DESIGN, DEVELOPMENT AND CHARACTERIZATION OF VERAPAMIL HYDROCHLORIDE MEMBRANE MODERATE TYPE TRANSDERMAL PATCHES

Dissertation submitted to

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY, CHENNAI-32

In partial fulfillment for the award of the degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

Register Number: 261210006

UNDER THE GUIDANCE

Dr. Rama, M.Pharm., Ph.D.
(Institutional Guide)

Dr. Lakshmi, Mpharm., Ph.D.
(Industrial Guide)

DEPARTMENT OF PHARMACEUTICS,
C.L.BAID METHA COLLEGE OF PHARMACY,
(An ISO 9001-2000 certified institute),
THORAIPAKKAM, CHENNAI-600097.

APRIL-2013

Rp Richer Pharmaceuticals

It is to certify that Smt. **G.Hema Navyatha** Studying Second year M.Pharmacy bearing registration number:561210006 at C.L.Baid Metha College of Pharmacy affiliated to The Tamilnadu Dr. M.G.R. Medical University, Chennai-32 have completed her project work successfully on topic "**Design, Development And Characterization Of Verapamil Hydrochloride Membrane Moderate Type Transdermal Patches**" during the period 2013-2014.

Manufacturing Unit: #5-5-36/23, IDA, Prasanthnagar, Kukatpally, Hyderabad - 500 072.
Ph: 040-64513413. Email: richerpharmaceuticals@gmail.com

Phone : 24960151, 24960425
E-mail : principal@clbaidmethacollege.com
Website : www.clbaidmethacollege.org

C.L. Baid Metha College of Pharmacy

An ISO 9001 - 2000 certified institution

Jyothi Nagar, Old Mahabalipuram Road
Thorapakkam, Chennai - 600 097.

Affiliated to The Tamilnadu Dr. M.G.R. Medical University, Chennai.
Approved by Pharmacy Council of India, New Delhi, and
All India Council for Technical Education. New Delhi.

CERTIFICATE

This is to certify that the dissertation work entitled **"DESIGN, DEVELOPMENT AND CHARACTERIZATION OF VERAPAMIL HYDROCHLORIDE MEMBRANE MODERATE TYPE TRANSDERMAL PATCHES"** submitted to **THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI-32** for the award of the degree **Master of pharmacy in Pharmaceutics** is a bonafide research work done by **Register No: 261210006** under my Guidance in the Department of Pharmaceutics, C.L.Baid Metha College of Pharmacy, Chennai-600097 during the academic year 2013-2014.

Place: Chennai-97

Date:

Dr. Rama, M.Pharm., Ph.D.
Assistant professor,
Department of pharmaceutics,
C.L.Baid Metha College of pharmacy,
Chennai-97

Phone : 24960151, 24960425
E-mail : principal@clbaidmethacollege.com
Website : www.clbaidmethacollege.org

C.L. Baid Metha College of Pharmacy

An ISO 9001 - 2000 certified institution

Jyothi Nagar, Old Mahabalipuram Road
Thorapakkam, Chennai - 600 097.

Affiliated to The Tamilnadu Dr. M.G.R. Medical University, Chennai.
Approved by Pharmacy Council of India, New Delhi, and
All India Council for Technical Education. New Delhi.

Prof. Dr. Grace Rathnam, M.pharm., PhD

Principal

CERTIFICATE

This is to certify that the dissertation work entitled **"DESIGN, DEVELOPMENT AND CHARACTERIZATION OF VERAPAMIL HYDROCHLORIDE MEMBRANE MODERATE TYPE TRANSDERMAL PATCHES"** submitted to **THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI-32** for the award of the degree **Master of Pharmacy in Pharmaceutics** is a bonafide research work done by **Register No: 261210006** under the guidance of **Dr. Rama, M.Pharm. Ph.D. Assistant professor,** Department of Pharmaceutics, C. L. Baid Metha college of Pharmacy, Chennai-600 097 during the academic year 2013-2014.

Place: Chennai -97
Date:

Prof. Dr. GRACE RATHNAM, M. Pharm., Ph.D.
Principal & HOD,
Department of Pharmaceutics,
C.L.Baid Metha college of Pharmacy
Chennai-97

DECLARATION

I hereby declare that the thesis entitled **"DESIGN, DEVOLOPMENT AND CHARECTERIZATION OF VERAPAMIL HYDROCHLORIDE MEMBRANE MODERATE TYPE TRANSDERMAL PATCHES"** has been originally carried out by me under the supervision and guidance of **Dr. Lakshmi, Mpharm., Ph.D.** (Industrial Guide) **Dr.Rama,M.Pharm., Ph.D.** (Institutional Guide) Asst.Professor, Department of Pharmaceutics, C.L.Baid Metha college of Pharmacy, Chennai-97, during the academic year 2013-2014.

Place: Chennai-97

Date:

Register No: 261210006,
Department of Pharmaceutics,
C.L.Baid Metha college of Pharmacy,
Chennai-97.

Dedicated to My

Beloved Parents

&

Husband

ACKNOWLEDGEMENT

I am currently extremely grateful to thank **Dr. GRACE RATHNAM, M.Phram., Ph.D**, principal, Head of Department, C.L.Baid Metha Collage of pharmacy for her excellent guidance, moral support, constant encouragement and constructive suggestions throughout my project work.

I am extremely thankful to my industrial guide **Dr. Lakshmi, M.Pharm, ph.D** for her support and encouragement throughout my project work.

I express my sincere to **Dr. RAMA, M.Pharm, Ph.D**, Assistant Professor, Department of Pharmaceutics, C.L.Baid Metha collage of pharmacy, Chennai, for her support, and encouragement throughout my project work.

Above all I thank **GOD** for showing me with plentiful blessing and for giving me strength and courage to complete this work.

CONTENTS

Introduction

1. INTRODUCTION

NOVEL DRUG DELIVERY SYSTEM

The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery system or by modifying the molecular structure and or physiological parameters inherent in a selected route of administration[1].

The goal of drug delivery is to produce drug concentrations that elicit desired pharmacological actions and to minimize the incidents and severity of unwanted adverse effects. To achieve this goal it would be advantageous and more convenient to maintain a dosing frequency at once or at most a twice- daily regimen.

In conventional oral drug delivery system, there is little or no control over the release of the drug and effective concentration at the target side can be achieved by intermittent administration of grossly excessive doses. This kind of dosing pattern results in constantly changing, unpredictable, and often subtherapeutic or supratherapeutic plasma concentrations, leading to marked side effective some case, moreover, the rate and extent of absorption of drug from conventional formulation may vary greatly depending on the factors such as physico-chemical properties of the drug, the presence of excipients, and various physiological factors.

Conventional dosages forms are rapidly absorbed with the ascending and descending portions of the concentrations versus time curves reflecting primarily the rate of absorption and elimination, respectively. Because of the rapid rate of absorption from conventional dosage forms, drugs are usually administered more than once daily with the frequency being dependent on biological half-life and

duration of pharmacological effect. The time of dosing may also be effected by therapeutic index of a drug.

Recently, several technical advancements have been made they have resulted in the development of new techniques for drug delivery . This techniques are capable of controlling the rate of drug delivery sustaining the duration of therapeutic activity and or targeting the delivery of drug to tissues[2].

Novel drug delivery system[3] can be broadly classified into two groups.

1. Sustained release drug delivery system (SRDDS).

2. Controlled release drug delivery system(CRDDS)

Sustained release drug delivery system:

SRDDS is described as pharmaceutical dosage form formulated to sustain the release of a therapeutic agent, such that its appearance in the systemic circulation is delayed and are prolonged and its plasma profile is sustained in duration. This leads to increase in duration of effects so that therapeutic effect is sustained.

Controlled release drug delivery system:

The objective in designing a controlled drug delivery system is to provide for the release of a pharmacologically active agent in a predetermined predictable and reproducible manner. The rationale behind controlled release formulations is that a drug is more effective and exhibits less side effects when its concentration in the circulation is kept constant at some optimum level for prolonged periods of time. Fig.1.illustrates the expected drug concentration profiles for different methods of drug administrations.

The plasma concentration of the drug reaches a maximum (peak) with conventional dosage forms and then decrease (valley) at the point where repeated

administrations becomes necessary to maintain the plasma concentrations. Very often the initial concentration Is above the therapeutically effective level that may increase the risk of side effects. Conventional dosage forms can thus result in a drug regimen in which the drug concentration oscillates between altering periods of drug overdose and drug in efficiency. Controlled release formulations are expected to remove the peaks and valleys of drug concentration in the blood thus providing for a more effective regimen. It should be pointed out here that constant drug concentrations are not always necessary for the best treatment of disease. For example treatment of diabetes with fluctuating levels of insulin requires self-modulated system, the rate of drug delivery can change continuously in response to the concentrations of a specific moiety in various triggered devices. Drug release does not takes place until it is activated by a specific a external moiety and more activated drug release takes place at a preprogrammed rate[4].

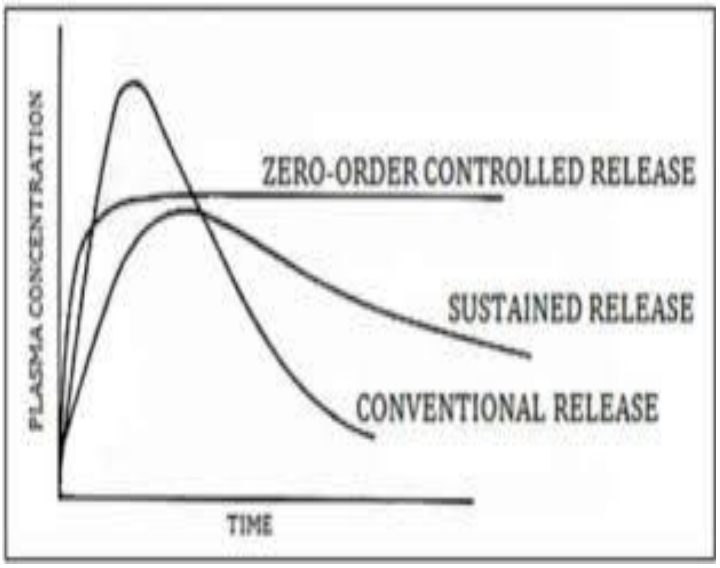


Figure 1: Drug level versus time profile showing differences between zero-order controlled release, slow first-order sustained release, and immediate release[5]

The term " Controlled release" implies predictability and reproducibility in drug release kinetics , which means that the release of drug ingredients from a controlled release drug delivery system proceeds at a rate profile i.e. not only predictable kinetically , but also reproducible from one unit to another.

In recent years considerable attention has been focused on the development of controlled release drug delivery systems. Controlled release drug delivery systems are designed to release one or more drugs continuously in a predetermined pattern for a fixed period of time either systemically or to a specified target organ. Drug release from this system should be at a desired predictable and reproducible rate. The primary objectives of controlled release drug delivery are to ensure safety and to improve efficacy of drugs as well as patient compliance. Controlled release drug delivery systems have been designed for oral parental, implantable and transdermal route.

The benefits of intravenous infusion closely duplicated, without its hazards by using the skin as the port of drug administration to provide continuous transdermal drug infusion into the systemic circulation.

Transdermal drug delivery systems (TDDS)[6] are defined as self contained, discrete dosage forms which, when applied to intact skin, deliver the drug(s), through the skin, at a controlled rate to systemic circulation. The transdermal route of administration is recognized as one of the potential route for the local and systemic delivery of drugs. In comparison to conventional pharmaceutical dosage forms, TDDS offer many advantages, such as elimination of first pass metabolism, sustained drug delivery, reduced frequency of administration, reduced side effects and improved patient compliance.

To provide continuous drug infusion through the intact skin, membrane moderated systems, adhesive diffusion controlled systems, matrix dispersion type systems and micro reservoir systems have been developed for the topical application on to the intact skin surface to control the delivery of drug and its subsequent permeation through the skin tissue. In membrane moderated systems, drug reservoir is encapsulated in a shallow compartment moulded from a drug impermeable metallic plastic laminate and a rate controlling polymeric membrane which may be micro porous or non-porous. The drug molecules are permitted to release only through the rate controlling polymeric membrane. Membrane moderated systems were developed in this investigation, as they are easy to fabricate in a wide range of

sizes and the constant release rate of the drug is the major advantage of membrane permeation controlled system.

Continuous intravenous infusion is recognized as a superior mode of drug delivery not only to bypass hepatic ‘’first-pass” elimination, but also to maintain a constant, prolonged and therapeutically effective drug level in the body. A closely monitored intravenous infusion can provide the advantage of drug into the systemic circulation and control of circulating drug levels. However this mode of drug delivery involves certain risks.

Recently there has been a growing recognition that the benefits of intravenous infusion can be closely duplicated without its hazards, by using the intact skin as the port of drug administration to provide continuous drug delivery into the systemic circulation[7]. This is known as the transdermal administration and the drug delivery systems are known as “transdermal therapeutic systems” or popularly as “transdermal patches”.

Transdermal drug delivery systems[8] are adhesive drug containing devices of defined surface area that deliver a predetermined amount of drug to the surface of intact skin at a programmed rate. These systems provide drug systemically at a predictable rate and maintain the rate for extended period of time thus eliminating numerous problems associated with oral dosing including product stability, bioavailability and the peaks and troughs of pulse dosing.

ADVANTAGES & DISADVANTAGES TRANSDERMAL DRUG DELIVERY SYSTEMS[9, 10, 11, 12:]

Advantages:

1. Transdermal medication delivers a steady infusion of a drug over an extended period of time. Adverse effects or therapeutic failures frequently associated with intermittent dosing can also be avoided.

2. Transdermal delivery can increase the therapeutic value of many drugs by avoiding specific problems associated with the drug e.g., gastro-intestinal irritation, low absorption, decomposition due to hepatic ‘’first- pass” effect, formation of metabolites that cause side effects, short half-life necessitating frequent dosing etc.

3. Due to the above advantage, it is possible that an equivalent therapeutic effect can be elicited via transdermal drug input with a lower daily dose of the drug than is necessary, if, for example, the drug is given orally.

4. The simplified medication regimen leads to improved patient compliance and reduced inter & intra – patient variability.

5. At times the maintenance of the drug concentration within the bio phase is not desired. Application and removal of transdermal patch produce the optimal sequence of pharmacological effect.

6. Self administration is possible with these systems.

7. The drug input can be terminated at any point of time by removing transdermal patch.

Disadvantages:

1. The drug must have some desirable physicochemical properties for penetration through stratum corneum and if the drug dose required for therapeutic value is more than 10 mg/day, the transdermal delivery will be very difficult.

2. Only relatively potent drugs are suitable candidates for TDDS because of the natural limits of drug entry imposed by the skin’s impermeability.

3. Some patients develop contact dermatitis at the site of application for one or more of the system components, necessitating discontinuation.

4. Clinical need is another area that has to be examined carefully before a decision is made to develop a transdermal product.

5. The barrier function of the skin changes from one site to another on the same person, from person to person and with age.

DRUG PERMEATION THROUGH SKIN:

Skin as a Site for drug infusion:

The skin of an average adult body covers a surface area of approximately 2 square meters and receives about one-third of the blood circulating through the body[13].The skin is a multilayered organ composed of many histological layers.

Structure and physiology of skin:

Macroscopically skin comprises of three layers

1. The epidermis,

2. The dermis,

3. The hypodermis.

Epidermis:

The epidermis is a stratified, squamous, keratinizing epithelium. The keratinocytes comprise the major cellular component and are responsible for the evolution of barrier function.

Microscopically, the epidermis can be divided into five distinct strata with stratum corneum forming the outer most layer of the epidermis, exposing to the external environment which correspond to the consecutive steps of keratinocyte differentiation.

Five strata of epidermis as shown in Figure 2.

The ultimate result of this differentiation process is formation of the functional barrier layer, the stratum corneum.

The five stratum include

1. Stratum basale
2. Stratum spinosum
3. Stratum granulosum
4. Stratum lucidum
5. Stratum corneum

Stratum basale:

The stratum basale or basal layer is responsibility for the continual renewal of the epidermis proliferation of the stem cells in stratum basale and creates new keratinocytes pushing the existing towards the surface thus they begin to differentiate finally achieving terminal differentiation in the stratum corneum.

Stratum spinosum:

The next layer of epidermis is the stratum spinosum named for the numerous spiny projections (desmosomes on the cell surface). The keratinocytes maintain a complete set of organelles and also include membrane coating granules (or lamellae bodies) which originate in the golgi.

Stratum Granulosum

The stratum granulosum is also called as granular layer characterized by numerous keratokyalin granules present in the cytoplasm of the more flattened, yet still viable, keratinocyte more lamellar bodies are also apparent and concentrate on the upper part of granulae cells. These contain stacks of flattened lipid vesicles.

Stratum Lucidum

The transition layer, the stratum lucidum comprises flattened cells which are not easy to visualize microscopically, the cellular organelles are broken down leaving only keratin filaments in the stratum granulosum, a inter filament matrix material in the intracellular compartment. The membrane coating granules fuse with the cell membrane and release their contents into the intercellular space.

These inter cellular lipids organize into multilamellar domains. Finally in the stratum corneum the outer most layer, protein is added to the inner surface of the cell membrane to form a cornified envelope that further strengthens the resistance of the cell.

Stratum corneum

It forms the primary barrier to dermatological delivery and consists of horny, flat, polyhedral shaped, non –nucleated cells approximately 40 µm in diameter and 0.5 µm thick called as corneocytes. These corneocytes are cell remnants of the terminally differentiated keratinocytes present in the upper layer of the viable epidermis.

These are surrounded by a layer of cross-linked proteins and covalently linked lipid. The intercellular lipids of the stratum cornuem include number of phospholipids comprising approximately equimolar mixture of ceramides, cholesterol and free fatty acids. These non-polar and somewhat rigid components of the stratum corneum play a critical role in barrier function to chemical penetration and permeation.

The diffusion pathways across the stratum corneum are

1. Inter cellular lipid
2. Pores
3. Hair follicles

Dermis:

The dermis is composed of network of collagen and elastin fibres embedded in a mucopolysaccharide matrix, that also contain blood vessels, lymphatics, and nerve endings and which provides physiological support for the epidermis.

Hypodermis:

Essential to the healthy function of the dermis and epidermis.

The hypodermis is mainly composed of fat cells that cushion the upper layer absorb nutrients, oxygen and moisture from the blood and remove toxic waste.

This subcutaneous layer contains glands and other skin structures, as well as sensory receptors involved in the sense of touch.

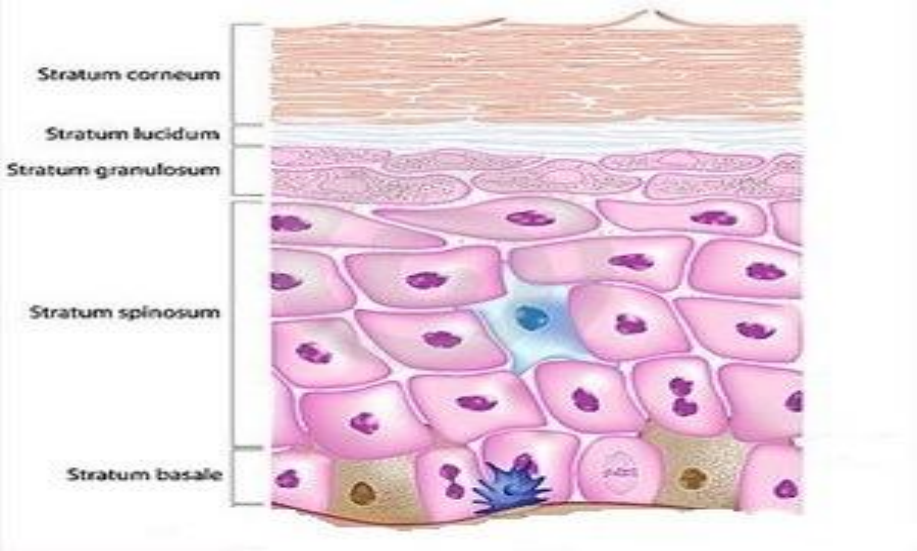


Figure 2: Structure of epidermis

The various skin tissue layers can be represented by a simplistic multilayer model as shown in Figure 3.

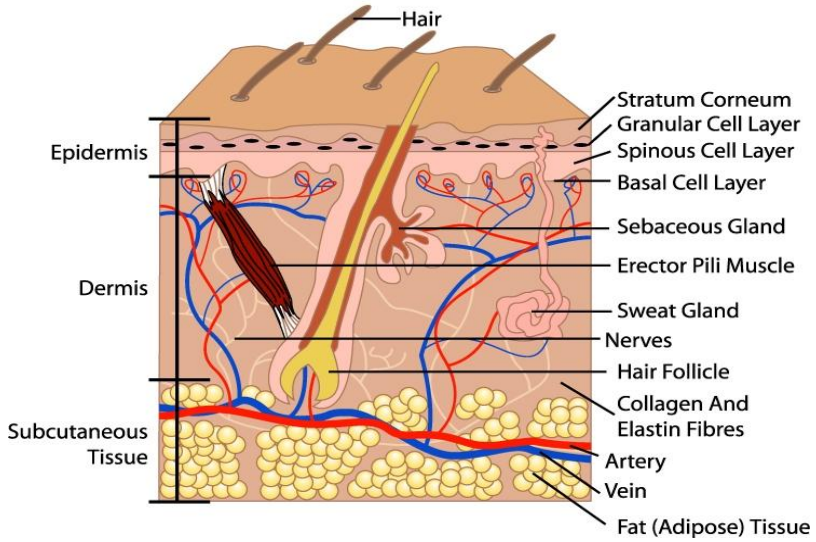


Figure 3: A cross-section of human skin

Skin as a membrane:

An average human skin surface is known to contain, on the average, 40-70 hair follicles and 200-250 sweat ducts on each square centimeter of skin area. These skin appendages, however, actually occupy, grossly, only 0.1% of the total human skin surface. Even though the foreign agents, especially the water-soluble ones, may be able to penetrate into the skin via these skin appendages at a rate which is faster than through the intact area of the stratum corneum, this trans-appendageal route of percutaneous absorption has, at steady state, a very limited contribution to the over all kinetic profile of transdermal permeation. Therefore, the transdermal permeation of most neutral molecules can, thus, be considered as, a process of passive diffusion through the intact stratum corneum in the interfollicular region. So, for the sake of mechanistic analysis of transdermal drug infusion[14] from stratum corneum the following model (figure 3) can be used. In the case that the skin serves as the point of administration for systemically active drugs, the drug applied topically will be absorbed, first into the systemic circulation and then transported to target tissues.

Mechanisms of Transdermal Permeation:

For a systemically active drug to reach a target tissue, it has to posses some physico-chemical properties which facilitate the sorption of the drug through the skin (Figure: 3), and also the uptake of the drug by the capillary network in the dermal papillary layer (Figure:5). Various events governing percutaneous absorption are shown in (Figure:4).

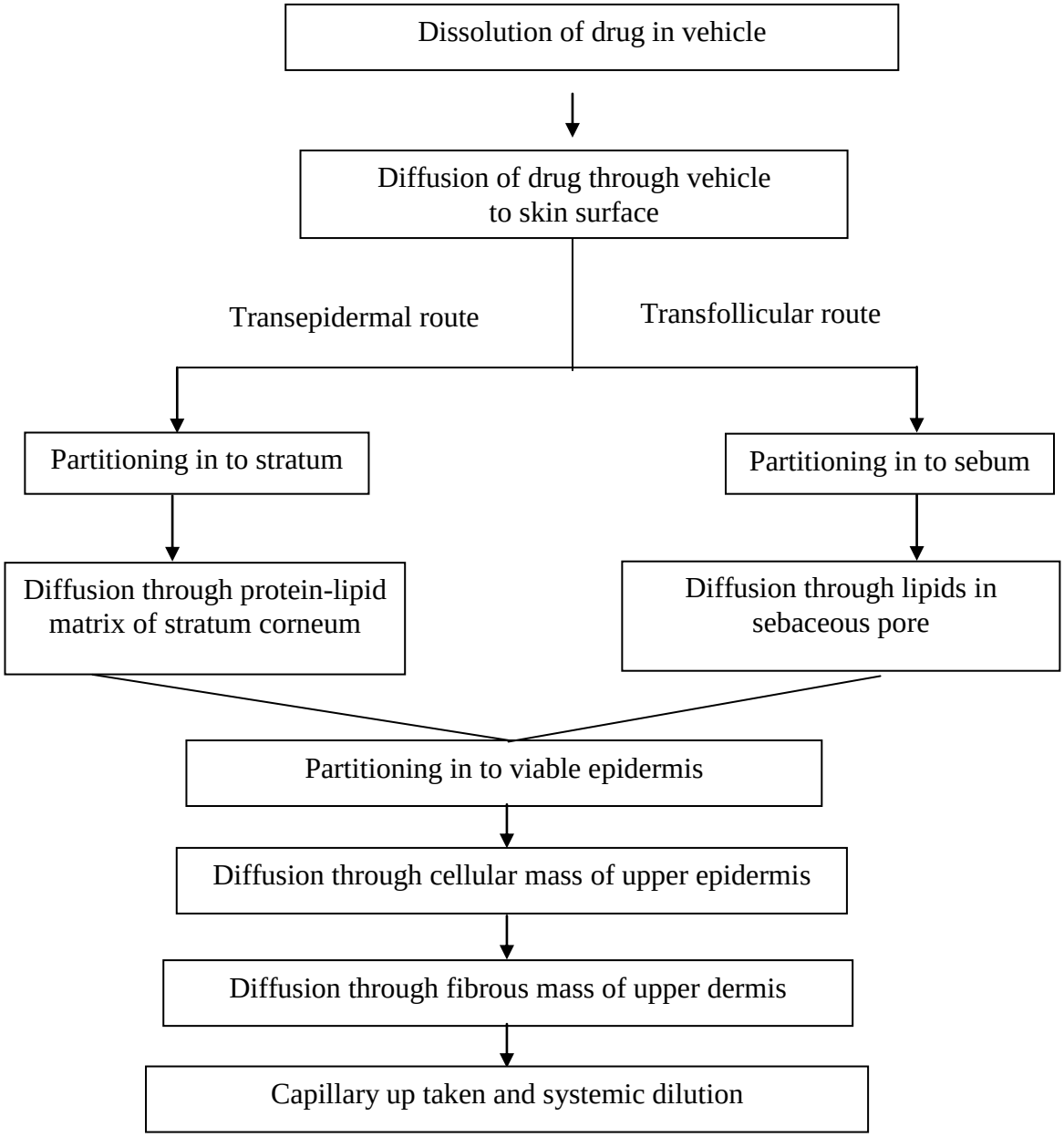


Figure 4: Events governing percutaneous absorption

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

$$\frac{dQ}{dt} = P_s (C_d - C_r) \text{ - - - - - } (1)$$

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

$$P_s = \frac{K_s D_{ss}}{h_s} \text{ - - - - - } (2)$$

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 since Ks; D_{ss} and h_s terms in equation (2) are constant under the given set of conditions.

A constant rate of drug permeation achieved, if $C_d > C_r$, then the equation (1) may be reduced to

$$\frac{dQ}{dt} = P_s . C_d \text{ - - - - - } (3)$$

And the rate of skin permeation (dQ/dt) becomes a constant, if the C_d value remains fairly constant throughout the course of skin permeation. To maintain the C_d at a constant value, it is critical to make the drug to be released at a rate (R_r) which is always greater than the rate of skin uptake (R_a), i. e., $R_r >> R_a$.

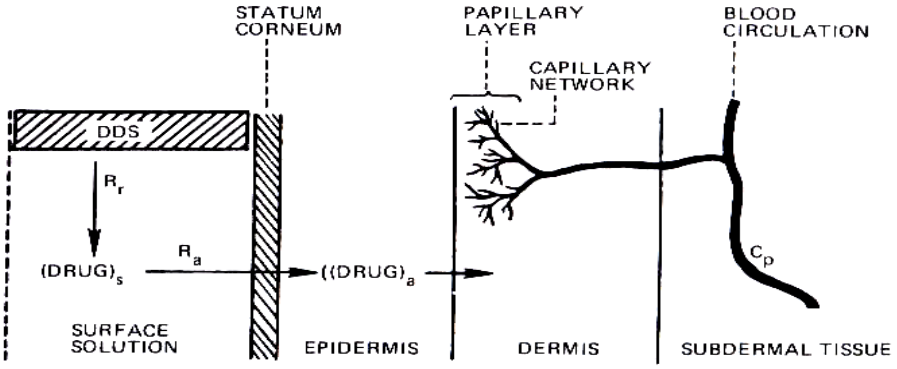


Figure 5: Diagrammatic illustration of the relationship between the rate of drug release (R_r) and the rate of drug uptake (R_a) by the skin

By doing so, the drug concentration on the skin surface (C_d) is maintained at a level which is always greater than the equilibrium (or saturation) solubility of the drug in the stratum corneum (C^e_s), i.e., $C_d >> C^e_s$; and a maximum rate of skin permeation $(dQ/dt)_m$,as expressed by equation (4),is thus reached:

$$\left(\frac{dQ}{dt}\right)_m = P_s C_s^e$$

Apparently, the magnitude of $(dQ/dt)_m$ is determined by the skin permeability coefficient (P_S) of the drug and its equilibrium solubility in the stratum corneum (C^e_s).

BASIC COMPONENTS OF TRANSDERMAL DRUG DELIVERY SYSTEM[15]

The components of transdermal patch includes:

1. Polymer matrix or matrices
2. The drug
3. Permeation enhancers and
4. Other excipients.

Polymer matrix or matrices:

It is the rate controlling polymeric membrane which regulates the release rate of drug during a predetermined time interval. The following criteria should be satisfied for a polymer to be used in the transdermal system[16].

1. Molecular weight, glass transition temperature and chemical functionality of the polymer should be such that the specific drug diffuses properly and gets released through it.
2. The polymer should be stable, non reactive with drug, easily manufactured and fabricated into the desired product and inexpensive.
3. The polymer and its degradation products must be non toxic or non antagonistic to the host.
4. The mechanical properties of the polymer should not deteriorate excessively when large amount of active agents are incorporated into it.

The Drug:

For successfully developing a transdermal drug delivery system, the drug should be chosen with great care. The following are some of the desirable properties of a drug for transdermal delivery[17].

A. Physicochemical Properties:

1. The drug should have molecular weight less than approximately 1000 Daltons.
2. The drug should have affinity for both lipophillic and hydrophilic phases. Extreme partitioning characteristics are not conducive to successful delivery via the skin.
3. The drug should have a low melting point.

B. Biological Properties:

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

Permeation Enhancers:

Three pathways are suggested for drug penetration through the skin: polar, non-polar, and polar/non-polar. The enhancers act by altering one of these pathways. The key to altering the polar pathway is to cause protein conformational change or solvent swelling. The key to altering the nonpolar pathway is to alter the rigidity of the lipid structure and fluidize the crystalline pathway (this substantially increases diffusion). The fatty acid enhancers increase the fluidity of the lipid portion of the stratum corneum[18, 19]. Some enhancers (binary vehicles) act on both polar and nonpolar pathways by altering the multi laminate pathway for penetrants. Enhancers can increase the drug diffusivity in the stratum corneum by dissolving the skin lipids or by denaturing skin proteins. The type of enhancer employed has a significant impact on the design and development of the product.

The success of dermatological drug products that are intended for systemic drug delivery, such as the transdermal, depends on the ability of the drug to penetrate through the skin in sufficient quantities to achieve its desired therapeutic

effect. The methods employed for modifying the barrier properties of the stratum corneum to enhance the drug penetration (and absorption) through the skin can be categorized as (1) Chemical and (2) physical methods of enhancement[20]

A. Chemical Enhancers:

Chemicals that promote the penetration of topically applied drugs are commonly referred to as accelerants, absorption promoters, or penetration enhancers. Chemical enhancers act by

1. Increasing the drug permeability through the skin by causing reversible damage to the stratum corneum.
2. Increasing (and optimizing) thermodynamic activity of the drug when functioning as co solvent.
3. Increasing the partition coefficient of the drug to promote its release from the vehicle into the skin.
4. Conditioning the stratum corneum to promote drug diffusion.
5. Promoting penetration and establish drug reservoir in the stratum corneum.

B. Physical enhancers:

The iontophoresis and ultra sound (also known as phonophoresis or sonophoresis) techniques are examples of physical means of enhancement that have been used for enhancing percutaneous penetration (and absorption) of various therapeutic agents.

Other Excipients:

A. Adhesives:

The fastening of all transdermal devices to the skin has been done by using a pressure sensitive adhesive. The pressure sensitive adhesive can be positioned on the face of the device or in the back of the device and extending peripherally. The adhesive used in transdermal drug delivery system should fulfill the following criteria[21].

1. Should not irritate or sensitize the skin or cause an imbalance in the normal skin flora during its contact time with the skin.
2. Should adhere to the skin aggressively during the dosing interval without its position being disturbed by activities such as bathing, exercise etc.
3. Should be easily removed
4. Should not leave an unwashable residue on the skin.
5. Should have excellent contact with the skin at macroscopic and microscopic level.

The face of adhesive system should also fulfill the following criteria.

a) Physical and chemical compatibility with the drug, excipients and enhancers of the device of which it is a part.

b) Permeation of the drug should not be affected.

B. Backing membrane:

Backing membranes are flexible and they provide a good bond to the drug reservoir, prevent drug from leaving the dosage form through the top, and accept printing. It is impermeable substance that protects the product during use on the skin e.g. metallic plastic laminate, plastic backing with absorbent pad and

occlusive base plate (aluminum foil),adhesive foam pad (flexible poly urethane) with occlusive base plate (aluminum foil disc) etc.

APPROACHES TO DEVELOPMENT OF TRANSDERMAL THERAPEUTIC SYSTEMS[22]:

Several technologies have been successfully developed to provide a rate control over the release and the transdermal permeation of drugs. These technologies can be classified into four approaches as follows:

1. **Membrane permeation – controlled systems**
2. **Adhesive dispersion – type systems.**
3. **Matrix diffusion – controlled systems.**
4. **Micro reservoir type or micro sealed dissolution controlled systems.**

1. Membrane Permeation – Controlled Systems:

In this type of system drug reservoir is encapsulated in a shallow compartment moulded from a drug impermeable metallic plastic laminate and a rate controlling polymeric membrane which may be micro porous or non-porous. The drug molecules are permitted to release only through the rate controlling polymeric membrane. In the drug reservoir compartment, the drug solids are either dispersed homogenously in a solid polymer matrix (e.g. Polyisobutylene adhesive) or suspended in an unbleachable, viscous liquid medium (e.g. Silicon fluids) to form a paste like suspension.

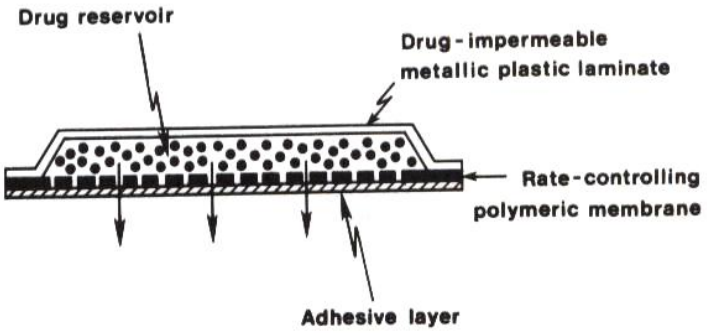


Figure 6: The cross-sectional view of a membrane moderated transdermal drug delivery system, showing various major structural components

The rate of drug release from this type of system can be tailored by varying the polymer composition, permeability coefficient and thickness of the rate limiting membrane and adhesive. The constant release rate of the drug is the major advantage of membrane permeation controlled system. Examples of this system are

a) Transderm – Nitro: Nitroglycerin releasing transdermal system for once a day medication in angina pectoris.

b) Transderm – Scop: Scopolamine releasing transdermal system for 72 hrs. Prophylaxis of motion sickness.

c) Catapres: Clonidine releasing transdermal system for 7 day therapy of hypertension.

d) Estraderm: Estradiol releasing transdermal system for treatment of menopausal syndrome for 3 – 4 days.

The membrane permeation controlled technology has also been used for controlled percutaneous absorption of prostaglandin derivatives.

2. Adhesive Dispersion – Type Systems:

This is a simplified form of the membrane permeation controlled system. As represented in Figure:6, the drug reservoir is formulated by directly dispersing

the drug in an adhesive polymer e.g. Poly (isobutylene) or poly (acrylate) adhesive and then spreading the medicated adhesive, by solvent casting or hot melt, on to a flat sheet of drug impermeable metallic plastic backing to form a thin drug reservoir layer.

On the top of the drug reservoir layer, thin layers of non medicated, rate controlling adhesive polymer of a specific permeability and constant thickness are applied to produce an adhesive diffusion – controlled delivery system. Examples are

Frandol tape: Releases Isosorbide dinitrate for once-a-day medication of angina pectoris.

Deponit: Delivers nitroglycerine for the treatment of angina pectoris.

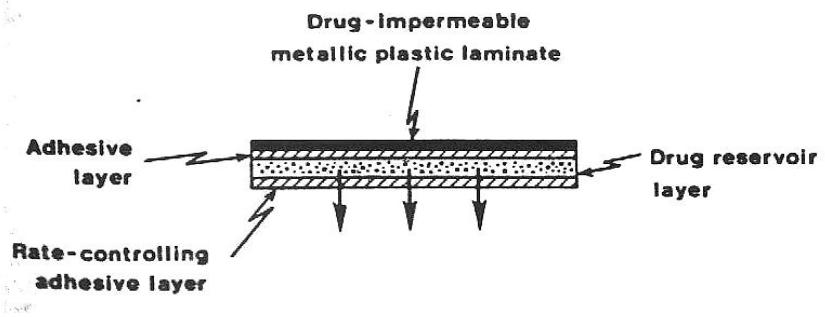


Figure 7: Adhesive diffusion-controlled transdermal drug delivery system

3. Matrix Diffusion- Controlled Systems:

In this approach, the drug reservoir is formed by homogenously dispersing the drug solids in a hydrophilic or lipophillic polymer matrix. The resultant medicated polymer is then moulded into a medicated disc with a defined surface area and controlled thickness. The dispersion of drug particles in the polymer matrix can be accomplished by either homogeneously mixing the finely ground drug particles with a liquid polymer or a highly viscous base polymer followed by cross-linking of the polymer chains or homogeneously blending drug solids with a rubbery polymer at an elevated temperature. The drug reservoir can

also be formed by dissolving the drug and the polymer in a common solvent followed by solvent evaporation in a mould at an elevated temperature and/or vacuum. This drug reservoir containing polymer disc is then pasted onto an occlusive base plate in a compartment fabricated from a drug impermeable plastic backing membrane. Instead of applying the adhesive polymer directly on the surface of the medicated disc as discussed earlier in the first two types of transdermal delivery systems, the polymer is spread along the circumference of the patch to form an adhesive rim around the medicated disc.

E.g., Nitro-Dur: Delivers nitroglycerin for the treatment of angina pectoris.

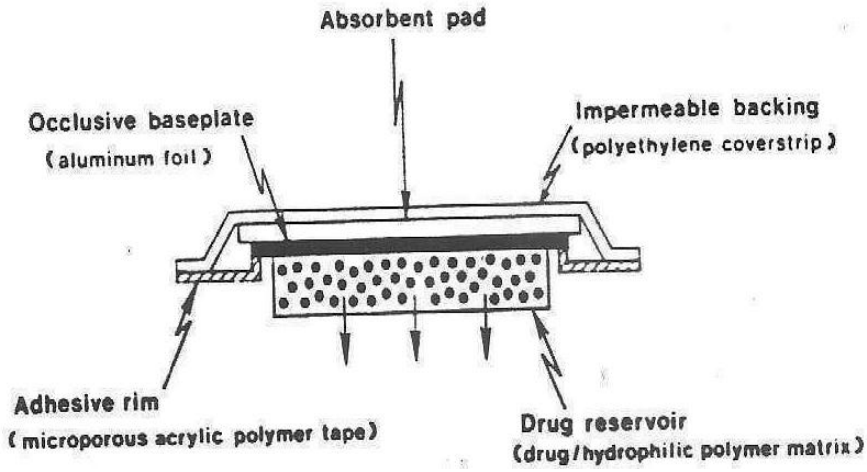


Figure 8: The cross-sectional view of a matrix dispersion-type transdermal drug delivery system, showing various major structural components.

4. Micro Reservoir Type or Micro Sealed Dissolution Controlled Systems

The micro reservoir type drug delivery system can be considered a combination of the reservoir and matrix diffusion type drug delivery systems. In this approach, the drug reservoir is formed by first suspending the drug solids in the aqueous solution of water soluble liquid polymer (e.g. Polyethylene glycol) and then dispersing the drug suspension homogenously in lipophillic polymer viz. silicone

elastomers by high energy dispersion technique to form several discrete, unleachable micro spheres of drug reservoirs. This thermodynamically unstable dispersion is quickly stabilized by immediately cross-linking the polymer chains in-situ, which produces a medicated polymer disc with a constant surface area and a fixed thickness. A transdermal therapeutic system is then produced by positioning the medicated disc at the centre and surrounding it with an adhesive rim.

E.g., Nitroglycerin: Releasing transdermal therapeutic system for once a day treatment of angina pectoris

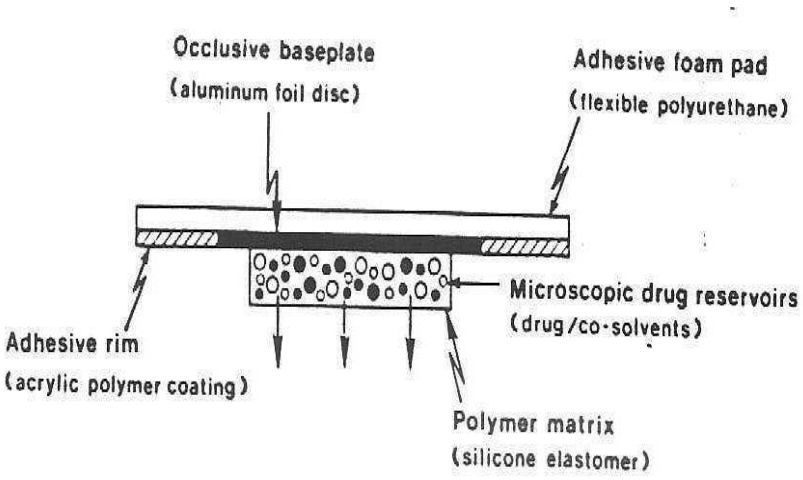


Figure 9: The cross-sectional view of a micro reservoir-type transdermal drug delivery system, showing various major structural components

Drug and excipient profile

2. DRUG AND EXCIPIENT PROFILE

VERAPAMIL HYDROCHLORIDE[23]

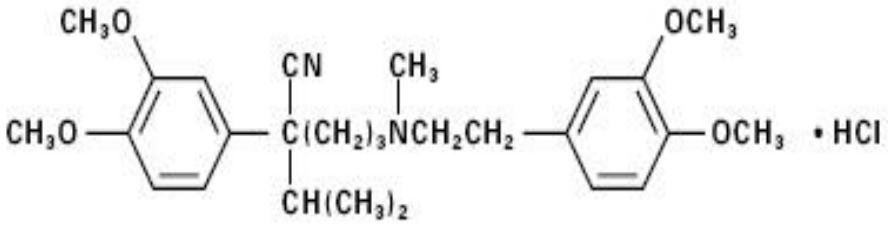
Name of the drug **:** Verapamil hydrochloride

Chemical name **:** 5-[(3, 4-Dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxy Phenyl)-2-isopropylvaleronitrile mono hydrochloride.

Formula **:** $C_{27}H_{38}N_2O_4$ HCl

Molecular weight **:** 491.06

Structure **:**



P^{Ka} **:** 8.6

Dose **:** The drug should be administered with food**.**

a) 240 mg each morning,

b) 180 mg each morning plus 180 mg each evening, or 240 mg each morning plus 120 mg each evening

c) 240 mg every twelve hours.

Dosage form : Tablets, capsules

Description : White crystalline powder, practically odorless and has a bitter taste.

Solubility : Soluble in water, freely soluble in chloroform, sparingly

Soluble in alcohol, Practically insoluble in ether.

Category : Antihypertensive

Brands Available : Isoptin, Calaptin, Veramil.

Pharmacology *:*

Mechanism of action :

Verapamil exerts antihypertensive effects by decreasing systemic vascular resistance, usually without orthostatic decreases in blood pressure or reflex tachycardia; bradycardia (rate less than 50 beats/min) is uncommon (1.4%).

It is a calcium ion influx inhibitor that experts its pharmacological effects by modulating the influx of ionic calcium across the cell membrane of the arterial smooth muscle as well as in conductile and contractile myocardial cells.

Pharmacokinetics:

Absorption:

About 90 % of Verapamil is absorbed from the gastro-intestinal tract. Absorption is rapid and the peak plasma concentration is reached 30-120 minutes following an oral dose. Verapamil undergoes extensive first-pass metabolism by the Liver. Bioavailability ranges from 20 to 35%.

Volume of distribution:

The volume of distribution is 2.4-6.2 lit/Kg.

Elimination half life:

The mean elimination half-life following single oral doses is 4-6 hours.

Metabolism:

Verapamil undergoes an extensive hepatic metabolism. Due to a large hepatic first-pass effect, bio-availability does not exceed 20 - 35% in normal subjects.

Elimination:

- Kidney: About 70% of the administered dose is excreted in urine within 5 days as metabolites, of which 3-4% is excreted as unchanged drug.
- Feces: About 16% of the ingested dose is excreted within 5 days in feces as metabolites.
- Breast milk: Verapamil may appear in breast milk.

Contraindication:

Verapamil HCl is contraindicated in:

1. Severe left ventricular dysfunction
2. Hypotension (systolic pressure less than 90 mmHg) or cardiogenic shock
3. Sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker)
4. Second- or third-degree Atrio-Ventricular block (except in patients with a functioning artificial ventricular pacemaker).

5. Patients with atrial flutter or atrial fibrillation and an accessory bypass tract (e.g., Wolff- Parkinson-White, syndromes).

6. Patients with known hypersensitivity to verapamil hydrochloride.

Drug Interactions:

Aspirin: In a few reported cases, co-administration of verapamil with aspirin has led to increased bleeding time greater than observed with aspirin alone.

Grapefruit juice: The intake of grapefruit juice may increase drug levels of verapamil.

Digitalis: Chronic verapamil treatment can increase serum digoxin levels by 50 to 75% during the first week of therapy, and this can result in digitalis toxicity. Maintenance and digitalization doses should be reduced when verapamil is administered, and the patient should be carefully monitored to avoid over or under digitalization.

Antihypertensive Agents: Verapamil administered concomitantly with oral antihypertensive agents (e.g., vasodilators, angiotensin-converting enzyme inhibitors, diuretics, beta blockers) will usually have an additive effect on lowering blood pressure.

Adverse reactions:

Cardiovascular: angina pectoris, atrio-ventricular dissociation, chest pain, myocardial infarction.

Digestive System: diarrhea, dry mouth, gastrointestinal distress.

Nervous System: cerebro vascular accident, confusion, insomnia, muscle cramps, psychotic symptoms,

Skin: Arthralgia and rash, hair loss hyperkeratosis, sweating, urticaria.

Special Senses: blurred vision, tinnitus.

Storage: Preserve in tight, light-resistant containers. Store at 25°C excursions permitted between 15–30°C.

POLYMER PROFILES

ETHYL CELLULOSE[24]

Chemical name : Cellulose Ethyl ether

Molecular formula : $C_{12}H_{23}O_6(C_{12}H_{22}O_5)_nC_{12}H_{22}O_5$

Melting point : 129-133°c.

Description : A taste less, free flowing white to light tan colored powder

Category : Coating agent, tablet binder, viscosity-increasing agent, and tablet filler.

Solubility : Ethyl cellulose is practically insoluble in glycerin, propylene glycol, and water. Ethyl cellulose that contains not less than 46.5% of ethoxyl groups is freely soluble in chloroform, ethanol (95%), ethyl acetate, methanol, and toluene.

Applications in pharmaceutical formulations:

The main use of ethyl cellulose in oral formulation is as a hydrophobic coating agent for tablets and granules. Ethyl cellulose coatings are used to modify the release of a drug, to make an unpleasant taste, (or) to improve the stability of a formulation.

Uses: 3-20% for sustained release tablets.

10-20% for micro encapsulation.

1- 3% for tablet loading.

1-3% for tablet granulation.

Safety: Ethyl cellulose is widely used in oral and topical pharmaceutical formulations. It is also used in food products. Ethyl cellulose is generally regarded as nontoxic, nonirritant and non-allergenic material. As ethyl cellulose is not considered to be a health hazard, the WHO has not specified an acceptable daily intake.

Storage Seal it and stored in dry place.

CELLULOSE ACETATE[25]

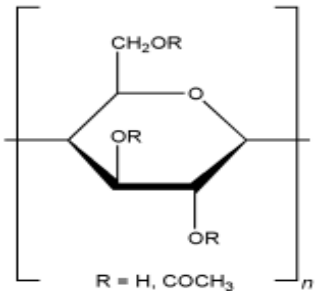
Nonproprietary Names

- BP: Cellulose acetate
- PhEur: Cellulosi acetas
- USPNF: Cellulose acetate

Synonyms

Acetyl cellulose; cellulose diacetate; cellulose triacetate.

Structural Formula



Functional Category

Coating agent; extended release agent; tablet and capsule diluent.

Applications in Pharmaceutical Formulation or Technology

Cellulose acetate is widely used in pharmaceutical formulations both in sustained-release applications and for taste masking.

Cellulose acetate is used as a semi permeable coating on tablets, especially on osmotic pump-type tablets and implants. This allows for controlled, extended release of actives. Cellulose acetate films, in conjunction with other materials, also offer sustained release without the necessity of drilling a hole in the coating as is typical with osmotic pump systems. Cellulose acetate and other cellulose esters have also been used to form drug loaded micro particles with controlled release characteristics. Cellulose acetate films are used in transdermal drug delivery systems and also as film coatings on tablets or granules for taste masking. For example, acetaminophen granules have been coated with a cellulose acetate based coating before being processed to provide chewable tablets. Extended release tablets can also be formulated with cellulose acetate as a directly compressible matrix former. The release profile can be modified by changing the ratio of active to cellulose acetate and by incorporation of plasticizer, but was shown to be insensitive to cellulose acetate molecular weight and particle size distribution. Therapeutically, cellulose acetate has been used to treat cerebral aneurysms, and also for spinal perimedullary arteriovenous fistulas.

Description

Cellulose acetate occurs as a white to off-white powder, free-flowing pellets, or flakes. It is tasteless and odorless, or may have a slight odor of acetic acid.

Glass transition temperature **:** 170–190°C

Melting point **:** melting range 230–300°C

Solubility **:** In general, cellulose acetates are soluble in acetone–water blends of varying ratios, dichloromethane–ethanol blends, dimethyl formamide, and dioxane. The cellulose acetates of higher acetyl level are generally more limited in solvent choice than are the lower acetyl materials.

Stability and Storage Conditions

Cellulose acetate is stable if stored in a well closed container in a cool, dry place. Cellulose acetate hydrolyzes slowly under prolonged adverse conditions such as high temperature and humidity, with a resultant increase in free acid content and odor of acetic acid.

Safety

Cellulose acetate is widely used in oral pharmaceutical products and is generally regarded as a nontoxic and nonirritant material.

Literature Review

3. LITERATURE REVIEW

- **Jatin Sood[26] *et al* (2013)** studied on matrix-type transdermal patches of verapamil hydrochloride (VPL) with combinations of hydroxyl propyl methyl cellulose (HPMC) and hydroxyl propyl cellulose (HPC) as matrix polymers and to investigate the influence of oleic acid (OA) on in vitro permeation of VPL through rat skin. The permeation studies were performed using Franz-type diffusion cells and full-thickness excised abdominal rat skin. The effect of the polymers on the drug release, percentage moisture loss, percentage moisture absorption, folding endurance, and thickness, were investigated. In vitro release studies showed zero-order release of the drug from all the patches, and the mechanism of release was diffusion mediated. Data was analysed using different release kinetic models. In vitro release profiles showed that from optimized combination the release of the drug was sustained and it extended over a period of 24 hr VPM 006 emerged as the most satisfactory formulation as far as its technological properties were concerned.

- **Gungor S[27] *et al* (2008)** developed on matrix-type transdermal patches of verapamil hydrochloride (VRP) with pectin as a matrix polymer to investigate the influence of several terpenes on in vitro permeation of VRP through rat skin and to evaluate pharmacodynamic activity of transdermal formulations in rats. Matrix-type transdermal patches containing VRP were prepared using pectin as a matrix agent and propylene glycol as a plasticizer agent. Terpenes such as nerolidol, d-limonene, eucalpytol, menthone, and menthol were also used as a chemical enhancer to improve the skin penetration of VRP. The permeation studies were performed using Franz-type diffusion cells and full-thickness excised abdominal rat skin. Effects of

terpenes on the permeation parameters of VRP were evaluated. In vitro skin permeation studies showed that nerolidol was the most promising enhancer among the enhancers examined in the present study, followed by d-limonene. Pharmacodynamic activity of the transdermal patches containing nerolidol or d-limonene was evaluated in rats by the measurement of systolic blood pressure for 360 min with the use of the tail cuff method. VRP transdermal patches significantly decreased the systolic blood pressure after 30 min and transdermal patches containing nerolidol and d-limonene maintained the decrease in blood pressure during the observation of 360 min.

- **Jawahar N[28] *et al* (2007)** investigated on prepare and evaluate Verapamil hydrochloride transdermal films and to study the effect of different formulation variables such as polymer concentration, polymer ratio, plasticizer concentration, permeation enhancer concentration, loading dose and thickness on the permeability and physico-chemical properties. The films were prepared by mercury substrate method employing chloroform as a solvent, cellulose acetate butyrate (CAB) and polyvinyl pyrrolidone (PVP) as polymers, dibutyl phthalate (DBP) as plasticizer, and isopropyl myristate (IPM) as permeation enhancer. The films were evaluated for film thickness, weight variation, tensile strength, drug content uniformity, moisture uptake, non-irritancy and stability. The drug diffusion through the films followed a pattern close to zero order type. The drug release profile was decreased with increased polymer concentration and film thickness. The films were comfortable with skin and stability studies indicated that the films had sufficient suitability and shelf-life.

- **Swarnlata S[29] *et al* (2006)** Developed Transdermal delivery of Timolol maleate for both reservoir as well as matrix system. The physically stable patches regarding drug contents, tensile strength, toughness and WVT were found for PVA 10% and HPMC: E.C (2:8) formulation. The reservoir system followed zero order while the matrix system followed first order release profile. Among both matrix systems PVA 10% patch have more permeability than HPMC: EC (2:8) patch.

- **Amnuaikit C[30] *et al* (2005)** Developed the suitable film formulations of Propranolol Hydrochloride (PPL) containing enhancers for transdermal use, polymeric film formulations were prepared by employing ethyl cellulose (E.C) and polyvinyl pyrrolidone (PVP) as a film former, and dibutyl phthalate (DBP) as a plasticizer. Terpenes such as menthol and cineole, and propylene glycol (PG) were also employed as a chemical enhancer to improve the skin penetration of PPL. In vitro skin permeation study showed that cineole was the most promising enhancer among the enhancers examined and suggested that the suitable compositions of film preparation would be E.C: PVP: PPL = 6:3:4 with 10% (w/w) cineole and 7:2:4 with 10% (w/w) PG and cineole, which provided high skin permeation rates at 93.81 ± 11.56 and 54.51 ± 0.52 μg/cm^2/h, respectively.

- **Mutalik S[31] *et al* (2004)** Prepared Glibenclamide transdermal patches using different ratios of ethyl cellulose (EC)/polyvinylpyrrolidone (PVP) and Eudragit RL-100 (ERL)/Eudragit RS-100 (ERS) by solvent evaporation technique. The patches were subjected to skin irritation test (by both visual observation and histopathological evaluation), oral glucose tolerance test and pharmacokinetic evaluation in mice. The results revealed that the patches successfully prevented the severe hypoglycemia in the initial hours, which is the major side effect associated with oral route. The patches maintained similar effect during long-term treatment also. The transdermal systems produced better improvement with all the tested biochemical parameters compared to oral administration. The better in-vivo performance of the transdermal patches of glibenclamide in comparison with oral administration could be due to day-to-day glycemic control on long-term application.

- **Meier M. M[32] *et al*(2004)** Studied the influence of plasticizer poly (caprolactone triol) (PCL-T) and pore forming agent water on cellulose acetate (CA) membrane morphology, porosity and the permeation coefficient of a model drug (paracetamol) . The addition of water, a non-solvent, during the membrane casting process was found to be a simple and effective way to change membrane porosity and consequently the drug permeation profile. When small quantities of non

solvent were used to obtain low porosity membranes, the presence of a plasticizer agent could be used to better modulate drug permeation. Combining the addition of PCL-T with the use of a non solvent resulted in a series of CA membranes with paracetamol permeation coefficient values in the range of ca. 10^{-7} to 10^{-5} cm s^{-1}.

- **Kusum Devi V[33] *et al* (2003)** developed Transdermal patches of verapamil hydrochloride were prepared using four different polymers (individual and combination): Eudragit RL100 (ERL100), Eudragit RS100 (ERS100), hydroxypropyl methylcellulose 15 cps (HPMC), and ethyl cellulose (EC), of varying degrees of hydrophilicity and hydrophobicity. The effect of the polymers on the technological properties, i.e., drug release, water vapor transmission rate (WVTR), and percentage moisture loss (ML), percentage moisture absorption (MA), folding endurance, and thickness, was investigated. Different formulations were prepared in accordance with the 2(3) factorial design, with ERL100 being the parent polymer. The patch containing ERL100 alone showed maximum WVTR, % MA, and % ML, which could be attributed to its hydrophilic nature. As expected, substitution with ERS100, HPMC, and EC decreased all the above values in accordance with their decreasing degree of hydrophilicity. In vitro release studies showed zero-order release of the drug from all the patches, and the mechanism of release was diffusion mediated. Moreover, the release of the drug was sustained and it extended over a period of 24 hr in all formulations. A12 emerged as the most satisfactory formulation insofar as its technological properties were concerned. Further, release and permeation of the drug from the most satisfactory formulation (A12) was evaluated through different biological barriers (shed snake skin, rabbit skin, and rat skin) to get an idea of the drug permeation through human skin. Shed snake's skin was found to be most permeable (82.56% drug release at 24 hr) and rat skin was least permeable (52.38%). Percutaneous absorption studies were carried out in rabbits. The pharmacokinetic parameters calculated from blood levels of the drug revealed a profile typical of a sustained release formulation, with the ability to maintain adequate plasma levels for 24 hr. [AUC: 3.09 mg/mL hr, Cmax: 203.95 microg/mL, Tmax: 8 hr]. It can therefore be concluded that the patch containing ERL100 and HPMC in the ratio 8:2 has achieved the objectives of transdermal drug

delivery system, such as avoidance of first pass effect, extended release, and reduced frequency of administration.

- **Wang F. G[34] *et al* (2002)** Casted the cellulose acetate membranes with acetone as a solvent at 22 and 40 °C. Polyethylene glycol (PEG, MW 600) was used as a pore forming agent. The in-vitro release rates of scopolamine base as a model drug through the membranes were evaluated in phosphate buffer solution (PBS, pH 7.4) at 32 °C. It was observed that the drug permeation through the cellulose acetate membranes was obviously affected by the incorporated PEG content and formed membrane morphology.

- **Nguyen V[35] *et al* (2000)** evaluated the effect of ethyl cellulose on the delivery of estradiol and norethindrone acetate. Transdermal systems were fabricated by utilizing drug-in-adhesive matrix technology and were evaluated for the delivery rate in-vitro using human cadaver skin. The conclusion is that ethyl cellulose has the ability to sustain the delivery rate of estradiol and norethindrone acetate over seven days.

- **K. L. K Paranjothy[36] *et al* (1997)** An attempt has been made to develop Transdermal patches of Verapamil HCI by using Sodium Carboxymethyl Guar as Polymer matrix, Propylene glycol as the plasticiser and Alupoly foil as the 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. The primary skin irritatancy tests have shown that the transdermal patches are non irritant.

- **Rao, P. R[37] *et al* (1997)** Studied the influence of casting solvent on the permeability of free films of ethyl cellulose with a view to develop a suitable rate controlling membrane for transdermal use The casting solvent showed a significant influence on the mechanical as well as permeability characteristics. It was concluded that the plasticized free films of ethyl cellulose casted from chloroform can be used as rate controlling membranes to develop transdermal drug delivery systems.

- **Bhatt, D C[38] *et al* (1995)** Conducted the diffusion studies of promethazine hydrochloride. The studies revealed that the films prepared from ethyl cellulose:povidone (polyvinylpyrrolidone) (80:20) gave zero order diffusion profile and it was suitable as a rate controlling membrane.

- **Phuapradit W[39] *et al*(1995)** Prepared some polymeric membranes and evaluated for mechanical properties and permeability to a model drug, theophylline. Cellulose acetate and ethyl cellulose membranes were effective in preventing the diffusion of theophylline. The addition of Eudragit RL-100 to cellulose acetate and ethyl cellulose membranes increased permeability but decreased mechanical strength.

- **Chowdary K. P[40] *et al*(1994)** Prepared membrane moderated transdermal drug delivery (TDD) systems, of various types of semisolid formulations and evaluated for their suitability as drug reservoirs for TDD systems by studying diffusion of diclofenac sodium from various bases through cellulose acetate (CA) membranes and rat abdominal skin alone and in combination. It was concluded that a membrane moderated TDD system for diclofenac sodium could be designed employing CA films as rate controlling membranes and sodium alginate and carbopol gels as drug reservoirs.

- **Bialik W[41] *et al* (1992)** Investigated the potential of the amphoteric substance, carboxyl betaine, to enhance the transdermal delivery of drugs, the compound was synthesized and incorporated into several matrices of varying thicknesses and drug concentrations; the release rate of chloramphenicol was evaluated in-vitro. Results indicated that carboxyl betaine enhances the release rate of the tested chemicals from thin films formed by cellulose acetate.

- **Baichwal M. R[42] *et al* (1988)** Conducted in-vitro and in-vivo studies of transdermal polymeric films comprised of ethyl cellulose and poly vinyl pyrrolidone (povidone; I), and containing either one, 2, or 4 mg of salicylic acid (II) per 2.5 sq cm, The study concluded that results of II release, regardless of I concentration or laminate thickness, showed this transdermal formulation to be promising.

- **Friedman M[43] *et al* (1980)** Studied diffusional mass transfer across a serial 2 or 3 unit laminate barrier of ethyl cellulose and polyethylene glycol membranes was studied using caffeine and salicylic acid as model drugs. The overall membrane diffusional resistance was found to be the sum of the intrinsic membrane resistances. When the resistance of one layer was much higher than that of the others, the permeability was then controlled by the single layer in the laminate.

- **Donbrow M[44] *et al* (1980)** studied drug release characteristics in laminated double layer film systems, with salicylic acid, tripelennamine, barbitone (barbital) or caffeine, dispersed in hydroxypropyl cellulose (I) and attached to ethylcellulose films containing various proportions of polyethylene glycol 4000 or hydroxypropyl cellulose to enhance permeability. Drug release in vitro followed zero order kinetics, rate constants being dependent on the thickness of the drug free membrane. Release rates were enhanced by addition of hydrophilic polymer to the drug free membrane.

- **Barry B. W[45] *et al* (1976)** Investigated the permeation across cellulose acetate of 3 estrogens, differing only in the number of hydroxyl groups attached to the nucleus, and a standard steroid, dexamethasone, using the lag time method for calculating diffusion parameters between 10DG and 40DG. The results implied that steroid diffusion occurred through aqueous membrane channels, but that it was impeded to various extents by both obstruction and polar interaction effects.

- **Barry B.W[46] *et al* (1976)** investigated permeation of hydrocortisone, dexamethasone, testosterone and progesterone across cellulose acetate membranes between 10DG and 40DG. The process depended mainly on membrane water partition coefficients of the steroids so that the least polar compound permeated the fastest.

- **Short P. M[47] *et al* (1970)** Investigated the effect of the surfactants upon the diffusion of testosterone through cellulose acetate membranes. Diffusion coefficients were calculated using a method that allows the measurements to be completed in a very short time. Possible mechanisms by which surfactants may

affect drug transport are discussed. In all cases examined, the surfactants reduced the diffusion coefficient of testosterone.

Scope and Objective of the Work

4. SCOPE AND OBJECTIVE OF THE WORK

Verapamil hydrochloride is a calcium ion influx inhibitor. It is widely used in the treatment of angina, hypertension, and supraventricular tachyarrhythmia. The plasma half-life of verapamil HCl is 2-7 hrs, which necessitates multiple dosing. It is approximately 90% absorbed from the gastrointestinal tract but is subject to considerable first pass metabolism and its bioavailability is around 20-30%. It undergoes variable and extensive first pass metabolism before entering into systemic circulation and varies with species. The transdermal administration of drugs, exhibiting oral first pass metabolism, may improve the bioavailability and reduces the dosing frequency when compared to the oral route.

Treatment for hypertension is a long term therapy where noncompliance is high. Hence prolonged release dosage forms are required for quality health care. The hypertension condition requires the continuous availability of antihypertensive drug in the systemic circulation. Due to its low biological half life (2-7hrs), Verapamil requires frequent administration. Sustained therapeutic action is necessary for alleviating patient's symptoms and is achieved by transdermal drug delivery systems. Transdermal drug delivery systems are designed to compliment pharmaceutical activity of the medicament in order to achieve the longer duration of action.

In the present investigation on membrane moderated therapeutic systems by employing Ethyl cellulose, Cellulose acetate polymeric films as a rate controlling membranes with an objective of developing transdermal formulations to obtain controlled release of Verapamil HCl.

Though the polymeric film and drug reservoirs have been studied for controlled release, no attempts were made to study the influence of casting solvent,

polymer film and drug reservoir on permeability of Verapamil HCl. The solvent employed in the preparation of polymer films is likely to influence the permeability of drug. In the present investigation the influence of four different solvents namely Acetone, Dichloromethane, Chloroform & Ethyl acetate was studied.

In the present work, Ethyl Cellulose, Cellulose acetate films were prepared and evaluated as rate controlling membrane for transdermal drug delivery systems. Solvent evaporation and Casting on mercury surface techniques were employed in the present work for the preparation of films. In each case films were prepared using solutions of the polymer in various solvents to evaluate the influence of the solvent used on the mechanical and permeability properties of the films.

The Major Objectives of the Investigation are as Follow:

1. To investigate the interactions existing among drug and polymers by FTIR spectral studies.
2. To evaluate the influence of casting solvent on the permeability of the Polymeric films.
3. To develop and design membrane moderated transdermal drug delivery systems for Verapamil HCl by using Ethyl Cellulose, Cellulose acetate polymers as rate controlling membrane.
4. To characterize the rate controlling membrane for
    a. Physical appearance.
    b. Thickness uniformity.
    c. Folding endurance.
    d. Water vapour transmission.
    e. Drug diffusion.
    f. Permeability Co efficient.
    g. Diffusion flux.

5. Preparation of a drug reservoir gel with different and combination of hydrophilic polymers.

6. To study the effect of permeation enhancers on permeability of Verapamil HCl.

7. To conduct the stability studies for the best gel formulation.

8. To develop the membrane moderated transdermal therapeutic system by optimizing the rate controlling membrane and casting solvent and studied the permeation of drug from the gels

Materials and Methods

5. MATERIALS & METHODS

Table 1: Materials

S.No	Materials	Manufacturer's Name
1.	Verapamil HCl	Hetero Drugs, Hyderabad
2.	Cellulose acetate(100-140 cps)	Himedia; Mumbai
3.	Ethyl cellulose (48-49.5%)	Himedia; Mumbai
4.	Acetone	Qualigens; Mumbai
5.	Ethyl acetate	S. D. Fine-Chem Ltd.; Mumbai
6.	Dichloromethane	S. D. Fine-Chem Ltd.; Mumbai
7.	Chloroform	S. D. Fine-Chem Ltd.; Mumbai
8.	Dibutyl phthalate	Ranbaxy Laboratories; New Delhi
9.	Propylene glycol	S. D. Fine-Chem Ltd.; Mumbai
10.	Ethanol	Qualigens; Mumbai
11.	Methanol	Qualigens; Mumbai
12.	Sodium carboxy methyl cellulose (200-300cps)	S. D. Fine-Chem Ltd.; Mumbai
13.	Carbopol 934	Arihanth traders; Mumbai
14.	Hydroxy propyl methyl cellulose(50 cps)	S. D. Fine-Chem Ltd.; Mumbai
15.	Methyl cellulose (28-32%)	S. D. Fine-Chem Ltd.; Mumbai
16.	Glycerin	S. D. Fine-Chem Ltd.; Mumbai
17.	Mercury	Qualigens; Mumbai
18.	Poly ethylene glycol 6000	Qualigens; Mumbai
19.	Poly vinyl pyrrolidone	Qualigens; Mumbai
20.	Dimethyl sulfoxide	Qualigens; Mumbai
21.	Poly ethylene glycol 400	Qualigens; Mumbai

Table 1: (Continued)

22.	Tween 20	Qualigens; Mumbai
23.	Sodium lauryl sulphate	Qualigens; Mumbai
24.	Hydrochloric Acid	Qualigens; Mumbai
25.	Sodium hydroxide	Qualigens; Mumbai
26.	Potassium di hydrogen ortho phosphate	Qualigens; Mumbai
27.	Potassium chloride	Qualigens; Mumbai
28.	Calcium chloride	Qualigens; Mumbai

Table 2: Equipments

S.No	Materials	Manufacturer's Name
1	U. V. Spectrophotometer	Elico; Hyderabad; Model: SL 159
2	Analytical Balance (200 D)	Dhona; Calcutta
3	Ultra Sonicator	PCI Limited; Mumbai
4	Magnetic Stirrer	Remi; Mumbai
5	Hot Air Oven	Lawrence & Mayo; Sec'bad
6	pH meter	Systronics Digital –DI-707
7	Fronz Diffusion cells	Labindia, Mumbai.

CALIBRATION CURVE FOR VERAPAMIL HCl

Accurately weighed 50mg of Verapamil HCl and was dissolved in ethanol in a 50 ml volumetric flask and the solution was made up to volume with ethanol.

The standard solution of Verapamil HCl was subsequently diluted with phosphate buffer of pH 7.4 to obtain a series of dilutions containing 2, 4, 6, 8 and 10 µg of Verapamil HCl per 1 ml of solution. The absorbance of the above dilutions was measured in Shimadzu double beam UV spectrophotometer at 278 nm using the phosphate buffer of pH 7.4 as a blank[48]. The concentrations of Verapamil HCl and

the corresponding absorbance values are given **Table 7**. The absorbance values were plotted against concentrations of Verapamil HCl as shown in **Figure 12**.

COMPATIBILITY STUDIES[49]

The IR spectra for the Verapamil, Cellulose acetate, Ethyl cellulose, were recorded on JASCO FT-Infra red spectrophotometer using KBr pellet technique (1:100) at the resolution rate of $4cm^{-1}$ and shown in the **figures 13,14,15**. Spectrum was integrated in transmittance mode at the wave number range 400 to 4000 cm^{-1}.

PREPARATION OF DRUG FREE FILMS

Cellulose Acetate and Ethyl Cellulose Films:

Solvent evaporation technique[50] was employed in the present work for the preparation of Cellulose acetate and Ethyl cellulose films. The composition of the films was showed in **Table 3**.

The polymer solutions were prepared by dissolving the polymer (2% w/v Cellulose acetate or 2% w/v Ethyl cellulose) in 20 ml of four different solvents namely, Acetone-Methanol (8:2), Chloroform-Methanol (8:2), Dichloromethane-Methanol (8:2), and Ethyl acetate-Methanol (8:2). Dibutyl phthalate at a concentration of 40% w/w of the polymer was used as a plasticizer. The resulting solution was made up to 50 ml with casting solvents separately. 20 ml of the polymer solution was poured in a Petri plate (9.4 cm diameter) placed on a horizontal flat surface. The rate of evaporation was controlled by inverting a funnel over the Petri plate. After 24 hours the dried films were taken out and packed in a aluminium foil.

Table 3: Composition of Ethyl Cellulose and Cellulose Acetate Drug Free Films

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Ethyl Cellulose (mg)	1000	1000	1000	1000	---	---	---	---
Cellulose Acetate (mg)	---	---	---	---	1000	1000	1000	1000
n-dibutylphthalate(ml)	40%w/w of polymer	40%w/w of polymer	40%w/w of polymer	40%w/w of polymer	40%w/w of polymer	40%w/w of polymer	40%w/w of polymer	40%w/w of polymer
Acetone + Methanol (ml) (8:2) up to	50	---	---	---	50	---	---	---
Dichloromethane + Methanol (ml) (8:2) up to	---	50	---	---	---	50	---	---
Chloroform+ Methanol (ml) (8:2) up to	---	---	50	---	---	---	50	---
Ethyl Acetate + Methanol (ml) (8:2) up to	---	---	---	50	---	---	---	50

DOSE DESIGN

The mathematical description of drug release that follow zero order kinetics is based on the equation[51].

$$\mathbf{K^{o}_{r}=K_eC_dV_dB_w}$$

Where, K^{0}_{r} is zero order rate constant for drug release,

K_e is first order rate constant for overall drug elimination,

C_d is desired drug level in the body,

V_d is volume space in which drug is distributed and

B_w is normal human body weight.

For **Verapamil Hydrochloride**[52] $t_{½}$ = 5.1 hr, V_d =4 l/kg and C_d = 0.05 µg/ml and therefore the desired drug release rate can be calculated as follows

K^{0}_{r} = (0.693/5.1)×0.05 ×4 ×70 =1.90 mg/h

For 24 hrs the required dose =1.90 X 24 = 45.6 mg=50mg

EVALUATION OF RATE CONTROLLING MEMBRANE

All the rate controlling membranes were evaluated for the following parameters**.**

Thickness:

The thickness of the films was measured by a 'Screwguage'. The mean of the five observations were calculated and the readings are shown in **Table 8**.

Tensile strength & Percentage of Elongation[53]:

Tensile strength was calculated using "Tensile meter". Percent elongation was calculated as the ratio of the difference in length after pulling to its initial length and the readings are shown in **Table 8**.

Folding Endurance[54]:

The folding endurance was measured manually for the prepared films. A strip of film (2x2 cm) was cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking give the exact value of folding endurance and the readings are shown in **Table 8**.

Water vapour Transmission (W.V.T) Rate[55]:

For the study vials of equal diameter were used as transmission cells. These cells were washed thoroughly and dried in an oven. About 1.0 gm of Calcium chloride was taken in the cell and the polymeric films measuring 3.14 cm^2 area were fixed over the brim with the help of an adhesive. The cells were weighed accurately and initial weight is recorded, and then kept in a desiccator containing saturated solution of KCl (about 200 ml.). The humidity inside the desiccator was measured by a hygrometer, and it was found to be in between 80 – 90 % RH. The cells were taken out and weighed after 18, 36 54 and 72 hrs.

From increase in weights the amount of water vapour transmitted and the rate at which water vapour transmitted were calculated by using the following formula

$$\text{Water Vapour Transmission Rate (W.V.T)} = \frac{WL}{S}$$

Where, W = Water vapour transmitted in gms.

L = Thickness of the film in cm.

S = Exposed surface area in cm^2

Figure 10: Hygrometer

The readings are shown in **Table 9**.

Drug Diffusion Study:

Drug diffusion study was conducted using Franz diffusion cell[56]. The receptor compartment was filled with 15 ml of phosphate buffer having pH 7.4 as diffusion media. Polymeric film was mounted on the donor compartment with the help of an adhesive.

10 ml of the 0.25% W/V of drug solution was poured into the donor compartment. Magnetic stirrer was set at 50 rpm and whole assembly was maintained at 32 $\pm$ 0.5°C. The amount of drug released was determined by withdrawing 1 ml of sample at regular time intervals for 3 hours. The volume withdrawn was replaced with equal volume of fresh buffer solution. Samples were analyzed for drug content using a U V spectrophotometer at 278 nm. The readings are shown in **Table 10**.

FORMULATION OF DRUG RESERVOIR GELS

Different drug reservoir gels were formulated as per the composition given in **Table 4**. The required quantities of polymer was weighed and transferred separately into a mortar. It was triturated with 10 ml of water. Specified amount of Verapamil hydrochloride, methylparaben and propylparaben were weighed accurately and dissolved in glycerin. The resulting drug solution was incorporated

into the polymer dispersion slowly with continuous trituration to obtain a gel. In case of carbopol gel, specified amount of carbopol 934 was soaked in 20 ml of water over night. Specified amount of Verapamil hydrochloride, methylparaben and propylparaben were weighed accurately and dissolved in glycerin. The resulting drug solution was incorporated into the polymer dispersion with stirring at 500 rpm, by a magnetic stirrer for 1 hr. The pH of above mixture was adjusted to neutral with tri ethanolamine (0.5%). The gel was transferred in to a measuring cylinder and the volume was made up to 20 ml with distilled water.

Table 4: Composition of Verapamil Hydrochloride Gels Containing Various Polymers

Ingredients	G_1	G_2	G_3	G_4
Verapamil hydrochloride **(**mg)	1000	1000	1000	1000
Sodium carboxy methyl cellulose (mg)	800	---	---	---
Carbopol 934 (mg)	---	800	---	---
Methyl cellulose (mg)	---	---	800	---
HPMC (mg)	---	---	---	800
Methylparaben(mg)	20	20	20	20
Propylparaben(mg)	10	10	10	10
Tri ethanolamine (0.5%)	---	q.s	---	---
Glycerin (ml)	2	2	2	2
Distilled water (ml) up to	20	20	20	20

EVALUATION OF DRUG RESERVOIR GELS

The drug reservoir gels formulated with HPMC, Sodium carboxy methyl cellulose, Methyl cellulose and Carbopol 934 were evaluated for the following parameters

Drug content:

The Verapamil hydrochloride gel (1gm containing 50 mg) was dissolved in 50 ml of phosphate buffer (pH 7.4) solutions. The absorbance was measured after suitable dilution at 278 nm respectively against the corresponding blank solution. The blank solutions were the gels free from drug. The readings are shown in **Table 11**.

pH and viscosity[57]:

The pH of the dispersion was measured using pH meter (Systronics Digital –DI-707).The pH of the gels were measured before and after the incorporation of the drug. Viscosity of the gels was determined using a Brook field viscometer. The readings are shown in **Table 11**.

Spreadability[58]:

Spreadability of formulation was determined with the apparatus proposed &fabricated by Multimer *et al.* It consists of wooden block provided with two glass slides. Lower slide was fixed on wooden block and upper slide with one end was tied to glass slide and other end tied to weight pan. A gel equivalent to 2.5 g was placed between two slides and 1000 g weight was placed over it for 5 minutes to press the sample to a uniform thickness. 100g of weight was added to pan. The time (in seconds) required by the top glass slide to travel a distance of 10cm is noted. This was taken as a measure of spreadability. Shorter time interval to cover the distance of 7.5 cm indicates better spreadability. The readings are shown in **Table 11**.

Physical stability by freeze thaw method[59]:

Stability testing was done by using freeze thaw cycling method. The temperature was altered every 24 hours between 25°C and -5°C for five cycles and samples were observed for physical stability, homogeneity and synersis

(spontaneous contraction of gel exuding some of the fluid medium). The readings are shown in **Table 11**.

Drug diffusion study[60]:

Drug diffusion study was conducted using Franz diffusion cell. The receptor compartment was filled with 15 ml of phosphate buffer having pH 7.4 as diffusion media. Cellulose acetate film was mounted on the dialysis membrane with the help of an adhesive. 1 gm of gel (50 mg of Verapamil hydrochloride) was placed on the film. Dialysis membrane was kept between the receptor compartment and the donor compartment. Magnetic stirrer was set at 50 rpm and whole assembly was maintained at 32 $\pm$ 0.5°C. The amount of drug released was determined by withdrawing 1 ml of sample at regular time intervals for 3 hours. The volume withdrawn was replaced with equal volume of fresh buffer solution. Samples were analyzed for drug content using a UV spectrophotometer at 278 nm. The readings are shown in **Table 12.**

FORMULATION AND EVALUATION OF GELS WITH COMBINATION OF POLY VINYL PYRROLIDINE AND POLY ETHYLENE GLYCOL 6000

Two different hydrophilic polymers polyvinyl pyrrolidone and poly ethylene glycol 6000 were incorporated into sodium carboxy methylcellulose gels to enhance the permeability of Verapamil hydrochloride. The composition of the resulting gels was showed in **Table 5**. These gels were also evaluated for drug content, pH and viscosity, spreadability, physical stability by freeze thaw method. The results are shown in **Table 13**. Diffusion data results are shown in **Table 14**.

Table 5: Composition of Verapamil Hydrochloride Gels Containing hydrophilic Polymers

Ingredients	G_1	G_5	G_6
Verapamil hydrochloride (mg)	1000	1000	1000
Na CMC (mg)	800	---	---
Na CMC**:** Povidone (1:1) (mg)	---	800	---
Na CMC**:** PEG 6000(1:1) (mg)	---	---	800
Methylparaben(mg)	20	20	20
Propylparaben(mg)	10	10	10
Glycerin (ml)	2	2	2
Distilled water (ml) up to	20	20	20

PREPARATION AND EVALUATION OF GELS CONTAINING PERMEATION ENHANCERS

Four different permeation enhancers namely 2% w/w of sodium lauryl sulphate, 2% w/v of poly ethylene glycol 400**,** dimethyl sulfoxide and tween 20 were incorporated into the gels. The composition of these gels was given in **Table 6**. These gels were also evaluated for drug content, pH and viscosity, spreadability, physical stability by freeze thaw method. The results are shown in **Table 15**. Diffusion data results are shown in **Table 16**.

Table 6: Composition of Verapamil Hydrochloride Gels Containing Various Permeation Enhancers

Ingredients	GP_1	GP_2	GP_3	GP_4
Verapamil hydrochloride (mg)	1000	1000	1000	1000
Na CMC **:** PEG 6000 (1:1) (mg)	800	800	800	800
Methylparaben(mg)	20	20	20	20
Propylparaben(mg)	10	10	10	10
Tween 20(ml)	0.4	---	---	---
Sodium lauryl sulphate (mg)	---	0.4	---	---
Dimethyl sulfoxide (ml)	---	---	0.4	---
Polyehylene glycol 400 (ml)	---	---	---	0.4
Glycerin (ml)	2	2	2	2
Distilled water (ml) up to	20	20	20	20

STABILITY STUDIES[61]

The accelerated stability studies were carried out for the selected gel formulations under following conditions of temperature and relative humidity for 6 weeks.

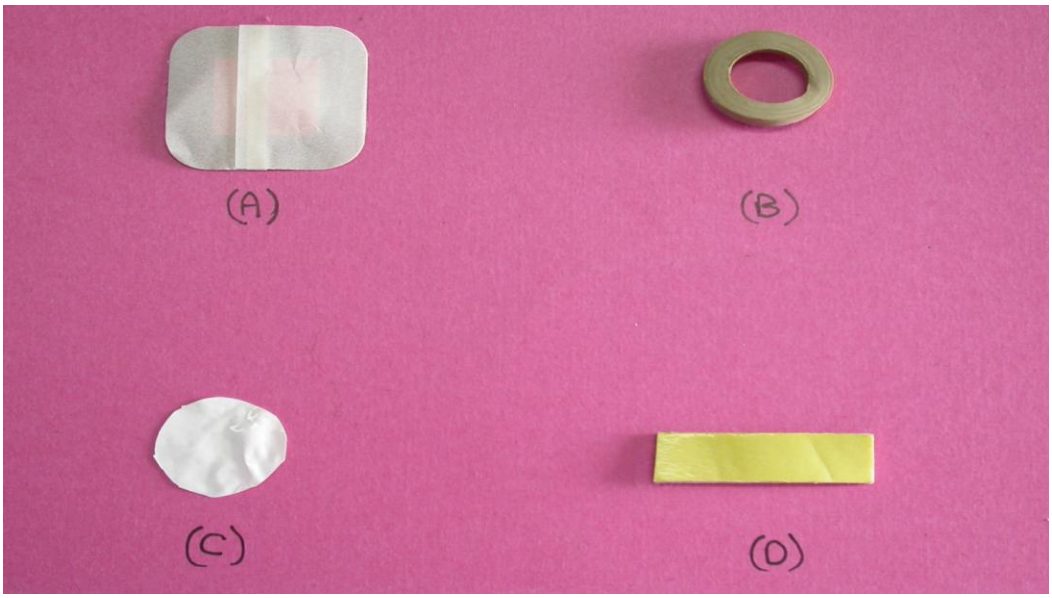
1. 25°C ± 2°C at 60±5%RH

2. 40°C ± 2°C at 75±5%RH

Known amounts of gels were taken out at regular time intervals of 1week for 6weeks and analyzed for drug content , physical appearance, pH, viscosity, extrudability, spreadability ,and degradation rate constant(K). the results are shown **Table 17** and **Table 18**.

DESIGN OF MEMBRANE MODERATED TRANSDERMAL THERAPEUTIC SYSTEM FOR OPTIMIZED FORMULATION

A circular silicon rubber ring with an internal diameter of 2.5 cm and a thickness of 3 mm was fixed on to a backing membrane (an imperforated adhesive strip; supplied by Johnson and Johnson Limited, Mumbai). This serves as a compartment for drug reservoir. 1 gm of medicated gel was taken into the compartment as a drug reservoir. Cellulose acetate membrane of known thickness was fixed on the ring with glue to form a membrane moderated therapeutic systems. A double sided adhesive strip was fixed on the rim of the ring above Cellulose acetate membrane. The design was shown in **figure 11**.



Components used in the design of membrane moderated TDD systems

A – Backing membrane
B – Silicone ring
C – Rate controlling CA membrane
D – Double sided adhesive tape

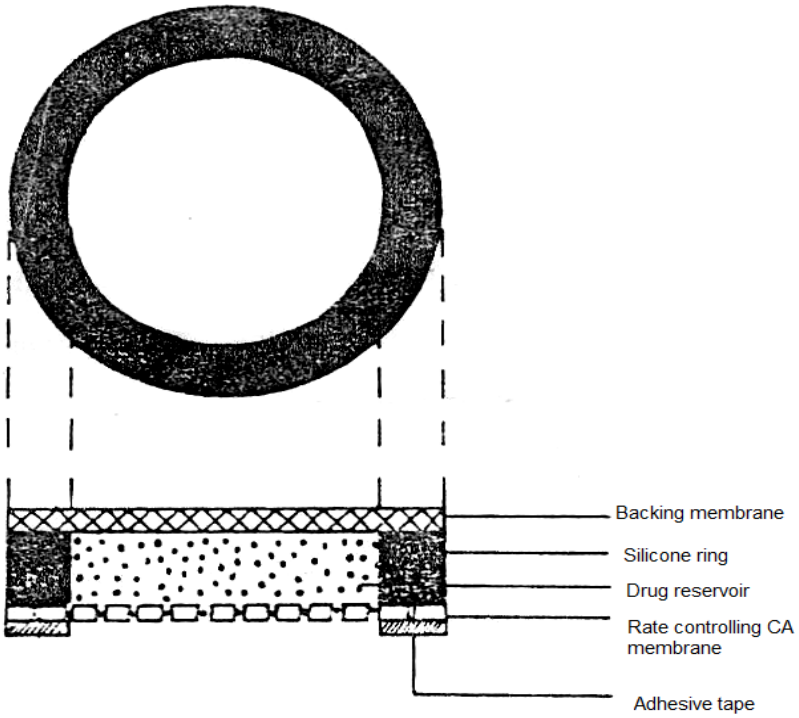


Figure 11: Sectional view of membrane moderated transdermal drug delivery system

***In vitro* studies[62]:**

Drug diffusion study was conducted using Franz diffusion cell. The receptor compartment was filled with 15 ml of phosphate buffer having pH 7.4 as diffusion media. The dialysis membrane was mounted between the donor and receptor compartment. The membrane moderated therapeutic systems of Verapamil hydrochloride was placed on the skin. Magnetic stirrer was set at 50 rpm and whole assembly was maintained at 32 $\pm$ 0.5°C. The amount of drug released was determined by withdrawing 1 ml of sample at regular time intervals for 24 hours. The volume withdrawn was replaced with equal volume of fresh buffer solution. Samples were analyzed for drug content using a UV spectrophotometer at 278 nm. The results are shown in **Table 19 and figure 23.** Further the order of drug release and mechanism of drug release was studied the values are shown in table 20 and fig 24, 25, 26 &27

Experimental Results

6. EXPERIMENTAL RESULTS

Table 7: Calibration Curve for the Estimation of the Verapamil HCl

Concentration (µg/ml)	Absorbance
0	**0**
2	**0.175±0.03**
4	**0.352±0.04**
6	**0.524±0.06**
8	**0.708±0.02**
10	**0.871±0.04**

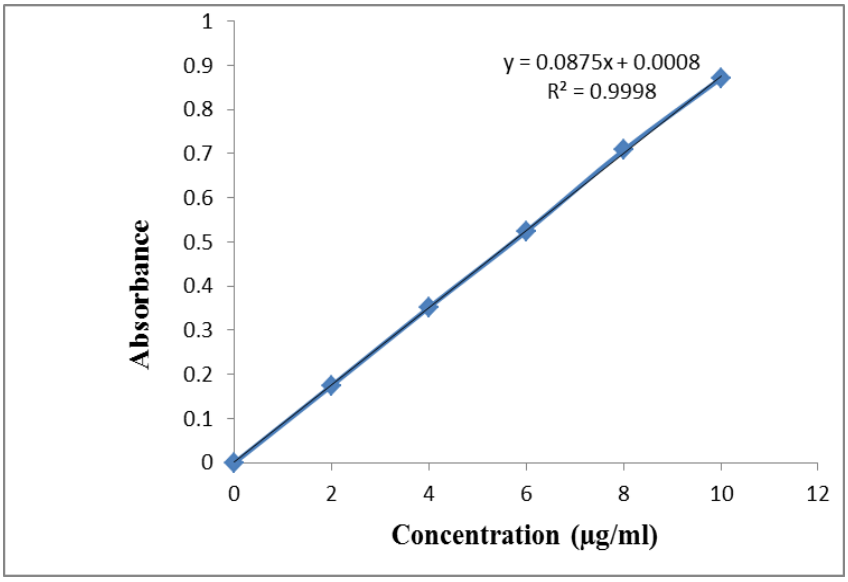


Figure: 12: Calibration Curve for the Estimation of Verapamil HCl

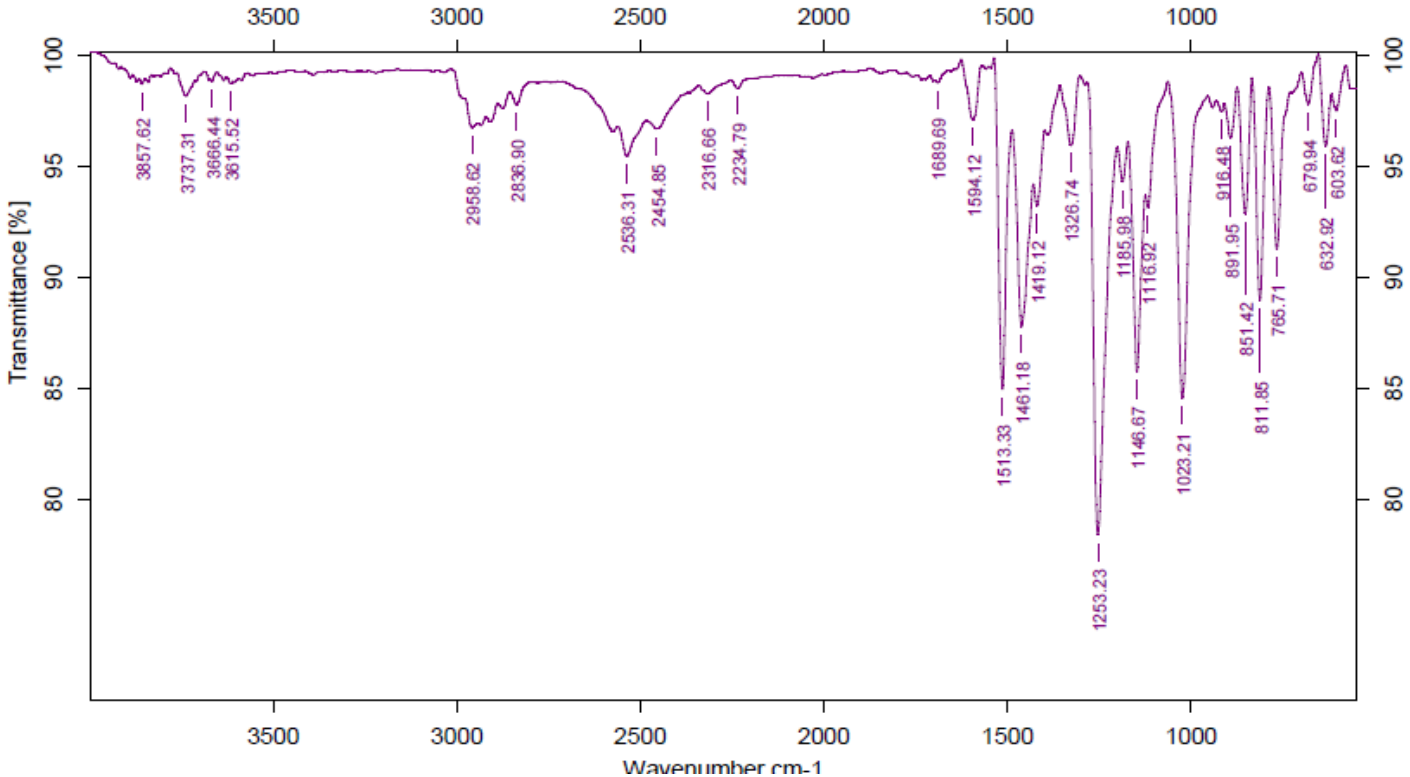


Figure 13: FTIR Spectra of Verapamil HCl

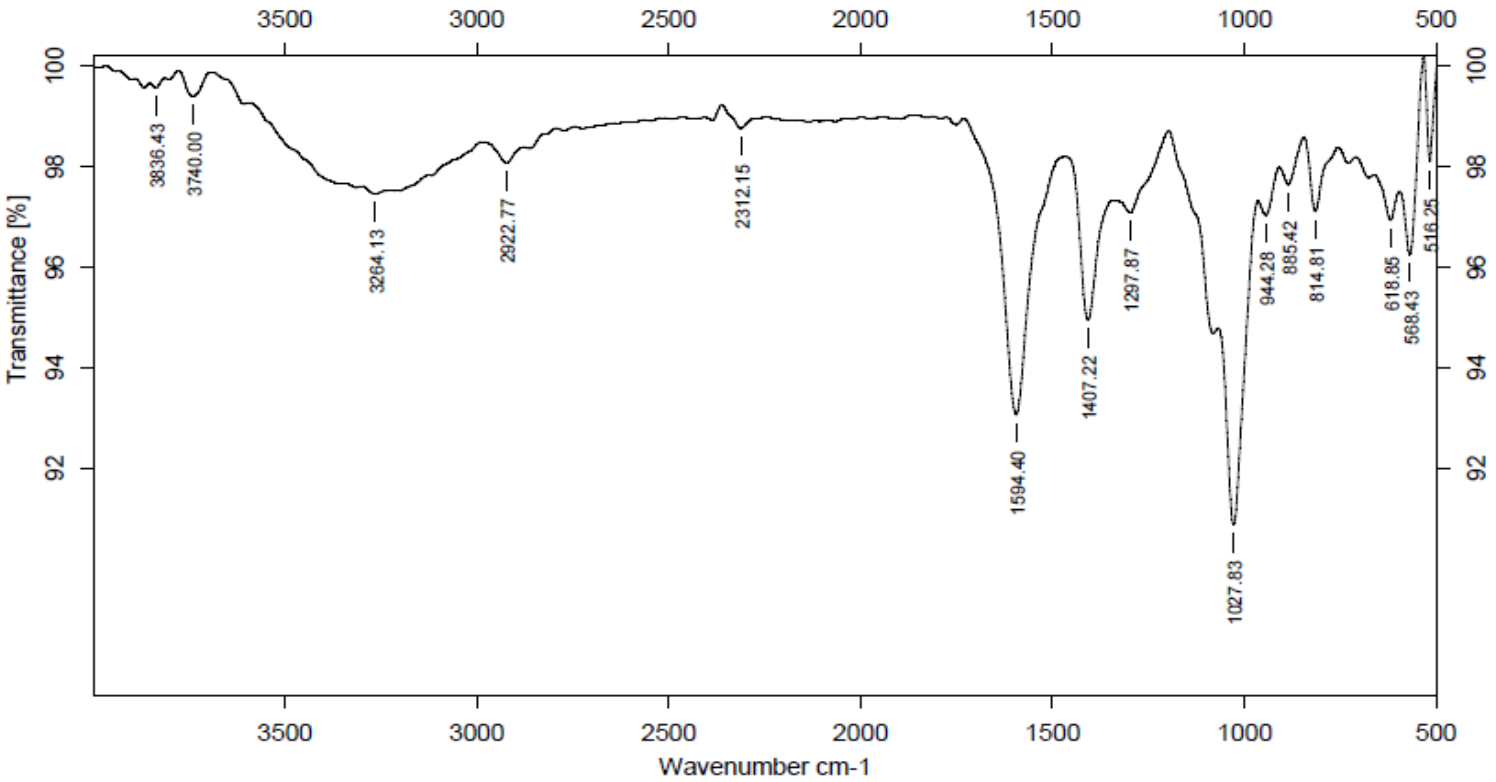


Figure 14: FTIR Spectra of Verapamil HCl with Cellulose acetate

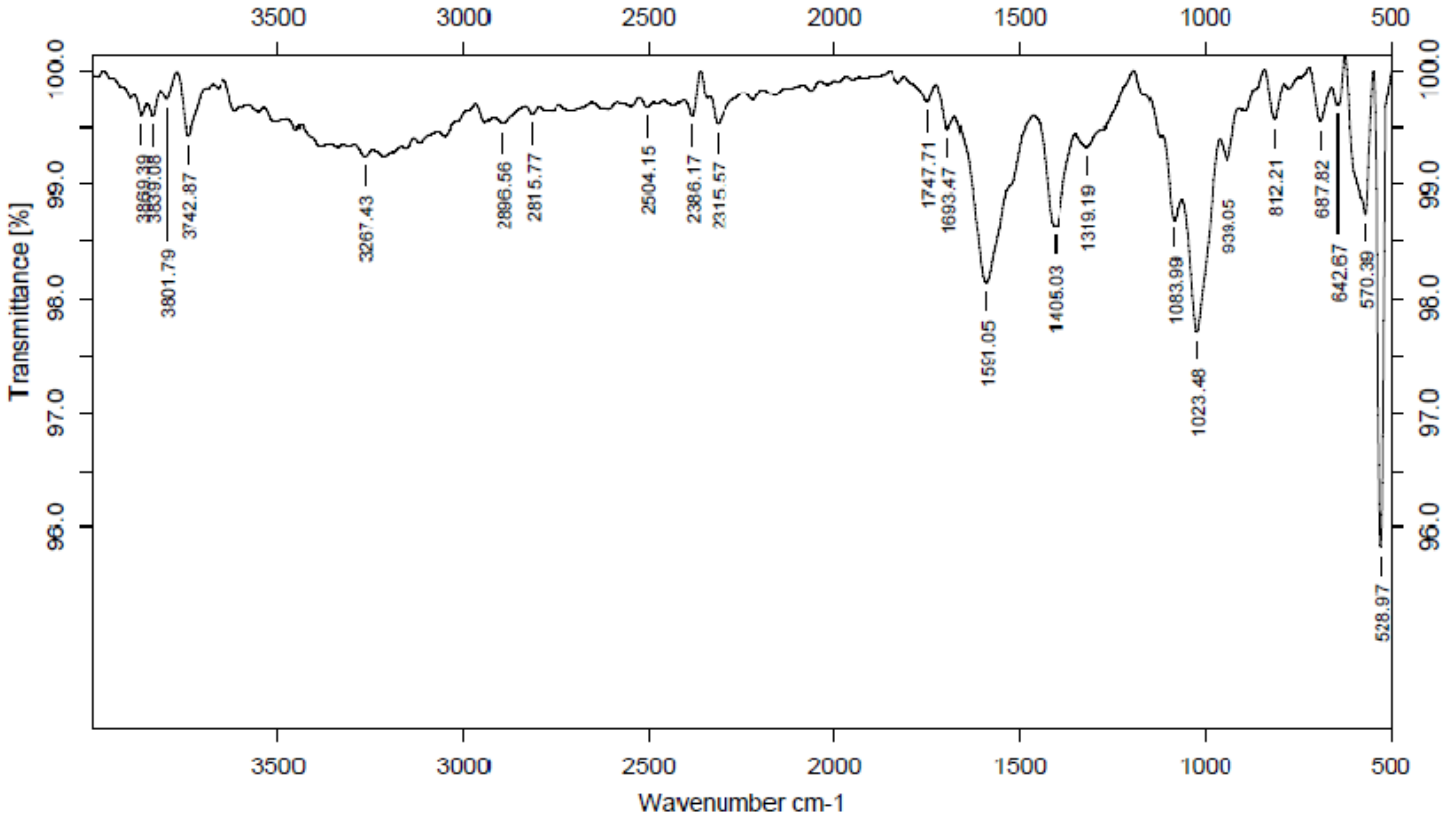


Figure 15: FTIR Spectra of Verapamil HCl with Ethyl cellulose

Table 8: Characterization of Prepared Films From F1to F8

Formulation	Thickness (µm)	Folding endurance	Tensile strength ($Kg.cm^2$)	Percentage elongation
F1	45.95±0.15	198	54.28±0.06	36.31±0.12
F2	45.30±0.17	223	48.29±0.10	40.55±0.16
F3	44.28±0.26	286	52.70±0.07	35.06±0.13
F4	46.70±0.26	164	66.18±0.05	44.05±0.15
F5	49.88±0.65	129	58.42±0.06	36.62±0.14
F6	54.25±0.37	196	48.36±0.07	38.41±0.13
F7	56.75±0.15	234	49.92±0.08	33.64±0.15
F8	51.40±0.28	132	57.21±0.05	37.74±0.12

Mean ± SD Values Where n=3

Table 9: Water Vapour Transmission Data of Prepared Films From F1 to F8

Time (hrs)	Amount of Water Vapour Transmitted (gm)							
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
0	0	0	0	0	0	0	0	0
18	0.208±0.04	0.197±0.02	0.151±0.01	0.306±0.02	0.290±0.01	0.27±0.02	0.245±0.02	0.298±0.04
36	0.412±0.05	0.394±0.08	0.306±0.05	0.610±0.08	0.576±0.05	0.51±0.01	0.486±0.01	0.596±0.04
54	0.618±0.04	0.592±0.04	0.453±0.06	0.911±0.04	0.868±0.04	0.77±0.05	0.734±0.05	0.890±0.025
72	0.838±0.08	0.783±0.04	0.606±0.07	1.118±0.04	1.152±0.05	1.03±0.08	0.975±0.08	1.189±0.05

Mean ± SD Values Where n=3

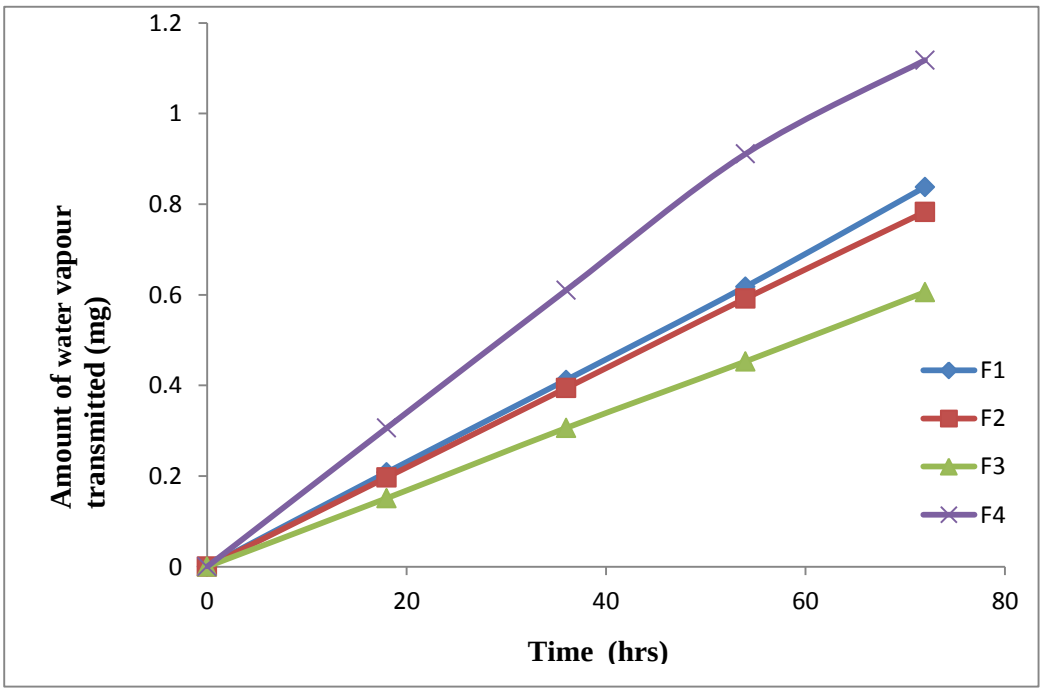


Figure 16: Water Vapour Transmission Profiles of Prepared Films

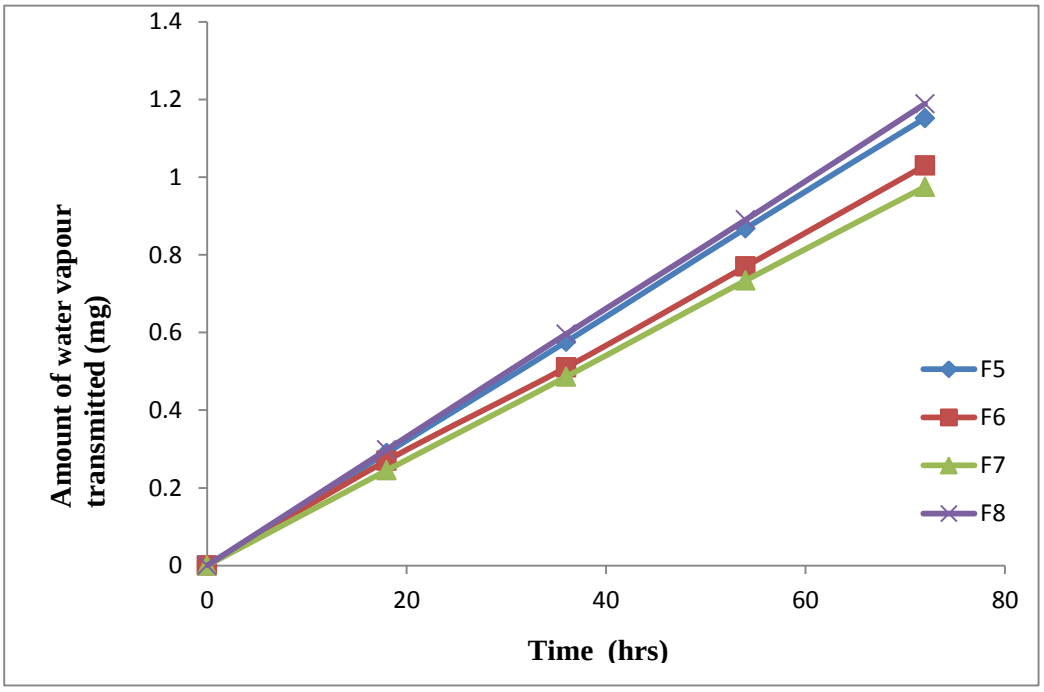


Figure 17: Water Vapour Transmission Profiles of Prepared Films From F5 to F8

Table 10: Diffusion data of drug solution through prepared films From F1 to F8

Time (h)	Amount of Verapamil HCl Diffused (mg)							
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
0	0	0	0	0	0	0	0	0
0.5	1.076±0.05	0.81±0.02	0.698±0.07	1.247±0.01	1.430±0.02	1.254±0.04	1.074±0.02	1.968±0.05
1	2.234±0.04	1.755±0.03	1.484±0.04	2.628±0.02	3.038±0.04	2.7328±0.06	2.327±0.04	4.205±0.02
1.5	3.589±0.04	2.79±0.04	2.357±0.05	4.187±0.04	4.871±0.05	4.300±0.01	3.714±0.07	6.666±0.05
2	5.070±0.02	3.96±0.02	3.36±0.08	5.925±0.02	6.837±0.02	6.0928±0.08	5.235±0.08	9.484±0.04
2.5	6.685±0.01	5.22±0.01	4.758±0.06	7.840±0.03	9.072±0.03	8.064±0.04	6.891±0.04	12.482±0.08
3	8.480±0.03	6.57±0.03	5.588±0.02	10.068±0.01	11.485±0.01	10.169±0.05	8.726±0.01	15.83±0.04

Mean ± SD Values Where n=3

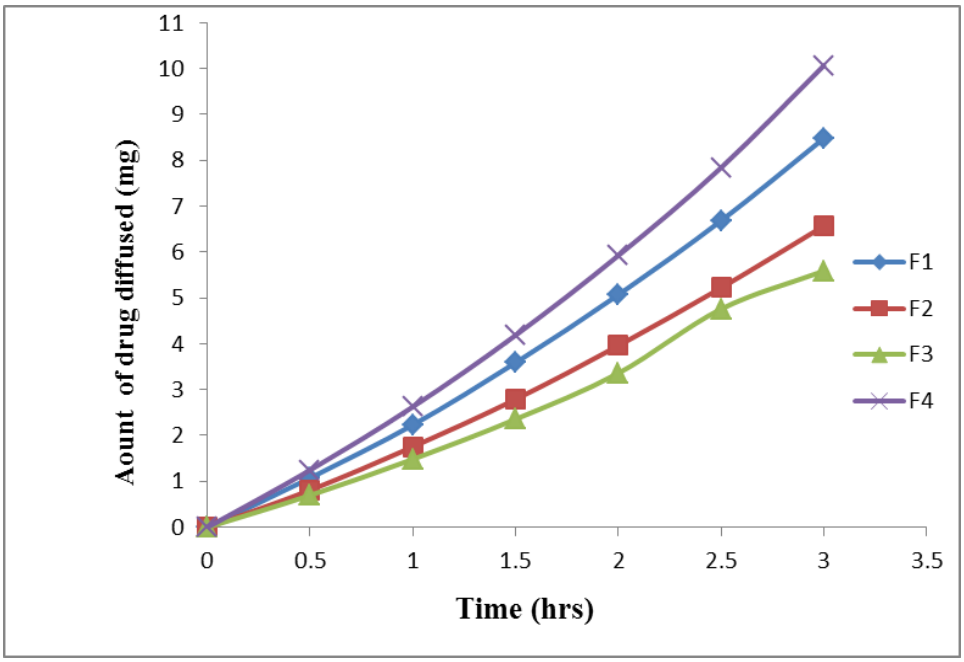


Figure 18: Diffusion Profiles of Prepared Films From F1 to F4

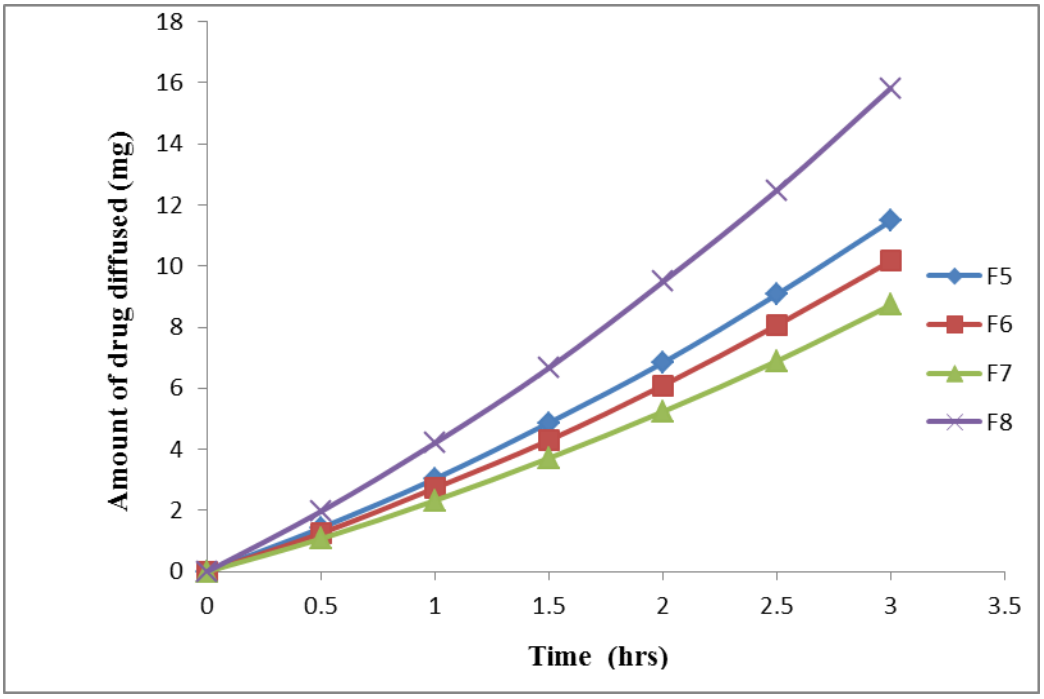


Figure 19: Diffusion Profiles of Prepared films for F5 to F8

Table 11: Characteristics of Verapamil HCl Gels Formulated with Different Polymers (G1 to G4)

Formulation	%Drug content	Viscosity (cps)	Spreadability (gm.cm/sec)	pH		Homogeneity	Synersis
				Before drug incorporation	After incorporation of drug.		
G1	98.56	1631	29.6	7.43	7.12	***	--
G2	99.82	4876	32.94	7.61	7.35	***	--
G3	99.65	1372	33.39	7.28	7.06	***	--
G4	99.46	1596	30.46	7.46	7.18	***	--

*** Excellent ** Good * Satisfactory -- Nill

Table 12: Diffusion Diffusion Data of Verapamil HCl Gel through Cellulose Acetate Films From G1 to G4

Time (h)	Amount of Verapamil HCl Diffused (mg)			
	G_1	G_2	G_3	G_4
0	0	0	0	0
0.5	0.05±0.01	0.03±0.05	0.02±0.05	0.01±0.08
1	0.56±0.04	0.39±0.07	0.23±0.06	0.17±0.04
1.5	1.50±0.05	1.26±0.11	1.19±0.01	1.11±0.04
2	2.52±0.06	2.41±0.08	2.36±0.02	2.19±0.05
2.5	3.56±0.02	3.29±0.02	3.15±0.06	3.09±0.02
3	4.58±0.03	4.15±0.06	4.09±0.04	3.98±0.01

Mean ± SD Values Where n=3

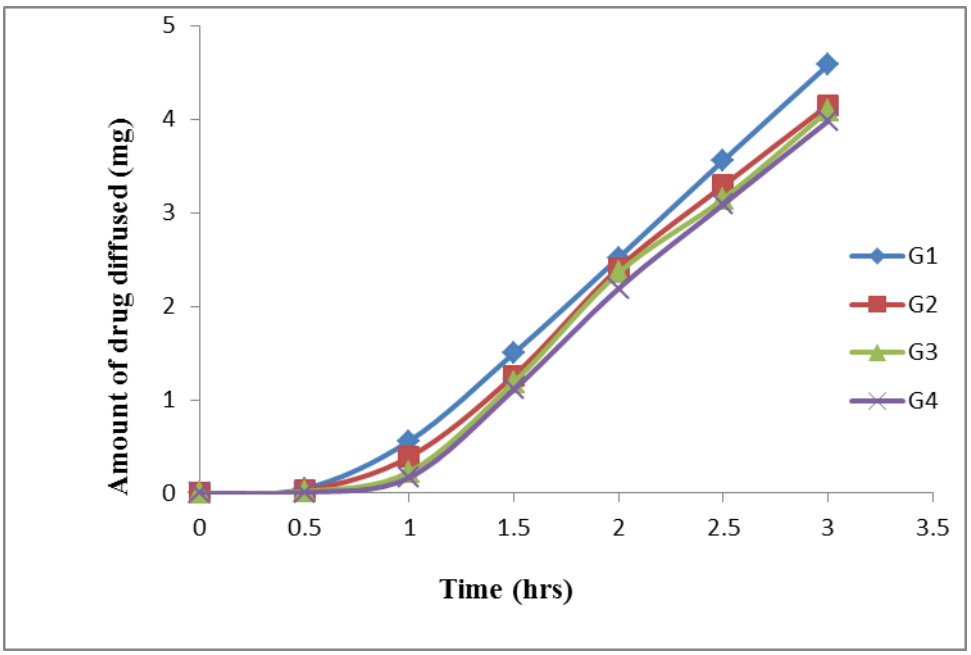


Figure 20: Diffusion Profiles of Verapamil HCl Gels through Cellulose acetate Film From G1 to G4

Table 13: Characteristics of Verapamil HCl transdermal Gels with combination of Hydrophilic Polymers (G5 &G6)

Formulation	%Drug content	Viscosity (cps)	Spreadability (gm.cm/sec)	pH		Homogeneity	Synersis
				Before drug incorporation	After incorporation of drug.		
G1	98.56	1631	29.6	7.43	7.12	***	--
G5	99.65	2895	31.42	7.52	7.31	***	--
G6	99.59	2685	30.88	7.45	7.23	***	--

*** Excellent ** Good * Satisfactory -- Nill

Table 14: Diffusion Data of Verapamil HCl Gels through Cellulose acetate Film (G5&G6)

Time(h)	Amount of Verapamil HCl Diffused (mg)		
	G1	G5	G6
0	0	0	0
0.5	0.05±0.01	0.49±0.05	0.68±0.07
1	0.56±0.04	1.39±0.02	1.62±0.08
1.5	1.50±0.05	2.45±0.04	2.59±0.06
2	2.52±0.06	3.52±0.02	3.65±0.05
2.5	3.56±0.02	4.43±0.04	4.69±0.09
3	4.58±0.03	5.37±0.05	5.58±0.04

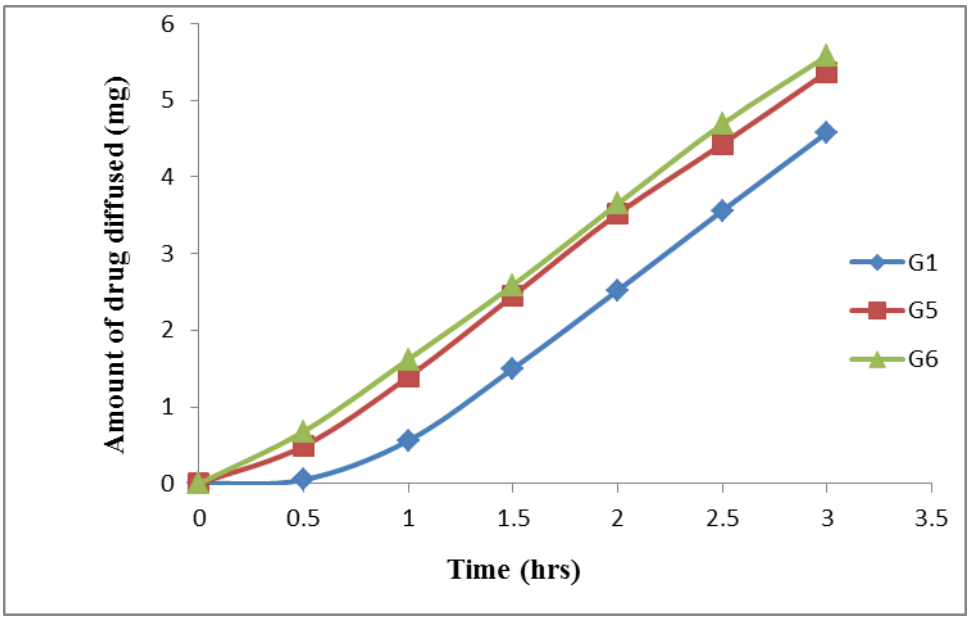


Figure 21: Diffusion Profiles of Verapamil HCl Gels through Cellulose acetate Film (G5&G6)

Table 15: Characteristics of Verapamil HCl Gels Containing Permeation Enhancers

Formulation	%Drug content	Viscosity (cps)	Spreadability (gm.cm/sec)	pH		Homogeneity	Synersis
				Before drug incorporation	After incorporation of drug.		
GP1	99.68	1100	29.06	7.33	7.32	***	--
GP2	99.52	1673	32.05	7.46	7.25	***	--
GP3	99.80	1010	33.78	7.60	7.14	***	--
GP4	99.88	993	32.46	7.41	7.23	***	--

*** Excellent ** Good * Satisfactory -- Nill

Table 16: Diffusion Data of Verapamil HCl Gels Containing Different Permeation Enhancers from Cellulose acetate Films (GP1 to GP4)

Time (h)	Amount of Verapamil HCl Diffused (mg)			
	GP1	GP2	GP3	GP4
0	0	0	0	0
0.5	0.89±0.04	0.80±0.02	0.72±0.05	0.68±0.03
1	1.82±0.05	1.65±0.03	1.55±0.01	1.46±0.02
1.5	2.83±0.03	2.66±0.06	2.51±0.02	2.36±0.06
2	3.89±0.06	3.68±0.05	3.48±0.03	3.17±0.02
2.5	4.56±0.08	4.01±0.08	3.98±0.02	3.86±0.01
3	5.80±0.06	4.73±0.05	4.48±0.06	4.22±0.03

Mean ± SD Values Where n=3

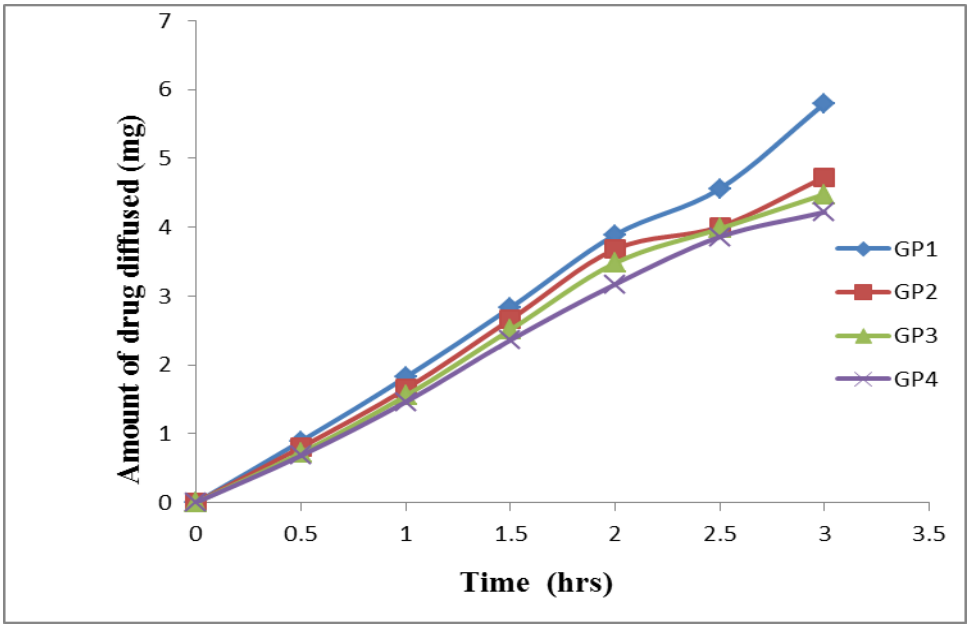


Figure 22: Diffusion Profiles of Verapamil HCl Gels Containing Different Permeation Enhancers through Cellulose acetate Films (GP1 to GP4)

Stability Studies

Table 17: Physicochemical Properties of Verapamil HCl Gel (GP1) Stored at 25°C ± 2°C at 75±5%RH.

Physicochemical properties		Time(weeks)						
S.No	**Parameter**	0	1	2	3	4	5	6
1	Drug content(%)	99.72	99.62	99.52	99.44	99.34	99.26	99.18
2	Viscosity(cps)	1100	1098	1096	1094	1092	1089	1085
3	pH	7.45	7.43	7.41	7.38	7.35	7.34	7.32
4	Spreadability (gm.cm/sec)	29.41	29.38	29.34	29.30	29.27	29.24	29.20
5	Homogenity	***	***	***	***	***	***	***
6	Degradation rate Constant(per day)	0.00005						

Table 18: Physicochemical Properties of Verapamil HCl Gel (GP1) Stored at 40°C ± 2°C at 75±5%RH.

Physicochemical Properties		Time(weeks)						
S.No	**Parameter**	0	1	2	3	4	5	6
1	Drug content(%)	99.72	99.58	99.46	99.34	99.22	99.12	99.04
2	Viscosity(cps)	1100	1097	1094	1091	1089	1087	1084
3	pH	7.45	7.41	7.38	7.35	7.33	7.31	7.29
4	Spreadability (gm.cm/sec)	29.41	29.38	29.36	29.33	29.31	29.28	29.24
5	Homogenity	***	***	***	***	***	***	***
6	Degradation rate constant(per day)	0.00007						

*** Excellent

Table 19: ***In vitro*** **study: Diffusion Data of Verapamil HCl Gel (GP1) Membrane Moderate Transdermal Therapeutic System For 24 hours**

S.No	Time (hrs)	GP1
1	0	0
2	1.0	1.76±0.03
3	2.0	3.63±0.04
4	3.0	5.56±0.02
5	4.0	7.60±0.01
6	5.0	9.63±0.02
7	6.0	11.88±0.01
8	7.0	13.49±0.04
9	8.0	15.24±0.02
10	9.0	17.41±0.03
11	10.0	19.32±0.02
12	11.0	21.30±0.01
13	12.0	23.13±0.04
14	13.0	25.12±0.03
15	14.0	27.17±0.02
16	15.0	29.28±0.03
17	16.0	31.34±0.03
18	17.0	33.56±0.04
19	18.0	35.84±0.02
20	19.0	37.14±0.03
21	20.0	39.37±0.02
22	21.0	41.86±0.01
23	22.0	43.06±0.02
24	23.0	44.78±0.03
25	24.0	45.3±0.04

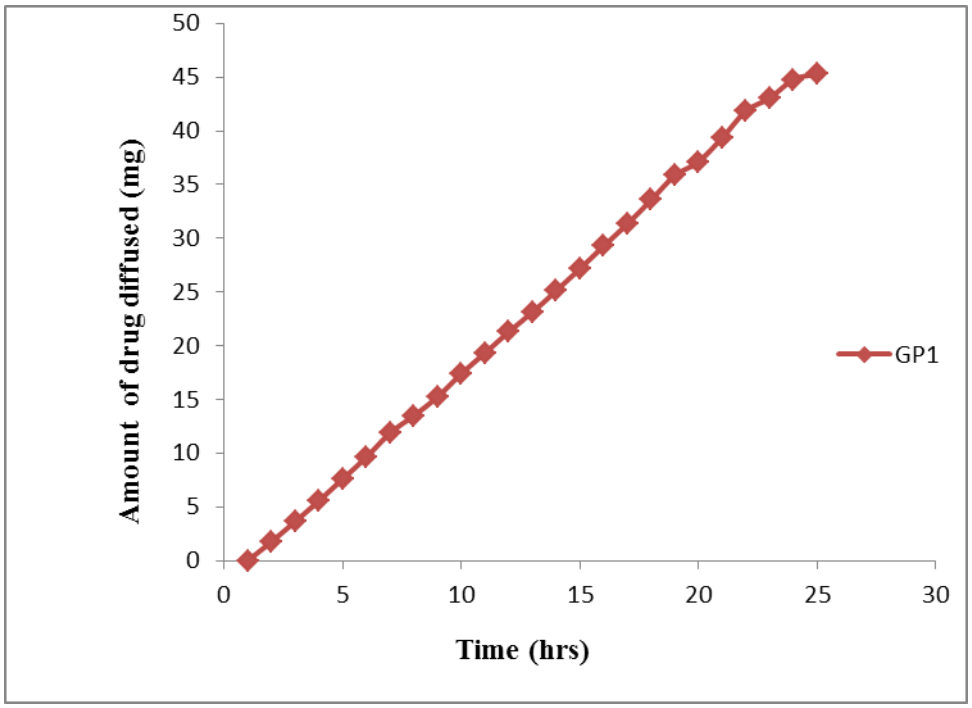


Figure 23: ***In vitro*** **Study: Diffusion Data of Verapamil HCl GP1 (GP1) Membrane Moderate Transdermal Therapeutic System For 24 hours**

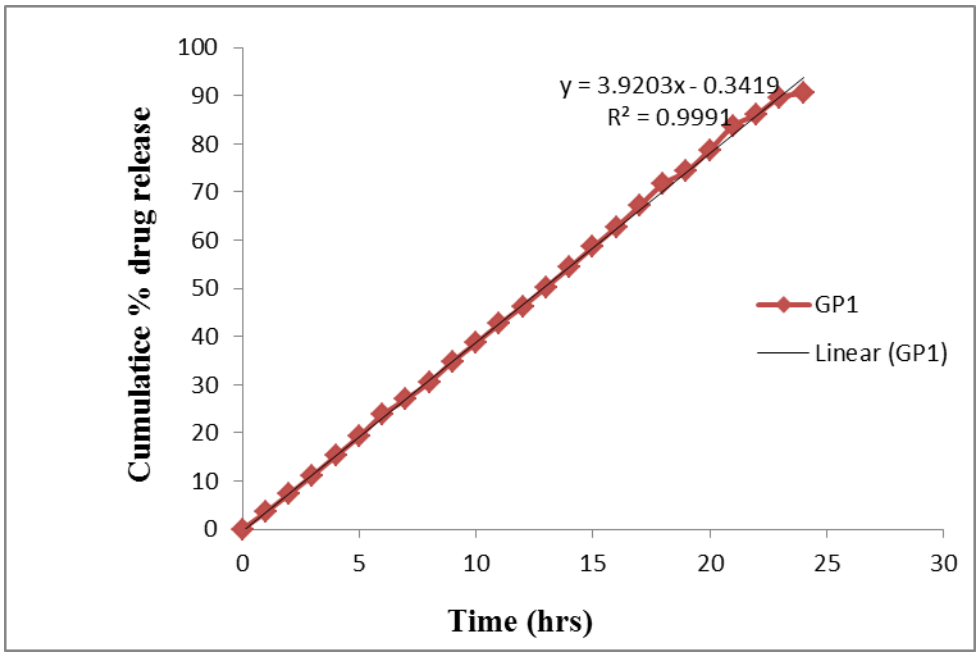


Figure 24: Zero Order Plot of Verapamil HCl Gel (GP1)

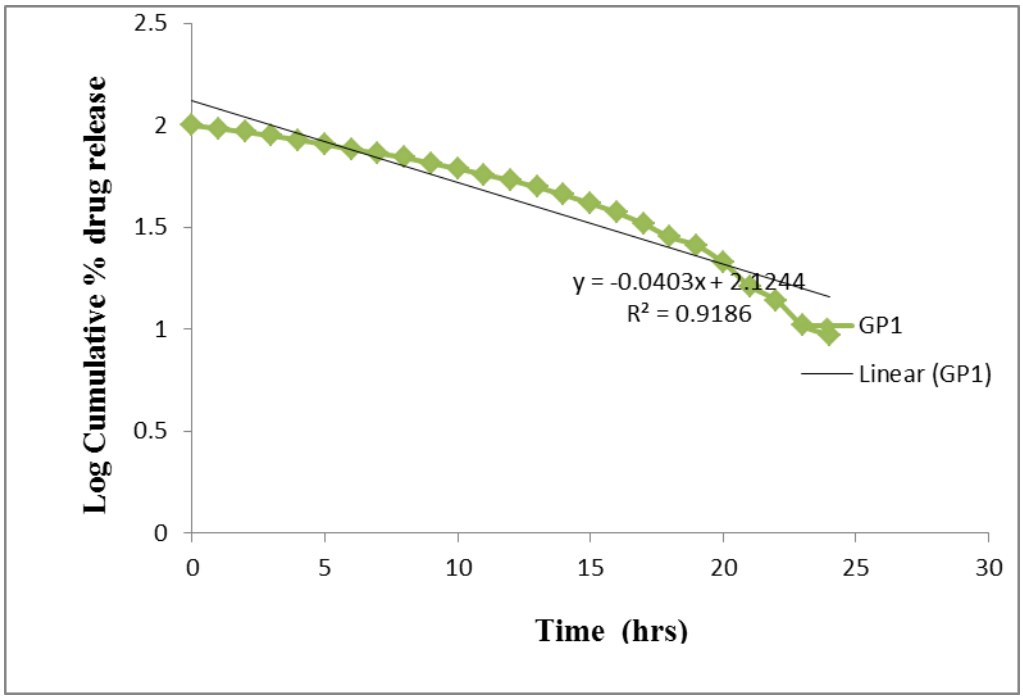


Figure 25: First Order Plot of Verapamil HCl Gel (GP1)

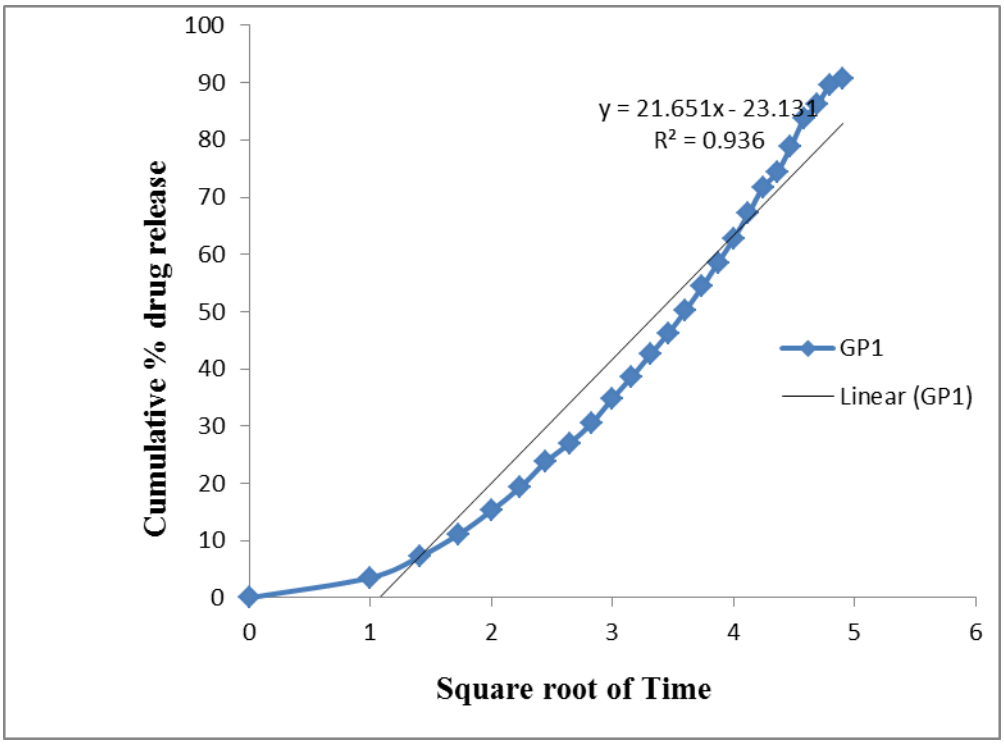


Figure 26: Higuchi Plot of Verapamil HCl Gel (GP1)

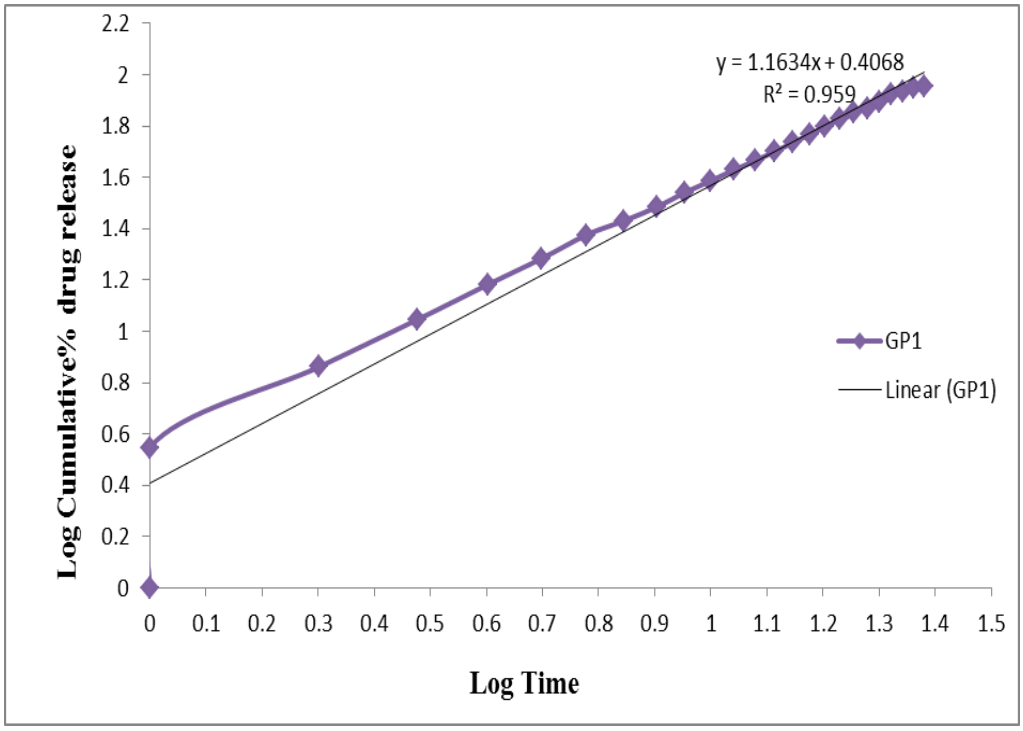


Figure 27: Peppas Plot of Verapamil HCl Gel (GP1)

Table 20: Diffusion Kinetics of Verapamil HCl Gel (GP1)

Formulation	Correlation coefficient (R) values				Diffusion exponent value(n)
	Zero order	First Order	Higuchi model	Peppas model	
GP1	0.9991	0.9186	0.936	0.959	1.1634

Discussion

7. DISCUSSION

Calibration curve:

The calibration curve was plotted against concentration versus absorbance for the drug Verapamil Hydrochloride with solvent saline phosphate buffer p^H 7.4. The table and figure were represented in 7 and 12. The straight line equation with saline phosphate buffer was found to be Y=0.0876x+0.0008 and R^2= 0.9998.

Compatibility studies:

The IR spectra of Verapamil HCl and its combination with cellulose acetate, ethyl cellulose were showed in Figure 13 to 15.

The Infrared absorption bands in the spectrum of the pure drug Verapamil HCl were as follows:

Table 20:

S.No	Region in cm^{-1}	Type of vibration	Functional group	Range of region
1.	1689.69 1594.12	C=C stretching	Aromatic ring	1500-1800
2.	2234.79	C≡N stretching	Alkyl nitrile	2200-2500
3.	1253.23 1185.98	C-O stretching	Aromatic Aliphatic	1100-1400
4.	1023.21	C-N stretching	Aliphatic	900-1200
5.	2958.62 2836.90	C-H stretching	Methyl	2800-3000
6.	2536.31	C-H stretching	Aldehyde	2500-2800

Compatibility studies of drug and polymer:

The compatibility between the drug and polymers were confirmed by FTIR.

The FTIR spectrum of the physical mixtures (drug with polymer ethyl celllulose and cellulose acetate) was compared with pure drug. From FTIR the principle peaks of Verapamil Hydrochloride alone observed at wavelength.

1594.12(C=C stretching), 2234.79 (C≡N stretching), 1023.21 (C-N stretching), 2536.31(C-H stretching). In the FTIR spectrum of the physical mixture of drug and polymers, the major peaks of drugs were observed at wavelength 1594.40 (C=C stretching), 2312.15 (C≡N stretching), 1083.99 (C-N stretching). From the spectrum it was clear that the peaks which were in pure drug were present in physical mixture this shows that there is no interaction between drug and polymers used.

Studies on polymeric films:

Solvent evaporation technique was employed for the preparation of ethyl cellulose and cellulose acetate films.

In each case films were prepared using 2% w/v solutions of the polymer in various solvents to evaluate the influence of the solvent used on the mechanical and permeability properties of the films. Acetone-methanol (8:2), chloroform-methanol (8:2), dichloromethane-methanol (8:2), and ethyl acetate-methanol (8:2) were used as solvents in the preparation of films.

The films prepared with polymer alone were found to be brittle. To prevent embitterment a plasticizer, dibutyl phthalate was tried at various concentrations ranging from 10-50% w/w of the polymer. Preliminary experiments indicated that lower concentrations of dibutyl phthalate were found to give rigid and brittle films where as higher concentrations gave soft films. Dibutyl phthalate at a concentration of 40% w/w of the polymer was found to give good flexible films.

Hence, dibutyl phthalate was included as a plasticizer in the preparation of ethyl cellulose and cellulose acetate films.

All the films prepared were evaluated for thickness uniformity, folding endurance, tensile strength, percentage elongation and the results were showed in Table 8. These films were found to be uniform in thickness and offered good mechanical strength and flexibility. Water vapour transmission studies indicated that the films were permeable to water vapour and the amount of water vapour transmitted at various time intervals was showed in Table 9 and in Figures 16 and 17.

The Verapamil HCl diffusion data was represented in Table 10 and in Figures 18 and 19. The result shows that the formulation F8 shows highest amount of drug release with Ethyl Acetate-Methanol solvent.

Studies on drug reservoir gels:

The design of membrane moderated transdermal drug delivery systems requires a suitable rate controlling membrane and a drug reservoir. The drug reservoir can be in either solid, semisolid or solution form. Out of the various semisolids dosage forms, the gels are becoming more popular due to ease of application and better percutaneous absorption, than other semisolids preparations. Gels can resist the physiological stress caused by skin flexion, blinking and mucociliary movement, adopting the shape of the applied area, and controlling drug release. With a view to design a suitable drug reservoir, various types of gel formulations were prepared and evaluated by studying drug diffusion from these formulations across the rate controlling membrane.

In the present study efforts were made to prepare transdermal gels of Verapamil HCl using polymers like Hydroxy Propyl Methyl Cellulose (HPMC), Sodium Carboxy Methyl Cellulose (NaCMC), Methyl Cellulose (MC) and Carbopol. Transdermal gels prepared with Carbopol and Hydroxy Propyl Methyl Cellulose were found to be white, translucent and homogenous. But gels prepared

with Sodium Carboxy Methyl Cellulose and Methyl Cellulose was found to be off white and homogenous.

Drug content values of the formulations were well with in the range between 98.56-99.82% (Table 11).The pH of all formulations was around the skin pH 7.06 to 7.61 reflecting no risk of skin irritation.

Viscosities of Verapamil HCl gels were presented in Table 12. All gels were found to exhibit plastic flow. It was observed that the gel formulations showed good homogeneity and spreadability and the data was presented in Table 12.

The results of the *in vitro* diffusion study from Verapamil HCl gels across the rate controlling membrane with dialysis membrane were reported in Table 12 and showed in Figure 20. The result shows that the amount of drug diffused through G1 formulation at the end of 3 hours was found to be 4.58±0.03mg.

The gel formulations can be graded in the following order with respect to the rates of release of selected drugs from them:

(HPMC) < (MC) < (Carbopol) < (NaCMC).

Based on diffusion data Sodium Carboxy Methyl Cellulose gels were selected for further studies.

Influence of hydrophilic polymers from Sodium carboxy methyl cellulose gels:

To enhance the permeability of selected drug, various hydrophilic polymers namely poly ethylene glycol 6000 (PEG 6000), poly vinyl pyrolidine (PVP) were incorporated in 1:1 ratio (Na CMC: polymer) in to the sodium carboxy methyl cellulose gels. Incorporation of hydrophilic polymers accelerated the permeability of selected drugs. Poly ethylene glycol 6000 offered more permeability when compared with poly vinyl pyrrolidine. Incorporation of poly ethylene glycol 6000 above 1:1 ratio yielded the gels with low viscosity, showed the leakage from

the rate controlling membrane. Hence the studies were restricted to 1:1 ratio. All gels were found to exhibit plastic flow.

It was observed that Verapamil HCl gel formulations showed good homogeneity and spreadability and the data was presented in Table 13.

The results of the *in vitro* diffusion study from different gels across the rate controlling membrane with dialysis membrane were reported in Table 14 and showed in Figure 21. The result shows that the amount of drug diffused through the G6 formulation at the end of 3 hours was found to be 5.58±0.04 mg .

From the diffusion data the gel formulations can be graded in the following order with respect to the rates of release of selected drugs from them:

(NaCMC) < (NaCMC +PVP) < (NaCMC+ PEG 6000).

Based on drug release G6 formulation (Na CMC+PEG 6000) was selected for further studies.

Influences of permeation enhancers on permeability of selected drugs:

The stratum corneum has evolved primarily for barrier function. This creates difficulties in the formulation of TDDS which aims to delivery the drug via skin in therapeutic quantities. The search for solutions to this problem led investigators to employ several enhancement techniques. One approach is the co administration of skin permeation enhancers. Ideally, permeation enhancers are a chemical entity which reduces reversibly the barrier resistance of the stratum corneum without damaging the viable cells. A large number of substances have been evaluated as permeation enhancers and research is extending with the growing need for safe, effective accelerants. The permeation enhancers such as sodium lauryl sulphate (SLS), poly ethylene glycol 400 **(**PEG 400), dimethyl sulfoxide (DMSO) and tween 20 were incorporated into gels (Drug +Na CMC + PEG 6000) with a view to improve permeability of selected drug.

It was observed that the Verapamil HCl gel formulations containing various permeation enhancers showed good homogeneity and spreadability. The data was presented in Table 15.

The results of the *in vitro* diffusion studies of Verapamil HCl gels containing various permeation enhancers across the rate controlling membrane with dialysis membrane were reported in Table 16 and showed in Figure 22. The result shows that for the GP1 formulation at the end of 3 hours the amount of drug diffused was found to be 5.80±0.04 mg.

Stability studies of Formulation GP1:

The results of stability studies were showed in Table 17 and 18. The stability studies were performed for six weeks. There were no significant changes in the drug content, physical appearance, pH, viscosity and spreadability.

Evaluation of membrane moderated transdermal therapeutic system:

***In vitro* study of Verapamil HCl membrane moderated transdermal therapeutic system:**

The results of the *in vitro* permeation study from Verapamil HCl membrane moderated transdermal therapeutic system were reported in Table 19 and were showed in Figure 23. The result shows that at the end of 24 hours the drug release was found to be 45.3mg. The diffusion data shows that the system followed zero order kinetics and showed in Figure 24. The correlation coefficient (R^2) values revealed that the diffusion profiles followed zero order kinetics and the mechanism of drug release was governed by peppas model the values were shown in Table 20. The diffusion exponent of peppas plots (slope) has a value of 1.1634 ($n \geq 1$), which indicates case II transport diffusion.

Summary and Conclusion

8. SUMMARY AND CONCLUSION

In the present work cellulose acetate and ethyl cellulose were prepared and evaluated as rate controlling membranes for transdermal drug delivery systems.

The results obtained in the present study thus indicated that the polymer and solvent used has significant influence on the water vapour transmission and drug diffusion of the films. Based on the diffusion rate the formulations can be arranged as

Cellulose Acetate > Ethyl Cellulose.

Among all the films, cellulose acetate films casted with ethyl acetate - methanol (8:2) showed high rate of drug release when compared to other films.

The cellulose acetate films casted with ethyl acetate: methanol (8:2) employing dibutyl phthalate (40% w/w of dry polymer) as plasticizer was used as rate controlling membranes in further studies.

In the present study efforts were made to prepare transdermal gels of Verapamil HCl using polymers like hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (Na CMC), methyl cellulose (MC) and carbopol.

The gel formulations can be graded in the following order with respect to the rates of release of selected drugs from them:

(HPMC) < (MC) < (Carbopol) < (NaCMC).

To enhance the permeability of selected drugs, various hydrophilic polymers namely poly ethylene glycol 6000(PEG 6000), poly vinyl pyrolidine

(PVP) were incorporated in 1:1 ratio (NaCMC: polymer) in to the sodium carboxy methyl cellulose gels. The gel formulations can be graded in the following order with respect to the rates of release of selected drugs from them:

(NaCMC) < (NaCMC +PVP) < (NaCMC+ PEG 6000).

The permeation enhancers such as of sodium lauryl sulphate (SLS), poly ethylene glycol 400 **(**PEG 400), dimethyl sulfoxide (DMSO) and tween 20 were incorporated into gels (Drug +NaCMC + PEG 6000) with a view to improve permeability of selected drugs.

The permeation enhancers used for increasing the permeation of drug could be arranged in the following increasing order according to their permeation rates:

Tween 20> SLS> DMSO > PEG 400.

The increased permeation rate in all these enhancers may be due to surfactant action. These results indicated that the non ionic surfactant tween 20 improves the permeability characteristics of Verapamil HCl when compared with the other permeation enhancers. The gels containing drug, sodium carboxy methyl cellulose: poly ethylene glycol 6000(1:1) and tween 20 were selected as drug reservoirs.

The membrane moderated therapeutic systems of Verapamil HCl was subjected to *in vitro* skin permeation studies, drug polymer interactions studies.

The results of the 24 hours *in vitro* permeation studies revealed that the drug diffusion was extended over a long period of time at a controlled rate in Verapamil HCl membrane moderated transdermal therapeutic systems.

Drug polymer interaction studies clearly indicating that the drug is not undergo any chemical interaction with the polymers.

Further the permeation, pharmacokinetic and pharmaodynamic of the optimized formulations has to be studied with animal models.

Bibliography

9. BIBLIOGRAPHY

1. Joseph, R, Robinson., and Vincent, H., L, Lee., controlled drug delivery, 2nd edition., Dedder., 1978;29:7.

2. Y, W, Chein., Novel drug delivery system., 2nd edition., marcel dekker., Inc., Newyork,1992, 1.

3. Joseph, R, Robinson., Sustained release drug delivery system., Remington pharmaceutical sciences., 18th edition ., 1990, 1682-1698.

4. Heller, J., Therapeutic drug carrier system., 10th edition ., Bailliere Tindall, 1993,23.

5. http://www.pharmainfo.net/reviews/controlled-released-system-review

6. Shaw, J. E., Chandrasekharan, S. K. and Campbell. The Influence of Skin Structure on Permeability: An Intersite and Interspecies Comparison with Hydrophilic Penetrants. P. J. Invest. Dermatol. 1976; 67: 677.

7. Monkhouse, D. C. and Huq, A. S. Development of matrix controlled transdermal delivery systems of pentazocine: In vitro/in vivo performance. Drug Develop. Ind. Pharm. 1988; 14: 183.

8. Carol, M. C., Erasmo, A. M., Rowena, S. W., Elizabeth, P. H. and Randall, M. Z., Drug Intelligence And Clinical Pharmacy.1987; 21: 642.

9. Guy, R. H., Hadgraft, J. and Bucks, D. A. W., Xenobiotica. 1987;17: 325.

10. Barry, B. W., Dermatological Formulations, Percutaneous Absorption, Marcel Dekker, New York 1983, 225.

11. Mishra, B., Pandit, J. K. and Bhattacharya, S. K. Recent trends in drug delivery systems: transdermal drug delivery. Ind. J. Exp. Biol. 1990; 28: 1001.

12. Harpin, V. A. and Rutter N. Immature Skin. J. Pediatr. 1983; 102: 419.

13. Jacob, S. A. and Francone, C. A., Structure and Function of Man, 2nd ed., W. B. Saunders Co., Philadelphia, 1970, 55.

14. Chien, Y. W., Drug Dev. Ind. Pharm. 1983;9:497.

15. Jain, N. K., Controlled and Novel Drug Delivery, CBS Publishers and Distributors, 2002, 107.

16. Kydonieus, A. F. Transdermal Delivery of Drugs, Vol I, (Keydonieus, A. F. and Berner, B, eds.), CRC Press, Florida, 1987,3.

17. Udupa N., Mutalik S., Kumar S, Agarwal S., Subramanian G., Ranjith AK., Life Sci. 2006; 79(16):1568.

18. Knuston, K, Potts, R. O., Guzek, D. B., Golden, G. M., Mckie, J. E., Lambert, W. J. and Higuchi, W. I. Effect of Experimental Temperature on the Permeation of Model Diffusants Across Porcine Buccal Mucosa. J. Control. Rel.1985; 2(10): 67.

19. Potts, R. O., Transdermal Drug Delivery, Hadgraft, J and Guy, R. H., Eds., Marcel Dekker, New York, 1989,23.

20. Feldman, RJ, Maibach, HI: Regional variation in percutaneous penetration of 14cortisol in man. J Invest Dermatol.1967; 48: 181–183.

21. Scheuplein, R. J. Mechanism of percutaneous absorption. Iv. Penetration of nonelectrolytes (alcohols) from aqueous solutions and from pure liquids. J. Invest. Dermatol.1965; 45: 334.

22. Chien, Y. W. and Valia K. H., Valia, Drug Dev. Ind. Pharm. 1984;10:575.

23. http://www.drugs.com/ppa/verapamil-hydrochloride.html

24. http://www.drugs.com/ppa/Ethyl cellulose.html

25. http://www.drugs.com/ppa/cellulose acetate.html

26. Jatin Sood, Varinder kaur, Pravin Pawar. Transdermal Delivery of Verapamil HCl: Effect of Penetration Agent on In Vitro Penetration through Rat Skin. Journal of Applied Pharmaceutical Science. 2013; 3(03): 044-051.

27. Gungor S, Bektaş A, Alp FI, Uydeş-Doğan BS, Ozdemir O, Araman A, Ozsoy Y. Matrix-type transdermal patches of verapamil hydrochloride: in vitro permeation studies through excised rat skin and pharmacodynamic evaluation in rats. Pharm Dev Technol. 2008; 13(4): 283-9.

28. Jawahar N, Anoop K. R, Prasad Ajish, Sarfaraz M. D, Gopal Rao M, Jayaprakash S. Evaluation of different formulation variables on transdermal films of verapamil hydrochloride. The Indian pharmacist, 2007; 6(60):67-69.

29. Swarnalta, S, Saraf, S and Dixit, V. K., www.priory.com/pme. htm, 2006.

30. Amnuaikit C, Ikeuch I, Ogawara K, Kimura T. Skin permeation of propranolol from polymeric film containing terpene enhancers for transdermal use. Int. J. Pharmaceutics 2005; 289 (1):167-78.

31. Mutalik S, Udupa N. Glibenclamide transdermal patches: Physicochemical, pharmacodynamic, and pharmacokinetics evaluations.J. Pharm. Sci. 2004; 6: 1577–94.

32. Donbrow, Meier and Samuelov. Zero order drug delivery from double-layered porous films: release rate profiles from ethyl cellulose, hydroxypropyl cellulose and polyethylene glycol mixtures. J. Pharmacy & Pharmacol, 1980; 32:463.

33. Kusum Devi V, Saisivam S, Maria GR, Deepti PU. Design and evaluation of matrix diffusion controlled transdermal patches of verapamil hydrochloride. Drug Dev Ind Pharm. 2003; 29(5):495-503.

34. Wang, F. J., Yang, Y. Y., Zhang, X. Z., Zhu, X, Chung, T. S. and Moochhala, S. Use of 2-hydroxypropyl-β-cyclodextrin as adjuvant for enhancing encapsulation and release characteristics of asiaticoside within and from cellulose acetate films. Materials Sci. and Eng. 2002; 20 (1-2): 93.

35. Nguyen, V, Mantelle, J, Kanios, D and Moncada, K. The study of Transdermal administration of ACE inhibitors and improved absorption of their prodrug. Noven Pharmaceuticals, Inc., Miami, Florida, 2000.

36. K. L. K Paranjothy, P. P Thampi. Development Of Transdermal Patches Of Verapamil Hydrochloride Using Sodium Carboxymethyl Guar As A Monolithic Polymeric Matrix And Their In vitro Release Studies. IJPS. 1997; 59(2): 49-54.

37. Rao P R, Diwan PV. Influence of casting solvent on permeability of Ethyl cellulose films for transdermal use. Eastern Pharmacist 1997; 46:135-39.

38. Bhatt D C,Agrawal G P. An approval to the formulation of a transdermal drug delivery system of promethazine hydrochloride. Eastern Pharmacist 1995; 38: 145-47.

39. Phuapradit, W., Shah, N. H., Railkar, A., Williams, L and Infeld, M. H. *In vitro* characterization of polymeric membrane used for controlled release application. Drug Develop. Industrial Pharmacy, 1995; 21 (8): 955.

40. Chowdary, K. P. and Naidu, R. A. prepared membrane moserated transdermal drug delivery systems of various types of semisolid formulations and evaluated. Indian Drugs. 1994; 31: 36.

41. Bialik, W. Studies on the influence of an amphoteric tenside-carboxylbetaine on in vitro release of chloramphenicol from thin films formed cellulose acetate. Pharmazie.1992; 47: 601.

42. Baichwal, M. R., Deshpande, S. G., Singh, P. K. and Venkitachalam, P. Studies on polymeric films for transdermal use. Ind. J. Pharma. Sci. 1988; 50: 153.

43. Friedman, M and Donbrow. Novel Drug Delivery. Systems. M, Pharmaceutisch Weekblad – Scientific Edition, 1980; 2:149.

44. Donbrow, M and Samuelov. Study of drug release characteristics in laminated double layer films. J. Pharmacy & Pharmacol. 1980; 32: 463.

45. Rafiee-Tehrani M, Safaii-Nikui N, Peteriet H, BeckertT. Drug development and industrial pharmacy. Drug Dev Ind Pharm. 2001; 27(5):431

46. Barry, B. W. and E L Eini, D. I. D. Study of permeation of hydrocortisone, dexamethasone, testosterone and progesterone across cellulose acetate membranes. J. Pharmacy & Pharmacol. 1976; 28: 224

47. Short, P. M., Abbs, E. T. and Rhodes, C. T. Effect of the surfactants upon the diffusion of testosterone through cellulose acetate membranes. J. Pharma. Sci. 1970; 59: 995.

48. O. Sipahigil, B. Dortunç. Preparation and in vitro evaluation of verapamil HCl and ibuprofen containing carrageenan beads. International Journal of Pharmaceutics. 2001; 228 (1–2): 119–128.

49. Das M K, Bhattacharya A, Ghosal S K. Transdermal delivery of trazodone hydrochloride from acrylic films prepared from aqueous latex. Indian J. Pharm. Sci. 2006; 68 (1): 41-6.

50. Kusum Devi V, Saisivam S, Maria G R , Deepti PU. Design and evaluation of matrix diffusion controlled transdermal patches of verapamil hydrochloride. Drug Dev. Ind. Pharm. 2003; 29 (5):495-503.

51. Rose marie,R and Dadiv,R. Drugs used for the treatment of myocardial ischemia.In,Joel,G H(ed),Goodman and Gilman's The Pharmacological Basis of Therapeutics. 10th edition. New York, McGraw-Hill medical Publishing Division, 2005; 767-777.

52. V. Sai Kishore and T. E. Gopala Krishna Murthy, Effect of casting solvent and polymer on permeability of propranolol hydrochloride through membrane controlled transdermal drug delivery system, Indian Journal Of Pharmaceutical Sciences. 2007;5: 646-650.

53. Khurana R, Ahuja A, Khar R.K. Development and evaluation of mucoadhesive films of miconazole nitrate. Indian J Pharm Sci. 2000; 62(6): 447-453.

54. Kulkarni RV, Doddayya H, Marihal S, Patil C, Habbu P. Comparative evaluation of polymeric films for transdermal applications. Eastern Pharmacist. 2000; 43: 109-12.

55. Raghuraman S, Velrajan R, Ravi B, Jeyabalan D, Benito J ,Shankar V. Design and evaluation of propranolol hydrochloride buccal films. Ind. J. Pharm. Sci. 2002; 64 (1): 32-6.

56. Paranjyothy K L K , Thampi P P. Development of transdermal patches of verapamil hydrochloride using sodium carboxy methyl guar as a monolithic polymer matrix and their *in vitro* studies. Indian J Pharm Sci. 1997; 59: 49-52.

57. Sankar V, Chandrasekaran A K, Durga S. Formulation and stability evaluation of diclofenac sodium opthalamic gels. Indian J. of Pharm.Sci. 2005; 67 (4): 473-76.

58. Sakarkar D M, Shrikhande V N. Studies on formulation development, characterization and transdermal permeation of nimesulide from emulgel. Int. J. Pharma. Excip. 2004; 3(3): 57-61.

59. Sreenivasa reddy M , Mutalik S. Preparation and evaluation of minoxidil gels for topical application in alopecia. Indian J.of Pharm. Sci. 2006; 68(4): 432-36.

60. Franz TJ. Transdermal Delivery. In, Kydonieus A(ed). Treatise on controlled drug delivery: Fundamentals, optimization, applications.4th edition ,New York, Marcel Dekker Inc. 1991; 341-43.

61. Nakhat PD,Wanjari VS,Yole PG.Pluronic lecithin organogels as vehical for topical delivery of drug. Int J Pharma Excip.2005; 1: 21-25.

62. Flynn GL,Durrheim H. Permeation through hairless mouse skin II:Membrane sectioning technique and influence on alkanol permeabilities. J. Pharma. Sci.1981; 70:52-6.