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FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES OF BUCLIZINE DIHYDROCHLORIDE

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1.1. ABSTRACT

The pharmaceutical industry has greatly benefited from transdermal medication administration. It is a patch that releases a specified dosage of medicine into the bloodstream through the skin. The fundamental benefit of transdermal medication administration is that it bypasses the gastrointestinal tract and the liver's first-pass effect. This allows drugs to be delivered directly into the systemic circulation. One benefit of transdermal drug administration over other methods is that the patch permits a controlled flow of the medication into the patient, often through a porous membrane that covers or melts a drug reservoir. Body heat is used to embed thin layers of medication in a binder. Using the solvent evaporation method, the current study aimed to create buclizine dihydrochloride transdermal films and assess physicochemical factors like thickness, weight change, moisture absorption, moisture content, folding strength, and drug content value. Five transdermal patches were created utilising various methyl cellulose concentrations. It was determined that the patch's thickness, weight homogeneity, and folding strength all rose as the polymer concentration did. With increasing polymer concentration, both the amount of moisture and the percentage of moisture absorption decreased.

KEYWORDS: Transdermal Patches, Skin, Buclizine Dihydrochloride, Ethyl cellulose.

2.1. INTRODUCTION

TDDS was created as a character enhancer even though many drugs are now administered orally since it no longer properly monitors when necessary. A medicine's systemic effect is attained through skin contact with delivered medication. as a means of administering drugs transdermally.[1] These are innovative dosage forms that deliver medication at cost-effective

rates and occasionally have a therapeutic effect on the skin's dermal tissue.[2] Despite being of paramount significance, drug divisions are transported in the blood throughout the body. A transdermal skin patch is a medicated adhesive plaster that is applied to the skin and releases a specific dose of medication via the skin before entering the bloodstream.[3]

2.1.2. The following advantages are offered by transdermal medicine administration techniques[4,5]

1. The potential for self-medication.
2. Less negative consequences.
3. The plasma medicine concentration is kept constant.
4. A reduction in the frequency of administration.
5. Has a broader range of applications and is easier to remember than nasal and oral cavity.

2.1.3. Disadvantages of transdermal medication delivery[6,7]

1. The possibility of allergic reactions.
2. High molecular weight medications are not therapeutically useful.
3. Delivery to Ion Pharmaceuticals, number.
4. There must be a sizable time lapse.

2.1.4. Skin anatomy and physiology

The three distinct but linked tissues that make up human skin are as follows:[8-11]

Stratified and vascular "epidermis" cells, "lower dermis connective tissue," and the subcutaneous layer.

- **Cutis**

The thickness of the epidermis varies, ranging from 0.8 mm at the base of the palm to 0.06 mm above the eyelid, depending on the size and number of cells in the cuticles. It has a healthy epidermis and a stratum corneum on the outside.

I. Corneal stratum

It is also known as the stratum corneum, the top layer of the skin. When fully hydrated, it swells to a thickness that is many times bigger than its dry thickness of around 10 mm. There are 10 to 25 layers in it. Keratinized dead cells are referred to as keratinocytes. It is flexible yet mostly waterproof. Drug penetration is significantly hampered by the stratum corneum. To mimic the architecture of the stratum corneum, a wall-like structure might be constructed.

In accordance with this paradigm, keratinized cells act as "bricks" consisting of proteins and lipids as "mortar." Lipids are organised using several bilayers. The lipid fractions' polar free fatty acids and cholesterol provide sufficient amphoteric material to preserve the bilayer structure.

ii) Viable Epidermis

Underneath the stratum corneum, the epidermis has a thickness that varies from 0.06 mm on eyelids to 0.8 mm on the palm. It has a light layer, layer seeds, spines, and bottoms, among other layers. The loss of horny, dead skin cells from the skin's surface is compensated for by the constant renewal of the epidermis by cells undergoing mitosis at the basal layer. Cells generated by the base layer move outward, change shape, and chemically undergo keratinization to create the stratum corneum's outermost layer.

- **Dermis**

The dermis is a 3 to 5 mm thick layer that contains blood arteries, lymphatic vessels, and nerves inside a matrix of connective tissue. Blood flow via the skin is essential for regulating body temperature. It provides the skin with nutrients and oxygen in addition to removing impurities and waste. The capillaries' 0.2 mm skin-surface penetration makes it easier for most molecules to get through the skin barrier. Blood maintains a steady level of concentration in skin with very poor permeability and the resulting concentration. Differentiation via the epidermis provides the required gradient of concentration for transdermal penetration.

- **Hypodermis**

The dermis and epidermis depend on subcutaneous tissue and layer for proper function. It serves as a location to store fat. This layer provides temperature regulation, mechanical support, and nutrient supply. There are large blood vessels, nerves, and even pressure-detecting organs that travel to the skin. When using solely topical drugs, the stratum corneum must be penetrated, and it is preferred to maintain the medication inside the layers of the skin since systemic circulation necessitates that the medication travel through these three layers during drug transport via the skin.

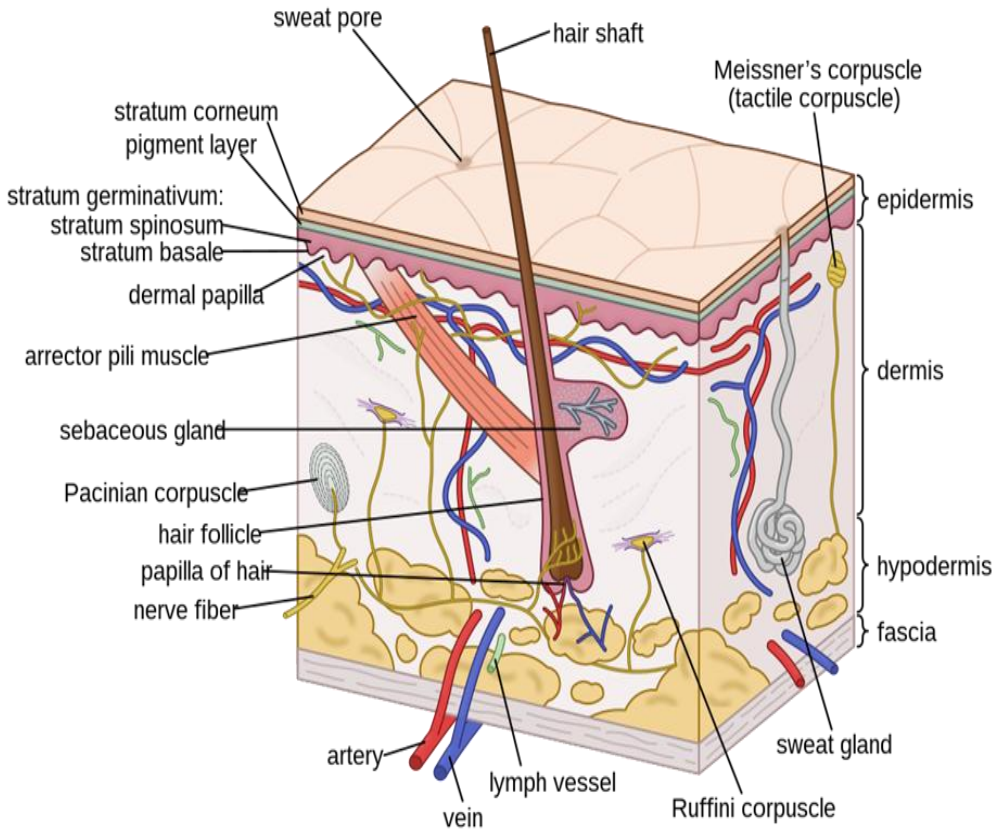


Figure 1: Structure of Human Skin.

2.1.5. Transdermal Bioavailability Influencing Factors[26-27]

Two main factors influence the bioavailability of Drugs that penetrate the skin:

- Physicochemical factors:-

Skin Moisturising

When in contact with water, skin permeability dramatically enhanced. Keeping hydrated is ideal. Skin permeability is increased by significant variables. Moisturiser usage is transdermal transfer as a result.

Temperature and pH

As the temperature changes, the drug's osmolarity rises by a factor of ten. As the temperature drops, the diffusion coefficient lowers. Depending on the pH and the pKa or pKb value, weak acids and weak bases separate. The percentage of the key medication combination's skin-surface concentration. Temperature and pH therefore have a significant impact on how well drugs are absorbed.

Diffusion coefficient

Drug penetration is influenced by this factor. The same temperature, The drug's diffusion coefficient is influenced by the drug's characteristics, its administration method, and interactions between these factors.

Drug concentration

Flux is proportional to concentration the slope through the fence and the concentration the gradient will be higher if the concentration of more drugs will cross the barrier.

Partition Coefficient

Optimal partitioning factor (K) is required for a good deed. High K drug is not ready leave the lipid part of the skin. In addition, the drug has Low K will not be impregnated.

Molecular size and shape

Drug absorption is inversely proportional to molecular weight, small molecules penetrate faster than adults.

- **Biological factors**

Skin state

Acids and alkalis, many solvents such as chloroform, methanol damages skin cells and promotes infiltrate. The patient's health status changes skin disease. Intact skin is a better barrier but the above conditions affect infiltrate.

Skin age

Young skin is more permeable than old skin. Children are more easily absorbed by the skin of poison. Thus, the age of the skin is one of the factors affect the penetration of drugs into TDDS.

Blood flow

Changes in the peripheral circulation can affect absorbed through the skin.

Skin metabolism

Skin metabolizing steroids, hormones, chemicals carcinogens and some drugs. Therefore, the metabolism of the skin determine the effectiveness of the impregnated drug through skin.

2.1.6. COMPONENTS OF TDDS[28]

The main ingredients of the transdermal patch are:

I. Release liner
II. Drug Reservoir
III. Adhesive
IV. Membrane
V. Backing

2.1.7. Transdermal Patches[29]

Products with a topical or transdermal formulation are meant for external use. The percutaneous drug delivery technology is utilised for systemic medication delivery, whereas the newer dermatological items are meant for. A transdermal device immediately injects medicine into the bloodstream through the skin. Due to the wide variety of medications that may be delivered through the skin to treat different disorders, this method of drug administration has gained popularity. Transdermal patches are being utilised to treat a variety of medical conditions, including pain management, quitting smoking, treating heart disease, replacing missing hormones, and managing motion sickness.

2.1.7.1. Types of Transdermal Patches[30-34]

a) Monolayer drugs in adhesives:
b) Multi-layer adhesive:
c) Steam patch:
d) Reservoir system:
e) Matrix system:
i. Drug in adhesive system
ii. Matrix Dispersion System
f) Microreservoir system:

3.1. MATERIALS AND METHODS

Materials

All the chemicals used in this research were of standard pharmaceutical grade.

- Buclizine Dihydrochloride (Drug was bought from the Yarrow Chem Products, L.B.S. Marg, Ghatkopar West, Mumbai.)
- Methyl Cellulose (Titan biotech Ltd., Bhiwadi, Rajasthan),

- Glycerine (Loba Chemicals, Mumbai.)
- HPMC (Loba Chemicals, Mumbai)
- Methanol (Nice Chemicals, Cochin) and
- Chloroform (SD Fine chemicals, Mumbai) were of analytical reagent grade.

Methods

- The drug buclizine dihydrochloride is used to treat allergies.
- The Transdermal Patch's composition included methyl cellulose.
- The plasticizer used was glycerol.
- DMSO is a penetration-enhancing agent.
- A solvent of chloroform:methanol (1:1) was used to dissolve the polymer.
- Constant swirling helped the medication dissolve evenly in the thick fluid.
- In a Petri dish with an inverted funnel covering, the resultant material was poured onto a surface of mercury that had been levelled. The Petri dish was left undisturbed at room temperature for one day.
- The patch was obtained intact by slowly lifting from the Petri dish and transdermal patches were cut into radius of 2cm2

4.1. EXPERIMENTAL STUDY

PREFORMULATION STUDIES OF SELECTED DRUG[12,13,14]

1. Detailed Description

As said, a powder that is white or almost white.

2. Solubility Determination

Buclizine hydrochloride solubility was assessed by combining 1 g of the drug with 10 ml of each of the following: pure water, chloroform, ethanol, and methanol. What was soluble at room temperature was decided.

3. Melting point

The melting point of the pure medication was determined using a melting point apparatus. The in question thermometer has previously undergone calibration. The process requires utilising a calibrated tube in a Thiele setup to heat the powdered material. The melting range is defined as the difference between the temperature at which a sample starts to melt and the

temperature at which it completely melts. The result was assessed in comparison to the reference values.

4. Partition Coefficient

An equal volume of n-octanol was added to a solution of buclizine dihydrochloride in water at a known concentration, and the mixture was agitated for an hour. Standing permit for four hours. After that, the aqueous phase and organic phase were separated and collected. A U.V. spectrophotometer was used to measure the concentration of BUZ at 230 against a blank after the appropriate dilution. By dividing the drug concentration in n-octanol by the drug concentration in the aqueous phase, the partition coefficient was calculated. On average, three readings were gathered.

5. Calibration curve for the estimation of Buclizine Dihydrochloride

Buclizine Dihydrochloride estimate calibration curve. In the investigation of quantification of Buclizine dihydrochloride, a spectrophotometric approach based on the measurement of absorbance at 230 nm of the ultraviolet region in phosphate buffer at pH 7.4 was utilised. In 100 ml of phosphate buffer saline (pH 7.4), 10 mg of buclizine dihydrochloride was accurately weighed, and 1% of tween 80 was added to the mixture. 5 hours were spent sonicating the mixture. After removing the samples from the volumetric flask holding drug concentrations of 1 to 6 ug/ml, UV absorbance was measured at 230 nm using phosphate buffer saline (pH 7.4) as a blank.

STUDIES ON FORMULATION

- **Solvent Evaporation Method**

1) Appropriately sized quantities of polymers were mixed with different solvent compositions. (Sonication for 1 to 2 hours)
2) The drug was then progressively increased to 40 mg. (Sonication for one hour)
3) Glycerol and DMSO were then added in the proper quantities as plasticizer and penetration enhancer, respectively.
4) After that, it was placed in a glass Petri dish. It was then placed in a hot air oven to dry out.
5) The rate of solvent evaporation was controlled by placing an inverted funnel over the Petri dish.

5.1. FORMULATION DESIGN

Ingredients	F1	F2	F3	F4	F5	
Buclizine Dihydrochloride(mg)	40	40	40	40	40	
Methyl Cellulose (mg)	60	60	70	80	80	
Chloroform(ml)	4	9	10	13	15	
Methanol(ml)	4	9	10	13	15	
DMSO(ml)	0.1	0.1	0.1	0.1	0.1	
Glycerol in % w/w	0.1	0.1	0.1	0.1	0.1	
HPMC In Parts(mg)	40	40	70	50	40	

6.1. EVALUATION & CHARACTERISTICS

Physical Appearance

Each transdermal film was visually inspected for transparency, stickiness, flexibility, and smoothness.

Thickness

Transdermal film thickness can be measured using a micrometre, dial gauge, screw gauge, or travelling microscope at various positions along the film.[15]

Uniformity of weight

Weight uniformity is investigated by weighing 10 randomly chosen patches separately and determining their average weight. The weight of a person shouldn't differ noticeably from the average weight.[16,17]

Folding endurance

Folding endurance refers to the ability to repeatedly fold a strip of a certain area at the same point until it breaks. The rating for folding endurance was determined by how many simultaneous folds a film could withstand without breaking.[18]

Drug Content

It is necessary to dissolve a certain patch area in a set volume of an appropriate solvent. Using the relevant technique (UV or HPLC), the drug content must be ascertained after the solution has been filtered through a filter material. Each digit represents the average over three samples.[19–21]

Percentage Moisture Absorption

The weighted films must be kept in desiccators at room temperature for 24 hours with saturated potassium chloride solution in order to maintain 84% RH. After 24 hours, the films

must be reweighed in order to quantify the percentage of moisture absorption following the steps below.[22-23]

[Final weight-Initial weight/Initial weight] / 100 is the formula for percentage moisture absorption.

Moisture Loss

Each of the manufactured films has to be weighed before being stored at 40°C in a desiccator with calcium chloride. The films must be reweighed after 24 hours in order to calculate the percentage of moisture loss using the formula below.[24]

% Moisture loss is calculated as [Initial wt - Final wt/ Final wt] x 100.

In-vitro drug diffusion studie

For these studies, a modified Franz diffusion cell[25] with a 50 ml receptor compartment capacity is employed. The donor and receptor compartments of the diffusion cell were linked to the artificial cellophane membrane. The prepared patches were cut into 1 cm2 squares, placed over adhesive taps, adhered to cellophane membranes, and then attached with rubber bands to glass tubes. Both the drug-releasing membrane and the receptor compartment of the diffusion cell were filled with phosphate buffer pH 7.4. The temperature was maintained at 32°C. At intervals of 10, 20, 30, 60, 120, 180, and 720 minutes, 3 ml samples were obtained, and the drug concentration was determined spectrophotometrically against a blank at a maximum wavelength of 270 nm. At each sample removal, an equivalent volume of phosphate buffer was added to the receptor phase to refill it.

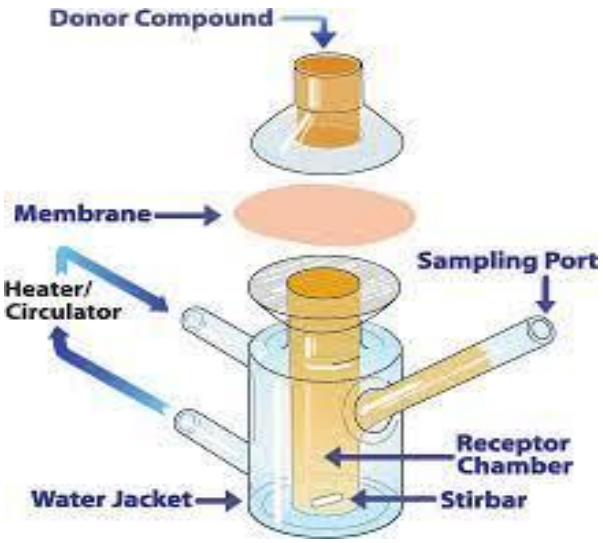


Figure 2: Franz Diffusion Cell.

7.1. RESULT AND DISCUSSIONS

Preformulation study of Buclizine Dihydrochloride

Detailed Description of Buclizine Dihydrochloride

Test	Specification	Result
Description	White or almost white, crystalline powder	White, crystalline powder.

Solubility of Buclizine Dihydrochloride

It was discovered that the buclizine dihydrochloride is not dissolved in phosphate Buffer & water. Very little soluble in methanol and sparingly soluble in water.

Solubility of Buclizine Dihydrochloride

Solvent	Descriptive terms
Distilled water	Insoluble
Chloroform	Sparingly soluble
Phosphate buffer pH 7.4	Insoluble
Ethanol	Very slightly soluble

Melting point

Melting point of Buclizine Dihydrochloride was found to be 230 to 240^{0}C. Result are shown as follows

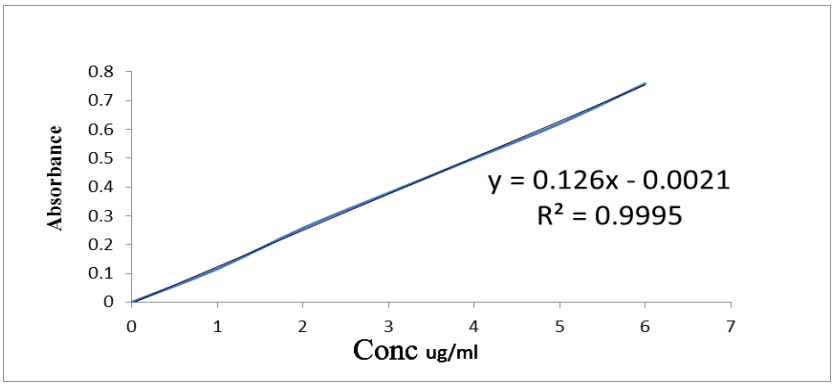
Partition coefficient

Partition coefficient of Buclizine Dihydrochloride was found to be 3.5 to 4.5, Result are shown as follows

Melting point and partition coefficient Buclizine Diydrochloride

Studies	Melting point (^{0}C)	Partition coefficient (P)
Results	**232**	**3.8**
Limits	**230-240$^{0\ C}$**	**4-5**

- **Calibration curve**



Graph No 1:- Calibration curve of Buclizine hydrochloride PBS pH 7.4.

Evaluation Tests

- **Physical Appearance**

The various batches of patches were all found to be opaque, non-sticky, flexible, smooth, and of a homogenous character.

Physical appearance of patches of Buclizine Dihydrochloride.

Formulation Batch	Stickiness	Smoothness	Flexibility	Transparency
F1	Non-sticky	Smooth	Flexible	Opaque
F2	Non –sticky	Smooth	Flexible	Opaque
F3	Non –sticky	Smooth	Flexible	Opaque
F4	Non –sticky	Smooth	Flexible	Opaque
F5	Non –sticky	Smooth	Flexible	Opaque

Weight uniformity, Folding Endurance, Thickness and Drug content of films of Buclizine Hydrochloride

The weight of patch, its folding endurance, thickness of patch & drug content of different batches of formulation of Buclizine dihydrochloride are given in the following table as follows:-

Weight, Folding Endurance, Thickness and Drug content of films of Buclizine Dihydrochloride

Formulation Batch	Weight* (mg)	Thickness* (mm)	Folding Endurance	Drug content (%)*
F1	361.5(±0.50)	0.065(±0.005)	>200	96.02(± 0.62)
F2	484.8(±0.82)	0.15(±0.008)	>200	97.65(±0.95)
F3	365.4(±0.87)	0.066(±0.006)	>300	99.10(± 0.70)
F4	365.3(±0.52)	0.124(±0.005)	>200	97.70(± 0.30)
F5	380.8(±0.80)	0.067(±0.008)	>300	92.00(±0.30)

Evaluation of % Moisture absorption, % Moisture loss

Percentage moisture absorption and percentage moisture loss was found to be acceptable. The results are shown as follows

Evaluation of % Moisture absorption, % Moisture loss of Buclizine Dihydrochloride

Formulation code	% Moisture absorption	% Moisture loss
F1	3.02(± 0.057)	1.22(± 0.98)
F2	1.52(± 0.042)	2.22(± 0.92)
F3	1.34(± 0.022)	2.34(± 0.72)
F4	1.45(± 0.036)	1.99(± 0.68)
F5	2.44(± 0.065)	1.85(± 0.42)

In-Vitro Drug Diffusion Studies

The cumulative percentage release of Buclizine Dihydrochloride from films F1, F2, F3, F4 & F5 were 89.04, 93.80, 96.98, 87.46 & 86.46 respectively at the end of 12 h. The batch F3 containing concentration of and DMSO was optimized, here DMSO act as a penetration enhancer. The results are given in below table.

In – Vitro Drug Release of Buclizine Dihydrochloride of batches F1 to F5

Time in Hrs.	F1	F2	F3	F4	F5
	% Cumulative drug release*	% Cumulative drug release *	% Cumulative drug release*	% Cumulative drug release *	% Cumulative drug release *
1	39.76	39.84	39.84	38.65	40.23
2	43.41	45.07	45.15	44.60	43.80
3	47.69	48.60	49.76	49.12	47.77
4	51.34	55.63	56.90	55.71	52.93
5	55.71	60.87	61.66	59.68	55.63
6	59.28	63.65	65.23	63.65	57.69
7	63.8	67.31	71.58	68.80	63.65
8	69.12	72.69	74.74	71.58	68.80
9	73.17	77.75	79.52	74.44	71.58
10	78.49	83.49	85.77	79.52	75.71
11	82.69	88.45	90.63	83.49	79.52
12	89.04	93.80	96.98	87.46	86.46

8.1. CONCLUSION

Transdermal medication administration has significantly improved medical procedures. It is a medical patch that releases a specified dosage of medicine into the bloodstream through the skin. Buclizine Dihydrochloride Transdermal Patch was created and assessed. Buclizine dihydrochloride patches totaling five were created.

Different evaluation tests were conducted, and results of formulations F1 to F5 were good in terms of their physical appearance, moisture absorption rate, moisture loss rate, weight uniformity, folding endurance, thickness, and drug content. The evaluation results reveal that Formulation F3 is superior to other formulations in terms of weight homogeneity, low moisture content, high folding durability, and reduced thickness. Additionally, compared to other formulations, they contain more drugs. F3 was therefore seen as An Optimised batch.

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