"PREPARATION AND CHARACTERIZATION OF TRANSDERMAL FILM OF VALSARTAN"

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IN

PHARMACEUTICAL TECHNOLOGY & BIOPHARMACEUTICS

BY

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CERTIFICATE

*This is to certify that **Mr. NEEL D. SHAH** has prepared his thesis entitled "Preparation and Characterization of Transdermal Film of Valsartan", in partial fulfillment for the award of M. Pharm. degree of the Nirma University, under our guidance. He has carried out the work at the Department of Pharmaceutics & Pharmaceutical Technology, Institute of Pharmacy, Nirma University.*

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DECLARATION

I declare that the thesis "Preparation and Characterization of Transdermal Film of Valsartan" has been prepared by me under the guidance of Dr. Tejal A. Mehta, Professor, and Mr. Jigar N. Shah, Assistant Professor, Department of Pharmaceutics & Pharmaceutical Technology, Institute of Pharmacy, Nirma University. No part of this thesis has formed the basis for the award of any degree or fellowship previously.

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Abstract

The aim of the present study was to prepare and evaluate a transdermal films of Valsartan for the drug Delivery. The low permeability of the skin is the rate-limiting step for delivery of most of the drugs. Transdermal films of Valsartan were formulated by using different polymer such as Hydroxy Propyl Methyl Cellulose (HPMC) and combination of hydrophilic - lipophilic polymers (HPMC: Eudragit RL 100) and (HPMC: Eudragit RS 100) by solvent evaporation Method. To study the effect of plasticizers such as PEG 400 and propylene glycol and effect of permeation Enhancers such as DMSO(Di Methyl Sulfoxide), Tween 80 and IPM(Iso Propyl Myristate) by using Keshary-Chein diffusion cell. The placebo and medicated films were evaluated for physicochemical properties like Tensile Strength, Folding Endurnce and also medicated films were evaluated for wt variation, Thickness, Drug Content, Moisture Uptake, Moisture Content, Tensile Strength, Strain and percent cumulative drug release. Physicochemical parameters were characterized, and dissolution studies of the formulated films were performed. In addition, partition coefficient in octanol/water system, and flux were also evaluated. Partition Co-efficient of drug was 1.498. Backing layers were prepared 5% Ethyl Cellulose as a polymer and 30% PEG 400 and 30 % Tri ethyl citrate as a plasticizer. Flux for the batches HPMC (4%), HPMC : ERL 100 (3 : 2) and HPMC : ERS 100 (2: 3) was according 4.10 ug/cm^2/hr, 9.10 ug/cm^2/hr, 7.28 ug/cm^2/hr. The release rate 75.23 of Batch N22 was higher than the other batches.

1. Aim of Present Investigation

Conventional delivery system which required multi-dose therapy is associated with certain drawbacks. So that newer approach to drug delivery is to deliver drug into systemic circulation at a predetermined rate , known as controlled release drug delivery systems.[1] The development of the newer drug molecule is costly and the development cost is estimated $ 300 million (around 1000 crores) and takes around 12 years to reach the market place. Whereas existing drug molecule can get a second life with newer drug delivery systems that can be developed in half of the time with 20%cost of the new drug discovery[2]

Skin covers 1.73m^2 areas and receives 1/3rd of circulating blood supply through the body at any given time and exhibits significance potential administration for dermatological preparation to elicit pharmacological action in the skin tissue.

The angiotensin II receptor antagonists (AIIRAs) are the first new class of antihypertensive agents to be introduced since the angiotensin converting enzyme (ACE) inhibitors. They have similarities to, but also important differences from, the ACE inhibitors. It is logical that the two classes will be compared. There are currently six AIIRAs licensed in Ireland and more under development. Losartan was the first to be approved for the treatment of hypertension in 1995. This has since been followed by valsartan, eprosartan, irbesartan, candesartan and telmisartan. AIIRAs are now being investigated for use in congestive heart failure. A niche for AIIRAs is evolving[3]

Valsartan is given orally in a dose of 40 mg to 320mg daily. This administration is due to pharmacokinetic parameters viz. short biological half life and high first pass metabolism of the drug. Thus there is a great need to develop a novel drug delivery system that can effectively deliver the drug in a systemic circulation with a good therapeutic plasma concentration[4].

Valsartan can not be administered via intravenous route because it caused arrhythmia and cardiac arrest[5]. Through Valsartan is administered via oral route , it is associated with various parameters like bioavailability (just 23%), intestinal metabolism and very high first pass metabolism.

The precision parameters like (bio availability, half life, and first pass metabolism) of Valsartan indicate it is an ideal candidate for development of transdermal delivery system. Thus transdermal route seems to be promising route for

delivering the drug effectively because of various advantage like avoidance of hepatic first pass metabolism, improved bioavailability maintain constant blood levels, decrease side effects etc. The present pharma market has many transdermal parches for drugs such as Clonidine, Scopolamine, Nitro glycerine, Fentyl, Estradiol, Testosterone, Oxybutynin, and Lidocaine etc[6]

To formulate the transdermal films, various polymers were tried like HPMC, Ethyl Cellulose and As well as combination with HPMC: Eudragit RL100 or HPMC: Eudragit RS 100. The effective of plasticizers like PEG 400 and Propylene Glycol as well as permeation enhancers like DMSO (Di methyl Sulfoxide), Tween 80 and IPM (Iso Propyl Myristate) on the film property were also evaluated.

2.1 : Introduction to skin

Skin is the most extensive and readily accessible organ in the body. In an average adult it covers an area of about 1.73 m2. And receives to be delivered transdermally, clinical needs, and drug pharmacokinetics are some of the important one third of circulating blood through the body at considerations in the development of transdermal any given time.

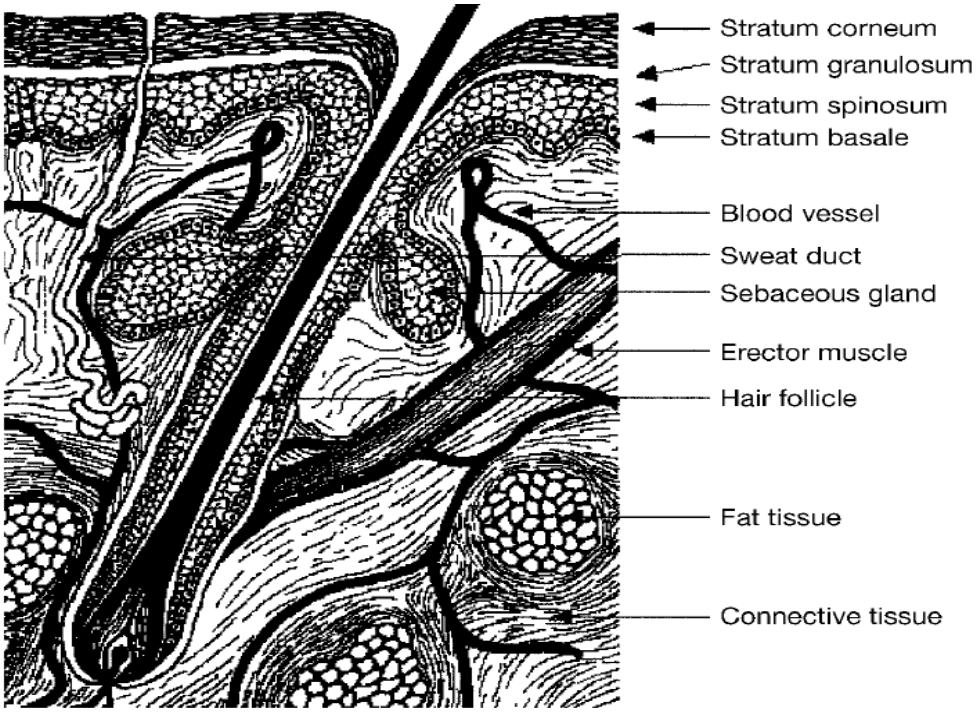
The skin became popular as a potential site for systemic drug delivery because it

- Avoid first-pass metabolism
- Avoid the problem of stomach emptying, pH effects and enzyme deactivation associated with gastrointestinal passage;
- The termination of delivery can be possible through removed of the device.

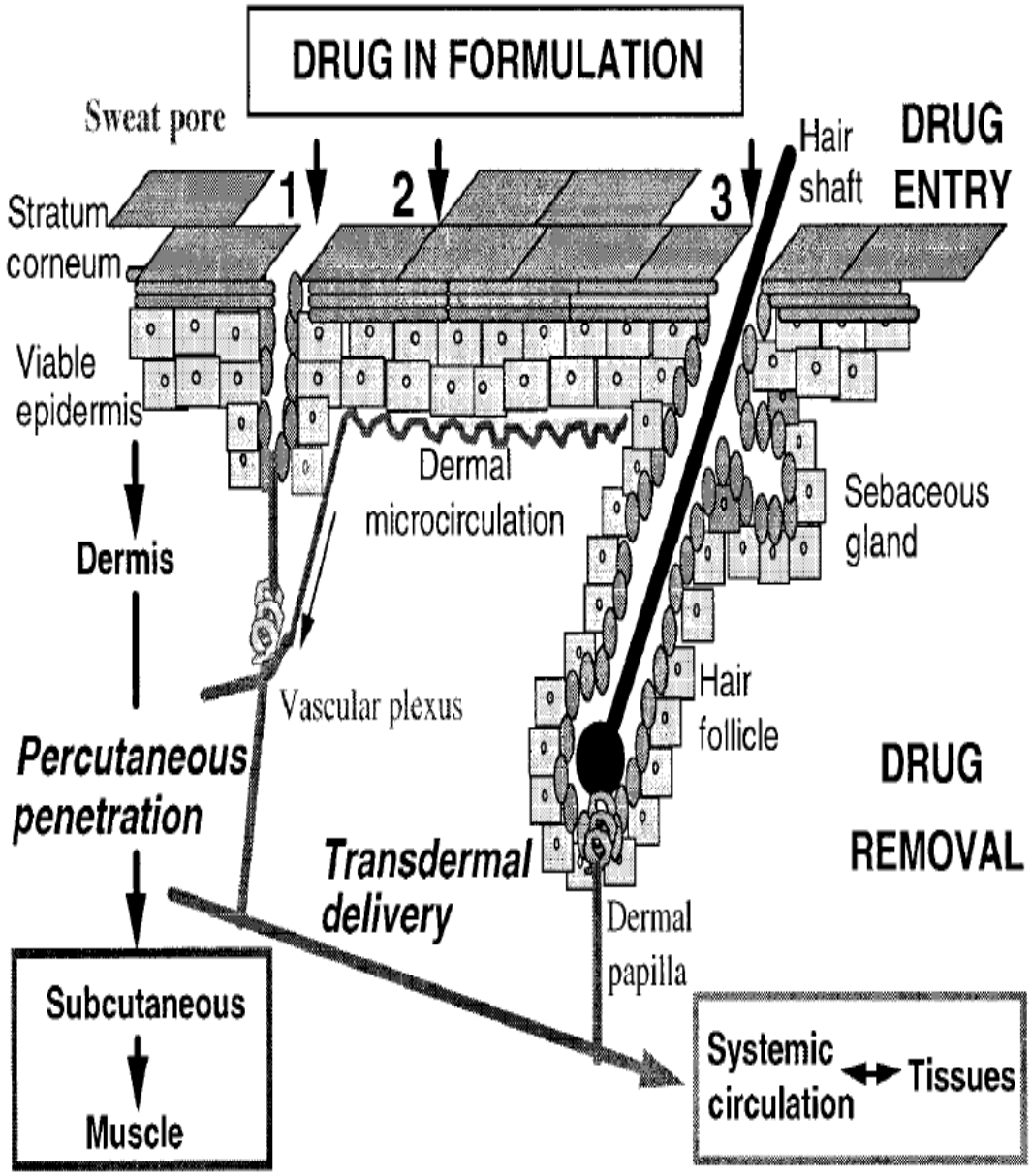
  The delivery of solutes through the skin is associated with various difficulties, like
  - The skin's FIRST – PASS metabolic effect;
  - Irritation and other toxicity caused by topical products;
  - The variability in percutaneous absorption owing to site, disease, age and species differences;
  - Inadequate definition of bioequivalence criteria;
  - The reservoir capacity of the skin; and
  - An incomplete understanding of the technology that may be used to facilitate or retard percutaneous absorption

2. 1. 1: Anatomy of the Skin[7,8]

The skin is the largest organ of the body, accounting for more than 10% of body mass, and the one that enables the body to interact most intimately with its environment. Figure shows a diagrammatic illustration of the skin.



The skin consists of four layers: the stratum corneum (nonviable epidermis), the remaining layers of the epidermis (viable epidermis), dermis, and subcutaneous tissues. There are also several associated appendages: hair follicles, sweat ducts, apocrine glands, and nails


DRUG IN FORMULATION
Sweat pore
1
2
3
Hair shaft
DRUG ENTRY
Stratum corneum
Viable epidermis
Dermis
Dermal microcirculation
Sebaceous gland
Vascular plexus
Hair follicle
Percutaneous penetration
Transdermal delivery
DRUG REMOVAL
Dermal papilla
Subcutaneous
Muscle
Systemic circulation
Tissues

2.1.2: Basic Function of the skin[9]

Protection

Our skin is a shield that protects us from:

- mechanical impact such as pressure and stroke
- thermic impact such as heat or cold
- environmental impact such as chemicals, the sun´s UV-radiation and bacteria

Regulation

The skin regulates our body temperature. The production of sweat, which evaporates on the skin´s surface, will cool us down.

As a Sensory organ-

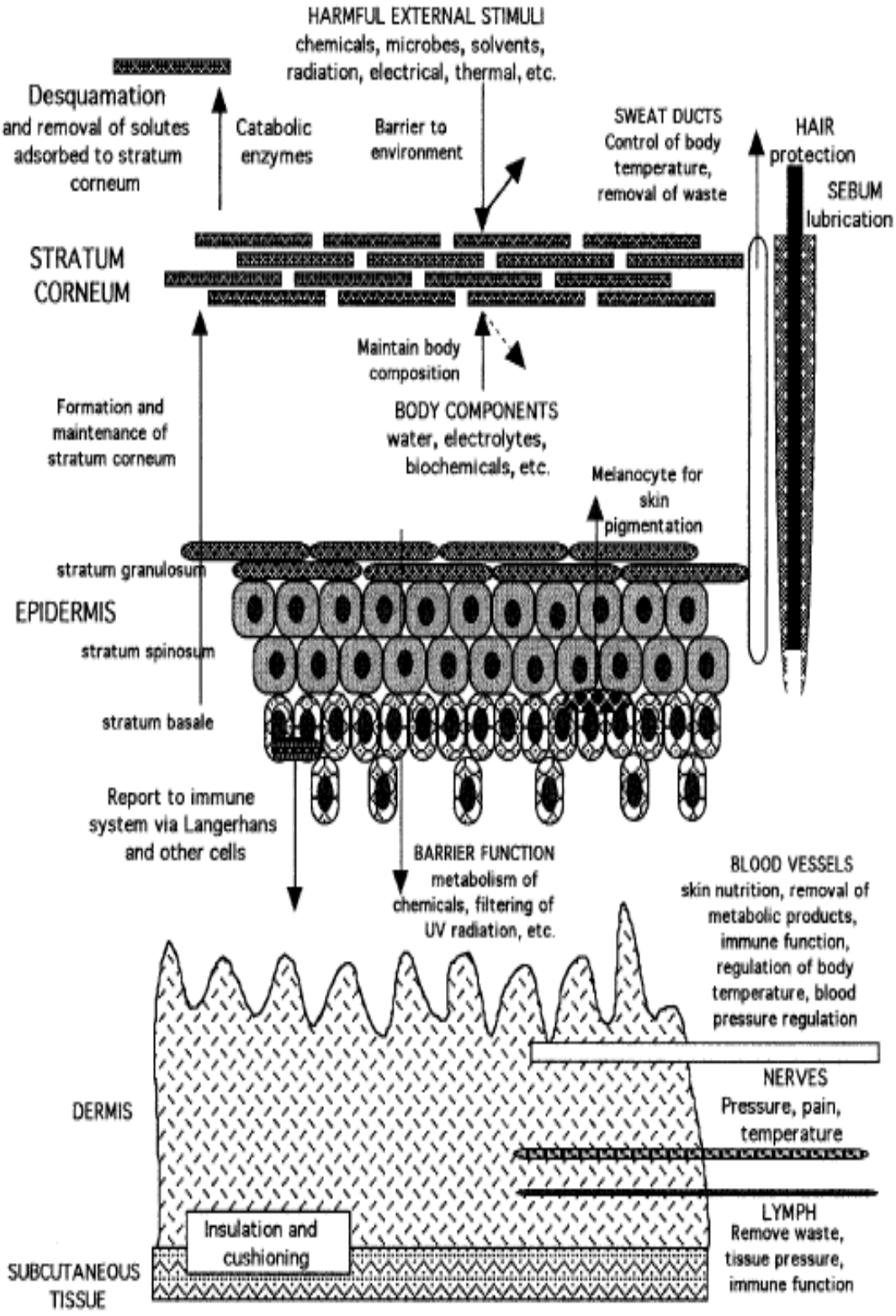
Skin is a major organ in terms of sensing environment influences, such as heat, pressure, pain and allergen. Finally, the skin is an organ that is in a continual state of regeneration and repair

An organ for maintaining the homeostasis of the body-

Skin maintains the homeostasis in terms of composition, heat regulation blood pressure control, and excretory roles. It has been argued that the basal metabolic rate of animals differing in size should be scaled to the surface area of the body to maintain a constant temperature through the skin's thermoregulatory control.:

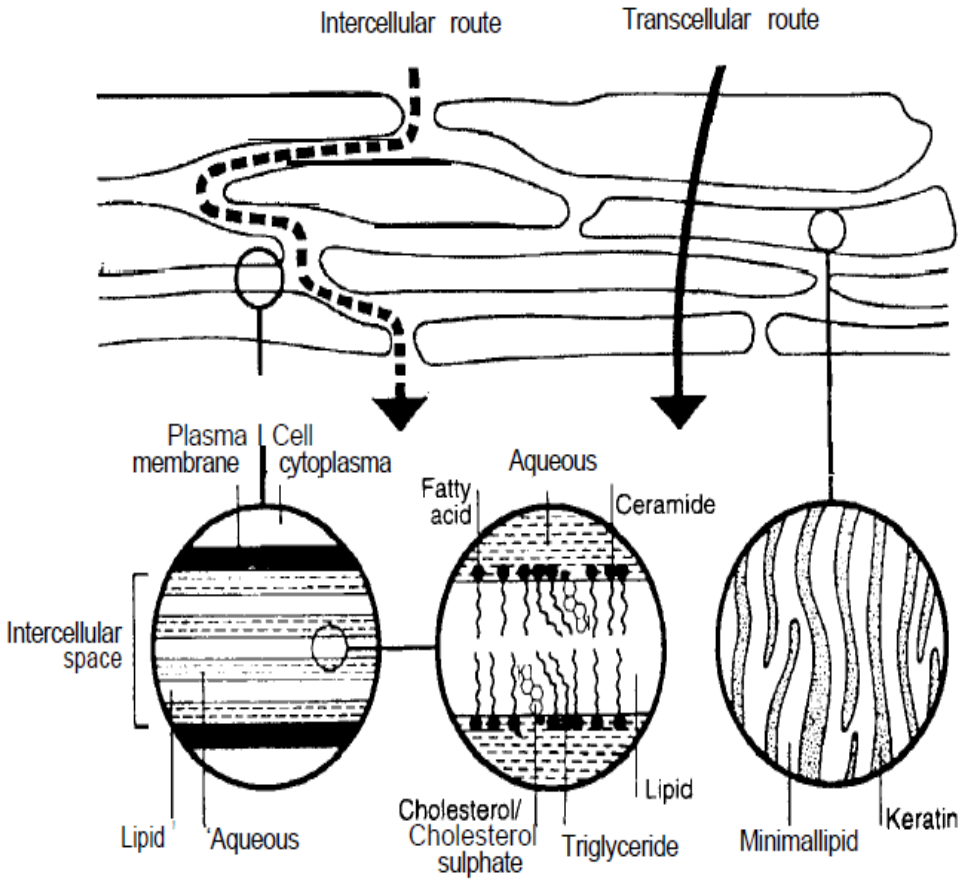
1. Protection: an anatomical barrier from pathogens and damage between the internal and external environment in bodily defense; Langerhans cells in the skin are part of the adaptive immune system.
2. Sensation: contains a variety of nerve endings that react to heat and cold, touch, pressure, vibration, and tissue injury; see somatosensory system and haptics.

3. Heat regulation: the skin contains a blood supply far greater than its requirements which allows precise control of energy loss by radiation, convection and conduction. Dilated blood vessels increase perfusion and heatloss, while constricted vessels greatly reduce cutaneous blood flow and conserve heat. Erector pili muscles are significant in animals.
4. Control of evaporation: the skin provides a relatively dry and semi-impermeable barrier to fluid loss. Loss of this function contributes to the massive fluid loss in burns.
5. Aesthetics and communication: others see our skin and can assess our mood, physical state and attractiveness.
6. Storage and synthesis: acts as a storage center for lipids and water, as well as a means of synthesis of vitamin D by action of UV on certain parts of the skin.
7. Excretion: sweat contains urea, however its concentration is 1/130th that of urine, hence excretion by sweating is at most a secondary function to temperature regulation.
8. Absorption: Oxygen, nitrogen and carbon dioxide can diffuse into the epidermis in small amounts, some animals using their skin for their sole respiration organ (contrary to popular belief, however, humans do not absorb oxygen through the skin).[8] In addition, medicine can be administered through the skin, by ointments or by means of adhesive patch, such as the nicotine patch or iontophoresis. The skin is an important site of transport in many other organisms.


HARMFUL EXTERNAL STIMULI
chemicals, microbes, solvents, radiation, electrical, thermal, etc.
Desquamation
and removal of solutes adsorbed to stratum corneum
Catabolic enzymes
Barrier to environment
SWEAT DUCTS
Control of body temperature, removal of waste
HAIR
protection
SEBUM
lubrication
STRATUM CORNEUM
Maintain body composition
Formation and maintenance of stratum corneum
BODY COMPONENTS
water, electrolytes, biochemicals, etc.
Melanocyte for skin pigmentation
stratum granulosum
EPIDERMIS
stratum spinosum
stratum basale
Report to immune system via Langerhans and other cells
BARRIER FUNCTION
metabolism of chemicals, filtering of UV radiation, etc.
BLOOD VESSELS
skin nutrition, removal of metabolic products, immune function, regulation of body temperature, blood pressure regulation
NERVES
Pressure, pain, temperature
DERMIS
LYMPH
Remove waste, tissue pressure, immune function
Insulation and cushioning
SUBCUTANEOUS TISSUE

2.1.3: Different type of Transdermal PermeationProcess [5,6,12]

Possible micro routes for drug penetration across human skin intercellular or transcellular[11]



1. Transcellular transport

   This pathway will provide a polar route through the membrane. The keratocyte is highly hydrated in nature which provide the aqueous environment for the transport of hydrophilic molecule.

2. Intracellular transport

   The lipid bilayers comprises around 1% of diffused area, yet providing the only continuous phase into the membrane. The importance of the lipid in regulating the body loss and controlling the permeation of the material in the body is well established.

3. Transappendangeal transport (Shunt Process)

The appendages (hair follicle, sweat ducts) occupy 0.1% of the skin which offers pores that bypass the barrier of the stratum corneum of the skin surface and hence contribute the total flux of the drug. Here the transport of substances occurs via the sweat glands and the hair follicles with their associates subaceous glands.

2.1.4 : Effect of different physical property on drug permeation

Partition coefficient	Partition in to the skin is the rate limiting factor in drug permeation $P_{octanol/water} < 1$ →Transcellular Pathway $P_{octanol/water}$ 1-3 →intercellular route is predominant $P_{octanol/water} > 3$ → Exclusively intercellular route
Molecular size	Should lie within the range of 100-500 Dalton
Ionization	For unionized species permeability co-efficient-high, solubility-low For ionized species permeability co-efficient-low, solubility-high
Solubility	Lipid molecule tend to permeate to skin faster than hydrophilic molecules but drug should be some hydrophilic, If drug is highly lipophilic, it result in rapid determination of drug
Other factors	Binding to skin component, influence of hydrogen bonding because tissue is hydrogen bond donating nature.

2.2 Introduction to Dosage Form

The drug delivery in to systemic circulation via skin has generated lot of interest during the last decade. A growing number of drugs are being developed and introduced to the market as transdermal patches. Transdermal administration of drugs can be used alternative to oral delivery. The choice of drugs delivered transdermally, clinical needs and drug pharmacokinetics are the some of the important considerations in the development of TDDS. Major advantage of transdermal delivery includes compliance, consistency of blood levels and reduced toxicity.[11] The risk of oral administration of many drug is that peak concentration (C_{max}) may lead to a breakthrough of the condition being treated. Transdermal delivery of the drug is also useful for the delivering the drugs that require sustain release.

Rationale for transdermal drug delivery [5, 6]

- Given that the skin offers such an excellent barrier to molecular transport, the rationale for this delivery strategy needs to be carefully identified.
- There are several instances in which the most convenient of drug intake methods (the oral route) is not feasible and when alternative routes must be sought.
- Although intravenous introduction of the medicament avoids many of these shortfalls (such as gastrointestinal and hepatic metabolism), its invasive and apprehensive nature (particularly for chronic administration) has encouraged the search for alternative strategies, and few anatomical orifices have not been investigated for their potential as optional drug delivery routes.

- Nevertheless, the transdermal mode offers several distinct advantages:

1) The skin presents a relatively large and readily accessible surface area (1–2 m^2) for absorption;
2) The application of a patch-like device to the skin surface is a non-invasive (and thus a patient compliant) procedure that allows

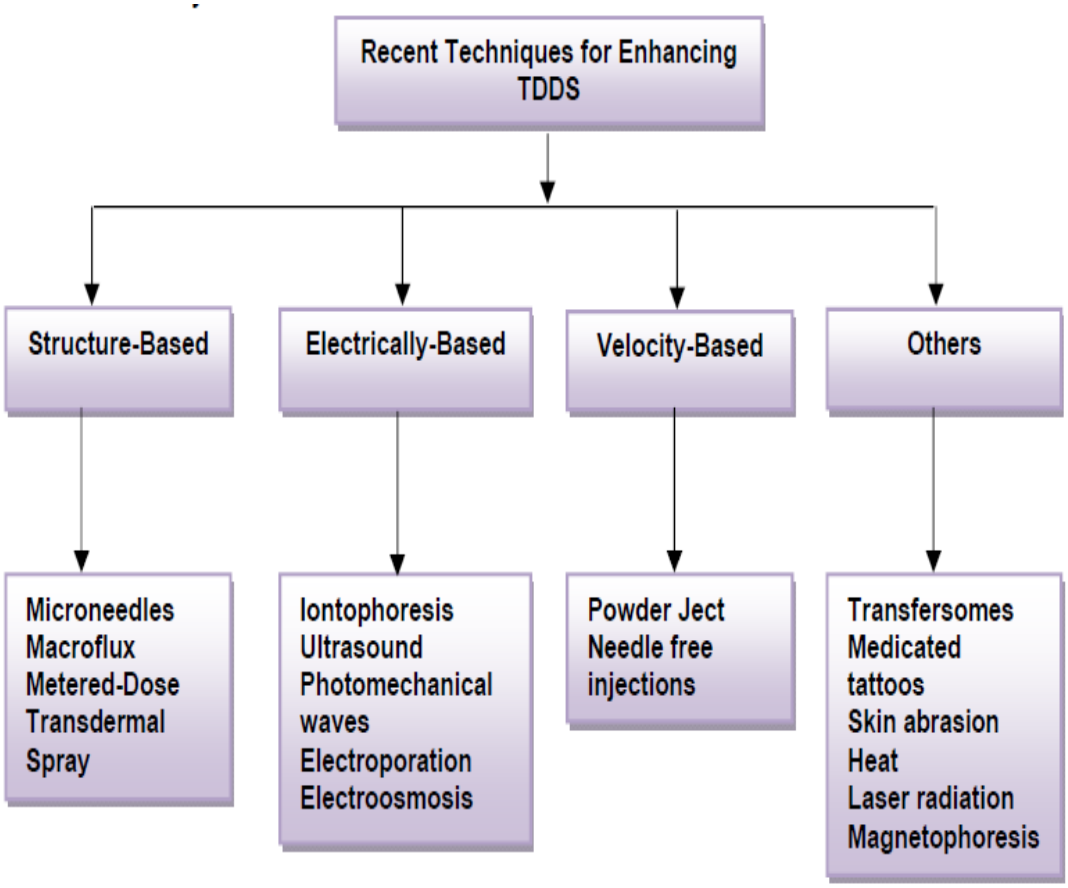
continuous intervention (i.e. system repositioning, removal or replacement).

3) In contrast to the traditional oral route, first-pass metabolism is minimized, which can often limit the tolerability and efficacy of many orally/parenterally delivery of drug
4) The Transdermal route provides a more-controlled, non-invasive method of delivery.
5) Some drugs degrade in the acidic environment of the stomach, and other drugs. Such as NSAID, can cause gastrointestinal bleeding or irritation.
6) The mixing of drugs with food in the stomach, and the pulsed,often erratic delivery of drugs to the intestine leads to variability in the plasma concentration-time profiles achieved for many drugs

Limitation of Transdermal drug Delivery system

- TDDS cannot deliver ionic drugs.
- TDDS cannot achieve high drug levels in blood/plasma.
- The metabolic enzymes in the skin can also pose a problem, so some drugs are almost completely metabolized before they reach the cutaneous vasculature.
- Cannot develop TDDS for drugs of large molecular size.
- Some drugs can be broken down before permeation through the SC by the bacteria that live the skin surface.
- TDDS cannot deliver drugs in a pulsatile fashion.
- Cannot develop TDDS, if drug or formulation causes irritation to skin.
- Diseased skin, as well as the disease, can also affect permeation rates.
- The adhesives may not adhere well to all types of skin and may be uncomfortable to wear.

Types of Transdermal System



Formulation considerations for passive transdermal delivery and ideal limits [11]

Potency of the drug	Daily systemic dose should be ≤ **20 mg**
Lipophilicity of drug	The **log p** should be in the range **1-4**
Molecular size	Drug molecular weight should be < **500 Da**
Irritation	Drug should not be direct irritate to skin
Melting point	Should be < **200 ° C**
Immunogenicity	Drug should not stimulate immune reaction to skin
Other parameters	Pharmacokinetic, indication, metabolism considerations

Basic Components of TDDS[12]

- Polymer matrix / Drug reservoir
- Drug
- Permeation enhancers
- Pressure sensitive adhesive (PSA)
- Backing layer
- Release liner
- Other excipients like plasticizers and solvents

Polymer matrix / Drug reservoir:

Polymers are the backbone of TDDS, which control the release of the drug from the device. Polymer matrix can be prepared by dispersion of drug in liquid or solid state synthetic polymer base. Polymers used in TDDS should have biocompatibility and chemical compatibility with the drug and other components of the system such as penetration enhancers and PSAs. Additionally they should provide consistent and effective delivery of a drug throughout the product's intended shelf life and should be of safe status[13.]

- **Natural Polymers**: e.g. cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan *etc*[14]
- **Synthetic Elastomers**: e.g. polybutadiene, hydrin rubber, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, butylrubber *etc*.
- **Synthetic Polymers**: e.g. polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate *etc*.

The polymers like cross linked polyethylene glycol, eudragits, ethyl cellulose, PVP and HPMC are used as matrix formers for TDDS. Other polymers like EVA, silicon rubber and polyurethane are used as rate controlling membrane.

Drug:

The transdermal route is an extremely attractive option for the drugs with appropriate pharmacology and physical chemistry. Transdermal patches offer much to drugs which undergo extensive first pass metabolism, drugs with narrow therapeutic window, or drugs with short half life which causes non- compliance due to frequent dosing. The foremost requirement of TDDS is that the drug possesses the right mix of physicochemical and biological properties for transdermal drug delivery[15-16]. It is generally accepted that the best drug candidates for passive adhesive transdermal patches must be non ionic, of low molecular weight (less than 500 Daltons), have adequate solubility in oil and water (log P in the range of 1-3), a low melting point (less than 200°C) and are potent (dose in mg per day).

Permeation Enhancers:

These are the chemical compounds that increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug candidate. Penetration enhancers interact with structural components of stratum corneum *i.e.*, proteins or lipids. They alter the protein and lipid packaging of stratum corneum, thus chemically modifying the barrier functions leading to increased permeability.[17]

THE PROPERTIES OF AN IDEAL PENETRATION ENHANCER
➢ Pharmacologically inert. ➢ Nontoxic, nonirritating, and no allergenic. ➢ Rapid onset of action, predictable and suitable duration of action for the drug used. ➢ Following the removal of the enhancer, the stratum corneum should immediately and fully recover its normal barrier property. ➢ The barrier function of the skin should decrease in one direction only, and efflux of endogenous materials should not occur. ➢ Chemically and physically compatible with the delivery system. ➢ Readily incorporated into the delivery system. ➢ Inexpensive and cosmetically acceptable.

List of different types of permeation enhancers [5, 6]

Penetration Enhancers	Properties
DMSO Dimethyl sulphoxide	• Use for both-hydrophilic and lipophilic permeants, it is an aprotic solvents which hydrogen bond with itself rather than with water. • Its metabolite will cause foul smell to breath
Pyrolidones	• It shows greater effects with hydrophilic permeants than with lipophilic permeants
Azones (<10%)	• Highly lipophilic and can be used for both hydrophilic and lipophilic permeants • Propylene Glycol is used as vehicle for delivering azones • It disrupts the packing arrangements of lipid domains within the stratum corneum
Alcohols. fatty alcohol and glycol	• Mainly ethanol is used • Also used as cosolvent for ensuring sink condition • Fatty alcohol mainly propylene glycol(1-10%)
Urea	• Act as hydrating agent to skin
Surfactants	• Anionic surfactants like SLS • Cationic surfactants like cetyl trimethyl ammonium bromide is used but all are toxic to skin
Phospholipids	• Used in a non vesicular form as penetration enhancer
Terpenes	• Terpenes and thir parent essential oil are the latest addition in the penetration enhancer

Pressure sensitive adhesives:

A PSA is a material that helps in maintaining an intimate contact between transdermal system and the skin surface. It should adhere with not more than applied finger pressure, be aggressively and permanently tacky, exert a strong holding force. Additionally, it should be removable from the smooth surface without leaving a residue. Polyacrylates, polyisobutylene and silicon based adhesives are widely used in TDDSs[18] .The selection of an adhesive is based on numerous factors, including the patch design and drug formulation. For matrix systems with a peripheral adhesive, an incidental contact between the adhesive and the drug and penetration enhancer should not cause instability of the drug, penetration enhancer or the adhesive. In case of reservoir systems that include a face adhesive, the diffusing drug must not affect the adhesive. In case of drug-in-adhesive matrix systems, the selection will be based on the rate at which the drug and the penetration enhancer will diffuse through the adhesive. Ideally, PSA should be physicochemical and biologically compatible and should not alter drug release.[19]

Backing Layer:

While designing a backing layer, the consideration of chemical resistance of the material is most important. Excipient compatibility should also be considered because the prolonged contact between the backing layer and the excipients may cause the additives to leach out of the backing layer or may lead to diffusion of excipients, drug or penetration enhancer through the layer. However, an overemphasis on the chemical resistance may lead to stiffness and high occlusivity to moisture vapor and air, causing patches to lift and possibly irritate the skin during long wear. The most comfortable backing will be the one that exhibits lowest modulus or high flexibility, good oxygen transmission and a high moisture vapor transmission rate. Examples of some backing materials are vinyl, polyethylene and polyester films[20].

Release Liner:

During storage the patch is covered by a protective liner that is removed and discharged immediately before the application of the patch to skin. It is therefore regarded as a part of the primary packaging material rather than a part of dosage form

for delivering the drug. However, as the liner is in intimate contact with the delivery system, it should comply with specific requirements regarding chemical inertness and permeation to the drug, penetration enhancer and water. Typically, release liner is composed of a base layer which may be non-occlusive (*e.g*. paper fabric) or occlusive (*e.g*. polyethylene, polyvinylchloride) and a release coating layer made up of silicon or teflon. Other materials used for TDDS release liner include polyester foil and metallized laminates[21].

Other excipients:

Various solvents such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir. In addition plasticizers such as dibutylpthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch[22]

Preparation of Different Types of Transdermal Patches:

Several system designs have been used in development and fabrication of TDDSs. The systems that have been introduced in market can be classified into following types[23]

· Drug in adhesive type

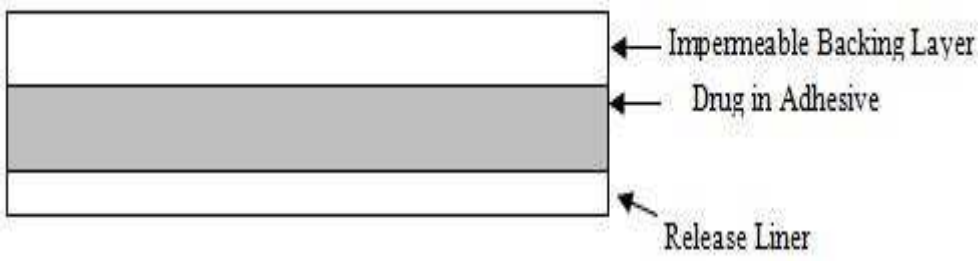
· Matrix type

· Reservoir type

· Membrane matrix hybrid

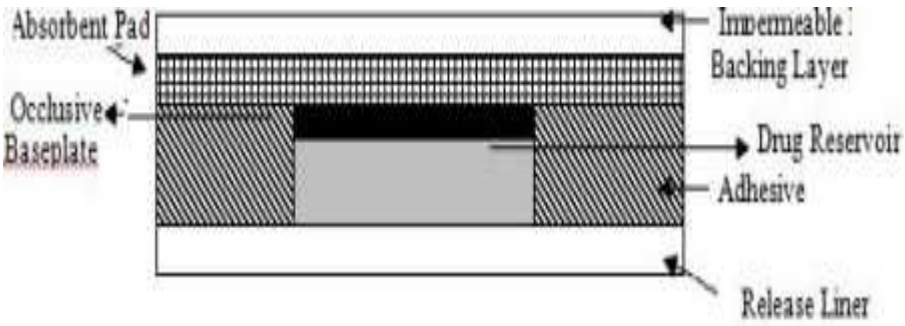
· Micro reservoir type

Drug in adhesive type transdermal patch(s):



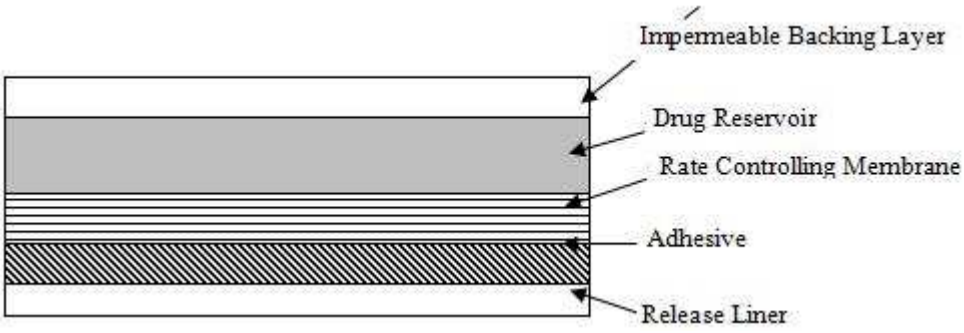
- The drug and other selected excipients, if any, are directly incorporated into the organic solvent based pressure sensitive adhesive solution, mixed, cast as a thin film and dried to evaporate the solvents, leaving a dried adhesive matrix film containing the drug and excipients.
- This drug in adhesive matrix is sandwiched between release liner and backing layer. Drug -in -adhesive patch may be single layer or multi layer. The multi layer system is different from single layer in that it adds another layer of drug-in-adhesive, usually separated by a membrane.

Matrix Type Transdermal Patch(s):



- Drug reservoir is prepared by dissolving the drug and polymer in a common solvent. The insoluble drug should be homogenously dispersed in hydrophilic or lipophillic polymer.
- The required quantity of plasticizer like dibutylpthalate, triethylcitrate, polyethylene glycol or propylene glycol and permeation enhancer is then added and mixed properly.
- The medicated polymer formed is then molded into rings with defined surface area and controlled thickness over the mercury on horizontal surface followed by solvent evaporation at an elevated temperature.
- The film formed is then separated from the rings, which is then mounted onto an occlusive base plate in a compartment fabricated from a drug impermeable backing. Adhesive polymer is then spread along the circumference of the film[24].

Reservoir Type Transdermal Patch(s):

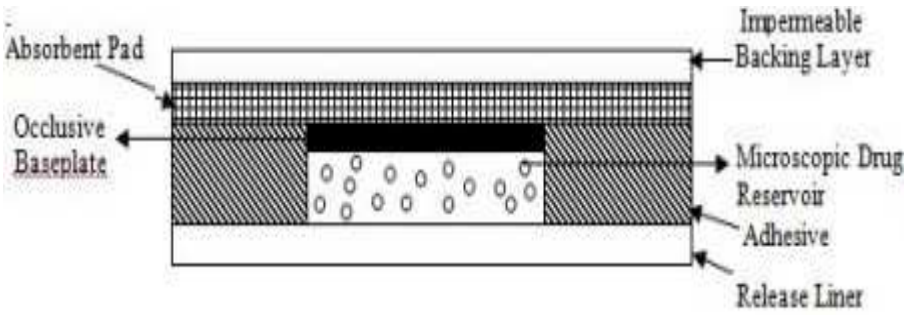


- The drug reservoir is made of a homogenous dispersion of drug particles suspended in an unleachable viscous liquid medium (e.g. silicon fluids) to form a paste like suspension or gel or a clear solution of drug in a releasable solvent (e. g. ethanol).
- The drug reservoir formed is sandwiched between a rate controlling membrane and backing laminate[25].
- The rate controlling membrane can be nonporous so that the drug is released by diffusing directly through the material, or the material may contain fluid filled micropores in which case the drug may additionally diffuse through the fluid, thus filling the pores.
- In the case of nonporous membrane, the rate of passage of drug molecules depends on the solubility of the drug in the membrane and the thickness of membrane. Hence, the choice of membrane material is dependent on the type of drug being used. By varying the composition and thickness of the membrane, the dosage rate per unit area of the device can be controlled.

.**Membrane matrix hybrid type patch(s):**

This is the modification of reservoir type transdermal patch. The liquid formulation of the drug reservoir is replaced with a solid polymer matrix (e.g. polyisobutylene) which is sandwiched between rate controlling membrane and backing laminate.

Micro reservoir type transdermal patch(s):



- The drug reservoir is formed by suspending the drug solids in an aqueous solution of water miscible drug solubilizer e.g. polyethylene glycol.
- The drug suspension is homogenously dispersed by a high shear mechanical force in lipophillic polymer, forming thousands of unleachable microscopic drug reservoirs (micro reservoirs).
- The dispersion is quickly stabilized by immediately cross linking the polymer chains in-situ which produces a medicated polymer disc of a specific area and fixed thickness. Occlusive base plate mounted between the medicated disc and adhesive form backing prevents the loss of drug through the backing membrane[2]

List of transdermal patches available in market[27 a-b]

Sr no	Drug	Trade name	Type of transdermal patch	Manufacturer	Indication
1	Fentanyl	Duragesic	Reservoir	Alza / Janssen Pharmaceutica	Moderate/ Severe pain
2		Deponit	Drug in adhesive	Schwarz Pharma	Angina Pectoris
		Minitran	Drug in adhesive	3M Pharmaceuticals	
		Nitrodisc	Micro reservoir	Searle, USA	
		Nitrodur	Matrix	Key Pharmaceuticals	
3	Nicotine	Prostep	Reservoir	ElanCorp	Smoking Cessation
		Nicotrol	Drug in adhesive	Cygnus Inc	
		Habitraol	Drug in adhesive	Novartis	
4	Testosterone	Androderm	Reservoir	GlaxoSmithKline	Hypogonadism in males
		Testoderm	Reservoir	Boehinger Ingelheim	
5	Clonidine	Catapres-	Membrane matrix hybrid type	Alza/Boehinger Ingelheim	Hypertension
6	Lidocaine	Lidoderm	Drug in adhesive	Cerner Multum, Inc.	Anesthetic
7	Estradiol	Climara	Drug in adhesive	3M Pharmaceuticals	Postmenstrual Syndrome
		Estraderm	Reservoir	Alza/Novartis	
		Esclim	Drug in adhesive	Women First Healthcare, Inc	
8	Scopolamine	Transderm Scop	Membrane matrix hybrid type	Alza/Novartis	Motion sickness

2.3 VALSARTAN[28-29]

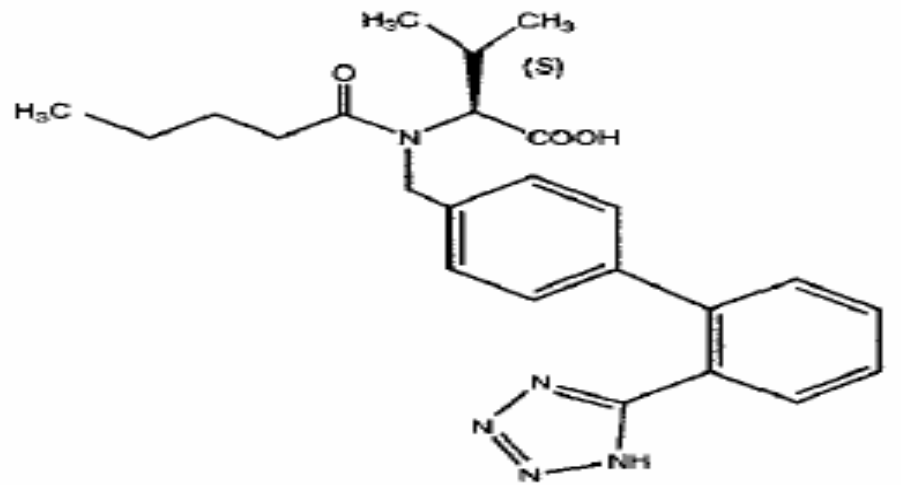
Generic Name : Valsartan

CAS No. : 137862-53-4

Chemical IUPAC Name : (2S)-3-methyl-2-[pentanoyl-[[4-[2-(2H-tetrazol-5-yl)phenyl]phenyl]methyl]amino] butanoic acid

Chemical Formula : $C_{24}H_{29}N_5O_3$

Chemical Structure :



Physical properties

State : Solid

Physical Characteristics : A practically white fine powder

Solubility : It is soluble in ethanol and methanol and slightly Soluble in water.

Molecular weight : 435.5 g.mol

Melting Point : 116 - 117°c

Stability : Stable under Ordinary condition

Half life : Around 6 hrs

λ_{max} : 250nm

Mechanism of Action

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressure agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Valsartan has much greater affinity (about 20,000-fold) for the AT_1 receptor than for the AT_2 receptor. The increased plasma levels of angiotensin II following AT_1 receptor blockade with valsartan may stimulate the unblocked AT_2 receptor. The primary metabolite of valsartan is essentially inactive with an affinity for the AT_1 receptor about one-200th that of valsartan itself.

Antihypertensive effect

- Valstaran blocks the vasoconstrictor and aldosterone secreting effects of AT_2 by selectively blocking the binding of AT_2 to AT_1 receptor in many tissue, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for AT_2 synthesis.
- There is an AT_2 receptor found in many tissue, but AT_2 is not known to be associated with cardiovascular homeostasis. Valsartan has much greater affinity (about 20,000-fold) for the AT_1 receptor than for the AT_2 receptor. The primary metabolite of valsartan is essentially inactive with affinity for the AT_1 receptor about 1 to 200^{th} that of valsartan itself.
- Blockage of the rennin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of AT_2 from AT_1, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, reaction also catalyzed by ACE. Because Valsartan does not inhibit ACE (

kininase)it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation. Blockage of the AT_2 receptors inhibits the negative regulatory feedback of AT_2 on rennin secretion, but the resulting increased plasma rennin activity and AT_2 circulating levels do not overcome the effect of valsartan on blood pressure.

Drug Interaction

- No clinical significant pharmacokinetic interactions were observed when valsartan was co administered with amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, and hydrochlorothiazide. The valsartan-amlodipine combination was more antihypertensive than either compound, but it did not lower the hyper tension when atenolol alone.
- Co administered of valsartan and warfarin did not change the pharmacokinetic of valsartan or the time-course of the anticoagulant properties of warfarin.
- CYP450 interaction: The enzymes responsible for valsartan metabolism have not been identified but do not seem to be CY450 isoenzyme. The inhibitory or induction potential of valsartan on CY450 is also unknown.

Amifostine	Additive hypotensive effects may occur. At chemotherapeutic doses of Amifostine, Valsartan should be withheld for 24 hours prior to Amifostine administration. Use caution at lower doses of Amifostine.
Lithium	Valsartan may increase serum Lithium concentrations. Monitor serum Lithium levels during concomitant therapy to avoid Lithium toxicity.
Rituximab	Additive hypotensive effects may occur. Increased risk of hypotension. Consider withholding Valsartan for 12 hours prior to administration of Rituximab.
Eltrombopag	Eltrombopag may increase the therapeutic and/or toxic effects of Valsartan. Increased Valsartan serum concentrations may be caused by inhibition of hepatic uptake and decreased metabolism. Consider dose modification, alternate therapy or monitor for changes in the therapeutic and toxic effects of Valsartan if Eltrombopag is initiated, discontinued or dose changed.

Over dose

The most likely manifestation of over dosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Valsartan is not removed from plasma by dialysis.

Storage condition

Store at 25 °C, Excusion permitted to 15-30°C.

Side-effects

Rarely anaemia, neutropenia; *very rarely* diarrhea, taste disturbance, syncope, fatigue, cough, headache, thrombocytopenia, epistaxis, arthralgia, myalgia, and hypersensitivity reactions (including rash, pruritus, vasculitis, and serum sickness)

CLINICAL INDICATIONS

Hypertension

Published data has shown the antihypertensive efficacy of this group of drugs to be similar to that of ACE inhibitors.1-8 Comparative studies with losartan, candesartan, valsartan, irbesartan and telmisartan have been conducted with thiazide diuretics, calcium antagonists and beta-blockers again showing equivalent blood pressure reductions. There is very little comparative data on eprosartan.6 Additive effects with other antihypertensives such as diuretics have been confirmed in clinical studies.9-12 It appears in some studies that the lower dose of AIIRA combined with a thiazide, produced a greater reduction in blood pressure than the maximum dose of the AIIRA alone.12 A combined preparation of losartan and hydrochlorothiazide became available in 1997 and may improve compliance.

Heart Failure

None of the AIIRAs are currently marketed in Ireland for heart failure although valsartan has been granted a licence. A recent consensus report notes that there is no conclusive evidence that AIIRAs are equivalent or superior to ACE inhibitors for heart failure.15,16 It recommends that these drugs are only considered in patients intolerant of ACE-inhibitors.

Pharmacodynamics

- Valsartan inhibits the presser effect of angiotensin II infusions. An oral dose of 80 mg inhibits the presser effect by about 80% at peak with approximately 30% inhibition persisting for 24 hours. No information on the effect of larger doses is available.
- Removal of the negative feedback of angiotensin II causes a 2- to 3-fold rise in plasma renin and consequent rise in angiotensin II plasma concentration in hypertensive patients. Minimal decreases in plasma aldosterone were observed after administration of valsartan; very little effect on serum potassium was observed.
- In multiple-dose studies in hypertensive patients with stable renal insufficiency and patients with renovascular hypertension, valsartan had no clinically significant effects on glomerular filtration rate, filtration fraction, creatinine clearance, or renal plasma flow.
- In multiple-dose studies in hypertensive patients, valsartan had no notable effects on total cholesterol, fasting triglycerides, fasting serum glucose, or uric acid.

Pharmacokinetics

Valsartan peak plasma concentration is reached 2 to 4 hours after dosing. Valsartan shows bi-exponential decay kinetics following intravenous administration, with an average elimination half-life of about 6 hours. Absolute bioavailability for Diovan is about 25% (range 10%-35%). The bioavailability of the suspension is 1.6 times greater than with the tablet. With the tablet, food decreases the exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (Cmax) by about 50%. AUC and Cmax values of valsartan increase approximately linearly with increasing dose over the clinical dosing range. Valsartan does not accumulate appreciably in plasma following repeated administration**.**

Metabolism and Elimination

Valsartan, when administered as an oral solution, is primarily recovered in feces (about 83% of dose) and urine (about 13% of dose). The recovery is mainly as unchanged drug, with only about 20% of dose recovered as metabolites. The primary metabolite, accounting for about 9% of dose, is valeryl 4-hydroxy valsartan. The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes. Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0.62 L/h (about 30% of total clearance).

Distribution

The steady state volume of distribution of valsartan after intravenous administration is small (17 L), indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (95%), mainly serum albumin.

2.4 INTRODUCTION TO POLYMERS

HYDROXYPROPYL METHYL CELLULOSE[30]

1. **Nonproprietary Names:**

   Ph Eur: Hypromellose

   USP: Hypromellose

   JP: Hydroxypropylmethylcellulose

   BP: Hypromellose

2. **Synonyms:**

   Cellulose, hydroxypropyl methyl ether: Hydroxypropylmethylcellulose: HPMC, Methocel, Methylcellulose propylene glyol ether; methyl hydroxypropylcellulose; Metalose; Pharmacoat.

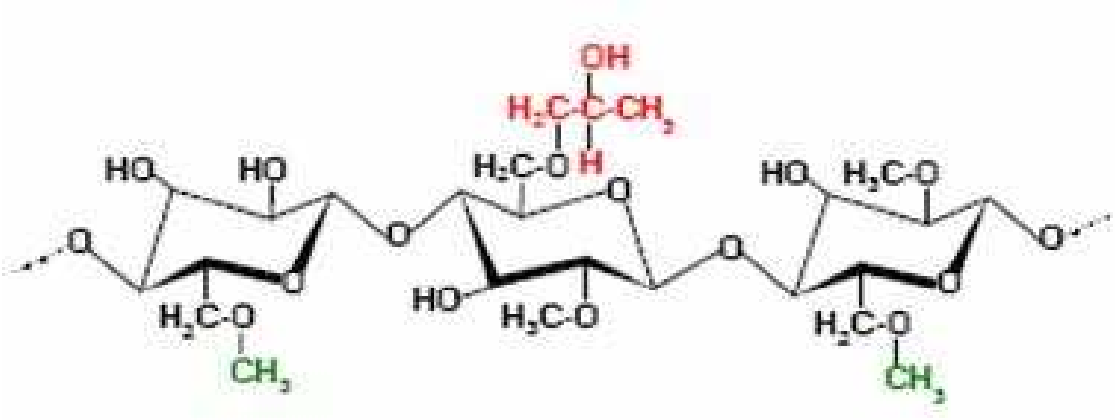
3. **Chemical name:**

   Cellulose, 2-hydroxypropyl methyl ether.

   Molecular weight:

   10000-1500000 approx.

4. **Structural formula:**



5. **Description:**

   Hypromellose is an odourless and tasteless, white or creamy-white fibrous or granular powder.

6. Functional category:

Coating agent, film former, rate controlling polymer for sustained release, stabilizing agent, suspending agent, tablet binder.

7. Applications:

- It is widely used in oral and topical pharmaceutical formulation.
- In oral products, it is primarily used as a tablet binder (2-5%w/w), film coating and as an extended- release tablet matrix (10-80% w/w).
- Depending upon the viscosity grade, concentration of 2-20% w/w are used for film forming solution to film coat tablet.
- It is also used as suspending agent and thickening agent in topical formulations.
- It is also used as an emulsifier in gel and ointment.
- As an adhesive in plastic bandages and as a wetting agent for hard contact lenses.

8. Stability and storage conditions:

It is a stable material, although it is hygroscopic after drying solution are stable at pH 3-11. Increasing temperature reduces the viscosity of solution. The gel point is 50-90 ℃, depending upon the grade and concentration of material. Aqueous solutions are comparatively enzyme resistant but liable to microbial spoilage and should be preserved with an antimicrobial preservative. Hypromellose powder should be stored in a well- closed container, in a cool, dry place**.**

ETHYL CELLULOSE[31]

1. Nonproprietary Names

• BP: Ethylcellulose

• PhEur: Ethylcellulosum

• USPNF: Ethylcellulose

2. Synonyms

Aquacoat ECD; Aqualon; E462; Ethocel; Surelease.

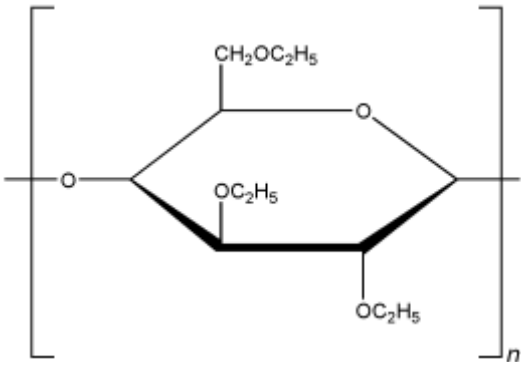
3. Chemical Name and CAS Registry Number

Cellulose ethyl ether [9004-57-3]

4. Empirical Formula and Molecular Weight

Ethylcellulose with complete ethoxyl substitution (DS = 3) is C12H23O6(C12H22O5)*n*C12H23O5 where *n* can vary to provide a wide variety of molecular weights. Ethylcellulose, an ethyl ether of cellulose, is a long-chain polymer of β-anhydroglucose units joined together by acetal linkages

5. Structural Formula



6. Functional Category

Coating agent; flavoring fixative; tablet binder; tablet filler; viscosity-increasing agent.

7. Applications in Pharmaceutical Formulation or Technology

Ethylcellulose is widely used in oral and topical pharmaceutical formulations

Use	Concentration (%)
Microencapsulation	10.0–20.0
Sustained-release tablet coating	3.0–20.0
Tablet coating	1.0–3.0
Tablet granulation	1.0–3.0

The main use of ethylcellulose in oral formulations is as a hydrophobic coating agent for tablets and granules. Ethylcellulose coatings are used to modify the release of a drug, mask an unpleasant taste, or to improve the stability of a formulation; for example, where granules are coated with ethylcellulose to inhibit oxidation. Modified-release tablet formulations may also be produced using ethylcellulose as a matrix former. Ethylcellulose, dissolved in an organic solvent or solvent mixture, can be used on its own to produce water-insoluble films. Higher-viscosity ethylcellulose grades tend to produce stronger and more durable films. Ethylcellulose films may be modified to alter their solubility, by the addition of hypromellose or a plasticizer.

8. Typical Properties

Density (bulk):

0.4 g/cm3

Glass transition temperature:

129–133°C

Moisture content:

Ethylcellulose absorbs very little water from humid air or during immersion, and that small amount evaporates readily.

Solubility:

Ethylcellulose is practically insoluble in glycerin, propylene glycol, and water. EC that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform, methyl acetate, and tetrahydrofuran, and in mixtures of aromatic hydrocarbons with ethanol (95%).Ethylcellulose that contains not less than 46.5% of ethoxyl groups is freely soluble in chloroform, ethanol (95%), ethyl acetate, methanol, and toluene.

Viscosity:

The viscosity of ethylcellulose is measured typically at 25°C using 5% w/v ethylcellulose dissolved in a solvent blend of 80% toluene : 20% ethanol (w/w). Grades of ethylcellulose with various viscosities are commercially available; They may be used to produce 5% w/v solutions in organic solvent blends with viscosities nominally ranging from 7 to 100 mPa s (7–100 cP). Specific ethylcellulose grades, or blends of different grades, may be used to obtain solutions of a desired viscosity. Solutions of higher viscosity tend to be composed of longer polymer chains and produce strong and durable films.

9. Stability and Storage Conditions

Ethylcellulose is a stable, slightly hygroscopic material. It is chemically resistant to alkalis, both dilute and concentrated, and to salt solutions, although it is more sensitive to acidic materials than are cellulose esters. Ethylcellulose is subject to oxidative degradation in the presence of sunlight or UV light at elevated temperatures. This may be prevented by the use of antioxidant and chemical additives that absorb light in the 230–340 nm range. Ethylcellulose should be stored at a temperature not exceeding 32°C (90°F) in a dry area away from all sources of heat. It should not be stored next to peroxides or other oxidizing agents.

10. Incompatibilities

Incompatible with paraffin wax and microcrystalline wax

.

11. Safety

Ethylcellulose is widely used in oral and topical pharmaceutical formulations. It is also used in food products. EC is not metabolized following oral consumption and is therefore a noncalorific substance. Because EC is not metabolized it is not recommended for parenteral products; parenteral use may be harmful to the kidneys. EC is generally regarded as a nontoxic, nonallergenic, and nonirritating material. As ECis not considered to be a health hazard, the WHO has not specified an acceptable daily intake.

EUDRAGIT[32]

The basis of our offerings are our Poly(meth)acrylates for pharmaceutical applications, which are known worldwide in the industry under the trade name EUDRAGIT®. These polymers allow the active in your solid dosage form to perform during the passage of the human body. The flexibility to combine the different polymers enables you to achieve the desired drug release profile by releasing the drug at the right place and at the right time and, if necessary, over a desired period of time. Other important functions are protection from external influences (moisture) or taste/odor masking to increase patient compliance. The range of our product portfolio provides full flexibility for your targeted drug release profiles by offering best performance for enteric, protective or sustained-release properties. EUDRAGIT® polymers are copolymers derived from esters of acrylic and methacrylic acid, whose physicochemical properties are determined by functional groups (R). EUDRAGIT® polymers are available in a wide range of different physical forms (aqueous dispersion, organic solution granules and powders).

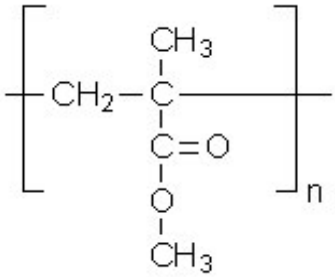
A distinction is made between

1. Poly(meth)acrylates; soluble in digestive fluids by salt formation EUDRAGIT® L, S, FS and E polymers with acidic or alkaline groups enable pH-dependent release of the active ingredient.

Applications: from simple taste masking through gastric resistance to controlled drug release in all sections of the intestine

2. Poly(meth)acrylates; insoluble but permeable in digestive fluids EUDRAGIT® RL and RS polymers with alkaline and EUDRAGIT® NE polymers with neutral groups enable controlled time release of the active ingredient by pH-independent swelling.

Applications: delayed and sustained drug release



Eudragit	Availability	Dissolution Property
RL 100	Granules	Insoluble
RL PO	Powder	Highly Permeability
RL 3D	30% Aqueous Dispersion	pH independent Swelling
RL 12,5	12.5 % Organic Solution	
RS100	Granules	Insoluble
RS PO	Powder	Highly Permeability
RS 3D	30% Aqueous Dispersion	pH independent Swelling
RS 12,5	12.5 % Organic Solution	
NE 30D	30% Aqueous Dispersion	Insoluble, Low permeability
NE 40D	40% Aqueous Dispersion	pH independent Swelling
NM 30D	30% Aqueous Dispersion	Insoluble

2.5 INTRODUCTION TO PLASTICIZERS

Polyethylene Glycol-400[33]

1. **Nonproprietary Names:**

BP: Macrogols

JP: Macrogol 400

PhEur: Macrogola

USPNF: Polyethylene glycol

2. **Synonyms:**

Carbowax; Carbowax Sentry; Lipoxol; Lutrol E; PEG;

3. **Chemical Name:**

α-Hydro-ω-hydroxypoly(oxy-1,2-ethanediyl)

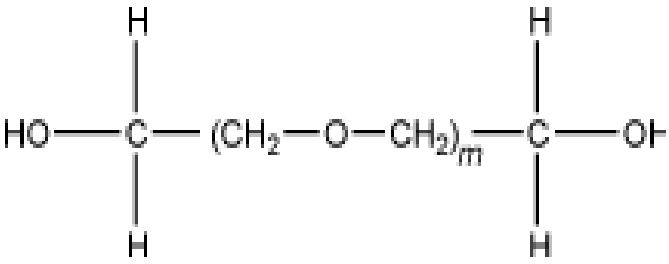
4. **Molecular Weight:**

380–420

5. **Emperical formula:**

HOCH2(CH2OCH2)*m*CH2OH where *m* represents the average number of oxyethylene groups. Alternatively, the general formula H(OCH2CH2)*n*OH may be used to represent polyethylene glycol, where *n* is a number *m* in the previous formula + 1.,m= 8.7, n= 9.7

6. **Structural formula:**



7. **Description:**

It occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight but characteristic odor and a bitter, slightly burning taste.

8. Functional Category:

Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

9. Application:

- Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral, and rectal preparations.
- It has been used experimentally in biodegradable polymeric matrices used in controlled-release systems.
- In concentrations up to approximately 30% v/v, PEG 300 and PEG 400 have been used as the vehicle for parenteral dosage forms.
- Polyethylene glycols are useful as plasticizers in microencapsulated products to avoid rupture of the coating film when the microcapsules are compressed into tablets.
- Polyethylene glycols have been used in the preparation of urethane hydrogels, which are used as controlled-release agents.
- It has also been used in insulin-loaded microparticles for the oral delivery of insulin.
- It has been used in inhalation preparations to improve aerosolization.

10. Stability and Storage Conditions:

Polyethylene glycols are chemically stable in air and in solution, although grades with a molecular weight less than 2000 are hygroscopic. Polyethylene glycols do not support microbial growth, and they do not become rancid. Polyethylene glycols and aqueous polyethylene glycol solutions can be sterilized by autoclaving, filtration, or gamma irradiation. Sterilization of solid grades by dry heat at 150°C for 1 hour may induce oxidation, darkening, and the formation of acidic degradation products. Ideally, sterilization should be carried out in an inert atmosphere.

Propylene Glycol[34]

1. Nonproprietary Names

• BP: Propylene glycol

• JP: Propylene glycol

• PhEur: Propylenglycolum

• USP: Propylene glycol

2. Synonyms

1,2-Dihydroxypropane; E1520; 2-hydroxypropanol; methyl ethylene glycol; methyl glycol; propane-1,2-diol.

3. Chemical Name and CAS Registry Number

1,2-Propanediol [57-55-6]

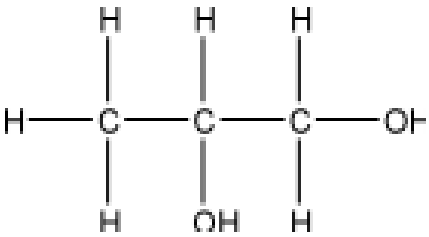
(−)-1,2-Propanediol [4254-14-2]

(+)-1,2-Propanediol [4254-15-3]

4. Empirical Formula and Molecular Weight

C3H8O2 76.09

5. Structural Formula



6. Functional Category

Antimicrobial preservative; disinfectant; humectant; plasticizer; solvent; stabilizer for vitamins; water-miscible co solvent.

7. Applications in Pharmaceutical Formulation or Technology

Propylene glycol has become widely used as a solvent, extractant, and preservative in a variety of parenteral and nonparenteral pharmaceutical formulations. It is a better

general solvent than glycerin and dissolves a wide variety of materials, such as corticosteroids, phenols, sulfa drugs, barbiturates, vitamins (A and D), most alkaloids, and many local anesthetics. As an antiseptic it is similar to ethanol, and against molds it is similar to glycerin and only slightly less effective than ethanol. Propylene glycol is commonly used as a plasticizer in aqueous film-coating formulations. Propylene glycol is also used in cosmetics and in the food industry as a carrier for emulsifiers and as a vehicle for flavours in preference to ethanol, since its lack of volatility provides a more uniform flavour

.

8. Description

Propylene glycol is a clear, colorless, viscous, practically odorless liquid with a sweet, slightly acrid taste resembling that of glycerin.

9. Typical Properties

Autoignition temperature: 371°C

Boiling point: 188°C

Density: 1.038 g/cm3 at 20°C

Flammability: upper limit, 12.6% v/v in air; lower limit, 2.6% v/v in air.

Flash point: 99°C (open cup)

Heat of combustion: 1803.3 kJ/mol (431.0 kcal/mol)

Heat of vaporization: 705.4 J/g (168.6 cal/g) at b.p.

Melting point: −59°C

Osmolarity: a 2.0% v/v aqueous solution is iso-osmotic with serum.

Refractive index: *n*20

D = 1.4324

Solubility:

miscible with acetone, chloroform, ethanol (95%), glycerin, and water; soluble at 1 in 6 parts of ether; not miscible with light mineral oil or fixed oils, but will dissolve some essential oils.

10. Stability and Storage Conditions

At cool temperatures, propylene glycol is stable in a well-closed container, but at high temperatures, in the open, it tends to oxidize, giving rise to products such as

propionaldehyde, lactic acid, pyruvic acid, and acetic acid. Propylene glycol is chemically stable when mixed with ethanol (95%), glycerin, or water; aqueous solutions may be sterilized by autoclaving. Propylene glycol is hygroscopic and should be stored in a well-closed container, protected from light, in a cool, dry place.

11. Incompatibilities

Propylene glycol is incompatible with oxidizing reagents such as potassium permanganate.

12. Method of Manufacture

Propylene is converted to chlorohydrin by chlorine water and hydrolyzed to 1,2-propylene oxide. With further hydrolysis, 1,2-propylene oxide is converted to propylene glycol.

13. Safety

Propylene glycol is used in a wide variety of pharmaceutical formulations and is generally regarded as a relatively nontoxic material. It is also used extensively in foods and cosmetics. Probably as a consequence of its metabolism and excretion, propylene glycol is less toxic than other glycols. Propylene glycol is rapidly absorbed from the gastrointestinal tract; there is also evidence that it is absorbed topically when applied to damaged skin. It is extensively metabolized in the liver, mainly to lactic and pyruvic acids and is also excreted unchanged in the urine. In topical preparations, propylene glycol is regarded as minimally irritant, although it is more irritant than glycerin.

14. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material Handled. Propylene glycol should be handled in a well-ventilated environment; eye protection is recommended. In the UK, the long-term (8-hour TWA) occupational exposure limit for propylene glycol vapor and particulates is 474 mg/m3 (150 ppm) and 10 mg/m3 for particulates.

2.6 INTRODUCTION TO PERMEATION ENHANCERS

Di methyl Sulfoxide[35]

1. Nonproprietary Names

• BP: Dimethyl sulfoxide

• PhEur: Dimethylis sulfoxidum

• USP: Dimethyl sulfoxide

2. Synonyms

Deltan; dimexide; dimethyl sulphoxide; DMSO; *Kemsol*; methylsulfoxide; *Rimso-50*; Sulphinylbismethane

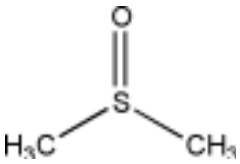
3. Chemical Name and CAS Registry Number

Sulfinylbismethane [67-68-5]

4. Empirical Formula and Molecular Weight

C_2H_6OS 78.13

5. Structural Formula



6. Functional Category

Penetration enhancer; solvent.

7. Applications in Pharmaceutical Formulation or Technology

Dimethyl sulfoxide is a highly polar substance that is aprotic, therefore lacking acidic and basic properties. It has exceptional solvent properties for both organic and inorganic components, which are derived from its capacity to associate with both ionic species and neutral molecules that are either polar or polarizable. Dimethyl

sulfoxide enhances the topical penetration of drugs owing to its ability to displace bound water from the stratum corneum; this is accompanied by the extraction of lipids and configurational changes of proteins.[1] The molecular interactions between dimethyl sulfoxide and the stratum corneum, as a function of depth and time, have been described.

8. Description

Dimethyl sulfoxide occurs as a colorless, viscous liquid, or as colorless crystals that are miscible with water, alcohol, and ether. The material has a slightly bitter taste with a sweet aftertaste and is odorless, or has a slight odor characteristic of dimethyl sulfoxide. Dimethyl sulfoxide is extremely hygroscopic, absorbing up to 70% of its own weight in water with evolution of heat.

9. Solubility:

Miscible with water with evolution of heat; also miscible with ethanol (95%), ether and most organic solvents; immiscible with paraffins, hydrocarbons. Practically insoluble in acetone, chloroform, ethanol (95%), and ether.

10. Stability and Storage Conditions

Dimethyl sulfoxide is reasonably stable to heat but upon prolonged reflux it decomposes slightly to methyl mercaptan and bismethylthiomethane. This decomposition is aided by acids, and is regarded by many bases. When heated to decomposition, toxic fumes are emitted. At temperatures between 40–60°C, it has been reported that DMSO suffers a partial breakdown, which is indicated by changes in physical properties such as refractive index, density, and viscosity. DMSO should be stored in airtight, light-resistant containers.

11. Incompatibilities

DMSO can react with oxidizing materials.

12. Method of Manufacture

Dimethyl sulfoxide is prepared by air oxidation of dimethyl sulfide in the presence of nitrogen oxides. It can also be obtained as a by-product of wood pulp manufacture for the paper and allied industries.

13. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. DMSO may cause irritation to the skin. Gloves and eye protection are recommended

Isopropyl Myristate[36]

1. Nonproprietary Names

• BP: Isopropyl myristate

• PhEur: Isopropylis myristas

• USPNF: Isopropyl myristate

2. Synonyms

Crodamol IPM; *Estol IPM*; isopropyl ester of myristic acid; *Kessco IPM 95*; *Lexol IPM-NF*;myristic acid isopropyl ester; *Rita IPM*; *Stepan IPM*; *Tegosoft M*; tetradecanoic acid, methylethyl ester; *Waglinol 6014*.

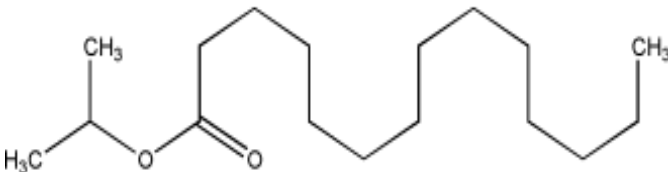
3. Chemical Name and CAS Registry Number

1-Methylethyl tetradecanoate [110-27-0]

4. Empirical Formula and Molecular Weight

C17H34O2 270.5

5. Structural Formula



6. Functional Category

Emollient; oleaginous vehicle; skin penetrant; solvent.

7. Applications in Pharmaceutical Formulation or Technology

Isopropyl myristate is a nongreasy emollient that is absorbed readily by the skin. It is used as a component of semisolid bases and as a solvent for many substances applied topically. Applications in topical pharmaceutical and cosmetic formulations include bath oils; make-up; hair and nail care products; creams; lotions; lip products; shaving products; skin lubricants; deodorants; otic suspensions; and vaginal creams.

8. Description

Isopropyl myristate is a clear, colorless, practically odorless liquid of low viscosity that congeals at about 5°C. It consists of esters of propan-2-ol and saturated high molecular weight fatty acids, principally myristic acid.

9. Solubility:

soluble in acetone, chloroform, ethanol (95%), ethyl acetate, fats, fatty alcohols, fixed oils, liquid hydrocarbons.

10. Stability and Storage Conditions

Isopropyl myristate is resistant to oxidation and hydrolysis and does not become rancid. It should be stored in a well-closed container in a cool, dry place and protected from light.

11. Incompatibilities

When isopropyl myristate comes into contact with rubber, there is a drop in viscosity with concomitant swelling and partial dissolution of the rubber; contact with plastics, e.g. nylon and polyethylene, results in swelling. Isopropyl myristate is incompatible with hard paraffin, producing a granular mixture. It is also incompatible with strong oxidizing agents.

12. Method of Manufacture

Isopropyl myristate may be prepared either by the esterification of myristic acid with propan-2-ol or by the reaction of myristoyl chloride and propan-2-ol with the aid of a suitable dehydrochlorinating agent. A high-purity material is also commercially available, produced by enzymatic etherification at low temperature.

13. Safety

Isopropyl myristate is widely used in cosmetics and topical pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material.

LD_{50} (mouse, oral): 49.7 g/kg

LD_{50} (rabbit, skin): 5 g/kg

3.1 Literature Review on Valsartan

Jinlong Yan et Al.[37] Electrochemical behavior of valsartan has been carried out in Britton–Robinson (B–R) buffer solution at pH 7.0 at the mercury film electrode (MFE) by cyclic, linear sweep, differential-pulse and square-wave voltammetry. The property of valsartan adsorption at the MFE using accumulation potential of +0.10 V was observed. The effects of experimental parameters on electrochemical process at the MFE were discussed. Differential-pulse adsorptive stripping and square-wave adsorptive stripping voltammeter for the valsartan determination were proposed, linearity was found in the range of 6.0×10^{-8} to 4.0×10^{-6} mol/L. The detection limits were 2.93×10^{-9} and 3.27×10^{-9} mol/L, respectively. The proposed methods were also applied to the commercial valsartan with good recoveries.

K.Venkates Kumar et Al.[38] Solubility is an important physicochemical factor affecting absorption of drug and its therapeutic effectiveness. Consequences of poor aqueous solubility would lead to failure in formulation development. The poor solubility of drug substances in water and their low dissolution rate in aqueous G.I.T fluid often leads to insufficient bioavailability. In the present investigation, an attempt was made to improve the solubility and dissolution rate of a poorly soluble drug, Valsartan by solid dispersion method using skimmed milk powder as carrier. Four different formulations were prepared with varying drug: carrier ratios viz.1:1, 1:3, 1:5 and 1:9 and the corresponding physical mixtures were also prepared. The formulations were characterized for solubility parameters, drug release studies and drug-polymer interactions by using phase solubility studies, dissolution studies; XRD analysis, FTIR spectrum, TLC analysis and UV overlay spectra. All the formulations showed marked improvement in the solubility behavior and improved drug release. Formulation containing drug:polymer ratio of 1:9 showed the best release with a cumulative release of 81.60% as compared to 34.91 % for the pure drug. The interaction studies showed no interaction between the drug and the carrier. It was concluded that skimmed milk powder as a carrier can be very well utilized to improve the solubility of poorly soluble drugs.

C.P. Jain et Al [39] In this investigation fast dissolving tablets of valsartan were prepared using different superdisintegrants by direct compression method. FDTs were evaluated for physicochemical properties and *in vitro* dissolution. Effect of disintegrant on disintegration behavior of tablet in artificial saliva, pH 5.8 was evaluated. Wetting time of formulations containing Crospovidone was least and tablets showed fastest disintegration. The drug release from FDTs increased with increasing concentration of superdisintegrants and was found to be highest with formulations containing Crospovidone. The release of valsartan from FDTs was found to follow non-Fickian diffusion kinetics.

3.2Literature Review on Transdermal Films

Ubaidulla U. et. al.[40] developed a matrix-type transdermal therapeutic system containing carvedilol with different ratios of hydrophilic and hydrophobic polymeric combinations by the solvent evaporation technique. The physicochemical compatibility of the drug and the polymers was studied by infrared spectroscopy and differential scanning calorimetry. The results suggested no physicochemical incompatibility between the drug and the polymers. In vitro permeation studies were performed by using Franz diffusion cells. The results followed Higuchi kinetics (r = 0.9953-0.9979), and the mechanism of release was diffusion mediated. Based on physicochemical and in vitro skin permeation studies, patches coded as F3 (ethyl cellulose:polyvinylpyrrolidone, 7.5:2.5) and F6 (Eudragit RL:Eudragit RS, 8:2) were chosen for further in vivo studies. The bioavailability studies in rats indicated that the carvedilol transdermal patches provided steady-state plasma concentrations with minimal fluctuations and improved bioavailability of 71% (for F3) and 62% (for F6) in comparison with oral administration. The antihypertensive activity of the patches in comparison with that of oral carvedilol was studied using methyl prednisolone acetate–induced hypertensive rats.

Shin S.C. et. al.[41] To enhance transdermal delivery of atenolol, ethylene–vinyl acetate (EVA) matrix of drug containing penetration enhancer was fabricated. Effect of penetration enhancer on the permeation of atenolol through the excised rat skin was studied. Penetrating enhancers showed the increased flux probably due to the enhancing effect on the skin barrier, the stratum corneum. Among enhancers used such as glycols, fatty acids and non-ionic surfactants, polyoxyethylene 2-oleyl ether showed the best enhancement. For the controlling transdermal delivery of atenolol, the application of EVA matrix containing permeation.

Melero A.et al.[42] The influence of propylen glycol (PG), ethanol, and oleic acid (OA) on nortriptyline hydrochloride (NTH) penetration through human epidermis was studied in vitro at two different pH values (5.5 and 7.4). The influence of lactic acid and polysorbate 80 was studied for a pH of 5.5. Permeation studies through Heat

Separated Epidermis, as well as the enhancing effect of the different vehicles, showed a pH dependency. A pH value of 5.5 in the donor solution decreases significantly the permeability coefficient (K_p) with respect to a pH value of 7.4 ($0.011 \pm 0.004 \times 10^{-6}$ versus $0.36 \pm 0.04 \times 10^{-6}$ cm/s). The vehicles showed an increasing enhancement effect in the order: polysorbate 80 > ethanol/PG/OA > PG > ethanol > ethanol/lactic acid > lactic acid at pH 5.5 while they reduced the permeation of NTH at pH 7.4. Considering the results obtained at pH 5.5, the maximum enhancement ratios were found for polysorbate 80 and the combination ethanol/PG/OA (10.72 and 3.90).

Larrucea E et. al.[43] studied influence of oleic acid (OA) on the in vitro percutaneous absorption of tenoxicam (TEN) and its combined effect with propylene glycol (PG) was studied using Franz-type diffusion cells. Furthermore, at defined concentrations of OA, complexes of the drug with cyclodextrins (MβCD and γCD) were added because their combined use may be an interesting approach to raise TEN flux. In addition, the amount of TEN retained in the skin after topical administration of several formulations was determined. It was found that OA content markedly increased TEN absorption when compared to the control gel; the highest drug flux was obtained by 15% of OA. The absorption rate of TEN increased in parallel with increasing OA concentration, due to the alteration of the stratum corneum caused by this enhancer. Moreover, the action of OA is likely to be strongly dependent on the vehicle used since drug penetration tended to increase with increasing PG content in the vehicle, especially at the high OA concentrations. Contrary to our expectations, addition of CD complexes did not produce a significant further enhancement.

Padula C. et .al[44] was developed an innovative drug delivery system, a water-based and vapor permeable film intended for dermal and/or transdermal delivery. The aim of this work was to modulate the delivery of the model drug lidocaine hydrochloride from the transdermal film across rabbit ear skin. The effect of drug loading, of film-forming polymer type and content, of adhesive and plasticizer on lidocaine transport across the skin was evaluated. Additional objective was to evaluate the effect of occlusion on the kinetics of lidocaine transport, by applying an occlusive backing on the surface of the transdermal film. From the data obtained it can be

concluded that the transdermal film acts as a matrix controlling drug delivery. The film-forming polymer molecular weight had a negligible effect on drug penetration, while its content was more effective. The choice of the adhesive seems to be the most important variable governing drug transport. In particular, the presence of lauric acid combined with a basic drug, such as lidocaine, can produce a relevant improvement in permeation, because of the formation of an ion pair. Concerning the kinetics, drug depletion is responsible for the declining permeation rates observed in the late times of permeation.

Giannakou S.A. et al.,[45] was worked to on the examination of efficacy to permeate human epidermis was examined in vitro. A preliminary study was carried out in order to estimate the effect of the type of enhancer, the concentration of enhancer and the concentration of gelling agent on the flux of nitrendipine, using a 2^3factorial design. The type of enhancer and the concentration of enhancer were further evaluated as they were found to be important for nitrendipine flux, while the concentration of the gelling agent was kept at its optimum level in all experiments. In order to increase further the flux of nitrendipine, the combination of two enhancers, glycerol monooleate (GMO) and *N*-methyl-2-pyrrolidone (NMP), which act via different mechanisms, at three concentration levels was examined, using the response surface method. The results indicate that higher flux values were obtained when NMP was greater than 4.5% w/w and GMO between 5.0 and 9.5% w/w, in the vehicle.

Aquil M et al.[46] was to fabricate Eudragit RL 100-polyvinyl acetate films and evaluate their potential for transdermal drug delivery in a quest to develop a suitable transdermal therapeutic system for pinacidil. The polymeric films (composed of Eudragit RL 100 and polyvinyl acetate in 2:8, 4:6, 6:4, 8:2 ratios in films P-1, P-2, P-3, P-4 respectively, together with 5% w/w of pinacidil and 5% w/w of dibutylphthalate in all the films) were cast on a glass substrate and evaluated for physicochemical parameters viz. thickness, weight, folding endurance (a measure of fragility), percent elongation at break (a measure of flexibility), drug content uniformity, water absorption capacity, moisture vapour transmission, drug-polymer interaction, in vitro drug release and skin permeation profiles. The films were also evaluated for appearance, smoothness and transparency. The film finally selected was assessed for its skin irritation potential, and its stability on storage under accelerated

temperature and humidity conditions. The values of thickness, weight, folding endurance, percent elongation at break, percentage water absorbed, moisture vapour transmission, cumulative amount of drug released and permeated for different films were in the following order: P-1 < P-2 < P-3 < P-4. The results suggest that Eudragit RL 100, a freely permeable polymer, has a major influence on the physicochemical profile of the films. The higher the quantity of Eudragit RL 100 in the film, the better its strength and flexibility as well as its higher drug release and skin permeation potential. The final optimized film (with a composition of Eudragit RL 100: polyvinyl acetate: pinacidil monohydrate: dibutylphthalate in 8.0:2.0:0.5:0.5 ratio) was found to be the best in terms of drug release (cumulative amount of drug released in 48 h was 96.09%) and skin permeation (permeability coefficient, 0.0164cm/h). There was no apparent drug-polymer interaction in the films.

Kanikkannan N et al.[47] was undertaken to prepare and evaluate monolithic drug-in-adhesive type transdermal patches of melatonin containing penetration enhancers such as fatty alcohols, fatty acids, and terpenes. The patches were prepared using Eudragit® E 100 as the adhesive polymer. The release profile of melatonin from control as well as enhancer-containing patches showed an initial burst of melatonin release for up to 4 hours and then a plateau after 8 hours. The release profiles of melatonin from patches containing various enhancers were similar to the control patch. However, the addition of enhancers in the patch increased the permeation of melatonin through hairless rat skin. The flux values of patches containing octanol, nonanoic acid, and myristic acid were higher than the control patch (no enhancer), but the differences were not statistically significant ($P > 0.05$). Decanol, myristyl alcohol, and undecanoic acid at 5% concentrations showed significantly higher flux values through hairless rat skin (enhancement ratios 1.7, 1.5, and 1.6 for decanol, myristyl alcohol, and undecanoic acid, respectively) ($P < 0.05$). Menthol and limonene at 5% w/w showed maximum permeation of melatonin among all enhancers studied (enhancement ratios = 2.1 and 2.0 for menthol and limonene, respectively) ($P < 0.001$). In general, there was about 4–6 hours of lag time observed before a steady state flux of melatonin was achieved.

3.3 Literature Review Eudragit RL 100 & RS 100

Das M. k. et Al.[48] Trazodone hydrochloride has not been previously investigated and reported for potential administration through transdermal route. Therefore, the present investigation was carried out to study the effect of polymeric composition, drug content and plasticizer on the permeation of trazodone hydrochloride across the mouse epidermis for the development of transdermal therapeutic system. The pseudolatex films with different combination of polymers, plasticizer and drug were prepared from aqueous colloidal polymer dispersions. The polymers used were Eudragit RL100 and RS100. Triethylcitrate was used as plasticizer. The in vitro release and skin permeation through mouse epidermis from the prepared films were studied using Keshary-Chien diffusion cell. The in vitro drug release increased with increasing amount of Eudragit RL100 in the film. It was observed that the maximum skin permeability was attained at a loading dose of 10% w/w in the film. The in vitro flux decreased gradually at higher concentration up to 13% w/w.

Aqil, M et al.[49]The aim of the present work was to develope and evaluate matrix type transdermal drug delivery systems (TDDS) of labetolol hydrochloride (L-HCL) effective for 48 hours. EXPERIMENTAL. The TDDS were prepared by solvent evaporation technique. Six formulations (carrying Eudragit RL100:Eudragit RS 100 in 7.5:4.5, 5.0:5.0, 3.5:8.5 in formulations X-1, X-2, X-3 and Eudragit RL100:PVP K-30 in 9.0:2.0, 5.0:5.0, 4.0:7.0 in formulations Y-1, Y-2, Y-3, respectively) were prepared. All formulations carried 36% w / w of L-HCL, 10-12% w / w of enhancer dimethyl sulfoxide and 2.5-7.5% w / w of plasticizer PEG 400 in methanol-acetone solvent system. The TDDS were evaluated by in vitro drug release, ex vivo skin permeation, stability and in vivo pharmacodynamic studies. RESULTS. The maximum drug release for X-series was 90.26% in 48 hours (X-1) and for Y-series, it was 83.24% (Y-1). Again formulations X-1 (Kp = 0.221x10-2 cm hr-1) and Y-1 (Kp = 0.210x10-2 cm hr-1) exhibited the best skin permeation potential in the respective series. This might be due to higher permeability characteristics of Eudragit RL100. A shelf life of 2.38 years was predicted for the TDDS.

Mukharjee B. et al[50] was designed to develop a suitable matrix type transdermal drug delivery system (TDDS) of dexamethasone using blends of two different polymeric combinations, povidone (PVP) and ethylcellulose (EC) and Eudragit with PVP. Physical studies including moisture content, moisture uptake, flatness to study the stability of the formulations and in vitro dissolution of the experimental formulations were performed to determine the amount of dexamethasone present in the patches were performed and scanning electron microscopy (SEM) photographs of the prepared TDDS were taken to see the drug distribution pattern. Drug–excipient interaction studies were carried out using Fourier transform infrared (FTIR) spectroscopic technique. In vitro skin permeation study was conducted in a modified Franz's diffusion cell. All the formulations were found to be suitable for formulating in terms of physicochemical characteristics and there was no significant interaction noticed between the drug and polymers used. In vitro dissolution studies showed that the drug distribution in the matrix was homogeneous and the SEM photographs further demonstrated this. The formulations of PVP:EC provided slower and more sustained release of drug than the PVP:Eudragit formulations during skin permeation studies and the formulation PVP:EC (1:5) was found to provide the slowest release of drug.

Kusum Devi V et al.[51] were prepared using four different polymers (individual and combination): Eudragit RL100 (ERL100), Eudragit RS100 (ERS100), hydroxypropyl methylcellulose 15cps (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 (A 12) 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%).

Khatun Masuda et al.[52] were prepared Polymeric films of Eudragit RS 100 by solvent casting method to explore the possibilities of using this polymer in transdermal therapeutic system (TTS). Naproxen was used as a model drug and incorporated in two different percent loading (8.3 % w/w and 20.8 % w/w of films). Effects of two plasticizers (PEG 1500 and PEG 4000) and two release modifiers (PVA and HPMC 15cps) on in vitro drug release from naproxen loaded Eudragit RS films were assessed. Drug release was found to be a function of drug load, PEG molecular weight and physico-chemical property of the release modifiers incorporated. At low drug load, highest amount of drug was released from flims containing PEG 1500 (more than 95%). However, a burst release was evident in case of all the experimental batches except that loaded with HPMC 15 cps. With this formulation, more than 75 % of active principle was released after 8 hours while only 12 % of naproxem was liberated in the first hour of dissolution

Talasila Eswara et al.[53] were prepared and evaluated cellulose acetate (CA), ethyl cellulose (EC), and Eudragit RS 100 (ERS100) films as rate-controlling membranes for transdermal drug delivery systems. 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. Dibutyl phthalate or propylene glycol at a concentration of 40% w/w of the polymer was used as a plasticizer in the preparation of CA and EC films. Dibutyl phthalate at a concentration of 15% w/w of the polymer was used as a plasticizer in the preparation of ERS100

films. The solvent evaporation technique was employed for the preparation of CA and EC films, and the casting solvent technique was employed for the preparation of ERS100 films. The dry films were evaluated for physical appearance, thickness uniformity, folding endurance, water vapor transmission (WVT), drug diffusion, and permeability coefficient. Both WVT and drug diffusion rate followed zero-order kinetics. The mechanism of drug release was governed by Peppas model.

Hemangi J. Et Al.[54] were prepared Matrix type Transdermal drug delivery system of Amlodipine besilate, an antihypertensive drug were prepared using different polymers like Carbopol 934, 940, HydroxyPropyl Methyl Cellulose and Eudragit L100 in varied ratios. The present study aims to formulate and evaluate Transdermal drug delivery for sustained release of Amlodipine besilate. Physicochemical parameter were characterized. The permeability studies indicates that the drug is suitable for Transdermal drug delivery. The patches were evaluated for various parameters like Thickness, Water-Vapor Permeability, Tensile Strength, Drug Content, Diffusion and Dissolution studies. The patches were further evaluated by DSC and SEM, to ensure uniform distribution of the drug and compatibility of drug with polymer. The Optimized formulation containing Carbopol 934: Eudragit L100 (3:7), with enhancer Hyaluronidase showed 84% drug release after 24 hours.

Mohamed Aqil et al.[55] were prepared the monolithic matrix type transdermal drug delivery system of metoprolol tartrate were prepared by the film casting on a mercury substrate and characterised *in vitro* by drug release studies, skin permeation studies and drug-excipients interaction analysis. Four formulations were developed, which differed in the ratio of matrix-forming polymers. Formulations MT-1, MT-2, MT-3 and MT-4 were composed of Eudragit RL-100 and polyvinyl pyrrolidone K-30 with the following ratios: 2:8, 4:6, 6:4 and 8:2, respectively. All the four formulations carried 10% (*m/m*) of metoprolol tartrate, 5% (*m/m*) of PEG-400 and 5% (*m/m*) of dimethyl sulfoxide in isopropyl alcohol:dichloromethane (40:60). Cumulative amounts of the drug released in 48 hours from the four formulations were 61.5, 75.4, 84.3 and 94.5%, respectively. The corresponding values for cumulative amounts of the permeated drug for the said formulations were 53.5, 62.5, 69.8 and 78.2%.

3.4 Literature Review of work done using polymer HPMC

Murthy NS et al.[56] Transdermal formulations containing theophylline and salbutamol sulfate (SS) were formulated using hydroxypropylmethylcellulose. Theophylline was loaded by adsorption with the aid of the coadsorbate sodium chloride. The formulations were subjected to in vitro release studies, and the dose of salbutamol and theophylline was optimized to yield the desired flux. The films were uniform and 93 ± 5.4 μm thick. The in vitro fluxes of theophylline and salbutamol sulfate from the formulation were 1.22 ± 0.4 mg/h/cm^2 and 13.36 ± 1.02 μg/h/cm^2, respectively. The formulation was subjected to pharmacodynamic studies in guinea pigs. The preconvulsive time (PCT) of guinea pigs increased significantly after 4 h, and the same was observed even after 24 h. Pharmacokinetic studies were carried out in healthy human volunteers. Theophylline was analyzed in saliva, and salbutamol was analyzed in the blood plasma. The T_{max} of the drugs was 3 h, and appreciable concentrations of the drugs above their MEC could be analyzed even after 12 h

Mi-Kyeong Kim et al.[57] A reservoir-type transdermal delivery system of testosterone (TS) was developed using an ethanol/water (70:30) cosolvent system as the vehicle. The maximum permeation rate achieved by 70% (v/v) of ethanol was further increased from 2.69 to 47.83 μg/cm^2/h with the addition of 1.0% dodecylamine as the skin permeation enhancer. The permeation rate of TS through the ethylene vinyl acetate (EVA) membrane was observed to increase as the vinyl acetate content in the copolymer increased. Addition of 1.0% (w/w) gelling agent, hydroxypropyl methlycellulose (HPMC), in the reservoir formulation resulted in desirable rheological properties with an insignificant effect on the skin permeation rate of TS. Thus, a new transdermal delivery system for TS was formulated using EVA membrane coated with a pressure-sensitive adhesive (Duro-Tak 87-2510) and HPMC as a gelling agent. This experimental patch showed comparable plasma concentration profiles in the in vivo study when compared with a commercial product, Androderm®. Moreover, the results suggested the possibility of further enhancing the permeation rate of TS by controlling the composition of the reservoir formulation.

Guyot M et al.,[58] Propranolol hydrochloride, a water-soluble drug, was incorporated in three transdermal delivery systems using three polymers (hydroxypropylmethylcellulose, polyisobutylene and Ucecryl®MC808). The influence of different factors (polymeric material, matrix thickness, drug content, thickness of the adhesive layer and presence of a dissolution enhancer) was investigated. Microscopic observations and DSC thermograms have permitted to demonstrate that propranolol was essentially dissolved in the HPMC matrix and dispersed in the two other matrix types. In vitro dissolution study was carried out according to European Pharmacopoeia. Release from HPMC matrices without adhesive coating was fast. Release from these matrices became more regular (reduction of the burst effect) and slow when they are coated with a 12 μm thick Ucecryl layer. Release from different PIB matrices was too slow to be suitable as TDDS for propranolol.

Patel J. et al.[59] was prepared Ketotifen fumarate, almost completely absorbed from the gastro-intestinal tract following oral administration, but bioavailability is reported to be only about 50% due to hepatic first-pass metabolism. The present study aims to prepare Transdermal patch for Ketotifen fumarate as asthmatic drug. Preparation of standard curve for Ketotifen fumarate in solution of 20% w/v PEG 400 in normal saline. Preparation of transdermal patches of Ketotifen fumarate using polymers : Eudragit L-100 and Ethyl cellulose in combination with Hydroxypropyl methyl cellulose, plasticized with polyethylene glycol 400. The patches were evaluated for various parameters like Thickness, Water-Vapor Permeability, Tensile Strength, Drug Content, Diffusion and Dissolution studies. Prepared patches exhibited Zero Order Kinetics and the permeation profile was matrix diffusion type.

Mehdizadeh A et al.[60] was designed to evaluate different matrix, drug-in-adhesive and reservoir formulations of fentanyl transdermal patches. The target was to design drug-in-adhesive patches (DIAPs); a full factorial design was used. Different types and amounts of liquid, pressure- sensitive adhesives (PSAs) were used and evaluated with respect to drug release and adhesive properties. A very simple but precise method, the simplified peel 180° test, was developed to measure and compare

adhesive properties of transdermal patches. The results showed that release kinetics obeyed the square root of time or Higuchi model, indicating the diffusion controlled release mechanism. It was found that the amount of fentanyl needed for each 10 cm2 three-days DIAP should be 3.3 mg. The respective amounts for reservoir and matrix patches were 2.5 and 5 mg. It was concluded that acrylic PSAs showed the best adhesion and release properties.

Aqil M. et al.[61] were prepared the monolithic matrix type transdermal drug delivery systems of pinacidil monohydrate (PM) by film casting technique on mercury substrate and characterized in vitro by drug release studies using paddle over disc assembly, skin permeation studies using Keshary and Chein diffusion cell on albino rat skin and drug-excipient interaction analysis. Four formulations were developed which differed in the ratio of matrix forming polymers, Eudragit RL-100 and PVP K-30, i.e. 8:2, 4:6, 2:8 and 6:4 and were coded as B-1, B-2, B-3 and B-4, respectively. All the four formulations carried 20% w/w of PM, 5% w/w of plasticizer, PEG-400 and 5% w/w of DMSO (based on total polymer weight) in isopropyl alcohol: dichloromethane (40:60) solvent system. Cumulative % of drug released in 48 h from the four formulations was 63.96, 55.95, 52.26 and 92.18%. The corresponding values for cumulative amount of drug permeated for the said formulations were 57.28, 50.35, 46.38 and 86.54%, respectively. On the basis of in vitro drug release and skin permeation performance, formulation B-4 was found to be better than the other three formulations and it was selected as the optimized formulation.

Jadhav R.T el Al.[62] were formulated Transdermal films of Diclofenac Sodium by using different polymer combinations such as hydrophilic (Poly vinyl alcohol: Poly vinyl pyrolidone), and combination of hydrophilic - lipophilic polymers (Ethyl cellulose: Poly vinyl pyrolidone). To study the effect of plasticizers such as dibutyl phthalate and propylene glycol by using Keshary- Chein diffusion cell. The placebo and medicated films were evaluated for physicochemical properties and also medicated films were evaluated for area variation, drug content and percent cumulative drug release. *In vitro* drug release study through cellophane membrane indicates that hydrophilic polymer showed higher release than the

hydrophilic - lipophilic combinations. The release rate found to follow first order rate kinetic. Primary irritation study shows that the transdermal films are non- irritant.

Shinde A J et Al.[63] The present work was designed to develop suitable transdermal matrix patches of tramadol hydrochloride, a non-steroidal anti-inflammatory drug, using hydroxy propyl methyl cellulose (HPMC), Eudragit RL-100 and Eudragit RS-100 with triethyl citrate as a plasticizeand dimethyl sulfoxide (DMSO) as a penetration enhancer. Different batches developed usin Eudragit RL-100 : HPMC and Eudragit RS-100 : HPMC in ratio of 2 : 8, 4 : 6, 6 : 4, and 8 : 2. Drug - excipients interaction study was further carried out using Fourier transform infrared (FTIR) spectroscopic technique. Physical evaluation was performed such as moisture content, moisture uptake, tensile strength, flatness, and folding endurance. *In vitro* diffusion studies were performed using cellulose acetate membrane (pore size 0.45 μ) in a Franz's diffusion cell. The concentration of diffused drug was measured using UV-visible spectrophotometer (JascoV-530) at λ_{max} 275 nm.

Chandra A et al[64] A reservoir-type transdermal patch for the delivery of ketorolac was studied. The low permeability of the skin is the rate-limiting step for delivery of most of the drugs. Studies were carried out to investigate the effect of pH, alcohols, and chemical permeation enhancers on the in vitro permeation of ketorolac. The reservoir core of the transdermal patch was filled with the hydrogel of a nonionic polymer, methocel K15M (hydroxyl propyl methylcellulose, HPMC) formulated at an optimized pH of 5.4. Enhanced in vitro permeation was achieved after the incorporation of the alcohols. Higher enhancement was produced by short-chain alcohols like ethanol and isopropyl alcohol (IPA). Propylene glycol (PG) along with other alcohols, viz. n-propanol, n-butanol, and n-pentanol, lagged behind. An exponential rise in permeation was observed in flux with an increase in the concentration of IPA. At 25% w/w IPA concentration, the observed ketorolac flux was 18.04 mg/cm2/h. Terpene containing eucalyptus oil was studied to determine its permeation enhancement capability. The increase in the concentration of eucalyptus oil enhanced the drug permeation and a maximum flux of 66.38 and 90.56 mg/cm2/h was achieved at 10 and 15% w/w concentrations.

R Sadashivaiah[65] Matrix-type transdermal drug delivery systems of haloperidol lactate were prepared using different ratios of ethyl cellulose (EC):polyvinyl pyrrolidone (PVP) (3:2, 2:3, 4:1, 1:2, 2:1, and 1:4) by solvent-evaporation technique. Physicochemical parameters were characterized, and dissolution studies of the formulated films were performed. In addition, solubility studies at various values of pH were carried out, and partition coefficient in octanol/water system, flux, and enhancement ratio were also evaluated. In vitro permeation studies were done using modified Franz diffusion cells through human cadaver skin utilizing 20% PEG 400 in normal saline. Permeation studies illustrated that 4% hyaluronidase enzyme was a good enhancer. The prepared films were subjected to scanning electron microscopy (SEM) and fourier transform infrared spectroscopy (FT-IR) spectral analysis. Higuchi and Peppas models were used for optimizing the formulation.

4. Experimental Work

4.1 Materials Used for the Present work

Materials		Company name
Drug	Valsartan	Torrent research Centre
Polymer	HPMC 50cps	S.D.Fine-Chem Ltd
	Eudragit RL-100 Eudragit RS-100	S.D.Fine-Chem Ltd
	PVA (Poly vinyl Alcohol)	S.D.Fine-Chem Ltd
	Ethyl Cellulose	
Solvent	Methanol	S.D.Fine-Chem Ltd
Plasticizer	PEG-400	S.D.Fine-Chem Ltd
	Propylene glycol	S.D.Fine-Chem Ltd
Penetration Enhancer	Dimethyl Sulphoxide(DMSO)	S.D.Fine-Chem Ltd
	Tween-80	CDH Laboratory
	IPM(Iso Propyl Myristate)	CDH Laboratory

Instruments used in Present Work

Instrument	**Manufacturing**
U.V- Visible Double Beam Spectrophotometer	UV 1800 Shimadzu scientific instrument, Japan
FT-IR Spectrophotometer	Jasco Corporation Ltd, India
pH meter	Analab Scientific Instrument Pvt Ltd.
Weighing Balance	Dhona 160-D
Vacuum Oven	Erection and Instrumentation Engineering
Magnetic Stirrer	EIE Instrument Pvt Ltd
Hot Air Oven	EIE Instrument Pvt Ltd
Tensile Tester	EIE Instrument Pvt Ltd
Diffusion Cell	Jencons Ltd
Dissolution Apparatus	Electrolab TDT-08L with electrolab Fraction Collection
Sonicator	Trans-o-Sonic D-Compact

4.2 Identification of Valsartan

1. Determination By Melting Point :

The thief tube method of melting point determination in liquid paraffin was used in the determination. The standard value and observed value are as shown below:

Reported Melting point	Obtained Melting Point
117°C	115°C to 120°C

Result:
Obtained melting point was similar to the reported melting point, this indicates the purity of the sample i.e. Valsartan

2. Partition coefficient drug in octanol /water system

Drug	Partition coefficient
Valsartan	1.498

Determination by FT-IR Spectroscopy

FT-IR spectra of drug were taken at moderate scanning speed between 4000-400cm^{-1} using FTIR. The wave number and the possibility of functional group present are as shown below:

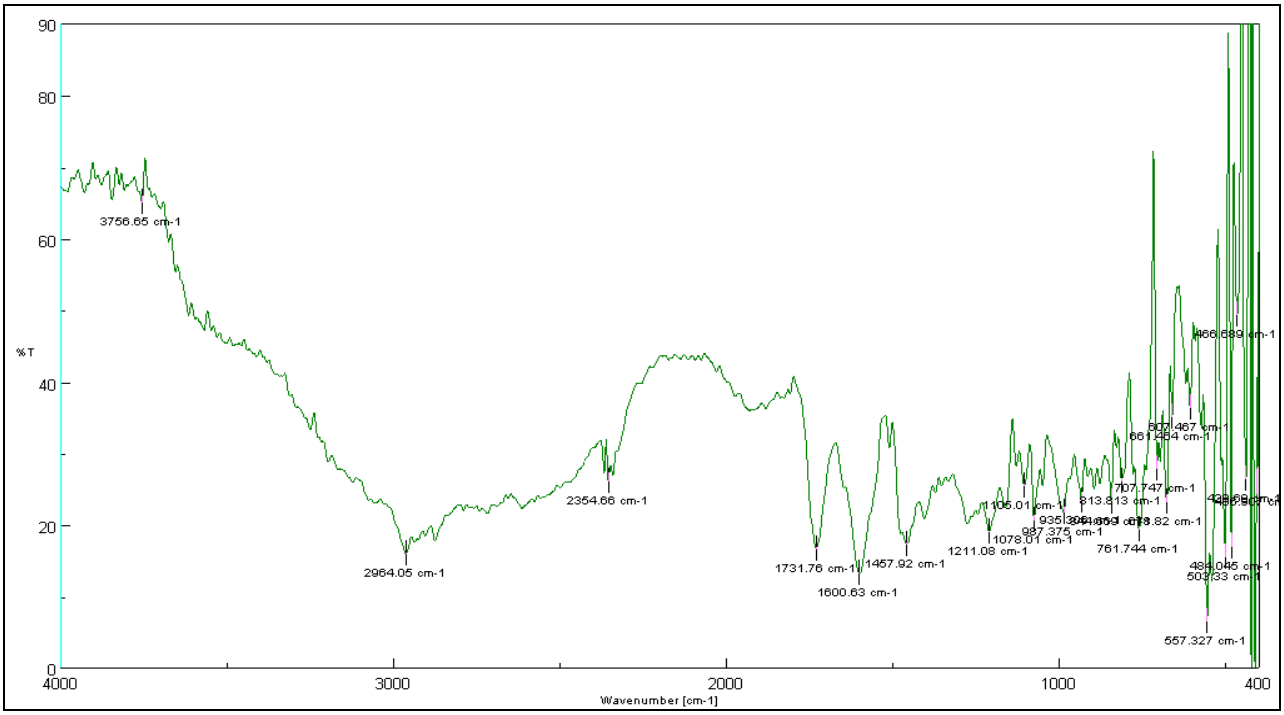


Fig 1: IR spectra of Valsartan

Type of Vibration	Obtained wave number (cm$^{-1)}$ (Drug Sample)
Methelene C-H stretch	2964
Ketone C-O stretch	1731
C-N stretching	1200
Carboxylic acid	3200-3400

Drug-Polymer compatibility Study

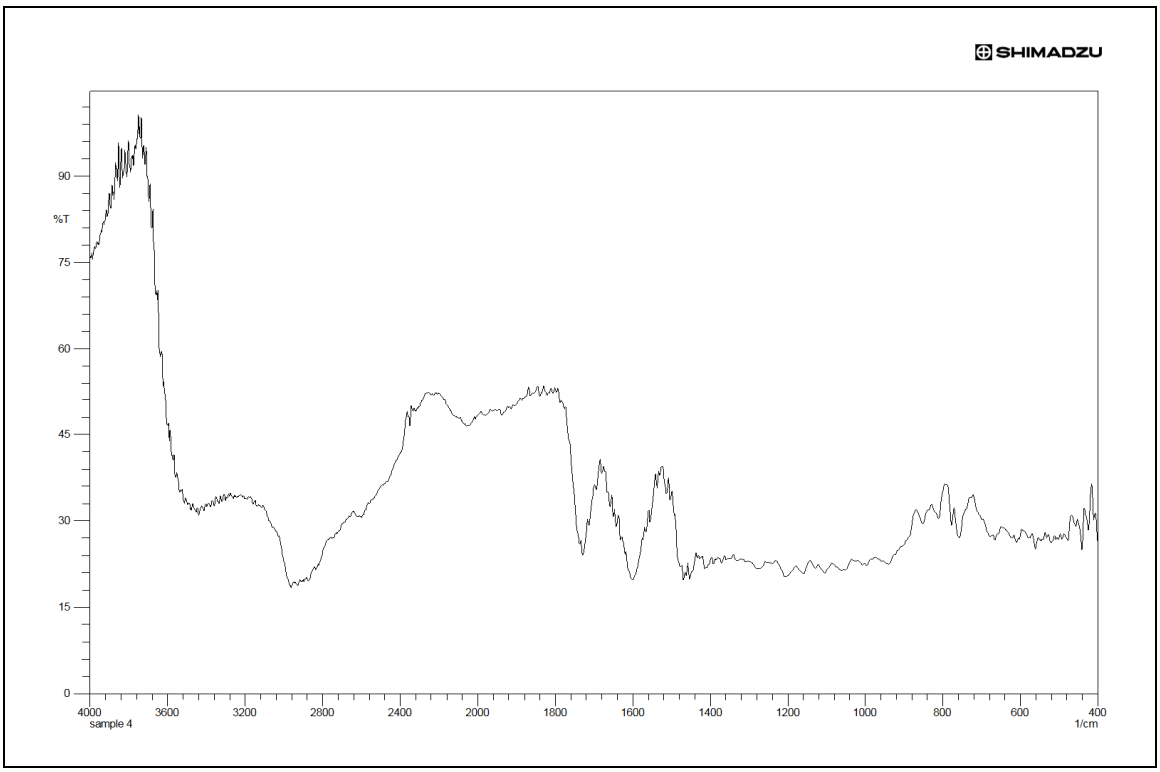


Fig 2 : IR Spectra of Valsartan + HPMC

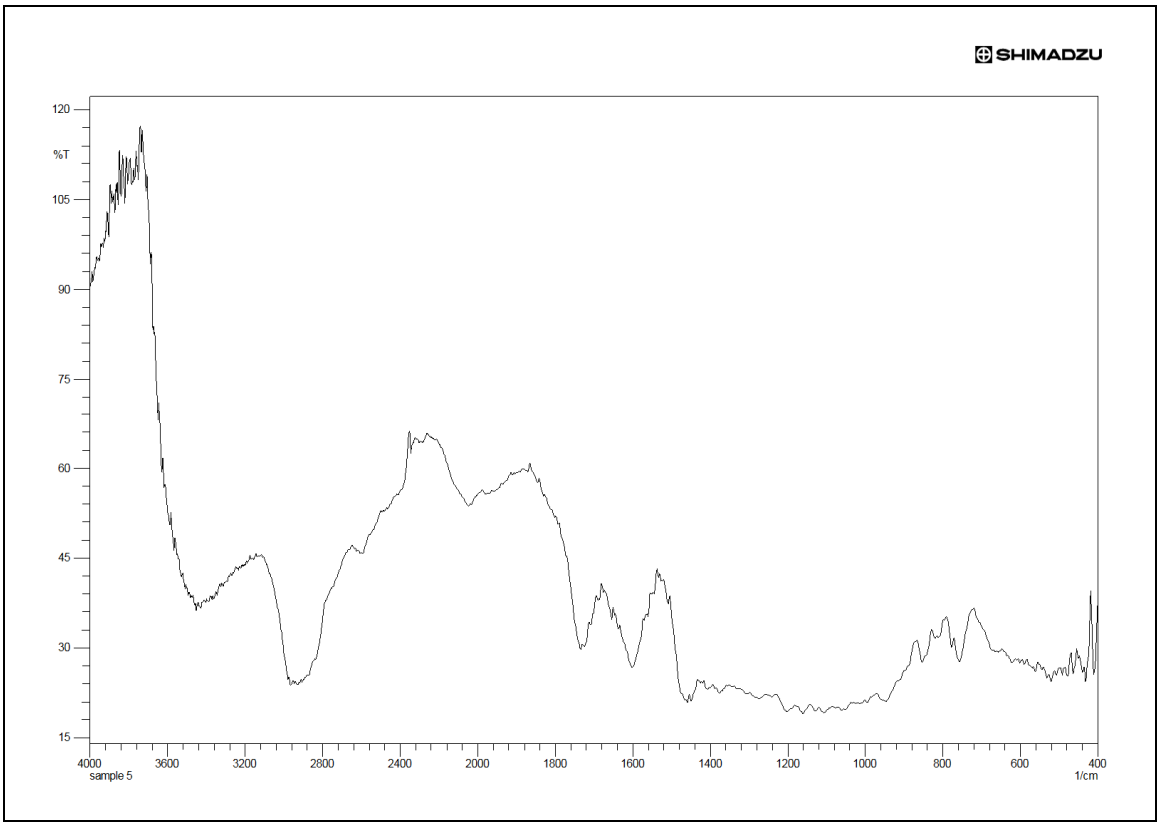


Fig 3 : IR Spectra of Valsartan + HPMC : ERL 100

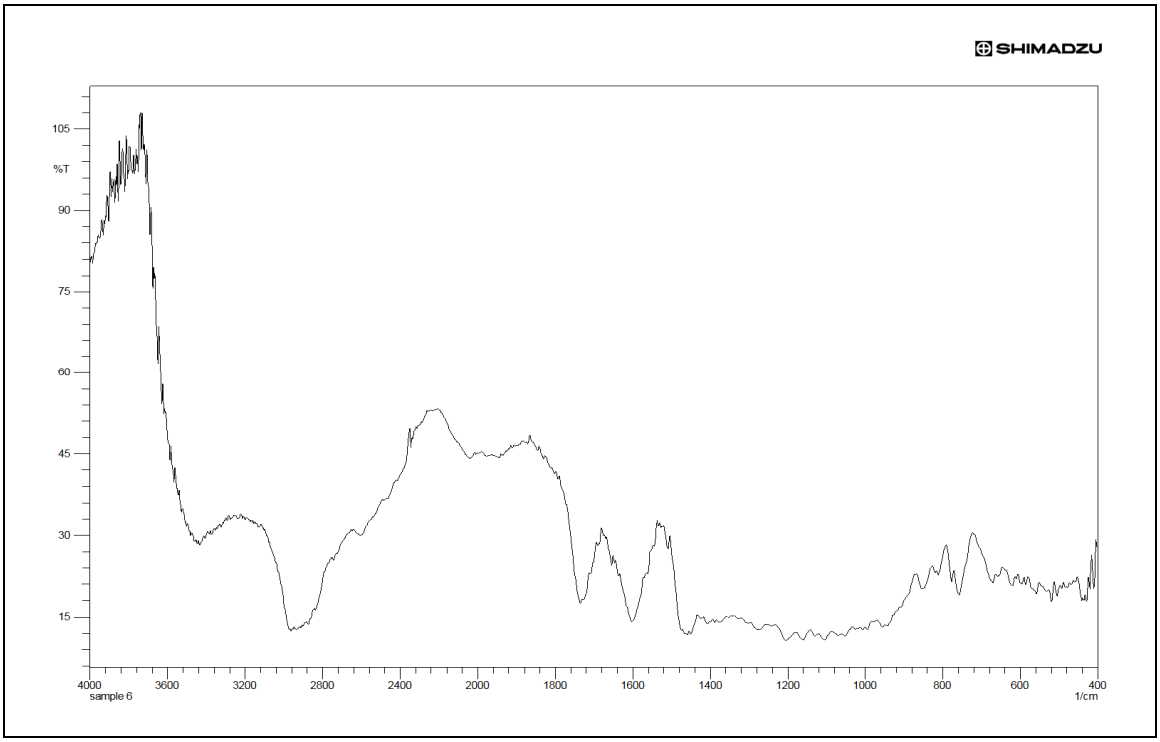


Fig 4 : IR Spectra of Valsartan + HPMC : ERS 100

Result:

To study the possible interaction between valsartan and polymeric materials of the films, infrared (IR) spectroscopy was carried out on pure substances and their physical Mixtures. The IR spectra were recorded using FTIR (Perkin Elmer FT-IR, Perkin Elmer Inst. USA) by KBr pellet method. The IR spectrum revealed that there was no interaction between drug and excipients.

Determination of UV Spectra

Concentration of Valsartan : 10µg/ml

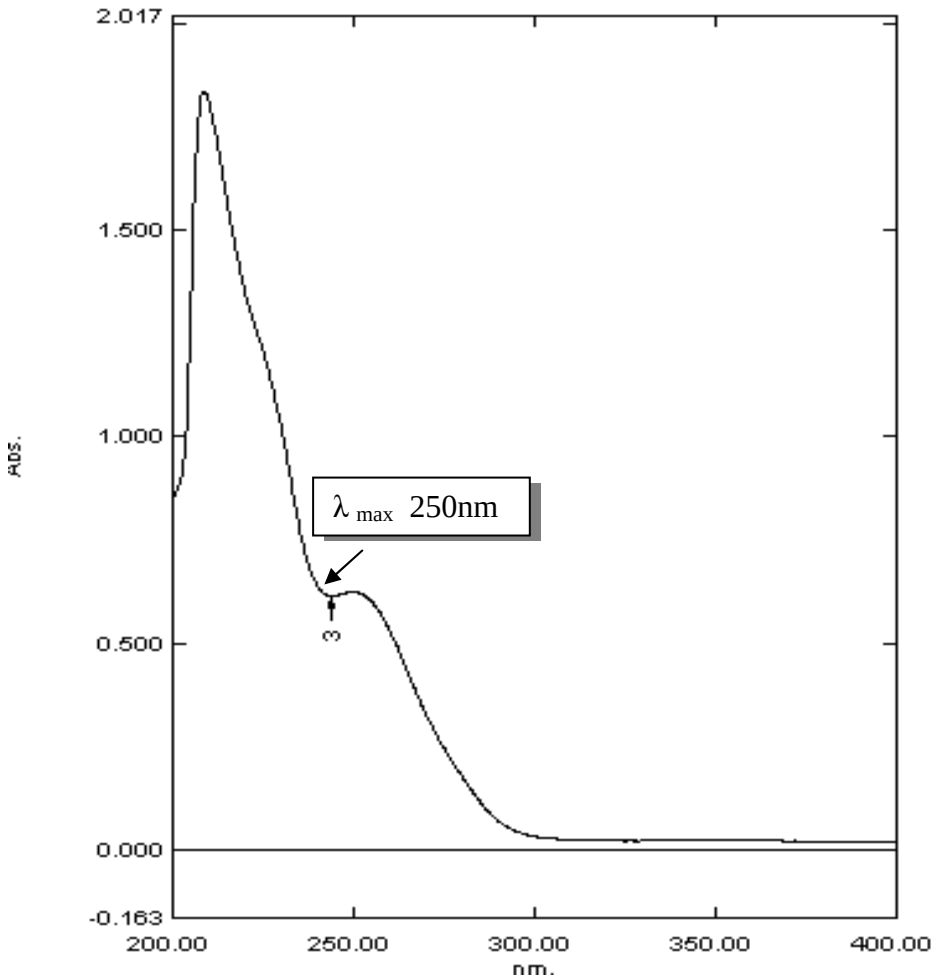


Fig 5 : U.V spectra of Valsartan in Phosphate Buffer.

Result

The obtained λ_{max} 250nm which indicate purity of the sample.

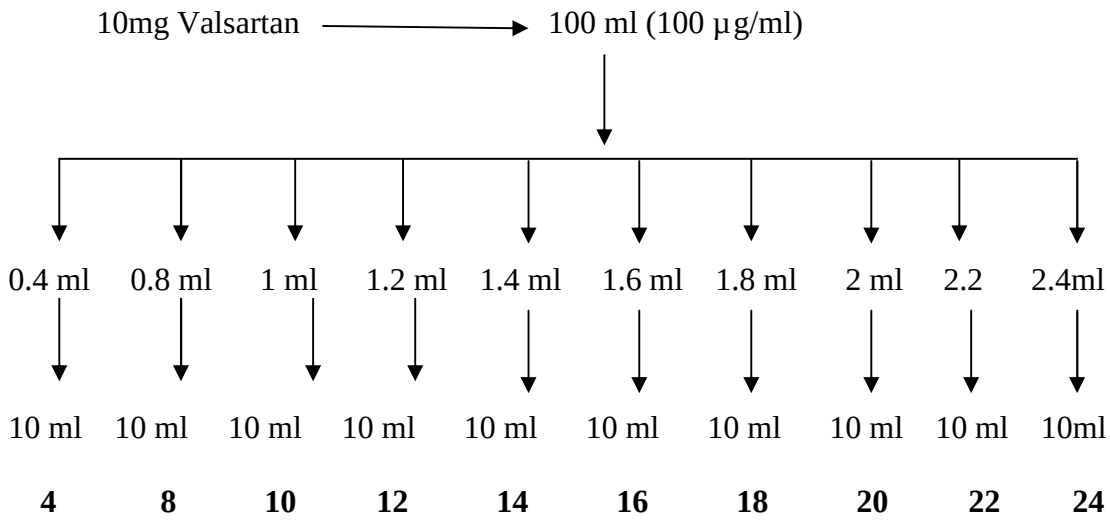
4.3 Estimation of Valsartan

Valsartan is official in United States Pharmacopoie 2007,

Stock Solution: Accurately weight VAL (10mg) was transferred to a 100 ml volumetric flask. Make up to 100 ml by phosphate buffer (7.4 pH).

Working Standard Solution:

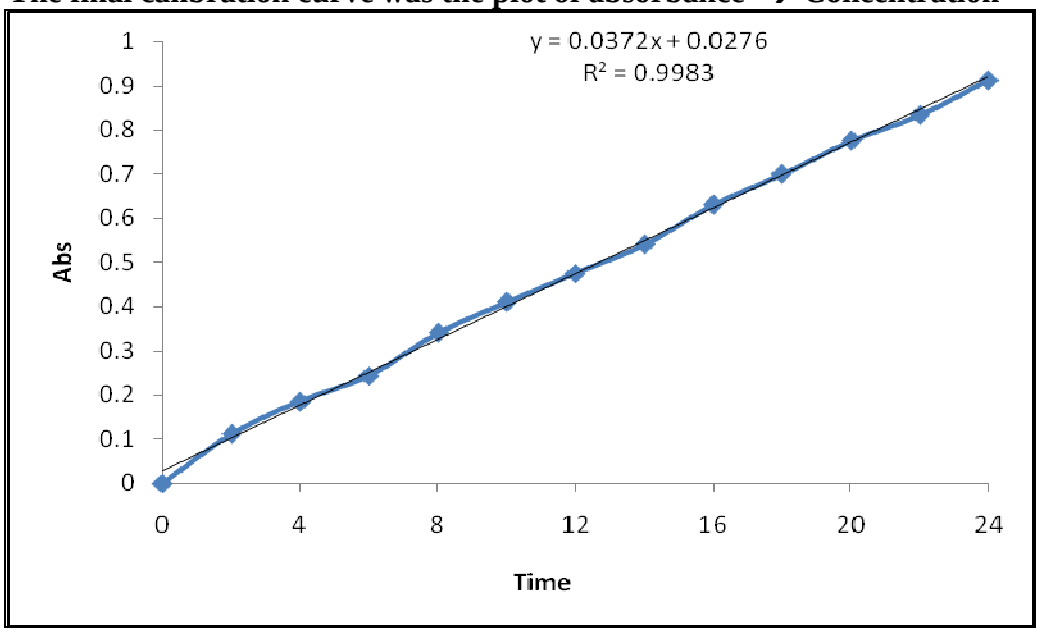
- Make different concentration ranging from 6 µg to 20µg as per dilution scheme mentioned into the figure.
- Take absorbance at 250nm in UV-Visible Spectrophotometer as follow :
- Dilution scheme for the estimation of Valsartan



Here all the dilution were made in Phosphate Buffer (pH7.4).
And Final Concentration was in (µg/ml).

Con (µg/ml)	Mean absorbance ± SD (N=3)
0	0
4	0.1845 ± 0.00050
6	0.2427 ± 0.00050
8	0.3405 ± 0.00065
10	0.4095 ± 0.0007
12	0.4753 ± 0.00070
14	0.5407 ± 0.00043
16	0.6305 ± 0.00052
18	0.7002 ± 0.00068
20	0.7757 ± 0.00115
22	0.8323 ± 0.00083
24	0.912 ± 0.00066

The final calibration curve was the plot of absorbance- → Concentration



Result

R^2	0.9983
Slope	0.0372
Intercept	0.0276

4.4 Preparation & Evaluation of Transdermal Film

4.4.1 Preparation of Transdermal Film:

In the present work transdermal film was prepared by the film casting method where, the drug was dissolved in the suitable solvent along with the polymer and plasticizer. Permeation Enhancer was added to improve the flux of the final formulation in desired amount, if needed. To cast film clear solution was allowed to evaporate in a suitable apparatus under controlled evaporation using funnel over the apparatus at room temperature until it was dried.

4.4.2 Physicochemical Evaluation:

Development of controlled release transdermal dosage form is a complex process involving extensive research. Transdermal patches have been developed to improve clinical efficacy of the drug and to enhance patient compliance by delivering smaller amount of drug at a predetermined rate. This makes evaluation studies even more important in order to ensure their desired performance and reproducibility under the specified environmental conditions. These studies are predictive of transdermal dosage forms and can be classified into following types:

- Physicochemical evaluation
- *In vitro* evaluation
- *In vivo* evaluation

Upon the success of physicochemical and *in vitro* studies, *in vivo* evaluations may be conducted.

Thickness: The thickness of transdermal film was determined by traveling microscope, dial gauge, screw gauge or micrometer at different points of the film.

Uniformity of weight: Weight variation was studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight[53].

Drug content determination: An accurately weighed portion of film (about 100 mg) was dissolved in 100 mL of suitable solvent in which drug was soluble and then the solution was shaken continuously for 24 h in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilution[48].

Moisture content: The prepared films were weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until they show a constant weight. The percent moisture content is calculated using following formula[48].

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \boldsymbol{X} 100$$

Moisture Uptake: Weighed films were kept in a desiccators at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in a desiccators until a constant weight is achieved. % moisture uptake is calculated as given below[48].

$$\% \text{ Moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \text{ X } 100$$

Flatness: A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip was cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness.

$$\% \text{ constriction} = \frac{I_1 - I_2}{I_1} \text{ X } 100 \qquad (1)$$

I_2 = Final length of each strip

I_1 = Initial length of each strip

Folding Endurance: Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until

it break. The number of times the films could be folded at the same place without breaking is folding endurance value.

Tensile Strength: To determine tensile strength, polymeric films are sandwiched separately by corked linear iron plates. One end of the films is kept fixed with the help of an iron screen and other end is connected to a freely movable thread over a pulley. The weights are added gradually to the pan attached with the hanging end of the thread. A pointer on the thread is used to measure the elongation of the film. The weight just sufficient to break the film is noted. The tensile strength can be calculated using the following equation.

$$\text{Tensile strength } (N/cm^2) = \frac{\text{force at break (kgF)} \times 980665}{\text{Area of sample } (cm^2) \times 10^5}$$

Water vapor transmission studies (WVT): For the determination of WVT, desiccators were used to place vials, in which 200 mL of saturated sodium bromide and saturated potassium chloride solution were placed. The desiccators were tightly closed and humidity inside the desiccators was measured by using hygrometer. The weighed vials were then placed in desiccators and procedure was repeated

$$WVT = W/ST \qquad (3)$$

W is the increase in weight in 24 h; S is area of film exposed (cm^2); T is exposure time

Partition coefficient of drug in octanol / water system

The partition coefficient of the drug was determined by taking equal volumes of 1-octanol and aqueous solution in a separating funnel.[8,9] In case of water-soluble drugs, a drug solution of 25 µg/mL was prepared in distilled water; and in case of water-insoluble drugs, a drug solution of 25 µg/mL was prepared in 1-octanol. Twenty-five milliliters of this solution was taken in a separating funnel and shaken with equal volume of 1-octanol/water system for 30 min and allowed to stand for 1 h. The mixture was then Centrifuged at 2000 rpm for 10 min, and concentration of drug in each phase was determined spectrophotometrically by measuring absorbance at 245 nm. The partition coefficient (Kp) was calculated from the equation.

$$\text{Partition coefficient (Kp)} = \frac{\text{Concentration of drug in organic phase}}{\text{Concentration of drug in aqueous phase}}$$

Permeability coefficient (P):

Permeability coefficient is the velocity of drug passage through the membrane in µg/cm^2/h. The permeability coefficient was calculated from the slope of the graph of percentage of drug transported versus time as,

P = slope * Vd/S

Where Vd = volume of donor solution;

S = surface area of tissue.

Flux (J): Flux is defined as the amount of material flowing through a unit cross-sectional barrier in unit time.

It is calculated by Flux (J) = P *CD

where CD = concentration of donor solution;

P = permeability.

In vitro permeation studies:

The amount of drug available for absorption to the systemic pool is greatly dependent on drug released from the polymeric transdermal films. The drug reached at skin surface is then passed to the dermal microcirculation by penetration through cells of epidermis, between the cells of epidermis through skin appendages.

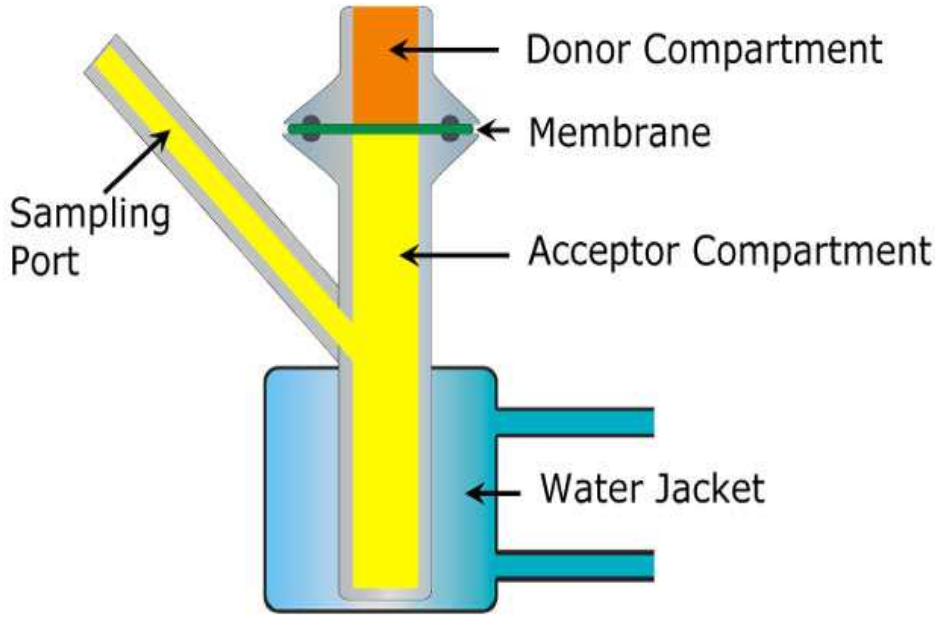


Fig: 6 Diffusion Cell

Usually permeation studies are performed by placing the fabricated transdermal patch with rat skin or synthetic membrane in between receptor and donor compartment in a vertical diffusion cell such as franz diffusion cell or keshary-chien diffusion cell. The transdermal system is applied to the hydrophilic side of the membrane and then mounted in the diffusion cell with lipophillic side in contact with receptor fluid. The receiver compartment is maintained at specific temperature (usually 32±5°C for skin) and is continuously stirred at a constant rate. The samples are withdrawn at different time intervals and equal amount of buffer is replaced each time. The samples are diluted appropriately and absorbance is determined spectrophotometrically. Then the amount of drug permeated per centimeter square at each time interval is calculated. Design of system, patch size, surface area of skin, thickness of skin and temperature etc. are some variables that may affect the release of drug.

In vitro release studies:

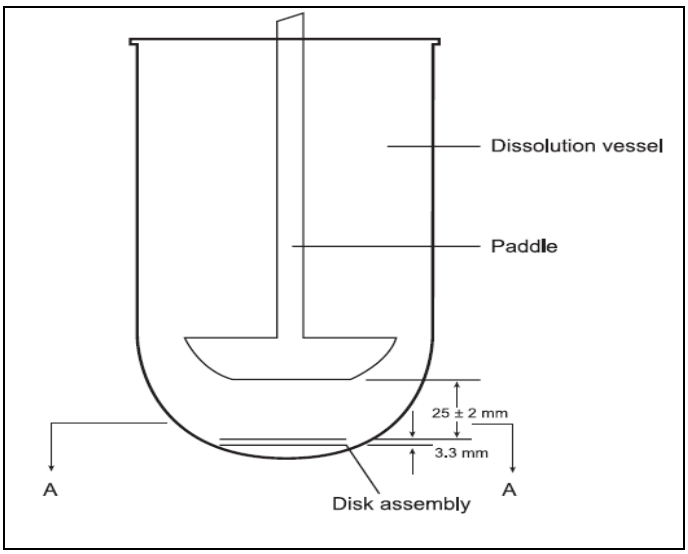


Fig: 7 Dissolution Apparatus

TDS are marketed in varying strengths, sizes, and shapes and contain significantly different amounts of drug for a given rate of drug delivery. TDS contain much larger amounts of drug than the amount of drug to be delivered in the body. The amount of drug varies several folds among different brands for the same amount of drug delivery (e.g., nitroglycerin patches). Several methods are described in the US Pharmacopoeia for in vitro drug release of TDS. However, some of the methods are complicated, cumbersome, and nonuniversal. The FDA has developed a simple, reproducible method of determining that in vitro release profile of a TDS. The method employs a "Watchglass-patch-teflon mesh" sandwich assembly and the paddle method. The US Pharmacopoeia has now adopted this procedure, which is referred as the paddle over disk method (Apparatus 5). The method is applicable to all brands, shapes, and strengths of all marketed TDS, and is also useful for product stability indications. According to specify in USP, three dissolution apparatuses can be used for TDDS drug release testing is:

Apparatus 5 (paddle over disk)

Apparatus 6 (cylinder)

Apparatus 7 (reciprocating cylinder)

4.5 Preliminary Trials

For the Formulation of effective transdermal film for the delivery of valsartan placebo films were prepared and studied first for flexibility, clarity, elasticity, tensile strength and ease of the removal from the molds. Here, films were prepared by film casting method using various polymers like HPMC, PVA, Eudragit RL100 and Eudragit RS 100.

HPMC in the concentration up to 4% was found to be insufficient to produce a transdermal Film using water as a solvent, but when methanol was used as a solvent, HPMC 4% concentration found to be sufficient to produce film. So practically HPMC in the concentration up to 4% found to be sufficient to produce a transdermal Film using methanol as a solvent. Ethyl cellulose in the concentration of 4% was tried but ethyl cellulose alone failed to produce a film with desired tensile strength and flexibility. As well as DBP was used as a plasticizer 30% to be taken for transdermal film but the at the end of drying process the film was not cast from the petridish so it could not be used for the process. So DBP was not to be used.

For the different type of polymers ratio like HPMC : Eudragit RL 100(4:1, 3:2, 2:3, 1:4) and HPMC : Eudragit RS 100 (4:1, 3:2, 2:3, 1:4) to be taken, and methanol as a solvent to be taken. Here HPMC : ERL100 (3:2) HPMC : ERS 100 (2:3) was the effective ratio for preparing transdermal film.

So in the preparation of HPMC (4%) ,methanol was used as a solvent and plasticizers like Propylene glycol and PEG-400 were employed while transdermal film containing ratio of HPMC:ERL100 and HPMC:ERS100 and methanol as a solvent, the permeation enhancers like DMSO, Tween 80 and IPM.

4.5.1 : Formulation of placebo Films using various polymers/ Plasticizers

Polymer / Plasticizer		Methanol as a Solvent		
		HPMC		
		3%	4%	5%
PG	20%	GH_{23}	GH_{24}	GH_{25}
	30%	GH_{33}	GH_{34}	GH_{35}
	40%	GH_{43}	GH_{44}	GH_{45}
PEG-400	20%	PH_{23}	PH_{24}	PH_{25}
	30%	PH_{33}	PH_{34}	PH_{35}
	40%	PH_{43}	PH_{44}	PH_{45}
DBP	20%	DH_{23}	DH_{24}	DH_{25}
	30%	DH_{33}	DH_{34}	DH_{35}
	40%	DH_{43}	DH_{44}	DH_{45}

4.5.2: Formulation of placebo Films using various Polymers / Plasticizers

Polymer / Plasticizer		Methanol as a Solvent							
		HPMC : ERL100				HPMC : ERS 100			
		4 : 1	3:2	2:3	1:4	4 : 1	3:2	2:3	1:4
PG	20%	GHL_{241}	GHL_{232}	GHL_{223}	GHL_{214}	GHS_{241}	GHS_{232}	GHS_{223}	GHS_{214}
	30%	GHL_{341}	GHL_{332}	GHL_{323}	GHL_{314}	GHS_{341}	GHS_{332}	GHS_{323}	GHS_{314}
	40%	GHL_{441}	GHL_{432}	GHL_{423}	GHL_{414}	GHS_{441}	GHS_{432}	GHS_{423}	GHS_{414}
PEG -400	20%	PHL_{241}	PHL_{232}	PHL_{223}	PHL_{214}	PHS_{241}	PHS_{232}	PHS_{223}	PHS_{214}
	30%	PHL_{341}	PHL_{332}	PHL_{323}	PHL_{314}	PHS_{341}	PHS_{332}	PHS_{323}	PHS_{314}
	40%	PHL_{441}	PHL_{432}	PHL_{423}	PHL_{414}	PHS_{441}	PHS_{432}	PHS_{423}	PHS_{414}

Evaluation

The transdermal films were evaluated for their tensile strength, elongation & folding Endurance.

4.5.3 : HPMC films with Propylene Glycol as Plasticizer,

BATCH	Tensile Strength ($N/cm^{2)}$	% Elongation	Folding Endurance
GH_{23}	0.432	86	87
GH_{33}	0.356	76	98
GH_{43}	0.321	20	97
GH_{24}	0.234	13	69
GH_{34}	0.654	38	68
GH_{44}	0.121	28	65
GH_{25}	0.287	22	112
GH_{35}	0.2	4	132
GH_{45}	0.355	15	105

4.5.4 : HPMC films with PEG-400 as Plasticizer,

BATCH	Tensile Strength (N/cm^2)	% Elongation	Folding Endurance
PH_{23}	0.234	52	112
PH_{33}	0.434	25	102
PH_{43}	0.441	86	120
PH_{24}	0.555	25	33
PH_{34}	0.865	21	143
PH_{44}	0.298	65	26
PH_{25}	0.143	3	98
PH_{35}	0.332	12	79
PH_{45}	0.109	43	83

4.5.5: HPMC - ERL100 with Propylene Glycol as Plasticizer,

BATCH	Tensile Strength (N/cm^2)	% Elongation	Folding Endurance
DHL_{241}	0.111	15	102
DHL_{341}	0.234	32	145
DHL_{441}	0.273	11	100
DHL_{232}	0.298	65	112
DHL_{332}	0.773	44	121
DHL_{432}	0.332	38	79
DHL_{223}	0.109	76	145
DHL_{323}	0.143	55	109
DHL_{423}	0.556	88	121
DHL_{214}	0.433	6	143
DHL_{314}	0.254	45	102
DHL_{414}	0.199	30	111

4.5.6: HPMC - ERL100 with PEG-400 as Plasticizer,

BATCH	Tensile Strength N/cm^2	% Elongation	Folding Endurance
PHL_{241}	0.432	15	121
PHL_{341}	0.109	32	104
PHL_{441}	0.654	11	99
PHL_{232}	0.234	65	132
PHL_{332}	0.766	22	145
PHL_{432}	0.111	31	100
PHL_{223}	0.341	5	96
PHL_{323}	0.178	66	92
PHL_{423}	0.323	86	58
PHL_{214}	0.286	34	112
PHL_{314}	0.132	12	98
PHL_{414}	0.188	73	109

4.5.7: HPMC - ERS100 with Propylene Glycol as Plasticizer,

BATCH	Tensile Strength (N/cm^2)	% Elongation	Folding Endurance
DHS_{241}	0.213	21	108
DHS_{341}	0.122	55	118
DHS_{441}	0.232	3	131
DHS_{232}	0.265	77	45
DHS_{332}	0.198	65	28
DHS_{432}	0.322	44	53
DHS_{223}	0.123	8	76
DHS_{323}	0.732	27	58
DHS_{423}	0.321	51	97
DHS_{214}	0.111	3	121
DHS_{314}	0.341	19	103
DHS_{414}	0.421	27	110

4.5.8: HPMC - ERS100 with PEG-400 as Plasticizer,

BATCH	Tensile Strength N/cm^2	% Elongation	Folding Endurance
PPS_{241}	0.411	86	121
PPS_{341}	0.323	38	100
PPS_{441}	0.343	20	106
PPS_{232}	0.165	13	33
PPS_{332}	0.132	52	65
PPS_{432}	0.236	28	76
PPS_{223}	0.376	22	91
PPS_{323}	0.657	4	86
PPS_{423}	0.181	15	78
PPS_{214}	0.209	22	108
PPS_{314}	0.36	42	118
PPS_{414}	0.229	10	131

The result of tensile strength shown in table 4.5.3 to 4.5.8 is represented graphically as under.

Fig 4.5.3 Tensile strength Vs HPMC –Propylene glycol film

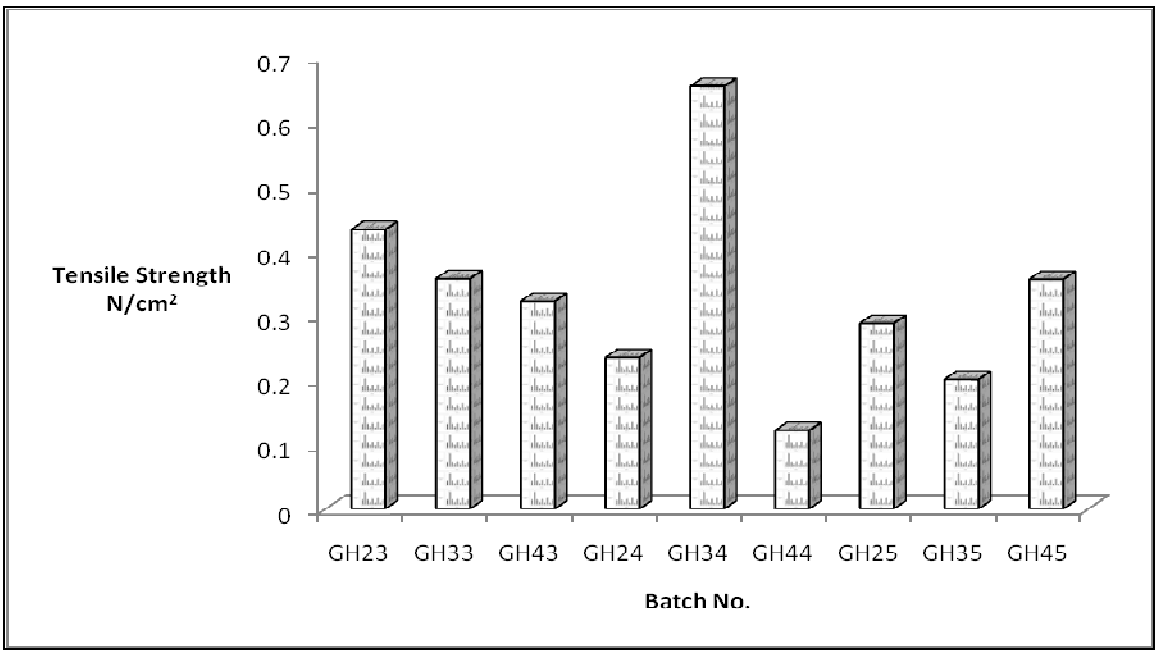


Fig 4.5.4 tensile strength Vs HPMC PEG-400 Film

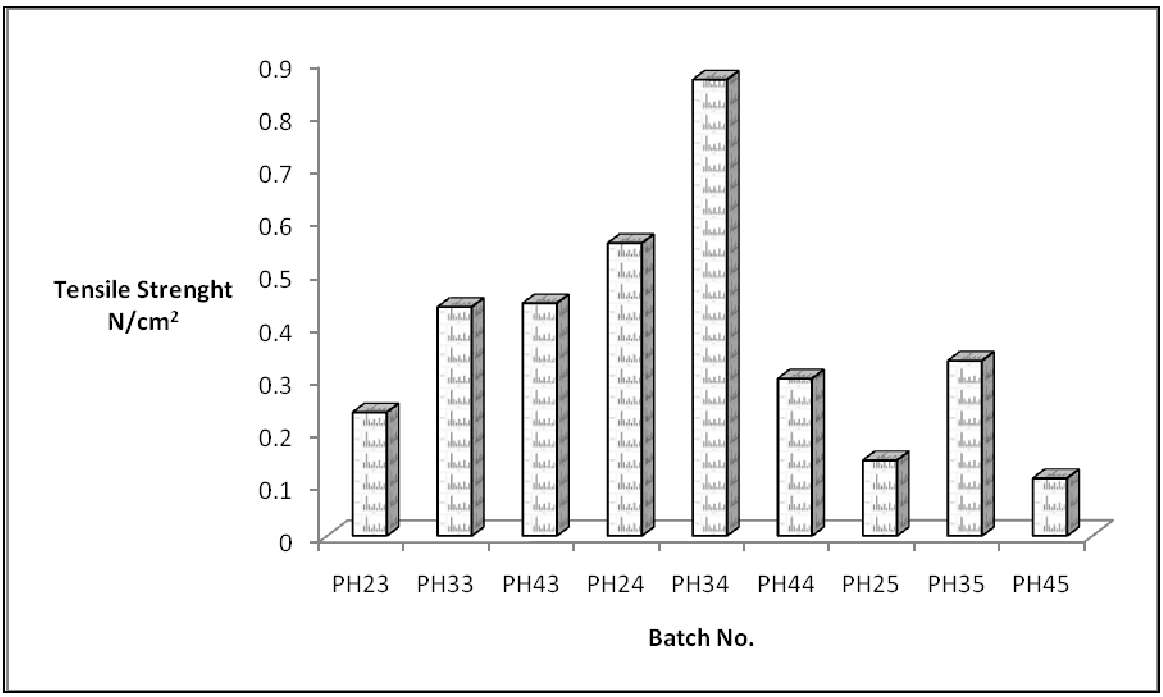


Fig 4.5.5 Tensile strength Vs HPMC-ERL 100 – Propylene Glycol Films

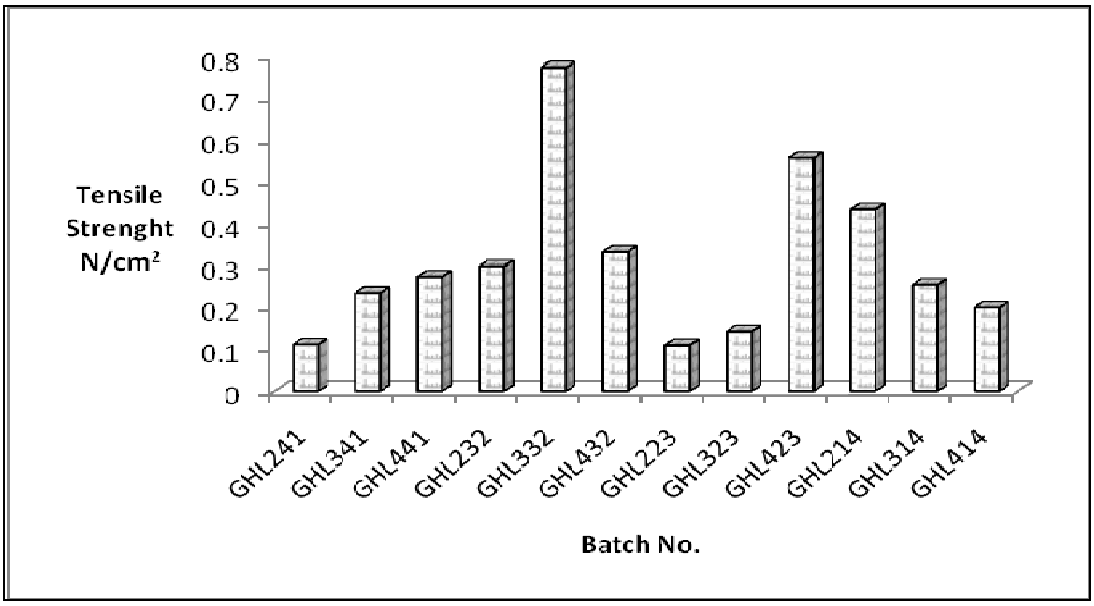


Fig 4.5.6 Tensile strength Vs HPMC-ERL 100-PEG-400 Films

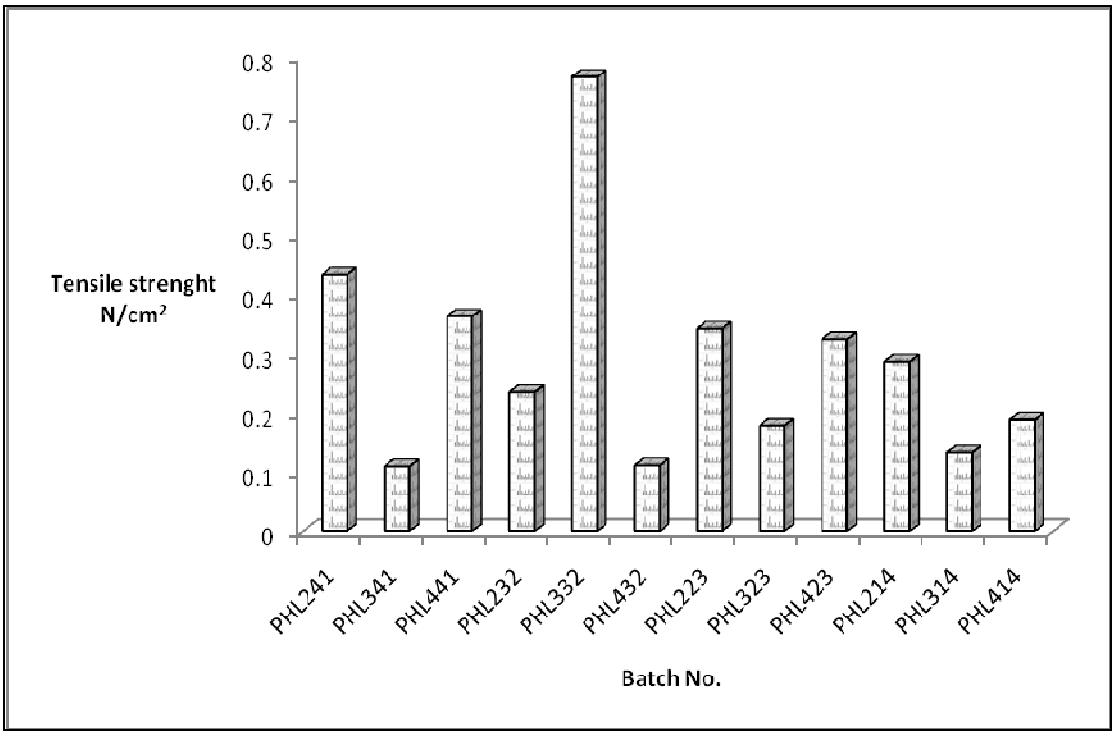


Fig 4.5.7 Tensile strength Vs HPMC-ERS 100 - Propylene Glycol Films

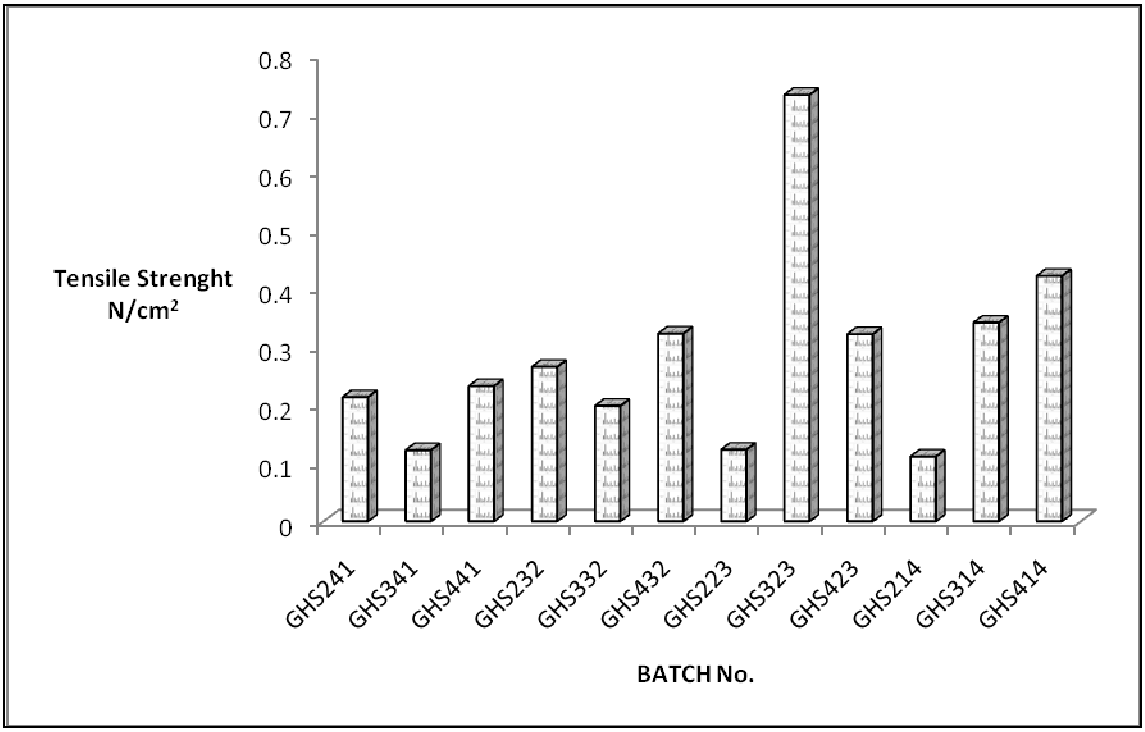
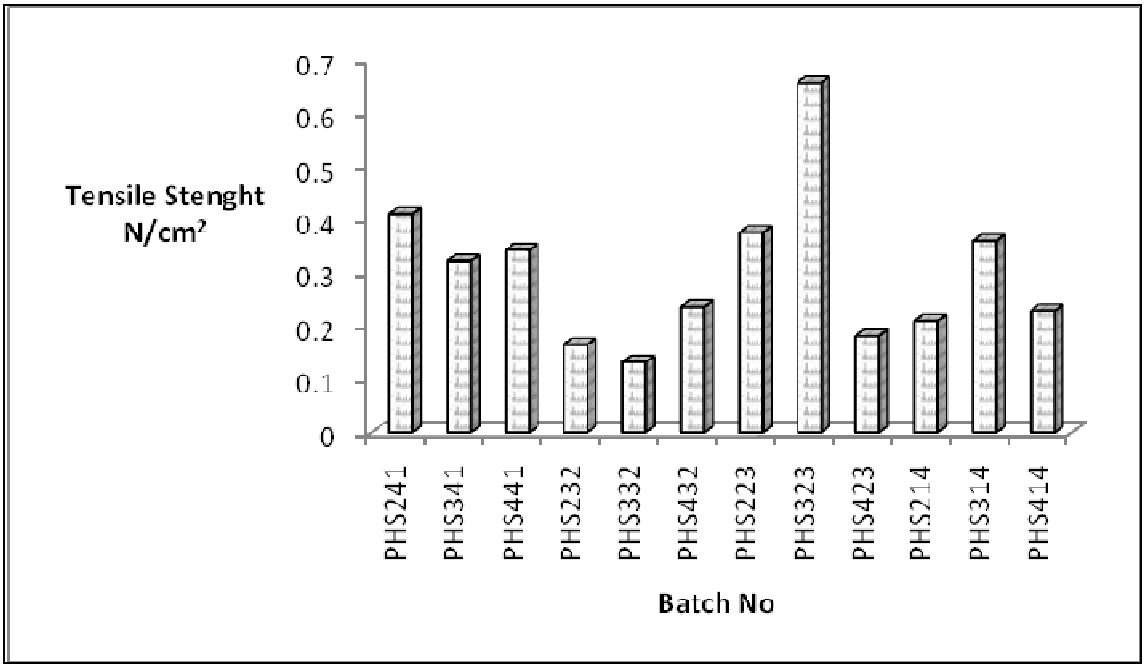


Fig 4.5.8 Tensile strength Vs HPMC-ERS 100 – PEG 400 Films



Result and Discussion

The graph presenting the tensile strenght of the various placebo films formulated is shown in figur 4.5.3 to 4.4.8. Study shown that HPMC using methanol as a solvent, in the concentration of 4% of polymer with the 30 % plasticizer (PG or PEG-400) is needed to formulate a film with desired flexibility and optimum tensile strenght. The DBP used as a plasticizer is not work properly in to the casting process. So DBP was not used for the preparation of film.

The ratio of HPMC and Eudragit RL 100 produced transdermal film at 3:2 ratio along with 30% plasticizer (PEG 400 or PG) with methanol as a solvent. And the ratio of HPMC and Eudragit RS 100 produced transdermal film at 2:3 ratio along with 30 % plasticizer (PEG 400 or PG) with methanol as a solvent. This may be due to the low boiling point of the solvent and good solubility of the polymer in the vehicle.

Thus batches shows the optimum results GH_{34}, PH_{34}, GHL_{332},PHL_{332},GHS_{323} and PHS_{323}, showed promising results and thus utilized further developing films of valsartan.

5. Formulation of transdermal films of valsartan

5.1 HPMC Films containing PEG-400 as a plasticizer

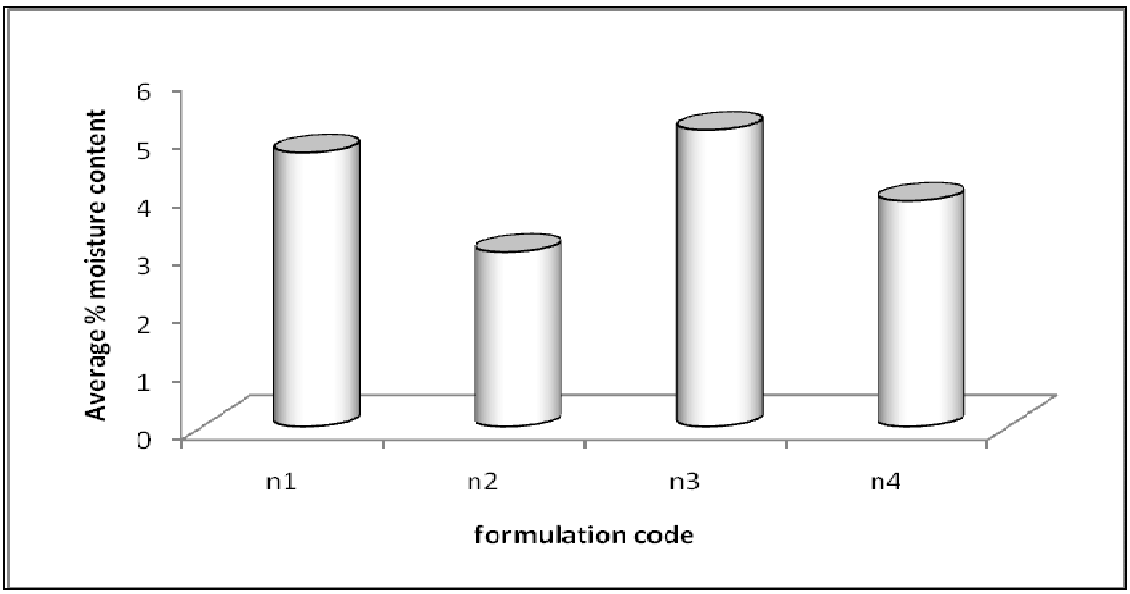
Ingredients	N1	N2	N3	N4
VALSARTAN	30mg/16cm^2	30mg/16cm^2	30mg/16cm^2	30mg/16cm^2
HPMC	4%	4%	4%	4%
PEG-400	30% w/w	30% w/w	30% w/w	30% w/w
DMSO	------	0.5%	------	------
TWEEN-80	-------	-----	0.5%	-----
IPM	-----	-----	-----	0.5%
METHANOL	q.s to 20ml	q.s to 20ml	q.s to 20ml	q.s to 20ml

5.1.1 Evaluation parameters

Batch	Tensile Strength (N/Cm^2)	% Elongation	Folding Endurance	Elastic Modulus (N/cm^2)	Strain	Thickness (mm)
N1	1.732 ± 0.12	11.78±1.12	89 ± 3	2.887±0.109	0.59±0.021	0.19±0.02
N2	1.798 ± 0.23	11.11±2.23	124 ± 5	1.997±0.213	0.9±0.013	0.23±0.01
N3	1.823 ± 0.14	12.45±0.27	117 ± 8	2.277±0.321	0.8±0.015	0.22±0.012
N4	1.773 ± 0.21	11.44±1.43	104 ± 7	2.216±0.172	0.8±0.024	0.25±0.021

Batch	Drug Content (mg)	Wt (mg)	WVP	% MU	%MC
N1	29.66±0.22	101	2.01	3±1.2	4.71±1.6
N2	30.02± 0.31	97	1.88	2.04±2.3	3±1.7
N3	30.11±0.42	93	1.97	5.37±1.5	5.10±2.2
N4	29.41±0.5	99	2.13	1.98±1.3	3.88±1.9

Figure 5.1 % Moisture content



5.1.2 In vitro drug permeation study of batch N1

Time (hr)	Abs	Dilution factor	Con µg/ml	Con mg/ml	%Drug permeated
0	0	0	0	0	0
1	0.1278	1	2.78	0.08	1.54
2	0.3219	1	7.95	0.24	4.40
3	0.4355	1	11.02	0.33	6.10
4	0.5578	1	14.33	0.43	7.93
5	0.6284	1	16.24	0.49	8.99
6	0.7649	1	19.93	0.60	11.03
24	0.2876	20	140.64	4.22	49.78

5.1.3 In vitro drug permeation study of batch N2

Time (hr)	Abs	Dilution factor	Con µg/ml	Con mg/ml	%Drug permeated
0	0	0	0	0	0
1	0.2321	1	5.56	0.17	3.08
2	0.3477	1	8.65	0.26	4.79
3	0.3923	1	9.86	0.30	5.46
4	0.4533	1	11.51	0.35	6.37
5	0.5238	1	13.41	0.40	7.42
6	0.6538	1	16.92	0.51	9.37
24	0.3576	20	177.87	5.34	62.96

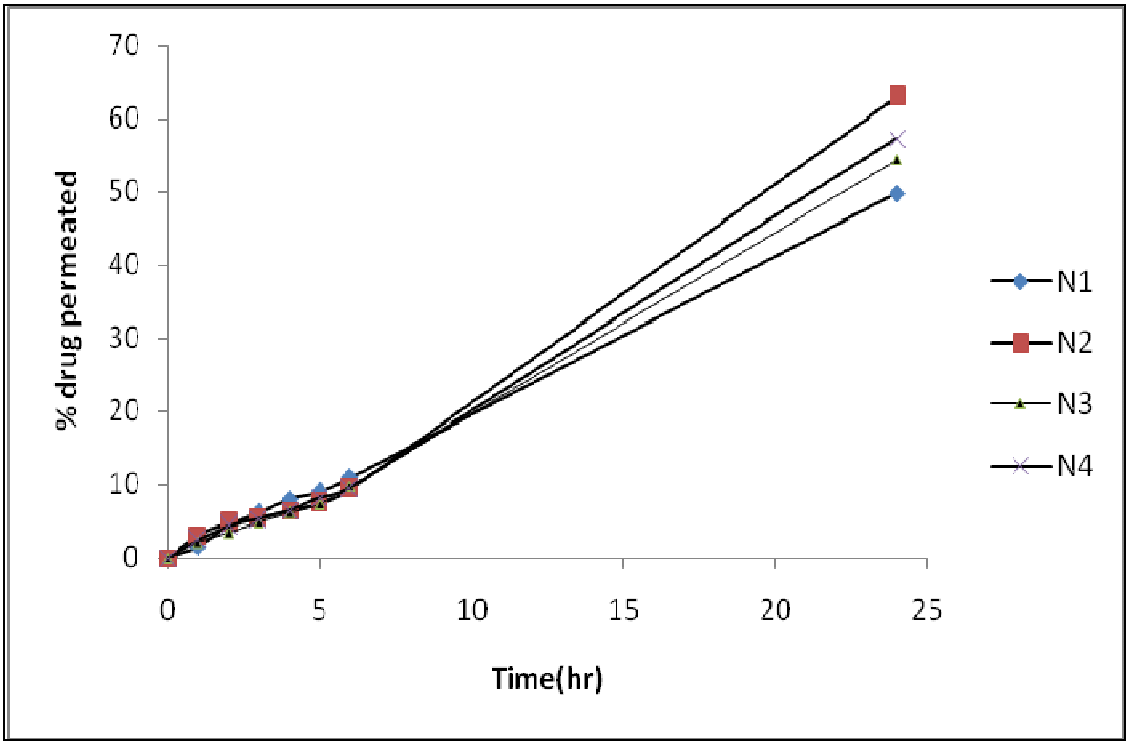
5.1.4 In vitro drug permeation study of batch N3

Time (hr)	Abs	Dilution factor	Con µg/ml	Con mg/ml	%Drug permeated
0	0	0	0	0	0
1	0.1643	1	3.75	0.11	2.08
2	0.2546	1	6.14	0.18	3.40
3	0.3465	1	8.62	0.26	4.77
4	0.4326	1	10.95	0.33	6.06
5	0.5176	1	13.24	0.40	7.33
6	0.6755	1	17.51	0.53	9.69
24	0.3124	20	153.83	4.61	54.45

5.1.5 In vitro drug permeation study of batch N4

Time (hr)	Abs	Dilution factor	Con µg/ml	Con mg/ml	%Drug permeated
0	0	0	0	0	0
1	0.1987	1	4.67	0.14	2.58
2	0.3128	1	7.71	0.23	4.27
3	0.3792	1	9.50	0.29	5.26
4	0.4534	1	11.51	0.35	6.37
5	0.5765	1	14.84	0.45	8.21
6	0.6658	1	17.25	0.52	9.55
24	0.3278	20	162.02	4.86	57.35

Figure 5.1' In vitro drug permeation study of batch N1 to N4



5.1.6 In vitro drug dissolution study of batch N1

Time (hr)	Abs	Con(µg/ml) after dilution	Con(µg/ml) before dilution	Con (mg/500ml)	Error	Cumulative (mg/500ml)	CPR
0	0	0	0	0	0	0	0
15	0.1544	3.255	16.277	8.138	0	8.138	27.13
30	0.2134	4.824	24.122	12.061	0.033	12.094	40.31
45	0.2754	6.473	32.367	16.184	0.081	16.264	54.21
60	0.3455	8.338	41.689	20.844	0.146	20.990	69.97
90	0.3909	9.545	47.726	23.863	0.229	24.092	80.31
120	0.4355	10.731	53.657	26.828	0.324	27.153	90.51
150	0.4677	11.588	57.939	28.969	0.432	29.401	98.00
180	0.4713	11.684	58.418	29.209	0.548	29.756	99.19
Dilution Factor - 5							

5.1.7 In vitro drug dissolution study of batch N2

Time (hr)	Abs	Con(µg/ml) after dilution	Con(µg/ml) before dilution	Con (mg/500ml)	Error	Cumulative (mg/500ml)	CPR
0	0	0	0	0	0	0	0
15	0.1872	4.128	20.638	10.319	0	10.319	34.40
30	0.2483	5.753	28.763	14.382	0.041	14.423	48.08
45	0.3262	7.824	39.122	19.561	0.099	19.660	65.53
60	0.3812	9.287	46.436	23.218	0.177	23.395	77.98
90	0.4316	10.628	53.138	26.569	0.270	26.839	89.46
120	0.4733	11.737	58.684	29.342	0.376	29.718	99.06
150	0.4758	11.803	59.016	29.508	0.494	30.002	100.01
180	0.4788	11.883	59.415	29.707	0.612	30.319	101.06
Dilution Factor - 5							

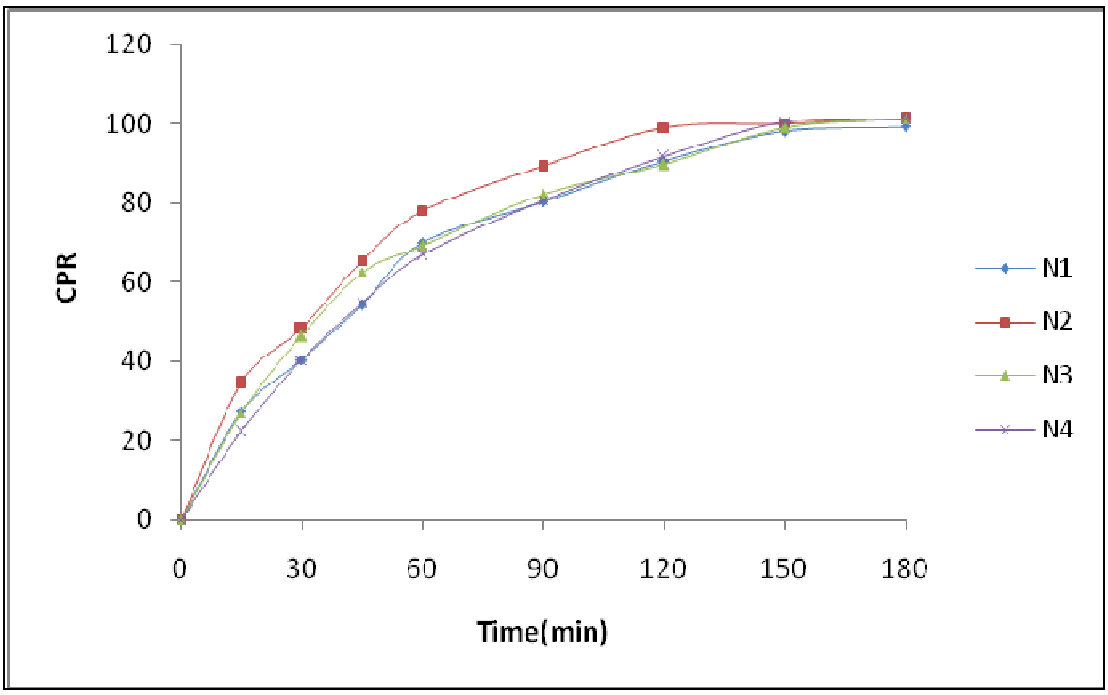
5.1.8 In vitro drug dissolution study of batch N3

Time (hr)	Abs	Con(µg/ml) after dilution	Con(µg/ml) before dilution	Con (mg/500ml)	Error	Cumulative (mg/500ml)	CPR
0	0	0	0	0	0	0	0
15	0.1541	3.247	16.237	8.118	0	8.118	27.06
30	0.2399	5.529	27.646	13.823	0.032	13.856	46.19
45	0.3125	7.460	37.301	18.650	0.088	18.738	62.46
60	0.3411	8.221	41.104	20.552	0.162	20.714	69.05
90	0.3987	9.753	48.763	24.382	0.245	24.626	82.09
120	0.4312	10.617	53.085	26.543	0.342	26.885	89.62
150	0.4723	11.710	58.551	29.275	0.448	29.724	99.08
180	0.4802	11.920	59.601	29.801	0.565	30.366	101.22
Dilution Factor - 5							

5.1.9 In vitro drug dissolution study of batch N4

Time (hr)	Abs	Con(µg/ml) after dilution	Con(µg/ml) before dilution	Con (mg/500ml)	Error	Cumulative (mg/500ml)	CPR
0	0	0	0	0	0	0	0
15	0.1321	2.662	13.311	6.656	0	6.656	22.19
30	0.2133	4.822	24.109	12.055	0.027	12.081	40.27
45	0.2783	6.551	32.753	16.376	0.075	16.451	54.84
60	0.3312	7.957	39.787	19.894	0.140	20.034	66.78
90	0.3921	9.577	47.886	23.943	0.220	24.163	80.54
120	0.4402	10.856	54.282	27.141	0.316	27.457	91.52
150	0.4788	11.883	59.415	29.707	0.424	30.132	100.44
180	0.4798	11.910	59.548	29.774	0.543	30.317	101.06
Dilution Factor - 5							

Figure 5.1" In vitro drug dissolution study N1 to N4



Result & Discussion:

Batches N1 to N4 were evaluated for the physical characterization. The prepared films were subjected to folding endurance, thickness, % elongation; Tensile Strength, WVT, % Moisture Uptake, % Moisture Content, wt variation, Drug Content, Strain, Elastic Modulus, In-vitro drug dissolution study and In-vitro drug permeation study are shown in table.

Here, HPMC films containing PEG-400 as a plasticizer and different type of penetration enhancers to be used like DMSO (Di methyl Sulfoxide), Tween-80 and IPM (Iso Propyl Myristate).HPMC films were thin, flexible, smooth & transparent. The method adopted was film casting method. The films have satisfactory results in thickness and wt variation. The Drug Content indicating that effective drug loading into the films. Folding endurance measured the ability of film to withstand rupture. It can be measures manually & result indicated that the films would not break and would maintain their integrity with general skin folding when used. Tensile Strength results indicate the Strength of films & the risk of film cracking, but no sign of cracking in prepared transdermal film was observed which might be attributed to the addition of plasticizer, PEG-400. Here Moisture uptake was found to increase concentration of hydrophilic polymer like HPMC. M.U of films was also low which could protect the formulations from microbial contamination & reduce bulkiness of films. Moisture Content was also low which provide the information regarding stability of the formulation & reduce brittleness during long storage. WVT study indicated that HPMC films were more permeated to water vapour.

The results of In vitro drug release are the most important parameter for the transdermal film. It can be shown that how much drug will behave in-vivo. The results of in-vitro skin permeation studies of transdermal films of valsartan using hairless rat abdomen skin as a skin membrane using Franz diffusion cell containing HPMC and PEG-400 as a film forming components are shown in figure. Cumulative amount of drug release from the formulations N1, N2, N3, and N4 batches, Here N1 batch have no permeation enhancer as compare to other three batches. So it shows that permeation enhancer was required to obtain desired permeation. The amount of drug permeated from formulation batch N2 was higher as compare to N3 and N4 batch. Here Tween-80 and IPM are less efficient than the DMSO as a Permeation enhancer.

So here, N2 batch is the best batch because Dimethyl sulfoxide is a highly polar substance that is aprotic, therefore lacking acidic and basic properties. It has exceptional solvent properties for both organic and inorganic components, which are derived from its capacity to associate with both ionic species and neutral molecules that are either polar or polarisable. The dissolution profile of films is shown in the figure. The dissolution profile were shown that all the batches effectively release almost all the drug content so that dissolution is not the rate limiting step for the drug permeation into the systemic circulation. Here dissolution of all the batches was shown nearer about 100% dissolution of the films.

5.2 HPMC Films containing Propylene Glycol as a plasticizer

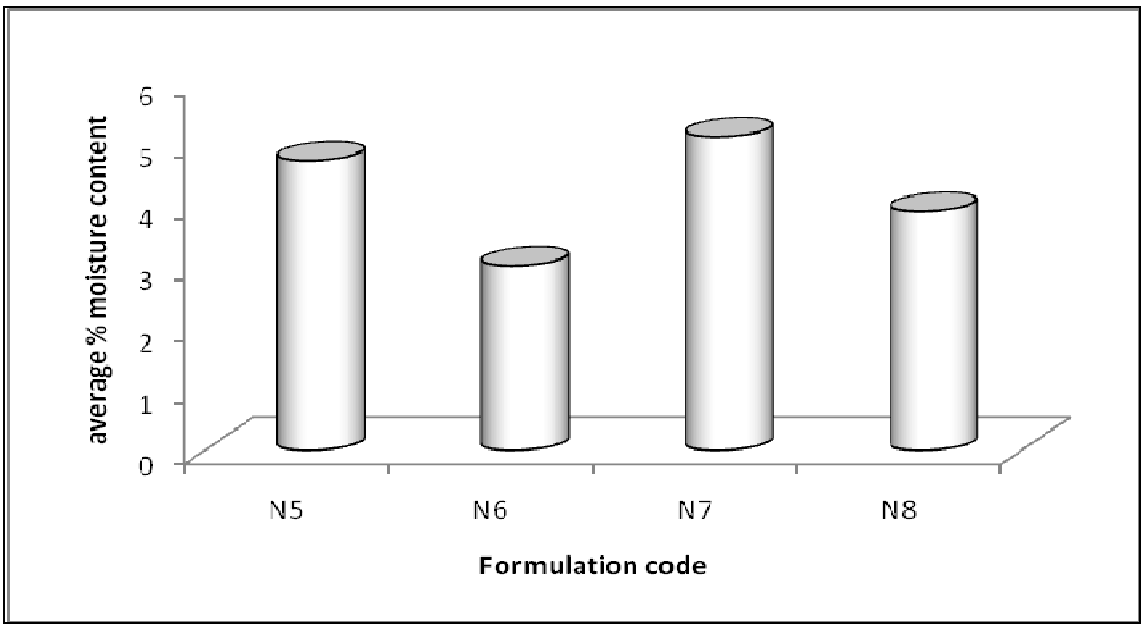
Ingredients	N5	N6	N7	N8
VALSARTAN	30mg/16cm^2	30mg/16cm^2	30mg/16cm^2	30mg/16cm^2
HPMC (4%)	4%	4%	4%	4%
PG	30% w/w	30% w/w	30% w/w	30% w/w
DMSO	------	0.5%	------	------
TWEEN-80	------	-----	0.5%	-----
IPM	-----	-----	-----	0.5%
METHANOL	q.s to 20ml	q.s to 20ml	q.s to 20ml	q.s to 20ml

5.2.1 Evaluation parameters

Batch	Tensile Strength (N/Cm^2)	% Elongation	Folding Endurance	Elastic Modulus (N/cm^2)	Strain	Thickness (mm)
N5	1.532 ± 0.31	13.13 ± 1.32	96 ± 4	1.709±0.121	0.89±0.011	0.20±0.021
N6	1.527 ± 0.2	13.80 ± 1.22	111 ± 5	1.913±0.213	0.79±0.042	0.25±0.01
N7	1.586 ± 0.3	14.47 ± 0.32	132 ± 8	1.324±0.342	1.19±0.024	0.19±0.024
N8	1.502 ± 0.25	12.79 ± 2.34	102 ± 6	1.678±0.276	0.88±0.015	0.23±0.015

Batch	Drug Content (mg)	Wt (mg)	WVP	% MU	%MC
N5	31.11±0.32	88	1.79	4.39±1.3	7.36±2.3
N6	29.79± 0.15	93	1.83	6.45±1.5	6.06±1.5
N7	30.07±0.52	94	1.81	6.31±1.4	6.93±1.8
N8	29.89± 0.47	91	1.97	3.26±2.1	4.21±1.1

Figure 5.2 % Moisture Content



5.2.2 In vitro drug permeation study of batch N5

Time (hr)	Abs	Dilution factor	Con µg/ml	Con mg/ml	%Drug permeated
0	0	0	0	0	0
1	0.1437	1	3.20	0.10	1.77
2	0.2587	1	6.25	0.19	3.46
3	0.3423	1	8.51	0.26	4.71
4	0.4189	1	10.58	0.32	5.85
5	0.4988	1	12.74	0.38	7.05
6	0.6538	1	16.92	0.51	9.37
24	0.2897	20	141.76	4.25	50.18

5.2.3 In vitro drug permeation study of batch N6

Time (hr)	Abs	Dilution factor	Con µg/ml	Con mg/ml	%Drug permeated
0	0	0	0	0	0
1	0.1787	1	4.14	0.12	2.29
2	0.2674	1	6.48	0.19	3.59
3	0.3421	1	8.50	0.26	4.70
4	0.4653	1	11.83	0.35	6.55
5	0.5367	1	13.76	0.41	7.62
6	0.6578	1	17.03	0.51	9.43
24	0.3723	20	185.69	5.57	65.73

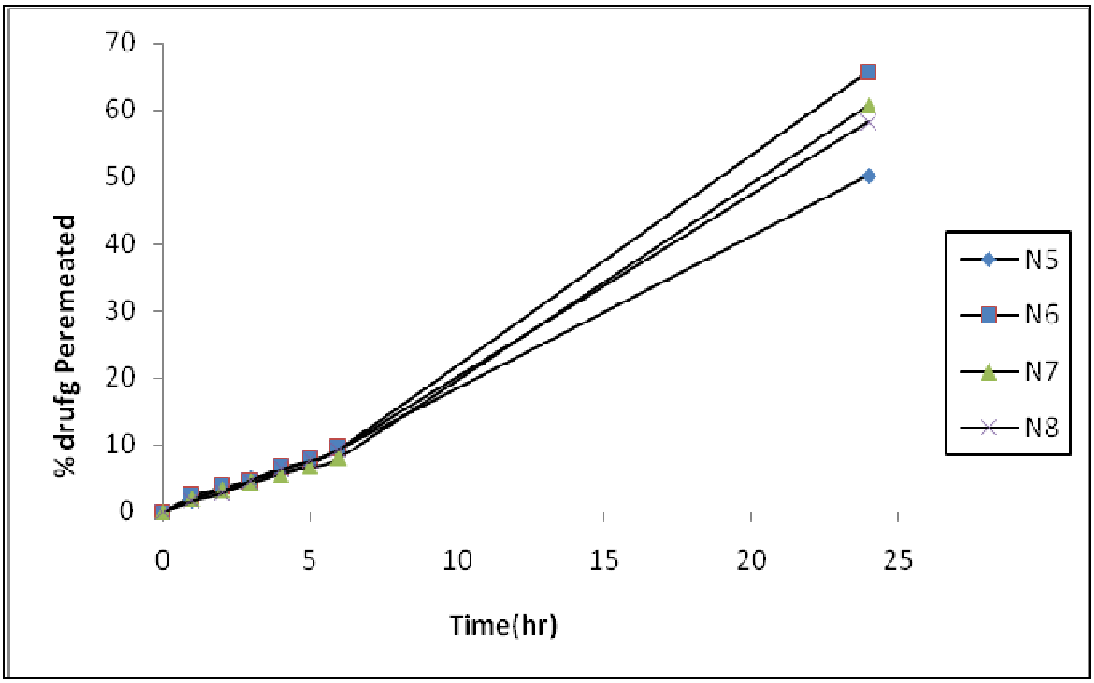
5.2.4 In vitro drug permeation study of batch N7

Time (hr)	abs	dilution factor	Con µg/ml	Con mg/ml	%drug permeated
0	0	0	0	0	0
1	0.1534	1	3.46	0.10	1.92
2	0.2437	1	5.84	0.18	3.23
3	0.3178	1	7.84	0.24	4.34
4	0.3987	1	10.03	0.30	5.55
5	0.4765	1	12.13	0.36	6.72
6	0.5654	1	14.54	0.44	8.05
24	0.345	20	171.17	5.14	60.59

5.2.5 In vitro drug permeation study of batch N8

Time (hr)	Abs	Dilution factor	Con µg/ml	Con mg/ml	%Drug permeated
0	0	0	0	0	0
1	0.1389	1	3.08	0.09	1.70
2	0.2134	1	5.02	0.15	2.78
3	0.3421	1	8.50	0.26	4.70
4	0.4476	1	11.35	0.34	6.28
5	0.5378	1	13.79	0.41	7.63
6	0.6479	1	16.76	0.50	9.28
24	0.3321	20	164.31	4.93	58.16

Figure 5.2 In vitro drug permeation study of batch N5 to N8



5.2.6 In vitro drug dissolution study of batch N5

Time (min)	Abs	Con(µg/ml) after dilution	Con(µg/ml) before dilution	Con (mg/500ml)	Error	Cumulative (mg/500ml)	CPR
0	0	0	0	0	0	0	0
15	0.1522	3.197	15.984	7.992	0	7.992	26.64
30	0.2241	5.109	25.545	12.773	0.032	12.805	42.68
45	0.2943	6.976	34.880	17.440	0.083	17.523	58.41
60	0.3519	8.508	42.540	21.270	0.153	21.423	71.41
90	0.3921	9.577	47.886	23.943	0.238	24.181	80.60
120	0.4288	10.553	52.766	26.383	0.334	26.717	89.06
150	0.4766	11.824	59.122	29.561	0.439	30.000	100.00
180	0.4803	11.923	59.614	29.807	0.557	30.365	101.22
Dilution Factor - 5							

5.2.7 In vitro drug dissolution study of batch N6

Time (min)	Abs	Con(µg/ml) after dilution	Con(µg/ml) before dilution	Con (mg/500ml)	Error	Cumulative (mg/500ml)	CPR
0	0	0	0	0	0	0	0
15	0.1323	2.668	13.338	6.669	0	6.669	22.23
30	0.1936	4.298	21.489	10.745	0.027	10.771	35.90
45	0.2436	5.628	28.138	14.069	0.070	14.139	47.13
60	0.2941	6.971	34.854	17.427	0.126	17.553	58.51
90	0.3655	8.870	44.348	22.174	0.196	22.370	74.57
120	0.4289	10.556	52.779	26.390	0.284	26.674	88.91
150	0.4812	11.947	59.734	29.867	0.390	30.257	100.86
180	0.4825	11.981	59.907	29.953	0.509	30.463	101.54
Dilution Factor - 5							

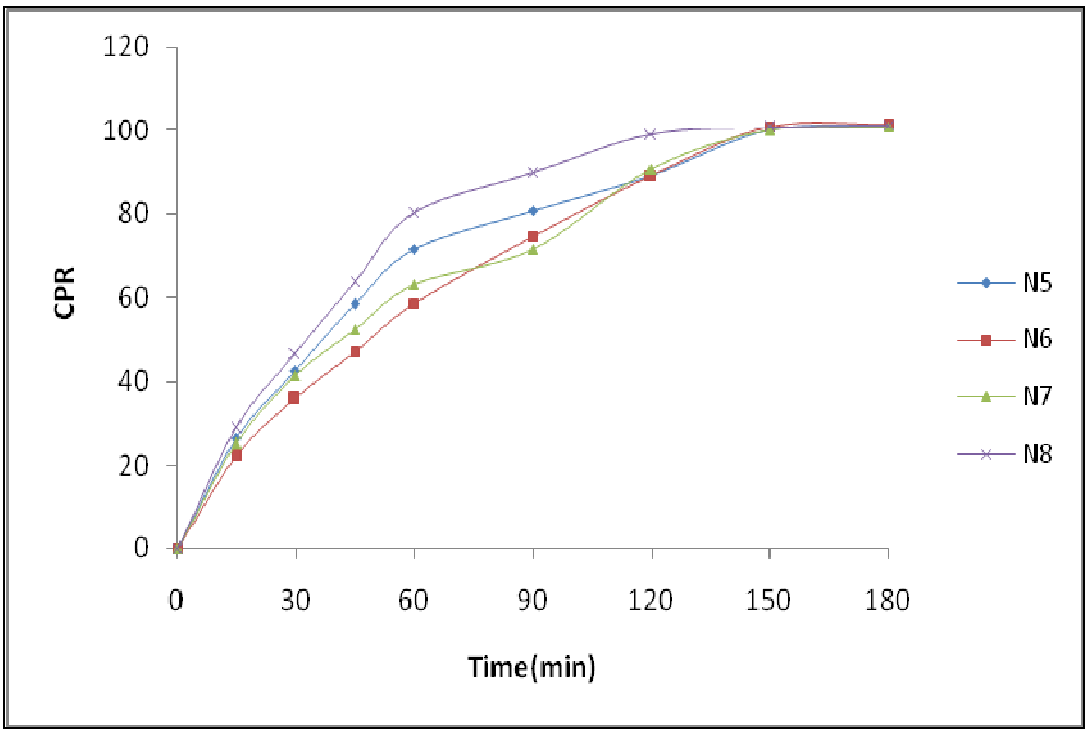
5.2.8 In vitro drug dissolution study of batch N7

Time (min)	Abs	Con(µg/ml) after dilution	Con(µg/ml) before dilution	Con (mg/500ml)	Error	Cumulative (mg/500ml)	CPR
0	0	0	0	0	0	0	0
15	0.1457	3.024	15.120	7.560	0	7.560	25.20
30	0.2187	4.965	24.827	12.414	0.030	12.444	41.48
45	0.2678	6.271	31.356	15.678	0.080	15.758	52.53
60	0.3145	7.513	37.566	18.783	0.143	18.926	63.09
90	0.3514	8.495	42.473	21.237	0.218	21.454	71.51
120	0.4359	10.742	53.710	26.855	0.303	27.158	90.53
150	0.4766	11.824	59.122	29.561	0.410	29.971	99.90
180	0.4789	11.886	59.428	29.714	0.528	30.242	100.81
Dilution Factor - 5							

5.2.9 In vitro drug dissolution study of batch N8

Time (min)	Abs	Con(µg/ml) after dilution	Con(µg/ml) before dilution	Con (mg/500ml)	Error	Cumulative (mg/500ml)	CPR
0	0	0	0	0	0	0	0
15	0.1634	3.495	17.473	8.737	0	8.737	29.12
30	0.2421	5.588	27.939	13.969	0.035	14.004	46.68
45	0.3189	7.630	38.152	19.076	0.091	19.167	63.89
60	0.3919	9.572	47.859	23.930	0.167	24.097	80.32
90	0.4327	10.657	53.285	26.642	0.263	26.905	89.68
120	0.4733	11.737	58.684	29.342	0.369	29.711	99.04
150	0.4789	11.886	59.428	29.714	0.487	30.201	100.67
180	0.4792	11.894	59.468	29.734	0.606	30.340	101.13
Dilution Factor - 5							

Figure 5.2" In vitro drug dissolution study of batch N5 to N8



Result & Discussion:

Batches N5 to N8 were evaluated for the physical characterization. The results of physical parameters are shown in the table. It was found that films show a good tensile strength along with satisfactory result of folding endurance, % elongation, elastic modulus, strain and WVT. Moisture content and Moisture uptake were low Which indicating protect the formulations from microbial contamination and information regarding stability of the formulation & reduce brittleness during long storage. The dissolution profile were shown that all the batches effectively release almost all the drug content so that dissolution is not the rate limiting step for the drug permeation into the systemic circulation.

In vitro drug release is the most important parameter for the transdermal film. It can be shown that how much drug will behave in-vivo. The results of in-vitro skin permeation studies of transdermal films of Valsartan using hairless rat abdomen skin as a skin membrane using Franz diffusion cell containing HPMC and PG as a film forming components are shown in figure. Here batches N5 to N8 have different penetration enhancers 0.5 % (blank, DMSO, Tween-80, IPM) to be used. N5 shows lower permeation because of absence of permeation enhancers as compare to other three batches N6, N7 and N8. So that 0.5% of DMSO Batch (N6) was used for the permeation in the HPMC Films using Propylene Glycol as a plasticizer.

5.3 HPMC: ERL100 films containing PEG-400 as a plasticizer

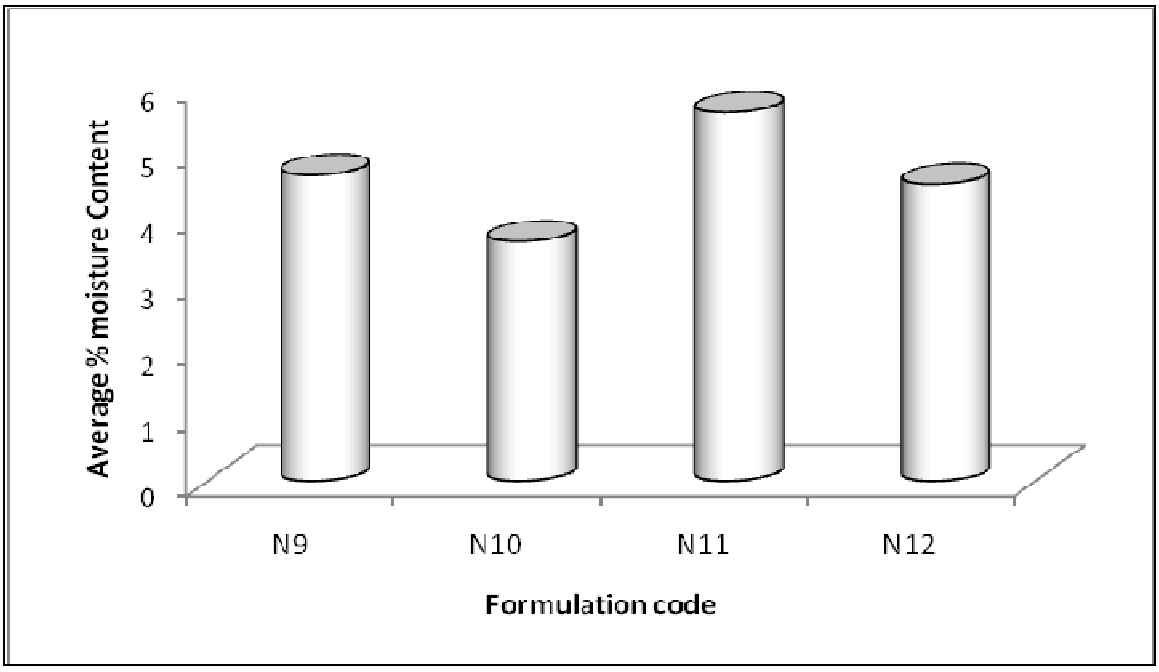
Ingredients	**N9**	**N10**	**N11**	**N12**
VALSATAN	30mg/16cm^2	30mg/16cm^2	30mg/16cm^2	30mg/16cm^2
HPMC : ERL 100	3:2	3:2	3:2	3:2
PEG-400	30% w/w	30% w/w	30% w/w	30% w/w
DMSO	------	0.5%	------	------
TWEEN-80	------	-----	0.5%	-----
IPM	-----	-----	-----	0.5%
METHANOL	q.s to 20ml	q.s to 20ml	q.s to 20ml	q.s to 20ml

5.3.1 Evaluation parameters

Batch	Tensile Strength (N/Cm^2)	% Elongation	Folding Endurance	Elastic Modulus (N/cm^2)	Strain	Thickness (mm)
N9	0.971±0.1	14.78 ±2.23	111±5	1.134±0.213	0.85±0.012	0.23±0.015
N10	1.322±0.32	14.81±1.42	128±8	1.383±0.412	0.95±0.032	0.22±0.021
N11	1.442±0.23	13.80±1.54	143±2	1.902±0.138	0.76±0.027	0.25±0.011
N12	1.331±0.16	13.13±2.65	102±5	2.053±0.152	0.64±0.015	0.31±0.014

Batch	Drug Content (mg)	Wt (mg)	WVP	% MU	%MC
N9	30.1 ±0.2	123	1.71	4.87±1.6	4.65±1.5
N10	28.89 ± 0.3	132	1.73	5.38±1.5	3.64±1.2
N11	29.3 ±0.1	118	1.69	3.30±2.1	5.6±2.5
N12	30.07 ±0.3	127	1.76	3.10±1.4	4.51±2.7

Figure 5.3 % Moisture Content



5.3.2 In vitro drug permeation study of batch N9

Time (hr)	Abs	Dilution factor	Con µg/ml	Con mg/ml	%Drug permeated
0	0	0	0	0	0
1	0.1546	1	3.49	0.10	1.93
2	0.2341	1	5.58	0.17	3.09
3	0.3245	1	8.02	0.24	4.44
4	0.4176	1	10.54	0.32	5.83
5	0.4983	1	12.72	0.38	7.04
6	0.5463	1	14.02	0.42	7.76
24	0.3544	20	176.17	5.29	62.36

5.2.3 In vitro drug permeation study of batch N10

Time (hr)	Abs	Dilution factor	Con µg/ml	Con mg/ml	%Drug permeated
0	0	0	0	0	0
1	0.1627	1	3.71	0.11	2.05
2	0.2531	1	6.09	0.18	3.37
3	0.3428	1	8.52	0.26	4.72
4	0.4362	1	11.04	0.33	6.11
5	0.5378	1	13.79	0.41	7.63
6	0.6264	1	16.18	0.49	8.96
24	0.4012	20	201.06	6.03	71.17

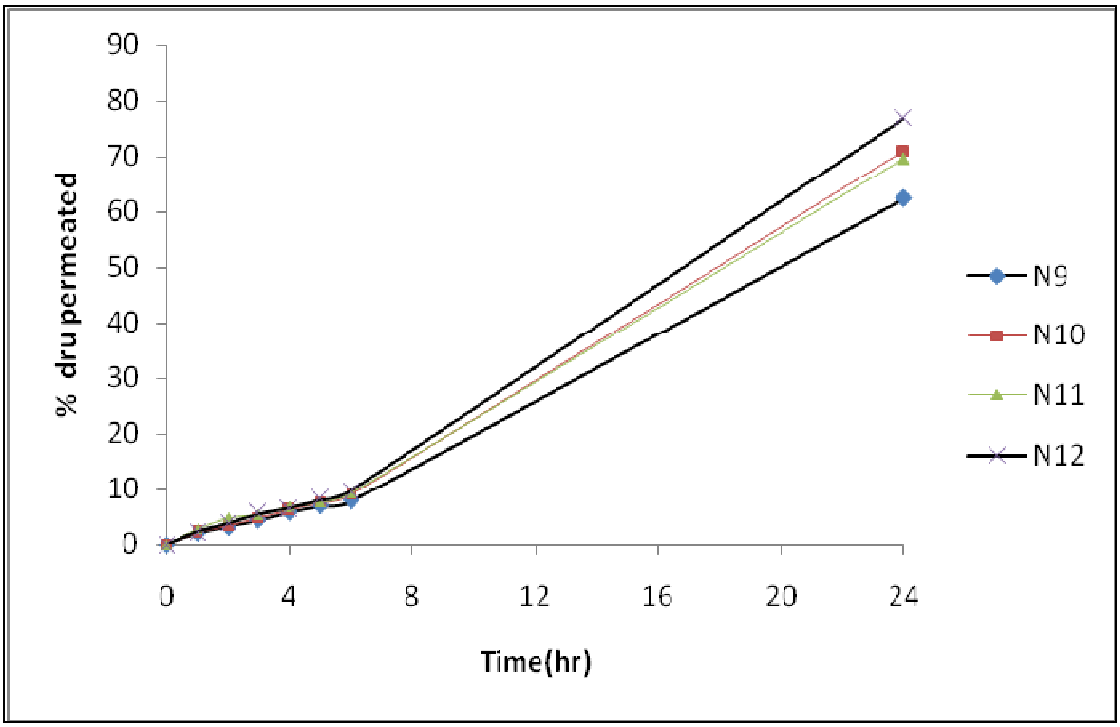
5.3.4 In vitro drug permeation study of batch N11

Time (hr)	Abs	Dilution factor	Con µg/ml	Con mg/ml	%Drug permeated
0	0	0	0	0	0
1	0.2176	1	5.17	0.16	2.86
2	0.3427	1	8.52	0.26	4.71
3	0.3921	1	9.85	0.30	5.45
4	0.4765	1	12.13	0.36	6.72
5	0.5438	1	13.95	0.42	7.72
6	0.6489	1	16.79	0.50	9.29
24	0.3922	20	196.28	5.89	69.48

5.3.5 In vitro drug permeation study of batch N12

Time (hr)	Abs	Dilution factor	Con µg/ml	Con mg/ml	%Drug permeated
0	0	0	0	0	0
1	0.1723	1	3.97	0.12	2.19
2	0.2879	1	7.04	0.21	3.89
3	0.3976	1	10.00	0.30	5.54
4	0.4628	1	11.76	0.35	6.51
5	0.5678	1	14.60	0.44	8.08
6	0.6748	1	17.49	0.52	9.68
24	0.4323	20	217.61	6.53	77.03

Figure 5.3' In vitro drug permeation study of batch N9 to N12



5.3.6 In vitro dissolution study of batch N9

Time (min)	Abs	Con(µg/ml) after dilution	Con(µg/ml) before dilution	Con (mg/500ml)	Error	Cumulative (mg/500ml)	CPR
0	0	0	0	0	0	0	0
15	0.1422	2.931	14.654	7.327	0	7.327	24.42
30	0.2314	5.303	26.516	13.258	0.029	13.287	44.29
45	0.3213	7.694	38.471	19.235	0.082	19.318	64.39
60	0.3988	9.755	48.777	24.388	0.159	24.548	81.83
90	0.4325	10.652	53.258	26.629	0.257	26.886	89.62
120	0.4812	11.947	59.734	29.867	0.363	30.230	100.77
150	0.4825	11.981	59.907	29.953	0.483	30.436	101.45
Dilution Factor - 5							

5.3.7 In vitro dissolution study of batch N10

Time (min)	Abs	Con(µg/ml) after dilution	Con(µg/ml) before dilution	Con (mg/500ml)	Error	Cumulative (mg/500ml)	CPR
0	0	0	0	0	0	0	0
15	0.1534	3.229	16.144	8.072	0	8.072	26.91
30	0.2743	6.444	32.221	16.110	0.032	16.143	53.81
45	0.3546	8.580	42.899	21.449	0.097	21.546	71.82
60	0.395	9.654	48.271	24.136	0.183	24.318	81.06
90	0.4531	11.199	55.997	27.999	0.279	28.278	94.26
120	0.4776	11.851	59.255	29.628	0.391	30.019	100.06
150	0.4789	11.886	59.428	29.714	0.510	30.224	100.75
Dilution Factor - 5							

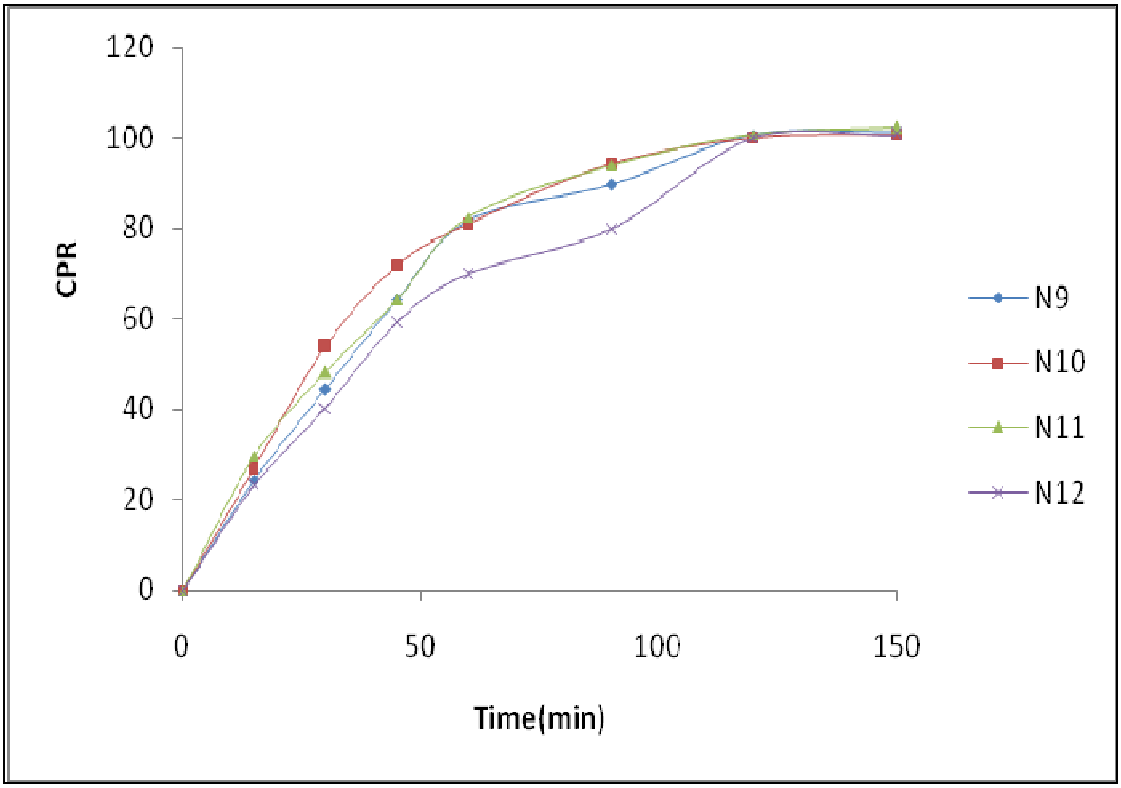
5.3.8 In vitro dissolution study of batch N11

Time (min)	Abs	Con(µg/ml) after dilution	Con(µg/ml) before dilution	Con (mg/500ml)	Error	Cumulative (mg/500ml)	CPR
0	0	0	0	0	0	0	0
15	0.1656	3.553	17.766	8.883	0	8.883	29.61
30	0.2487	5.763	28.816	14.408	0.036	14.444	48.15
45	0.3213	7.694	38.471	19.235	0.093	19.329	64.43
60	0.4023	9.848	49.242	24.621	0.170	24.791	82.64
90	0.4523	11.178	55.891	27.945	0.269	28.214	94.05
120	0.4812	11.947	59.734	29.867	0.380	30.247	100.82
150	0.4855	12.061	60.306	30.153	0.500	30.653	102.18
Dilution Factor - 5							

5.3.9 In vitro dissolution study of batch N12

Time (min)	Abs	Con(µg/ml) after dilution	Con(µg/ml) before dilution	Con (mg/500ml)	Error	Cumulative (mg/500ml)	CPR
0	0	0	0	0	0	0	0
15	0.1354	2.750	13.750	6.875	0	6.875	22.92
30	0.2134	4.824	24.122	12.061	0.028	12.089	40.30
45	0.2987	7.093	35.465	17.733	0.076	17.808	59.36
60	0.3454	8.335	41.676	20.838	0.147	20.984	69.95
90	0.3897	9.513	47.566	23.783	0.230	24.013	80.04
120	0.4789	11.886	59.428	29.714	0.325	30.039	100.13
150	0.4794	11.899	59.495	29.747	0.444	30.191	100.64
Dilution Factor - 5							

Figure 5.3" In vitro drug dissolution study of batch N9 to N12



Result & Discussion:

Batches N9 to N12 were evaluated for the physical characterization. But here the two polymers were mixed in various proportions (formulations N9 to N12) to study the influence of polymeric compositions on the drug release from mixed films as function of HPMC/ Eudragit RL (3:2) ratio. The drug release increased with increasing amount of the more hydrophilic Eudragit RL. Eudragit RL100 is copolymer of acrylic and esters with a low content (2.5-5%) of quaternary ammonium groups. The ammonium groups are responsible for the permeability and swelling of these water-insoluble films. The higher proportion of quaternary ammonium groups in Eudragit RL100 resulted in rapid hydration and drug release. A suitable proportion of RL100 and HPMC may be used to achieve prolonged release of the drug.

The prepared films were subjected to folding endurance, thickness, % elongation; Tensile Strength, WVT, % Moisture Uptake, % Moisture Content, wt variation, Drug Content, Strain, Elastic Modulus, In-vitro drug dissolution study and In-vitro drug permeation study are shown in table. The films have satisfactory results in thickness and wt variation. The Drug Content indicating that effective drug loading into the films. Folding endurance measured the ability of film to withstand rupture. It can be measures manually & result indicated that the films would not break and would maintain their integrity with general skin folding when used. Tensile Strength results indicate the Strength of films & the risk of film cracking. Moisture uptake was found to increase concentration of hydrophilic polymer like HPMC. M.U of films was also low which could protect the formulations from microbial contamination & reduce bulkiness of films. Moisture Content was also low which provide the information regarding stability of the formulation & reduce brittleness during long storage. WVT study indicated that HPMC films were more permeated to water vapour.

The dissolution profile were shown that all the batches effectively release almost all the drug content so that dissolution is not the rate limiting step for the drug permeation into the systemic circulation. The result of In vitro drug release is the most important parameter for the transdermal film. It can be shown that how much drug will behave in-vivo. The results of in-vitro skin permeation studies of transdermal films of valsartan using hairless rat abdomen skin as a skin membrane using Franz diffusion cell containing HPMC: ERL 100 and PEG-400 as a film forming

components are shown in figure. Here batch N9, without penetration enhancer having less permeation as compare to other batch. The combination of two polymers having three different penetration enhancers (DMSO, Tween 80, IPM). The amount of drug permeated from Batch N12 was higher as compare to batches N9, N10 and N11 indicating that permeation enhancer required to obtain desire flux. Thus batch N12, 0.5% IPM as a permeation enhancer and 30% PEG-400 was the premising result for the permeation. DMSO and Tween 80 were less efficient as compare to IPM.

5.4 HPMC: ERL100 films containing Propylene Glycol as a plasticizer

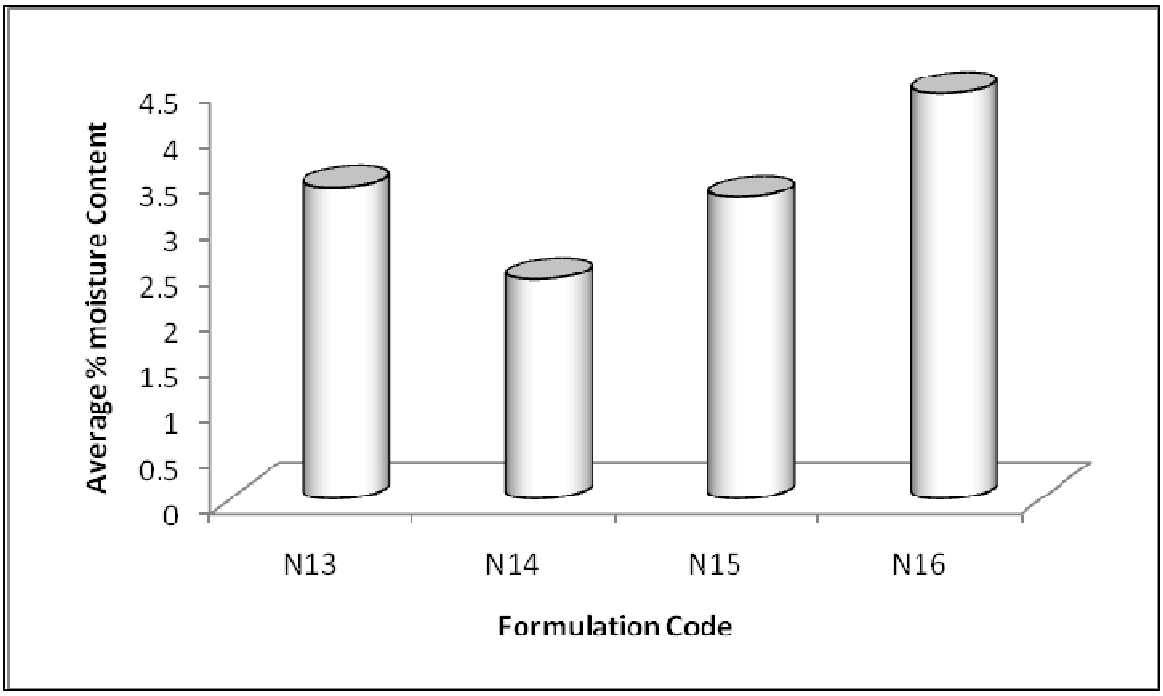
Ingredients	N13	N14	N15	N16
VALSARTAN	30mg/16cm^2	30mg/16cm^2	30mg/16cm^2	30mg/16cm^2
HPMC : ERL 100	3:2	3:2	3:2	3:2
PG	30% w/w	30% w/w	30% w/w	30% w/w
DMSO	-----	0.5%	------	------
TWEEN-80	-----	-----	0.5%	-----
IPM	-----	-----	-----	0.5%
METHANOL	q.s to 20ml	q.s to 20ml	q.s to 20ml	q.s to 20ml

5.4.1 Evaluation parameter

Batch	Tensile Strength (N/Cm^2)	% Elongation	Folding Endurance	Elastic Modulus (N/cm^2)	Strain	Thickness (mm)
N13	1.923±0.23	14.81±1.23	132±4	2.403± 0.321	0.80±0.027	0.17 ±0.021
N14	1.973±0.14	14.78± 2.31	109±6	2.198± 0.243	0.89±0.012	0.200.011
N15	1.952±0.42	15.78 ±2.43	123±2	3.223 ±0.148	0.60±0.016	0.27 ±0.015
N16	1.962±0.16	15.33 ±3.11	110±4	2.182 ±0.265	0.90±0.017	0.25±0.016

Batch	Drug Content (mg)	Wt (mg)	WVP	% MU	%MC
N13	29.87 ±0.4	113	1.89	3.53±1.3	3.41±2.2
N14	29.92±0.3	122	1.72	4.16±1.7	2.40±2.4
N15	29.33±0.2	117	1.80	3.41±1.4	3.30±1.6
N16	30.12 ±0.2	129	1.84	3.84±2.1	4.44±1.8

Figure 5.4 % Moisture Content



5.4.2 In vitro drug permeation study of batch **N13**

Time (hr)	Abs	Dilution factor	Con µg /ml	Con mg/ml	%Drug permeated
0	0	0	0	0	0
1	0.1387	1	3.07	0.09	1.70
2	0.2534	1	6.10	0.18	3.38
3	0.3346	1	8.30	0.25	4.59
4	0.4261	1	10.77	0.32	5.96
5	0.5127	1	13.11	0.39	7.26
6	0.6388	1	16.52	0.50	9.14
24	0.3021	20	148.35	4.45	52.51

5.4.3 In vitro drug permeation study of batch **N14**

Time (hr)	Abs	Dilution factor	Con µg/ml	Con mg/ml	%Drug permeated
0	0	0	0	0	0
1	0.1428	1	3.18	0.10	1.76
2	0.2315	1	5.51	0.17	3.05
3	0.3548	1	8.84	0.27	4.89
4	0.4327	1	10.95	0.33	6.06
5	0.5364	1	13.75	0.41	7.61
6	0.6028	1	15.55	0.47	8.60
24	0.3763	20	187.82	5.63	66.48

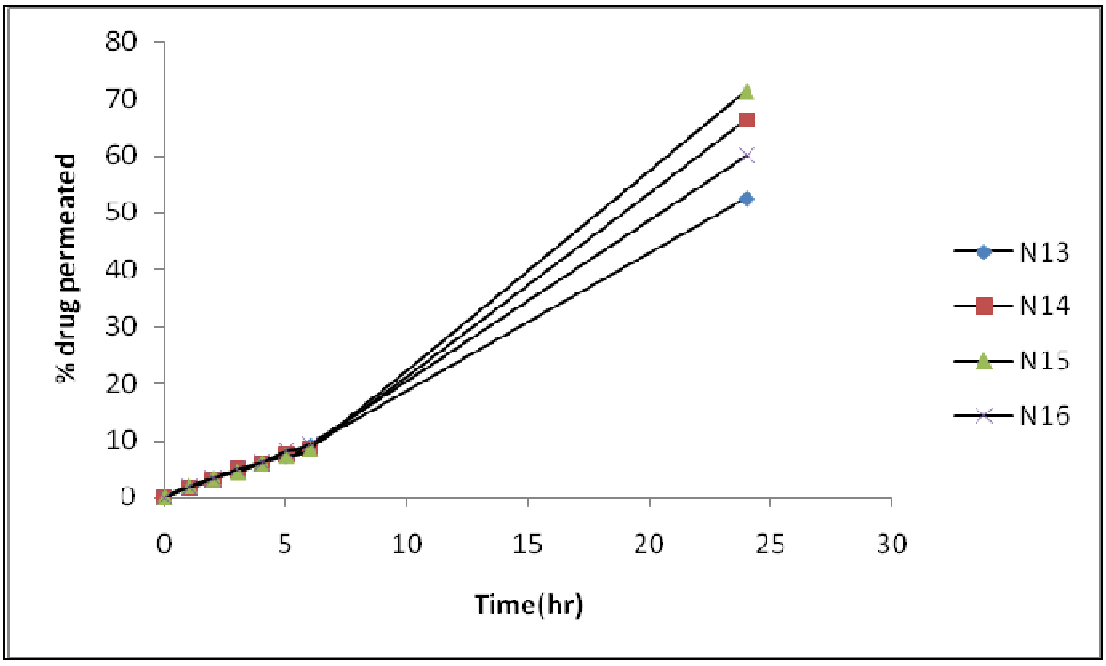
5.4.4 In vitro drug permeation study of batch **N15**

Time (hr)	Abs	Dilution factor	Con µg/ml	Con mg/ml	%Drug permeated
0	0	0	0	0	0
1	0.1635	1	3.73	0.11	2.07
2	0.2537	1	6.11	0.18	3.38
3	0.3276	1	8.11	0.24	4.49
4	0.4352	1	11.02	0.33	6.10
5	0.5172	1	13.23	0.40	7.32
6	0.5988	1	15.44	0.46	8.54
24	0.4021	20	201.54	6.05	71.34

5.4.5 In vitro drug permeation study of batch **N16**

Time (hr)	Abs	Dilution factor	Con µg/ml	Con mg/ml	%Drug permeated
0	0	0	0	0	0
1	0.1476	1	3.31	0.10	1.83
2	0.2533	1	6.10	0.18	3.38
3	0.3628	1	9.06	0.27	5.01
4	0.4377	1	11.08	0.33	6.13
5	0.5768	1	14.84	0.45	8.22
6	0.6544	1	16.94	0.51	9.38
24	0.3421	20	169.63	5.09	60.05

Figure 5.4' In vitro drug permeation study of batch N13 to N16



5.4.6 In vitro drug dissolution study of batch **N13**

Time (min)	Abs	Con(µg/ml) after dilution	Con(µg/ml) before dilution	Con (mg/500ml)	Error	Cumulative (mg/500ml)	CPR
0	0	0	0	0	0	0	0
15	0.1632	3.489	17.447	8.723	0	8.723	29.08
30	0.2438	5.867	29.335	14.668	0.035	14.702	49.01
45	0.3124	7.457	37.287	18.644	0.094	18.737	62.46
60	0.3765	9.162	45.811	22.906	0.168	23.074	76.91
90	0.4435	10.944	54.721	27.360	0.260	27.620	92.07
120	0.4789	11.886	59.428	29.714	0.369	30.083	100.28
150	0.4802	11.920	59.601	29.801	0.488	30.289	100.96
Dilution Factor - 5							

5.4.7 In vitro drug dissolution study of batch **N14**

Time (min)	Abs	Con(µg/ml) after dilution	Con(µg/ml) before dilution	Con (mg/500ml)	Error	Cumulative (mg/500ml)	CPR
0	0	0	0	0	0	0	0
15	0.1532	3.223	16.117	8.059	0	8.059	26.86
30	0.2312	5.298	26.489	13.245	0.032	13.277	44.26
45	0.2936	6.957	34.787	17.394	0.085	17.479	58.26
60	0.3421	8.247	41.237	20.618	0.155	20.773	69.24
90	0.4257	10.471	52.354	26.177	0.237	26.414	88.05
120	0.4699	11.646	58.231	29.116	0.342	29.458	98.19
150	0.4809	11.939	59.694	29.847	0.458	30.306	101.02
180	0.4834	12.005	60.027	30.013	0.578	30.591	101.97
Dilution Factor - 5							

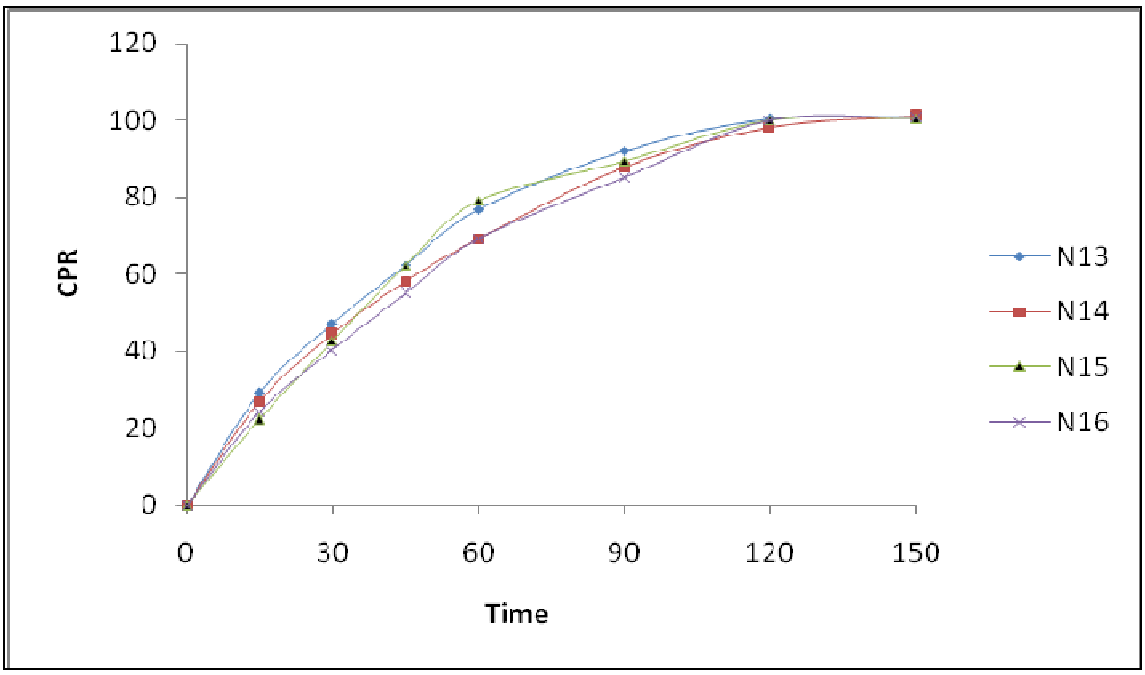
5.4.8 In vitro drug dissolution study of batch **N15**

Time (min)	Abs	Con(µg/ml) after dilution	Con(µg/ml) before dilution	Con (mg/500ml)	Error	Cumulative (mg/500ml)	CPR
0	0	0	0	0	0	0	0
15	0.1322	2.665	13.324	6.662	0	6.662	22.21
30	0.2241	5.109	25.545	12.773	0.027	12.799	42.66
45	0.3126	7.463	37.314	18.657	0.078	18.735	62.45
60	0.3865	9.428	47.141	23.570	0.152	23.723	79.08
90	0.4321	10.641	53.205	26.602	0.247	26.849	89.50
120	0.4779	11.859	59.295	29.648	0.353	30.001	100.00
150	0.4787	11.880	59.402	29.701	0.472	30.172	100.57
Dilution Factor - 5							

5.4.9 In vitro drug dissolution study of batch **N16**

Time (min)	Abs	Con(µg/ml) after dilution	Con(µg/ml) before dilution	Con (mg/500ml)	Error	Cumulative (mg/500ml)	CPR
0	0	0	0	0	0	0	0
15	0.1422	2.931	14.654	7.327	0	7.327	24.42
30	0.2134	4.824	24.122	12.061	0.029	12.090	40.30
45	0.2789	6.566	32.832	16.416	0.078	16.494	54.98
60	0.3423	8.253	41.263	20.632	0.143	20.775	69.25
90	0.4134	10.144	50.718	25.359	0.226	25.585	85.28
120	0.4789	11.886	59.428	29.714	0.327	30.041	100.14
150	0.4802	11.920	59.601	29.801	0.446	30.247	100.82
Dilution Factor - 5							

Figure 5.4" In vitro drug dissolution study of batch N13 toN16



Result & Discussion:

Batches N13 to N16 were evaluated for the physical characterization. But here the two polymers were mixed in various proportions (formulations N13 to N16) to study the influence of polymeric compositions on the drug release from mixed films as function of HPMC/Eudragit RL100(3:2) ratio. The transdermal films show satisfactory result of effective tensile strength and % elongation. The moisture content and moisture uptake were also low which reduce bulkiness as well as brittleness. The dissolution profile were shown that all the batches effectively release almost all the drug content so that dissolution is not the rate limiting step for the drug permeation into the systemic circulation.

The result of In vitro drug release is the most important parameter for the transdermal film. It can be shown that how much drug will behave in-vivo. The results of in-vitro skin permeation studies of transdermal films of valsartan using hairless rat abdomen skin as a skin membrane using Franz diffusion cell containing HPMC : ERL 100 and PG as a film forming components are shown in figure. 0.5% of Tween-80 was given a best permeation as compare to DMSO and IPM. So batch N15 was given satisfactory result because of the the polymeric mixture of hydrophilic polymers.

5.5 HPMC: ERS 100 films containing PEG-400 as a plasticizer

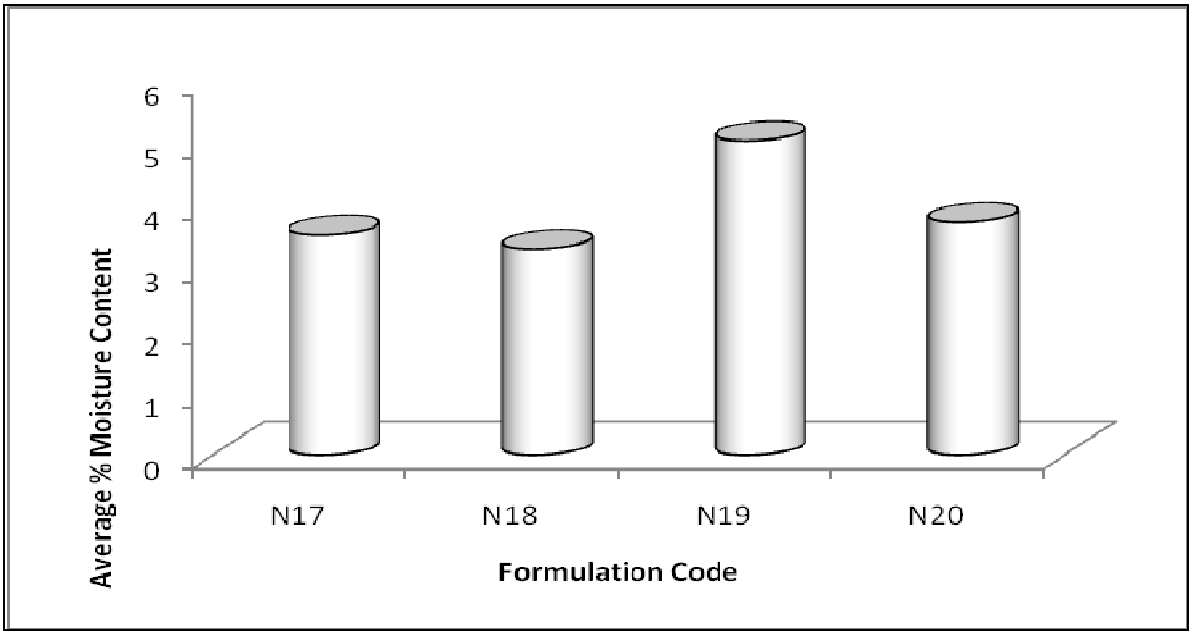
Ingredients	N17	N18	N19	N20
VALSARTAN	30mg/16cm^2	30mg/16cm^2	30mg/16cm^2	30mg/16cm^2
HPMC : ERS 100	2:3	2:3	2:3	2:3
PEG-400	30% w/w	30% w/w	30% w/w	30% w/w
DMSO	-----	0.5%	----	----
TWEEN-80	-----	-----	0.5%	-----
IPM	-----	-----	-----	0.5%
METHANOL	q.s to 20ml	q.s to 20ml	q.s to 20ml	q.s to 20ml

5.5.1 Evaluation parameter

Batch	Tensile Strength (N/Cm^2)	% Elongation	Folding Endurance	Elastic Modulus (N/cm^2)	Strain	Thickness (mm)
N17	1.867 ± 0.21	12.79 ±2.23	95±3	2.332 ±0.324	0.80 ± 0.032	0.18± 0.02
N18	1.981 ± 0.15	13.80 ±1.32	120±6	2. 113 ±0.143	0.93 ± 0.012	0.15±0.013
N19	1.792 ± 0.34	13.13 ±1.54	112±7	2.703 ±0.261	0.66 ±0.023	0.2±0.03
N20	1.872 ± 0.27	11.11 ±1.76	102±2	2.084 ±0.176	0.89 ±0.027	0.19±0.013

Batch	Drug Content (mg)	Wt (mg)	WVP	% MU	%MC
N17	30.13 ± 0.5	109	1.63	3.53±1.8	3.53±2.1
N18	29.97 ±0.2	117	1.69	2.54±1.9	3.30±1.5
N19	29.15 ±0.4	113	1.79	3.47±1.4	5.04±1.3
N20	30.01 ±0.1	129	1.73	3.07±1.7	3.73±1.7

Figure 5.5 % Moisture Content



5.5.2 In vitro drug permeation study of batch N17

Time (hr)	Abs	Dilution factor	Con µg/ml	Con mg/ml	%Drug permeated
0	0	0	0	0	0
1	0.2188	1	5.20	0.16	2.88
2	0.3433	1	8.53	0.26	4.72
3	0.4487	1	11.38	0.34	6.30
4	0.5537	1	14.22	0.43	7.87
5	0.6138	1	15.84	0.48	8.77
6	0.6577	1	17.03	0.51	9.43
24	0.2786	20	135.85	4.08	48.09

5.5.3 In vitro drug permeation study batch N18

Time (hr)	Abs	Dilution factor	Con µg/ml	Con mg/ml	%Drug permeated
0	0	0	0	0	0
1	0.1532	1	3.46	0.10	1.91
2	0.2132	1	5.02	0.15	2.78
3	0.3218	1	7.95	0.24	4.40
4	0.4325	1	10.94	0.33	6.06
5	0.5165	1	13.21	0.40	7.31
6	0.6239	1	16.12	0.48	8.92
24	0.4098	20	205.64	6.17	72.79

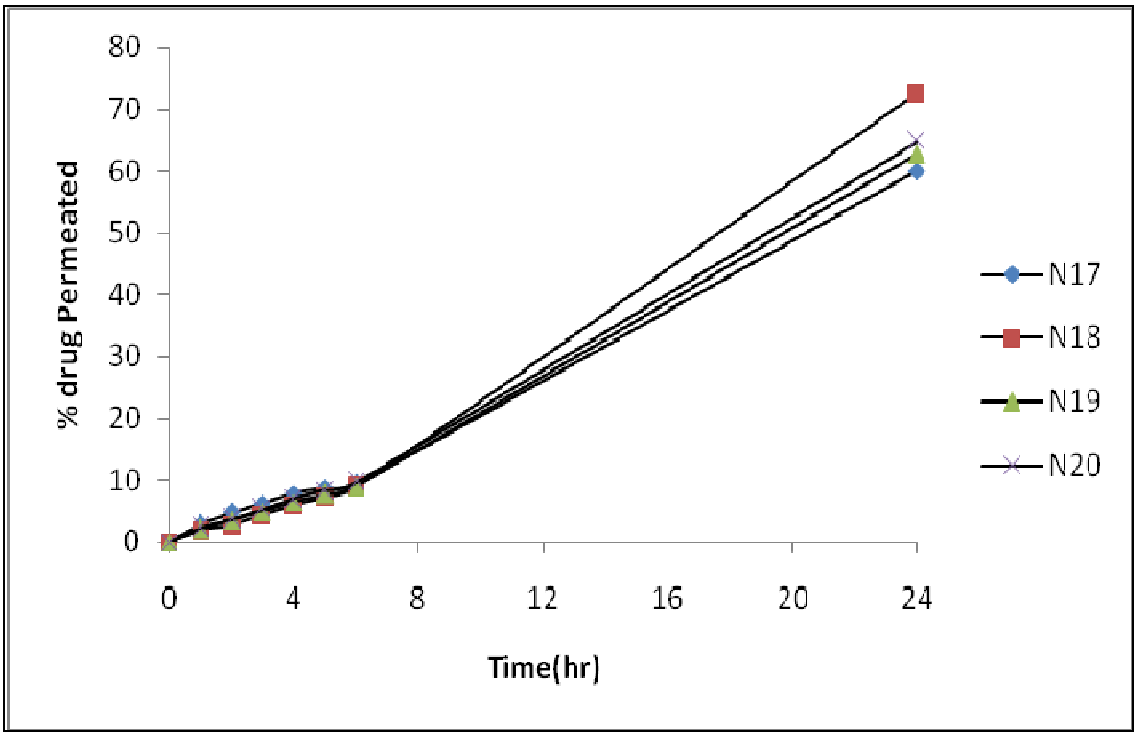
5.5.4 In vitro drug permeation study batch N19

Time (hr)	Abs	Dilution factor	Con µg/ml	Con mg/ml	%Drug permeated
0	0	0	0	0	0
1	0.1623	1	3.70	0.11	2.05
2	0.2642	1	6.39	0.19	3.54
3	0.3543	1	8.83	0.26	4.89
4	0.4641	1	11.80	0.35	6.53
5	0.5437	1	13.95	0.42	7.72
6	0.6283	1	16.24	0.49	8.99
24	0.3567	20	177.39	5.32	62.79

5.5.5 In vitro drug permeation study batch N20

Time (hr)	Abs	Dilution factor	Con µg/ml	Con mg/ml	%Drug permeated
0	0	0	0	0	0
1	0.1823	1	4.23	0.13	2.34
2	0.2745	1	6.67	0.20	3.69
3	0.3823	1	9.59	0.29	5.31
4	0.5021	1	12.82	0.38	7.10
5	0.5932	1	15.29	0.46	8.46
6	0.6758	1	17.52	0.53	9.70
24	0.3675	20	183.14	5.49	64.83

Figure 5.5' In vitro drug permeation study batch N17 to N20



5.5.6 In vitro drug dissolution study of batch N17

Time (min)	Abs	Con(µg/ml) after dilution	Con(µg/ml) before dilution	Con (mg/500ml)	Error	Cumulative (mg/500ml)	CPR
0	0	0	0	0	0	0	0
15	0.1323	2.902	14.508	7.254	0	7.254	24.18
30	0.2436	5.862	29.309	14.654	0.029	14.683	48.94
45	0.3543	8.806	44.029	22.015	0.088	22.102	73.67
60	0.412	10.340	51.702	25.851	0.176	26.027	86.76
90	0.4309	10.843	54.215	27.108	0.279	27.387	91.29
120	0.4689	11.854	59.269	29.634	0.388	30.022	100.07
150	0.4704	11.894	59.468	29.734	0.506	30.240	100.80
Dilution Factor - 5							

5.5.7 In vitro drug dissolution study of batch N18

Time (min)	Abs	Con(µg/ml) after dilution	Con(µg/ml) before dilution	Con (mg/500ml)	Error	Cumulative (mg/500ml)	CPR
0	0	0	0	0	0	0	0
15	0.1541	3.481	17.407	8.703	0	8.703	29.01
30	0.2319	5.551	27.753	13.876	0.035	13.911	46.37
45	0.2981	7.311	36.556	18.278	0.090	18.368	61.23
60	0.3628	9.032	45.160	22.580	0.163	22.743	75.81
90	0.4213	10.588	52.939	26.469	0.254	26.723	89.08
120	0.4672	11.809	59.043	29.521	0.360	29.881	99.60
150	0.4677	11.822	59.109	29.555	0.478	30.032	100.11
180	0.4689	11.854	59.269	29.634	0.596	30.230	100.77
Dilution Factor - 5							

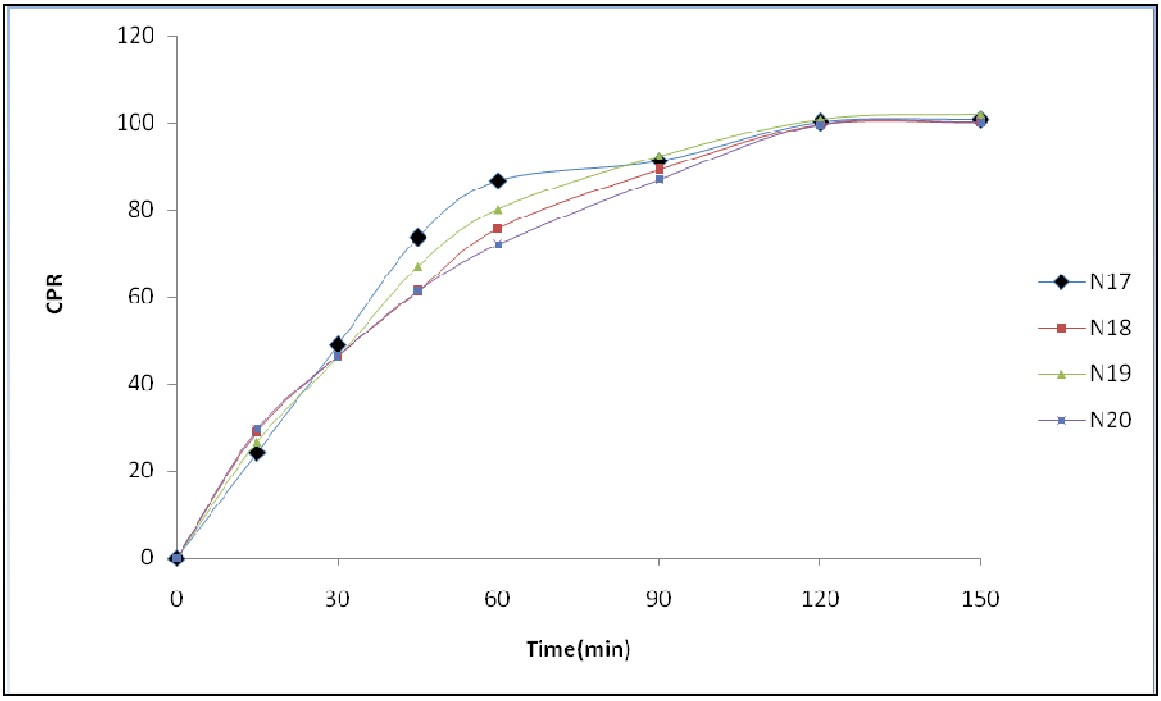
5.5.8 In vitro drug dissolution study of batch N19

Time (min)	Abs	Con(µg/ml) after dilution	Con(µg/ml) before dilution	Con (mg/500ml)	Error	Cumulative (mg/500ml)	CPR
0	0	0	0	0	0	0	0
15	0.1435	3.199	15.997	7.999	0	7.999	26.66
30	0.2311	5.529	27.646	13.823	0.032	13.855	46.18
45	0.3245	8.013	40.066	20.033	0.087	20.121	67.07
60	0.3821	9.545	47.726	23.863	0.167	24.030	80.10
90	0.4358	10.973	54.867	27.434	0.263	27.696	92.32
120	0.4722	11.941	59.707	29.854	0.373	30.226	100.75
150	0.4756	12.032	60.160	30.080	0.492	30.572	101.91
Dilution Factor - 5							

5.5.9 In vitro drug dissolution study of batch N20

Time (min)	Abs	Con(µg/ml) after dilution	Con(µg/ml) before dilution	Con (mg/500ml)	Error	Cumulative (mg/500ml)	CPR
0	0	0	0	0	0	0	0
15	0.1565	3.545	17.726	8.863	0	8.863	29.54
30	0.2319	5.551	27.753	13.876	0.035	13.912	46.37
45	0.2987	7.327	36.636	18.318	0.091	18.409	61.36
60	0.3453	8.566	42.832	21.416	0.164	21.580	71.93
90	0.4123	10.348	51.742	25.871	0.250	26.121	87.07
120	0.4671	11.806	59.029	29.515	0.353	29.868	99.56
150	0.4678	11.824	59.122	29.561	0.471	30.033	100.11
Dilution Factor - 5							

Figure 5.5"In vitro drug dissolution study of batch N17 to N20



Result & Discussion:

Batches N17 to N20 were evaluated for the physical characterization. But here the two polymers were mixed in various proportions (formulations N17 to N20) to study the influence of polymeric compositions on the drug release from mixed films as function of Eudragit RS/HPMC ratio. As the Eudragit RS100 content increased, the release rate constant decreased to. Eudragit RS100 is copolymers of methacrylic acid esters with a low content (2.5-5%) of quaternary ammonium groups. whereas the lower proportion of ammonium groups in Eudragit RS100 is responsible for controlling the release of TZN. A suitable proportion of RS100 and HPMC may be used to achieve prolonged release of the drug.

The prepared films were subjected to folding endurance, thickness, % elongation; Tensile Strength, WVT, % Moisture Uptake, % Moisture Content, wt variation, Drug Content, Strain, Elastic Modulus, In-vitro drug dissolution study and In-vitro drug permeation study are shown in table. The films have satisfactory results in thickness and wt variation. The Drug Content indicating that effective drug loading into the films. Folding endurance measured the ability of film to withstand rupture. It can be measures manually & result indicated that the films would not break and would maintain their integrity with general skin folding when used. Tensile Strength results indicate the Strength of films & the risk of film cracking. Moisture uptake was found to increase concentration of hydrophilic polymer like HPMC. M.U of films was also low which could protect the formulations from microbial contamination & reduce bulkiness of films. Moisture Content was also low which provide the information regarding stability of the formulation & reduce brittleness during long storage. WVT study indicated that HPMC films were more permeated to water vapour.

The result of In vitro drug release is the most important parameter for the transdermal film. It can be shown that how much drug will behave in-vivo. The results of in-vitro skin permeation studies of transdermal films of valsartan using hairless rat abdomen skin as a skin membrane using Franz diffusion cell containing HPMC : ERS 100 (2:3) and PEG-400 as a film forming components are shown in figure.The dissolution profile were shown that all the batches effectively release almost all the drug content so that dissolution is not the rate limiting step for the drug permeation into the systemic circulation. Batch N18 was shown satisfactory result of

permeation. Dimethyl sulfoxide is a highly polar substance that is aprotic, therefore lacking acidic and basic properties. It has exceptional solvent properties for both organic and inorganic components, which are derived from its capacity to associate with both ionic species and neutral molecules that are either polar or polarizable.

5.6 HPMC: ERS 100 films containing Propylene Glycol as a plasticizer

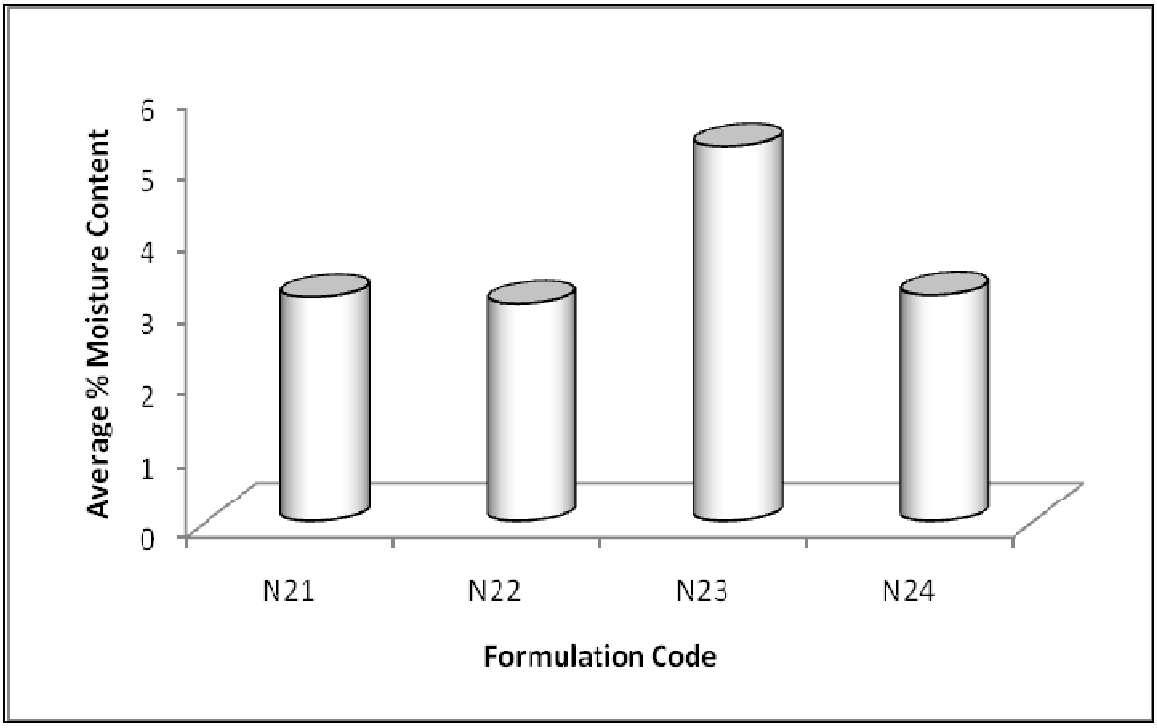
Ingredients	N21	N22	N23	N24
VALSARTAN	30mg/16cm^2	30mg/16cm^2	30mg/16cm^2	30mg/16cm^2
HPMC : ERS 100	2:3	2:3	2:3	2:3
PG	30% w/w	30% w/w	30% w/w	30% w/w
DMSO	------	0.5%	------	------
TWEEN-80	-------	-----	0.5%	-----
IPM	-----	-----	-----	0.5%
METHANOL	q.s to 20ml	q.s to 20ml	q.s to 20ml	q.s to 20ml

5.6.1 Evaluation parameter

Batch	Tensile Strength (N/Cm^2)	% Elongation	Folding Endurance	Elastic Modulus (N/cm^2)	Strain	Thickness (mm)
N21	1.798±0.3	14.80 ±1.42	134±4	2.101 ±0.241	0.89±0.031	0.16±0.014
N22	1.781±0.2	13.76 ±2.31	140±3	2.231± 0.351	0.79±0.023	0.13±0.021
N23	1.793±0.1	14.24±2.52	127±8	2.685± 0.153	0.66±0.025	0.19±0.012
N24	1.772±0.4	14.55 ±1.25	118±7	2.213± 0.255	0.80±0.035	0.12±0.016

Batch	Drug Content (mg)	Wt (mg)	WVP	% MU	%MC
N21	29.89 ± 0.3	123	1.57	3.25±1.9	3.14±1.5
N22	29.67±1.1	127	1.59	3.14±1.4	3.05 ±1.6
N23	29.11±0.6	119	1.53	2.50±1.2	3.25±2.1
N24	30.2±0.9	122	1.69	2.43±1.6	3.17±1.4

Figure 5.6 % Moisture Content



5.6.2 In vitro drug permeation study of batch N21

Time (hr)	Abs	Dilution factor	Con µg/ml	Con mg/ml	%Drug permeated
0	0	0	0	0	0
1	0.1263	1	2.74	0.08	1.52
2	0.2134	1	5.02	0.15	2.78
3	0.3245	1	8.02	0.24	4.44
4	0.4536	1	11.51	0.35	6.37
5	0.5437	1	13.95	0.42	7.72
6	0.6698	1	17.36	0.52	9.61
24	0.3213	20	158.56	4.76	56.13

5.6.3 In vitro drug permeation study of batch N22

Time (hr)	Abs	Dilution factor	Con µg/ml	Con mg/ml	%Drug permeated
0	0	0	0	0	0
1	0.2316	1	5.54	0.17	3.07
2	0.3564	1	8.89	0.27	4.92
3	0.4376	1	11.08	0.33	6.13
4	0.5748	1	14.79	0.44	8.19
5	0.6548	1	16.95	0.51	9.38
6	0.7638	1	19.90	0.60	11.01
24	0.4236	20	212.98	6.39	75.39

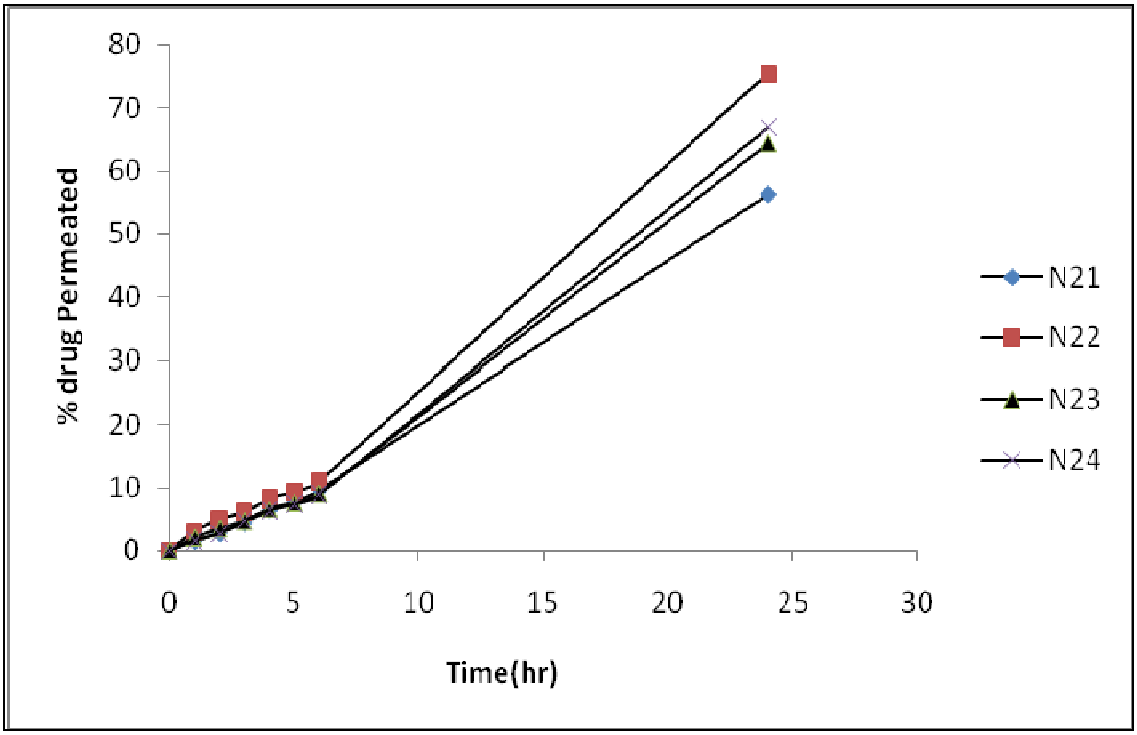
5.6.4 In vitro drug permeation study of batch N23

Time (hr)	Abs	Dilution factor	Con µg/ml	Con mg/ml	%Drug permeated
0	0	0	0	0	0
1	0.1637	1	3.74	0.11	2.07
2	0.2632	1	6.37	0.19	3.52
3	0.3427	1	8.52	0.26	4.71
4	0.4732	1	12.04	0.36	6.67
5	0.5402	1	13.85	0.42	7.67
6	0.6374	1	16.48	0.49	9.12
24	0.3647	20	181.65	5.45	64.30

5.6.5 In vitro drug permeation study of batch N24

Time (hr)	Abs	Dilution factor	Con µg/ml	Con mg/ml	%Drug permeated
0	0	0	0	0	0
1	0.1328	1	2.91	0.09	1.61
2	0.2143	1	5.05	0.15	2.79
3	0.3432	1	8.53	0.26	4.72
4	0.4564	1	11.59	0.35	6.41
5	0.5265	1	13.48	0.40	7.46
6	0.6254	1	16.16	0.48	8.94
24	0.3786	20	189.04	5.67	66.92

Figure 5.6' In vitro drug permeation study of batch N21 to N24



5.6.6 In vitro drug dissolution study of batch N21

Time (min)	Abs	Con(µg/ml) after dilution	Con(µg/ml) before dilution	Con (mg/500ml)	Error	Cumulative (mg/500ml)	CPR
0	0	0	0	0	0	0	0
15	0.1462	3.271	16.356	8.178	0	8.178	27.26
30	0.2412	5.798	28.989	14.495	0.033	14.527	48.42
45	0.3289	8.130	40.652	20.326	0.091	20.416	68.05
60	0.3982	9.973	49.867	24.934	0.172	25.106	83.69
90	0.4453	11.226	56.130	28.065	0.272	28.337	94.46
120	0.4702	11.888	59.441	29.721	0.384	30.105	100.35
150	0.4733	11.971	59.854	29.927	0.503	30.430	101.43
Dilution Factor - 5							

5.6.7 In vitro drug dissolution study of batch N22

Time (min)	Abs	Con(µg/ml) after dilution	Con(µg/ml) before dilution	Con (mg/500ml)	Error	Cumulative (mg/500ml)	CPR
0	0	0	0	0	0	0	0
15	0.1627	3.710	18.551	9.275	0	9.275	30.92
30	0.2519	6.082	30.412	15.206	0.037	15.243	50.81
45	0.3321	8.215	41.077	20.539	0.098	20.636	68.79
60	0.3921	9.811	49.056	24.528	0.180	24.708	82.36
90	0.4521	11.407	57.035	28.517	0.278	28.795	95.98
120	0.4622	11.676	58.378	29.189	0.392	29.581	98.60
150	0.4698	11.878	59.388	29.694	0.509	30.203	100.68
180	0.4703	11.891	59.455	29.727	0.628	30.355	101.18
Dilution Factor - 5							

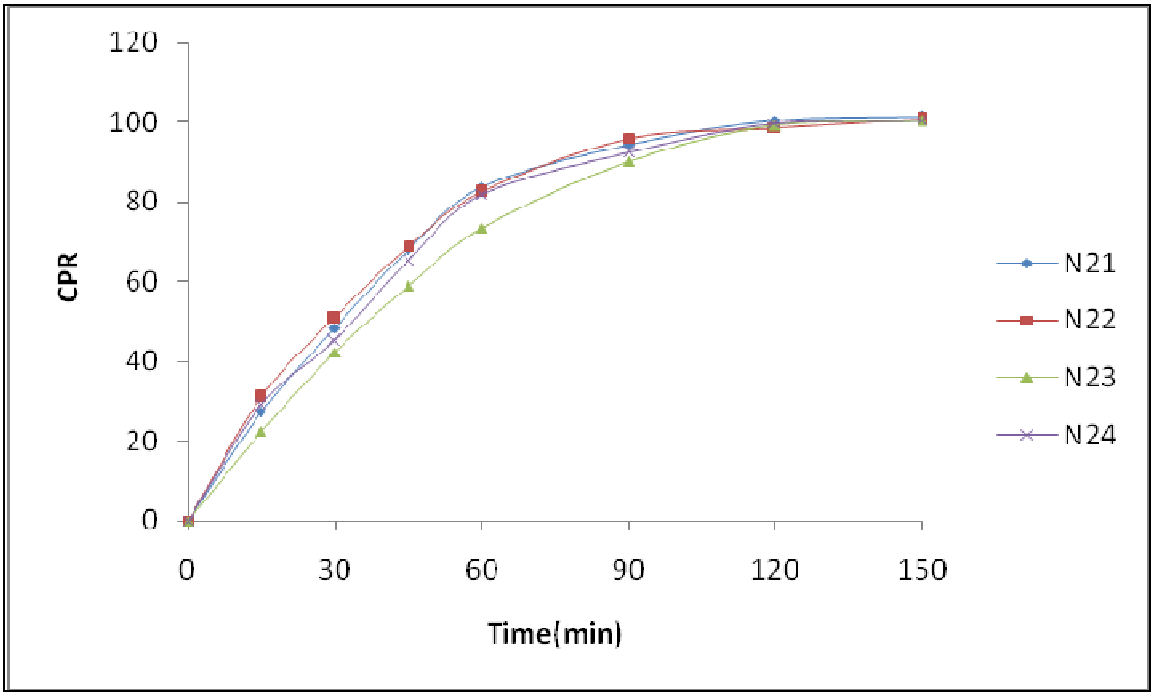
5.6.8 In vitro drug dissolution study of batch **N23**

Time (min)	Abs	Con(µg/ml) after dilution	Con(µg/ml) before dilution	Con (mg/500ml)	Error	Cumulative (mg/500ml)	CPR
0	0	0	0	0	0	0	0
15	0.1237	2.673	13.364	6.682	0	6.682	22.27
30	0.2137	5.066	25.332	12.666	0.027	12.693	42.31
45	0.2876	7.032	35.160	17.580	0.077	17.657	58.86
60	0.3521	8.747	43.737	21.868	0.148	22.016	73.39
90	0.4267	10.731	53.657	26.828	0.235	27.064	90.21
120	0.4656	11.766	58.830	29.415	0.343	29.757	99.19
150	0.4688	11.851	59.255	29.628	0.460	30.088	100.29
Dilution Factor - 5							

5.6.9 In vitro drug dissolution study of batch **N24**

Time (min)	Abs	Con(µg/ml) after dilution	Con(µg/ml) before dilution	Con (mg/500ml)	Error	Cumulative (mg/500ml)	CPR
0	0	0	0	0	0	0	0
15	0.1547	3.497	17.487	8.743	0	8.743	29.14
30	0.2258	5.388	26.941	13.471	0.035	13.506	45.02
45	0.3165	7.801	39.003	19.501	0.089	19.590	65.30
60	0.3896	9.745	48.723	24.362	0.167	24.529	81.76
90	0.4356	10.968	54.840	27.420	0.264	27.685	92.28
120	0.4669	11.801	59.003	29.501	0.374	29.875	99.58
150	0.4689	11.854	59.269	29.634	0.492	30.126	100.42
180	0.4699	11.880	59.402	29.701	0.611	30.311	101.04
Dilution Factor - 5							

Figure 5.6"In vitro drug dissolution study of batch N21 to N24



Result & Discussion:

Batches N21 to N24 were evaluated for the physical characterization. The results of physical parameters are shown in the table. It was found that films show a good tensile strength along with satisfactory result of folding endurance, % elongation, elastic modulus, strain and WVT. Moisture content and Moisture uptake were low which indicating protect the formulations from microbial contamination and information regarding stability of the formulation & reduce brittleness during long storage. The dissolution profile were shown that all the batches effectively release almost all the drug content so that dissolution is not the rate limiting step for the drug permeation into the systemic circulation.

The results of In vitro drug release are the most important parameter for the transdermal film. It can be shown that how much drug will behave in-vivo. The results of in-vitro skin permeation studies of transdermal films of valsartan using hairless rat abdomen skin as a skin membrane using Franz diffusion cell containing HPMC : ERL 100, PG-400 as a film forming components are shown in figure. The cumulative amount of drug permeated from batch N22 indicating that the penetration enhancer was required to desired flux. So that batch containing N22, 0.5% of DMSO was given desired permeation and more effective as compare to Tween 80 and IPM.

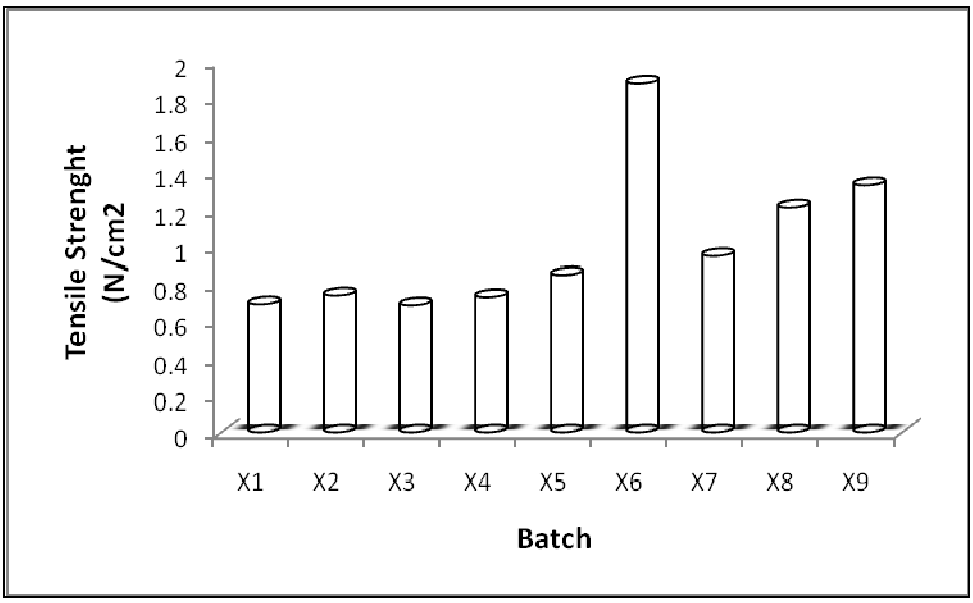
5.7 Formulation of backing layer

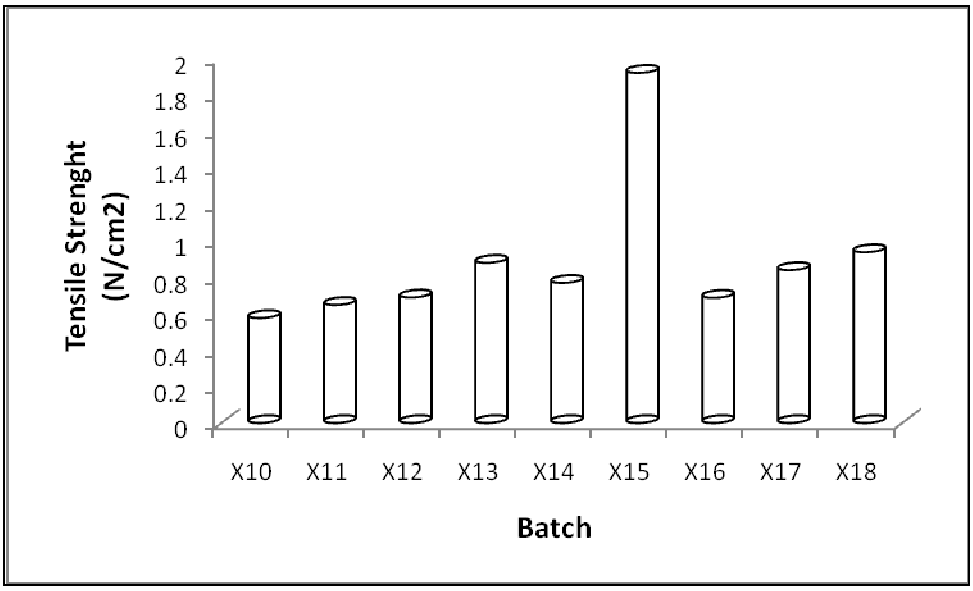
Polymer / Plasticizer		(Acetone : IPA) up to 50ml		
		Ethyl Cellulose		
		3%	4%	5%
PEG 400	20%	X1	X2	X3
	30%	X4	X5	X6
	40%	X7	X8	X9
TEC	20%	X10	X11	X12
	30%	X13	X14	X15
	40%	X16	X17	X18

5.7.1 Evaluation parameter

Batch	Tensile Strength (N/cm^2)	Batch	Tensile Strength (N/cm^2)
X1	0.689	X10	0.576
X2	0.737	X11	0.648
X3	0.683	X12	0.689
X4	0.727	X13	0.879
X5	0.847	X14	0.769
X6	1.879	X15	1.921
X7	0.948	X16	0.687
X8	1.213	X17	0.839
X9	1.328	X18	0.937

Tensile Strength of Batches X1 to X18





Result & Discussion

There is different type of backing layers to be used. Here, Ethyl Cellulose was widely used as a baking layer. Different concentration of polymers with different concentration of plasticizers like (PEG 400 & TEC) were tried. Tensile Strength results indicate the Strength of films & the risk of film cracking, Here the film was given a satisfactory result of tensile strength so that batch X6 and X 15 was given a good tensile strength as compare to other batches. So the 5% of Ethyl Cellulose with 30% of PEG 400 and TEC(tri ethyl citrate) was the best batch for the backing layer.

5.8 Effect of Polymer

Ingredients	N2	N6	N12	N15	N18	N22
VALSARTAN	30mg/16cm^2					
HPMC	4%		--	--	--	--
HPMC : ERL 100	--	--	3:2		--	--
HPMC : ERS 100	--	--	--	--	2:3	
PEG-400	30% w/w	--	30% w/w	--	30% w/w	--
PG	--	30% w/w	--	30% w/w	--	30% w/w
DMSO	0.5%	0.5%	--	--	0.5%	0.5%
TWEEN-80	--	--	--	0.5%	--	--
IPM	--	--	0.5%	--	--	--
METHANOL	q.s to 20ml					

Figure 5.8

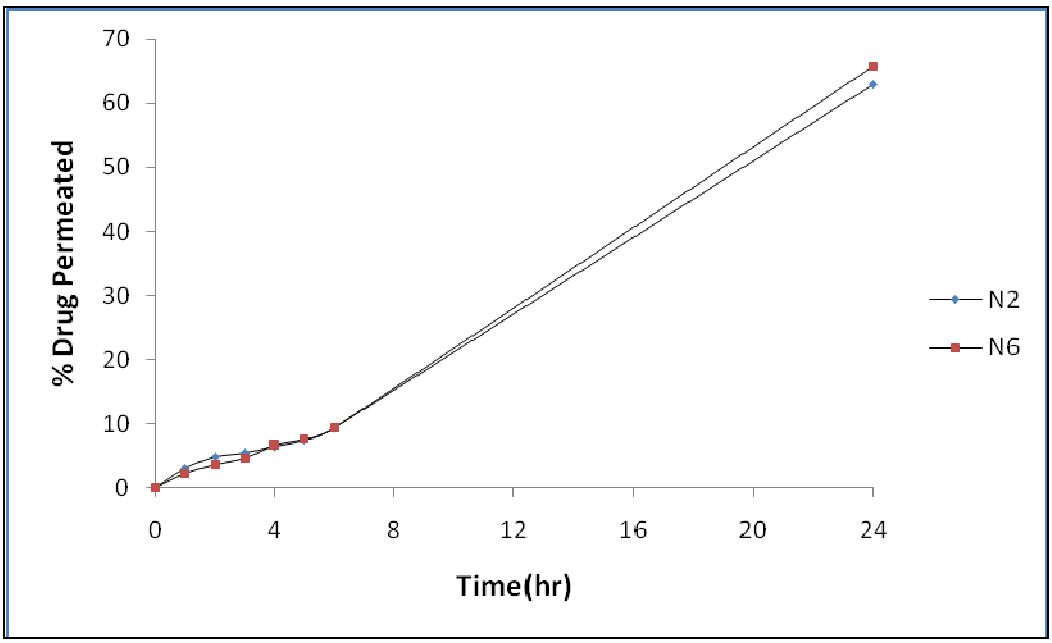


Figure 5.8'

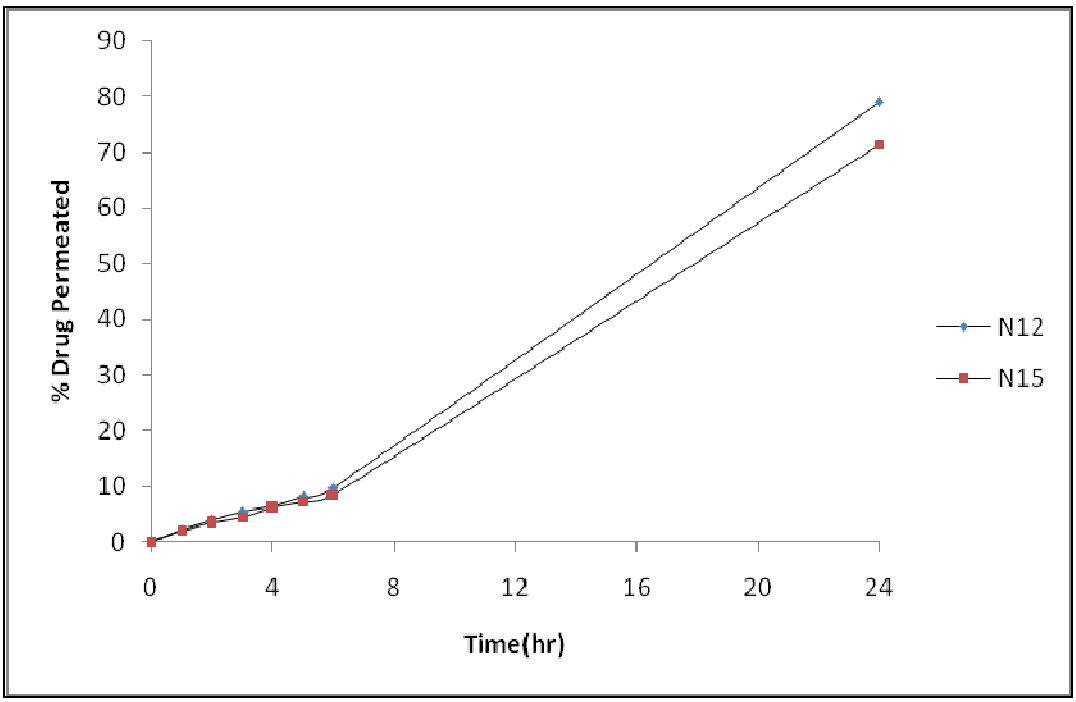
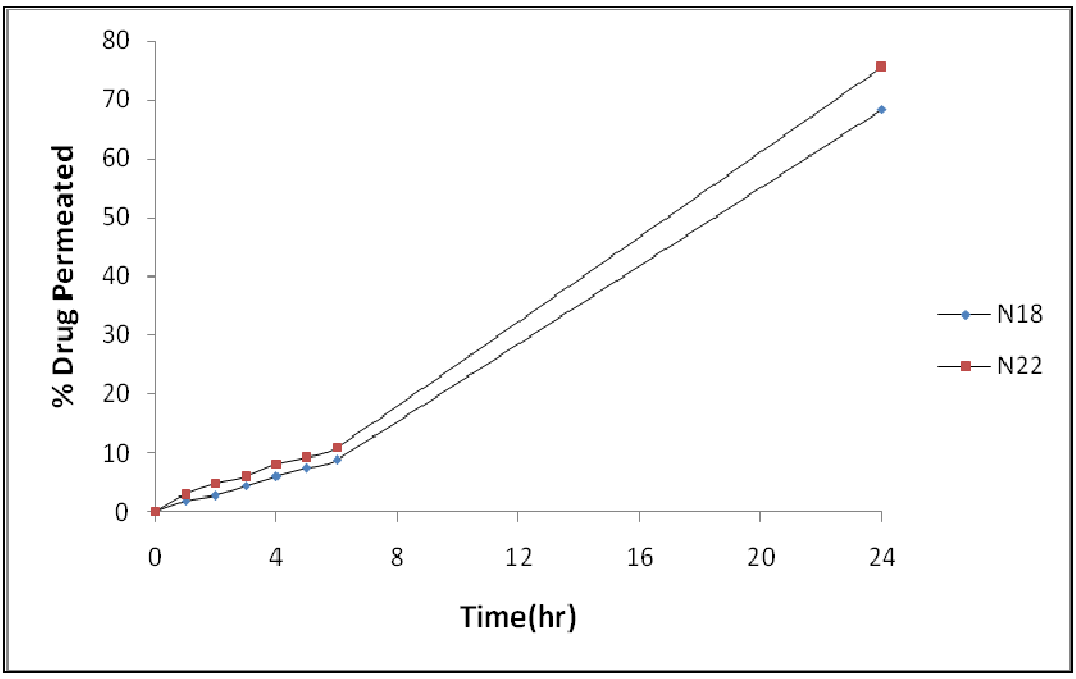


Figure 5.8"



Result & Discussion:

Here effect of polymers to be evaluated. There are three types of polymers to be taken. Single HPMC and combination with ERL 100 and ERS 100.The ratio of plasticizer and penetration enhancer remain same. The results of in-vitro skin permeation studies of batch N2 and N6, N12 and N15, N18 and N22 was given in the figure. From the permeation profile of the drug, 8 batches of HPMC having less permeation as compare with the combination with ERL 100 and ERS 100. The combination of HPMC : ERL100 (3 : 2) and HPMC : ERS 100 (2 :3). Because of The hydrophilic property of HPMC is low so combination of ERL 100 and ERS 100 was increase the hydrophilic property. Thus we can conclude that N12 containing HPMC : ERL 100 (3 : 2) as a polymer and PEG 400 as a plasticizer and N22 HPMC: ERS 100 (2 : 3) are promising formulation for the transdermal films.

5.9 Effect of plasticizers

Ingredients	N2	N12	N18	N6	N15	N22
VALSARTAN	30mg/16cm^2					
HPMC	4%	--	--	4%	--	--
HPMC : ERL 100	--	3:2	--	--	3:2	--
HPMC : ERS 100	--	--	2:3	--	--	2:3
PEG-400	30% w/w			--	--	--
PG	--	--	--	30% w/w		
DMSO	0.5%	--	0.5%	0.5%	--	0.5%
TWEEN-80	--	--	--	--	0.5%	--
IPM	--	0.5%	--	--	--	--
METHANOL	q.s to 20ml					

Figure 5.9

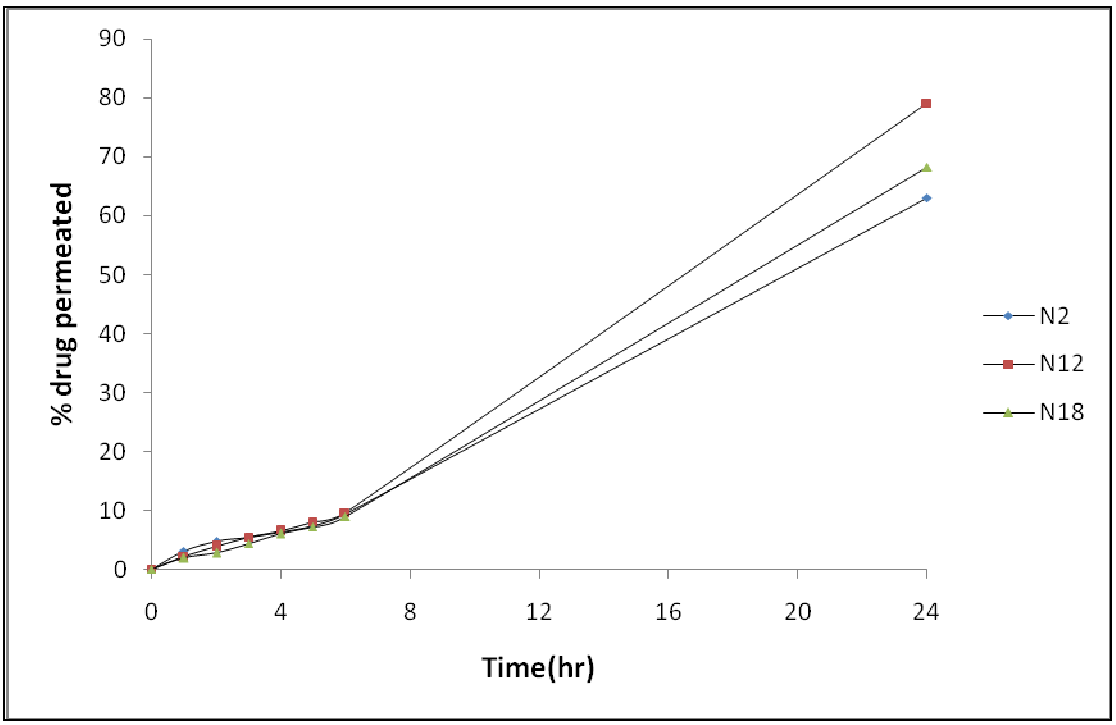
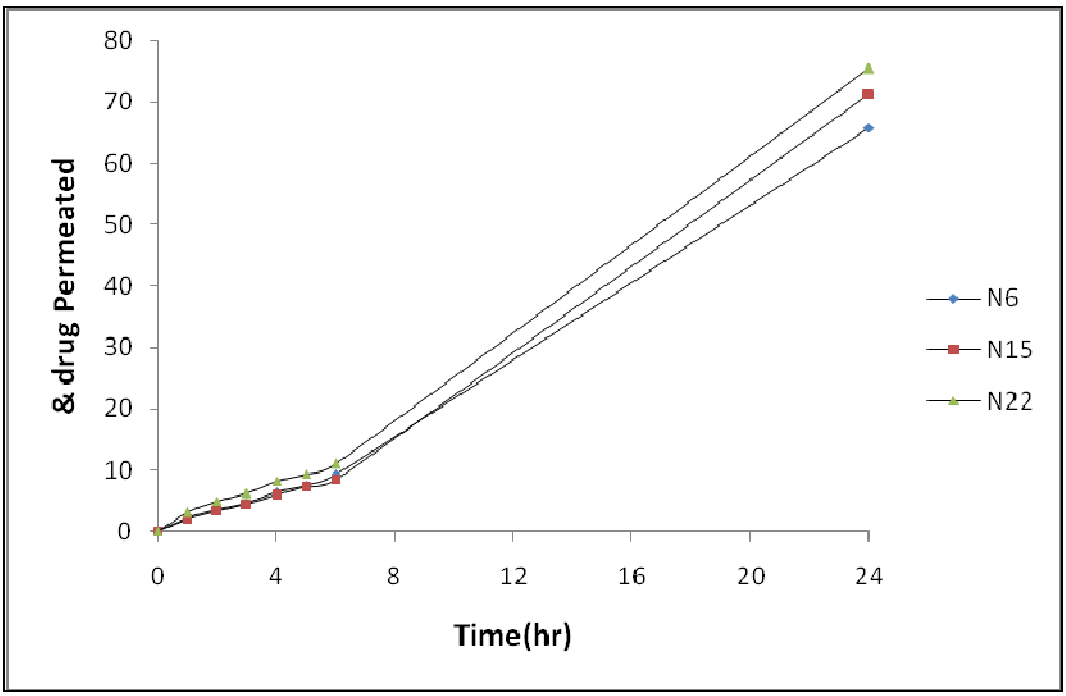


Figure 5.9'



Result & Discussion

Here effect of plasticizer to be evaluated. There are two types of plasticizer to be taken like PEG 400 and PG. The ratio of polymer and penetration enhancer remains same. The results of in-vitro skin permeation studies of batches N2, N12,and N18 having PEG 400 as a plasticizer and batches N6, N15 and N22 having PG as a plasticizer was given in the figure. Polyethylene glycols are more stable, hydrophilic substances that are essentially non-irritant to the skin as compare to PG. They do not readily penetrate the skin, although the polyethylene glycols are water-soluble and are easily removed from the skin by washing. So that the N12 batch is the best formulation for the HPMC : ERL100 polymers and N22 batch is the best batch formulation for HPMC : ERS 100 polymers.

5.10 Effect of penetration enhancer

Ingredients	N2	N6	N12	N15	N18	N22
VALSARTAN	30mg/16cm^2					
HPMC	4%	4%	--	--	--	--
HPMC : ERL 100	--	--	3:2	3:2	--	--
HPMC : ERS 100	--	--	--	--	2:3	2:3
PEG-400	30% w/w	--	30% w/w	--	30% w/w	--
PG	--	30% w/w	--	30% w/w	--	30% w/w
DMSO	0.5%	0.5%	--	--	0.5%	0.5%
TWEEN-80	--	--	--	0.5%	--	--
IPM	--	--	0.5%	--	--	--
METHANOL	q.s to 20ml					

Figure 5.10

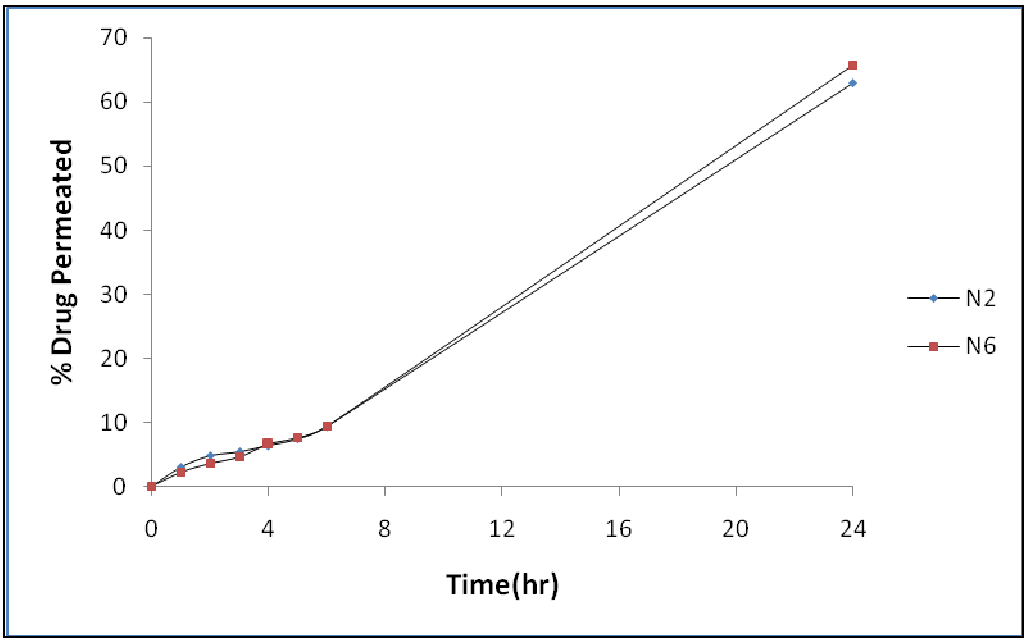


Figure 5.10'

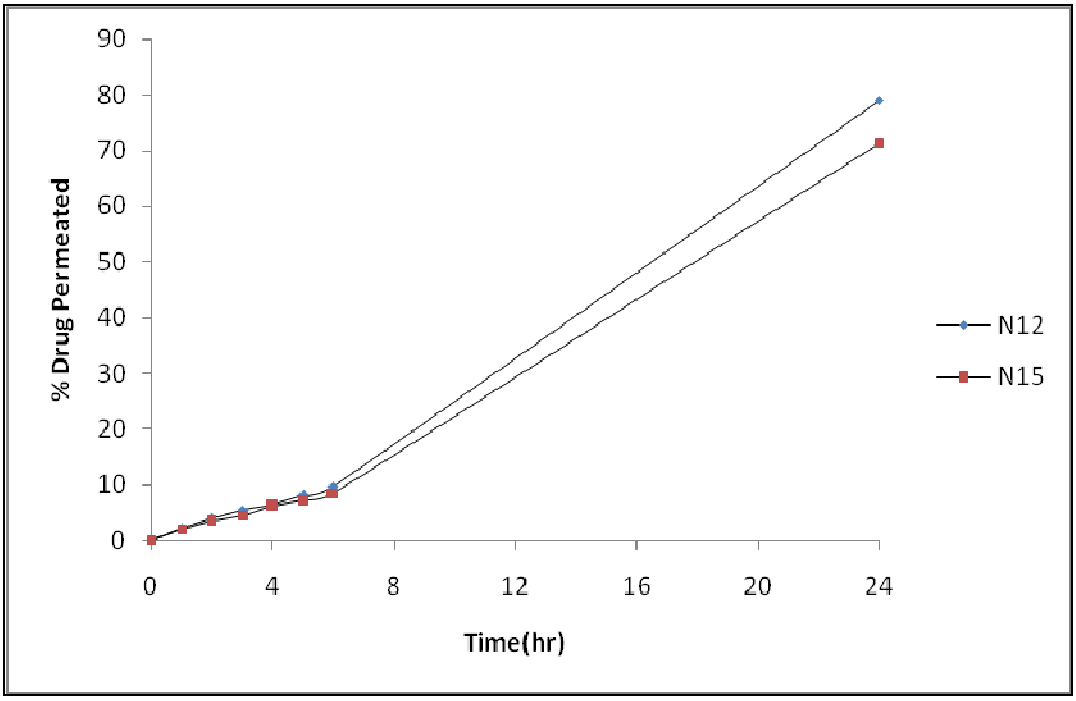
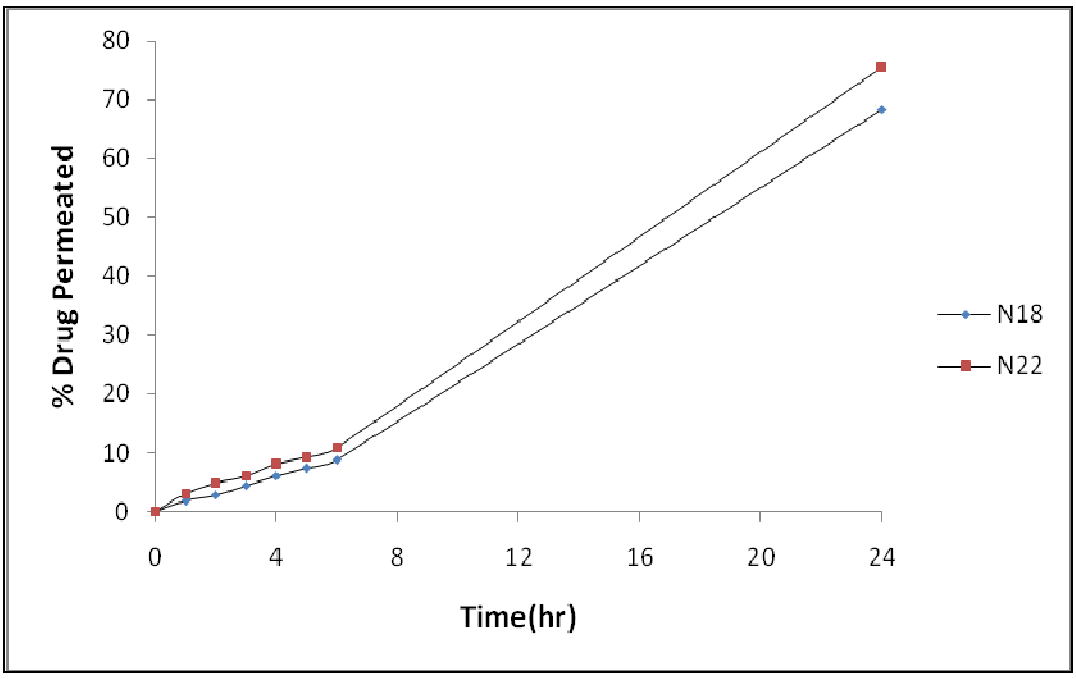


Figure 5.10"



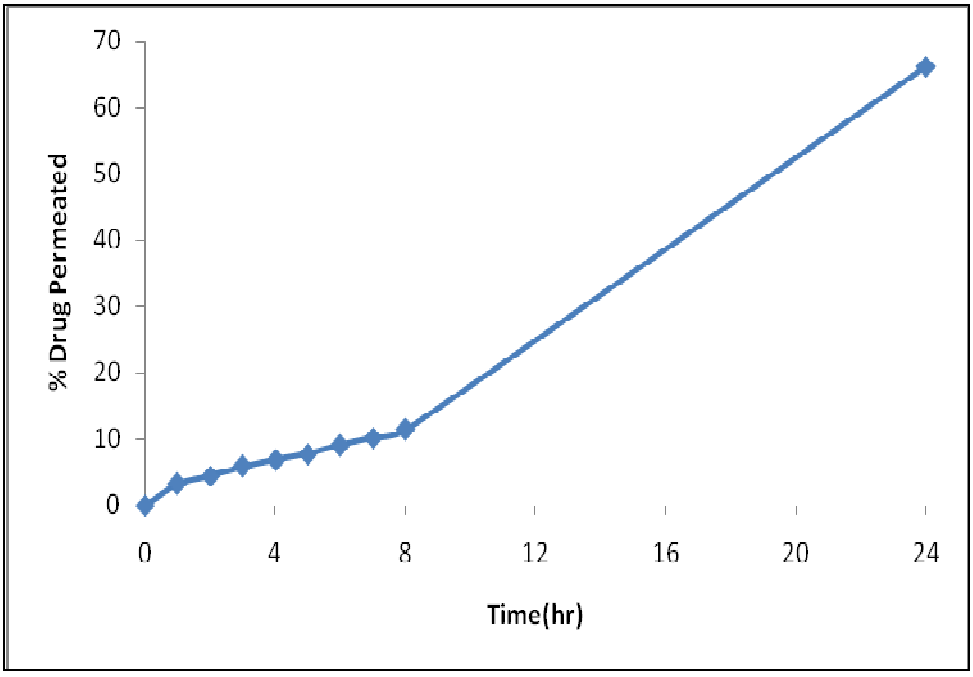
Result and Discussion:

Here effect of penetration Enhancer to be evaluated. There are three types of Enhancers to be taken for preparation of transdermal films like DMSO, tween 80 and IPM. The ratio of polymers and plasticizers remain same. The results of in-vitro skin permeation studies of batch N2 and N6, N12 and N15, N18 and N22 was given in the figure. Here DMSO was given a best result of the formulations as compare to other two penetration enhancers. Because DMSO use for both-hydrophilic and lipophilic permeants, it is an aprotic solvents which hydrogen bond with itself rather than with water.Its metabolite will cause foul smell to breath. While Isopropyl myristate is a nongreasy emollient that is absorbed readily by the skin. So as compare to Tween 80 DMSO and IPM having best permeation. Thus we conclude that batch N12 and batch N22 having best formulation using IPM and DMSO as a penetration enhancers.

5.11 Calculating flux for the final batches.

Batch N6

Time (hr)	Abs	Dilution factor	Con µg/ml	Con mg/ml	%Drug permeated
0	0	0	0	0	0
1	0.2412	1	5.80	0.17	3.21
2	0.3213	1	7.94	0.24	4.39
3	0.4187	1	10.57	0.32	5.85
4	0.4839	1	12.33	0.37	6.83
5	0.5436	1	13.95	0.42	7.72
6	0.6321	1	16.34	0.49	9.04
7	0.7129	1	18.52	0.56	10.25
8	0.7945	1	20.73	0.62	11.47
24	0.3746	20	186.91	5.61	66.16

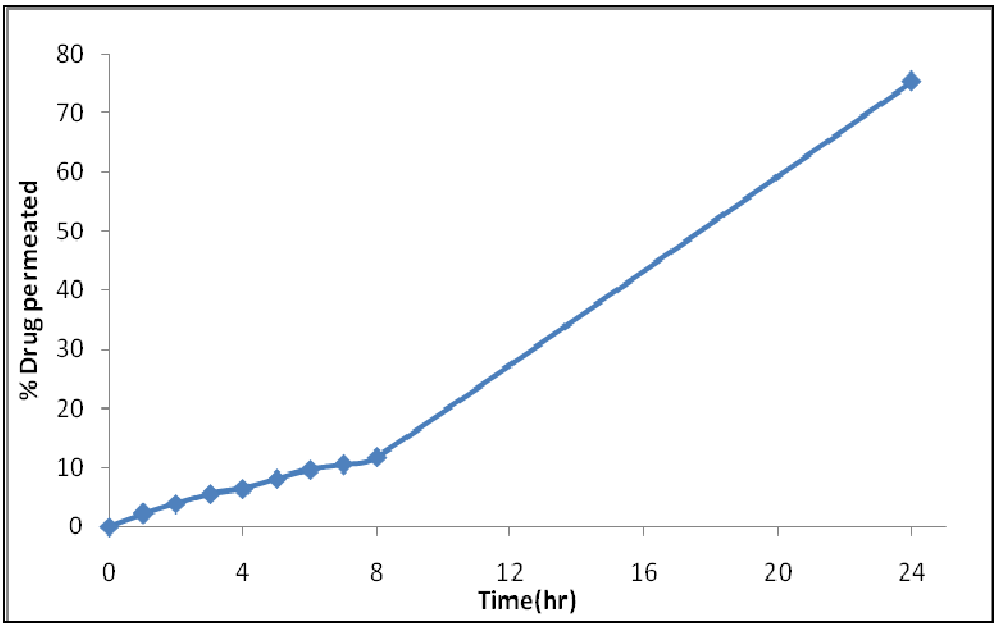


Result :

Calculated	Equation	Value
Permeability coefficient(P)	slope * Vd/Area	3.16
Flux (j)	p *CD	4.17

Batch N12

Time (hr)	Abs	Dilution factor	Con µg/ml	Con mg/ml	%Drug permeated
0	0	0	0	0	0
1	0.1723	1	3.97	0.12	2.19
2	0.2879	1	7.04	0.21	3.89
3	0.3976	1	10.00	0.30	5.54
4	0.4628	1	11.76	0.35	6.51
5	0.5678	1	14.60	0.44	8.08
6	0.6748	1	17.49	0.52	9.68
7	0.7328	1	19.06	0.57	10.55
8	0.8129	1	21.22	0.64	11.75
24	0.4231	20	212.71	6.38	75.30

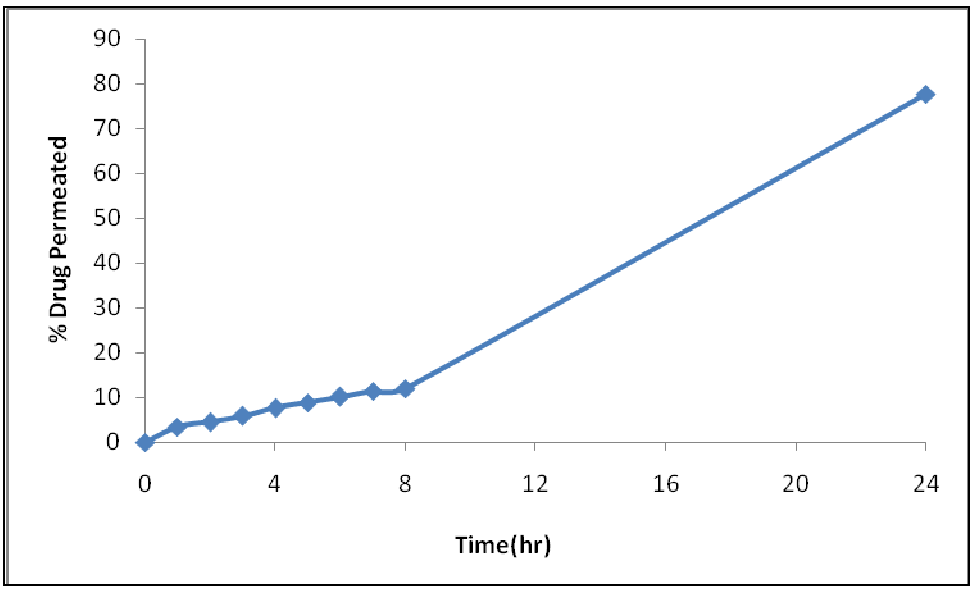


Result :

Calculated	Equation	Value
Permeability coefficient(P)	slope * Vd/Area	3.37
Flux (j)	p *CD	9.70

Batch N22

Time (hr)	Abs	Dilution factor	Con µg/ml	Con mg/ml	%Drug permeated
0	0	0	0	0	0
1	0.2541	1	6.14	0.18	3.40
2	0.3267	1	8.08	0.24	4.47
3	0.4132	1	10.42	0.31	5.77
4	0.5378	1	13.79	0.41	7.63
5	0.6186	1	15.97	0.48	8.84
6	0.7023	1	18.24	0.55	10.09
7	0.7931	1	20.69	0.62	11.45
8	0.8324	1	21.75	0.65	12.04
24	0.4356	20	219.36	6.58	77.65



Result :

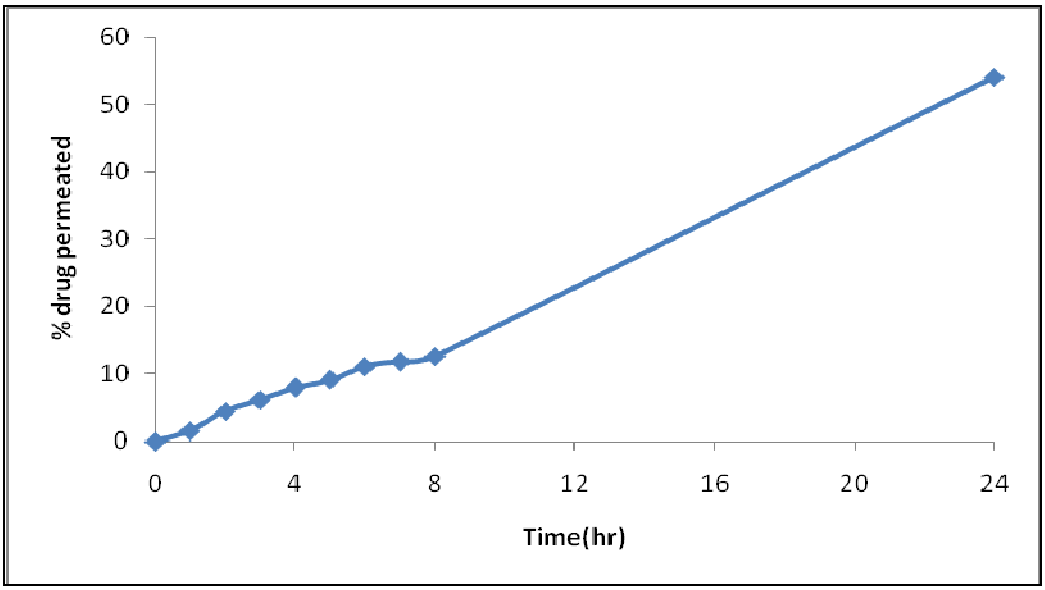
Calculated	Equation	Value
Permeability coefficient(P)	slope * Vd/Area	3.86
Flux (j)	p *CD	7.48

5.11 Comparative Evaluation of gel over the Transdermal film

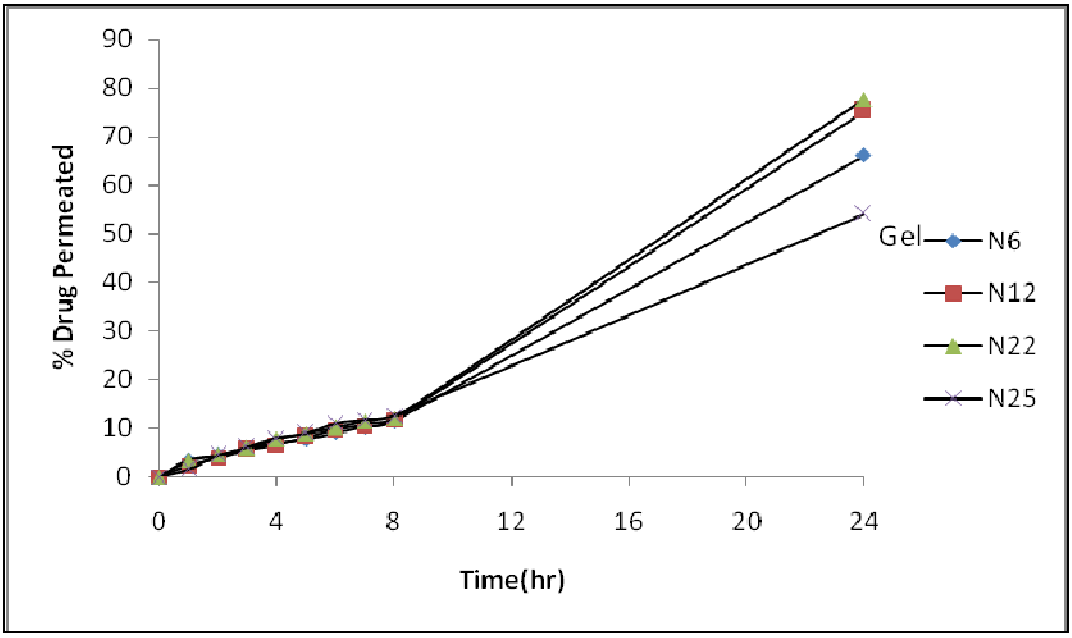
Ingredients	Quantity Taken
Valsartan	200mg
Carbopol	2gm
Propylene Glycol	2gm
Methanol	q.s
Triethanolanine	q.s
Distilled Water	q.s

In- Vitro Drug Permeation Study for Batch N25

Time (hr)	Abs	Dilution factor	Con µg/ml	Con mg/ml	%Drug permeated
0	0	0	0	0	0
1	0.1278	1	2.78	0.08	1.54
2	0.3219	1	7.95	0.24	4.40
3	0.4355	1	11.02	0.33	6.10
4	0.5578	1	14.33	0.43	7.93
5	0.6284	1	16.24	0.49	8.99
6	0.7649	1	19.93	0.60	11.03
7	0.8126	1	21.22	0.64	11.74
8	0.8678	1	22.71	0.68	12.57
24	0.3892	10	97.73	2.93	54.09



In-Vitro Drug permeation profile of Batch N6, N12, N22, N25



Result & Discussion

The comparison study of transdermal fims was to be taken with formulation of gel of valsartan. 30mg of gel was formulated using Carbopol-934 as a gelling agent. The gel was evaluated for its permeation profile through the hairless rat abdomen skin. The comparative results of in vitro drug permeation studies of valsartan gel 30mg and permeation profile of other batches was shown in the figure. The amount of permeated in the drug was lower as compared with other three batches N6, N12 & N22.It indicating that the transdermal films having a good satisfactory results as compare to gel.

6. SUMMARY

Valsartan is given orally in a dose of 40 mg to 320mg daily. This administration is due to pharmacokinetic parameters viz. short biological half life and high first pass metabolism of the drug. Thus there is a great need to develop a novel drug delivery system that can effectively deliver the drug in a systemic circulation with a good therapeutic plasma concentration. Valsartan can not be administered via intravenous route because it caused arrhythmia and cardiac arrest[5]. Through Valsartan is administered via oral route, it is associated with various parameters like bioavailability (just 23%), intestinal metabolism and very high first pass metabolism.

The precision parameters like (bio availability, half life, and first pass metabolism) of Valsartan indicate it is an ideal candidate for development of transdermal delivery system. Thus transdermal route seems to be promising route for delivering the drug effectively because of various advantage like avoidance of hepatic first pass metabolism, improved bioavailability maintain constant blood levels, decrease side effects etc.

The films were made by the film casting method and they were evaluated for thickness, mechanical properties such as tensile strength and folding endurance, In-vitro dissolution study, In vitro diffusion study, Moisture content etc. Transdermal films of valsartan were prepared using different polymers, plasticizers and permeation enhancers. Different polymers like HPMC, ERL 100 and ERS 100 alone and the combination with HPMC: ERL 100 and HPMC : ERS 100 with different plasticizers like PEG 400 and Propylene Glycol were tried. For the preliminary trials PEG 400, PG and DBP were used. But DBP did not give premising result for preparing the films because it could not casted from the petri dish.

It was found that 4 % HPMC along with 30% of PEG 400 and Propylene glycol were required to prepared the transdermal films using methanol as a solvent. In the of combination with HPMC : ERL 100 (3 : 2) and HPMC : ERS 100 (2 :3) were tried using 30% PEG 400 and 30 % Propylene Glycol.

In Vitro drug permeation study showed that the permeation enhancers were required to improve the permeation of the drug. Here three types of enhancers were used like DMSO, Tween 80 and IPM. DMSO was found more effective in batch (N6) containing HPMC (4%) and batch (N22) containing HPMC : ERS 100 (2 : 3).Because

of the DMSO is polar substance that is aprotic and lacking acidic and basic property. The optimized three batches were evaluated for flux. And according to evaluation parameters batch N22 containing Propylene as a plasticizer and DMSO as permeation enhancers was found best as compare to others. The backing membrane was prepared by using ethyl cellulose as a polymer and PEG 400 and TEC (Tri ethyl citrate). Then Final batch was compared with gel. The permeation study showed that drug release from optimized batch was faster than gel.

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Valsartan is given orally in a dose of 40 mg to 320mg daily. This administration is due to pharmacokinetic parameters viz. short biological half life and high first pass metabolism of the drug. Thus there is a great need to develop a novel drug delivery system that can effectively deliver the drug in a systemic circulation with a good therapeutic plasma concentration. Valsartan can not be administered via intravenous route because it caused arrhythmia and cardiac arrest[5]. Through Valsartan is administered via oral route, it is associated with various parameters like bioavailability (just 23%), intestinal metabolism and very high first pass metabolism.

The precision parameters like (bio availability, half life, and first pass metabolism) of Valsartan indicate it is an ideal candidate for development of transdermal delivery system. Thus transdermal route seems to be promising route for delivering the drug effectively because of various advantage like avoidance of hepatic first pass metabolism, improved bioavailability maintain constant blood levels, decrease side effects etc.

The films were made by the film casting method and they were evaluated for thickness, mechanical properties such as tensile strength and folding endurance, In-vitro dissolution study, In vitro diffusion study, Moisture content etc. Transdermal films of valsartan were prepared using different polymers, plasticizers and permeation enhancers. Different polymers like HPMC, ERL 100 and ERS 100 alone and the combination with HPMC: ERL 100 and HPMC : ERS 100 with different plasticizers like PEG 400 and Propylene Glycol were tried. For the preliminary trials PEG 400, PG and DBP were used. But DBP did not give premising result for preparing the films because it could not casted from the petri dish.

It was found that 4 % HPMC along with 30% of PEG 400 and Propylene glycol were required to prepared the transdermal films using methanol as a solvent. In the of combination with HPMC : ERL 100 (3 : 2) and HPMC : ERS 100 (2 :3) were tried using 30% PEG 400 and 30 % Propylene Glycol.

In Vitro drug permeation study showed that the permeation enhancers were required to improve the permeation of the drug. Here three types of enhancers were used like DMSO,

Tween 80 and IPM. DMSO was found more effective in batch (N6) containing HPMC (4%) and batch (N22) containing HPMC : ERS 100 (2 : 3).Because of the DMSO is polar substance that is aprotic and lacking acidic and basic property. The optimized three batches were evaluated for flux. And according to evaluation parameters batch N22 containing Propylene as a plasticizer and DMSO as permeation enhancers was found best as compare to others. The backing membrane was prepared by using ethyl cellulose as a polymer and PEG 400 and TEC (Tri ethyl citrate). Then Final batch was compared with gel. The permeation study showed that drug release from optimized batch was faster than gel.