# DEVELOPMENT, CHARACTERIZATION AND STATISTICAL OPTIMIZATION OF ALMOTRIPTAN MALATE LOADED TRANSDERMAL PATCHES FOR THE TREATMENT OF MIGRAINE

A Dissertation submitted to
**THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY**
**CHENNAI- 600 032**

In partial fulfillment of the requirements for the award of the Degree of
**MASTER OF PHARMACY**
**IN**
**BRANCH - I- PHARMACEUTICS**

**Submitted by**
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**COIMBATORE – 641044**

**OCTOBER 2017**

# CERTIFICATE

This is to certify that the M.Pharm dissertation entitled "**Development, Characterization and Statistical Optimization of Almotriptan Malate Loaded Transdermal Patches for the Treatment of Migraine**" being submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai was carried out by **Ms. Naseem A.K (Reg. 261510154)** in the Department of Pharmaceutics, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, under my direct supervision, guidance and to my fullest satisfaction.

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***May the ALMIGHTY bless and guide us all to the right path.***

# CONTENTS

# ABBREVIATIONS

| | |
|---|---|
| AEG-1 | Astrocyte elevated gene-1 |
| BNF | British national formulary |
| CNS | Central Nervous System |
| DBP | Dibutyl Phthalate |
| DCM | Dichloromethane |
| DOE | Design of Experiment |
| DMSO | Dimethyl Sulphoxide |
| DNA | Deoxyribonucleic acid |
| EC | Ethyl Cellulose |
| FDA | Food & Drug Approval |
| FTIR | Fourier Transform Infrared Spectroscopy |
| ERL 100 | Eudragit R L 100 |
| ERS 100 | Eudragit R S 100 |
| HPMC | Hydroxy Propyl Methyl Cellulose |
| 5-HT 1 | 5-hydroxytryptamine 1 |
| GIT | Gastrointestinal Tract |
| IP | Indian Pharmacopoeia |
| IUPAC | International Union of Pure and Applied Chemistry |
| KBr | Potassium Bromide |
| MAO | Monoamino oxidase |
| MC | Methyl Cellulose |
| MTDH | Metadherin |

| | |
|---|---|
| NSAID | Non-Steroidal Anti-inflammatory Drug |
| ODT | Orally disintegrating tablet |
| PEG | Polyethylene Glycol |
| PG | Propylene Glycol |
| PGCP | Plasma glutamate carboxypeptidase |
| Ph Eur | European Pharmacopoeia |
| PVA | Poly Vinyl Alcohol |
| PVP | Poly Vinyl Pyrrolidine |
| RH | Relative Humidity |
| SSG | Sodium starch glycolate |
| TDDS | Transdermal Drug Delivery System |
| USP | United State Pharmacopoeia |
| UV | Ultraviolet |
| WVTR | Water vapour transmission rate |

# INTRODUCTION

The development of a new drug molecule is a time consuming procedure and requires approximately 125 million dollars. This is beyond the scope of pharmaceutical companies in developing countries like India. But it is possible to give a new life to the existing molecules by formulating them in the form of novel drug delivery systems. Therefore, in recent years, considerable attention has been focused on the development of new drug delivery systems. The therapeutic efficacy and safety of the drugs administered by convention methods can be improved by more precise spatial and temporal placement within the body, thereby reducing both the size and number of doses through a controlled drug delivery.

**Rate Controlled Drug Delivery** (Chein, 1998)

For many decades, medication of an acute disease or a chronic illness has been accomplished by delivering drugs to patients via various pharmaceutical dosage forms like tablets, capsules, pills, injectables, suppositories etc. as carriers. Though, these conventional drug delivery systems are still the primary pharmaceutical products, recently several advancements have been made towards development of new techniques of drug delivery. These techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue. The novel drug delivery systems would provide one or more of the following benefits:

- Controlled administration of a therapeutic dose at a desirable delivery rate.
- Maintenance of drug concentration within an optimal therapeutic range for prolonged duration of treatment
- Maximization of efficacy dose relationship
- Reduction of adverse effects
- Minimization of need for frequent dose intake
- Enhancement of patient compliance

Continuous i.v. infusion is recognised as the superior mode of drug administration as it bypass hepatic first pass metabolism and maintain constant & prolonged drug level in the body. However this type of administration involves certain risks & need for close medical supervision of drug administration, thus using skin as a port of drug entry i.v. infusion could be duplicated (Misra, 2004).

Transdermal is a route of administration wherein active ingredients are delivered across ***(trans)*** the skin ***(dermal)*** for systemic distribution. In a broad sense, the term TDDS includes all topically administered drug formulations (patch, ointment, cream, gel, specially formulated sprays, etc.) intended to deliver the active ingredient into the general circulation. In the past, the most commonly applied systems were topically applied creams & ointments for dermatological disorders.

Transdermal systems are ideally suited for diseases that demand chronic treatment such as cardiovascular diseases, which require prolonged medication & sometimes lifelong therapy is advised. The extensive vital research work of last 25 years has generated around 10 marketed transdermal patches & a large number of patents. Commercially available transdermal patches are limited in number but this small group of marketed products represents many important classes: antianginal (Nitroglycerin, Isosorbide dinitrate), antihypertensive (Clonidine), antiemetics (Scopolamine), hormones (Estradiol, Testosterone), opioids (Fentanyl) and anticholinergics (Nicotine).

**Transdermal Patches (**Sandhu Premjeet *et al.,* 2011**)**

A transdermal patch or skin patch is a **medicated adhesive pad** (a flat mass of soft material used for protection, stuffing or comfort) that is placed on the skin to deliver a specific dose of medication through the skin into the bloodstream.

An advantage of a transdermal drug delivery route over other types of medication delivery such as oral, topical, intravenous, intramuscular, etc. is that

the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive.

Theoretically, transdermal patches works in a very simple way. A drug is applied in a relatively high dosage to the inside of patch, which is worn on the skin for an extended period of time. Through a diffusion process, the drug enters the bloodstream directly though the skin. Drug is placed in large amount in the patches to keep the concentration gradient suitable for absorption because the active ingredients act at low dosage. Since there is high concentration on the patch and low concentration in the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow.

**Benefits & Drawbacks of TDDS** (Kamal Saroha *et al.,* 2016)

There are some discomforts associated with TDDS but its advantages outweigh the discomforts.

**Possible discomforts of TDDS:**

- TDDS could be unsuitable for drugs that irritate or sensitize skin.
- The natural limits of drug entry imposed by the skin's permeability indicate that only relatively potent drugs are suitable for transdermal delivery.
- Transdermal therapy is not feasible for ionic drugs.
- It cannot deliver drug in pulsatile fashion.
- Some drugs e.g. scopolamine transdermal patch placed behind the ear, it is uncomfortable.
- Long time adhere is difficult.

**Advantages of TDDS:**

- The ease of usage makes it possible for patients to self-administer these systems.
- In case of an emergency, drug therapy can be terminated quickly by removal of the application from the surface of the skin.
- They are noninvasive, avoiding the inconvenience of parenteral therapy.
- Provides ease of rapid identification of medication in non responsive patients, unconscious or comatose patients.
- They can avoid GIT difficulties during absorption caused by gastrointestinal pH, enzymatic activity & drug interaction with food, drink or any other orally administered drug.
- Suitable in instances like vomiting or diarrhoea where oral route is not desirable.
- Since the composition of skin structurally and biologically is the same in almost all the humans, there is minimal inter & intra patient variation.
- Hepatic first pass metabolism, salivary metabolism and intestinal metabolism are avoided.
- Extends the activity of drugs with short biological half-lives, which would otherwise require frequent dosing, through the reservoir of drug present in the delivery systems and its controlled release characteristics.
- Due to reduced frequency of dosing there is better patient compliance.
- Therapeutic failures associated with irregularities in the dosing with conventional therapies can be avoided.
- Less chance of over or under dosing as the result of prolonged preprogrammed delivery of drug at the required therapeutic rate.

**Table 1 Ideal properties of TDDS**

| Properties | Range |
|---|---|
| Shelf life | Should be up to 2.5 years |
| Patch size | Should be less than 40 $cm^2$ |
| Dose frequency | Once in a day - once in a week |
| Appearance | Should be clear or white in color |
| Packaging properties | Should be easily removable of release liner & have minimum number of steps required to apply |
| Skin reaction | Should be non-irritating & non sensitizing |
| Release Properties | Should have consistent pharmacokinetic & pharmacodynamic profiles over time |

**Factors Affecting TDDS**

**Biological factors**

- ***Skin condition***: Acids and alkalies, many solvents like chloroform, methanol damage the skin cells and promotes penetration. Diseased state of patient alters the skin conditions.
- ***Skin age***: The young skin is more permeable than older. Children's are more sensitive for skin absorption of toxins.
- ***Regional skin site***: Thickness of skin, nature of stratum corneum and density of appendages vary site to site. These factors affect significantly penetration.
- ***Species Differences***: The skin thickness, density of appendages and keratinization of skin vary species to species, so affects the penetration.
- ***Skin metabolism***: Skin metabolizes steroids, hormones, chemical carcinogens and some drugs. So skin metabolism determines efficacy of drug permeated through skin.
- ***Blood supply***: Changes in peripheral circulation can affect transdermal absorption.

**Physicochemical factors**

- ***Temperature and pH*:** The drug permeation increases ten folds with temperature variation. The diffusion coefficient decreases as temperature falls. Weak acids and weak bases dissociate depending on the pH and pKa or pKb values. The proportion of unionized drug determines the drug concentration in skin.
- ***Diffusion coefficient***: Drug penetration depends on diffusion coefficient of drug. At a constant temperature the diffusion coefficient of drug depends on properties of drug, diffusion medium and interaction between them.
- ***Drug concentration***: The flux is proportional to the concentration gradient across the barrier and concentration gradient will be higher if the concentration of drug will be more across the barrier.
- ***Skin hydration***: In contact with water the skin permeability increases significantly. Hydration is the most important factor increasing the skin permeation. So humectants are used in transdermal delivery.
- ***Partition coefficient***: The optimal partition coefficient (K) is required for good action. Drugs with high K are not ready to leave the lipid portion of skin. Also drug with low K will not be permeated.
- ***Molecular size and shape***: Drug absorption is inversely related to molecular weight. Small molecules penetrate faster than larger ones.

**Basic Components of Transdermal System** (Mishra, 2004)

Following are the basic components which generally are used in the formulations of almost all type of transdermal patches.

**Drug**

The drug, of which transdermal system will be designed, should possess some physicochemical characteristics. It will be in direct contact with the release liner. The structure of skin also affects skin penetration. Drugs, which are

efficacious in only a few milligrams per day, are considered as candidates for transdermal delivery. Pro-drugs can be used to reduce the melting point and change the partition coefficient of drugs so as to increase the permeation through the skin. The drug should be non- irritating and non-allergenic to human skin as very little can be done, if the drug is a strong irritant.

**Table 2 Ideal properties of drug for TDDS**

| Properties | Range |
|---|---|
| Dose | Should be low (generally <20mg/day) |
| Elimination half life of drug in hour | Should be 10 or less |
| Molecular weight | Should be less than 500 Dalton |
| Partition Coefficient | Log P (Octanol-Water) should be in the range of 1 to 3 |
| Drug reaction | Should be non-irritating and non sensitizing |
| Oral Bioavailability | Should be low |
| Therapeutic Index | Should be low |
| pH of saturated aqueous solubility | 5-9 |

**Polymer matrix or matrices**

Polymers are the foundation of transdermal system. The selection of polymer and design are of prime importance. Considerations for polymer selection in transdermal delivery system:

- It should be stable and non-reactive with the drug moiety.
- It should be easily available, fabricated and manufactured in to desired formulations.
- The properties of polymer e.g. molecular weight, glass transtition

temperature, melting point and chemical functionality etc. should be such that drug can easily diffused through it and with other components of system.

- The mechanical properties should not change if large amount of drug incorporate.
- It should provide consistent release of drug throughout the life of system.

**Semi permeable (release) membrane**

It takes place in reservoir type and multi-layer patch systems. These membranes control the rate of drug diffusion out of the patch and into the skin. Important properties to consider include the membrane composition and thickness.

**Adhesives**

It serves to adhere the components of the patch together along with adhering the patch to the skin. Adhesive should enable the transdermal system to easily adhere to the skin and should not be irritant or allergen for skin. Generally, pressure-sensitive adhesives are used in transdermal systems.

**Backing layer**

The backing is the outermost layer of the patch, which protects the system from external effects while the patch is worn and ensures integrity of the system in the storage period. For this purpose, the materials impermeable for drug molecule are used as backing layer. The backing layer must be inert and not compatible with the drug and other substances used in the formulation and it should have low water vapour transmission rate so as to promote skin hydration and thus greater skin permeability of drug. Important considerations include occlusivity, patient comfort and cosmetic appearance.

**Release liners**

Generally, patch is covered by protective liner during storage until it is used. The release liner protects the adhesives and drug formulations. It is removed prior to patch application. Ideally, it should be easily peeled from the adhesive layer and should not damage the structure of adhesive layer. Since release liner is in intimate contact with the transdermal system, it should be physically as well as chemically inert. The release liner is composed of a base layer which may be non-occlusive (e.g. paper fabric) or occlusive (e.g. polyethylene, polyvinylchloride) and a release coating layer made up of silicon or Teflon. Important considerations when choosing a liner include: adhesive, drug formulations and release forces.

**Solvents**

Various solvents are used to solve or disperse the polymer and adhesive or drug used in preparation of the transdermal systems.

**Plasticizers**

Plasticizers are generally non-volatile organic liquids or solids with low melting temperature and when added to polymers, they cause changes in definite physical and mechanical characteristics of the material. One of the many advantages of plasticizers used in transdermal formulations is the controlling of the release rate of therapeutic compound which can be done by the selection of the plasticizer type and the optimization of its concentration in the formulation.

The reasons for the use of plasticizers in transdermal drug delivery systems are the improvement of film forming properties and the appearance of the film, decreasing the glass transition temperature of the polymer, preventing film cracking, increasing film flexibility and obtaining desirable mechanical properties. In transdermal systems, plasticizers are used to improve the brittleness of the polymer and to provide flexibility. Upon addition of plasticizer, flexibilities of polymer macromolecules or macromolecular segments increase as a result of loosening of tightness of intermolecular forces.

**Penetration enhancers**

The compounds which promote the penetration of topically applied drugs are commonly referred as **absorption promoters, accelerants, or penetration enhancers.** These are incorporated into a formulation to improve the diffusivity and solubility of drugs through the skin that would reversibly reduce the barrier resistance of the skin.

**Table 3 Mostly used components in TDDS**

| Components | Mostly Used |
|---|---|
| Polymer matrices | • **Natural/Semi Synthetic Polymer** Gelatin, Gum Arabic, Methyl cellulose, Arabino galactan, Starch, Shellac, Proteins, HPMC, Sodium CMC, Natural rubber, Zein<br>• **Synthetic Elastomers** Neoprene, Polysilozane Silicone rubber, Chloroprene, Hydrin rubber, Acrylonitrile, Butyl rubber, Nitrile Rubber<br>• **Synthetic Polymers** Polyethylene, Polystyrene, Acetal copolymer, Polyvinyl chloride, Polyester, Epoxy Polyamide Polyvinyl acetate, Ethylene vinyl acetate copolymer, Eudragits |
| Semi permeable membrane | Ethylene-vinyl acetate copolymer, Silicones, High density polyethylene, Polyester elastomers, Cellulose nitrate, Cellulose acetate |
| Pressure sensitive adhesives | Acylates<br>Polyisobutylene adhesives<br>Polysiloxan adhesives |
| Backing laminates | Polyethylene film, Polyester film, Polyolefin film, Aluminum vapor coated layer, Ethylene vinyl acetate, |

| Components | Mostly Used |
|---|---|
| | Polypropylene,<br>Polyvinylidene chloride, Polyurethane |
| Release liners | Polyester foil, Metalized laminate, Silicone, Fluorosilicone,<br>Perfluorocarbon polymers |
| Solvents | Chloroform, Methanol, Acetone, Isopropanol, DCM |
| Plasticizers | Phthalate esters, Phosphate esters, Fatty acid esters,<br>Glycol derivatives such as PEG 200, PEG 400 |
| Penetration enhancers | • **Lipophilic Solvents**<br>Dimethyl formamide, 2-Pyrrolidone, DMSO<br>• **Surface Active Agents**<br>Dimethyl formamide, 2-Pyrrolidone Sodium lauryl sulfate, Dodecyl methyl sulfoxide<br>• **Two Component Systems**<br>PG, Oleic acid, 1-4 Butadiol, Linoleic acid, Tweens, Spans |

**Approaches to Development of TDDS** (Vyas *et al.,* 2002)

Several technologies have been successfully developed to provide rate control over the release and the transdermal permeation of drugs. There are two concepts in the design of TDDS namely, rate programmed systems and physical stimuli activated systems.

**Rate programmed systems**

- Drug in reservoir
- Drug in matrix

- Drug in adhesive
- Drug in micro reservoir

**Physical stimuli activated system**

- Structure based system
- Velocity based system
- Electrically based system

**Polymer Membrane Permeation Controlled TDDS**

In this system, the drug reservoir is encapsulated in a compartment moulded from a drug impermeable backing layer and a rate controlling polymeric membrane. In the drug reservoir compartment, the drug particles are either dispersed in a solid polymeric matrix or suspended in an unleachable viscous liquid medium. On the external surface of the polymeric membrane, a thick layer of drug compatible adhesive polymer such as silicone or polyacrylate adhesive is applied to provide an intimate contact between device and skin surface. Several TDDS formulations have been marketed from this technology. E.g.

- Transderm - Scop (Ciba / Alza)
- Transderm-Nitro (Ciba /Alza)
- Estraderm (Novartis)
- Nicoderm (Alza)
- Catapress-TTS (Boehringer/ Ingelheium)
- Durogesic (Janssens)

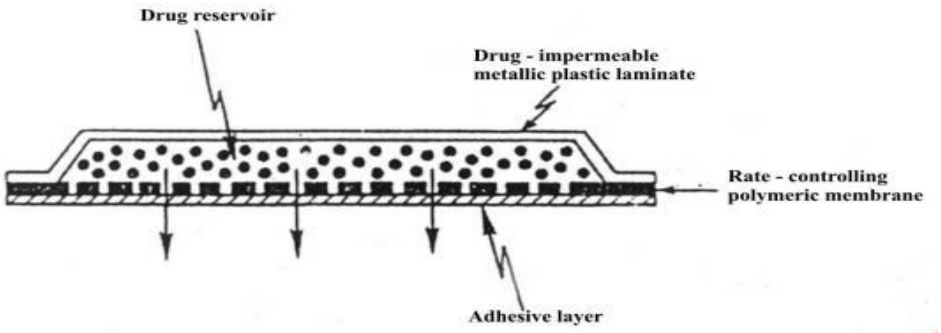



**Figure 1 Membrane permeation controlled TDDS**

**Matrix Diffusion Controlled Systems (Monolith or Matrix Systems)**

The drug reservoir in this type of devices is formed by homogeneously dispersing the drug particles in a hydrophilic or lipophilic polymer and the medicated polymer is then moulded into a medicated disc with a defined surface area and thickness. This medicated disc is then glued to a base plate, which is sealed to a drug impermeable backing. Most of these systems do not have an adhesive overlay but instead possess a peripheral adhesive ring. E.g., NTS (Hercom), ProStep (Parke-Davis).

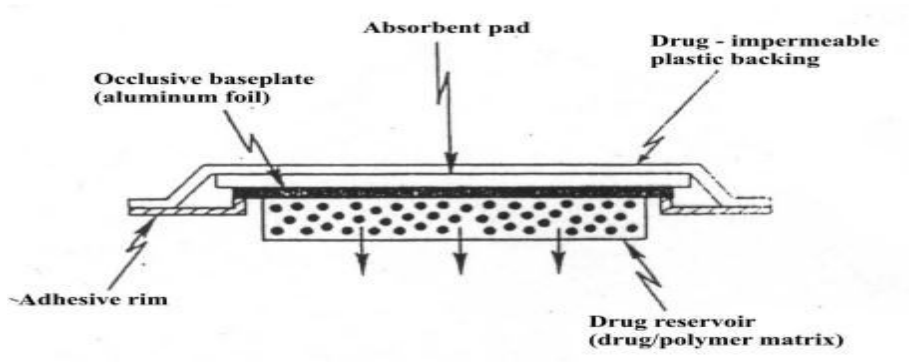



**Figure 2 Matrix diffusion controlled TDDS**

**Drug reservoir gradient controlled TDDS**

To overcome non-zero drug release profile, polymer matrix drug dispersion type TDDS can be modified to have the drug loading level varied in an incremental manner, forming a gradient of drug reservoir along the diffusional path across the multi laminate adhesive layer, E.g. NitroDur (Alza).

**Adhesive Diffusion-Controlled TDDS**

In this, the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer on a flat sheet of drug impermeable backing to form a thin drug reservoir layer. Layers of non-medicated rate controlling adhesive polymer of constant thickness are applied to produce an adhesive diffusion controlled drug delivery system. E.g.

- Deponit (Wyeth / Schwartz)
- Frandol Tape (Toaeiyo)
- Minitran (3 M Riker)
- Habitrol (Novartis)
- Nicotinell (Novartis)

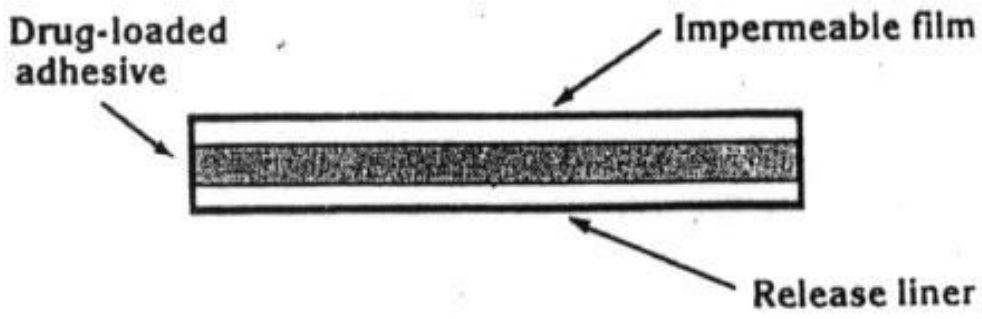



**Figure 3 Adhesive diffusion controlled TDDS**

**Micro-reservoir / Micro sealed Controlled TDDS**

These systems are a combination of the reservoir and matrix dispersion type drug delivery systems. In these systems, drug dispersion is prepared by suspending the drug in an aqueous polymer solution and then the drug suspension is dispersed homogeneously into lipophilic polymer by high shear mechanical force to form microscopic spherical reservoir with the drug entrapped. This unstable dispersion is stabilized by cross-linking the polymer chains by the addition of polymeric cross-linking agents. This matrix is then attached to adhesive form (flexible) backings. The system has a peripheral adhesive ring, E.g., Nitro Disc (nitroglycerin) (Searle).

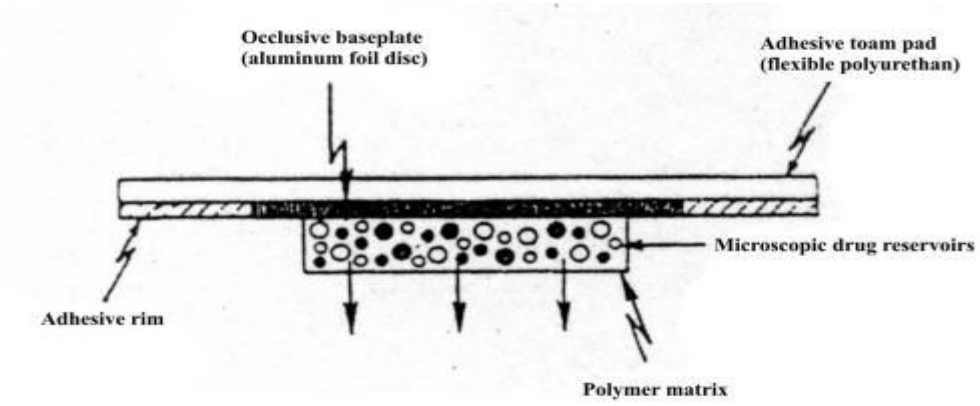



**Figure 4 Micro-reservoir controlled TDDS**

**Skin, the Integumentary System**

**Structure Of Skin** (Breathnach, 1971)

The skin is the largest organ of human body approximately weighing 16% of bodys weight. The skin of an average adult body covers a surface area of approximately 2 $m^2$ and receives about one-third of the blood circulating through the body**.** It is the major interface between the environment and the human organs and so it serves many specialised functions. It regulates body temperature to protect against hypothermia and hyperthermia. It protects from the invasion of noxious substances, UV light, heat and micro-organisms. Skin is used for the

delivery of drug because skin has large surface area; there is systemic access through underlying circulatory and lymphatic networks.

The skin is made up of multiple layers, epidermis, dermis and hypodermis and it contains appendages that include sweat glands, sebaceous glands, and hair follicles.

The superficial epidermis is a stratified epithelium largely composed of keratinocytes. Within the epidermis, there are several other cell populations, namely melanocytes, which donate pigment to the keratinocytes, Langerhans' cells, which have immunological functions and Merkel cells. Stratum corneum forming the outermost layer of the epidermis is the rate-limiting barrier to percutaneous drug transport. In fact, the stratum corneum is a remarkably more formidable barrier to drug transport than the epithelial barriers of gastrointestinal, nasal, buccal, vaginal, or rectal delivery routes.

The inferior layer is the hypodermis, which is largely made up of adipose tissue and mainly functions as an insulator and cushion. Above this layer is dermis, which is about 2-3mm thick and consist of connective tissue, which adhere to the epidermis and the hypodermis. The dermis is responsible for the skin pliability and mechanical resistance and it's also involved in the regulation of body temperature. It contains the sense organs for touch, pressure, pain and temperature. The dermis is considered to be the primary site of material exchange between the skin and blood as it has a dense network of capillaries. The is known as transdermal administration.

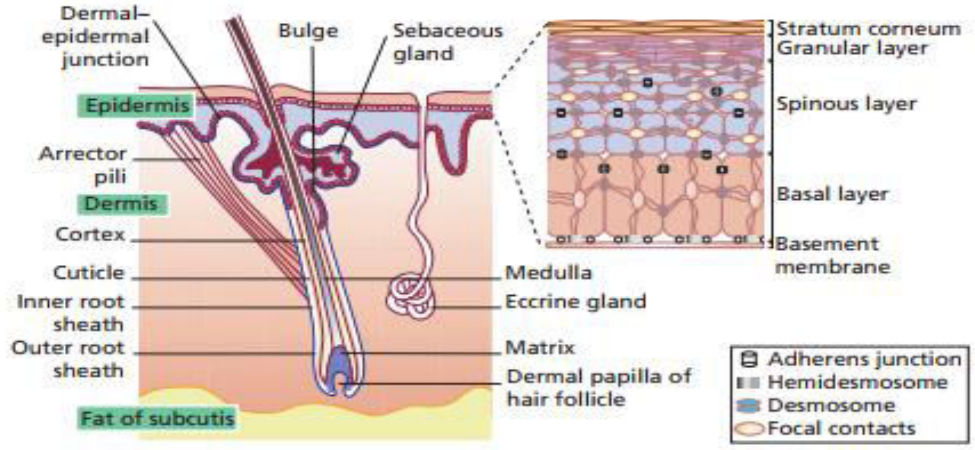



**Figure 5 Skin and its appendages**

**Drug Delivery Routes across Human Skin**

Percutaneous absorption of drug molecules is of particular importance in the case of transdermal drug delivery systems because the drug has to be absorbed to an adequate extent and rate to achieve and maintain uniform, systemic, therapeutic levels throughout the duration of use. In general, once drug molecules cross the stratum corneal barrier, passage into deeper dermal layers and systemic uptake occurs relatively quickly and easily.

Drug molecules can penetrate through skin via three pathways:

- Sweat ducts
- Hair follicles
- Sebaceous glands

Or directly across the stratum corneum. The human skin is a readily accessible surface for drug delivery as it contains 10-70 hair follicles and 200-250 sweat ducts per $cm^2$ of the skin.

**Principles of Transdermal Permeation** (Misra, 2004)

Transport of hydrophilic or charged molecules is especially difficult

attributable to the lipid-rich nature of the stratum corneum and its low water content; this layer is composed of about 40% lipids, 40% protein, and only 20% water. Transport of lipophilic drug molecules is facilitated by their dissolution into intercellular lipids around the cells of the stratum corneum. Absorption of hydrophilic molecules into skin can occur through 'pores' or openings of the hair follicles and sebaceous glands, but the relative surface area of these openings is barely 1% of the total skin surface. This small surface area limits the amount of drug absorption.

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 permeation through viable epidermis.
- Uptake of drug by capillary network in the dermal papillary layer.
- Effect on target organ

The rate of permeation, dq/dt, across various layers of skin tissues can be expressed as,

$$\mathbf{dq / dt = P_s ( C_d - C_r ) \text{ ---------- (1)}}$$

Where, $C_d$ and $C_r$ are the concentrations of a skin penetrant in the donor phase (stratum corneum) and in the receptor phase (systemic circulation) respectively; and $P_s$ is the overall permeability coefficient of the skin.

$$\mathbf{Ps = K_s.D_{ss} / h_s \text{ --------- (2)}}$$

Where, $K_s$ = Partition coefficient of the penetrant

$D_{ss}$ = Apparent diffusivity of penetrant

$h_s$ = Thickness of skin

Thus, permeability coefficient ($P_s$) may be a constant, if $K_s$, $D_{ss}$ and $h_s$ terms in equation (2) are constant under a given set of conditions. A constant rate of drug permeation is achieved, if $C_d >> C_r$.

Then, the equation (1) may be reduced to,

**$dq / dt = P_s.C_d$---------- (3)**

The diffusional resistance encountered, limit the molecular penetration through the various regions of the skin. The total diffusional resistance (Rskin) to permeation through the skin has been described by Chien as,

**$(R_{skin}) = R_{sc}. R_e. R_{pd}$**

Where, R is the diffusional resistance, and subscripts sc, e and pd refer to stratum corneum, epidermis and papillary layer of the dermis respectively. Of these layers the greatest resistance is put up by the stratum corneum and tends to be the rate-limiting step in percutaneous absorption.

**Migraines** (Estemalik *et al.,* 2013)

Migraines are intense headaches, sometimes causing loss of energy or strength.

**Types of Migraine**

The most common types of migraine are

**Classical migraines**:

A migraine with aura involving number of different sensations that ranges from visual disturbances to physical sensations.

**Common migraines**:

A migraine without aura characterized by moderate to severe throbbing

and unilateral pain.

Other types of migraine include **basilar artery migraine, abdominal migraine, hemiplegic migraine, menstrual migraine, chronic migraine and cluster migraine.**

**The Signs of Migraine**

The associated symptoms that can prevent an individual from continuing with their daily life, and these can occur with or without the headache.

- Intense throbbing headache, often unilateral;
- Nausea, loss of appetite and / or vomiting. May also experience diarrhoea;
- Photophobia (excessive sensitivity to light and aversion to bright light);
- Phonophobia (an unusual fear of sound);
- Other common aura symptoms you may experience include: tingling or pins and needles in the limbs, an inability to concentrate, confusion, and difficulty in speaking, paralysis or loss of consciousness (in very rare cases).

These symptoms, often called 'aura', can occur before an attack happens lasting from a few minutes up to an hour. However, this is usually only experienced by about 20 - 30% of people.

The symptoms of a migraine can vary from person to person and during different attacks. Migraine attacks may differ in their frequency, duration and severity, although, normally they last between 4 and 72 hours, and most people are symptom-free between attacks.

**The Causes of Migraine**

Disruption of normal brain functioning is believed to be the underlying

cause of the migraine pain and aura. The vascular theory suggests that migraines results from the widening of blood vessels surrounding the brain.

In recent years the understanding of migraine within the medical world has greatly improved, recognizing that migraine is a disorder that involves many aspects of physiology, including the CNS, neurotransmitters and other chemicals within the brain. Migraine is thought to be caused by a release of neurotransmitters (chemical messengers) through nerve endings in the trigeminal system located in the brain. When a migraine attack has been triggered, this is then thought to expand the blood vessels in the brain.

Recent research confirms a genetic link to migraine; people with a DNA variant on chromosome 8 between two genes - PGCP and MTDH / AEG-1 have been found to have a significantly greater risk of developing migraine. It appears that this DNA variant regulates the levels of glutamate – a chemical, known as a neurotransmitter, that transports messages between nerve cells in the brain; an accumulation of this chemical in the brain can cause migraine attacks. Research into preventing the buildup of glutamate and other causes in migraine is still ongoing.

**The Triggers of Migraine**

Migraine sufferers have their own individual triggers. The most common migraine 'triggers' are:

- Lack of food or infrequent meals (e.g. missing meals)
- Changes in the weather (e.g. strong winds, extreme heat or cold)
- Stress
- Changing sleep patterns (e.g. weekend lie-ins or shift work), sleeping more or less than usual
- Certain medications

- Certain foods (including products containing caffeine, tyramine, alcohol, monosodium glutamate)
- Hormonal factors (e.g. monthly periods, the contraceptive pill, HRT or the menopause; migraines tend to intensify during puberty and disappear during menopause)
- Overtiredness/over-exertion (both physical and mental)
- Extreme emotions (e.g. anger, or grief)
- Environmental factors (e.g. loud noise, bright / flickering lights, strong smells, hot stuffy atmospheres, etc.)

**The Five Stages of Migraine**

In adults a migraine attack actually comes in 4 or 5 phases- that roll on from each other; however not everyone has all five phases.

1. **Warning phase** (known as **prodrome**) can occur hours or even days before the aura or headache begins. It is considered as an integral component of the migraine process. It acts as a warning sign that a migraine is imminent. Prodromes are characterized by mood changes, food cravings, feeling tired or hyperactive, or excessive yawning. Some people may also experience fatigue or stiffness in the neck.
2. **Aura** includes a wide range of neurological symptoms – sensory disturbances, motor disturbances, verbal disturbances and visual disturbances.
3. **Attack phase** involves head pain which can be severe and even unbearable. It is usually one sided, but some sufferers get the pain on both sides of the head, or over the forehead, but not usually at the back of head.

4. **Resolution** (known as **postdrome**) may last up to 48 hrs. Most attacks slowly fade away, but some stop suddenly after the sufferer is sick or cries a lot. Sleep seems to be the best 'cure' for many sufferers, who find that even an hr or 2 can be enough to end an attack.

5. **Recovery** (**hangover or run over phase**): is the final stage and can takes hrs or even days for this hangover type feelings to disappear

In children the migraine attack is often shorter and it may therefore not be possible to fully make out the different phases.

**The Medications for Migraine**

Although there is no miracle cure for migraine, it is possible to bring the condition under control using a wide range of treatments that are available. Effectiveness of these treatments can vary between individuals. Migraine treatment falls into 2 main groups: 'acute' and 'preventive' medication. Patients with frequent attacks usually require both.

***Acute (abortive or rescue) therapies*** reverse, or at least stop, the progression of a headache that has started. The choice of abortive medications for an individual patient depends on the severity of the attacks, associated symptoms such as nausea and vomiting, co morbid problems and the patient's treatment response.

Simple analgesics alone or in combination with other compounds have provided relief for mild to moderately severe headaches and sometimes even for severe headaches. Acute treatment is most effective when given within 15 minutes of pain onset and when pain is mild. Analgesics used in migraine include acetaminophen, NSAIDs and narcotic analgesics (e.g.: oxycodone, morphine sulfate).

For more severe pain, 5-HT 1 agonists (triptans) and / or opioid analgesics are used, either alone or in combination with dopamine antagonists (prochlorperazine). The use of abortive medications must be limited to 2-3 days a week to prevent development of a rebound headache phenomenon.

Intravenous metoclopramide can be an effective therapy for acute migraine, but the optimal dosing has not been established.

***Preventive (prophylactic) therapy*** given even in the absence of a headache aims to reduce the frequency and severity of the migraine attack, make acute attacks more responsive to abortive therapy, and perhaps also improve the patient's quality of life.

Propranolol, timolol, methysergide, valproic acid and topiramate have been approved by the FDA for migraine prophylaxis. The 3 classes of prophylactic drugs include**-** antiepileptics, antidepressants and antihypertensives.

***Complementary or alternative*** can often provide relief and / or help migraineurs to manage their migraine. Mindfulness based stress reduction and home meditation have been studied as a method to reduce the pain and improve health related quality of life in patients with chronic pain syndromes.

Biofeedback, cognitive behavioral therapy and relaxation therapy are frequently effective against migraine headaches and may be used adjunctively with pharmacologic treatments. For those with neck tension or back problems, acupuncture, massage and osteopathy can be of benefit. Occipital nerve stimulators may be helpful in patients whose headaches are refractory to other forms of treatment.

**Migraine - Specific Oral Medications**

Migraine - specific oral medications include mainly 2 categories **triptans** and **ergot alkaloids**. The specific ergot alkaloids include ergotamine and **dihydroergotamine**.

The triptans share a common mechanism of action, but they differ in their routes of administration, onset of action and duration of action. Routes of administration include oral, intranasal, subcutaneous, and intramuscular. Transdermal patches have proved effective for the delivery of Sumatriptan, and

one such product has received FDA approval.

All the triptans are most effective when taken early during a migraine attack and all may be repeated in 2 hrs as needed, with a maximum of 2 doses daily. Triptans should not be used more than 3 days weekly, to avoid transformed migraine and medication overuse headache.

The mechanism of action for triptans has not been completely outlined, but there are two possibilities that have been proposed. The first recommend that triptans may activate serotonin ($5HT_{1B/1D}$) on presynaptic trigeminal nerve endings to inhibit the release of vasodilating peptides. The second focuses on the direct vasoconstrictor actions of direct 5-HT agonists and the possible prevention of vasodilation that would lead to activation of nerve endings in the cerebral vasculature that produce pain.

The safety of triptans is well established, and the risk of de novo coronary vasospasm from triptan use is exceedingly rare. However, triptans should not be taken by patients with known or suspected coronary artery disease, as they may increase risk of myocardial ischemia, infarction, or other cardiac or cerebrovascular events.

**Table 4: Currently available triptan medications**

| Triptan | Available Dose Forms |
|---|---|
| Alsuma ® (sumatriptan) | injectable |

| | |
|---|---|
| Amerge® (naratriptan) | Oral |
| Axert® (almotriptan) | Oral |
| Frova® (frovatriptan) | Oral |
| Imitrex® (sumatriptan) | Oral, injectable, intranasal |
| Maxalt® (rizatriptan) | Oral, also available in an orally disintegrating tablet |
| Relpax® (eletriptan) | Oral |
| Onzetra ™ Xsail (sumatriptan) | intranasal |
| Sumavel® (sumatriptan) | Needless injectable device |
| Treximet® (sumatriptan/naproxen) | Oral |
| Zembrace ™ (sumatriptan) | injectable |
| Zomig® (zolmitriptan) | Oral, also available in an orally disintegrating tablet, intranasal |

# RESEARCH OBJECTIVE

Almotriptan Malate is a highly selective serotonin 5-HT1B/1D receptor agonist. According to the FDA Clinical Review, Almotriptan Malate is effective in the acute treatment of moderate to severe migraine attacks in adult and adolescent patients with a history of migraine with or without aura. Several studies have reported that Almotriptan Malate has the best sustained pain-free rate and the lowest adverse events rate of all the triptans. It is consistently one of the preferred triptans in multi attribute decision-making analyses.

Almotriptan Malate is administered as oral tablets (basically 12.5 mg) and although its absorption is good after oral administration, the mean absolute bioavailability is 69.1%**.** As mentioned, the bioavailability of Almotriptan Malate is somewhat limited after oral dosing. Parenteral dosing is an alternative, but it involves obvious inconveniences. Bearing in mind the pharmacokinetic properties of this agonist and its superior efficacy and tolerability profile in comparison to other triptans*,* an alternative route of Almotriptan Malate delivery, such as transdermal administration, could represent a new and valid pharmaceutical form. Furthermore, it is well known that Almotriptan Malate involves a much lower risk of adverse events than Sumatriptan, Zolmitriptan and Rizatriptan, making it a better tolerated and more cost-effective choice for triptan-naïve patients (Calatayud-Pascual *et al.,* 2011).

Many studies conducted in vivo have demonstrated that the transdermal administration of triptans is possible. In view of the above facts, in the present investigation, an attempt was made to develop matrix type transdermal patches of Almotriptan Malate using suitable combination of hydrophilic polymer like

HPMC K 15M with hydrophobic polymers like ERS 100 and EC. These polymers were used due to its low toxicity, biocompatible, exhibits minimal cell adhesion, good chemical stability and film-forming ability. So the aim of the present research work is to formulate and optimize a stable and sustained release transdermal formulation by using various polymers in order to avoid the first-pass effect and to obtain great therapeutic efficacy.

**Specific objectives of investigation**

- To design the formula for transdermal patches, preliminary trials were conducted with different concentration of different polymer combination.
- To select the best polymer combination.
- To carry out the compatibility studies of drug and selected polymer combinations.
- To incorporate selected model drug candidates in the formula and prepare patches.
- To characterize the formulated patches for the physico-mechanical characteristics.
- To carry out the in vitro drug release studies of the formulated patches through dialysis membrane using Franz diffusion cell.
- To design the optimized formulation by simple $2^2$ factorial designs by using statistical software.
- To check the stability of the formulated patches.
- To evaluate the drug release kinetics for the best formulation among the other patches

# PLAN OF RESEARCH WORK

- Literature survey on TDDS, Almotriptan Malate, migraine and antimigraine drugs
- Selection of polymers
- Designing the formula for preparing transdermal patches
- Preformulation studies
- Formulation of Almotriptan Malate loaded transdermal patches
- Characterization of the formulated patches including physico mechanical studies, in vitro drug release studies etc
- Statistical optimization to determine the best prepared formulation
- Stability studies
- Drug release kinetic studies of the best formulated patches

# LITERATURE REVIEW

1. **Srilakshmi *et al.,* (2017)** developed matrix type transdermal therapeutic system containing Irbesartan, an angiotensin receptor blocker, with different ratios of hydrophilic and hydrophobic polymeric concentration by solvent evaporation technique. The prepared patch showed satisfactory physiochemical characteristics of weight uniformity, thickness, folding endurance, moisture absorption for stability of the formulation and drug content were uniform in all patches. *In vitro* study was carried out by using Franz diffusion cell having cellophane membrane & determined the amount of drug present in the formulated patch. On the basis of the *in vitro* drug release and drug content result, formulation F5 was concluded as an optimized formulation, which had its maximum percentage of drug release.

2. **Rahul Shivajirao Solunke *et al.,* (2016)** formulated and evaluated TDDS of an anti – diabetic drug, Repaglinide, using polymers such as HPMC & Eudragit RLPO by solvent casting technique. Repaglinide with a shorter half-life and low bioavailability undergoing extensive first pass metabolism has chosen for TDDS to maintain its therapeutic level. The prepared formulations were evaluated for different physicochemical characteristics like weight variation, folding endurance, flatness, pH of patches, % moisture content, % moisture uptake, % elongation, % drug content & % drug release. The in-vitro drug release data has shown that the drug release followed zero order kinetics & Higuchi model, Based on the result of evaluation parameters obtained from the formulation, F2 is considered as an optimized formulation which showed high percentage of drug release (98.20% at 14 hour) with diffusion mediated mechanism.

3. **Apoorva Srivastava *et al.,* (2016)** formulated TDDS of Timolol maleate, an anti-hypertensive drug using various polymers such as EC, ERS100 & ERL100 by solvent casting method. To improve the patch performance and drug release permeation enhancers like Tween 80 or Span 80 were added whereas glycerin was used as a plasticizer. It was observed that F5 follows the zero order as their $R^2$ values were higher than other model. It was concluded that this formulation released drug in control manner and it is the ideal method of drug release to achieve pharmacological prolonged action.

**4.** **Anil kumar *et al.,* (2016)** prepared Almotriptan chewable tablets using 3 various superdisintegrants cross povidone, cross caramellose and sodium starch glycolate and other ingredients in varying concentrations and were subjected to weight variation, drug content uniformity, lock length, dissolution, drug excipients interaction and short-term stability studies. The results of % compressibility index and hausner's ratio for the entire formulation showed fair flow properties. The entire tablet passes weight variation test, as the average % weight variation was within the Pharmacopeial limit - 7.5%. The concentration of the drug in all the formulations with different polymers was found to be 97.35 – 99.58%. It was within the IP limits. The overall results indicated that formulation F6 with cross caramellose (7.5%) had a higher edge compared to other formulations containing super disintegrants and palatability is good.

**5.** **Bhavani Boddeda *et al.,* (2016)** prepared and evaluated patches of synthetic antifungal agent, Fluconazole. Preliminary trials were conducted with different polymer combination (PVA: PVP, HPMC K4M: PVP, HPMC K15M: PVP, HPMC K100M: PVP and EC: PVP). In this F2 & F4 were selected depending on their parameters such as tensile strength and

folding endurance. By using 2 different grades of HPMC and PVP concentrations as levels, HPMC & PVP as factors, the formulation were incorporated in $2^2$ factorial designs by using DOE software. The drug release through the transdermal patches of Fluconazole followed first order kinetics with diffusion controlled mechanism.

6. **Sirisha Yella *et al.,* (2016)** prepared orally disintegrating tablets of Almotriptan and determined the effect of various diluents and super disintegrants in various ratios on drug release. The formulation was developed to increase the bioavailability of the drug using optimization technique and effect of various excipients has been studied to obtain an optimized formulation. Diluents such as microcrystalline cellulose, spray dried lactose, mannitol and starch were employed and super disintegrants such as cross povidone, cross carmellose sodium and sodium starch glycolate were used in different ratios. All the formulations were evaluated or precompression and post compression parameters, in which precompression studies showed statisfaction. Formulation F23 having diluents as mannitol and superdisintegrants as SSG (8%) showed maximum drug release of 100.03% within 20 min among all the other formulation. From the optimized formulation the drug release kinetics was found to follow first order kinetics.

7. **Shyam P. Bihade *et al.,* (2014)** focused on the development and evaluation of Eletriptan transdermal patches. Matrix types transdermal patches were prepared using HPMC K100LV / K15M grades polymers. The solvent used for the preparation was water. PEG 400 was used as plasticizer. The drug release of the optimized batch F1 was found to be 86.43% providing sustained transdermal delivery for prolonged periods in the management of migraine.

8. **Soujanya *et al.,* (2014)** developed a transdermal therapeutic system for Lornoxicam using various polymers like EC and HPMC and natural permeation enhancers like Eugenol and Cineole by solvent casting method. The prepared patches were evaluated for physicochemical properties, *in vitro* drug release, ex vivo skin permeation studies and *in vivo* studies. The interactions between Lornoxicam and polymers were investigated by FTIR. The *in vitro* release studies revealed that the release was sustained up to 24h and it followed zero order kinetics. Finally, the best formulation (L3) selected through *in vitro* study was subjected to ex vivo skin permeation using rat skin and *in vivo* studies in rabbits. The patch was also subjected to skin irritation and anti inflammatory activity and found that there was no skin irritation and edema levels were lowered in the albino rats.

9. **Jayesh *et al.,* (2014)** prepared and optimized Nifedipine transdermal patch by using D-optimal mixture design. The prepared transdermal patches were evaluated for various parameters like drug excipients compatibility study, physicochemical evaluation, mechanical properties, *in vitro* drug release and *in vitro* permeation study. The result of evaluation parameters demonstrated a successful development of transdermal patch with PVP and EC as rate controlling polymer. For optimization, PVP & EC content were selected as the independent variables whereas amount of drug release, cumulative amount of drug permeated at 24h, permeation flux were taken as dependent variable. The optimized transdermal patch was prepared with 90.91 % PVP and 9.09 % EC. This developed optimized transdermal patch showed prolonged sustained release of Nifedipine with high permeation rate, promising improved patient compliance and bioavailability.

10. **Prabhakar *et al.,* (2014)** developed Azelnidipine transdermal patches by solvent casting method using different amounts and combination of HPMC E15, EC and ERS100 and studied the effect of DMSO on drug permeation across the rat abdominal skin. The prepared patches were subjected to physicochemical studies such as drug content, weight variation, thickness, moisture absorption, moisture loss, WVTR and folding endurance. The prepared films were smooth, flexible, uniform thickness and content of drug. Ex-vivo studies showed that as an increasing DMSO concentration increased cumulative amount of drug released.

11. **Karva *et al.,* (2013)** developed a quantitative estimation of Almotriptan Malate in pharmaceutical formulation. The stock solution of the drug was prepared and subsequent suitable dilution was prepared in 0.1N HCl to obtain standard curve. The standard curve showed 2 absorption maxima, one at 283.000 nm and the other at 283.00 nm. The drug obeyed Beer Lambert's law in the concentration range of 10-100 µg/ml with R value 0.9998 at 283.00 nm. Results were been validated as per ICH guidelines.

12. **Narayana Charyulu *et al.,* (2013)** designed and evaluated melt in mouth films of Almotriptan using polymers pullulan, carrageenan, xanthum gum and guar gum as the film forming agents, glycerol as the plasticizer, sorbitol as the sweetener and glycolate as the disintegrants. This formulation was found to have quick onset of action which can be a merit for managing the severe migraine attack and also aiding in enhanced bioavailability. The films prepared by solvent casting technique were evaluated for physicochemical characterization, *in vitro* disintegration and *in vitro* drug release studies.

13. **Akhila Alladi *et al.,* (2012)** formulated and evaluated taste masked Almotriptan ODT by using 2 taste masking agents namely Eudragit EPO and Precirol A To5 and different superdisintegrants in different ratios. Due to its bitter taste formulating Almotriptan into an ODT was a challenge. The effect of different superdisintegrants at different concentration on in-vitro release was studied. Almotriptan release from ODT was directly proportional to the concentration of the superdisintegrants used. The optimized formulation was found to release the drug in minimum time and is found to be stable.

14. **Michail Vikelis *et al.,* (2012)** developed the iontophoretic sumatriptan patch. Two trials have been performed to evaluate the pharmacokinetic profile of transdermal iontophoretic delivery of sumatriptan which indicated that the administration of sumatriptan transdermally is fast, consistent, and well tolerated without typical triptan-related adverse effects. The long-term safety and efficacy of the sumatriptan patch was examined in a subsequent open-label, extension study. Patch number containing 120 mg of Sumatriptan Succinate, was selected for further development under the commercial name Zelrix™. This device consists of a thin patch containing two shallow wells filled with chemicals that act as electrodes, each with nonwoven pads placed on top. They concluded that this could be a non-invasive process where no disruption of the skin takes place and the rate and amount of medication delivery is controlled by a microprocessor, which can be activated by the user.

# DRUG PROFILE

## ALMOTRIPTAN MALATE

**Indications:**

Acute treatment of migraine attacks in patients with or without aura

**Class:**

Selective serotonin (5-$HT_{1B/1D}$) receptor agonist

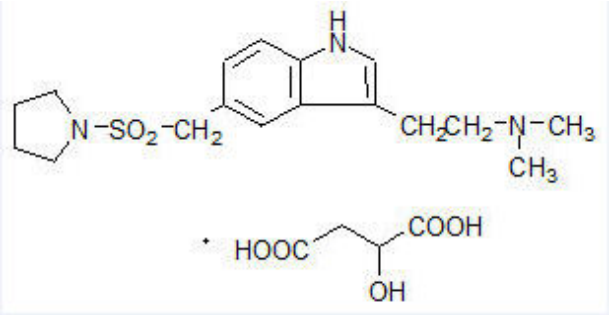
**Chemical name:**

1-[[[3-[2-(Dimethylamino)ethyl]-1H-indol-5-yl]-methyl]-sulfonyl]-pyrrolidine-hydroxybutanedioate(1:1)

**Molecular formula:** $C_{17}H_{25}N_{3O}2_{S}$-$C_4H_6O_5$

**Molecular mass:** 469.56 g/mol

**Structural formula:**




**Physical Form:**

White to slightly yellow crystalline powder

**Solubility:**

Freely soluble in water and methanol but practically insoluble in ethanol and methylene chloride.

**pKa:** 8.77 at 22 ± 2°C

**Melting Point:** 167 – 173°C

**pH:** 1% solution in purified water has pH 4.1

**Partition Coefficient:**

A partition coefficient of 0.008 between octanol and water was determined, when measured at the normal pH value (5.4 -6.3) for purified water.

**Dosage:**

Recommended dose in adults and adolescents (age 12 – 17 yrs) is 6.25mg – 12.5mg, with 12.5mg as the most effective dose in adults. If after the initial dose, the headache returns, another dose may be taken after 2 hours. The maximum daily dose should not exceed 25mg. In case of hepatic or renal impairment dose should be adjusted in to a starting dose of 6.25mg and a maximum of 12.5mg over a 24hr period.

**Dosage form:** White, coated, circular, biconvex tablets

**Dosage strength:** 6.25mg and 12.5mg

**Overdosage:** Hypertension or any other cardiovascular symptoms can occur

**Pharmacokinetic data:**

- **Absolute bioavailability**: 70%
- **Protein binding**: 35%
- **Mean apparent volume of distribution**: 180-200 liters (approx)
- **Metabolism**: Major route – MAO mediated oxidative deamination (approx 27% of dose) & CYP450 mediated oxidation (approx 12% of dose), Minor route – flavin monooxygenase
- **Biological half life**: 3-4hrs
- **$C_{max:}$** 49.5 – 64 mcg/L

**Pharmacology**:

Binds to serotonin 5- $HT_{1B/1D}$ receptor on extra cerebral, intra cranial blood vessels which leads to vasoconstriction of cranial (brain) blood vessels, thus affecting redistribution of blood flow. Significantly it increases cerebral blood flow and reduces blood flow through extra cerebral cranial vessels. A single dose

of almotriptan has no clinically significant effect on blood pressure or heart rate in both young and elderly healthy volunteers. However larger doses seem to slightly increase blood pressure but not beyond clinical relevance.

**Contraindications:**

- Ischemic or Vasospastic Coronary Artery Disease
- Cardiovascular Syndromes
- Peripheral Vascular Disease
- Uncontrolled Hypertension
- Ergot derived medications
- Any other 5-$HT_1$agonists
- Hemiplegic or Basilar Migraine
- Hypersensitivity

**Storage:** Store at room temperature between $20^0$C - $25^0$C ($68^0$F – $77^0$F)

# POLYMER PROFILE

**HYDROXY PROPYL METHYL CELLULOSE** (Wade *et al.*, 1994)

**Nonproprietary names:**

Hypromellose (BNF)**,** Methyl hydroxyl propyl cellulosum (Ph Eur)

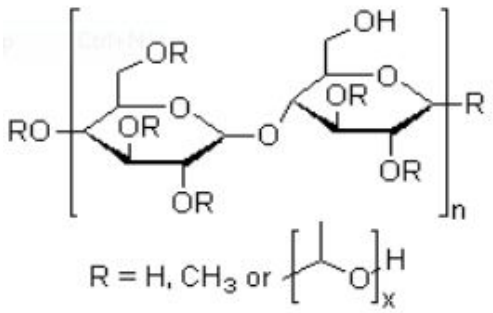
**Synonyms:**

- Cellulose hydroxyl propyl methyl ether
- Metolose
- Methylcellulose propylene glycol ether
- Methyl hydroxypropyl cellulose
- Methocel

**IUPAC name:**

(2R,3R,4S,5R,6R)-2,3,4-trimethoxy-6-(methoxymethyl)-5-[(2R,3R,4S,5R,6R)-3,4,5- trimethoxy-6-(methoxymethyl)oxan-2-yl]oxyoxane

**Chemical structure:**




**Molecular formula:** $C_{56}H_{108}O_{30}$

**Molecular weight**: 1261.45 g/mol

**Description:**

HPMC absorbs moisture from the atmosphere. The Ph.Eur 1992 describes HPMC as a partly O methylated and O-(2-hydroxypropylated) cellulose. It is available in several grades which vary in viscosity and extent of subscription. HPMC defined in the USP XXII specifies the substitution type by appending a four digit number to the non proprietary name, e.g. HPMC1828 .the first two digits refer to the approximate percentage content of the methoxy group & the second digits refer to the approximate percentage content of the hydroxyl propyl group calculated on a dried basis.

**Appearance:**

White to creamy- white fibrous or granular powder

**Odor:**

Odorless and tasteless

**Melting point:**

Browning temperature 190–200°C; charring temperature 225–230°C.

**Acidity / alkalinity:**

pH= 5.5–8.0 (1% w/v aqueous solution)

**Nominal viscosity:** 15000 mPa s

**Density :** 0.25-0.70 g/cm$^3$

**Solubility:**

Soluble in cold water forming a viscous colloidal solution, a mixture of ethanol & DCM, a mixture of water and alcohol and a mixture of methanol and DCM and practically insoluble in ethanol (95%), chloroform and ether.

**Different grades:**

HPMC K4M, HPMC K15M, HPMC K100

**Storage:**

HPMC powder should be stored in well closed container, in a cool, dry, place.

**Functional category:**

- Coating agent
- Film-former
- Rate controlling polymer for sustained release
- Stabilizing agent
- Suspending agent
- Tablet binder
- Viscosity increasing agent

**Applications in pharmaceutical formulations and technology:**

HPMC is widely used in oral and topical pharmaceutical formulations. In oral products, HPMC is primarily used as tablet binder, in film coating and as an extended release tablet matrix. Depending upon the viscosity grades, concentration between 2 -10%w/w are used as film forming solutions to film coat tablets. Lower viscosity grades are used in aqueous film coating solution while higher viscosity grades are used with organic solvents. HPMC is also used as suspending agent and thickening agent in topical formulations especially in ophthalmic preparations. Compared with MC, HPMC produces solutions of greater clarity, with fewer undispersed fibers present, and is therefore preferred in formulation for ophthalmic use. Concentration of between 0.45%-1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solution. HPMC is also used as an emulsifier, suspending agent and stabilizing agent in topical gels and ointments. In addition, HPMC is used as adhesive in plastic bandages and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

**EUDRAGIT RS 100** (Abhijit Sonje *et al.*, 2013)

**Nonproprietary names:**

Methacrylic acid copolymer, polymeric methacrylates

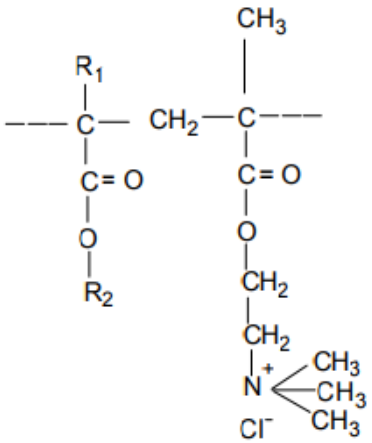
**Synonyms:**

- Trimethyl ammonium ethyl methacrylate chloride
- Methyl methacrylate
- Ethyl acrylate polymer

**IUPAC name:**

Ethyl prop-2-enoate; methyl 2-methylprop-2-enoate; trimethyl-[2-(2-methylprop-2-enoyloxy)ethyl]azanium; chloride

**Chemical structure:**




$R_1$ = H, $CH_3$

$R_2$ = $CH_3$, $C_2H_5$

**Molecular formula:** $C_{19}H_{34}ClNO_6$

**Molecular weight:** 407.932 g/mol

**Description:**

It is a 5% trimethylammoniummethacrylate chloride and is copolymers of acrylic and methacrylic acid esters containing some quaternary ammonium groups. The ammonium groups are present as salts and make the polymers permeable.

**Appearance:**

Colorless, clear to cloudy granules

**Odor:**

Slight amine like odor

**Viscosity:**

5-15 cps

**Density:**

0.825 g/ml

**Solubility:**

Soluble in acetone, ethanol, methanol, propanol, DCM, ethyl acetate whereas practically insoluble in ether, 1 N sodium hydroxide and water.

**Storage:**

Protect from warm temperatures and from moisture. They tend to form lumps at warm temperatures, but this has no influence on the quality. The lumps are easily broken up again.

**Functional category:**

- Film former

- Tablet binder
- Tablet diluents
- Suspending agent
- Film former
- Emulsifying agent
- Emulsion stabilizer
- Stabilizing agent

**Applications in pharmaceutical formulations and technology:**

Eudragit exhibits favourable behaviour, such as no toxicity, positive charge and controlled release profile this makes them suitable for ophthalmic applications. Eudragit provide good drug release barrier with good adhesive strength or buccal and sublingual drug delivery. Sustained intestine drug deliveries was developed that could bypass the stomach and release the loaded drug for longer periods into the intestine by coating of Eudragit polymer. ERS 100 vaginal suppositories containing sildenafil and other excipients give adequate release. Anti sense oligodeoxynucleotides were successfully delivered by nanoparticles prepared by ERL 100 and ERS 100.

**ETHYL CELLULOSE**

**Nonproprietary names:** Ethyl-cellulose, Ethocel

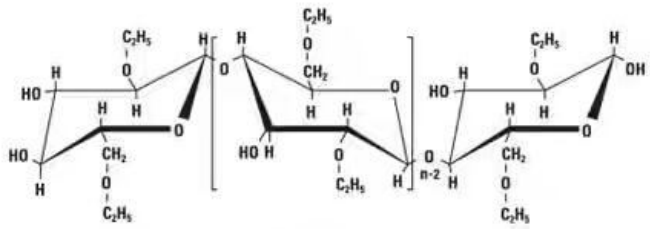
**Synonyms:**

- Aquacoat
- Aqualon
- E462
- Ethocel
- Surelease

**IUPAC name:**

2-[4, 5-diethoxy-2-(ethoxymethyl)-6-methoxyoxan-3-yl]oxy-6-(hydroxymethyl) -5-methoxyoxane-3,4-diol

**Chemical structure:**



**Molecular formula:** $C_{20}H_{38}O_{11}$

**Molecular weight:** 454.513 g/mol

**Description:**

Ethyl cellulose is a hydrophobic ethyl ether of cellulose. It is a derivative of cellulose in which some of the hydroxyl groups on the repeating glucose units are converted into ethyl ether groups.

**Appearance:** free-flowing white to tan powder

**Odor:** Odorless and tasteless powder

**Melting point:** 160-210°C

**Viscosity:** 18.00 – 24.00 cp

**Density:** 1.07-1.18 g/cm$^3$

**Solubility:**

Practically insoluble in water, in glycerol and in propane-1, 2-diol but soluble in varying proportions in certain organic solvents depending upon the ethoxyl content. Ethyl cellulose containing 46 - 48% or more of ethoxyl groups is freely soluble in chloroform, in methanol, in toluene and in ethyl acetate. Freely soluble in mixture of aromatic hydrocarbons with alcohol.

**Storage:**

Stored between 70$^0$C-30°C in a dry area away from all sources of heat and away from bright light. Store in a well closed container.

**Functional category**

- Coating agent
- Flavouring
- Tablet binder and filler
- Film former
- Rate controlling polymer for sustained release
- Stabilizing agent
- Suspending agent
- Viscosity increasing agent

**Applications in pharmaceutical formulations and technology:**

Ethyl cellulose is a non-toxic, stable, compressible, inert, hydrophobic polymer that has been widely used to prepare pharmaceutical dosage forms. It is a

stabilizer and thickener for foods. It is currently used in pharmaceutical applications for micro encapsulation of actives, controlled-release matrix systems, taste masking, solvent and extrusion granulation, tablet binding, and as a controlled-release coating for tablets and beads. It is directly extracted from plant fiber and is then chemically modified. It is a kind of cellulose ether and it shows good thermo stability and electric properties. The film made from EC has quite good permeability; it has been used widely as industrial air filter.

# PLASTICIZER PROFILE

## POLYETHYLENE GLYCOL

**Non proprietary name:**

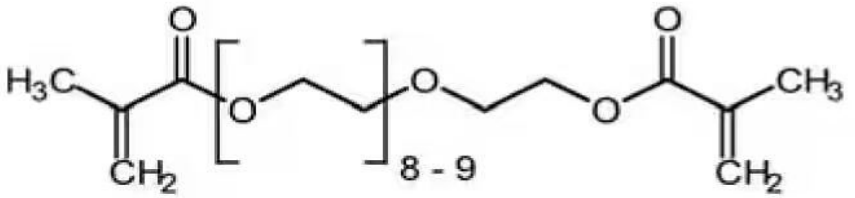
- Macrogol 300
- Macrogol 1540
- Macrogol 4000

**Synonym:**

- PEG
- Macrogol
- Polyoxyethylene glycol

**IUPAC name:** α-Hydro-ω-hydroxypoly-(oxy-1, 2-ethanediyl)

**Chemical structure:**




**Structural formula:**

$HOCH_2(CH_2OCH_2)_nCH_2OH$, where n=average number of oxyethylene groups. In PEG 400 n is in the range 8-10

**Molecular weight:** 380-420 g/mol

**Description:** Clear, colorless or slightly yellowish, viscous liquids. The odor is slight but characteristics, and the taste is bitter and slightly burning.

**Viscosity:** 6.8-8.0

**Density:** 1.13 $g/cm^3$

**Solubility:**

Soluble in water, alcohol, glycol, glycerol, acetone and benzene.

**Storage:**

Stored in well closed container. Storage under nitrogen will reduce the possibility of oxidation.

**Functional category:**

- Suppository base
- Solvent
- Tablet lubricant
- Capsule lubricant
- Ointment base
- Pharmaceutical aid

**Applications in pharmaceutical formulations and technology:**

It is a low molecular weight grade of polyethylene glycol. It is widely used as plasticizers in conjunction with film forming polymers. Their presence in film tends to increase their water permeability, and may reduce protection against low pH in enteric coating films. PEGs are useful as plasticizers in micro-encapsulated products to avoid rupture of the coating film when microcapsules are compressed into tablets. They are used as water miscible vehicles for the contents of soft gelatin capsules. However, they may cause hardening of the shell by preferential absorption of moisture from the gelatin shells. In concentration up to 30% they have been used as vehicles in parenteral dosage forms. The aqueous solubility or dissolution characteristics of poorly soluble compounds can be enhanced by making solid dispersions with an appropriate PEG. In aqueous vehicles, PEGs can be used to adjust viscosity and consistency. When used in conjunction with other emulsifiers, PEGs can act as emulsion stabilizers. As suppository bases, PEGs offer many advantages over fats, such as physical stability or better storage, high melting point thus withstanding exposure to warmer climates and are readily miscible with rectal fluids.

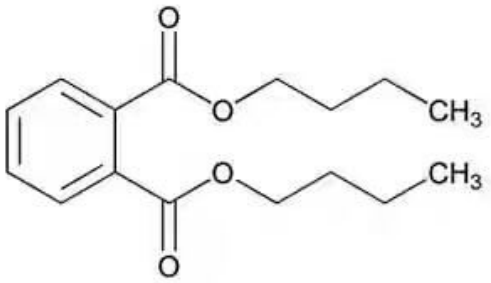
**DIBUTYL PHTHALATE**

**Synonyms:**

- Di-n-butyl phthalate
- 1, 2-benzenedicarboxylic acid
- Phthalic acid di-n-butyl ester
- 1, 2-benzene dicarboxylate
- n-butyl phthalate
- Palatinol C
- Butyl phthalate
- DBP
- DBP (ester)
- Phthalic acid
- Dibutyl ester

**IUPAC name:** Dibutyl benzene-1,2-dicarboxylate

**Chemical structure:**




**Molecular formula:** $C_{16}H_{22}O_4$

**Molecular weight:** 278.34 g/ mol

**Description:** Colorless to faint yellow oily liquid with a slight aromatic odor

**Melting point:** $-35^0C$

**Boiling point:** $340^0C$

**Partition coefficient:** log P 4.72

**Relative density:** 1.045 g/cm3 at $20^0C$

**Solubility:**

It is almost insoluble in water but miscible with most common organic solvents. Very soluble in alcohol, ether, acetone & benzene.

**Storage:**

Stored in a tightly closed container in a cool dry well-ventilated place. Optimum storage temperature is between $2^0$C-$8^0$C.

**Functional category:**

- Plasticizer
- Anti foaming agent
- Ectoparasiticide
- Additives or adhesives or printing inks
- Putative endocrine disruptor
- Gelling aid

**Applications in pharmaceutical formulations and technology:**

The primary use of DBP is as a plasticizer in polyvinyl acetate emulsions. It is used in combination with other plasticizers in PVC applications to increase flexibility and workability. It is also found in fiberglass and rubbers. DBP is further used as plasticizers in adhesives, paints, lacquers and grouts. It is also used as a solvent in a number of other miscellaneous application and as a medium for reactions in a number of chemical processes for the manufacture of other substances. It is also used as an additive to adhesives or printing inks. DBP is used as an ectoparasiticide & also a putative endocrine disruptor. It is found in soil, air, water, plants and animals. DBP can also be used as a gelling aid, as a solvent, as an antifoam agent or as a lubricant. Its properties as lubricant are used in particular in textile manufacturing. DBP is also used in the coatings industry as a primary plasticizer solvent for nitrocellulose lacqers.

# MATERIALS AND EQUIPMEMTS

**Table 5 List of materials used**

| Materials | Source |
|---|---|
| Almotriptan Malate | Azakem Laboratories, Hyderabad |
| HPMC K 15M | Yarrow Chem Products, Mumbai |
| ERS 100 | Yarrow Chem Products, Mumbai |
| EC | Hi Media Laboratories Pvt. Ltd, Mumbai |
| PEG 400 | Hi Media Laboratories Pvt. Ltd, Mumbai |
| DBP | SDFCL, Mumbai |
| DCM | Qualigens Fine Chemicals, Mumbai |
| Methanol | SDFCL, Mumbai |
| Glycerin | PAXMY Speciality Chemicals, Chennai |

**Table 6 List of equipments used**

| Equipments | Model / Company |
|---|---|
| Circular moulds | Borosil Glass Works LTD. |
| Digital balance | Sri Mahalakshmi Scientific Co., Coimbatore |
| Digital micrometer | Aerospace |
| Franz diffusion cell | Self – fabricated |
| FT – IR spectrophotometer | Jasco FTIR 4100 |
| Heating mantle | Guna Enterprises, Chennai |
| Hot air oven | Inlab Equipment (Madras) Pvt. Ltd. |
| Magnetic stirrer | Remi Motors |
| pH meter | Systronics, Ahmadabad |
| UV - Visible spectrophotometer | Jasco v 530 |

# EXPERIMENTAL METHODS

## PREFORMULATION STUDIES

The aim of preformulation study is to generic information useful to the formulator in developing stable and bioavailable dosage form. The use of preformulation parameter maximizes the chances in formulation for an acceptable, safe, efficacious and stable product and at the same time provides the basis for optimization of the drug product quality.

### Solubility Profile of Almotriptan Malate

The solubility of Almotriptan Malate was tested in various solvents. A definite quantity (10mg) of drug was dissolved in 10ml of each solvent at room temperature. The solubility was observed by visual inspection.

### Development of Calibration Curve of Almotriptan Malate

**Preparation of pH 6.5 Phosphate Buffer** (IP 2007 Vol 1)

Dissolved 60.5g of disodium hydrogen phosphate and 46g of potassium dihydrogen phosphate in water; 100ml of 0.02M disodium edetate and 20mg of mercuric chloride was added and was diluted with water to produce 1000ml.

### Calibration Curve of Almotriptan Malate

100mg of Almotriptan Malate was accurately weighed into 100ml volumetric flask and dissolved in methanol. The volume was made up to 100ml with pH 6.5 phosphate buffer solution to get a concentration of 1000µg/ml. From this 10ml was withdrawn and diluted to 100ml with pH 6.5 phosphate buffer solution to get a concentration of 100µg /ml. From this standard stock solution 0.2ml, 0.4ml, 0.5ml, 0.8ml and 1ml were withdrawn and volume was made up to using pH 6.5 phosphate buffer solution to get a concentration of 2, 4, 6, 8 and 10µg/ml. Absorbance of these solutions were measured against blank of pH 6.5 phosphate buffer solution at 227nm.

**Compatibility Studies of Drug & Excipients** (Sagar S.Jadhav *et al*., 2013)

The FTIR studies were carried out by KBr disc pellet method. 10mg of the samples and 400mg of KBr were taken in a mortar and triturated. A small amount of the triturated sample was taken into the pellet marker. It was compressed at 10kg /cm² using a hydraulic press. The pellet was taken on the sample holder. It was then scanned from 4000$cm^{-1}$ to 400$cm^{-1}$ in FTIR spectrophotometer. Samples were prepared for drug and excipients also. The spectra obtained were compared and interrupted for functional group peaks.

**FORMULATION OF ALMOTRIPTAN MALATE LOADED TRANSDERMAL PATCHES** (Prabhakar *et al.,* 2014)

In the present study, matrix-type transdermal patches of Almotriptan Malate for its low (6.25mg) and high dose (12.5mg) were prepared by solvent evaporation technique. A glass mould of diameter 9.6cm having surface area 72.34cm$^2$ were used for casting the patches. The total amount of drug to be loaded in the patch was calculated by measuring the total area of the petri dish in which the patch will be casted.

**Almotriptan Malate Loaded HPMC K 15M - ERS 100 Transdermal Patches**

Polymeric solutions of HPMC K 15M and ERS 100 were prepared using DCM and methanol in 1:1 ratio (20ml) and specified amount of Almotriptan Malate and DBP were added and stirred well in a magnetic stirrer for 30min to get a homogenous solution. 5 ml of the casting solution was poured into glass a mould which was lubricated with glycerin; entrapped air bubbles were removed and dried at room temperature for 24hours for solvent evaporation. The rate of solvent evaporation was controlled by inverting a glass funnel over the petriplate. After 24hours the patches were removed by peeling and cut into circle of radius 2.1cm having surface area 13.85cm$^2$. These patches were kept in desiccator for 2 days for further drying and wrapped in aluminium foil, packed in self-sealing covers. Same procedure was followed for preparing transdermal patches of high dose of Almotriptan Malate.

**Table 7 Composition of formulations A1 & A2**

| Ingredient | | Quantity | |
|---|---|---|---|
| | | **Formulation A1** | **Formulation A2** |
| Drug | Almotriptan Malate | 6.25 mg | 12.5 mg |
| Polymers | HPMC K 15 M | 400 mg | 400 mg |
| | ERS 100 | 600 mg | 600 mg |
| Plasticizer | DBP | 0.8 ml | 0.8 ml |
| Solvent | DCM | 10 ml | 10 ml |
| | Methanol | 10 ml | 10 ml |

**Drug Loaded HPMC K 15M – EC Transdermal Patches**

Matrix patches containing Almotriptan Malate were prepared by dissolving polymers HPMC K15M and EC in suitable solvents namely DCM and methanol. PEG 400 is used as plasticizer. The beakers were kept on the magnetic stirrers for continuous stirring to get a homogenous solution. The solution was poured into a petri plate which was lubricated with glycerin and covered with a funnel in inverted position. The solvent was allowed to evaporate at ambient conditions for 24hours. After 24hours the patches were removed by peeling and cut into circle of radius 2.1cm having surface area 13.85cm$^2$. These patches were kept in desiccator for 2 days for further drying and wrapped in aluminium foil, packed in self-sealing covers. High dose of Almotriptan Malate were also prepared.

**Table 8 Composition of formulations B1 & B2**

| Ingredient | | Quantity | |
|---|---|---|---|
| | | **Formulation B1** | **Formulation B2** |
| Drug | Almotriptan Malate | 6.25 mg | 12.5 mg |
| Polymers | HPMC K 15M | 150 mg | 150 mg |
| | EC | 150 mg | 150 mg |
| Plasticizer | PEG 400 | 0.5 ml | 0.5 ml |
| Solvent | DCM | 10 ml | 10 ml |
| | Methanol | 10 ml | 10 ml |

**Drug Loaded HPMC K 15M Transdermal Patches**

The transdermal patches of Almotriptan Malate were prepared using HPMC K15M polymer by solvent evaporation method. 250mg of HPMC K15M polymer was weighed accurately and kept aside. The specified amount of the drug was weighed accurately and is dissolved in 20ml of distilled water. The beakers were kept for continuous stirring at room temperature. While stirring the polymer is added into the beaker slowly. As the drug & polymer both are hydrophilic in nature they get completely dissolved in solvent. PEG 400 is added to the solution. The whole solution was mixed thoroughly with the help of a magnetic stirrer for 30minutes. An inverted funnel was placed over the plate to avoid sudden evaporation. Then the petri plates were kept for 12 hours in hot air oven at $40^{o}$ C for drying & the dried patches were taken out, cut to a circle of radius 2.1 cm having surface area 13.85 $cm^2$ and preserved in aluminum foil for further studies. Same composition was used for the other dose of the drug.

**Table 9 Composition of formulations C1 & C2**

| Ingredient | | Quantity | |
|---|---|---|---|
| | | **Formulation C1** | **Formulation C2** |
| Drug | Almotriptan Malate | 6.25 mg | 12.5 mg |
| Polymers | HPMC K 15M | 250 mg | 250 mg |
| Plasticizer | PEG 400 | 1 ml | 1 ml |
| Solvent | Water | 20 ml | 20 ml |

**CHARACTERIZATION OF ALMOTRIPTAN MALATE LOADED**

**TRANSDERMAL PATCHES** (Ashok *et al.,* 2010)

**Physical Appearance**

All the prepared patches were visually inspected for colour, clarity, flexibility and smoothness.

**Thickness**

The thicknesses of the drug loaded patches were measured at 3 different points by using a digital micrometer and the mean value was calculated.

**Folding Endurance**

The folding endurance was measured manually for the prepared patches. The prepared drug loaded patches were folded until it breaks or it develops cracks.

**Drug Content**

An area of the films was cut and was dissolved in sufficient quantity of methanol. The solvent is selected in which the drug is freely soluble. The medium was stirred with a Teflon coated magnetic bead at 500rpm for 24 hrs. The solution was filtered through a Whatmann filter paper. After filtration, the absorbance of the diluted solution was measured spectrophotometrically with proper dilution at wavelength of 227nm against the reference solution consisting of placebo films (contains no drug) and the drug content in the film was calculated.

**Weight Uniformity**

The prepared patches are dried at 60°C for 4hrs before testing. Weight variation is studied by individually weighing 5 randomly selected patches from each formulation and calculating the average weight. The weights were taken in an electronic digital balance. The individual weight should not deviate significantly from the average weight.

**Surface pH**

Surface pH of the patch was determined by allowing them to swell in closed petridish at room temperature for 1hr in 0.5 ml of double distilled water. The surface pH was then noted by bringing a combined glass electrode near the surface of the patch and allowing it to equilibrate for 1 minute.

**Swellability**

The patches of specific area was weighed and put in a petridish containing 10 ml of double distilled water and were allowed to imbibe. Increase in weight of the patch was determined at preset time intervals, until a constant weight was observed.

The degree of swelling (S) was calculated using the formula:

$$S\ (\%) = \frac{Wt - Wo}{Wo} X100$$

Where S is the percent swelling

$W_t$ is the weight of patch at time t

$W_o$ is the weight of patch at time zero

**Percentage Moisture Absorption**

The films were weighed accurately and kept in a desiccator containing anhydrous calcium chloride. After 3 days, the films were taken out and reweighed. The study was performed at room temperature.

The moisture uptake/ absorption was calculated using the formula:

$$Percentage\ moisture\ uptake = \frac{\text{Final weight - Initial weight}}{\text{Initial weight}} X100$$

**Percentage Moisture Loss**

The films were weighed accurately and placed in the desiccator containing 100ml of saturated solution of potassium chloride, which maintains 80-90% RH. After 3 days, the films were taken out and reweighed. The study was performed at room temperature.

The moisture content/ loss was calculated using the formula:

$$\textit{Percentage moisture content} = \frac{\text{Initial weight - Final weight}}{\text{Final weight}} X 100$$

**Water Vapour Transmission Rate**

Glass vials of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried to a constant weight in an oven. About 1 g of fused calcium chloride as a desiccant was taken in the vials and the polymeric patches were fixed over the brim with the help of an adhesive tape like silicon adhesive grease and the adhesive was allowed to set for 5 minutes. Then, the vials are accurately weighed. These preweighed vials were stored in a desiccator containing saturated solution of potassium chloride to maintain 84% RH. The vials are again weighed at the end of every 1st day, 2nd day, 3rd day up to 7 consecutive days and an increase in weight was considered as a quantitative measure of moisture transmitted through the patch.

The rate of water vapor transmitted was calculated using following formula:

$$WVTR = (W_f - W_I) / (A \times T) \times 100$$

Where $W_f$ is the final weight

$W_I$ is the initial weight

A is the area of film exposed ($cm^2$)

T is the exposure time

***In-Vitro* Drug Release Study**

*In-vitro* permeation studies were performed through dialysis membrane-50 (Hi Media) by using self fabricated Franz diffusion cell apparatus with a cross sectional area of 13.84 $cm^2$. The Franz Diffusion cells used generally consists of donor (for placing drug or formulation) and receptor (for collecting drug samples) compartment. The diffusion cell consists of a sampling port and temperature maintaining jacket. The receptor compartment was filled with phosphate buffer pH 7.4 and it was stirred magnetically by placing small magnetic bead. The synthetic cellophane membrane was mounted between donor and receptor compartment of the diffusion cell.

The formulated patches were cut into size of 2.1 cm radius and placed over the drug release membrane in such a way that the drug releasing surfaces face towards the receptor compartment. The donor cell was fixed using clips. The whole assembly was fixed on a magnetic stirrer and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 rpm and was maintained at 37 ± 0.5° C by circulating the constant temperature water through outer jacket of the diffusion cells.

One ml of receptor solution was withdrawn at different time intervals over 12hours. The receptor phase was replenished with an equal volume of phosphate buffer pH 7.4 at each sample withdrawal . The samples were analyzed spectrophotometrically at 227 nm taking phosphate buffer pH 7.4 as blank. The cumulative percentage of drug permeated per square centimeter of patches at various time intervals were calculated and were plotted against time.

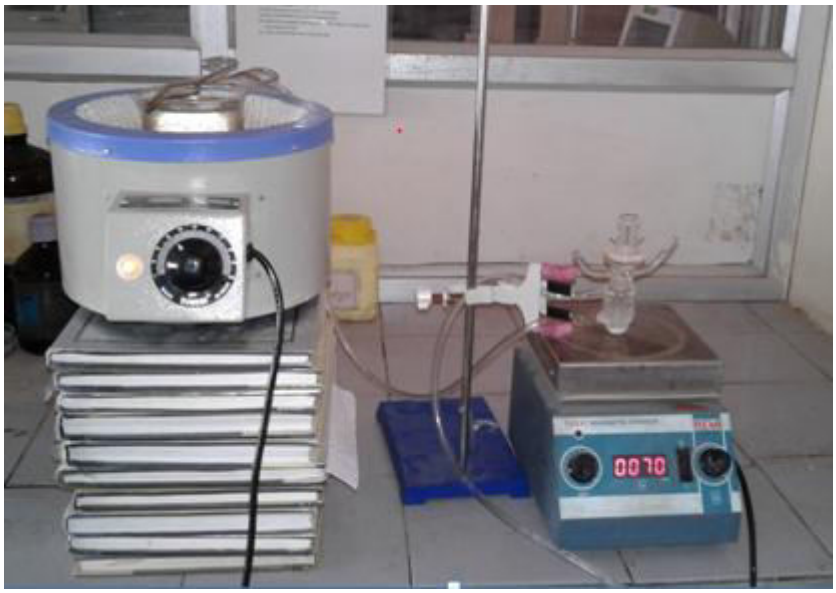


**Figure 6 Franz diffusion cell**

**EXPERIMENTAL STATISTICAL DESIGN** (Deore *Et Al.,* 2013)

Minitab 18 trial version was used for the effect of analysis of each variable on the designated response. Surface plots were made for the analysis of each response coefficient for its statistical significance. The significant polynomial equations were used to validate the statistical design.

From the above formulations prepared the best one was selected after their characterization and were subjected for experimental design & data analysis. In this design, 2 independent factors were evaluated, each at 2 levels and according to a $2^2$ factorial design and considering these two variables, 4 runs had been performed for both low and high doses of Almotriptan Malate. The different concentration of the polymers HPMC K 15M and ERS 100 were chosen as independent variables. Drug content, moisture absorption, moisture loss and cumulative % drug release at 12 hr were taken as dependent variables.

The effect of mixture component on dependent variables were modeled using the following equation

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_{12} + b_{22}X_{22}$$

Where Y is predicated response,

$b_0$ is the arithmetic mean of all responses,

$b_1$ & $b_2$ are the estimated coefficient for factors A & B respectively.

**Table 10 Independent factors selected for statistical optimization**

| Independent Factors | Levels | |
|---|---|---|
| | (-) | (+) |
| HPMC K 15M (A) | 400 mg | 600 mg |
| ERS 100 (B) | 400 mg | 600 mg |

**EFFECT ON AGING**

The effect of aging on physical appearance is studied by packing the best polymeric films in properly sealed aluminium foil and then storing them in a desiccator at 40±0.5°c and 75±5% RH for 60 days. The patches were then characterized for drug content and drug release study at regular intervals (0, 30 and 60 days).

***IN-VITRO* DRUG RELEASE KINETIC STUDY**

Drug release rate kinetics of Almotriptan Malate loaded transdermal patches was calculated by using a software, Microsoft Office Excel Add - In. The *in-vitro* drug permeation data obtained of optimized formulation was fitted to zero order kinetics (cumulative amount of drug released versus time), first order kinetics (log cumulative percentage of drug remaining vs. time), Higuchi model (cumulative percentage drug release versus square root of time), Korsmeyer-pappas model (log cumulative percentage drug release versus log time) to assess the kinetic modeling of drug release and the model with the higher correlation coefficient (i.e. higher $R^2$) was considered to be the best fit model (Allena *et al.,*2012).

# RESULTS & DISCUSSIONS

## PREFORMULATION STUDIES

### Solubility Profile of Almotriptan Malate

Solubility studies were carried out to select a suitable solvent to dissolve the drug and to select the dissolution medium.

**Table 11: Solubility studies**

| Solvent | Solubility |
|---|---|
| Water | Soluble |
| Phosphate buffer pH 6.5 | Soluble |
| Dichloromethane | Soluble |
| Methanol | Soluble |

### Development of Calibration Curve of Almotriptan Malate

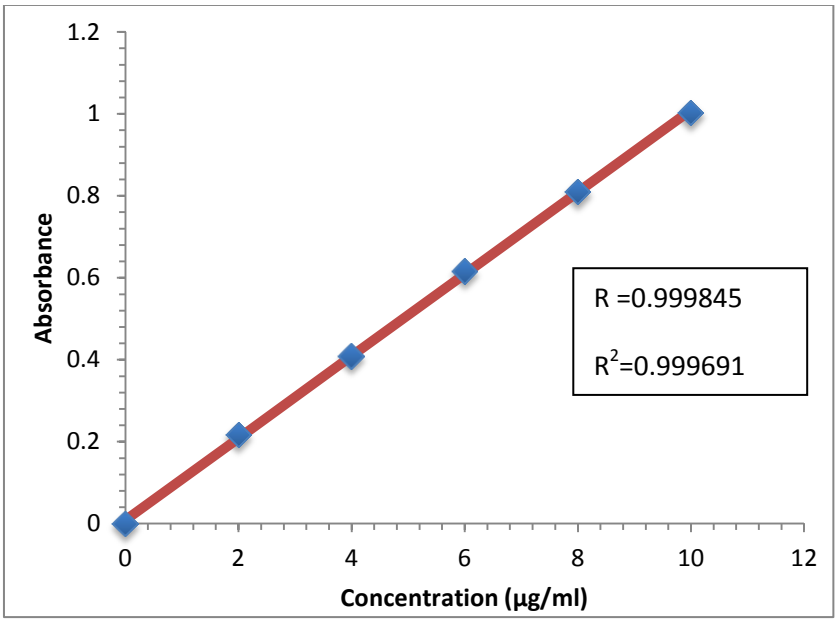
### Calibration Curve of Almotriptan Malate

In the validation studies, it was found that the estimation of Almotriptan Malate by spectrophotometric method at 227 nm has good reproducibility, at the concentration between 2-10 µg/ml. Correlation between concentration and absorbance was found to be 0.999845 which is closer to 1.

**Table 12 Calibration curve of Almotriptan Malate**

| Concentration (µg/ml) | Absorbance |
|---|---|
| 0 | 0 |
| 2 | 0.2166 |
| 4 | 0.4085 |
| 6 | 0.6155 |
| 8 | 0.8098 |
| 10 | 1.0031 |

**Graph 1 Calibration curve of Almotriptan Malate**



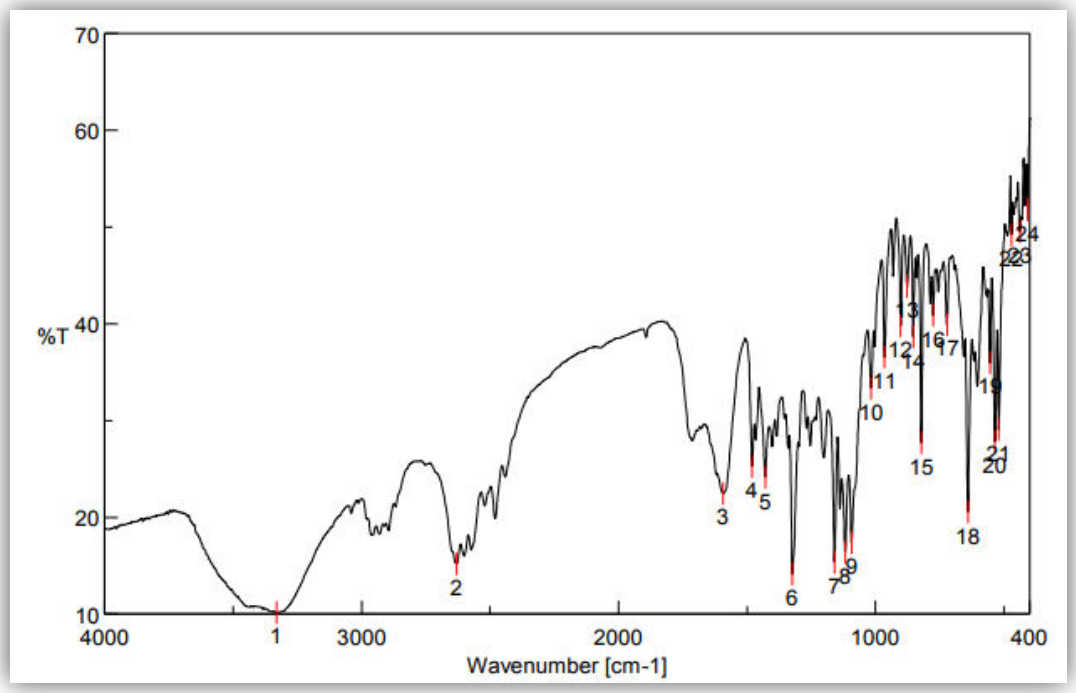

**Compatibility Studies of Drug & Excipients**

In the present study, physical mixture of Almotriptan Malate in solid form along with different polymers were prepared and analyzed by FTIR to find out the compatibility between the drug and polymers. The IR spectra of Almotriptan Malate along with the physical mixture of Almotriptan Malate with different polymers are shown from the graph 2-5, which showed that the drug and excipients are chemically compatible, as there were no abnormal peaks.

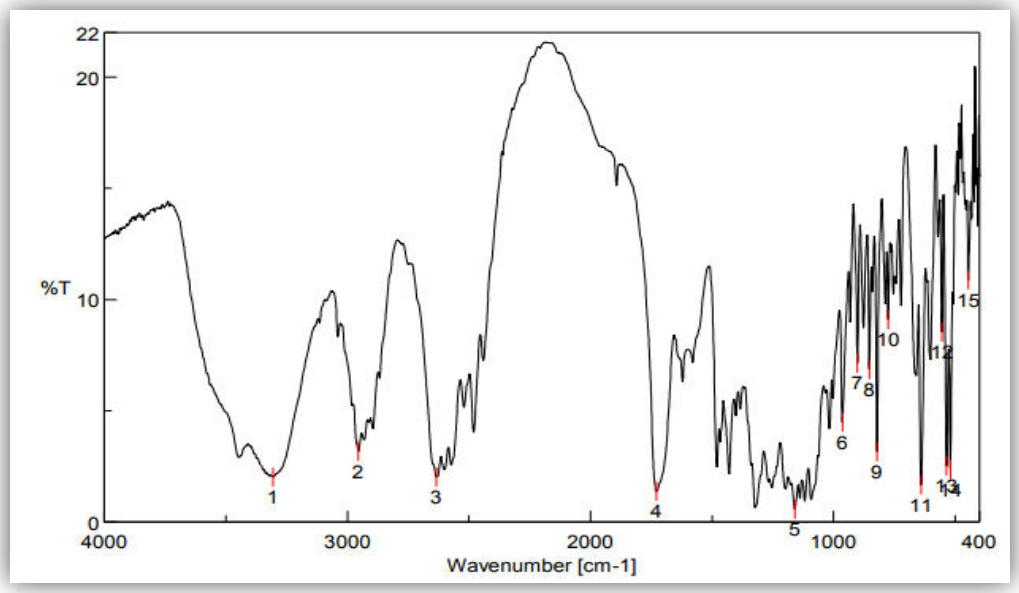
**Table 13 FTIR interpretation of Almotriptan Maleate**

| FTIR Interpretation of Drug Almotriptan Maleate | | | | | |
|---|---|---|---|---|---|
| **Samples** | **Functional group** | | **Type of vibration** | **Characteristic absorption ($cm^{-1}$)** | **Test absorption ($cm^{-1}$)** |
| Almotriptan Malate | CH | | Stretching | 2840-3000 | 2976.59 |
| | | | Bending | 1350-1480 | 1433.82 |
| | NH | | stretching | 3400-3500 | 3429.78 |
| | C=C | | | 1400-1600 | 1433.82 |
| | S=O | | | 1030-1060 | 1038.45 |
| | COOH | OH | | 2500-3300 | 2563.21 |
| | | C-O | | 1210-1320 | 1229.12 |

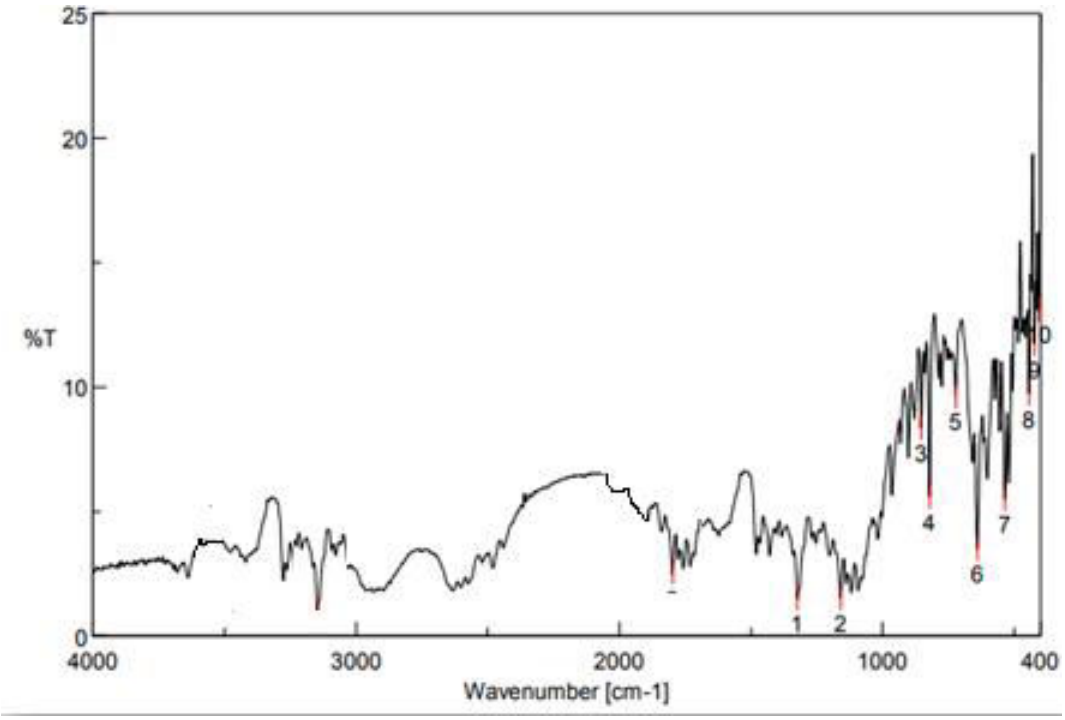
**Graph 2 FTIR of Almotriptan Malate**



**Graph 3 FTIR of Almotriptan loaded HPMC K15M - ERS 100 patches**




**Graph 4 FTIR of Almotriptan loaded HPMC K 15M - EC patches**



**Graph 5 FTIR of Almotriptan loaded HPMC K 15M patches**

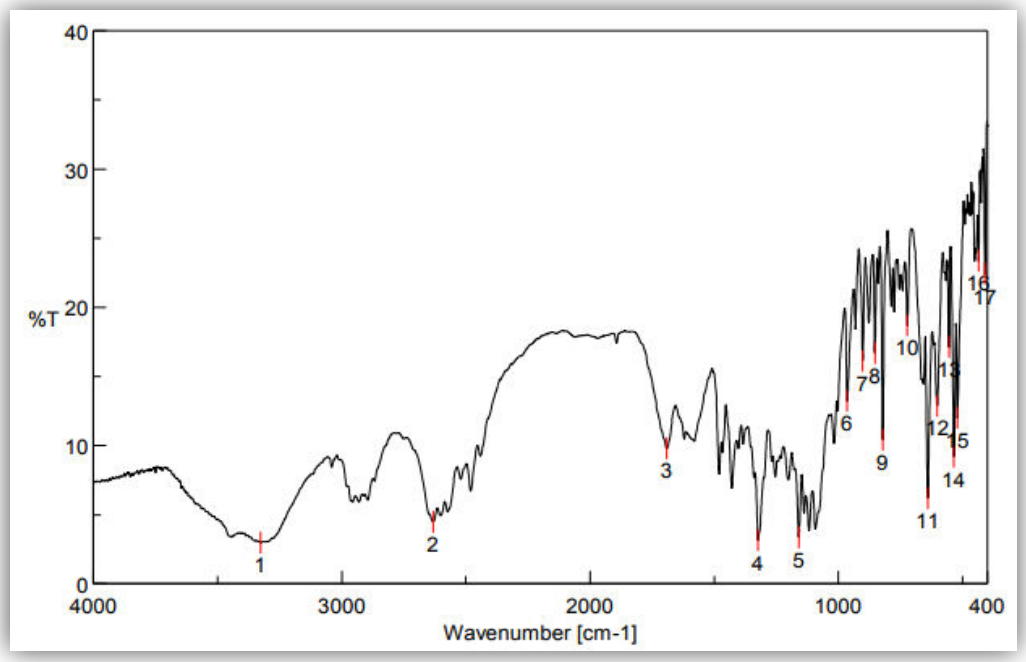


**Table 14 Comparison of FTIR data of drug and polymers in samples**

| Formulation components | Functional group | Characteristic absorption($cm^{-1}$) | Patch 1(HPMC K 15M-ERS 100) | Patch 2(HPMC K 15M-EC) | Patch 3(HPMC K 15M) |
|---|---|---|---|---|---|
| Almotriptan Malate | CH Stretching | 2840-3000 | 2954.41 | 2936.98 | 2782.36 |
| | CH Bending | 1350-1480 | 1728.87 | 1322.98 | 1322.93 |
| | NH Stretching | 3400-3500 | 3428.66 | 3499.45 | 3325.64 |
| | C=C | 1400-1600 | 1728.87 | 1586.67 | 1690.3 |
| HPMC K 15M | OH stretching | 3700-3584 | 3305.39 | 3566.34 | 3325.64 |
| | C-H stretching of alkyl group | 2840-2960 | 2954.41 | 2855.50 | 2632.36 |
| | C-H scissoring | 2695-2830 | 2633.32 | 2732.56 | 2632.36 |
| ERS 100 | OH stretching of COOH group | 2500-3300 | 3305.39 | - | - |
| | C-H stretching of alkane | 2890 | 2954.51 | - | - |
| | C=O stretching of carbonyl group | 1540-1870 | 1728.87 | - | - |
| EC | O-H stretching | 3200-3600 | - | 3325.64 | - |
| | C-H | 2700-3800 | - | 2632.36 | - |
| | C-O-C stretch | 1085-1150 | - | 1159.01 | - |
| | C=C | 1610-1660 | - | 1690.3 | - |

## FORMULATION OF ALMOTRIPTAN LOADED TRANSDERMAL PATCHES

**Calculation of total drug loading** (John *et al.*, 2014)

The formulation of the patch was made in such a way that each small circular patch of 2.1cm radius (which is the radius of the Franz diffusion cell) contains desired amount of the drug. The total amount of drug to be loaded in the patch was calculated by measuring the total area of the petri dish in which the patch will be casted. The calculation was done as follows;

***Total amount of drug to be loaded = (area of the petri dish in which the patch is moulded / area of small circular patch) × desired drug amount***

**Table 15 Calculation of total amount of drug to be loaded**

| Desired drug content | 6.25 mg | 12.5 mg |
|---|---|---|
| Area of the small circular patch (which is the area of Franz diffusion cell) | 13.8474cm $^2$ | 13.8474cm $^2$ |
| Area of the petri dish in which the patch is moulded | 72.3456 cm$^2$ | 72.3456 cm$^2$ |
| Total amount of drug to be loaded | (72.3456 / 13.8474) × 6.25 = 32.65mg | (72.3456 / 13.8474) × 12.5 = 65.31mg |

Hence 32.65 mg and 65.31 mg of the drug were added in each formulation in order to get 6.25 mg and 12.5 mg per small circular patch respectively.

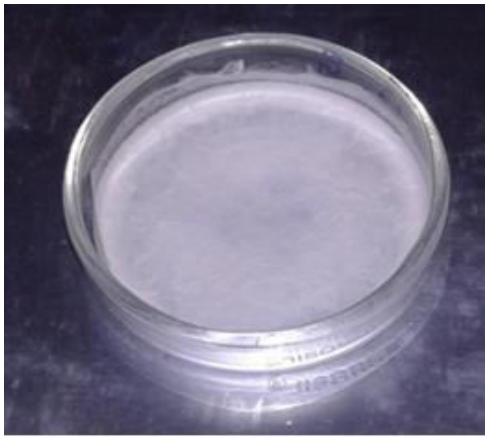


**Figure 7 Prepared formulation A1**

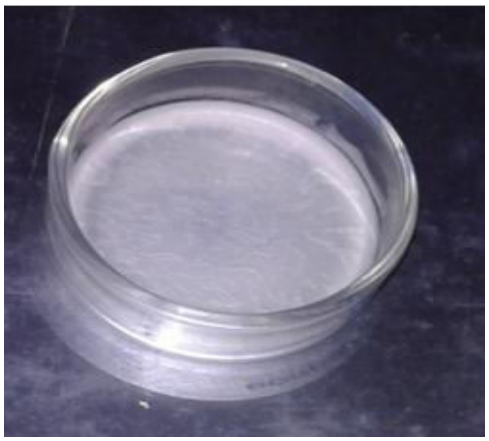


**Figure 8 Prepared formulation A2**

**Figure 9 Prepared formulation B1**

**Figure 10 Prepared formulation B2**

**Figure 11 Prepared formulation C1**

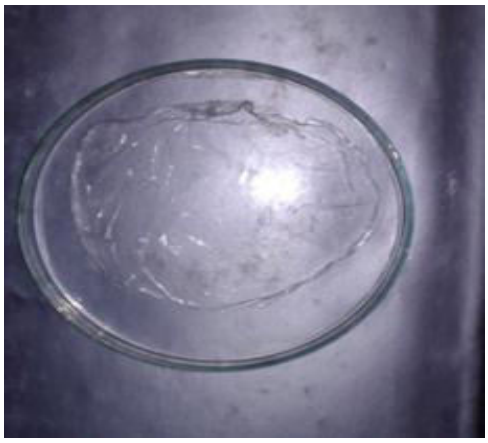


**Figure 12 Prepared formulation C2**

## CHARACTERIZATION OF ALMOTRIPTAN LOADED TRANSDERMAL PATCHES

Transdermal patches of Almotriptan Malate were successfully prepared by solvent casting technique using HPMC K 15M as the hydrophilic polymer, ERS 100 and EC as the hydrophobic polymer and DBP & PEG 400 as plasticizer. All the prepared formulations were evaluated for physicochemical characteristics, *in-vitro* drug release studies and *in-vitro* drug release kinetic studies.

### Physical Appearance

Physical appearances of the films were evaluated. All the films were easily removable from the mould without any recrystallization. All the systems were thin, flexible, smooth and without the entrapment of air but formulation having only the polymer HPMC K 15M were found to be clear and transparent. The method adopted for casting the systems was found satisfactory.

**Table 16 Physical characters of formulated transdermal patches**

| Formulation | Formulation code | Evaluation Parameters | | | |
|---|---|---|---|---|---|
| | | Colour | Flexibility | Smoothness | Stickiness |
| Almotriptan loaded HPMC – ERS100 patches | F A1 | White | Flexible | Smooth | Non - sticky |
| | F A2 | White | Flexible | Smooth | Non - sticky |
| Almotriptan loaded HPMC – EC patches | F B1 | White | Flexible | Smooth | Non - sticky |
| | F B2 | White | Flexible | Smooth | Non - sticky |
| Almotriptan loaded HPMC patches | F C1 | Clear & transparent | Flexible | Smooth | Sticky |
| | F C2 | Clear & transparent | Flexible | Smooth | Sticky |

### Thickness

Thickness of each film of all formulation was found to be uniform. Thickness ranged from 0.103 mm to 0.332 mm.

**Folding Endurance**

Folding endurance test results indicated that the patches did not show any cracks even after folding 300 times and thus showing good elasticity, maintaining the integrity with general skin folding.

The folding endurance measures the ability of patch to withstand rupture.

**Drug Content**

Drug content in each small circular patches were analyzed spectrophotometrically and it was observed that all the formulations showed a satisfactory drug content values ranging from 88 – 99% ensures the uniform reproducible sustained release of the drug from the patch.

**Weight Uniformity**

From each batch, the weight of five patches was taken on a digital balance. It was observed that weight of the entire film sample in each formulation was uniform.

**Surface pH**

The surface pH for all the formulations was well within the optimum range of 5-6 and hence no skin irritation was expected to occur after applications of the patches.

**Table 17 Physical characteristics of formulated transdermal patches**

| Formulation | Formulation code | Evaluation Parameters | | | | |
|---|---|---|---|---|---|---|
| | | Thickness (mm) | Folding endurance | Drug content (%) | Weight uniformity (mg) | Surface pH |
| Almotriptan loaded HPMC – ERS100 patches | F A1 | 0.232 | >300 | 99.85 | 350 | 5 |
| | F A2 | 0.334 | >300 | 98.92 | 480 | 5.11 |
| Almotriptan loaded HPMC – EC patches | F B1 | 0.128 | >300 | 95.77 | 370 | 5.88 |
| | F B2 | 0.256 | >300 | 96.8 | 450 | 5.24 |
| Almotriptan loaded HPMC patches | F C1 | 0.128 | >300 | 88.58 | 230 | 6 |
| | F C2 | 0.116 | >300 | 94.43 | 300 | 6.14 |

**Swellability**

The percentage of swelling of Almotriptan Malate loaded HPMC K 15M-ERS 100 patches was around 30 and the other formulations also showed considerable swelling. Hydrophilic polymer showed considerable swelling, as it increased the surface wettability and consequently water penetration within the matrix.

In the swelling study it was observed that as time increased, the swelling index was also increased, because weight gain by patch was increased proportionally with the rate of hydration up to certain time. The consequence of water uptake could be the formation of empty spaces within the patch that could make its structure less resistant to mechanical stresses.

**Percentage Moisture Absorption**

Percentage moisture absorption for HPMC-ERS 100, HPMC-EC and HPMC alone was found in the range of 14.72 %, 9.5 % and 4.94% respectively; this may be due to hydrophilic and hydrophobic nature of the polymer.

The lower moisture content in the formulations made the patches to remain stable and become a completely dried and brittle film and also protects the material from microbial contamination and bulkiness (Ashok *et al.,* 2010).

**Percentage Moisture Loss**

From moisture loss study it was found that formulation showed maximum amount of moisture loss due to HPMC K 15M as it undergo moisture loss in dry condition. Inspite of the moisture loss, patches were found to maintain their physical stability.

The low percentages of moisture loss help them to remain stable and free from completely drying and brittle (Ashok *et al.,* 2010).

**Water Vapour Transmission Rate**

Patches having ERS 100 as the hydrophobic polymer showed least transmission rate than that of patches with EC. All the formulations were permeable to water vapour. Low water vapor transmission rate also indicates high degree of stability even in high humid conditions (Ashok et al., 2010).

**Table 18 Physico-chemical characteristics of formulated transdermal films**

| Formulation | Formulation code | Evaluation Parameters | | | |
|---|---|---|---|---|---|
| | | Swellability (%) | % Moisture Loss (%) | % Moisture Absorbed (%) | WVTR ($g/h/cm^2$) |
| Almotriptan loaded HPMC – ERS100 patches | F A1 | 28.76 | 6.42 | 14.72 | $2.97\times10^{-4}$ |
| | F A2 | 30.4 | 5.4 | 11.75 | $3.8\times10^{-4}$ |
| Almotriptan loaded HPMC – EC patches | F B1 | 16.78 | 4.35 | 9.6 | $5.25\times10^{-4}$ |
| | F B2 | 20 | 3.56 | 5.87 | $4.7\times10^{-4}$ |
| Almotriptan loaded HPMC patches | F C1 | 20.98 | 4.28 | 4.94 | $5.98\times10^{-4}$ |
| | F C2 | 29.54 | 4.51 | 3.334 | $6.25\times10^{-4}$ |

### *In-Vitro* Drug Release Study

The cumulative percent drug release was higher in case of Eudragit containing polymer matrix as it released 3.39 $mg/cm^2$ /12 hrs and 6.08 $mg/cm^2$ /12 hrs for low dose (6.25 mg) & high dose (12.5 mg) of Almotriptan Malate. The reason for high release from ERS 100 polymer could be explained by the hydrophobic nature of this polymer and the existence of the quaternary ammonium groups which could affect the release from the patches because of the hydration and swelling of the patches. Eudragit (Polymethyl methacrylate) is known to have larger cavity size in its polymeric network and thus it may involve a faster mode of diffusion of Almotriptan Malate from the ERS 100: HPMC K 15M formulations as compared to the EC: HPMC K 15M formulations.

Release of the drug from transdermal patches is controlled by the chemical properties of the drug and delivery form, as well as physiological and physicochemical properties of the biological membrane. The process of drug release in most controlled release devices is governed by diffusion and the polymer matrix has strong influence on the diffusivity as the motion of a small molecule is restricted by the three-dimensional network of polymer chains.

**Table 19 Cumulative drug release profile for Almotriptan Malate loaded HPMC K 15M-ERS 100 patches.**

| Time (hr) | Cumulative Amount of Drug Released (mg) | | Cumulative Percentage Amount of Drug Released (%) | |
|---|---|---|---|---|
| | Formulation A1 | Formulation A2 | Formulation A1 | Formulation A2 |
| 1 | 0.12 | 0.19 | 1.98 | 1.52 |
| 2 | 0.25 | 0.37 | 4.02 | 2.99 |
| 3 | 0.77 | 1.34 | 12.33 | 10.78 |
| 4 | 1.63 | 2.54 | 26.16 | 20.32 |
| 5 | 1.89 | 3.28 | 30.32 | 26.31 |
| 6 | 2.16 | 3.75 | 34.64 | 30.01 |
| 7 | 2.37 | 4.00 | 38.02 | 32.02 |
| 8 | 2.62 | 4.51 | 42.06 | 36.12 |
| 9 | 3.02 | 5.0 | 48.32 | 40.23 |
| 10 | 3.14 | 5.5 | 50.25 | 44.03 |
| 11 | 3.26 | 5.7 | 52.31 | 46.2 |
| 12 | 3.39 | 6.0 | 54.26 | 48.3 |

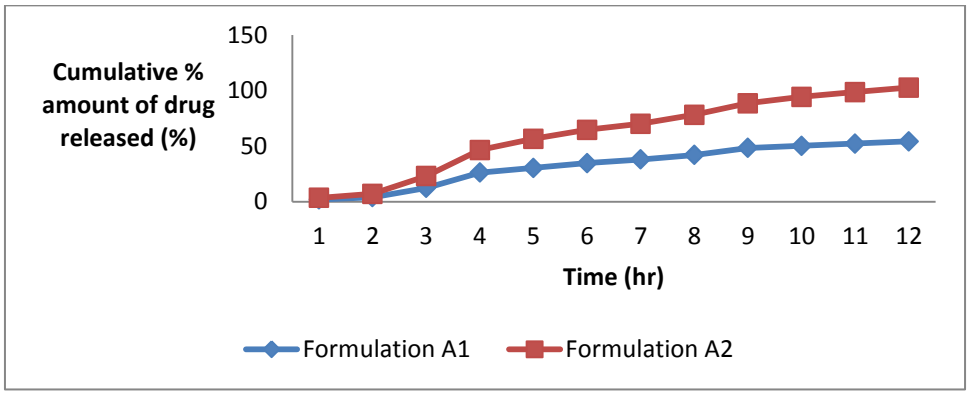
**Table 20 Cumulative drug release profile for Almotriptan Malate loaded HPMC K 15M-EC patches**

| Time (hr) | Cumulative Amount of Drug Released (mg) | | Cumulative Percentage Amount of Drug Released (%) | |
|---|---|---|---|---|
| | Formulation B1 | Formulation B2 | Formulation B1 | Formulation B2 |
| 1 | 0.12 | 0.22 | 1.86 | 1.82 |
| 2 | 0.31 | 0.45 | 4.96 | 3.62 |
| 3 | 0.67 | 1.04 | 10.86 | 8.38 |
| 4 | 1.58 | 2.79 | 25.32 | 22.32 |
| 5 | 1.92 | 3.58 | 30.85 | 28.68 |
| 6 | 2.02 | 3.91 | 32.32 | 31.33 |
| 7 | 2.41 | 4.27 | 38.62 | 34.23 |
| 8 | 2.56 | 5.07 | 41 | 40.62 |
| 9 | 2.73 | 5.14 | 43.68 | 41.12 |
| 10 | 2.85 | 5.27 | 45.63 | 42.23 |
| 11 | 2.89 | 5.44 | 46.32 | 43.52 |
| 12 | 2.97 | 5.54 | 47.63 | 44.35 |

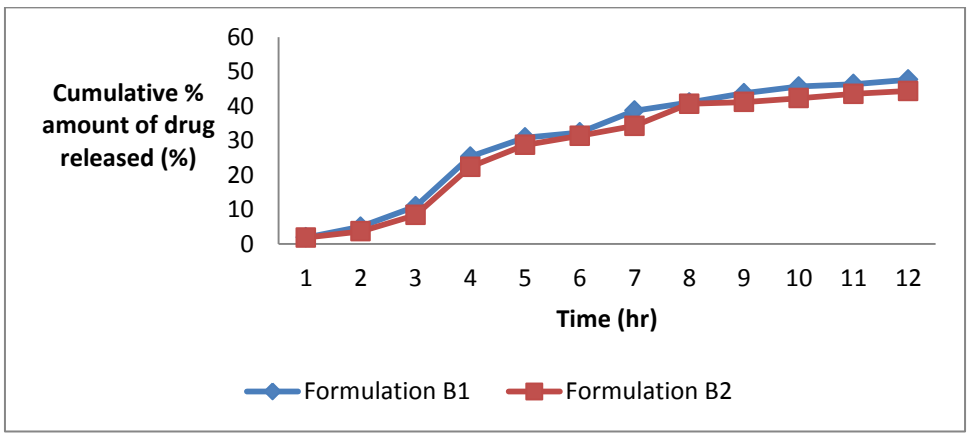
**Table 21 Cumulative drug release profile for Almotriptan Malate loaded HPMC K 15M patches**

| Time (hr) | Cumulative Amount of Drug Released (mg) | | Cumulative Percentage Amount of Drug Released (%) | |
|---|---|---|---|---|
| | Formulation C1 | Formulation C2 | Formulation C1 | Formulation C2 |
| 1 | 0.08 | 0.16 | 1.37 | 1.28 |
| 2 | 0.21 | 0.4 | 3.46 | 3.2 |
| 3 | 0.39 | 0.535 | 6.28 | 4.28 |
| 4 | 0.98 | 1.765 | 15.68 | 14.12 |
| 5 | 1.40 | 2.27 | 22.45 | 18.18 |
| 6 | 1.58 | 2.53 | 25.32 | 20.25 |
| 7 | 1.68 | 3.02 | 26.98 | 24.23 |
| 8 | 2.12 | 3.5 | 33.98 | 28.12 |
| 9 | 2.45 | 4.01 | 39.29 | 32.12 |
| 10 | 2.51 | 4.27 | 40.25 | 34.23 |
| 11 | 2.66 | 4.79 | 42.68 | 38.32 |
| 12 | 2.83 | 5.16 | 45.36 | 41.28 |

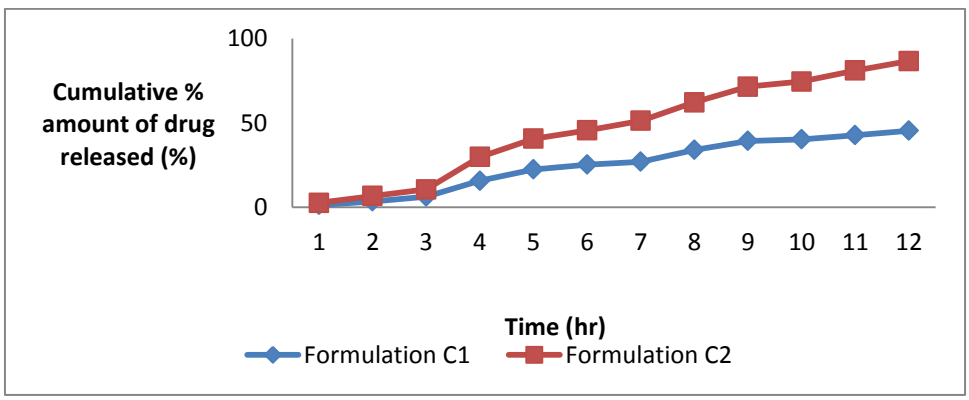
**Graph 6 Cumulative drug release profile for Almotriptan Malate loaded HPMC K 15M-ERS 100 patches**




**Graph 7 Cumulative drug release profile for Almotriptan Malate loaded HPMC K 15M-EC patches**




**Graph 8 Cumulative drug release profile for Almotriptan Malate loaded HPMC K 15M patches**



**EXPERIMENTAL STATISTICAL DESIGN**

The aim of present work was to achieve optimized formulations for Almotriptan loaded transdermal patches by determining the effects of some important factors (variables) and their interactions during the process of preparation. Among all combinations HPMC K 15M:ERS 100 loaded with Almotriptan Malate gave better results. Hence these formulations were selected and incorporated in $2^2$ factorial design and evaluated for further studies. Two of the most significant factors (concentration of HPMC K 15M and ERS 100) had been chosen as the independent variables. In the next step, for determining the low and high levels of each factor, some formulations were made. According to a $2^2$ factorial design and considering these two variables, 4 experiments each for low and high doses of Almotriptan had been performed. The effect of these variables on drug content, moisture absorption, moisture loss and cumulative amount of drug release at 12 hr were investigated as optimization response parameters in the current study.

**Table 22 $2^2$ full factorial experimental design layout for low dose (6.25 mg) of Almotriptan Malate**

| Formulation Code | HPMC K 15M (mg) (A) | E RS100 (mg) (B) | Drug Content (%) | Moisture Absorption (%) | Moisture Loss (%) | Cumulative % Drug Release At 12hr (%) |
|---|---|---|---|---|---|---|
| F1 | 600 | 400 | 98.89 | 13.36 | 7.42 | 45.50 |
| F2 | 400 | 600 | 99.85 | 14.72 | 6.42 | 54.26 |
| F3 | 600 | 600 | 99.90 | 16.8 | 8.6 | 45.71 |
| F4 | 400 | 400 | 99.00 | 10.43 | 5.432 | 50.33 |

**Table 23 $2^2$ full factorial experimental design layout for high dose (12.5 mg) of Almotriptan Malate**

| Formulation Code | HPMC K 15M (mg) (A) | E RS100 (mg) (B) | Drug Content (%) | Moisture Absorption (%) | Moisture Loss (%) | Cumulative % Drug Release At 12hr(%) |
|---|---|---|---|---|---|---|
| F5 | 600 | 400 | 97.90 | 15.9 | 6.1 | 36.80 |
| F6 | 400 | 600 | 98.92 | 11.75 | 5.4 | 48.30 |
| F7 | 600 | 600 | 98.90 | 17.4 | 7.9 | 39.56 |
| F8 | 400 | 400 | 98.20 | 10.56 | 3.9 | 44.72 |

**The polynomial equations for the dependent responses of low dose (6.25 mg) of Almotriptan Malate are as follows:**

| | | |
|---|---|---|
| Drug content | = | 98.16 - 0.002150 HPMC K 15M + 0.002650 ERS 100 + 0.000004 HPMC K 15M*ERS 100 |
| Moisture absorption | = | -7.410 + 0.02315 HPMC K 15M + 0.02995 ERS 100 - 0.000021 HPMC K 15M*ERS 100 |
| Moisture loss | = | 0.2480 + 0.008020 HPMC K 15M + 0.003020 ERS 100 + 0.000005 HPMC K 15M*ERS 100 |
| Cumulative % drug release | = | 37.25 + 0.01305 HPMC K 15M + 0.05685 ERS 100 - 0.000093 HPMC K 15M*ERS 100 |

**The polynomial equations for the dependent responses of high dose (12.5 mg) of Almotriptan Malate are as follows:**

| | | |
|---|---|---|
| Drug content | = | 98.48 - 0.004300 HPMC K 15M + 0.000800 ERS 100 + 0.000007 HPMC K 15M*ERS 100 |
| Moisture absorption | = | -1.260 + 0.02360 HPMC K 15M + 0.002850 ERS 100 + 0.000008 HPMC K 15M*ERS 100 |
| Moisture loss | = | -2.300 + 0.008000 HPMC K 15M + 0.004500 ERS 100 + 0.000007 HPMC K 15M*ERS 100 |
| Cumulative % drug released | = | 50.12 - 0.03140 HPMC K 15M + 0.02610 ERS 100 - 0.000020 HPMC K 15M*ERS 100 |

**Fig.13 : Surface Plot for low Dose (6.25 mg) of Almotriptan Malate**

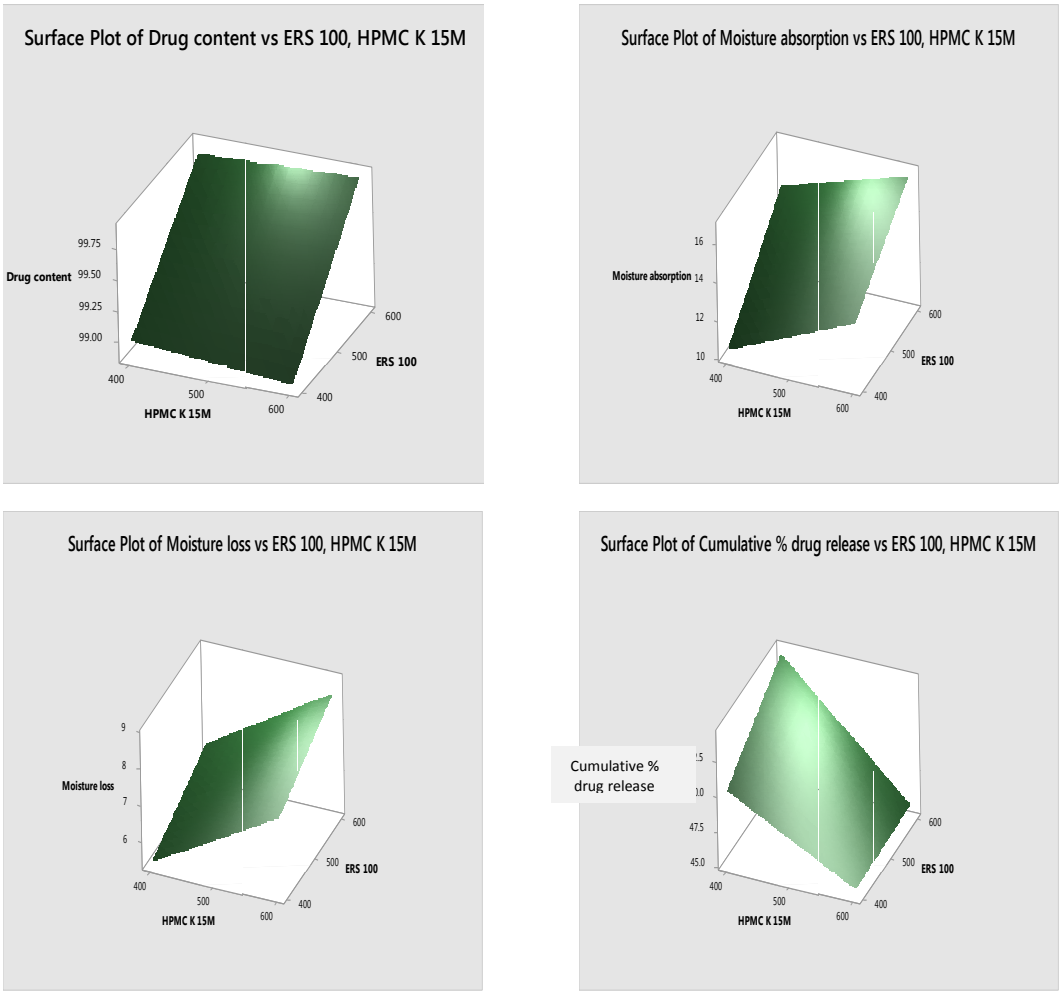
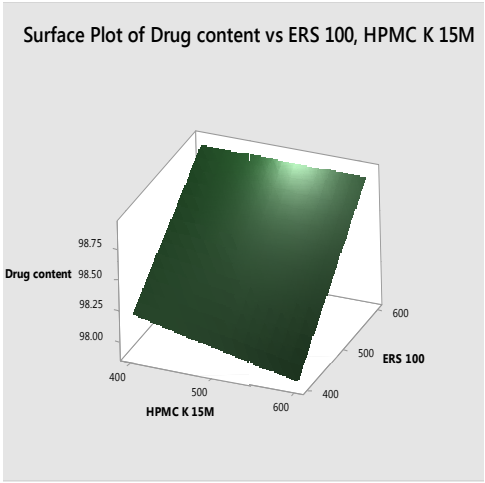
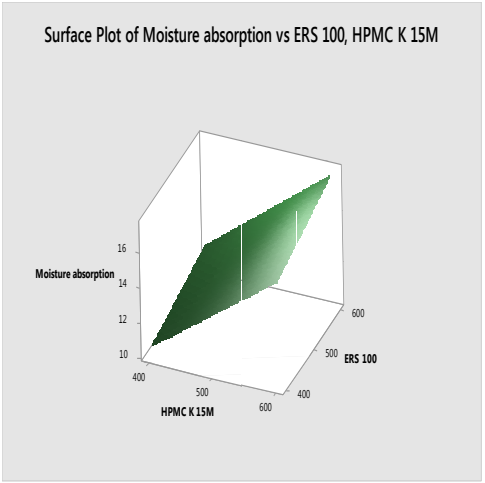
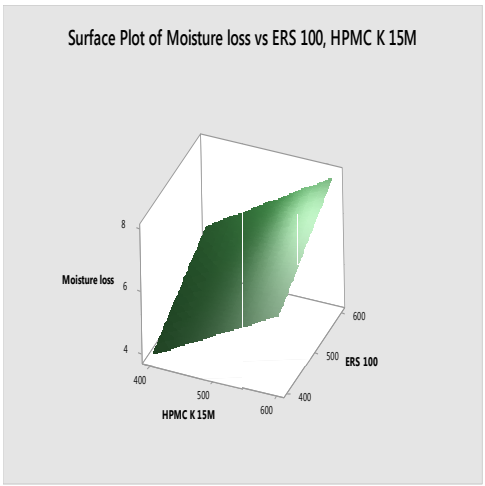
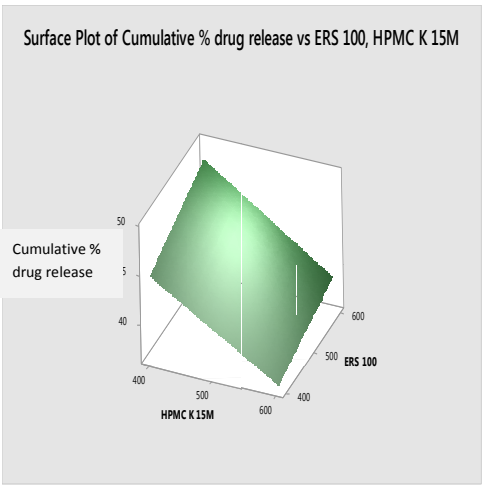



**Fig.14 : Surface Plot for high dose ( 12.5 mg) of Almotriptan Malate**


Surface Plot of Drug content vs ERS 100, HPMC K 15M
Drug content
98.75
98.50
98.25
98.00
400
500
600
HPMC K 15M
400
500
600
ERS 100


Surface Plot of Moisture absorption vs ERS 100, HPMC K 15M
Moisture absorption
16
14
12
10
400
500
600
HPMC K 15M
400
500
600
ERS 100


Surface Plot of Moisture loss vs ERS 100, HPMC K 15M
Moisture loss
8
6
4
400
500
600
HPMC K 15M
400
500
600
ERS 100


Surface Plot of Cumulative % drug release vs ERS 100, HPMC K 15M
Cumulative % drug release
400
500
600
HPMC K 15M
400
500
600
ERS 100

**EFFECT ON AGING**

Transdermal patches of the best formulated Almotriptan Malate patches was found to be physically and chemically stable and showed no significant change in terms of physical characteristics, surface pH, folding endurance, percentage drug content and percentage drug release. It is evident from the stability study that the films are stable under normal shelf-conditions. There were no significant physical and chemical changes in the optimized batch after 2 months. Elasticity of patches was found to be maintained.

**Table 24 % drug content & % cumulative drug release during stability study**

| Time in days | % drug content | | % cumulative drug release at 12hr | |
|---|---|---|---|---|
| | Formulation A1 | Formulation A2 | Formulation A1 | Formulation A2 |
| 0 | 99.85 | 98.92 | 54.26 | 48.3 |
| 30 | 99.79 | 98.80 | 54.20 | 48 |
| 60 | 99 | 99.30 | 53 | 47.6 |

***In- Vitro* Drug Release Kinetics Study**

It was observed that the best formulation i.e. that of Almotriptan Malate loaded HPMC K 15M-ERS 100 followed the zero order kinetics. The correlation coefficient (R) values were higher in zero order model when compared to other order model. So, it was concluded that this formulation follows zero order kinetics, which release drug in control manner and it is the ideal method of drug release to achieve pharmacological prolonged action.

In order to determine the release mechanism that provides the best description to the pattern of drug release, the in vitro release data were fitted to zero order, first order, and Higuchi matrix. The release data were also kinetically analyzed using the Korsemeyer–Peppas model.

The release exponent (n) describing the mechanism of drug release from the matrices was calculated by regression analysis using the following equation.

$$M_t / M_\infty = Kt^n$$

Where $M_t / M_\infty$ is a fraction of drug released at time t, k is the release rate constant and n is the release exponent. For both the formulations the values of release exponent "n" obtained by applying Peppas equation was greater than 0.45, thus it was observed that the mechanism of drug release was Non Fickian diffusion, the type of release was anomalous transport.

The n value is used to characterize different release, $0.45 \leq n$ corresponds to a Fickian diffusion mechanism, $0.45 < n < 0.89$ to non-Fickian transport (anomalous), $n = 0.89$ to Case II transport, and $n > 0.89$ to Super Case II transport.

**Table 25 Drug release kinetics data of FA1**

| Formulation A1 | | | | | |
|---|---|---|---|---|---|
| **Time (hr)** | **Square root of time** | **Log time** | **Cumulative amount of drug released** | **Cumulative % amount of drug released** | **Log cumulative % amount of drug released** |
| 1 | 1 | 0 | 0.12 | 1.98 | 0.2966 |
| 2 | 1.4142 | 0.3010 | 0.25 | 4.02 | 0.60422 |
| 3 | 1.7320 | 0.4771 | 0.77 | 12.33 | 1.0909 |
| 4 | 2 | 0.6020 | 1.63 | 26.16 | 1.4176 |
| 5 | 2.2360 | 0.6989 | 1.89 | 30.32 | 1.4817 |
| 6 | 2.4494 | 0.7781 | 2.16 | 34.64 | 1.5395 |
| 7 | 2.6457 | 0.8450 | 2.37 | 38.02 | 1.5800 |
| 8 | 2.8284 | 0.9030 | 2.62 | 42.06 | 1.6238 |
| 9 | 3 | 0.9542 | 3.02 | 48.32 | 1.6841 |
| 10 | 3.1622 | 1 | 3.14 | 50.25 | 1.7011 |
| 11 | 3.3166 | 1.0413 | 3.26 | 52.31 | 1.7185 |
| 12 | 3.4641 | 1.0791 | 3.39 | 54.26 | 1.7344 |

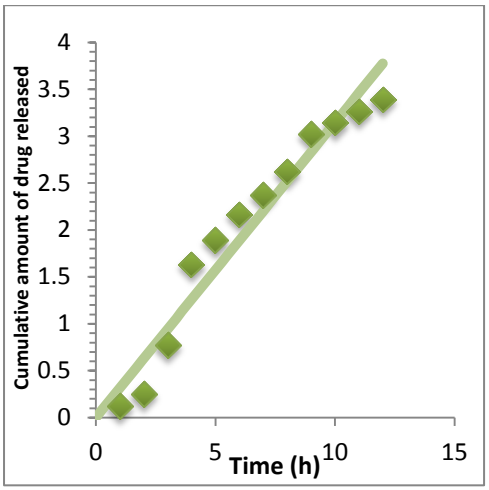
**Table 26 Drug release Kinetics data of FA2**

| Formulation A2 | | | | | |
|---|---|---|---|---|---|
| **Time (hr)** | **Square root of time** | **Log time** | **Cumulative amount of drug released** | **Cumulative % amount of drug released** | **Log cumulative % amount of drug released** |
| 1 | 1 | 0 | 0.19 | 1.52 | 0.1818 |
| 2 | 1.4142 | 0.3010 | 0.37 | 2.99 | 0.4756 |
| 3 | 1.7320 | 0.4771 | 1.34 | 10.78 | 1.03261 |
| 4 | 2 | 0.6020 | 2.54 | 20.32 | 1.3079 |
| 5 | 2.2360 | 0.6989 | 3.28 | 26.31 | 1.4201 |
| 6 | 2.4494 | 0.7781 | 3.75 | 30.01 | 1.4772 |
| 7 | 2.6457 | 0.8450 | 4.00 | 32.02 | 1.5054 |
| 8 | 2.8284 | 0.9030 | 4.51 | 36.12 | 1.5577 |
| 9 | 3 | 0.9542 | 5.0 | 40.23 | 1.6045 |
| 10 | 3.1622 | 1 | 5.5 | 44.03 | 1.6437 |
| 11 | 3.3166 | 1.0413 | 5.7 | 46.2 | 1.6646 |
| 12 | 3.4641 | 1.0791 | 6.0 | 48.3 | 1.6839 |

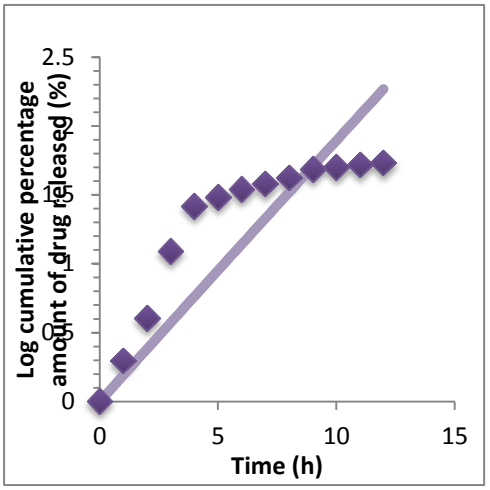
**Table 27 Release kinetic modeling of drug release**

| **Formulation code** | **Regression Constant Value ($R^2$)** | | | | **n value** |
|---|---|---|---|---|---|
| | **Zero Order** | **First Order** | **Higuchi's Model** | **Korsemeyer Peppas Model** | |
| A1 | 0.9462 | 0.5855 | 0.6265 | 0.9250 | 0.631 |
| A2 | 0.9674 | 0.6592 | 0.6137 | 0.9457 | 0.704 |

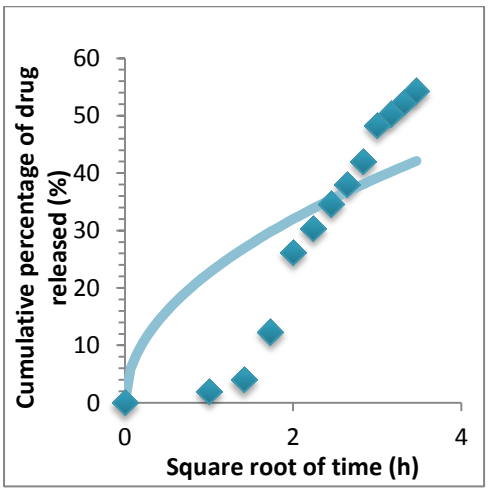
**Graph 9 Zero order plot for FA1**



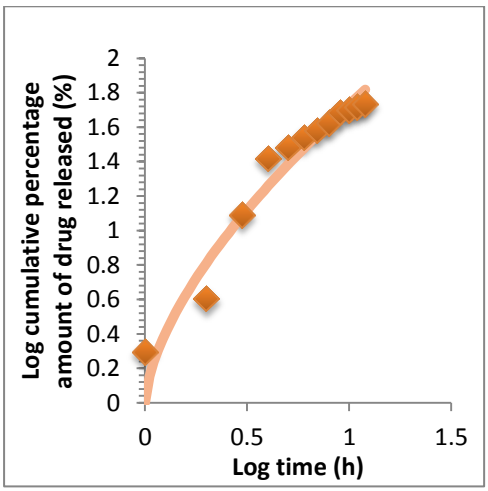

**Graph 10 First order plot for FA1**



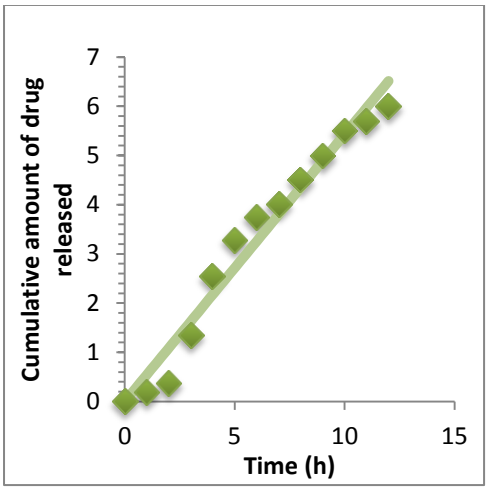

**Graph 11 Higuchis plot for FA1**



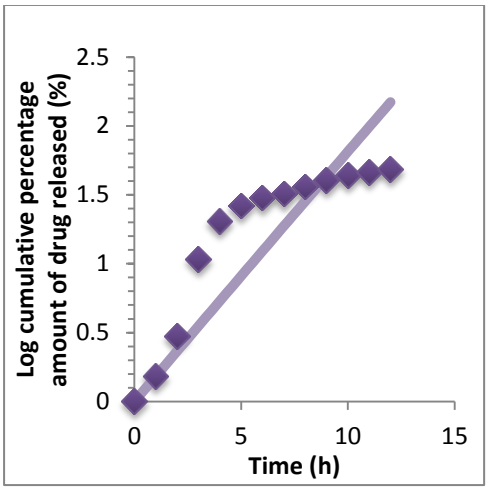

**Graph 12 Korsemeyer-Peppas plot for FA1**



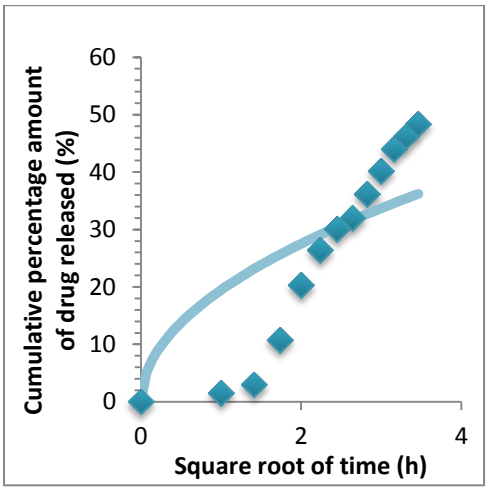
**Graph 13 Zero order plot for FA2**



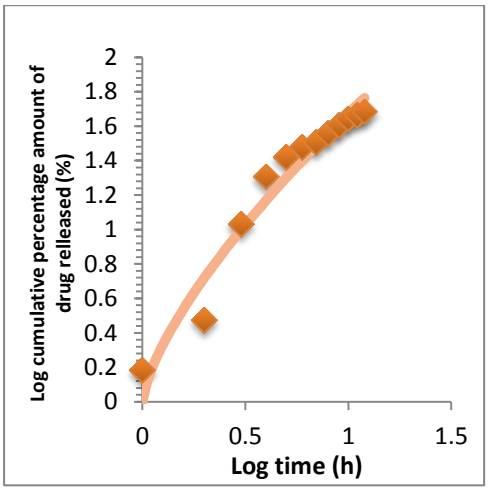

**Graph 14 First order plot for FA2**




**Graph 15 Higuchis plot for FA2**




**Graph16 Korsemeyer-Pepppas plot for FA2**



# SUMMARY & CONCLUSION

Transdermal delivery represents an attractive alternative to oral drug delivery. TDDS has been accepted as a potential non invasive route of drug administration, with advantages of prolonged therapeutic effect, reduced side effects, improved bioavailability, better patient compliance and easy termination of drug therapy. Thus it is anticipated that TDDS, the most suitable system for a long term treatment or for a multi –dose treatment can be designed to deliver drug at appropriate rates to maintain suitable plasma drug levels for the therapeutic efficacy by using skin as the port of entry of drugs.

Almotriptan Malate, the highly selective serotonin 5-$HT_{1B/1D}$ receptor agonist, used in the acute treatment of moderate to severe migraine attacks in adults and adolescent patients with a history of migraine with or without aura, is reported to have the best sustained pain-free rate and the lowest adverse events rate of all the triptans. Furthermore, it is well known that Almotriptan Malate involves a much lower risk of adverse events than Sumatriptan, Zolmitriptan and Rizatriptan, making it a better tolerated and more cost-effective choice for triptan-naïve patients and thus making interest in the development of a new route for the therapeutic administration of this drug.

So the present research work was aimed to develop matrix type transdermal patches of Almotriptan Malate using polymers HPMC K 15M, ERS 100 and EC and plasticizers DBP & PEG 400 via solvent casting method for low dose (6.25 mg) & high dose (12.5 mg) of drug. This formulation would help to avoid non-compliance of the tablet dosage form.

The spectra of drug and physical mixtures of drug-polymers were taken by using FTIR spectrophotometer and confirmed the absence of incompatibility between drug (Almotriptan Malate) and the physical mixture of polymers (HPMC K15M, ERS 100 and EC). Thus, concluded that Almotriptan Malate can be formulated in to a transdermal patch with the above mentioned polymers.

Incorporation of plasticizer at an optimum concentration yielded smooth and flexible patches. There were no significant difference in thickness and average weight among each group and thus indicated that the patches were uniform throughout. Surface pH of all the films were found to be in the range of 5-6, indicating that irritation will not occur on the skin after applications of the patches.

Swellability of the patches due to presence of polymer was measured by its weight gain or water uptake and the transdermal patches showed good swelling and maintained the integrity of formulation which is required for bio-adhesion. The quantity of moisture transmitted through unit area of a patch in unit time found out, helped us to know the permeation characteristics. Low water vapor transmission rate also indicates high degree of stability even in high humid conditions.

To check the moisture sensitiveness of the patch during their storage, percentage moisture loss test was carried out & to check the physical stability and integrity of the films at high humid conditions, percentage moisture absorption test was carried out. The low percentages of moisture loss and moisture absorption helps the patches to remain stable and free from completely drying and brittle and also protect the patches from microbial contamination.

Based on *in-vitro* drug studies, Almotriptan Malate loaded with polymers HPMC K 15M-ERS 100 with DBP as plasticizer was considered as the best formulation, in both high and low doses of drug, (6.25 mg & 12.5 mg) which exhibited the drug release of 3.39 mg/cm$^2$ /12 hrs and 6.08 mg/cm$^2$ /12 hrs respectively. The patches were found to be stable for 2 months with respect to Almotriptan Malate content and there was no significant change in physico-chemical and drug release characteristics of the films.

The present study demonstrated the optimization of Almotriptan Malate loaded transdermal patches by statistical 2 level 2 factorial design using

Minitab18 software. The independent variables selected were HPMC K 15M and ERS 100. The effect of these variables on drug content, %moisture absorption, %moisture loss and cumulative % drug release at 12hr were investigated as optimization response parameters in the current study. It provides flexibility and giving importance for each response individually. Optimization aided in understanding the interaction of formulation parameters, which can be exemplified by increase in both the polymer concentration decreases drug release and it was found that concentration of HPMC K 15M were found to have individual effect on moisture uptake and loss i.e. when its concentration increased moisture absorption and loss also increased.

Release data were analyzed as per the zero order model, first order model, Higuchi model, and Korsemeyer-Peppas model to assess the drug release kinetics and mechanism from the patches. Analysis of the release data as per zero order and first order kinetic models indicated that the drug release from TDDS patches formulated followed zero order kinetics. The correlation coefficient values were higher in zero order model when compared to first order model. When the release data were analyzed as per Peppas equation, the release exponent 'n', used to characterize different release mechanisms was found in the range 0.45- 0.89 in the case of TDDS patches indicating non-fickian (anomalous) diffusion as the release mechanism from these patches.

From the present investigation, it may be concluded that such matrix type transdermal patches of Almotriptan Malate may provide sustained transdermal delivery for prolonged periods in the management of migraine, which can be a good way to bypass the extensive hepatic first pass metabolism. The result of the study showed the feasibility of formulating rate-controlled transdermal films of Almotriptan Malate for effective control and prophylaxis of migraine. Further in-vivo investigations are required to correlate in-vitro permeation studies for the development of suitable transdermal system of Almotriptan Malate.

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