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OPTIMIZATION AND IN VITRO EVALUATION OF TRANSDERMAL PATCH OF SUMATRIPTAN

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ABSTRACT

In the present study the prime objective was to develop transdermal patches loaded with sumatriptan in order to improve its bioavailability by sustaining the drug release. Transdermal patches were prepared using Hydroxy propyl methyl cellulose (HPMC K) as the hydrophilic matrix and ethyl cellulose (EC) as the lipophilic component. The elasticity of the patches was attained using oleic acid (30% polymeric weight) as the plasticizer. EC and HPMC were used in 3 different ratios to obtain the most optimum formulation. All the prepared patches were subjected to visual inspection for examining the physical appearance. The physical appearance of the patches gave satisfactory results. All the prepared patches were found to be smooth, non-sticky, opaque, homogeneous, and flexible in nature. The pH levels of the patches ranged between 5.29 ± 0.006 to 5.69 ± 0.015 suggesting their suitability of human use and possibly suggesting that no skin irritation would be produced on application of the patches. The thickness of the transdermal patches ranged from 0.513 ± 0.004 mm to 0.689 ± 0.004 mm. This difference in the thickness could be attributed to the nature and concentrations of polymers, i.e., an increase in the concentration of the hydrophilic polymer HPMC led to an increased thickness of the transdermal patch. The formulated transdermal patches displayed weight variations between 39.33 ± 0.577 mg and 54.66 ± 0.577 mg.

KEYWORDS: Vitro, Evaluation, transdermal, patch, sumatriptan.

INTRODUCTION

Controlled release medication may be defined as the permeation-moderated transfer of an active material from a reservoir to a target surface to maintain a predetermined concentration or emission level for a specified period of time. Transdermal drug delivery system can be defined as the controlled release of drugs through intact skin. Controlled release technology has received increasing attention in the face of a growing awareness that substances are frequently toxic and sometimes ineffective when administered or applied by conventional means. The transdermal route now ranks with oral treatment as the most successful innovative research area in drug delivery, with around 40 % of the drug delivery candidate products under clinical evaluation related to transdermal or dermal system.

1.1 The structure of skin and drug permeation

The skin is the largest organ in a human body, accounting for over 10% of the whole body mass. It enables the body to interact with its environment and more importantly provides protection. Basically, the human skin consists of the epidermis, dermis and hypodermis embedded with hair shafts and gland ducts (Figure 1). The epidermis is the major barrier against drug permeation, and it is comprised of five layers: stratum corneum (horny layer), stratum lucidum, stratum granulosum (granular layer), stratum spinosum (spinous layer) and stratum germinativum (basal layer). As the cells approach the stratum corneum (SC) layer they flatten and their metabolic activity declines.

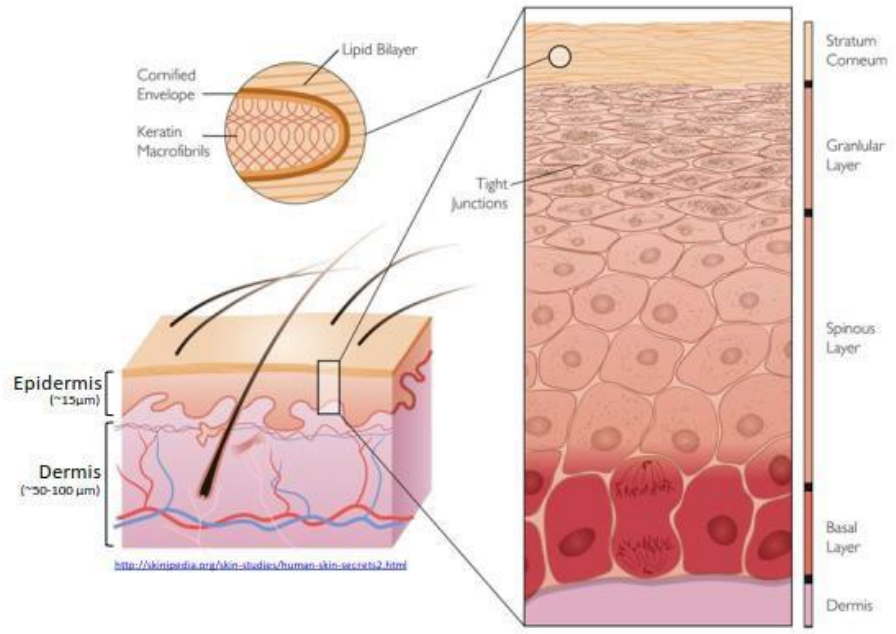

Figure 1.1: Anatomy of the skin.

Finally, all the cells in the SC are deceased, anucleate, and metabolically inactive and upward migration continues as cells at the surface desquamate .The two most important pathways for drugs to permeate through the skin are trans-epidermal pathway and appendageal or shunt route. The overall flux of drugs across the skin is the sum of the individual flux through these parallel pathways, which depend on different physicochemical and geometrical properties. It was reported that the available diffusional area of the shunt route is about 0.1% of the total skin area. Although the fraction of appendages is relatively small, in some cases, these sites might still provide the main portal of entry into the subepidermal layers of the skin for ions and large polar molecules. For small nonelectrolyte molecules, it was reported that the shunt route was dominant only in the non-steady-state phase of percutaneous absorption, but makes a negligible contribution to overall flux in the steady-state permeation period. It was found that the contribution of shunt route in thesteady-state transport of polar and nonpolar steroids was less than 10% and there was a poor correlation between appendageal density and percutaneous absorption when different skin regions were compared.

However, some papers also reported that the appendages could be a potential pathway for steady-state permeation of a wide range of drugs. Transdermal delivery of drugs is a result of partitioning and diffusion of drug molecules in the SC, viable epidermis, and papillary layer of the dermis, with the microcirculation usually providing an infinite sink. The main barrier to permeation of water is in the external layers of the epidermis, particularly the SC. And the SC is the rate-limiting barrier to percutaneous absorption of most compounds in most conditions. However, for very lipophilic drugs, the rate limiting step may change from diffusion through to clearance from the SC. The SC has a multilayer structure, in which keratin-rich epidermal cells are embedded in an intercellular lipid-rich matrix. This two-compartment arrangement has been referred to as a bricks (corneocytes) and mortar (intercellular domain) analogy. The SC usually has 15 to 20 layers of corneocytes and the thickness varies from 10 to 15 µm in dry state.

After hydration, the SC swells and may reach to as much as around 40 µm thickness. The SC lipids content accounts for 5 to 15% of the dry tissue weight, which mainly comprise ceramides, cholesterol and fatty acids, together with smaller amounts of cholesteryl sulfate, sterol/wax esters, triglycerides, squalene, n-alkanes, and phospholipids. SC lipids localize mainly in the intercellular space with little in the corneocytes. Besides lipids, some proteins and enzymes also exist in the intercellular space. Freeze-fracture electron microscopy studies

of the SC showed that intercellular lipids form a bilayers structure. The lipids pack into lamellae, with the hydrocarbon chains mirroring each other and the polar groups dissolving in an aqueous layer. The intercellular bilayers are in pairs and firmly bind together, possibly by the action of molecules such as acyl ceramides. Adjacent bilayers may mutually contribute chains to an intermediate structure as a monolayer. Small-angle X-ray diffraction studies (SAXS) of hydrated human SC demonstrated that SC lipids develop in two lamellar structures.

In addition, SC intercellular lipids exhibit a phenomenon of complex polymorphism. According to wide-angle X-ray diffraction studies (WAXS) of human SC, lipid alkyl chains arrange into orthorhombic perpendicular and (pseudo)hexagonal packings, with some in the liquid state. Cholesterol may also be present in the form of small crystals in human SC. As the result, the SC intercellular domain comprises a mixture of crystalline, lamellar gel, and lamellar liquid crystalline lipid phases. It was reported that intact intercellular lamellae are present at all levels in human SC and their appearance does not differ significantly between different anatomical locations.

In order to understand how the physiochemical properties of drugs can influence transdermal drug delivery, it is necessary to determine the predominant route of drug permeation through the stratum corneum. Drug molecules that come in contact with the skin can penetrate through three pathways (Figure 2): 1) through the sweat ducts, 2) via hair follicles and sebaceous glands, or 3) directly across the stratum corneum. It is generally accepted that the sweat ducts provide minimal contribution (permeation of ~0.1%) to the steady flux of most drugs, therefore the majority of skin penetration enhancements have focused on transporting drugs across the stratum corneum. However, drug molecules must travel a very intricate and specific pathway through the stratum corneum. A molecule that transverse through the stratum corneum must partition into and diffuse through the corneocytes. In order to move to the next corneocyte, the drug molecule must migrate through multiple lipid layers in between each corneocyte.

The partitioning into and diffusion across continuous hydrophilic and hydrophobic domains is unfavorable for most drugs. As a result, the majority of techniques and methods used to optimize transdermal drug delivery are directed towards the manipulation and alteration of the well-ordered stratum corneum.

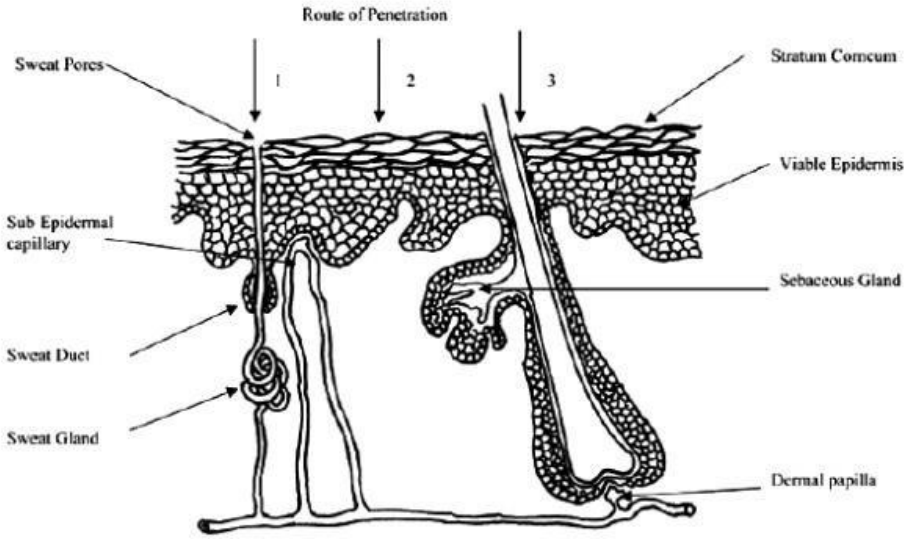

Figure 1.2 Illustration of skin depicting routes of penetration of the drug: 1) through sweat ducts; 2) through stratum corneum; 3) via hair follicles.

Drug permeation across the stratum corneum obeys Fick's first law (Equation 1.1). The steady-state flux (J) is related to the diffusion coefficient (D) of the drug over the membrane thickness (h), the partition coefficient (P) between the stratum corneum and drug vehicle, and drug concentration (C0) which is assumed to be constant. Since the skin thickness and drug concentration are considered constant, techniques used to successfully increase the rate of drug release through the stratum corneum focus on increasing D and P. More importantly, the combination of enhancing both D and P will result in multiplicative effect.

1.2 Transdermal patch

A transdermal patch is a medicated adhesive patch placed on skin to deliver a time released dose of medication through the skin for treating topical or systematic illness.

Since early 1990, this dosage form of transdermal therapeutic system has been available in the pharmaceutical market.[1] A recent approach to drug delivery is to deliver the drug into systemic circulation at predetermined rate using skin as a site of application. A transdermal drug delivery is a formulation or device that maintains the blood concentration of the drug within therapeutic window ensuring that drug levels neither fall below the minimum effective concentration nor exceed minimum toxic dose.[2] Such a system offers variety of significant clinical benefits over other systems, such as tablet and injections. For example, it provides controlled release of the drug and produces a steady blood- level profile leading to reduced systemic side effects and, sometimes, improved efficacy over other dosage form. In addition

transdermal dosage form is userfriendly, convenient, painless, and offers multi-day dosing, it generally leads to improved patient compliance.[3] It offers many important advantages over oral drug delivery, e.g., gastrointestinal and hepatic first pass metabolism, reduces variation in delivery rates, avoids interference due to presence of food, controls absorption rate, suitable for unconscious patients, and enables fast termination of drug delivery, if needed.[4]

1.3 Criteria of Drug to be candidate for Transdermal Drug Delivery

Basically, not every drug or chemical is a candidate for transdermal drug delivery. The choice of drug is the most important decision in the successful development of a transdermal product. The most important drug properties that affect its diffusion through the devices as well as the skin include molecular weight, chemical functionality and melting point. It is generally accepted that the best drug candidates for passive adhesive transdermal patches must be nonionic, low molecular weight (less than 500 Daltons), have adequate solubility in oil and water (log P in the range of 1 to 3), a low melting point (less than 200 °C), short plasma half-life, and are potent (dose is less than 50 mg per day, and ideally less than 10 mg per day). Given these operating parameters, the number of drug candidates for passive transdermal patches is low, owing to the challenge of diffusing across the bilayers in the tortuous stratum corneum. But, many new opportunities still exist for novel passive transdermal patch products. The new transdermal technologies that were introduced in the previous section challenge the paradigm that there are only a few drug candidates for transdermal drug delivery. With the active and micropore-creating transdermal technologies, molecular size is not a limiting factor. The same applies for other physiochemical drug properties, such as ionization state, melting point, and solubility. Finally, the active and micropore-creating technologies also enable therapeutic delivery of drugs at doses higher than 10 mg. Clearly, the opportunities for transdermal drug delivery have been greatly expanded through the application of new formulation technologies and active delivery systems. Now, a much wider set of drug compounds, including macromolecules, have the possibility to be delivered transdermally at therapeutic levels than was possible just a decade ago. Of course, the use of a TDD technology for any drug must be clinically beneficial.

1.4 Factors Affecting Transdermal Drug Delivery

Apart from minor factors such as individual variations, age, site of application, occlusion, temperature, race, and disease states, there are other physical related factors that affect the permeation of drugs through the skin as described in the Fick's equation: dQ/dt = ÞCDA/l

Where, dQ/dt is the rate of drug penetration, Þ is the partition coefficient between stratum corneum and vehicle, C is the concentration of drug in the vehicle, D is the average diffusion coefficient, A is the surface area of application of the drug, l is the thickness of the skin barrier.

(a) Partition Coefficient: For an individual drug, this is measured as the octanol-water ratio (or log P). It is a measure of lipophilicity verses hydrophilicity. In skin permeation studies, the steady-state rate of permeation across the skin can be expressed by the equation below: $dQ/dt = P_s(C_d-C_r)$

Where *Cd* and *Cr* are, respectively, the concentration of drug in the donor compartment and in the receptor compartment and *Ps* is the permeability coefficient of the skin defined by the equation below:

$$Ps = Ks.Ds/h$$

Where *Ks* is the partition coefficient for the interfacial partitioning of the drug from the device (vehicle) to the skin, *Ds* is the diffusivity of the drug through the skin, h is the thickness of the skin.

(b) Diffusion

This is the process by which a substance moves from one area to another. It is driven by thermal agitation and requires a concentration gradient. In other words, the area that a substance is going to must have a lower concentration of the drug than the area it is coming from. Lipophilic substances diffuse easily through stratum corneum lipids, but have much more difficulty with the aqueous layers below. If transport slows too much in any layer of tissue (example, stratum corneum, epidermis, dermis) diffusion slows, causing a build up in the outer layers.

(c) Concentration

This is the amount of substance per unit volume of vehicle. The importance of solubility is the reason a solvent carrier is typically used despite its reduction in partition coefficient. For example, corticosteroid's partition coefficient is reduced twofold by the addition of 50 % ethanol to saline, but its solubility is increased 100 fold, giving a 40 fold penetration enhancement. The solubility issue can become a problem if the vehicle evaporates before the drug has fully partition into the skin, causing precipitation. Thus, it is necessary to also

incorporate a small amount of a less volatile solvent such as fatty acid, terpenes, isopropyl myristate into a transdermal formulation.

(d) Surface Area

Large surface area of contact between the drug formulation and the stratum corneum exposes more drug molecules to the lipid skin layer and so increases the rate of drug permeation.

1.5 Types of Transdermal Patches

1. Single-layer drug –in-adhesive
2. Multi-layer drug-in-adhesive
3. Drug reservoir-in-adhesive
4. Drug matrix-in-adhesive

1.6 Benefits of transdermal drug delivery systems

1. Provides safe, convenient and pain less self administration systems for patients
2. Beneficial for patients on polymedication
3. Provide constant rate of drug release
4. Bypass metabolic problems like presystemic metabolism thereby improves therapeutic efficacy
5. Decreases dosing frequency of the drug
6. Very helpful in long term treatment regimes

1.7 Basic components of transdermal systems

1. Polymer matrix
2. Rate controlling membrane
3. Adhesive
4. Release liners
5. Backing laminate
6. Penetration enhancers
7. Drug
8. Plasticizers and solvents

1.8 Method of Transdermal drug delivery

(a) Use of Chemical Enhancers

The enhancement of skin has been tested with water, surfactants, essential oils, dimethyl sulfoxide (DMSO), and alcohols. Barry and coworkers proposed the lipidprotein partitioning (LPP) theory to describe how enhancers affect skin permeability. By disrupting the intercellular bilayer lipid structure and interacting with intracellular proteins of the stratum corneum, chemical enhancers improve the partitioning of a drug, coenhancer, or cosolvent into the stratum corneum.

One of the safest and most widely used chemical enhancer to increase permeation is water. It is hypothesized that the increased hydration of the skin may lead to swelling and to the opening of the structure which can increase permeation. Other types of enhancers have shown increase in permeability by disordering the lipid structure of the stratum corneum. The diffusion coefficient of the drug is increased as microcavities are formed in the lipid bilayers. In other cases, enhancers can create permeable "pores" that provide less resistance for polar molecules. Penetration of chemical enhancers has also been found to interact with the keratin in the corneocytes. The surfactants interact and bind with keratin to disrupt the order within the corneocytes thereby diffusion coefficient. One of the major side effects of chemical enhancers is irritation to the skin at potent levels, which is not surprising since the chemicals disrupt organized lipid structures, cell membranes, and their components. The toxicity associated with many enhancers have limited their usefulness in clinical applications, however there has been a move towards investigating potential generally regarded as safe (GRAS) enhancers by the FDA, such as essential oils and terpenes.

(b) Iontophoresis

This method of transdermal drug delivery involves low level electric current applied either directly or indirectly to the skin in order to enhance its permeation. The electrical charge primarily drives drug molecules through the skin via sweat ducts since they provide less electrical resistance than the stratum corneum. The reason for the increased permeation can be attributed to one or all of the following: electrophoresis (for charged solutes), electro-osmosis (for uncharged solutes), and electropertubation (for both charged and uncharged solutes). Electrophoresis drives charge molecules across the skin by direct interaction with the applied electric field, therefore small highly charged particles are delivered more rapidly. In electroosmosis, the delivery of molecules occurs as they are dragged by the electrically

induced solvent flow. The flow of the solvent is induced by the net flux of cations from the anode to the cathode. The electroosmotic flow of water is generated by the preferential movement of mobile cations in the cells (i.e. Na+) instead of fixed anions proteins in the skin.

Typically, a few milliamperes of current are applied to a small area of the skin, generating no pain beyond mild erythema. The Phoresor^{TM} was the first iontophoretic system approved by the FDA in the late 1970s as a therapeutic device. Currently, iontophoretic systems are approved for administering drugs into the body for specialized medical purposes, such as diagnosis of medical conditions and glucose monitoring. Despite the straight forward application, many parameters can affect the design of an iontophoretic device, including but not limited to electrode type, current intensity, pH of system, and competitive ion effect. Currently, there are many requirements for a successful iontophoretic device. For example, the device must: (1) be sufficiently high powered to provide desired delivery rate; (2) not produce any permanent harmful effects on skin permeability; (3) establish proportionality between flux and applied current/voltage; and (4) maintain constant current/voltage over time.

In addition, iontophoresis is limited by the electric current that can be used on humans (regulated at 0.5mA/cm^2)

(c) ***Electroporation***

This method of transdermal delivery is similar to iontophoresis, in which it uses electrical current to aid the delivery of drug molecules through the skin. In the case of electroporation, extremely high voltage pulses, rather than milliamperes of current, are used to induce skin perturbation. The high voltage creates transient pores which may account for the skin permeability. The increased skin permeability is related to the electroporation process, which is the formation of aqueous pathways across the lipid bilayer by a pulsed electric field. This technology can enhance the skin permeability to molecules of greater hydrophilicity and sizes compared to other methods.

High voltages (≥100 V) over short durations (milliseconds) are normally applied. The pulses can be administered painlessly using closely spaced electrodes to minimize the electric field in the nerve-free stratum corneum. With the application of high voltages, transdermal transport can be reduced to a few seconds opening opportunities for rapidresponse delivery systems. Transdermal transport has been shown to increase by orders of magnitude with

partial to full reversibility within minutes to hours. However, with the use of high voltage, there is a greater chance of cell damage if the pulses duration or intensity is too great. In addition, electroporation requires specialized and cumbersome equipment.

(d) *Microneedles*

This method of transdermal drug delivery involves piercing the skin with very short needles. Solid microneedles (~50-100µm) encapsulated or coated with drug formulations for controlled or rapid release. Microneedles increase permeability and delivery of drugs transdermally by creating micron-scale pathways into the skin, driving drugs into the skin as coated cargo. Their effects are targeted in the stratum corneum, although they do pierce across the epidermis and into superficial dermis. Microneedles treatment have been reported to be painless by volunteers and generally well tolerated. This technique has great promise because they appear to be capable of delivering a broad range of drugs. A notable limitation is the diffusion rate of large compounds through micron-scale pathways. When rapid delivery is required, it may be necessary use an additional force to drive the drugs into the skin.

REVIEW OF LITERATURE

1. **Zhong et al (2024)**[5] developed dissolving microneedles (MNs) using polyvinyl alcohol (PVA) and poly (1-vinylpyrrolidone-co-vinyl acetate) (P(VP-co-VA)) as matrix materials for transdermal delivery of rizatriptan benzoate (RB) for acute migraine treatment. *In-vitro* permeation studies were conducted to assess the feasibility of the as-fabricated dissolving MNs to release RB. Drug skin penetration were tested by Franz diffusion cells, showing an increase of the transdermal flux compared to passive diffusion due to the as-fabricated dissolving MNs having a sufficient mechanical strength to penetrate the skin and form microchannels. The pharmacological study *in vivo* showed that RBloaded dissolving MNs significantly alleviated migraine-related response by upregulating the level of 5-hydroxytryptamine (5-HT) and down-regulating the levels of calcitonin gene-related peptide (CGRP) and substance P (SP).
2. **Afreen et al**[6] design a suitable transdermal therapeutic system for venlafaxine hydrochloride (VFH) with the objective to prolong the release to be used for controlled release drug delivery. Eudragit RSPO membrane in different concentrations was cast to achieve controlled release of the drug. The absence of physiochemical interactions between VFH and the polymers was confirmed by Fourier transform infrared spectroscopy. The physicochemical parameters and in-vitro drug release studies of

formulations were performed and data of optimized formulation were fitted to various kinetic models.

3. **Durgapal et al**[7] reported the formulation and evaluation of buccal patches of venlafaxine using different polymers like Ethyl cellulose, Hydroxypropyl methylcellulose (HPMC) K4M, Eudragit S100 in various proportion and combination, where propylene glycol and dibutylpthalate are used as plasticizer. All formulations are formulated by solvent casting technique. Venlafaxine; an antidepressant drug has high first pass metabolism so buccal route is excellent for its systemic delivery thereby rendering great bioavailability. Preformulation studies were conducted before formulation and formulated patches were subjected for evaluation of various physicochemical parameters like thickness, wt. uniformity, pH, content uniformity, folding endurance, percentage swelling, tensile strength, vapour transmission rate, percentage moisture loss and mucoadhesion force. In vitro drug release study was carried out using Franz diffusion cell.
4. **Rajula et al**[8] prepared transdermal delivery system for venlafaxine using hydrophilic (HPMC E15) and hydrophobic (ERS100 and ERL 100) polymers in 1:5, 2:4, 3:3, 4:2, 5:1 ratios by solvent casting technique with 15 % v/w propylene glycol as plasticizer. The drug permeation studies revealed that drug permeation increased proportionally with increasing HPMC ratio where ERS 100 as hydrophobic polymer but in case of ERL 100 as hydrophobic polymer proportional increase was not obtained this may be due to increased diffusion path length.
5. **Pawar et al**[9] formulate nanoethosome formulation containing naringin to overcome lower bioavailability, biodistribution and metabolism. The use of nanoethosomes as vesicle drug carrier having ability to increase solubility, improve biodistribution, slows the biotransformation which improves the activity of naringin for treating neurological disorder. The ethosomes were formulated by varying the variables such as concentrations of soya lecithine, polyethylene glycol, and ethanol. The formulations were evaluated with entrapment efficiency, and particle size. Results specify that prepared nanoethosomes of naringin shows decreased particle size, better entrapment efficiency as compared to rigid ethosomes.
6. **Ghosal et al**[10] studied the outcome of the concentration of polycaprolactone (PCL), the concentration of polyvinyl alcohol (PVA) and the concentration of hydroxypropyl methylcellulose (HPMC) on the average particle size of microspheres and the drug

entrapment efficiency of naringin-loaded polycaprolactone microspheres based oral suspension.

7. **Yang et al**[11] prepared naringin-loaded microsphere/sucrose acetate isobutyrate (Ng-m-SAIB) hybrid depots, reduce the burst release of naringin (Ng), and improve osteogenesis. The morphology and size distributions of electrosprayed Ng-microspheres were characterized by scanning electron microscopy (SEM). The Ng-microspheres and Ng-m-SAIB depots were characterized by Fourier transform infrared spectroscopy (FTIR) and *in vitro* release studies.
8. **Huang et al**[12] prepared poly-(ε-caprolactone) (PCL) microspheres with diverse exterior architectures by electro-spraying solution of polymer in host and guest solvent. With increase in PCL concentration collapsed particles gets converted to regular uniform microspheres and ultimately to fibers. Non-solvent induced phase separation leads to surface pores formation, which could be varied through change in guest solvent or amount of non-solvent.
9. **Lauro et al**[13] Formulated naringin and naringenin gastro-resistant microparticles using CAP as coating material and spray-drying technique. The influence of parameters such as the composition of the feed solution and polymer concentration on the particle yield, behavior and morphology was investigated. The microparticles were characterized by scanning electron microscopy (SEM), fluorescence microscopy (FM), and differential scanning calorimetry (DSC). In vitro dissolution studies, carried out using a pH change method, revealed that gastro-resistant naringin- and naringenin-loaded microparticles are obtainable from2% buffer aqueous feed solutions in different polymer/drug ratios (1:1, 3:1, 5:1) by spray-drying.
10. **Mohanty et a**[14] prepared combination liposomal formulations of Naringin (NAR), sulforaphane (SFN), and phenethyl isothiocyanate (PEITC) with 1,2dipalmitoyl-sn-glycero3-phosphocholine/cholesterol/1,2-distearoyl-snglycero-3 phosphoethanolamine -020CN (15:4:1 M ratio) was determined to be 79.8 ± 4.2, 46.5 ± 3.6, and 78.5 ± 3.2%, respectively. The CLFs were characterized by differential scanning calorimetry, Xray diffraction, dynamic light scattering, and Fourier transform infrared spectroscopy. The physicochemical results showed that the preparations were monodisperse (PDI 0.062−0.248) in water with an average size from 140.5 to 165.6 nm and a zeta potential of −47.3 to −53.3 mV. Dissolution studies in vitro showed a slower release of PEITC (>90%, 6 h) in comparison to that of SFN (3 h). Here, we are the first to report the

antiarthritic activity of CLF of NAR + SFN and NAR + PEITC in the Freund's complete adjuvant (FCA)-induced arthritic model.

11. **Bavarsad et al**[15] prepared and characterized films formed from blends of chitosan and soy PC for topical delivery of griseofulvin. The topical films composed of chitosan and soy PC were prepared by means of casting and solvent evaporation technique. The properties of the films were characterized regarding mechanical properties, swelling, ability to transmit vapor, drug release, thermal behavior and antifungal efficacy against Microsporum gypseum and Epidermophyton floccosum.
12. **Rastogi et al**[16] prepared matrix type transdermal patches of Glibenclamide were prepared by solvent casting technique using various combinations of hydrophobic (ethyl cellulose) and hydrophilic (Polyvinylpyrrolidone) polymer, with or without permeation enhancer (vegetable oils). Percentage cumulative drug release from the in vitro study depicted the effect of polyvinyl pyrrolidone, on increasing its concentration with respect to ethyl cellulose increases the release of Glibenclamide from the matrix. Significant effect of vegetable oils on the lipid and protein framework of the skin was seen which results in approximately 1.3 fold times increase of Glibenclamide flux. The hypoglycemic activity revealed the significant reduction in blood glucose levels (≈55% at 12th hour) from the transdermal patches which proves the sustained release of Glibenclamide over a prolonged period of time.
13. **Patel et al**[17] formulated transdermal patches using Eudragit RL 100, Eudragit RS 100, Polyvinyl pyrollidone (PVP) as polymers, glycerol and propylene glycol as a plasticizers and Span 80 as a permeation enhancer by solvent casting method with aim of to study the release kinetics of drug with a view to reduce the dose frequency, improving patient compliance, greater therapeutic efficacy and to prevent its first pass metabolism to achieve a controlled drug release and overcome some draw backs such as gastric disturbance, hepato toxicity with improved bioavailability. The prepared transdermal patches were then evaluated for uniformity of thickness, weight variation, hardness, surface pH, tensile strength, swelling index (%), folding endurance, water vapor permeability, drug content. In vitro drug release studies of formulated patches were performed by studying the diffusion through human cadaver skin.
14. **Paranjothy and Thampi**[18] have developed of transdermal patches of verapamil hydrochloride using sodium carboxy methyl guar as a monolithic polymer matrix and their *in vitro* release studies. Propylene glycol used as a plasticiser and alupoly foil used as a backing membrane. A comparison of various polymers and plasticisers were also

made. *In vitro* release studies through mouse skin have shown that sodium carboxymethyl guar as a suitable polymer.

15. **Sankar et al**[19] have prepared transdermal drug delivery system of nifedipine, prepared drug free polymeric film of ethyl cellulose [EC], to explore their suitability for transdermal application as the rate controlling membrane. Castor oil, glycerol was incorporated at a concentration of 30 % w/w, 40% w/w of dry polymer, as plasticizer.

DRUG PROFILE

Sumatriptan[20]

Sumatriptan is a serotonin receptor agonist commonly used to treat migraines and sometimes cluster headaches.

IUPAC Name: 1-{3-[2-(dimethylamino)ethyl]-1H-indol-5-yl}-Nmethylmethanesulfonamide

Chemical Structure:

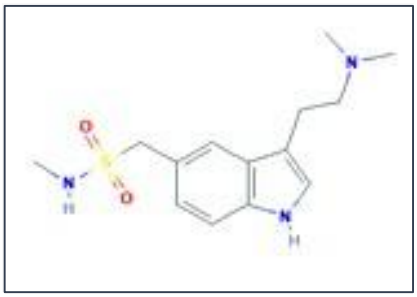

Figure 4.1Chemical structure of sumatriptan.

Chemical Formula: $C_{14}H_{21}N_3O_2S$

Molar Mass: **295.4**

Indication: A combination sumatriptan and naproxen tablet is indicated for the treatment of migraines with or without auras in patients 12 years of age and older. Sumatriptan nasal powder, nasal spray, subcutaneous injection, and tablets are indicated to treat migraines with or without auras in adults. One of the subcutaneous formulations of sumatriptan is also indicated to treat cluster headaches in adults, while the other subcutaneous formulation is not.

Pharmacodynamics: Sumatriptan constricts cranial blood vessels and prevents the release of vasoactive peptides. The dose of sumatriptan varies widely by route of administration and in most cases, no more than 2 doses should be given daily. Medication overuse headaches may occur in patients who use sumatriptan frequently.

Mechanism of action: Sumatriptan is an agonist of 5-HT_{1B} and 5-HT_{1D}. This agonism leads to constriction of cranial blood vessels and inhibits the release of proinflammatory neuropeptides. Sumatriptan decreases carotid arterial blood flow, but increases blood flow velocity in the internal carotid artery and middle cerebral artery.

Absorption: A 6mg subcutaneous injection of sumatriptan reaches a C_{max} of 69.5ng/mL (95% CI of 62.8-76.9ng/mL) with a T_{max} of 0.17h (95% CI of 0.08-0.33h), an AUC of 9.0h*ng/mL (95% CI of 7.5-10.9h*ng/mL), and a bioavailability of 100%.

Volume of distribution: Sumatriptan has a volume of distribution of 50±8L for a 6mg subcutaneous dose, or 2.7L/kg.

Protein binding: Sumatriptan is 14%-21% bound to protein in circulation.

Metabolism: Sumatriptan is predominantly metabolized by monoamine oxidase A. The main metabolites are the inactive indole acetic acid and indole acetic acid glucuronide.

Route of elimination: 22±4% is excreted in the urine as unchanged sumatriptan and 38±7% in urine as indole acetic acid approximately 40% is excreted in the feces.

Half life: Subcutaneous sumatriptan has a half life of 1.9h (95% CI of 1.7-2.0h). Oral sumatriptan has a half life of 1.7h (95% CI of 1.4-1.9h).[3] Rectal sumatriptan has a half life of 1.8h (95% CI of 1.6-2.2h). Intranasal sumatriptan has a half life of 1.8h (95% CI of 1.7-2.0h).

Toxicity: Symptoms of overdose include convulsions, tremor, paralysis, inactivity, ptosis, erythema of the extremities, abnormal respiration, cyanosis, ataxia, mydriasis, salivation, and lacrimation.

RESEARCH ENVISAGED

4.1 Research envisaged

In recent years, various drug delivery systems have been developed which provide sustained release therapy via a sub-dermal insert. Systems have been disclosed which also provide drug delivery systems suitable for transdermal drug administration. Many of the serotonin agonist drugs possess the properties necessary to be effective in a transdermal drug delivery system. The properties include high potency, proper physicchemical characteristics, good dermal penetration and lack of dermal irritation.

Sumartriptan has been widely prescribed drug for management of migraine. The transdermal delivery through patches has been widely investigated for improving the bioavailability of drugs.

4.2 Objective of Study

In the proposed research work, it was hypothesized to formulate transdermal patches containing sumatriptan with the following objective.

1. Transdermal patches loaded with sumatriptan are expected to improve the bioavailability of the drug by improving its half life.
2. The patches would be prepared using a blend of Eudragit RL100 and Ethylcellulose in varying ratio.
3. An enhanced duration of action might be achieved through the patches.
4. The prepared transdermal patches will be evaluated for various parameters like weight variation, thickness, folding endurance, drug content, percentage of moisture content, *in-vitro* release study etc.

PLAN OF WORK

1. Literature review
2. Procurement of drugs and excipients
3. Preformulation studies of sumatriptan

a. Organoleptic characters
b. Melting point
c. Solubility profile
d. Calibration curve
e. FTIR
f. Drug-excipient compatibility study by FTIR

4. Preparation of transdermal patches using solvent casting method
5. Optimization of patch formulation

a. Eudragit concentration on release duration
b. Ethyl cellulose concentration on release duration

6. Characterization of transdermal patch

a. Thickness
b. Weight variation
c. Folding Endurance

d. Drug content

e. *In vitro* drug release

MATERIAL AND METHODS

LIST OF MATERIAL

S.N	Item	Source
1	Sumatriptan	Yarrow Pharmaceuticals, Mumbai
2	HPMC	CDH
3	Ethyl cellulose	Oxford
4	HCl	Rankem
5	Methanol	Rankem
6	Acetone	Finar
7	Oleic acid	Oxford
8	Potassium dihydrogen phosphate	Oxford
9	Dipotassium hydrogen phosphate	Oxford

LIST OF EQUIPMENT

S.N	Item	Make
1	Hot air oven	Biotechnics
2	Magnetic stirrer	Biotechnics
3	pH meter	Labtronics
4	UV-Visible spectrophotometer	Labtronics
5	Franz diffusion cell	Fabricated

PREFORMULATION STUDIES[21]

Preformulation studies provide the necessary information of the drug for ascertaining its utilization with excipients for developing a particular formulation. They also fulfill the purpose of authenticating the drug using certain parameters.

6.1 Organoleptic Evaluation

The color, odor and appearance of the obtained drug sample were observed with the help of the sensory organs.

6.1.1 Solubility (at room temperature, qualitative)

Solubility was observed in different solvents like water, HCl, ethanol and acetone. A small amount of drug was taken in test tube and 1mL of solvent was added to it. The contents were shaken for some time and observed for any dissolved particles remaining in the test tube.

6.1.2 Identification Test

FT-IR spectrum of the sample of sumatriptan was obtained and examined for the presence of characteristic peaks and matched with that of the reference spectra in databases for confirmation of the identity of the drug.

6.1.3 Melting point determination

Melting point was determined by open capillary method and is uncorrected. A small quantity of powder was placed into fusion tube and placed in the melting point apparatus. The temperature of the apparatus was gradually increased and the temperature at which the powder started to melt and the temperature at which all the powder got melted was recorded.

6.2 Compatibility analysis

The FTIR spectra of the pure drug and a physical mixture of the drug and the polymers under study were obtained and observed for deletion of the characteristic peaks of the drug.

6.3 Partition Coefficient[22]

This study was performed by using butanol as oil phase (30ml) and water as aqueous phase (30ml). The 2 phases were mixed by keeping them in a separating funnel and 5 mg of drug was added in it then 2 phases were separated from each other when it was shaken continuously and then separated from each other by separating funnel. Both phases were taken in a conical flask and then analyzed against their respective blank solution and the partition coefficient was calculated by following formula.

$\mathbf{K_{o/w}}$ **=** Concentration of drug in butanol/ Concentration of drug in water

6.4 Determination of λ_{max}

Accurately weighed 5 mg of sumatriptan was dissolved in 5 mL of water in a 10 mL volumetric flask. 1 mL of this solution was taken in to a 10 mL volumetric flask and volume made up to the mark with phosphate buffer pH 6.8.[23] The resulting solution was then scanned between 200-400 nm using UV spectrophotometer. The λ_{max} was found to be 225 nm. The solution was stored for 3 days at room temperature and rescanned to observe any changes in wavelength.

6.5 Preparation of Calibration Curve in phosphate buffer pH 6.8

Accurately weighed 10 mg of sumatriptan was taken in 10 mL volumetric flask and dissolved in water to the mark resulting in a stock solution of 1000 µg/mL. 1 mL of the above stock

solution was taken in another 10 mL volumetric and volume was made up with phosphate buffer pH 6.8 to mark resulting in a solution of 100 µg/mL. Aliquots of 1-6 mL of stock solution were taken into a series of 10 mL volumetric flask and volume was made up to the mark using phosphate buffer pH 6.8 and were analyzed at 225 nm using UV spectrophotometer. A standard curve was constructed against absorbance and concentration.

FORMULATION STUDY

6.6 Formulation of transdermal Patches[24]

Sumatriptan loaded transdermal patches were formulated utilizing the solvent casting method using a petridish of area 38.46 cm^2. Polymers were accurately weighed and dissolved in 10 mL of water-ethanol (1:1) solution, stirrer for 30 min on a magnetic stirrer and kept aside to form clear solution (Table 6.1). Sumaritptan was accurately weighed and was dissolved in the above solution and mixed until clear solution was obtained. Oleic acid (30% w/w of total polymer) was added to be used as plasticizer and eucalyptus oil (10% w/w of total polymer) was added as the permeation enhancer. The resulted uniform solution was cast on the petri dish, which was lubricated with glycerin and dried at room temperature for 24 h. An inverted funnel was placed over the petridish to prevent fast evaporation of the solvent. After 24 h, the dried patches were taken out and stored in a desiccator for further studies.

Table 6.1: Formula for Sumatritan loaded transdermal patches.

Ingredients	Sumatriptan (mg)	HPMC (mg)	EC (mg)	Oleic acid (%w/w)
P1	135	100	50	30
P2	135	125	50	30
P3	135	150	50	30
P4	135	100	75	30
P5	135	125	75	30
P6	135	150	75	30
P7	135	100	100	30
P8	135	125	100	30
P9	135	150	100	30

Calculation of dose[25]

Area of petridish = 38.465 cm^2
No. of films of 4 cm^2 in whole plate = 9
Amount of drug in each film = 15 mg
Total amount of drug required = 135 mg
Label claim of films = 15 mg

6.7 Evaluation of Transdermal Patches[26]

6.7.1 Physical appearance

The formulated patches were evaluated for homogeneity, transparency, clarity, color, and smoothness.

6.7.2 Uniformity of weight test

The patches were subjected to mass variation by individually weighing each formulated patch and checking the weight of patch against the average weight of the formulated patches. Measurement of patch weight was carried out using a calibrated analytical balance. The determination was carried out for each formulation in triplicate.

6.7.3 Thickness

The thickness of each patch was measured by the use of vernier caliper at six different positions of the patch and the average was calculated.

6.7.4 Surface pH

The surface pH of the transdermal patches was measured using a calibrated pH meter. In a test tube, 1 mL of distilled water and a 1 cm^2 portion of transdermal patch was kept at room temperature (25 ± 2°C) for 2 h. The water from the test tube was decanted and the wet patch was used for surface pH analysis. The pH electrode was placed at three different places at the swollen part of the patch for calculating the average pH.

6.7.5 Folding endurance

Folding endurance was determined by repeatedly folding one patch from the same place till it cracked or broke. The number of times the film could be folded from the same place without breaking/ cracking represented the value of folding endurance.

6.7.6 Drug content test

Three pieces of 4 cm^2 were collected by cutting off zones from different parts of patch from each patch. These pieces were dissolved in 10 ml ethanol and were placed on vortex shaker for 1 h to dissolve completely the patches. The resultant solutions were filtered through the whatman paper and then 0.1 mL solution was withdrawn into another volumetric flask (10 mL) and dilution was made up to 10 mL. The absorbance of this solution was observed at 225 nm using UV-Visible spectrophotometer and the drug content was calculated.

6.7.7 Percent moisture content

The prepared transdermal films were weighed individually and kept in desiccators containing fused calcium chloride at room temperature for the duration of 24 hours. After 24 hours, the films were re-weighed and the percentage moisture content was determined by the given formula

$$\% = \frac{hh}{hh} 100$$

6.7.8 *In-vitro* permeation study

In-vitro permeation studies of the transdermal patches were carried out by using Franz diffusion cell with a receptor compartment capacity of 30 ml. The formulated patch of surface area of 4 cm^2 was placed in between the dialysis membrane and the donor compartment and then dialysis membrane was mounted between the donor and receptor compartment of diffusion cell. The receptor compartment of diffusion cell was filled with phosphate buffer saline pH 7.4. The whole assembly was fixed on a magnetic stirrer and the solution in the receptor compartment was constantly and continuously stirred magnetic beads at 50 rpm; the temperature was maintained at 37±0.5ºC. The 1 ml aliquots were withdrawal at different time intervals (0, 2, 4, 6, 8, 12 and 24 h) and analyzed the drug content by UV at 225 nm by appropriated dilution. The receptor phase was replenished with an equal volume of phosphate buffer (37ºC) at each sample withdrawal, the cumulative amount of drug permeated per square centimeter of patches were plotted against time.

RESULTS AND DISCUSSION

The objective of this study was to prepare transdermal patches containing sumatriptan and perform the in vitro evaluation of the formulations. The observation and interpretation of results obtained from the study are reported here.

7.1: Preformulation Studies

The physical characterization of the drug was performed according to the reported procedure and the results obtained are presented Table 7.1 and 7.2.

Table 7.1: Physical Characteristics of sumatriptan.

Test	Specification	Observation
Color	White to Off white	White
Odor	Odorless	Odorless
Appearance	Crystalline Powder	Crystalline powder

Table 7.2: Solubility of sumatriptan.

Solvent	Observation
Water	Soluble
Methanol	Soluble
Ethanol	Slightly soluble
Phosphate buffer	Soluble

7.2 Melting point

The melting point of sumatriptan was determined by capillary method, melting point of sumatriptan was found to be 172-174°C. Melting point compared with USP standards that showed that drug is pure.

7.3 Loss on Drying

Loss on drying of sumatriptan was determined by heating the drug to constant weight in hot air oven (Table 7.3)

Table 7.3: Loss on drying observed for sumatriptan pure drug.

Test	Specification	Observation
LOD	NMT 0.5%	0.30%

7.4 Calibration curve of sumatriptan

Calibration curve of sumatriptan was determined by plotting absorbance versus concentration (µg/ml) at 225 nm.

Table 7.4: Calibration curve data.

Concentration (µg/mL)	Absorbance
0	0
5	0.41
10	0.295
15	0.438
20	0.565
25	0.699

The linear regression analysis for the calibration curve was Abs = 0.0277(concentration) + 0.0118 with a regression coefficient of 0.9986.

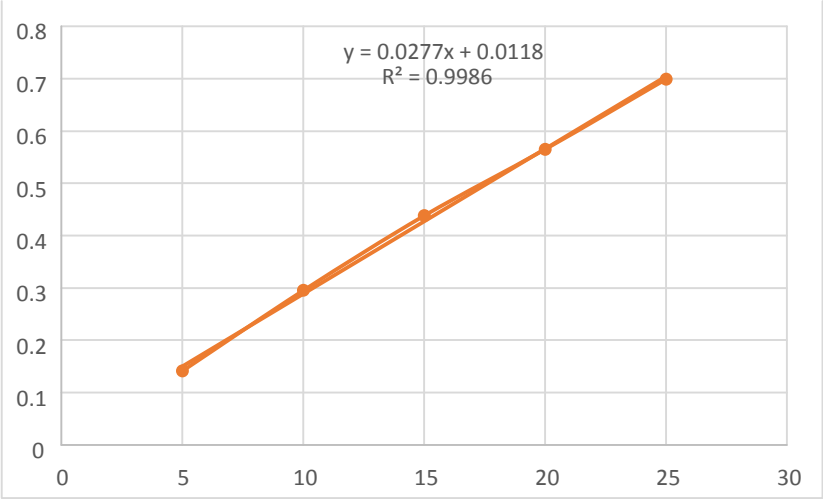

Figure 7.1: Calibration curve of sumatriptan.

7.5 Drug-polymer compatibility study

The FTIR spectra of the pure drug and physical mixture of drug and excipient were recorded in between 400-4000 wave number (cm^{-1}). Deletion of the peaks of the pure drug in the mixture spectra is usually taken as an indication of incompatibility of the drug and excipients. On comparison of the FTIR spectra of the drug and the mixture it was observed that no peak was deleted and only the intensities of the existing peaks changed which might be due to the coupling of absorption frequencies. This provides an evidence of compatibility between the drug and the matrix forming polymers.

The FT-IR spectra (Figure 7.2) exhibits the major peaks of the functional groups present in Sumatriptan. All these peaks were observed in the FT-IR spectra of the physical mixture of drug and excipients (Figure 7.3) also providing evidence for the absence of any chemical incompatibility between pure drugs with the excipients. The functional groups which cause the occurrence of the peaks are presented in Table 7.5.

Table 7.5: Major peaks occurring in the FT-IR spectra of sumatriptan.

S.No.	Wave Number	Peak Occurs Due to...
1	3271	N-H stretching
2	2925-2970	C-H stretching (alkyl)
3	1560	Aromatic C=C bending
4	1300	C-N stretching

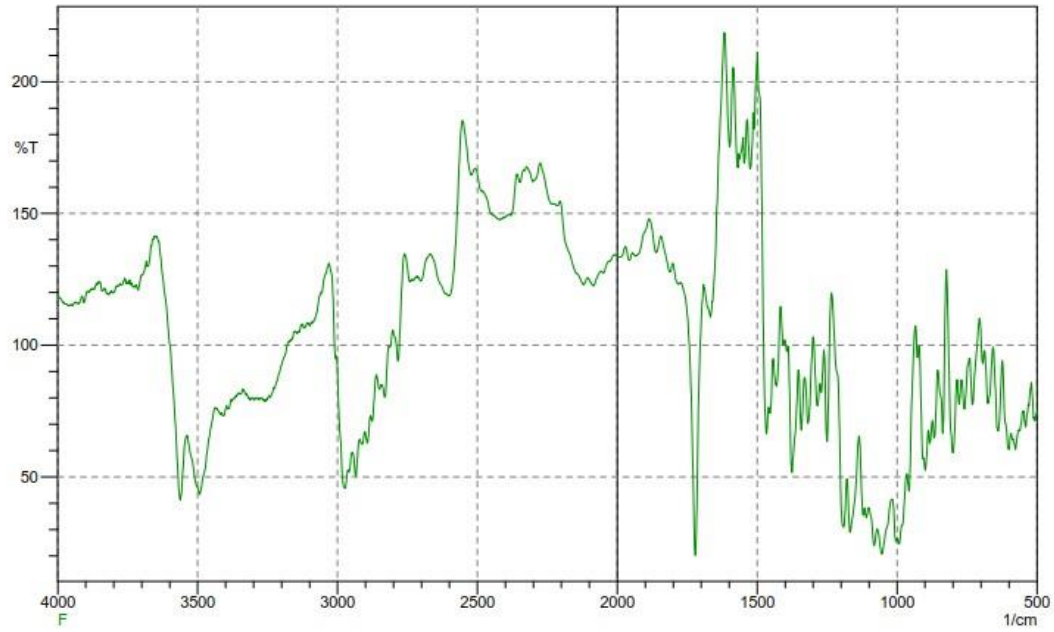

Figure 7.2: FTIR spectra of sumatriptan.

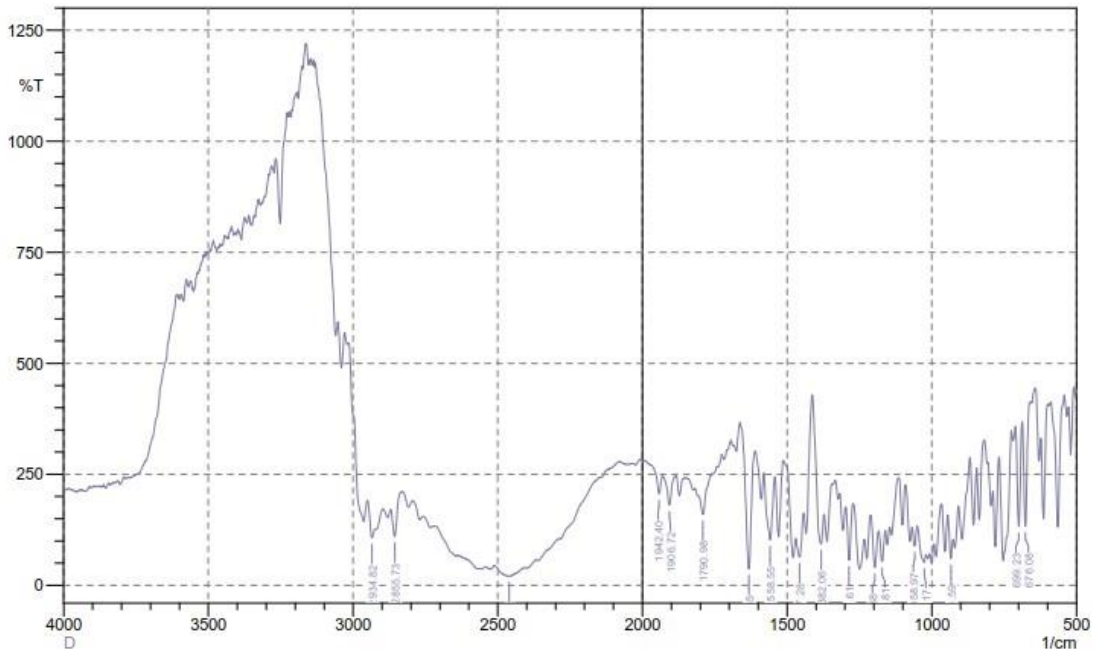

Figure 7.3: FTIR spectra of physical mixture (sumatriptan+HPMC+ethylcellulose).

7.6 Transdermal patch formulation

Transdermal patches containing sumatriptan were prepared using Hydroxy propyl methyl cellulose (HPMC) as the hydrophilic matrix and ethyl cellulose (EC) as the lipophilic component. The elasticity of the patches was attained using oleic acid (30% polymeric weight) as the plasticizer. Solvent casting method is the most widely used and the simplest

method for formulation of transdermal patches. The use of inverted funnel allows for controlled evaporation of the solvents from the patch. EC and HPMC were used in 3 different ratios to obtain the most optimized formulation.

The evaluation of the patches was done for various physical parameters as per procedure and the results are reported in Table 7.6.

All the prepared patches were subjected to visual inspection for examining the physical appearance. The physical appearance of the patches gave satisfactory results. All the prepared patches were found to be smooth, non-sticky, opaque, homogeneous, and flexible in nature.

Formulation	Thickness (mm)	Average weight (mg)	Moisture loss (%)	Drug content (%)	Folding Endurance	Surface pH
P1	0.513 ± 0.004	39.33 ± 0.577	7.24 ± 0.158	94.75 ± 0.404	75.33 ± 1.527	5.29 ± 0.006
P2	0.538 ± 0.003	44.66 ± 1.154	7.89 ± 0.058	95.58 ± 0.231	77.33 ± 0.577	5.69 ± 0.021
P3	0.589 ± 0.003	47.66 ± 0.577	10.15 ± 0.058	97.26 ± 0.115	83.66 ± 0.577	5.58 ± 0.02
P4	0.527 ± 0.004	45.66 ± 1.527	7.3 ± 0.100	94.72 ± 0.600	80.33 ± 1.152	5.62 ± 0.040
P5	0.565 ± 0.004	48.33 ± 0.577	7.75 ± 0.058	95.75 ± 0.265	77.33 ± 0.577	5.68 ± 0.031
P6	0.628 ± 0.003	51.66 ± 0.577	10.36 ± 0.158	97.32 ± 0.153	83.66 ± 1.152	5.71 ± 0.026
P7	0.535 ± 0.003	48.33 ± 0.577	7.15 ± 0.058	94.74 ± 0.6	74.66 ± 0.577	5.46 ± 0.025
P8	0.611 ± 0.002	54.00 ± 1.732	8.09 ± 0.058	95.85 ± 0.100	80.33 ± 0.577	5.39 ± 0.021
P9	0.689 ± 0.004	54.66 ± 0.577	9.93 ± 0.1	97.38 ± 0.208	83.33 ± 1.152	5.65 ± 0.015

As shown in the table 7.6 the pH levels of the patches ranged between 5.29 ± 0.006 to 5.69 ± 0.015 suggesting their suitability of human use and possibly suggesting that no skin irritation would be produced on application of the patches.

The thickness of the transdermal patches ranged from 0.513 ± 0.004 mm to 0.689 ± 0.004 mm. This difference in the thickness could be attributed to the nature and concentrations of polymers, i.e., an increase in the concentration of the hydrophilic polymer HPMC led to an increased thickness of the transdermal patch (Figure 7.4).

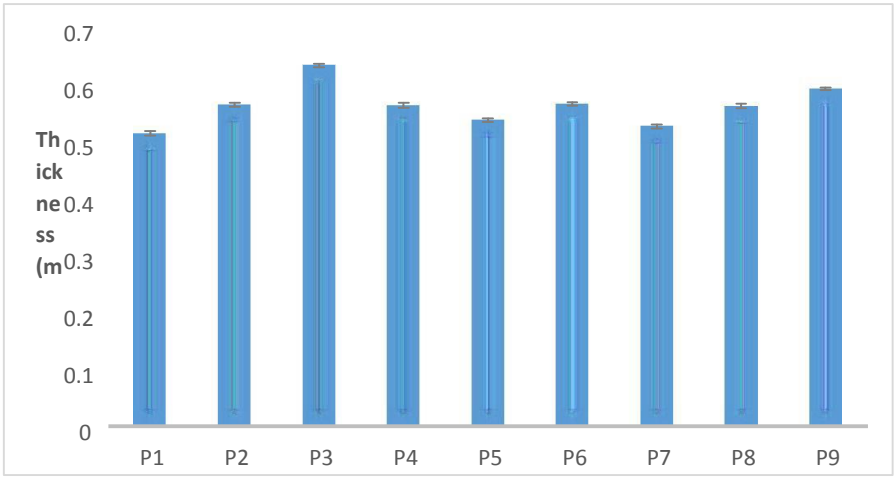

Figure 7.4: Variation in thickness of the transdermal patch formulations.

The formulated transdermal patches displayed weight variations between 39.33 ± 0.577 mg and 54.66 ± 0.577 mg. It was revealed from the weight variation data that the increase in the concentration of HPMC resulted in an increased weight of patches. This might be due to the fact that HPMC possesses a greater affinity for water and greater moisture uptake, causing an increased patch weight. The HPMC polymer is more hygroscopic in nature in comparison to EC; it might cause water retention in the patches, thereby resulting in increased weight of patches.

The moisture content of the formulated transdermal patches varied from 7.24 ± 0.158 % to 9.93 ± 0.158 %. Once again, the formulations containing greater amounts of HPMC resulted in an increase in moisture content. As HPMC is hydrophilic and it can cause absorption, as well as retention, of water in transdermal patches (Figure 7.5).

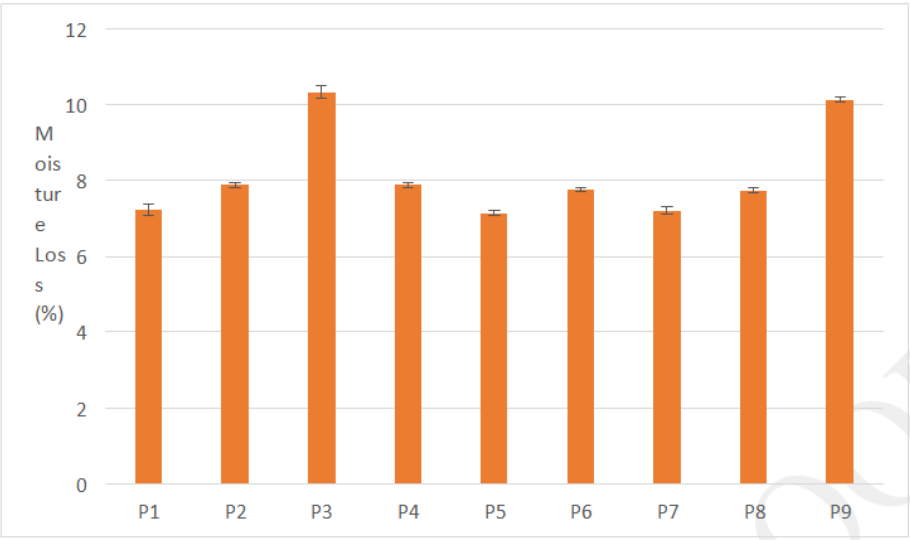

Figure 7.5: Variation in moisture content of the transdermal patch formulations.

Folding endurance is of utmost importance for patches because greater folding endurance prevents patches from being easily broken or damaged, and patches are considered to meet good quality. All the formulated transdermal patches exhbited high folding endurance (>70 times). This reveals that all transdermal patches meet the standard patch requirements. Different concentrations of the polymers (HPMC and EC) did not considerably affect the folding endurance of the transdermal patches though higher HPMC content increased the folding endurance. Oleic acid was used as a plasticizer for obtaining flexible patch formulation.

All the transdermal patch formulations exhibited uniform drug content and with a minimum variability within the batch. The drug content ranged from 94.75 ± 0.6 % to 97.38 ± 0.208 % (Figure 7.6). This drug content range is deemed suitable for transdermal application.

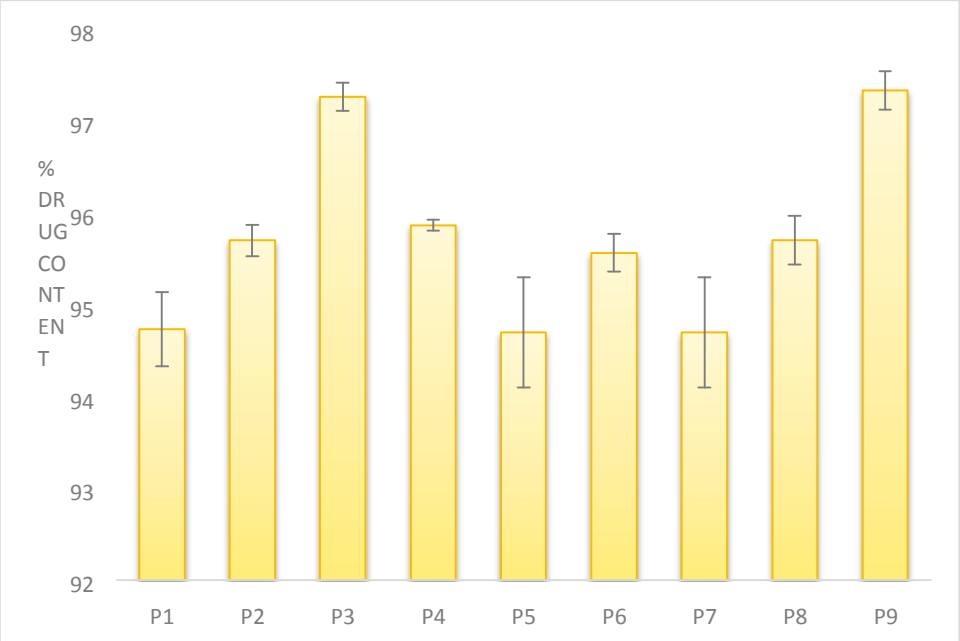

Figure 7.6: Drug content in the formulated transdermal patches.

From the above figure it was very clear that increase in the concentration of HPMC caused an increase in drug loading in the patch which may be due to the fact that HPMC being a hydrophilic polymer had affinity for sumatriptan which is also having good water solubility. The retention of water by HPMC in turn led to the higher loading of sumatriptan.

7.7 *In-vitro* permeation study

The amount of drug that permeated or released from the transdermal patches was determined using Franz diffusion cell.

The *in vitro* drug release study depicted that the highest amount of drug was released from **P9** (90.21 ± 1.286 %) while the lowest was released from **P1** (62.39 ± 1.066 %) at the end of 24 hours of release study. Faster drug release was observed from formulated patches containing greater amounts of the lipophilic polymer, EC (Figure 7.7).

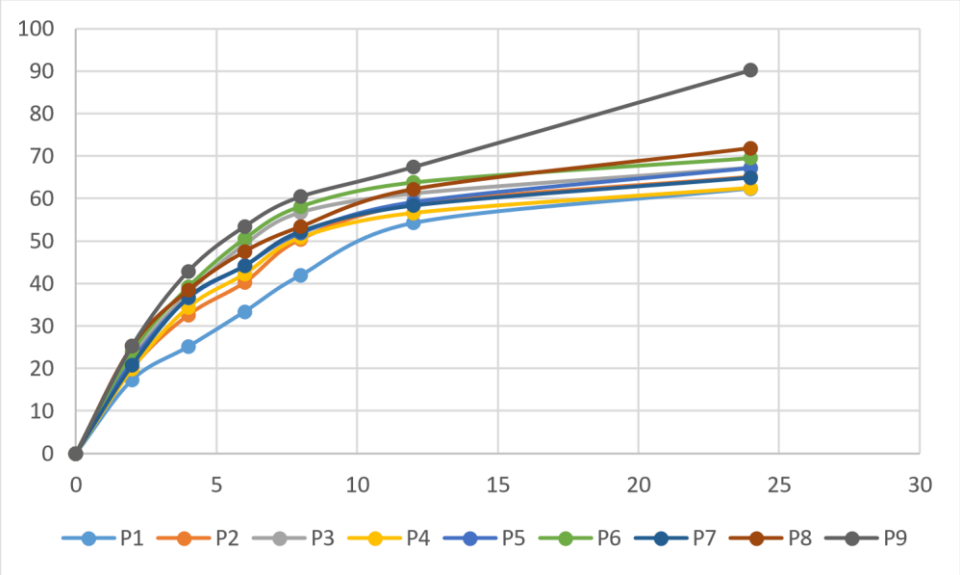

Figure 7.7: Release of sumatriptan from transdermal patches (*in vitro*).

SUMMARY AND CONCLUSION

8.1 Summary

In the present study the prime objective was to develop transdermal patches loaded with sumatriptan in order to improve its bioavailability by sustaining the drug release. Transdermal patches were prepared using Hydroxy propyl methyl cellulose (HPMC K) as the hydrophilic matrix and ethyl cellulose (EC) as the lipophilic component. The elasticity of the patches was attained using oleic acid (30% polymeric weight) as the plasticizer. EC and HPMC were used in 3 different ratios to obtain the most optimum formulation.

All the prepared patches were subjected to visual inspection for examining the physical appearance. The physical appearance of the patches gave satisfactory results. All the prepared patches were found to be smooth, non-sticky, opaque, homogeneous, and flexible in nature.

The pH levels of the patches ranged between 5.29 ± 0.006 to 5.69 ± 0.015 suggesting their suitability of human use and possibly suggesting that no skin irritation would be produced on application of the patches.

The thickness of the transdermal patches ranged from 0.513 ± 0.004 mm to 0.689 ± 0.004 mm. This difference in the thickness could be attributed to the nature and concentrations of polymers, i.e., an increase in the concentration of the hydrophilic polymer HPMC led to an increased thickness of the transdermal patch.

The formulated transdermal patches displayed weight variations between 39.33 ± 0.577 mg and 54.66 ± 0.577 mg. It was revealed from the weight variation data that the increase in the concentration of HPMC resulted in an increased weight of patches. The moisture content of the formulated transdermal patches varied from 7.24 ± 0.158 % to 9.93 ± 0.158 %.

All the formulated transdermal patches exhibited high folding endurance (>70 times). This reveals that all transdermal patches meet the standard patch requirements.

All the transdermal patch formulations exhibited uniform drug content and with a minimum variability within the batch. The drug content ranged from 94.75 ± 0.6 % to 97.38 ± 0.208 %

The *in vitro* drug release study depicted that the highest amount of drug was released from **P9** (90.21 ± 1.286 %) while the lowest was released from **P1** (62.39 ± 1.066 %) at the end of 24 hours of release study.

8.2 CONCLUSION

The primary objective of the present investigation was formulating transdermal patched loaded with sumatriptan, for management of inflammation. The formulation was achieved using Hydroxypropylmethylcellulose (HPMC) and ethylcellulose (EC) as the polymeric release controlling matrix. The formulation was expected to overcome the problems of poor bioavailability, poor distribution and high metabolism associated with oral administration of sumatriptan. The ability of the formulated transdermal patches to sustain the release of sumatriptan for more than 24 hours was conclusive enough that the problems associated with the oral administration were taken care of. The formulation **P9** released the highest amount of drug and presented highest drug loading.

Thus is could be concluded that **P9** was the best formulation with sufficient strength and drug release that would be able to effectively manage migraine pain throughout the day.

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