properties of Drug

- The drug should have a molecular weight less than approximately 1000 g/mol
- The drug should have affinity for both lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conducive to successful drug delivery via the skin.

- iii. The drug should have a low melting point (< 200°C)

Biological properties of Drug

- The drug should be potent with a daily dose of the order of a few mg/day.
- The half life ($t_{1/2}$) of the drug should be short.
- The drug must not induce a cutaneous irritant or allergic response.
- Drugs, which degrade in the GI tract or are inactivated by hepatic firstpass effect, are suitable candidates for transdermal delivery.
- Tolerance to the drug must not develop under the near zero-order release profile of transdermal delivery.
- Drugs, which have to be administered for a long period of time or which cause adverse effects to non-target tissues can also be formulated for transdermal delivery.

c) Permeation Enhancers¹³

These are the compounds, which promote skin permeability by altering the behaviour of skin as barrier to the flux of a desired penetrant. The flux, J, of drugs across the skin can be written as:

$$J = D \frac{dc}{dx} \text{ ----- (1)}$$

Where,

D is the diffusion coefficient and is a function of the size, shape and flexibility of the diffusing molecule as well as the membrane resistance;

C is the concentration of the diffusing species;

x is the spatial coordinate.

Thus enhancement of flux across membranes depends on the considerations of:

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

Permeation enhancers are hypothesized to affect one or more of the layers to achieve skin penetration enhancement. A large number of compounds have been investigated for their ability to enhance stratum corneum permeability. These conveniently classified under the following main headings:

Solvents:

These compounds increase penetration possibly by

- Swelling the polar pathways in the skin.
- Fluidization of lipids.

Examples include water alcohols-methanol and ethanol; alkyl methyl Sulphoxides-dimethyl Sulphoxide, alkyl homologs of methyl Sulphoxide,

dimethyl acetamide and dimethyl formamide; pyrrolidones-2-pyrrolidone; laurocapram (Azone), miscellaneous solvents-propylene glycol, glycerol, silicone fluids, isopropyl palmitate.

Surfactants:

These compounds are proposed to enhance polar pathway transport, especially of hydrophilic drugs.

The ability of a surfactant to alter penetration is a function of the head group and the hydrocarbon chain length. These compounds are, skin irritants, therefore, a balance between penetration enhancement and irritation have to be considered. Anionic surfactants can penetrate and interact strongly with the skin. Once these surfactants have penetrated the skin, they can induce large alterations. Cationic surfactants are reportedly more irritant than the anionic surfactants and they have not been widely studied as skin permeation enhancers. Of the three major classes of surfactants, the nonionics have long been recognized as those with the least potential for irritation and have been widely studied. Examples of commonly used surfactants are:

Anionic Surfactants: Dioctyl sulphosuccinate, Sodium lauryl sulphate, Decadecylmethyl sulphoxide etc.

Nonionic Surfactants: Pluronic F127, Pluronic F68, etc.

Bile Salts : Sodium taurocholate, Sodium deoxycholate, Sodium tauroglycocholate.

Miscellaneous chemicals: These include urea, a hydrating and keratolytic agent; N,N-dimethyl-m-toluidamide; Calcium thioglycolate; Anticholinergic agents.

Some potential permeation enhancers have recently been described but the available data on their effectiveness are sparse. These include eucalyptol, di-o-methyl-beta-cyclodextrin and soyabean casein.

d) other excipients:

Adhesives:

The fastening of all Transdermal devices to the skin has so far been done by using a pressure sensitive adhesive. The pressure sensitive adhesive can be positioned on the face of the device or in the back of the device and extending peripherally.

Both adhesive systems should fulfill the following criteria.

- Should not irritate or sensitize the skin or cause an imbalance in the normal skin flora during its contact time with the skin.
- Should adhere to the skin aggressively during the dosing interval without its position being disturbed by activities such as bathing, exercise etc.
- Should be easily removed.
- Should not leave an unwashable residue on the skin.

MATERIALS Table : List of Material Used In the Formulation Development

Material	source
Hesperidin	Procured From Torrent Pharma, India. Provided by SURA LABS , Dilsukhnagar, Hyderabad.
Ethyl Cellulose	Merck Specialities Pvt Ltd
HPMC	Merck Specialities Pvt Ltd
Eudragit RSPO	Merck Specialities Pvt Ltd
PEG-400 (ml)	Merck Specialities Pvt Ltd
Chloroform	Merck Specialities Pvt Ltd
Dimethylsulphoxide	Merck Specialities Pvt Ltd
Dibutyl phthalate	Merck Specialities Pvt Ltd

METHODOLOGY:**a) Determination of absorption maxima:**

100mg of Deflazacort pure drug was dissolved in 100ml of Methanol (stock solution) 10ml of above solution was taken and make up with 100ml by using 0.1 N HCL (100µg/ml). From this 10ml was taken and make up with 100 ml of 0.1 N HCL (10µg/ml). and pH 6.8 Phosphate buffer UV spectrums was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400nm.

b) Preparation calibration curve:

100mg of Deflazacort pure drug was dissolved in 100ml of Methanol (stock solution) 10ml of above solution was taken and make up with 100ml by using 0.1 N HCL (100µg/ml). From this 10ml was taken and make up with 100 ml of 0.1 N HCL (10µg/ml). The above solution was subsequently diluted with 0.1N HCL to obtain series of dilutions Containing 10, 20, 30, 40 and 50 µg/ml of Deflazacort per ml of solution. The absorbance of the above dilutions was measured at 244 nm by using UV-Spectrophotometer taking 0.1N HCL as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

9.2. Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$$\tan \theta = h / r \quad \tan \theta = \text{Angle of repose}$$

$$h = \text{Height of the cone ,}$$

$$r = \text{Radius of the cone base}$$

Formulation composition for tablets

INGREDIENTS (mg)	FORMULATION CHART								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Deflazacort	6	6	6	6	6	6	6	6	6
Ethyl Cellulose	5	10	15	-	-	-	-	-	-
Eudragit S 100	-	-	-	5	10	15	-	-	-
Hydroxypropyl Cellulose	-	-	-	-	-	-	5	10	15
Lactose	71	66	61	71	66	61	71	66	61
PVP K30	10	10	10	10	10	10	10	10	10
Magnesium stearate	4	4	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4	4	4
Total Tablet Weight	100	100	100	100	100	100	100	100	100

All the quantities were in mg

RESULTS AND DISCUSSION:

Initially the drug was tested by UV to know their significant absorption maximum which can be used for the diffusion study of the drug.

8.1. Analysis of drug:**A. UV scan:**

The lambda max of Hesperidin was found to be 330 nm.

B. construction of calibration curve:

Table 8.1: Standard graph of Hesperidin

Concentration (µg/ml)	Absorbance (at 330 nm)
0	0
10	0.107
20	0.226
30	0.334
40	0.449
50	0.556

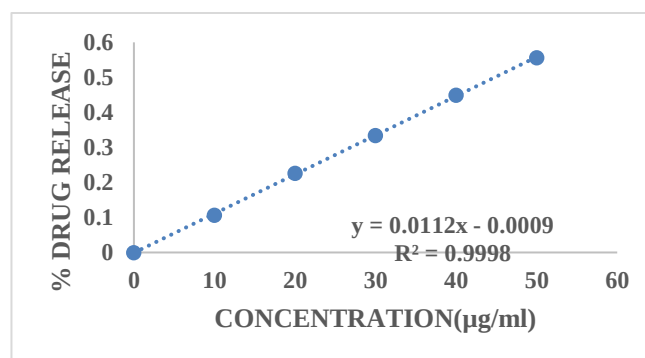


Figure 8.1: Standard calibration curve of Hesperidin

8.2. Preformulation study

Totally, nine formulation trials were done with the aim to achieve the successful matrix type Hesperidin transdermal patches. The blend trials prepared for the drug was evaluated for various physical parameters and content uniformity of drug by UV.

A. Colour, odour, taste and appearance

Table 8.2: Results of identification tests of drug

Parameter	Hesperidin
Color	White
Odor	Odorless
Taste	Bitter
Appearance	A white powder

B. Melting point determination:

Table 8.3: Results of melting point determination tests of drug

Drug	Reported melting point
Hesperidin	305-306 °C

C. Determination of solubility:

Table 8.4: Solubility Determination

solvent	Drug solubility(mg/ml)
Distilled water	48.93
Ph 7.4 phosphate buffer	60.31

8.3 Evaluation of Patch

The formulations F1 to F9 were varying in thickness when compared to other formulations which is due to the variation in the polymer concentration. Which shows the increase in polymer concentration increases the thickness of patch. For all other formulations it was found to be in between 0.041 ± 0.007 to 0.051 ± 0.004 mm.

All formulations from F1 to F9 shows weight variation in between 80 ± 9.85 to 89 ± 4.96 mg.

Folding endurance from formulations F1 to F9 was found to be in between 70 ± 1.84 to 79 ± 2.51 which can withstand the folding of the skin.

All formulations showed % drug content from 97.1 ± 2.10 to 99.74 ± 1.57 .

Table 8.5: Evaluation of patches

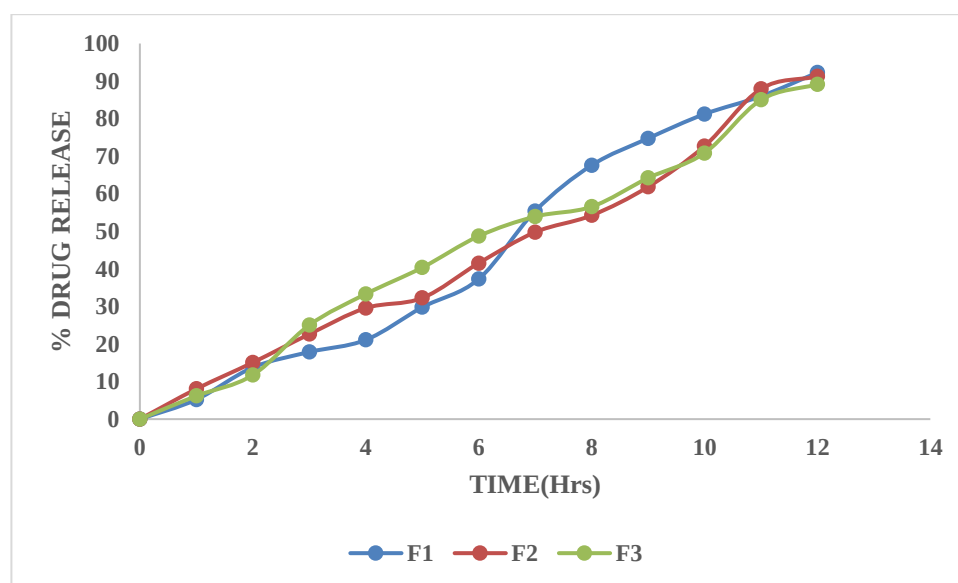
Formulation Code	Average weight(mg)	Thickness (mm)	Folding endurance	Flatness (%)	Appearance	% Drug Content
F1	85 ± 1.51	0.046 ± 0.003	71 ± 0.51	100	Transparent	97.1 ± 2.10
F2	88 ± 5.63	0.049 ± 0.008	76 ± 1.93	99	Transparent	98.28 ± 0.45
F3	81 ± 2.48	0.051 ± 0.004	75 ± 2.62	100	Transparent	97.69 ± 2.21
F4	85 ± 5.14	0.041 ± 0.009	70 ± 1.84	100	Transparent	98.1 ± 2.61
F5	87 ± 9.81	0.049 ± 0.004	72 ± 3.11	99	Transparent	99.2 ± 3.87
F6	89 ± 4.96	0.041 ± 0.007	79 ± 2.51	100	Transparent	98.35 ± 0.59
F7	80 ± 9.85	0.047 ± 0.001	74 ± 2.63	99	Transparent	99.11 ± 2.34
F8	86 ± 3.68	0.045 ± 0.009	77 ± 2.04	100	Transparent	99.74 ± 1.57
F9	84 ± 7.92	0.048 ± 0.006	72 ± 2.69	100	Transparent	98.48 ± 0.44

***In vitro* diffusion study:**

All the formulation *in vitro* diffusion study was carried out by using Franz type diffusion cell under specific condition such as temp maintained at 32 ± 0.5 °C. The diffusion was carried out for 12 h and 5 ml sample was withdrawn at an interval of 1 h.

Table 8.6: *In vitro* drug permeation of Hesperidin

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	5.22	8.04	6.18	4.86	5.65	3.71	6.41	8.92	5.89
2	13.75	15.07	11.73	8.92	12.23	8.47	9.66	12.36	10.53
3	17.87	22.61	25.02	14.04	17.44	15.45	13.37	17.31	22.07
4	21.09	29.57	33.31	21.16	23.08	21.02	18.56	24.08	37.47
5	29.77	32.24	40.34	35.86	39.88	28.44	24.22	28.01	42.88
6	37.28	41.52	48.71	39.03	45.44	34.78	31.94	36.45	49.81
7	55.39	49.77	53.93	46.49	52.63	41.67	37.37	41.18	53.99
8	67.57	54.24	56.54	55.22	68.97	51.26	45.03	49.12	61.04
9	74.73	61.83	64.19	67.53	77.53	59.63	54.01	68.06	67.87
10	81.21	72.68	70.83	74.37	83.51	63.97	67.83	79.01	74.02
11	85.96	87.91	84.99	88.11	95.46	73.08	78.99	83.46	80.12
12	92.26	91.22	89.15	93.62	99.73	82.23	85.15	87.87	85.25

**Figure: 8.2 Cumulative % drug permeation of Hesperidin patch (F1, F2 and F3)**

The formulations F1 to F3 were prepared by different concentrations of Ethyl Cellulose (25, 50 and 75mg) in 2*2 cm² patch, the drug release or drug permeation from the patch was dependence on the concentration of polymer in the matrix. At low polymer concentration the drug permeation is more within 12 hours it was total amount of drug was permeated. The 25 mg concentration of polymer was showed maximum drug released at 12 hors 92.26%. Hence in that 3 formulation F1 formulations showed total drug release at desired time period.

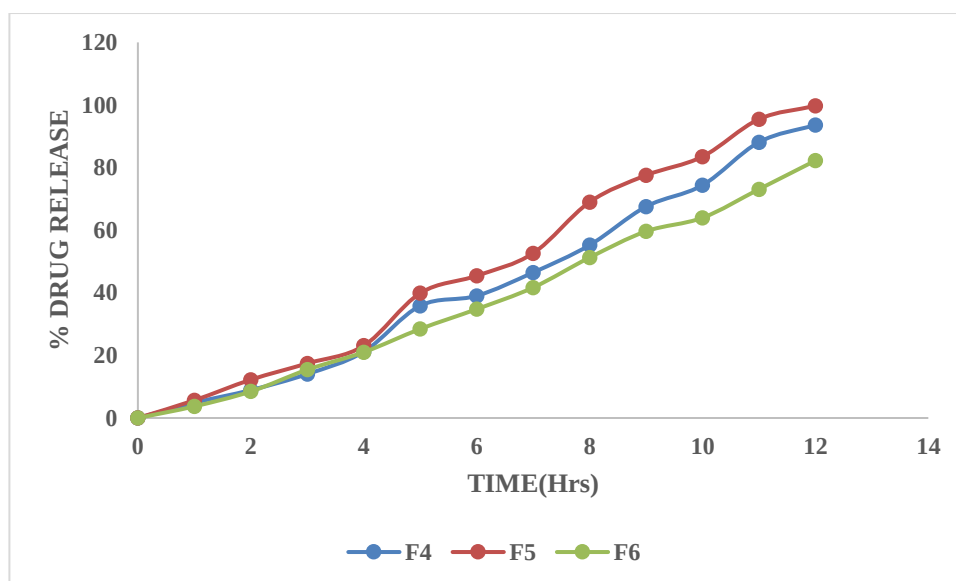


Figure: 8.3 Cumulative % drug permeation of Hesperidin patch (F4, F5 and F6)

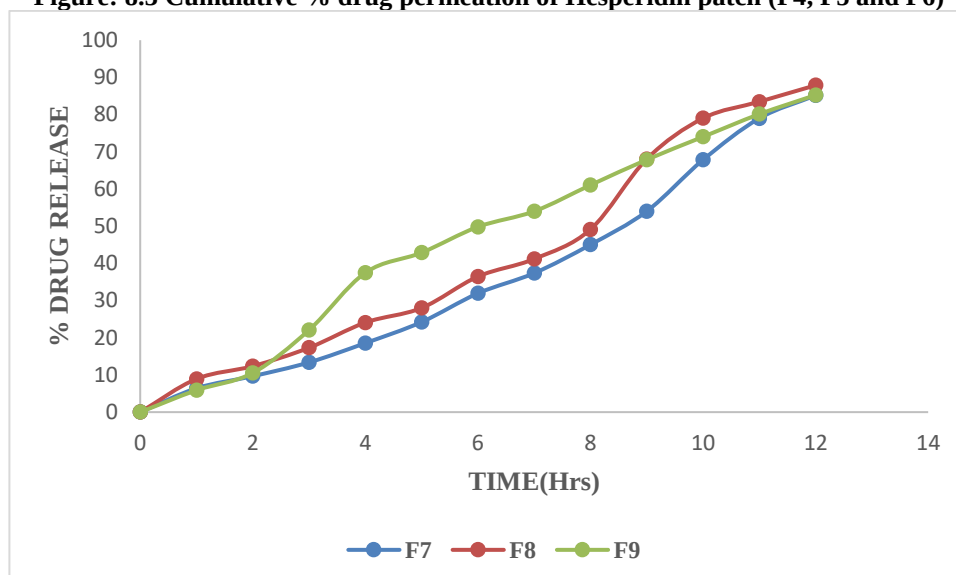


Figure: 8.4 Cumulative % drug permeation of Hesperidin patch (F7, F8 and F9)

The formulations F4 to F6 were prepared by different concentrations of HPMC (25, 50 and 75mg) in 2*2 cm² patch the drug release or drug permeation from the patch was dependence on the concentration of polymer in the matrix. The 50mg (F5) concentration of polymer was showed maximum drug release 99.73 within 12 hours.

CONCLUSION:

The present study was successfully conducted to formulate and evaluate a transdermal drug delivery system (TDDS) of Hesperidin, aiming to improve its bioavailability and provide sustained drug release. Various formulations were prepared using suitable polymers and plasticizers, and evaluated for physicochemical parameters such as thickness, tensile strength, moisture content, drug content uniformity, and in vitro drug release. Among the developed formulations, the optimized batch demonstrated desirable mechanical properties and a controlled drug release profile over an extended period, indicating its potential for effective

transdermal delivery. The results suggest that Hesperidin can be effectively delivered through the transdermal route, potentially overcoming its limitations related to poor oral bioavailability and enhancing therapeutic efficacy.

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