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Research Article

Formulation and evaluation of Transdermal Patch for the treatment of Migraine

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Abstract

A migraine is a specific kind of headache disorder that primarily affects the head. It can range in severity from mild to severe and is often accompanied by other symptoms like vomiting, nausea, illness, dizziness that gets worse with movement, photophobia, sonophobia, severe disability, or other types of nature. Triptans that are administered intravenously can be used to treat migraines and irritated injection sites. Transdermal delivery means that the medications will be administered through the skin in a precise, regulated manner. Our study aims to identify all possible transdermal patch combination and application for the treatment of migraines. The drug rizatriptan belongs to a group of drugs known as selective serotonin receptor agonists. It functions by constricting blood vessels in the brain, preventing the transmission of pain signals to the brain, and preventing the production of several naturally occurring compounds that produce pain, nausea, and other migraine symptoms. Verapamil belongs to the group of drugs known as calcium-channel blockers. It works by relaxing the blood vessels in order to reduce the workload of the heart. The Lambda max Rizatriptan and Verapamil is 278.9nm and 228nm respectively. They are soluble in most of the solvents. When used with verapamil, rizatriptan's transdermal patch improves patient compliance in those with hypertension. P2 patch shows the optimized results.

Keywords: Migraine, Rizatriptan, Verapamil, Bioavailability, Transdermal patch.

1. INTRODUCTION [1-8]

The word migraine came from the Greek word "hemikrania" that means "half of the skull" as in the majority of migraines the patient will present with a unilateral headache that is throbbing or pulsating in character. Migraine can frequently be accompanied by headache nausea or vomiting, sensitivity to light, sound, or smell, and auras that indicate an impending headache. Many migraine sufferers experience early morning awakenings when their attack is already advanced and accompanied by nausea and vomiting. As a result, a unique, non-invasive, non-oral delivery technology needs to be developed for the rapid and effective treatment of migraines. A transdermal patch, also known as a skin patch, is an adhesive patch applied to the skin which contains medication that is supposed to be absorbed into the bloodstream through the skin. The United States Pharmacopoeia (USP) states that 'transdermal systems' are created to transport the drug(s) to the systemic circulation through the skin. However, the article also makes clear that patches used to localise the effects of medications are typically characterised as "plasters" or "tapes". The FDA first granted approval for transdermal patch products in 1981. Transdermal delivery allows for constant infusion of medications with short biological half-lives, eliminates pulsed entrance into the systemic circulation, and offers controlled, ongoing drug administration. Compared to conventional injection and oral procedures, TDDS has many benefits. It lessens the burden that taking medication orally frequently places on the liver and digestive system. It improves patient compliance and reduces dangerous pharmacological side effects brought on by transient overdose.

Merits and Demerits of TDDS

Merits of TDDS

1. Reduced frequency of dose due to improved bioavailability and longer duration of action.
2. Consistent blood drug levels made possible by steady drug penetration over the skin; frequently an objective of therapy.
3. Lessened side effects, and additionally, toxicity from a medicine given transdermally could be mitigated by taking the patch off.
4. Topical patches are an easy, non-invasive approach to get drugs into your body.
5. This method of drug delivery is efficient for medications that are extensively destroyed by the liver, poorly absorbed from the gut, or broken down by the stomach acids.
6. For those who cannot or do not want to take drugs or vitamins orally, transdermal patches provide an alternative.
7. It is quite helpful for individuals who are queasy or unconscious.

8. Topical patches are practical and affordable; one aspect of particular note in some patches is that they only need to be applied once a week. Patient adherence to pharmacological therapy can be helped by such a straightforward dose schedule.

Transdermal patches have been effective in minimizing first-pass drug degradation effects and in creating novel therapeutic applications for currently available medications.

Demerits as well as limitations of TDDS

1. A lot of medications, especially those with hydrophilic components that penetrate the skin too slowly, might not work as intended.
2. Local erythema, itching, and oedema can be brought on by the medication, the adhesive, or any excipients in the patch formulation.
3. Ionic medicines cannot be delivered using TDDS.
4. TDDS is unable to achieve high drug concentrations in plasma or blood.
5. Drugs with large molecular sizes cannot be created using TDDS.
6. Pulsatile medication delivery is not possible with TDDS.
7. If a medicine or formulation irritates skin, TDDS cannot be established.
8. According to Latheeshjlal et al. (2011), the barrier function of the skin varies from one place to another on the same individual, from person to person, and also with age.

2. RESEARCH OBJECTIVE

Most of the medication are given by oral route. It is most prevalent and commonly preferred route of drug administration. The effectiveness of about 74% of medications, which are taken orally, is determined to be unsatisfactory.

- The primary objective of the proposed work is to develop a dosage form that would enhance the controlled release of a medicine, and a transdermal drug delivery system has been developed to achieve this.
- The ease of administration is a considerable benefit.
- To overcame some key limitations, such as poor bioavailability caused by hepatic metabolism (first pass) and the propensity to cause swift spikes in blood levels (both high and low), necessitating high and/or frequent doses, which may be both expensive and inconvenient.

In order to overcome these challenges, new drug delivery systems must be developed.

3. METHODOLOGY. [8-26]

3.1 Procurement of Drugs and Excipients.

Table 1: List of material used.

Sr. No.	Drugs and Excipients	Source
1.	Rizatriptan	ZIM laboratories, Ltd.
2.	Verapamil	Arrow chemicals, Mumbai.
3.	Ethyl cellulose	S.D. Fine chemicals, Mumbai.
4.	Poly Vinyl Pyrrolidone	S.D. Fine chemicals, Mumbai.
5.	Ethanol	S.D. Fine chemicals, Mumbai.
6.	Chloroform	S.D. Fine chemicals, Mumbai.
7.	Dibutyl Phthalate	S.D. Fine chemicals, Mumbai.

Table 2: List of equipment used

Sr.No.	Equipment	Source
1.	Calibrated Weighing Balance	Contech Instruments Ltd, Navi Mumbai.
2.	Magnetic Stirrer	Remi Lab world.
3.	UV Spectrophotometer	Shimado UV-Spectrophotometer.
4.	FTIR	Shimado IR spectroscopy.

3.2 Preformulation Study

3.2.1 Colour, Odour, Taste and Appearance.

The colour, odour, and appearance of the drug sample had been evaluated.

3.2.2 Determination of solubility.

Rizatriptan and verapamil's solubility has been evaluated by dissolving excess quantities of the drugs in the solvent.

3.2.3 Melting point determination.

Melting point apparatus was used to determine the drug sample's melting point using the capillary method. Small quantity of drug was taken in capillary tube (fused at one end) and placed in melting point apparatus, and the melting temperature was recorded.

3.2.4 Determination of lambda max.

The calibration curve was created using distilled water. To obtain a concentration of 1000 PPM, 100 mg of the drug were dissolved in water and diluted up to 100 ml, which is referred to as stock solution. To achieve various concentrations, this stock solution undergone further dilution. Utilising a UV spectrophotometer, resultant solutions were examined for the presence of max between 200 and 400 nm.

3.2.5 Fourier Transform Infrared (FTIR).

The Shimado Affinity-1 FT-IR equipment was used to carry out the FT-IR study. The medication, excipients, polymers, and physical combination all had overlapping peaks. Any brand-new items or significant spectrum changes were noted.

3.3 Dose Calculation of Drugs.

Transdermal dose = Oral dose × Bioavailability

Transdermal dose of Rizatriptan = 10 × 45/100

= 4.5 mg

Transdermal dose of Verapamil = 120 × 20/100

= 24 mg

3.4 Method of Preparation.

Various methods for the preparation of transdermal patches are

I. Mercury substrate method.
II. Solvent casting method.
III. Solvent evaporation method.
IV. Free film method.
V. Asymmetric TPX membrane method.
VI. IPM membrane method.
VII. Aluminium backed adhesive film method.
VIII. Preparation of TDDS by using Proliposomes.
IX. Circular Teflon mould method.

The given patch is prepared by Mercury Substrate method. This method is consisting of following steps :

➢ **Preparation of Casting Solution.**

Ethyl cellulose and poly vinyl pyrrolidone were precisely weighed and dissolved in a chloroform : ethanol combination using the given procedure. The plasticizer dibutyl phthalate was added after that drug had been dispersed in the polymeric solution. To get a consistency resembling semisolid, the solution was agitated.

➢ **Preparation of Transdermal Patch.**

The resulting material was poured into a surface of mercury that had been levelled in a Petri dish with an inverted funnel covering it. The petri dish had been untouched and kept at room temperature for one day. The patch has been removed intact from a Petri dish carefully, and the transdermal patch was then cut into a 2cm^2 radius.

3.5 Formulation Development.

All the formula are prepared in order to get patch which meet the requirements.

Table 3: Formula of transdermal patch.

Patch code → / Ingredients ↓	P1	P2	P3	P4	P5	P6	P7
Rizatriptan (mg)	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Verapamil (mg)	24	24	24	24	24	24	24
Ethyl Cellulose (mg)	400	400	400	00	50	100	150
PVP (mg)	50	100	150	400	400	400	400
Ethanol (ml)	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Chloroform (ml)	18.0	18.0	18.0	18.0	18.0	18.0	18.0
Dibutyl phthalate (ml)	0.4	0.4	0.4	0.4	0.4	0.4	0.4

Figure 1: Formulation of Transdermal Patch.

3.6 Evaluation Parameters.

3.6.1 Physical appearance.

Visual evaluations for colour, clarity, flexibility, and smoothness were made for each prepared patch.

3.6.2 Film thickness.

At three different points on the drug-loaded patches, the thickness of the patches was measured using a screw gauge micrometre. For each drug-loaded patch, the average and standard deviation of the three measures were calculated.

3.6.3 Weight variation.

The patches were subjected to weight variation by individually weighing 10 randomly selected patches. Such determinations were carried out for each formulation.

3.6.4 Folding endurance.

This was discovered by folding multiple times one film till it broke in the same place. The value of folding endurance was determined by how many times the film could be folded in the same place without breaking or cracking.

3.6.5 Drug content uniformity.

A transdermal patch sized 2x2 cm was dissolved in 100 cc of solvent and constantly shaken for 24 hours. Next, the entire solution was ultrasonicated for 15 minutes. Following filtration, spectrophotometry was used to calculate the drug's content.

3.6.6 Tensile strength.

The tensile strength of the patch had been evaluated by using the tensiometer. It consists of two load cell grips of which the lower one was fixed and upper one was movable. Film strips with the dimensions of 2 × 2 cm were fixed between these cell grips, and force should be gradually applied until the film get broke.

3.6.7 Percentage moisture content.

The formed films must be weighed individually and kept at room temperature in a desiccator together with fused calcium chloride for 24 hours. The films must be reweighed after 24 hours in order to calculate the percentage moisture content using the formula below.

% Moisture = (Initial weight - Final weight) / Final weight ×100

4. RESULT

4.1 Preformulation Study.

Table 4: Preformulation Study.

Sr. No.	Parameters	Rizatriptan	Verapamil
1.	Colour	White to off-white	White
2.	Odour	Odourless	Odourless
3.	Appearance	Crystalline powder	Crystalline powder

4.2 Determination of solubility.

Table 5: Solubility of drug in different solvents.

Sr. No.	Solvent	Rizatriptan	Verapamil
1.	Water	Soluble	Soluble
2.	Ethanol	Soluble	Soluble
3.	Chloroform	Soluble	Soluble
4.	Methanol	Soluble	Soluble

4.3 Melting point determination.

- Melting point of Rizatriptan - 178 to 180℃
- Melting point of Verapamil - < 25℃

4.4 Determination of Lambda Max.

- Lambda Max of Rizatriptan – 278.9nm

Table 6: Absorbance of Rizatriptan.

Sr. No.	Concentration (µg/ml)	Absorbance
1.	10	0.241
2.	20	0.562
3.	30	0.834
4.	40	1.180
5.	50	1.399

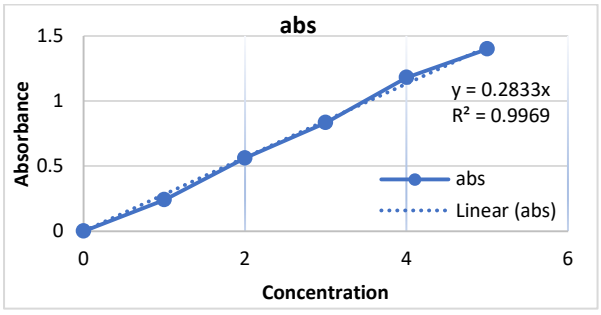

Figure 2: Calibration Curve of Rizatriptan Benzoate.

Lambda Max of Verapamil – 228nm

Table 7: Absorbance of Verapamil.

Sr. No.	Concentration(µg/ml)	Absorbance
1.	10	0.355
2.	20	0.648
3.	30	0.925
4.	40	1.235
5.	50	1.463

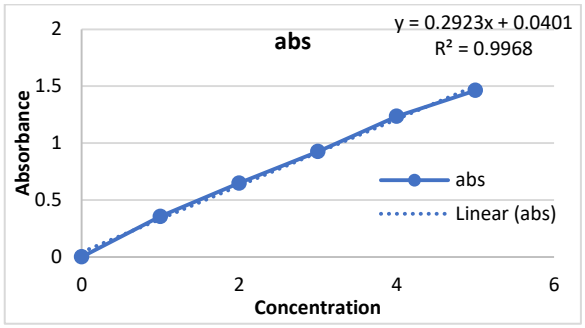

Figure 3: Calibration Curve of Verapamil Hydrochloride.

4.5 Fourier Transform Infrared (FTIR).

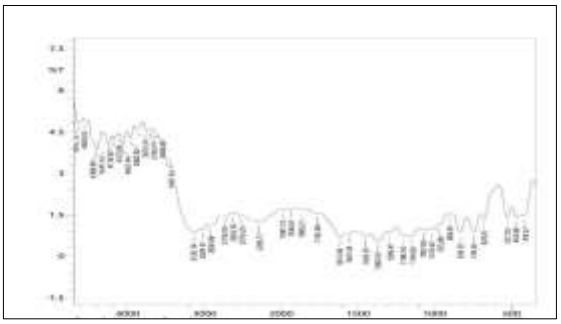

Figure 4: FTIR of Rizatriptan Benzoate.

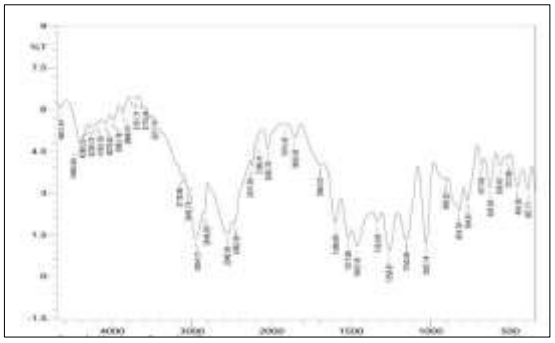

Figure 5: FTIR of Verapamil Hydrochloride.

4.6 Evaluation Parameters.

Table 8: Results of Evaluation Parameters.

Evaluation parameters	P1	P2	P3	P4	P5	P6	P7
Physical appearance.	Whitish yellow, Flexible, smooth	Whitish yellow, Flexible, smooth	Whitish yellow, Flexible, smooth	Whitish yellow, Flexible.	Whitish yellow, Flexible, smooth	Whitish yellow, Not Flexible	Whitish yellow, Not Flexible
Film thickness (mm)	0.132	0.153	0.175	0.120	0.139	0.148	0.258
Weight variation(g)	0.430	0.562	0.658	0.416	0.494	0.537	0.729
Folding endurance.	83 ± 15	79 ± 7	75 ± 9	87 ± 13	82 ± 12	76 ± 18	73 ± 14
Drug content uniformity.	76.2 ± 0.59	80.3 ± 0.045	75.01 ± 0.028	73.9 ± 0.012	81.10 ± 0.018	71.8 ± 0.097	83.052 ± 0.15
Tensile strength (kg/cm^2)	1.90	2.91	2.98	1.25	2.16	2.65	4.31
Percentage moisture content(%)	2.97 ± 0.4	3.35 ± 0.3	3.55 ± 0.7	2.28 ± 0.8	3.02 ± 0.4	3.05 ± 0.7	4.15 ± 0.9

5. DISCUSSION

All patches were evaluated successfully in which we found that the all patches had same physical parameters except P6 and P7 i.e., they were not flexible in nature. P3 and P7 patch were had a high tensile strength and thickness than the other patches.

From the table above, it can be assumed that patch thickness, weight uniformity, and folding endurance also increase and the percentage moisture content, moisture uptake, and medication release all decreases as the concentration of polymer increases.

In comparison to other patches, P2 patch result are displayed within a standard range.

6. RESEARCH OUTCOMES

There are several patches available for the treatment of migraines, but rizatriptan and verapamil cannot be used in combination before. In patients with migraine, the rizatriptan transdermal patch is efficacious and well tolerated. The side effect of Rizatriptan i.e., hypertension can be treated with verapamil when given together. All of the requirements for a transdermal patch are satisfied by the P2 formula.

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Conflicts of Interest

The authors have no known conflict of interest concerning the present article.

Abbreviations

Abs - Absorbance.

AUC - Area Under Curve.

ERL100 - Eudragit RL100.

DMSO - Dimethyl Sulfoxide.

EC - Ethyl Cellulose.

FTIR - Fourier Transform Infrared.

HPMC - Hydroxyl Propyl Methyl Cellulose.

ICHD - International Classification of Headache Disorders.

MA - Percentage Moisture Absorption.

ML - Percentage Moisture Loss.

NT - Neurotransmitter.

PPM - Parts Per Million.

PVP - Poly Vinyl Pyrrolidone.

TDDS - Transdermal Drug Delivery System.

USP - United States Pharmacopoeia.

UV - Ultra Violet.

WVTR - Water Vapor Transmission Rate.

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