DESIGN AND CHARACTERIZATION OF TRANSDERMAL DELIVERY OF REPAGLINIDE

Dissertation submitted to

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

in partial fulfillment of the requirement for the award of degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

March – 2010

DEPARTMENT OF PHARMACEUTICS

COLLEGE OF PHARMACY

MADURAI MEDICAL COLLEGE

A.Abdul Hasan Sathali, M.Pharm,
Professor and Head,
Department of pharmaceutics,
College of pharmacy,
Madurai Medical College,
Madurai-625 020

CERTIFICATE

This is to certify that the Dissertation entitled **"DESIGN AND CHARACTERIZATION OF TRANSDERMAL DELIVERY OF REPAGLINIDE"** submitted by **Mr. P.BALAJI** in partial fulfillment of the requirement for the degree of **Master of Pharmacy** in **Pharmaceutics** is a bonafide work carried out by him, under my guidance and supervision during the academic year 2009 – 2010 in the Department of Pharmaceutics, Madurai Medical College, Madurai-20.

I wish him success in all his endeavors.

Place: Madurai

Date: **(A.Abdul Hasan Sathali)**

CHAPTER I

INTRODUCTION

Oral administration of drugs has been practiced for centuries and, most recently, through tablets and capsules. Injectables came into being approximately 130 years ago, but have only become acceptable since the development of a better understanding of sterilization [1]. Topical application has also been used for centuries, predominantly in the treatment of localized skin diseases. Oral delivery is by far the easiest and most convenient way of delivering drugs especially when repeated and routine administration is required. Therefore, to achieve as well as to maintain the drug concentration within therapeutically effective range needed for treatment, it is often necessary to take this type of drug delivery system several times a day. This results in significant fluctuations in plasma drug concentration levels leading to marked side effects in some cases.

The next era of health care will demand more accommodating delivery systems for sensitive drug classes. Patient compliant, noninvasive and sustained delivery will become the key feature desirable of any drug delivery system.

Modified release drug delivery system can be divided into four categories [2].

a) Delayed release.

b) Sustained release.

   i. Controlled release.

   ii. Extended release.

c) Site specific targeting.

d) Receptor targeting.

a) Delayed release:

These systems are those that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form. Examples of delayed release systems include repeat action tablets and capsules and enteric coated tablets where timed release is achieved by a barrier coating.

b) Sustained release:

The term “sustained release” describes a pharmaceutical dosage form formulated to retard the release of a therapeutic agent such that its appearance in the systemic circulation is delayed and/ or prolonged .The onset of its pharmacologic action is often delayed and the duration of its therapeutic effect is sustained.

i) Controlled release:

The term “controlled release” implies the release of drug ingredient(s) from controlled-release drug delivery system proceeds at a rate profile that is not only predictable kinetically, but also reproducible from one unit to another.

ii) Extended release:

Pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate and necessarily reduce the dosage frequency by two folds.

c) Site specific targeting:

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is adjacent to or in the diseased organ or tissue.

d) Receptor targeting:

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug within an organ or tissue. Site specific targeting and receptor targeting systems satisfy the aspect of drug delivery and are also considered to be controlled drug delivery systems.

Controlled drug delivery systems:

In the mid- to late 1960s, the term "controlled drug delivery" came into being to describe new concepts of dosage-form design. These concepts usually involved controlling drug dissolution, but also had additional objectives. The primary objectives of a controlled-release system have been to enhance safety and extend duration of action. Today, we also have controlled-release systems designed to produce more reliable absorption and to improve bioavailability and efficiency of delivery.

Controlled drug delivery systems hold the major credibility because of its obvious advantages of [3],

a) Increase in patient compliance.

b) Reduction in total dose administered, thereby,

- Minimize or eliminate local and systemic side effects.
- Minimize drug accumulation with chronic use.
- Obtain less potentiation or reduction in drug activity with chronic use.

c) Improve efficiency in treatment.

- Cure or control condition more promptly.
- Reduces fluctuation in plasma drug concentration.
- Improve bioavailability of some drugs.
- Possibly reduced patient care time.
- Improved patient compliance.

Some of the disadvantages of controlled drug delivery systems are as follows,

- Longer time to achieve therapeutic blood concentrations.
- Dose dumping.
- Sustained concentration decline in overdose cases.
- Lack of dosage flexibility.
- Usually, greater expense.
- Enhanced first pass effect.

Various forms of controlled drug delivery systems are [4]

- Oral drug delivery systems.
- Mucosal drug delivery systems.
- Nasal drug delivery systems.

- Ocular drug delivery systems.
- Transdermal drug delivery systems.
- Parenteral drug delivery systems.
- Vaginal drug delivery systems.
- Intrauterine drug delivery systems.
- Systemic delivery of peptide based pharmaceuticals.

Innovations in the area of drug delivery are taking place at a much faster as compared to last two decades. Improved patient compliance and effectiveness are inextricable aspects of a new drug delivery system [5]. A large contribution to these novel systems appeared as modifications of the active drug or use of formulation excipients to modulate drug pharmacokinetics, safety, efficacy and metabolism. A more radical approach has been to explore newer interfaces on the body for introducing therapeutics. One such approach, transdermal drug delivery, makes use of human skin as a port of entry for systemic delivery of drug molecules.

Transdermal drug delivery systems:

Transdermal delivery systems are specifically designed to obtain systemic blood levels and have been used in the U.S. since the 1950s. Transdermal permeation, or percutaneous absorption, can be defined as the passage of a substance, such as a drug, from the outside of the skin through its various layers into the bloodstream.

The first commercially available prescription patch was approved by the U.S.Food and Drug Administration in December 1979 [6], which administered scopolamine for motion sickness.

There are now more than 35 transdermal products, containing atleast 13 approved molecules. According to a report by Jain PharmaBiotech, the value of the global market for transdermal delivery was $12.7 billion in the year 2005 and is expected to increase to $21.5 billion in the year 2010 and $31.5 billion in the year 2015 [7] . Nowadays, the transdermal route has become one of the most successful and innovative focus for research in drug delivery, with around 40% of the drug candidate being under clinical evaluation related to transdermal or dermal systems [8].

Factors limiting the success of transdermal technology include local skin irritation and other adverse reactions associated with certain drugs and formulation, limitation on the dose of drug that can be delivered transdermally, a lag time associated with the delivery of the drug across the skin, resulting in a delay in onset of action, variation of absorption rate based on site of application, skin disease, and variation in adhesive effectiveness in different individuals.

Over the last 25 years, the transdermal patch has become a proven technology accepted as offering a variety of significant clinical benefits over other dosage forms. Drug delivery direct to the systemic circulation via the application to the skin appears to be a desirable alternative to oral delivery for several good reasons [9]:

- Improved patient compliance.

- Patients have difficulty in swallowing tablets and capsules and some patients are tempted to crush tablets to assist in swallowing which destroys any controlled release characteristics of the tablets.
- Many orally delivered drugs irritate the gastrointestinal mucosa and a large number undergo extensive ‘first-pass’ inactivation by the liver.
- A controlled delivery of drugs through the skin can provide less fluctuation in the circulating drug levels.
- Greater flexibility of dosage in that dosing can be easily terminated by removal of the TDDS.

The non-invasive character of TDDS makes it accessible to a wide range of patient populations and a highly acceptable option for drug dosing.

.

CHAPTER II

TRANSDERMAL DRUG DELIVERY SYSTEM – A REVIEW.

"Transdermal drug delivery system is a non invasive, self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at a controlled rate to the systemic circulation".

Recently, the transdermal route has vied with oral treatment as the most successful innovative research area in drug delivery. In the USA, out of 129 drug delivery candidate products under clinical evaluation, 51 are transdermal or dermal systems; 30% of 77 candidate products in preclinical development represent such drug delivery. The worldwide transdermal market approaches £2 billion, yet is based on only ten drugs — scopolamine (hyoscine), nitroglycerine, clonidine, estradiol (with and without norethisterone or levonorgestrel), testosterone, fentanyl and nicotine, with a lidocaine patch soon to be marketed.

Advantages of Transdermal Drug Delivery System (TDDS):

- Prolonged therapy and continuous drug delivery is possible with once daily or multiday patches.
- Enables utilization of drugs with short-half-life and low therapeutic index due to sustained therapeutic effect of transdermal drug delivery system and Provides more consistent treatment of chronic disease.
- Facilitates more predictable drug absorption due to avoidance of GI tract variables (pH, motility, transit time, presence of food)

- Avoidance of “Hepatic first pass effect” and reduction of dose for some drugs.
- Provides an alternative route when oral dosing is unsuitable.
- Minimizes fluctuations in plasma drug concentration through controlled drug input, thereby abatement of side effects.
- Noninvasive, More convenient, Painless, Lower risk of complications and Suitable for outpatient use.
- Reduces dosing frequency and improves patient compliance.
- Removed easily and cessation of drug input in case of toxicity.

Limitations of Transdermal Drug Delivery System:

- Drug candidates with molecular weight more than 500 daltons fail to penetrate stratum corneum.
- Drugs with very low or high partition coefficient are non-conducive for transdermal drug delivery system.
- Drugs with high melting point fail to cross stratum corneum due to their low solubility in both water and fat.
- Drugs that require high blood levels cannot be administered.
- Adhesives used may not adhere well to all types of skin.
- Drugs or ingredients used in formulation may cause skin irritation (or) sensitization.
- Transdermal drug delivery systems may not be economical to some patients.

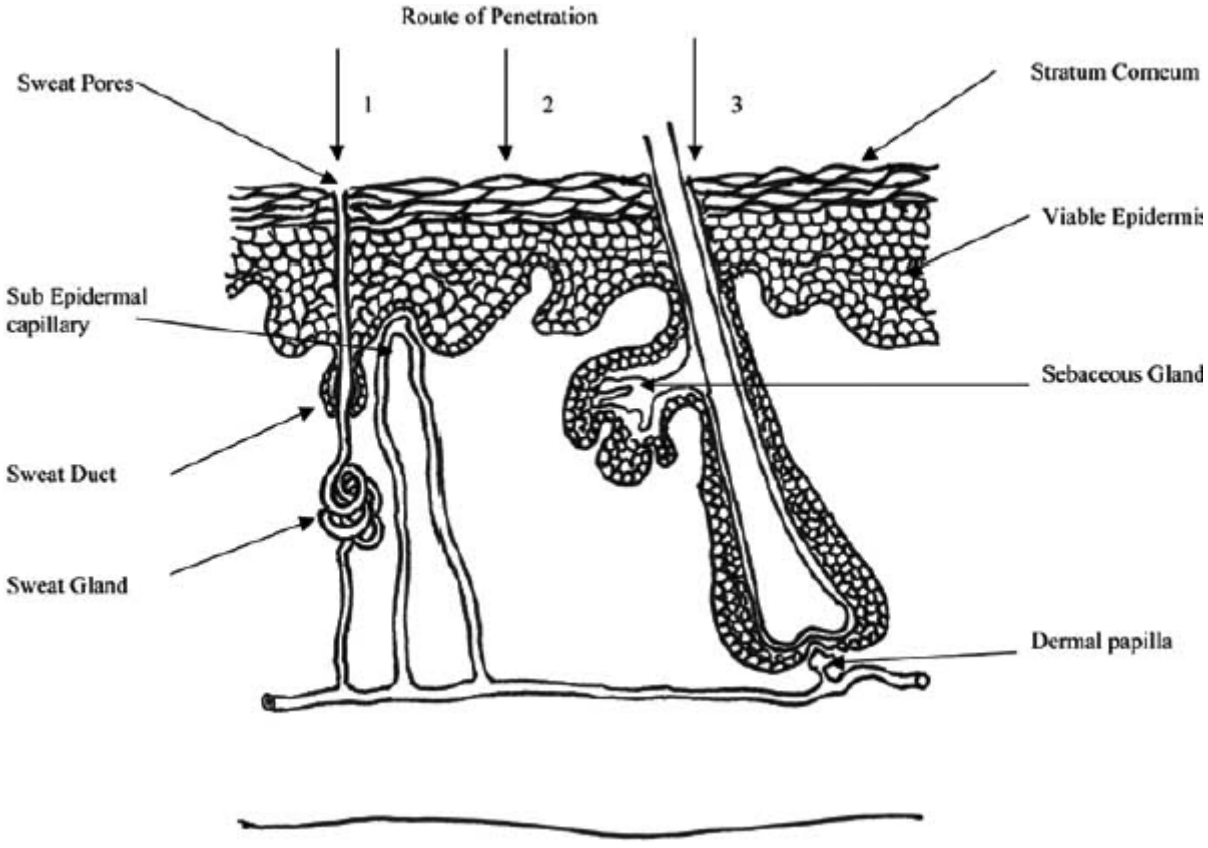
Skin – An effective barrier for permeation:

The skin is one of the most extensive and readily accessible organs of the human body. It receives about one-third of the blood circulation through the body. The skin is a very effective barrier for the permeation of most xenobiotics. Only a very little drug actually arrives at the site action.

Skin is a multilayered tissue consisting of Epidermis, Dermis and Hypodermis.

Stratum corneum (or) horny layer is the outermost layer of epidermis, which restricts the inward and outward movement of chemical substances. These are compacted, flattened, dehydrated and keratinized cells which are physiologically inactive.

Figure - 1



Stratum corneum has two distinct chemical regions,

i) The mass of intracellular protein

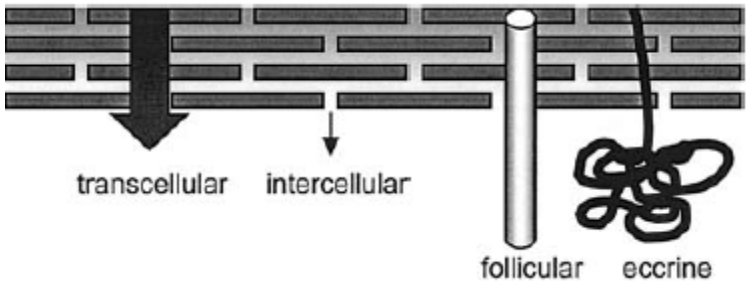
ii) The intercellular lipoidal medium.

The epidermis rests on the much thicker (2000 µm) dermis. The dermis essentially consists of about 80% protein in a matrix of mucopolysaccharide ground substance. Also contained within the dermis are lymphatics, nerves and epidermal appendages such as hair follicles, sebaceous glands and sweat glands.

Pathways involved in drug permeation:

Percutaneous absorption (or) permeation involves passage of drug (or) chemicals through the epidermis itself (Transepidermal absorption) or diffusion through shunts offered by relatively widely distributed hair follicles and eccrine glands (transappendegeal).

Figure - 2



Transepidermal (or Transcorneal) penetration includes intracellular and intercellular penetration, hydrophilic drugs generally seen to permeate through intracellular pathway. As stratum corneum hydrates, water accumulates near the outer surface of the protein filaments. Polar molecules appear to pass through this immobilized water. Non polar substances

permeate through intercellular penetration. These molecules diffuse into the non-aqueous lipid matrix imbibed between the protein filaments.

In Transappendegeal permeation (shunt pathway) the drug molecule may transverse through the hair follicles, the sebaceous pathway of pilosebaceous apparatus or the aqueous pathway of the salty sweat glands.

The transdermal permeation can be visualized as composite of a series in sequence as:

1. Adsorption of a penetrant molecule onto the surface layers of stratum corneum.
2. Diffusion through stratum corneum and through viable epidermis.
3. Finally through the papillary dermis into the microcirculation.

The viable tissue layer and the capillaries are relatively permeable and the peripheral circulation is sufficiently rapid. Hence diffusion through the stratum corneum is the rate limiting step.

Basic components of TDDS:

- Polymer matrix / Drug reservoir.
- Drug.
- Permeation enhancers.
- Adhesives.
- Backing laminates.
- 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 shelf life and should be of safe.

The following criteria should be satisfied for a polymer to be used in transdermal formulations,

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

The polymers utilized for TDDS can be classified as:

- **Natural Polymers**: e.g. cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan etc.

- **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, polyvinylpyrrolidone and hydroxypropylmethylcellulose 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 more benefits 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.

Drug selection for TDDS:

The ideal characteristics for a drug candidate to be formulated as Transdermal formulation are as follows

Parameters	Ideal characteristics

Aqueous solubility.	>1mg/ml
Lipophilicity	10<Kw/o<1000
Molecular weight.	<500 daltons
Melting point.	<200^{o}c
PH of aqueous saturated solution.	5 to 9
Dose deliverable	<10mg/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 viz proteins or lipids. They alter the protein and lipid packaging of stratum corneum, thus chemically modifying the barrier functions leading to increased permeability.

Types of permeation enhancers	Mechanism of permeation	Examples
Solvents	By swelling of polar pathway. By fluidizing lipids.	Methanol, ethanol, Alkyl methyl sulfoxides – dimethylsulfoxide, pyrrolidones, miscellaneous solvents – propylene glycol etc.
Surfactants	By enhancing the polar pathway By irritating the skin.	Anionic surfactants – Dioctylsulphosuccinate, Sodium lauryl sulphate, Decodecylmethyl

		sulphoxide etc. Nonionic surfactants – Pluronic F127, Pluronic F68,
Bile salts		Sodium taurocholate, Sodium deoxycholate, Sodium tauroglycocholate.
Binary systems	By opening up the heterogeneous multilaminate pathway.	Propylene glycol – oleic acid and 1, 4-butane diol-linoleic acid.
Miscellaneous chemicals		Urea, N,N-dimethyl-m-toluamide, Eucalyptol, soya bean casein.

Adhesives:

The fastening of all transdermal devices to the skin has so far been done by using a pressure sensitive adhesive. The pressure sensitive adhesive can be positioned on the face of the device or in the back of the device and extending peripherally. Both the adhesive systems should fulfill the following criteria

- Should not irritate or sensitize the skin.
- Should adhere to the skin aggressively.
- Should be easily removed.
- Should not leave an unwashable residue on the skin.
- Should have an excellent contact with the skin at macroscopic and microscopic level.

Some widely used pressure sensitive adhesives include polyisobutylenes, acrylics and silicones.

Backing Laminate:

Backing membranes are flexible and they provide a good bond to the drug reservoir, prevent drug from leaving the dosage form through the top and accept printing. 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. It is an impermeable substance that protects the product during use on the skin e.g. metallic plastic laminate, plastic backing with absorbent pad and occlusive base plate (aluminium foil), adhesive foam pad (flexible polyurethane) with occlusive base plate (aluminium foil disc) etc.

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 metalized laminates.

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.

Methods of preparation:

Mercury casting method:

In this method mercury is taken in a Petri dish of appropriate size, in which drug containing polymer solution is poured into the dish over the mercury. A funnel is placed in an inverted position over the mercury plate and it is left over night and then the film is separated.

Moulding method:

In this homogeneous drug containing polymer solution is poured in mould of appropriate size and volume and it is left overnight and the film is separated.

Preparation of different types of Transdermal patches:

The systems that have been introduced in market can be classified into following types:

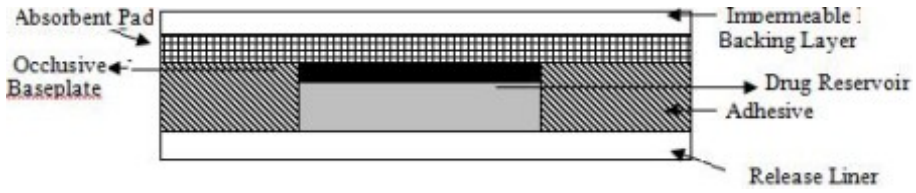
- Matrix type
- Reservoir type
- Micro reservoir type
- Drug in adhesive type

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.

Figure - 3

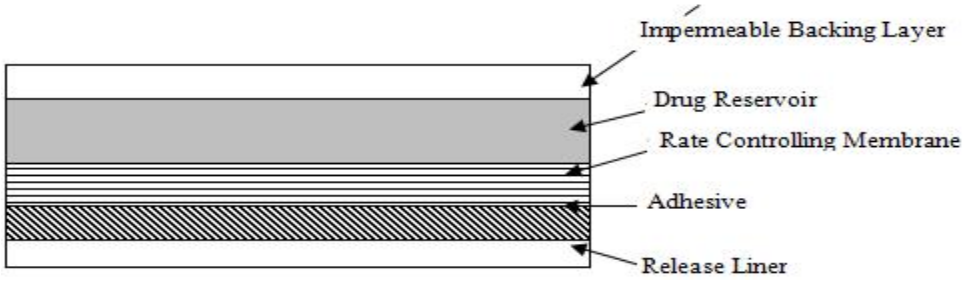


The dispersion of drug particles in the polymer matrix can be accomplished by either homogenously mixing the finely ground drug particles with a liquid polymer or a highly viscous base polymer followed by cross linking of polymer chains or homogenously blending drug solids with a rubbery polymer at an elevated temperature. This system is exemplified by development of Nitro-Dur.

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.

Figure - 4



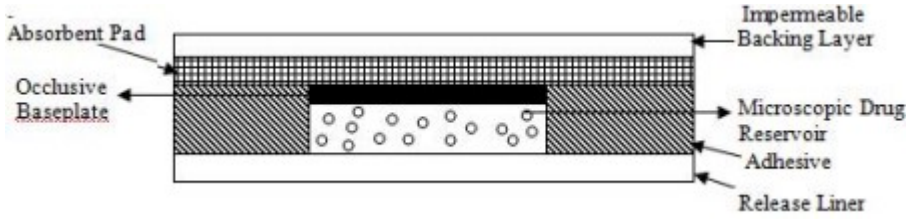
The rate controlling membrane can be nonporous so that the drug is released by diffusing directly through the material, or the material may contain fluid filled micropores in which case the drug may additionally diffuse through the fluid, thus filling the pores. In the case of nonporous membrane, the 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.

Rate controlling membrane may be prepared by solvent evaporation method or compression method. Examples of marketed preparations are Duragesic, Estradem and Androderm.

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. This system is exemplified by development of Nitrodisc.

Figure - 5

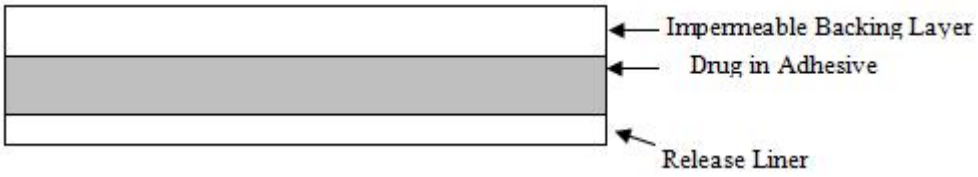


Drug in adhesive type transdermal patch(s):

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.

Figure - 6



Some examples of suitable pressure sensitive adhesives are polysiloxanes, polyacrylates and polyisobutylene. These pressure sensitive adhesives are hydrophobic in nature and are prepared as solutions of polymer dissolved in organic solvents. Hence, this type of system is preferred for hydrophobic drugs as it is to be incorporated into organic solvent based hydrophobic adhesive. Examples of marketed preparations of drug-in-adhesives patches are Climara, Nicotrol and Deponit.

Evaluation of Transdermal patches:

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

Physicochemical Evaluation:

Various physicochemical evaluations for transdermal drug delivery systems are as follows.

- Thickness
- Uniformity of weight.
- Drug content determination.
- Moisture content.
- Moisture uptake.
- Flatness.
- Folding endurance.
- Tensile strength.
- Water vapor transmission studies.
- Adhesive studies.
    - Peel Adhesion properties
    - Tack properties.
    - Thumb tack test
    - Rolling ball test.
    - Quick stick (Peel tack) test.
    - Probe tack test.
    - Shear strength properties or creep resistance.

In vitro release studies:

Drug release mechanisms and kinetics are two characteristics of the dosage forms which play an important role in describing the drug dissolution profile from a controlled release dosage forms and hence their in vivo performance.

There are various methods available for determination of drug release rate of TDDS.

- Paddle over disc. (USP apparatus 5)
- The Cylinder modified USP Basket (USP apparatus 6).
- The reciprocating disc (USP apparatus 7)

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. 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.

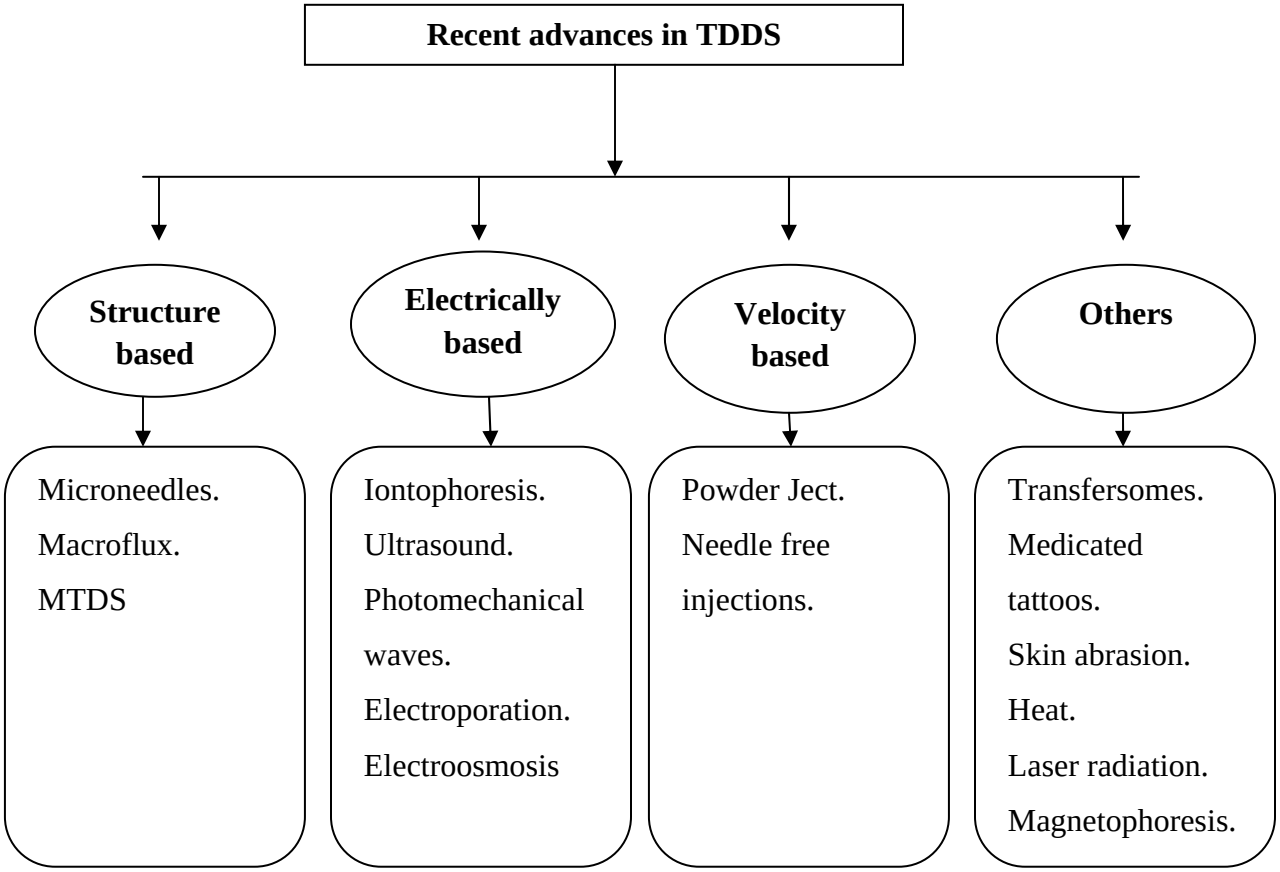
In vivo Studies:

In vivo evaluations are the true depiction of the drug performance. The variables which cannot be taken into account during in vitro studies can be fully explored during in vivo studies. In vivo evaluation of TDDS can be carried out using:

- Animal models.
- Human volunteers.

Current developments in Transdermal technologies:

Several approaches have been tried to overcome the primary barrier, viz., stratum corneum to facilitate the passage of a drug through the skin. These approaches can be classified as follows.



CHAPTER III

LITERATURE REVIEW

1. **Raju.R.Thenge et al.,** developed a matrix type transdermal patches lercanidipine hydrochloride. The transdermal patches were prepared by solvent casting method. The patches were evaluated for physical appearance, Thickness, weight variation, folding endurance, percentage moisture content, in-vitro drug release study and ex-vivo skin permeation study. Ex- vivo permeation studies revealed that extent of drug release was higher in case of (polymers ERS 100 and HPMC) than (polymers ERS 100 and EC) [24].

2. **Satyanarayan pattnaik et al .,** investigated polymer matrix Transdermal films of Alfuzosin Hydrochloride using statistical experimental design. Various physicochemical parameters of the transdermal films were evaluated. Influence of polymers on the cumulative amount of alfuzosin hydrochloride permeated per cm2 of human cadaver skin at 24 h (Q24), permeation flux (J) and steady state permeability coefficient (PSS) were studied using experimental design. Ratio of EC and PVP was found to be the main influential factor for all the dependent variables studied. Drug loading dose was also found to influence the cumulative amount released but to a lesser extent [25].

3. **Kevin c. Garala et al .,** studied about *in-vitro* characterization of monolithic matrix transdermal systems using HPMC/Eudragit S 100 polymer blends. Monolithic matrix transdermal systems containing tramadol HCl were prepared using various ratios of the polymer blends of hydroxy propyl methyl cellulose (HPMC) and Eudragit S 100 (ES) with triethyl citrate as a plasticizer. A 32 full factorial design was employed. 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 experimental results shows that the transdermal drug delivery system (TDDS) containing ES in higher proportion gives sustained the release of drug [26].

4. **Liang Fang et al .,** prepared transdermal formulations of Indomethacin. The patches were prepared using MASCOS 10 (polyacrylic acid type) pressure sensitive adhesive was used to prepare a drug-in-adhesive type patch containing a variety of permeation enhancers. The results showed that the presence of IPM, oleic acid and Tween 80 did not increase Indomethacin permeation from the transdermal patches compared with the transdermal patches containing azone and *L*-menthol ($P > 0.05$). 5% azone and 5% *L*-menthol were the permeation enhancers of choice for the percutaneous absorption of Indomethacin [27].

5. **N. Udupa et al.,** investgated Glibenclamide Transdermal Patches for Physicochemical, Pharmacodynamic, and Pharmacokinetic Evaluations. matrix type transdermal patches containing glibenclamide were prepared using different ratios of ethyl cellulose (EC)/polyvinylpyrrolidone (PVP) and Eudragit RL-100 (ERL)/Eudragit RS-100 (ERS) by solvent evaporation technique. All the prepared formulations were subjected to physicochemical studies (thickness, weight variation, drug content, moisture content and uptake, and flatness), in vitro release and in vitro permeation studies through mouse skin. The pharmacokinetic evaluation showed that the patches could maintain almost steady-state

concentration of drug within the pharmacologically effective range for prolonged period of time [28].

6. **H.O. Ammar et al.,** investigated membrane mediated transdermal sytems of aspirin. The study comprised formulation of aspirin in different topical bases. Release studies revealed that hydrocarbon gel allowed highest drug release. In vitro permeation studies revealed high drug permeation from hydrocarbon gel. Several chemical penetration enhancers were monitored for augmenting the permeation from this base. Combination of propylene glycol and alcohol showed maximum enhancing effect [29].

7. **Yun-seek Rhee et al .,** investigated of monolithic matrix patch system containing Tulobuterol. The effect of functional groups in acrylic adhesive on tulobuterol uptake, release rate and permeation rate across rat skin were investigated. These results indicate that there was an interaction between secondary amino group of tulobuterol and the carboxy group of the acrylic poltmer therefore the drugs chemical structure and functional groups in pressure sensitive adhesives must be considered in order to formulate a transdermal patch system [30].

8. **Mohd. Aqil et al.,** studied in-vivo characterization of monolithic matrix patches of Pinacidil monohydrate. The transdermal patches were prepared by solvent casting technique using Eudragit RL 100 and PVP K30. All the formulations were evaluated for physico-chemical parameters. The in - vivo studies showed a significant fall in BP with all formulations [31].

9. **Ramesh Panchagnula et al.,** developed reservoir type transdermal patches of naloxone. Ex vivo permeation studies were performed by employing porcine and rat skins. Further stability of the formulation was established for 3 months at accelerated stability conditions as per ICH guidelines. Based on ex vivo data, the surface area (SA) of the patch was predicted to be 39.6 cm2 in order to achieve therapeutic blood levels. Upon single dose administration, the steady-state levels were maintained from 4–48 h, which proves the clear advantage of transdermal delivery system over the current mode of administration [32].

10. **J.-C. Olivier et al.,** performed In vitro comparative studies of two marketed transdermal nicotine delivery systems: Nicopatch® and Nicorette®. Release profiles were obtained using the FDA paddle method, and skin permeation profiles using Franz-type diffusion cells. Using the first method, nicotine release followed the polymer matrix diffusion-controlled process, as suggested by the linear Q versus $t_{1/2}$ relationship. Cumulative amounts released from Nicopatch were twice the amounts released from Nicorette, but the released fractions were almost equal for both TDS (~50%). Using diffusion cells, skin permeation rates were constant over the time: they were not significantly different between both TDS and close to in vivo claimed releases [33].

11. **Soodabeh Davaran et al.,** developed a novel prolonged-release nicotine transdermal patch. An inclusion complex formed between the nicotine and ß-cyclodextrine (ß -CD) was used in drug depot. The usefulness of a specially cross-linked polyvinyl alcohol (cross-PVA) membrane was investigated as a rate controlling membrane. The influence of

carbopol polymers, type C-934P and C-940 and propylene glycol on transdermal permeation of nicotine through the rat skin was investigated. The results indicated a maximum flux of 42 μg cm^{-2} h^{-1} after 48 h from the patches made from C-934P when the propylene glycol concentration was 15% and the nicotine ß-CD mole ratio in the inclusion complex was 3:1 [34].

12. **P. Santi et al .,** developed a bioadhesive transdermal film of oxybutynin. Transdermal films were prepared by dissolving in water an adhesive (Plastoid®), a film-forming polymer (polyvinyl alcohol), a plasticizer (sorbitol) and the drug. The mixture was then spread on siliconized paper and oven-dried.Permeation experiments were conducted in Franz-type diffusion cells using rabbit ear skin as barrier. Oxybutynin showed good permeation characteristics across the skin. When the film was applied in occlusive conditions the release profiles were much higher than in non-occlusive conditions, reaching 50% of drug permeated after 24 h [35].

13. **M. Aqil et al.,** prepared matrix type transdermal delivery of pinacidil monohydrate. The monolithic matrix type transdermal drug delivery systems of pinacidil monohydrate (PM) were prepared with Eudragit RL-100 and PVP K-30, by film casting technique on mercury substrate and characterised 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 [36].

14. **Charles M. Heard et al.,** investigated adhesive transdermal patch of primaquine with national starch. This work investigated the permeation of primaquine across full-thickness excised human skin from two acrylate transdermal adhesives. Primaquine base was formulated with National Starch 387-2516 and 387-2287. The patches were applied to cadaver skin in Franz-type diffusion cells and the permeation of primaquine determined over a 24-h period. Relatively high fluxes were found. It was determined that a simple patch with a diameter of ~13 cm^2 could deliver a therapeutic in vivo dose [37].

15. **M. Guyot et al.,** developed matrix type propranolol adhesive patch. 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. The best release modulation was obtained from Ucecryl matrices. In all matrices types, propylene glycol accelerated propranolol release rate [38].

16. **Toshikiro Kimura et al.,** investigated Skin permeation of propranolol from polymeric film containing terpene enhancers for transdermal use. polymeric film formulations were prepared by employing ethyl cellulose (EC) and polyvinyl pyrrolidone (PVP) as a film former and dibutyl phthalate (DBP) as a plasticizer. Terpenes such as menthol and cineole, and propylene glycol (PG) were also employed as a chemical enhancer to improve the skin penetration of propranolol hydrochloride. The uniformity of drug

content was evidenced by the low S.D. values for each film preparation. Cineole showed better results when compared with menthol and propylene glycol [39].

17. **Ayman El-Kattan et al.,** discussed the kind of skin model that will be used to evaluate the drug permeation; the mathematical model that will be used to characterize the permeation of the drug across the skin and the diffusion apparatus that will be used to conduct the permeation study [40].

18. **Dae – duk kim et al.,** a reservoir-type testosterone transdermal delivery system. A reservoir-type transdermal delivery system of testosterone (TS) was developed using an ethanol/water (70:30) cosolvent system as the vehicle. The permeation studies were performed with keshary chien cell. 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 [41].

19. **Charles M. Heard et al.,** investigated Triclosan release from transdermal adhesive formulations. Model patches were prepared using DuroTak® 2287, 2516 and 2051 acrylic polymer adhesives loaded with 0, 30 and 50 mg per 0.785 cm^2 triclosan and dissolution was measured over a 12-h period. There was no apparent difference between the adhesives at the 30 mg patch loading, but at 50 mg, the trend for increased release was 2051 > 2516 > 2287 [42].

20. **S.S. Agrawal et al.,** investigated transdermal controlled administration of verapamil Hcl. Transdermal drug delivery (TDD) systems of Verapamil Hcl using hydrophilic polymers -- polyvinyl alcohol (PVA) and polyvinyl pyrrolidone (PVP) and different concentrations of an enhancer, d-limonene were developed. In-vitro permeation profiles across the guinea-pig dorsal and human cadaver skins using a Keshary-Chien diffusion cell are reported [43].

21. **Janardhanan Bagyalakshmi et al.,** developed membrane moderated transdermal patches of ampicillin sodium. The membrane-type transdermal systems were prepared using a drug with various antinucleant polymers - hydroxypropyl methylcellulose (HPMC), methylcellulose (MC), cellulose acetate phthalate,chitosan,sodium alginate(SA), and sodium carboxymethylcellulose -in an ethanol: pH 4.7 buffer volatile system by the solvent evaporation technique with HPMC as the rate-controlling membrane for all the systems. The in vivo study of the ampicillin sodium patch exhibited a peak plasma concentration Cmax of 126 μg/mL at Tmax 4 hours [44].

22. **Udhumansha Ubaidulla et al.,** prepared monolithic matrix patches of Carvedilol using hydrophilic and hydrophobic polymers. Matrix-type transdermal therapeutic system containing carvedilol with different ratios of hydrophilic and hydrophobic polymeric combinations by the solvent evaporation technique. Based on physicochemical and in vitro skin permeation studies, patches coded as F3 (ethyl cellulose: polyvinyl pyrrolidone, 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 [45].

23. **S. Narasimha Murthy et al .,** investigated Physical and Chemical Permeation Enhancers in Transdermal Delivery of Terbutaline Sulphate. The study was designed to control the release

of matrix type transdermal delivery systems of TS using HPMC. Because of the low permeability of the drug, enhancers had to be used in the formulations. The in vitro diffusion studies were carried out in a modified Keshary-Chien diffusion cell using distilled water as the receptor medium [46].

24. **V.G.Jamakandi et al.,** investigated formulation, characterization and evaluation of matrix type transdermal patches of nicorandil. Different grades of HPMC were used for development of transdermal patches. All the prepared formulations were subjected to physicochemical studies (thickness, weight variation, drug content, moisture content and uptake, and flatness), in vitro release and in vitro permeation studies through mouse skin [47].

25. **Stanislaw Janicki et al.,** investigated the penetration of terpenes from matrix-type transdermal systems through human skin. Polyurethane matrices containing up to 39% of the terpenes eucalyptol, L-limonene, D-limonene, dipentene or terpinolene were produced. Release of the terpenes directly to the acceptor fluid, as well as through isolated human epidermis and dermis, was studied. For all terpenes the penetration was slower in the presence of epidermis. Release and penetration through the epidermis and dermis were

fastest for dipenetene (mixture of D-limonene and L-limonene), being at least 3–4 times faster than for D-limonene and L-limonene [48].

CHAPTER IV

OBJECTIVE OF THE STUDY [49]

Transdermal delivery of drugs through the skin to the systemic circulation provides a convenient route of administration for a variety of clinical indications. Several TDDS containing drugs such as clonidine, estradiol, fentanyl, nicotine, nitroglycerin, oxybutynin and scopoloamine are available in the United States. This mode of drug delivery is more beneficial for chronic disorders such as Diabetes mellitus which require long term drug administration to maintain therapeutic drug concentration in plasma.

Transport of drugs or compounds via skin is a complex phenomenon, which allows the passage of drugs or compounds into and across the skin. The skin is one of the most extensive and readily accessible organs of the human body. It receives about one-third of the blood circulation through the body. Hence the skin has been explored as the port of entry of drugs. Innovations in the area of drug delivery are taking place at a much faster pace as compared to the last two decades.

Antidiabetic drugs like sulphonylureas, Meglitinides, Biguanides and Thiazolidinediones are used in the treatment of Type II diabetes mellitus. Though these drugs are absorbed orally their bioavailability varies widely because of extensive presystemic metabolism.In the transdermal matrix drug delivery system the polymer matrix binds with the drug and controls the release of the drug from the patch.(eg : Nitrodur, Duragesic)

A review by Beverley J. Thomas and Barrie C. Finnin showed that current transdermal drug delivery (TDD) relies primarily upon occlusive patches, and is now considered to be a mature technology. This method is capable of delivering drugs, the use of which would be limited through, for example, poor oral bioavailability, side effects associated with high peaks or poor compliance due to the need for frequent administration.

Transdermal drug delivery has been investigated and developed in order to

- Avoid hepatic first pass effect.
- Minimize fluctuations in plasma drug concentration.
- Improve drug bioavailability.
- Reduce dosing frequency and improve patient compliance.

Repaglinide, a blood glucose lowering drug of Meglitinide class is used in the management of Type II diabetes mellitus. It is subjected to hepatic first pass metabolism following oral administration with systemic bioavailability of about 56% [50]. Because of its short half life (1 hour), the drug has to be given frequently at 0.5 to 4 mg. The conventional therapy with oral pharmaceutical dosage forms may result in high fluctuations in therapeutic plasma drug concentration with some unwanted side effects. Hence, an attempt has been made to develop Transdermal patches of Repaglinide that could provide desired delivery of the drug at a constant and predictable rate which would be beneficial for the safe and effective management of Type II diabetes mellitus.

CHAPTER V

PLAN OF WORK

The work plan involves formulation and evaluation of matrix type transdermal patches of Repaglinide.

Part – I

1. Determination of λmax of Repaglinide.

2. Preparation of standard calibration curve of repaglinide.

Part – II

1. Formulation of transdermal patches of repaglinide by solvent casting method.

Part – III

1. Evaluation of transdermal patches.

a) Characterization of the transdermal patches.

- Physical appearance.
- Weight uniformity.
- Thickness of the film.
- Folding endurance.
- Percentage moisture content

- Estimation of drug content.

b) *In-vitro* drug release studies.

- Paddle over disc method (USP apparatus 5)

c) *In-vitro* permeation studies.

- Franz diffusion cell method using rat skin membrane.

Part – IV

1. Surface morphological study of transdermal patch before and after in- vitro permeation studies using scanning electron microscopy.

Part – V

1. Compatibility studies of drug and polymers using Fourier transformer infrared spectroscopy (FTIR).

Part – VI

1. Stability studies of Transdermal patches of repaglinide using environmental chamber.

CHAPTER VI

MATERIALS AND EQUIPMENTS

Drugs and Chemicals

1. Repaglinide	-	Gift sample from Actavis Pharma, Chennai.
2. PVP	-	Gift sample from Intermed Pharma, Chennai.
3. HPMC (5cps)	-	Gift sample from Intermed Pharma, Chennai.
4. Dibutyl phthalate	-	Loba Chemie private limited.
5. Tween 60	-	CDH lab
6. Potassium dihydrogen phosphate	-	CDH lab
7. Disodium hydrogen phosphate	-	CDH lab
8. Sodium chloride	-	CDH lab
9. Methanol	-	Astron chemicals limited
10. Dichloromethane	-	CDH lab
11. Chloroform	-	S. D fine chemicals.

Equipments used

1. Petriplate with Mercury	-	Borosil
2. Electronic weighing balance	-	A & D company, Japan.
3. Hot air oven	-	Sico
4. Vernier caliper	-	Linker
5. Dissolution apparatus	-	Lab India 2000
6. Franz diffusion cell	-	Universal scientifics
7. UV-Visible spectrophotometer	-	Schimadzu UV – 1700
8. Environmental chamber	-	Equipment madras pvt., ltd
9. Scanning electron microscope	-	JEOL-JFC-1600.
10. FT-IR	-	Schimadzu 8400 S.

CHAPTER VI

MATERIALS AND EQUIPMENTS

Drugs and Chemicals

1. Repaglinide	-	Gift sample from Actavis Pharma, Chennai.
2. PVP	-	Gift sample from Intermed Pharma, Chennai.
3. HPMC (5cps)	-	Gift sample from Intermed Pharma, Chennai.
4. Dibutyl phthalate	-	Loba Chemie private limited.
5. Tween 60	-	CDH lab
6. Potassium dihydrogen phosphate	-	CDH lab
7. Disodium hydrogen phosphate	-	CDH lab
8. Sodium chloride	-	CDH lab
9. Methanol	-	Astron chemicals limited
10. Dichloromethane	-	CDH lab
11. Chloroform	-	S. D fine chemicals.

Equipments used

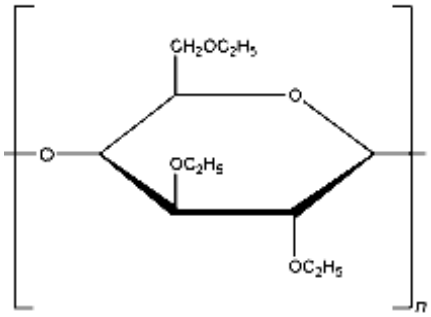
1. Petriplate with Mercury	-	Borosil
2. Electronic weighing balance	-	A & D company, Japan.
3. Hot air oven	-	Sico
4. Vernier caliper	-	Linker
5. Dissolution apparatus	-	Lab India 2000
6. Franz diffusion cell	-	Universal scientifics
7. UV-Visible spectrophotometer	-	Schimadzu UV – 1700
8. Environmental chamber	-	Equipment madras pvt., ltd
9. Scanning electron microscope	-	JEOL-JFC-1600.
10. FT-IR	-	Schimadzu 8400 S.

CHAPTER VIII

EXCIPIENTS PROFILE [56],[57],[58]

ETHYL CELLULOSE

Synonyms	:	Aquacoat ECD; Aqualon; E462; Ethocel; Surelease.
Nonproprietary names	:	BP: Ethylcellulose, PhEur: Ethylcellulosum, USPNF: Ethylcellulose
Chemical name	:	Cellulose ethyl ether
Empirical formula	:	$C_{12}H_{23}O_6\,(C_{12}H_{22}O_5)n\,C_{12}H_{23}O_5$
Structural formula	:	



Description	:	Ethylcellulose is a tasteless, free-flowing, white to light tan colored powder.
Functional categories	:	Coating agent; flavoring fixative; tablet binder; tablet filler; viscosity- increasing agent.

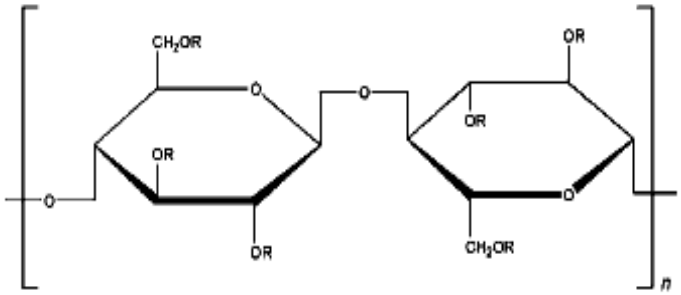
Properties

Loss on drying	:	≤ 3.0%
Residue on ignition	:	≤ 4.0%
Ethoxyl groups	:	44.0–51.0%
Melting point	:	165^0C to 180^0 C
Solubility	:	Ethylcellulose is practically insoluble in glycerin, propylene glycol, and water. Ethylcellulose 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%).
Specific gravity	:	1.12–1.15 g/cm^3
Nominal viscosity	:	6–10 mPa s
Stablility and storage	:	Ethylcellulose is a stable, slightly hygroscopic material. Ethylcellulose is subject to oxidative degradation in the presence of sunlight or UV light at elevated temperatures.

HYDROXY PROPYL METHYL CELLULOSE (5 cps)

Synonyms	:	Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; Tylopur
Nonproprietary names	:	BP: Hypromellose, PhEur: Hypromellosum, USP: Hypromellose.
Chemical name	:	Cellulose hydroxypropyl methyl ether.
Molecular weight	:	10,000 to 1,500,000

Structural formula :



where R is H, CH_3, or $CH_3CH(OH)CH_2$

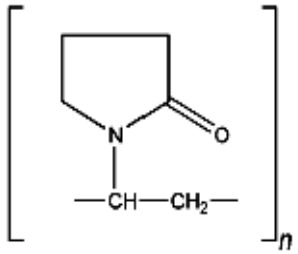
Description	:	Hypromellose is an odorless and tasteless, white or creamy white fibrous or granular powder.
Functional categories	:	Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

Properties

Ash	:	1.5–3.0%,
Loss on drying	:	≤ 5.0%
Methoxy content	:	27.0% to 30.0%
Hydroxypropoxy	:	4.0% to 7.5%
Melting point	:	Browns at 190–200^{o}C; chars at 225–230^{o}C and Glass transition temperature is 170–180^{o}C.
Solubility	:	soluble in cold water, practically insoluble in chloroform, ethanol and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol.
Specific gravity	:	1.26.
Nominal viscosity	:	5 centipoise. (2% w/v aqueous solution)
Stablility and storage	:	HPMC is a stable material, although it is hygroscopic after drying.

POLYVINYL PYROLLIDONE (PVP K30)

Synonyms	:	Kollidon; Plasdone; polyvidone; 1-vinyl-2-pyrrolidinone polymer.
Nonproprietary names	:	JP: Povidone, PhEur: Povidonum.
Chemical name	:	1-Ethenyl-2-pyrrolidinone homopolymer
Empirical formula	:	(C6H9NO)n
Molecular weight	:	2,500 to 3,000,000
Structural formula	:	



Description	:	Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with K-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres. Povidone K-90 and higher K-value povidones are manufactured by drum drying and occur as plates.
Functional categories	:	Disintegrant; dissolution aid; suspending agent; tablet binder, film forming agent, viscosity-enhancement agent, lubricator and adhesive.

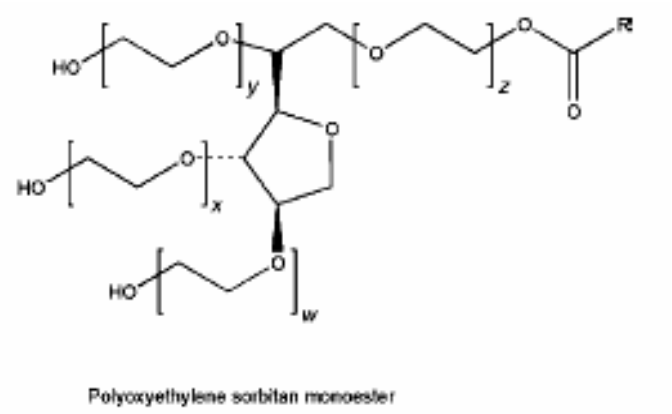
Properties

Water content	:	≤ 5.0%
Residue on ignition	:	≤ 0.1%
Vinyl pyrrolidinone	:	≤ 0.2%
Melting point	:	softens at 150^0 c
Solubility	:	freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil.
Moisture	:	3.5%
Nominal viscosity	:	5.5–8.5 mPa s (10% w/v aqueous povidone solution)
Stability and storage	:	It is stable to a short cycle of heat exposure around 110 –130^0C; steam sterilization of an aqueous solution does not alter its properties. Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

.

TWEEN 60

Synonyms	:	Capmul POE-S; Cremophor PS 60; Crillet 3; Drewpone 60K; Durfax 60
Nonproprietary names	:	BP: Polysorbate 60, USPNF: Polysorbate 60, PhEur: Polysorbatum 60
Chemical name	:	Polyoxyethylene 20 sorbitan monostearate.
Empirical formula	:	$C_{64}H_{126}O_{26.}$
Molecular weight	:	1312
Structural formula	:	



Polyoxyethylene sorbitan monoester

w +x+ y+ z = 20 (Polysorbate 60)

Description : Polysorbates have a characteristic odor and a warm, somewhat bitter tasted yellow colour oily liquid although it should be noted that the absolute color intensity of the products may vary from batch to batch and from manufacturer to manufacturer.

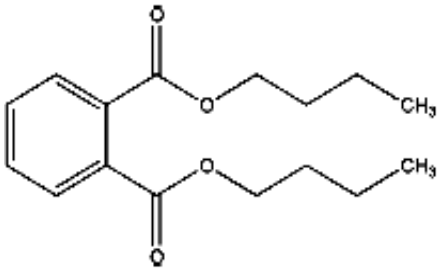
Functional categories	:	Emulsifying agent; nonionic surfactant; solubilizing agent; wetting, dispersing/suspending agent.

Properties

Flash point	:	149^0c
HLB value	:	14.9
Stearic acid	:	40.0 to 60.0%
Hydroxyl value	:	81 to 96.
Solubility	:	Freely soluble in ethanol and water.
Specific gravity	:	1.1
Surface tension.	:	42.5 (at 20^0c)
Nominal viscosity	:	600
Stability and storage	:	Polysorbates are stable to electrolytes and weak acids and bases; gradual saponification occurs with strong acids and bases. Prolonged storage can lead to the formation of peroxides. Polysorbates should be stored in a well-closed container, protected from light, in a cool, dry place.

DIBUTYL PTHALATE

Synonyms	:	Araldite 502; benzenedicarboxylic acid; benzene-o-dicarboxylic acid di-n-butyl ester; butyl phthalate; Celluflex DBP; Genoplast B; Hatcol DBP; Hexaplast M/B;
Nonproprietary names	:	BP: Dibutyl Phthalate, PhEur: Dibutylis phthalas
Chemical name	:	Dibutyl benzene-1,2-dicarboxylate
Empirical formula	:	$C_{16}H_{22}O_4$
Molecular weight	:	278.34
Structural formula	:	



Description	:	Dibutyl phthalate occurs as an odorless, oily, colorless, or very slightly yellow-colored, viscous liquid.
Functional categories	:	Film-former; plasticizer; solvent.

Properties		
Flash point	:	171^0c
Boiling point	:	340^0c
Refractive index	:	1.491 to 1.495
Solubility	:	very soluble in acetone, benzene, ethanol (95%), and ether; soluble 1 in 2500 of water at 20^0C.
Relative density	:	1.043–1.048
Dynamic viscosity	:	20 mPa s
Stability and storage	:	Dibutyl phthalate should be stored in a well-closed container in a cool, dry, location. Containers may be hazardous when empty since they can contain product residues such as vapors and liquids.

CHAPTER IX

EXPERIMENTAL DETAILS

Preparation of standard calibration curve

Preparation of dissolution medium [59]

(30% v/v)Methanolic isotonic phosphate buffer pH 7.4

2.38 gms of disodium hydrogen phosphate, 0.19 gms of potassium dihydrogen ortho phosphate and 8.0 gms of sodium chloride are weighed and dissolved in sufficient amount of water to produce 700 ml. To this 300 ml of methanol is added to produce 1000ml of methanolic isotonic phosphate buffer pH 7.4.

100 mg Repaglinide is weighed and dissolved in a small quantity of methanol in a 100 ml standard flask and made up to the volume with 30%v/v methanolic isotonic phosphate buffer (IPB) pH 7.4. From this primary stock solution 10 ml is pipetted out and made up to 100 ml with methanolic IPB pH 7.4 to form the secondary stock solution resulting in the concentration of100 µg/ml.

From the secondary stock solution 5ml, 10ml, 15ml, 20ml …50ml samples are pipetted into 100 ml volumetric standard flasks separately and made up to the volume with methanolic IPB pH 7.4 to get concentrations of 5 µg/ml, 10 µg/ml, 15 µg/ml, 20 µg/ml…50 µg/ml of drug respectively.

λ max is found by scanning the repaglinide solution under UV-Visible spectrophotometer. The absorbance is measured at λ max for different concentrated solutions to obtain standard calibration curve. Standard calibration curve is plotted by taking concentration in x-axis and absorbance in y-axis.

The calibration curve is useful in estimation of drug content, concentration of drug released during in-vitro release studies and in-vitro permeation studies.

Formulation of repaglinide transdermal patches

The solvent casting technique on mercury substrate is used to formulate the matrix type transdermal patches of repaglinide. Transdermal formulations of Repaglinide are prepared using ethyl cellulose/polyvinyl pyrrolidone (EC/PVP) and ethyl cellulose/hydroxyl propyl methyl cellulose (EC/HPMC) with three different total polymer weights like 200mg, 300mg, 400mg each having requisite ratios polymer mixture as shown in table

Table - 1

Formulation of repaglinide loaded transdermal patches

Sl.no	Formulations	Ingredients				
		Polymer	Weight in mg	Ratio	Dibutyl phthalate in % w/w of polymers	Tween 60 in % w/w of polymers.
1	EPA1	EC/PVP	200	4.5:0.5	30	5
2	EPA2	EC/PVP	200	4 : 1	30	5
3	EPA3	EC/PVP	200	3 : 2	30	5
4	EPB1	EC/PVP	300	4.5:0.5	30	5
5	EPB2	EC/PVP	300	4 : 1	30	5
6	EPB3	EC/PVP	300	3 : 2	30	5
7	EPC1	EC/PVP	400	4.5:0.5	30	5
8	EPC2	EC/PVP	400	4 : 1	30	5
9	EPC3	EC/PVP	400	3 : 2	30	5
10	EHA1	EC/HPM	200	4.5:0.5	30	5
11	EHA2	EC/HPM	200	4 : 1	30	5
12	EHA3	EC/HPM	200	3 : 2	30	5
13	EHB1	EC/HPM	300	4.5:0.5	30	5
14	EHB2	EC/HPM	300	4 : 1	30	5
15	EHB3	EC/HPM	300	3 : 2	30	5
16	EHC1	EC/HPM	400	4.5:0.5	30	5
17	EHC2	EC/HPM	400	4 : 1	30	5
18	EHC3	EC/HPM	400	3 : 2	30	5

*****The drug concentration is kept constant in all the formulations.

*EP – Ethyl cellulose/PVP.

*EH - Ethyl cellulose/HPMC.

*A - 200 mg.

*B - 300mg.

*C - 400 mg.

The transdermal patches are formulated such that each patch contains 1mg/cm^2 drug concentration.

The solvent used to dissolve EC/PVP is chloroform and for EC/HPMC the solvent mixture is methanol: dichloromethane (6:4) [25],

To the polymeric solution known weight of drug (repaglinide 25 mg) is added and mixed slowly with a glass rod for 30 minutes until a homogenous drug polymer solution is formed. Then dibutyl phthalate (plasticizer) and Tween 60 (permeation enhancer) of requisite quantity are added and mixed thoroughly.

The resulting homogenous drug-polymeric solution is poured on a mercury substrate (area of 25 cm^2) in a petridish and dried at room temperature. The rate of evaporation of solvent was controlled by inverting a funnel over the petridish. The dried films are taken out after 24 hours and subjected for evaluation.

Evaluation of transdermal patches [25],[28],[47]

a) Characterization of the transdermal patches [60]

Physical appearance

All the transdermal patches are visually inspected for color, clarity, flexibility and smoothness.

Weight uniformity

Four patches from each batch are accurately weighed using a digital balance. The average weight and the standard deviation values are calculated from the individual weights.

Thickness of the films

The thicknesses of the drug loaded polymeric films are measured using a digital vernier caliper. The measurements are made at five different points, four at the corners and one at the centre of the patch. The average and standard deviation of five readings were calculated for each formulation.

Folding endurance

Folding endurance of patches is determined by repeatedly folding the small strip of film at the same place till it breaks. The number of times, the film could be folded at the same place till it breaks will give the value of folding endurance.

Percentage moisture content

The prepared films are weighed individually and kept in a desiccator containing silica gel at room temperature for 24 hours. The films were again weighed and the percentage moisture content is calculated using the formula:

Percentage moisture content = [(Initial weight – Final weight)/Final weight] x 100

Estimation of drug content

Transdermal patches of specified area and weight are cut into small pieces and are transferred into 100mL standard flask. About 5mL of methanol is added to dissolve the patch and then made upto 100mL with methanolic isotonic phosphate buffer pH 7.4. Similarly, a blank is also prepared using drug free patch. The solutions are filtered and the absorbance is measured at λmax (281.5) nm using UV visible spectrophotometer.

b) *In-vitro* drug release studies [61], [62], [63]

The in-vitro drug release study for the transdermal patches are carried out using modified paddle over disc assembly USP 23, Apparatus 5. The disc apparatus consists of mesh screen made of stainless steel clamped in the watch glass using nylon clips.

The transdermal patch of area 3.14 cm^2 is pasted over a small piece of aluminium foil (backing layer) to prevent two dimensional release. The transdermal patch with backing layer is placed between inert stainless steel mesh and watch glass exposing the patch to the medium. It is also ensured that the patch does not float inside the disc assembly.

The disc assembly containing transdermal patch is placed at the bottom of the dissolution vessel, with the mesh facing upwards, under the rotating paddle. The dissolution medium used is 900 ml of methanolic isotonic phosphate buffer pH 7.4. The apparatus was equilibrated to the temperature of 37 ± 0.5^0c operated at 50 ± 1 rpm. The dissolution study is carried out for 12 hours. 10 ml of samples are withdrawn at regular intervals of 1 hour and the same volume of corresponding dissolution medium was replenished to maintain sink condition.

The amount of repaglinide released is determined by measuring the absorbance of the samples at 281.5 nm using UV-Visible spectrophotometer. Each test is performed in triplicate.

c) In-vitro permeation studies [47]**,** [61], [64].

The in-vitro skin permeation experiments are conducted using vertical type Franz diffusion cells having receptor compartment capacity of 15 ml.

Preparation of rat skin membrane

Permeation studies are carried out after obtaining ethical committee clearance. Wister strains of male albino rats weighing between 180-200 gms are used for this

study. Membrane for the permeability studies is full thickness skin from the dorsal region of the rats. The hair present over the skin is removed by trimming and careful shaving so that the skin is not damaged. The skin is excised from rat after sacrificing. The subcutaneous fat present on the skin samples are removed by soaking the skin samples in hot water (60^{o}c) for 45 seconds. The excised skin samples are then stored in frozen condition until use.

Permeation studies

The receptor compartment is filled with 15 ml of methanolic isotonic phosphate buffer pH 7.4. The transdermal patches with backing membrane are firmly pressed onto the centre of the rat skin. Once adhesion to the skin surface had been confirmed, the skin is quickly mounted on the diffusion cell receptor compartment such that the patch was tightly secured over the flange aperture. The donor compartment is then placed in position and the two halves of the cell are clamped together. The whole assembly was placed over a magnetic stirrer. The dissolution medium in the receptor compartment was stirred constantly and continuously using a magnetic bead.

The samples are withdrawn at regular time intervals of 1 hour and analyzed for drug content. Receptor phases are replenished with equal volume of dissolution medium at each time interval. The cumulative amounts of drug permeated per square centimeter of patches were plotted against time. From the graph flux (J) is determined.

Scanning electron microscopy [28]

The surface morphology of the transdermal patches before and after in-vitro skin permeation experiments were analyzed by scanning electron microscopy

FTIR studies [28]

The possibility of drug - excipient interaction is investigated by FTIR. The FTIR graph of pure drug and physical mixture of drug – polymer are recorded.

Stability studies [65]

Stability studies are performed on the formulated transdermal patches at 40 ± 2^{o}c and relative humidity of 75% ± 5% maintained. The drug content of the different formulations are evaluated every week using UV-Visible spectrophotometer and physical appearance is also examined.

CHAPTER X

RESULTS AND DISCUSSION

Standard calibration curve for repaglinide

Known concentration of repaglinide in methanolic isotonic phosphate buffer is scanned to find the λmax and it was found to be 281.5 nm. Calibration curve for repaglinide were prepared in methanolic isotonic phosphate buffer pH 7.4 in the concentration range of 5 to 50µg/ml at 281.5 nm. The correlation coefficient was found to be 0. 0.998725148. The results are presented in the table -2. Calibration plots of repaglinide are shown in Fig – 7

Formulation of repaglinide transdermal patches

Matrix-type transdermal patches containing repaglinide and variable combinations of EC/PVP and EC/HPMC were prepared as per the composition given in table - 1. Excellent film forming ability of these polymeric combinations were already reported [(ref)].These polymeric combinations produced smooth patches compared to patches prepared by a single polymer.

Evaluation of transdermal patches

a) Characterization of the transdermal patches

Physical appearance

All the polymers used for the formulation of transdermal patches showed good film forming properties.

The patches formed were thin, flexible, smooth and transparent. The method used for casting the film on a mercury substrate was found to be satisfactory.

Weight uniformity

The results of weight variation tests of the patches are shown in the table-2. The weights of the patches ranged from 246.36 ± 1.46 mg to 482.24 ± 1.15 mg for EC/PVP formulations and 237.23 ± 0.64 mg to 467.02 ± 0.65 mg for EC/HPMC formulations.

From the results it has been found that there is less variation in weight between different patches of a same batch suggesting uniform distribution of drug and polymer over the mercury surface.

Thickness of the patches

The results of thickness of the patches are shown in the table-3. The thickness of the patch ranged from 0.078 ± 0.007 mm to 0.148 ± 0.009 mm for formulations prepared with EC/PVP and 0.069 ± 0.004 mm to 0.131 ± 0.015 mm for formulations prepared with EC/HPMC.

The thickness of patches were found to increase in the following order,

EC/PVP 200 mg – EPA1< EPA2< EPA3.

EC/PVP 300 mg – EPB1< EPB2< EPB3.

EC/PVP 400 mg – EPC1< EPC2< EPC3.

EC/HPMC 200 mg – EHA1< EHA2< EHA3.

EC/HPMC 300 mg – EHB1< EHB2< EHB3.

EC/HPMC 400 mg – EHC1< EHC2< EHC3

From the results it was found that thickness increases with increase in concentration of hydrophilic polymers (PVP and HPMC). The thickness of the patch over five different areas was found to be uniform, suggesting even distribution of drug and polymer over the mercury surface.

Folding endurance

The results of folding endurance were shown in table-3. The folding endurance of EC/PVP patches ranged from 14.33 ± 0.471 to 27.66 ± 2.624 and that of EC/HPMC patches ranged from 11.66 ± 2.054 to 26.66 ± 2.054 respectively. The results from the table also showed that increasing concentration of hydrophilic polymers showed increasing folding endurance. All the patches showed good flexibility and folding endurance properties.

Percentage moisture content [25]

The results of moisture content studies are shown in the table-4. The moisture content in the formulations was found to be low and ranged from 1.68 to 2.74 for EC/PVP patches and 1.39 to 2.58 for EC/HPMC patches.

The moisture content of the transdermal patches were found to be in the following order,

EC/PVP 200 mg – EPA1< EPA2< EPA3.

EC/PVP 300 mg – EPB1< EPB2< EPB3.

EC/PVP 400 mg – EPC1< EPC2< EPC3.

EC/HPMC 200 mg – EHA1< EHA2< EHA3.

EC/HPMC 300 mg – EHB1< EHB2< EHB3.

EC/HPMC 400 mg – EHC1< EHC2< EHC3

It was found that the moisture content increases with increase in concentration of hydrophilic polymers PVP and HPMC. The presence of little moisture content helps to maintain the formulation stable and prevent them from becoming completely dried and brittle.

Estimation of drug content

The results of drug content analysis were shown in table-5. The drug content of the patches ranged from 96.45 ± 0.942% to 100.76 ± 1.414%. The results suggest that the method employed to prepare the patches shown uniformity in drug content with minimum variations and also the results showed that the drug has been uniformly distributed.

b) *In-vitro* drug release studies

The results of in-vitro drug release studies from the transdermal patches are shown in the tables- 6, 7, 8, 9, 10, 11 and in figures 9, 10, 11, 12, 13 and 14 respectively. The formulations with total polymer weight 200mg containing EC/PVP in the ratio (3:2) and EC/HPMC in the ratio (3:2) exhibited greatest (100.82 ± 3.78 and 89.25 ± 1.93 respectively) percentage of drug release in 12 hours, whereas lowest release were observed with the formulations with total polymer weight 400 mg containing EC/PVP in the ratio (4.5:0.5) and EC/HPMC in the ratio (4.5:0.5) (46.14 ± 2.47 and 46.73 ± 1.34 respectively) in 12 hours.

Effect of hydrophilic polymers [25] [57]

The order of drug release from all the formulations increased in the following order.

EC/PVP 200 mg – EPA1 (80.03 ± 1.369) < EPA2(91.01 ± 3.79) < EPA3 (100.82 ± 3.78)

EC/PVP 300 mg – EPB1(60.23 ± 1.31) < EPB2 (63.03 ± 1.32) < EPB3 (70.47 ± 3.08).

EC/PVP 400 mg – EPC1 (46.14 ± 2.47) < EPC2 (52.87 ± 1.34) < EPC3 (60.30 ± 1.20)

EC/HPMC 200mg –EHA1 (80.79 ± 1.50) < EHA2 (82.43 ± 2.15) < EHA3(89.25 ± 1.93)

EC/HPMC 300mg – EHB1 (51.20 ± 1.20) < EHB2 (57.53 ± 2.34) < EHB3(62.71 ± 1.70)

EC/HPMC 400mg – EHC1 (46.73 ± 1.34) < EHC2(49.63 ± 1.43) < EHC3 (53.28 ± 1.50)

The formulations EPA3, EPB3, EPC3 and EHA3, EHB3, EHC3 showed more release during initial hours due to the presence of more amount of hydrophilic polymers.

From the studies it has been found that the formulations with increasing concentration of hydrophilic polymers like PVP and HPMC showed increase in dissolution rate substantially. The increase in rate of drug release is because of the ability of hydrophilic polymers to absorb water and hydrate the polymer matrix thereby promoting dissolution. The hydrophilic polymers present in the patches would leach out and create more pores and channels for the drug to diffuse out of the patches.

It has also been reported that PVP act as antinucleating agent reduces the crystallization of the drug. Thus they play a significant role in improving the solubility of a drug in the matrix by sustaining the drug in an amorphous form so that it undergoes rapid solubilization which accounts for the increased release of the drug

with an increase in the PVP concentration in the patches. HPMC causes easy hydration and swelling of polymer matrix leading to fast release of drug [58].

Effect of hydrophobic polymer [58]

The formulations EPA1, EPB1, EPC1, EHA1, EHB1 and EHC1 which contained more concentration of ethyl cellulose showed retarded drug release.

The order of retardation of drug release from EC/PVP and EC/HPMC is as follows,

EPC1(46.14±2.47) < EHC1(46.73±1.34) < EHB1(51.20±1.20) < EPB1 (60.23±1.31) < EPA1(80.03±1.69) < EHA1 (80.79±1.50).

This retarded drug release from the formulations containing higher concentration of ethyl cellulose may be because of hydrophobic nature of the polymer which has less affinity for water. This results in decrease in the thermodynamic activity of the drug in the patch and hence decreased drug release. The presence of ethyl cellulose a hydrophobic polymer controls the release of drug and maintains the integrity of the patch.

c) *In-vitro* permeation studies

Selection of formulation for permeation studies [25] [28]

The formulations which showed highest release (EPA3-100.82 ± 3.78% and EHA3 - 89.25 ± 1.93 %), lowest release (EPC1 – 46.14 ± 2.47% and EHC1- 46.73 ± 1.34 %) and intermediate release (EPB3-70.47 ± 3.08 % and EHB3- 62.71 ± 1.70 %) in 12 hours were selected for in-vitro skin permeation studies in rat abdominal skin.

The results of in-vitro permeation studies have been shown in the table-12, 13 and figures 15, 16. The formulation EPA3 with EC: PVP (3:2, 200mg – total polymer weight) and EHA3 with EC/HPMC showed higher permeation of 95.19% and 97.59% respectively in12 hours. The process of drug release was governed by diffusion and the polymer matrix had a strong influence on the diffusivity as the motion of a small molecule is restricted by the three-dimensional network of polymer chains.

The initial increased release of drug may be as a result of initial rapid dissolution of PVP (hydrophilic polymer) in the patch when it comes in contact with the hydrated skin, which results in accumulation of high amounts of drug on the skin surface and thus leads to saturation of the skin with the drug molecules.

The steady state plasma concentration data of repaglinide is not available and in this event peak plasma concentration value, which is supposed to be within therapeutic window, may be considered as required plasma concentration for calculation of desired drug input rate. The mean peak plasma concentration (Cmax) of repaglinide is 65.8ng/mL and the total clearance (Cl_T) is 0.633 L/h/kg. Hence, the required rate of drug input can be calculated as follows [25]:

:

Required rate of drug input

= Required plasma concentration × Clearance = 41.673 µg/h.

The results of flux achieved from the formulations are given in the table 14. From the results it has been found out that the formulations EPA3, EPB3, EHA3 and EHB3 with

flux of 68.92, 48.12, 62.66 and 51.87 µg/hr/cm^2 meets the required flux but the release was found to be rapid, whereas the formulations EPC1and EHC1 showed a sustained release with a flux of 26.88 µg/hr/cm^2 and 26.07 µg/hr/cm^2 respectively. Hence by increasing the surface area of the formulations EPC1and EHC1 to 2 cm^2 the required target flux may be achieved with sustained effect.

Scanning electron microscopy

The results of scanning electron microscopy were shown in the figure 17, 18. The shows the microstructure of EC/HPMC transdermal patch before and after the drug permeation experiments. The films prior to in-vitro skin permeation studies showed uniform smooth surface. After the permeation studies the surface became rough and pores were formed on the surface of the patch due to diffusion of drug. The patches did not loose integrity after the release, further indicating that the drug was released from the patches predominantly through diffusion.

FTIR studies

The possible drug – polymer interaction was studied by IR-spectroscopy. The results of IR spectroscopy were shown in the figures 19, 20, 21, 22, 23, 24. The IR spectral analysis of repaglinide pure drug alone showed that principal peaks were observed at wave numbers 3309.24, 2935.64, 1686.88, 1569.14 and 760.02. In the IR spectra of the physical mixture of repaglinide, EC and PVP the major peaks of repaglinide were 3307.84, 2934.06, 1687.64, 1567.78 and 760.68.Further in the physical mixture of EC, HPMC and repaglinide major peaks of repaglinide were

observed at 3309.62, 2934.43, 1688.97, 1568.12 and 759.33 suggesting that there is no interaction between the polymers and drug used in the present study. This study also further indicates that the polymers do not alter the performance characteristics of the drug from the patches.

Stability studies

The formulations were subjected to stability studies for a time span of one month. The formulations were evaluated for physical appearance and drug content. There was no significant change in physical appearance and drug content. It was found that the formulations remained stable during the process of storage. The results are presented in the table 15.

CHAPTER XI

SUMMARY AND CONCLUSION

- In the present work an attempt has been made to formulate and evaluate the transdermal patches of repaglinide using various blends of polymer.
- The polymeric combinations EC/PVP and EC/HPMC used for the formulation of transdermal patches showed good film forming property.
- The patches formed were thin, flexible, smooth and transparent.
- The weight variation tests showed less variation in weight and suggesting uniform distribution of drug and polymer over the mercury surface.
- The thicknesses of the transdermal patches were found to increase on increasing concentration of hydrophilic polymers like PVP and HPMC.
- All the patches showed good flexibility and folding endurance properties. The result suggests that the formulations with increased hydrophilic polymer concentration showed long folding endurance.
- The moisture content in the patches were found to be low and formulations with more hydrophilic polymer concentrations showed more percentage moisture content.
- The drug content analysis showed minimum variations suggesting uniform distribution of drug.
- The in-vitro drug release studies showed that formulations EPA3, EPB3, EPC3, EHA3, EHB3 and EHC3 with increased concentration of hydrophilic polymer showed rapid release.

- Formulations EPC1 and EHC1 showed sustained release.
- The in-vitro permeation studies showed that the required target flux is achieved with formulations EPC1 and EHC1 which also produces a sustained release of the drug.
- Surface morphological studies by SEM showed the patch showed uniform smooth surface and did not loose integrity after release.
- The results of compatibility studies by FTIR showed no interaction between the drug and polymers.
- The result of stability studies no change in the physical appearance and drug content suggesting that the formulations remained stable during storage.

It is concluded that solvent casting method using mercury substrate is useful for successful development of matrix type transdermal patches. The sustained release of drug from the transdermal patches suggests that the frequency of administration may be reduced. Further, the transdermal patches may improve the bioavailability of the drug by avoiding hepatic first pass metabolism.

Hence we can conclude that the polymer matrix provide sustained delivery of drug and these systems can be used to deliver drugs with short half life and low therapeutic index through transdermal drug delivery systems.

Fig - 9 Comparison of invitro release of EC/PVP patches -200 mg

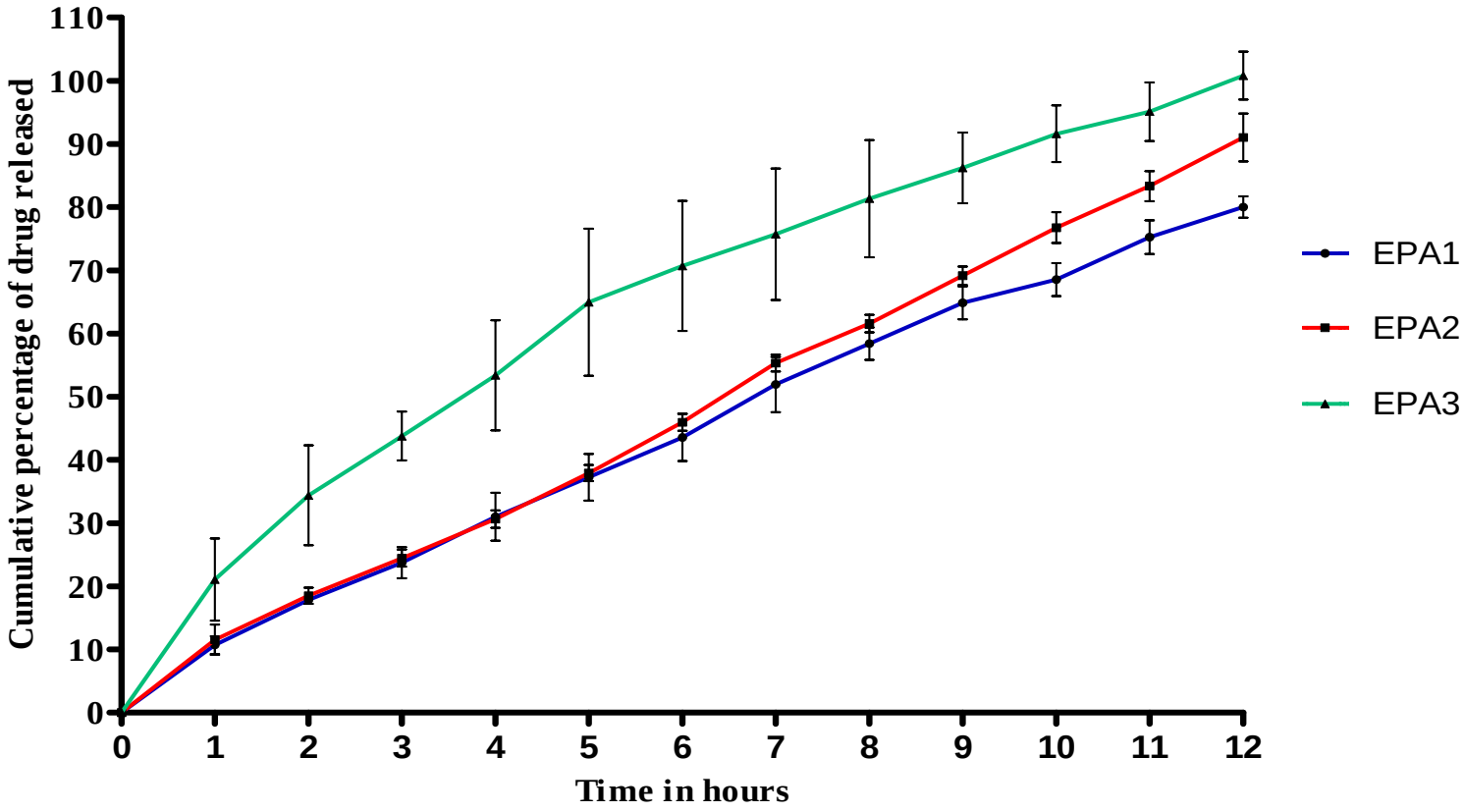


Fig - 10 Comparison of invitro release of EC/PVP patches -300 mg

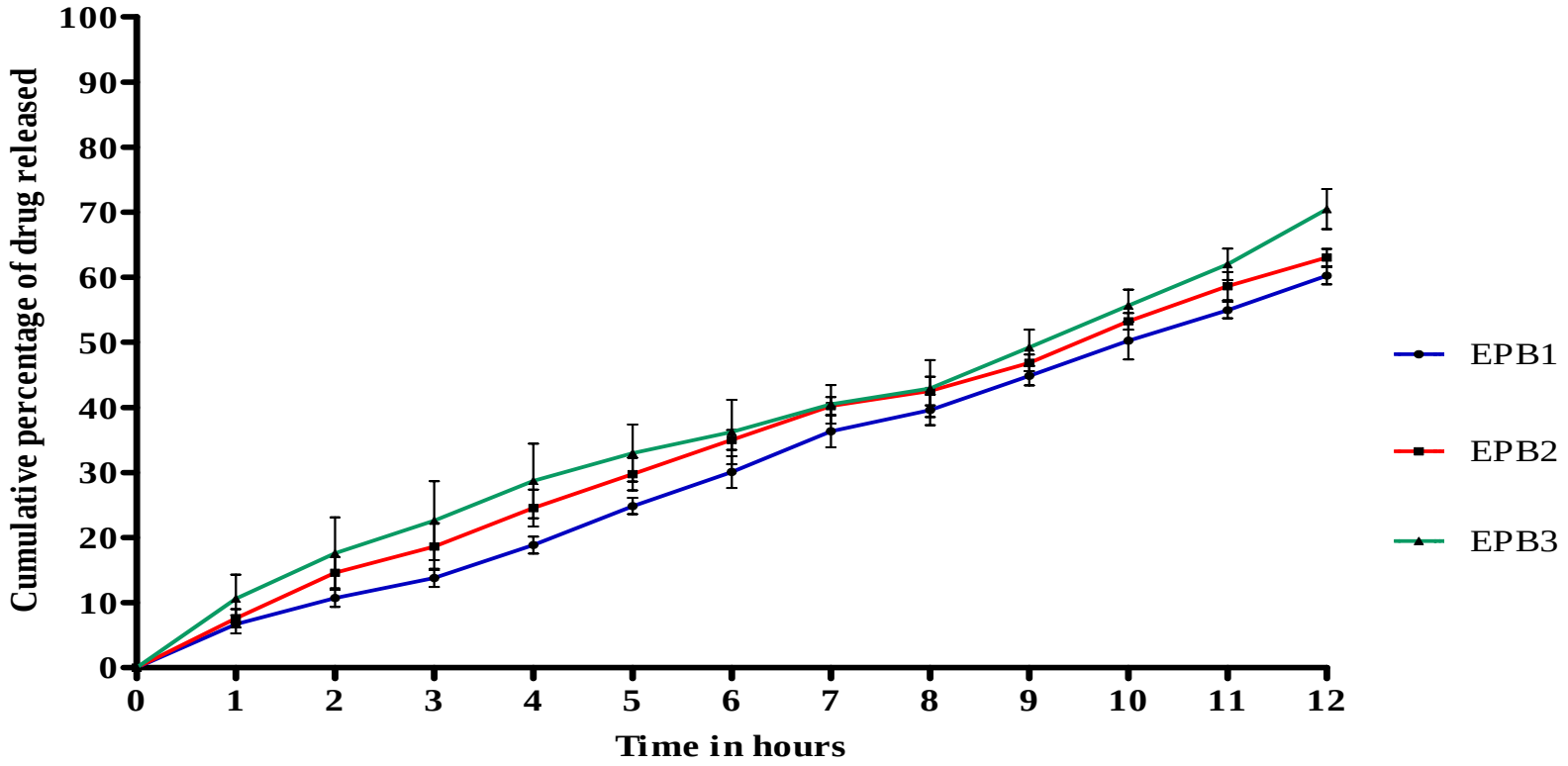


Fig - 11 Comparison of invitro release of EC/PVP patches -400 mg

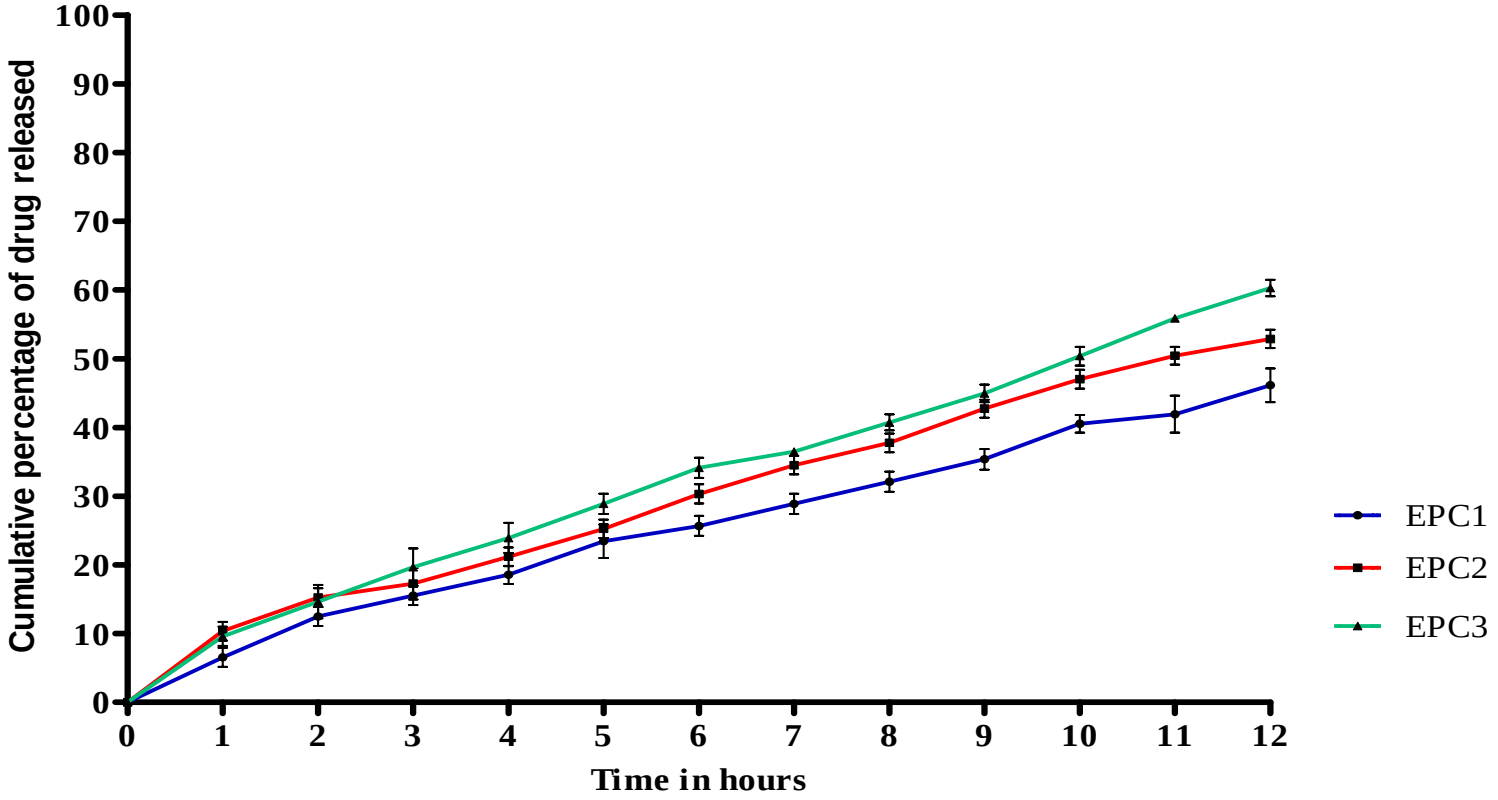


Fig - 12 Comparison of invitro release of EC/HPMC patches -200 mg

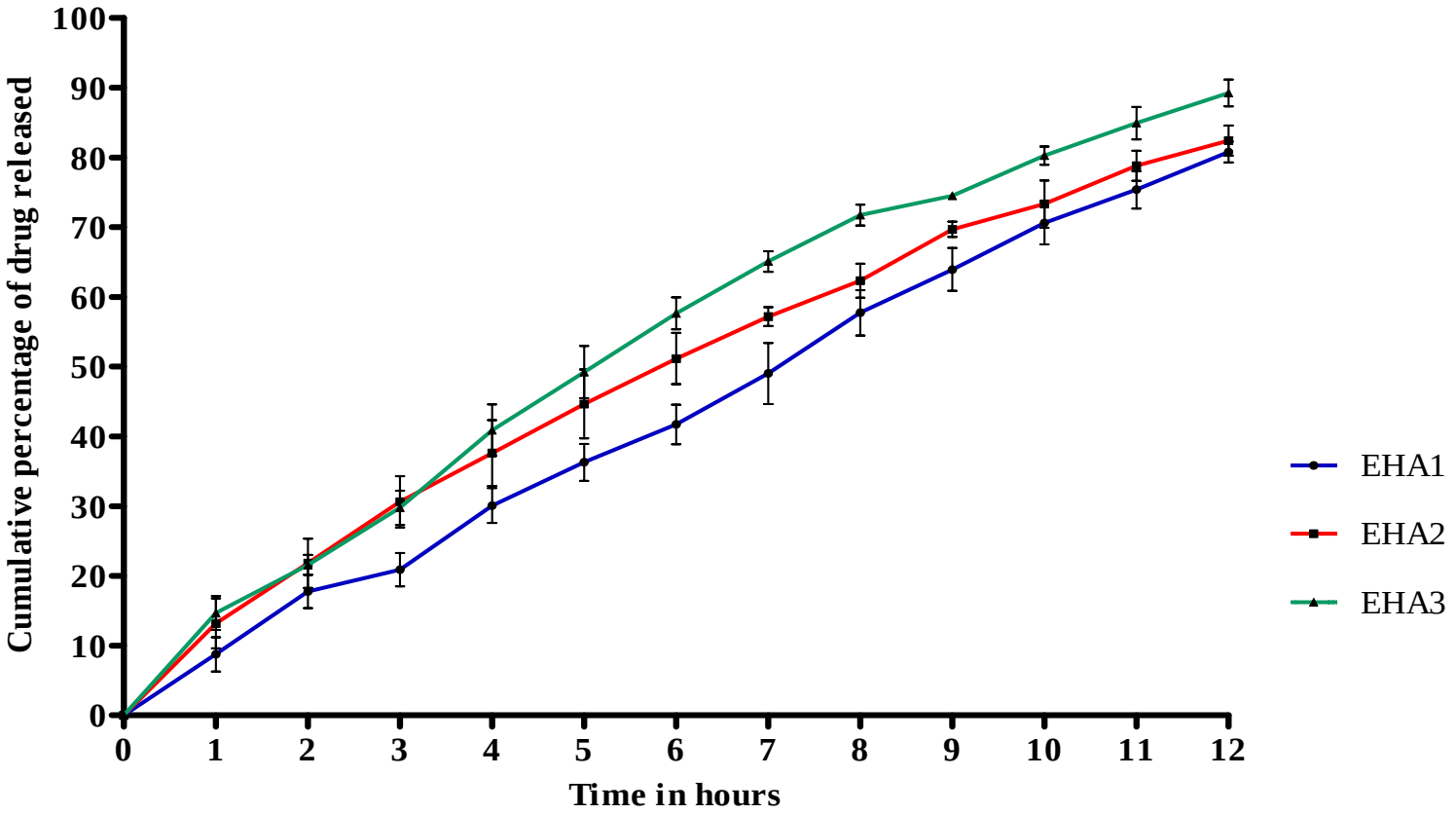


Fig - 13 Comparison of invitro release of EC/HPMC patches - 300 mg

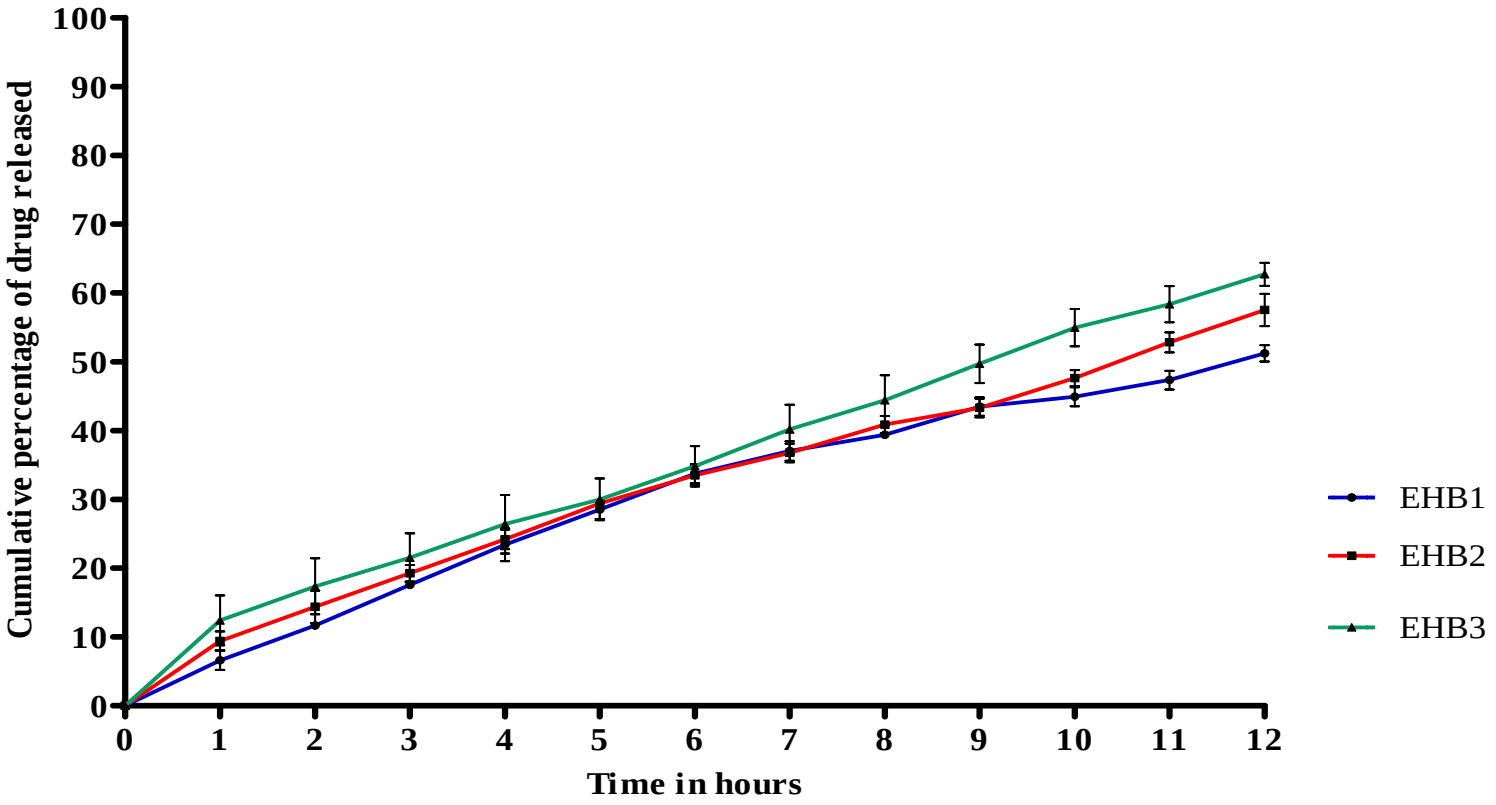


Fig - 14 Comparison of invitro release of EC/HPMC patches - 400 mg

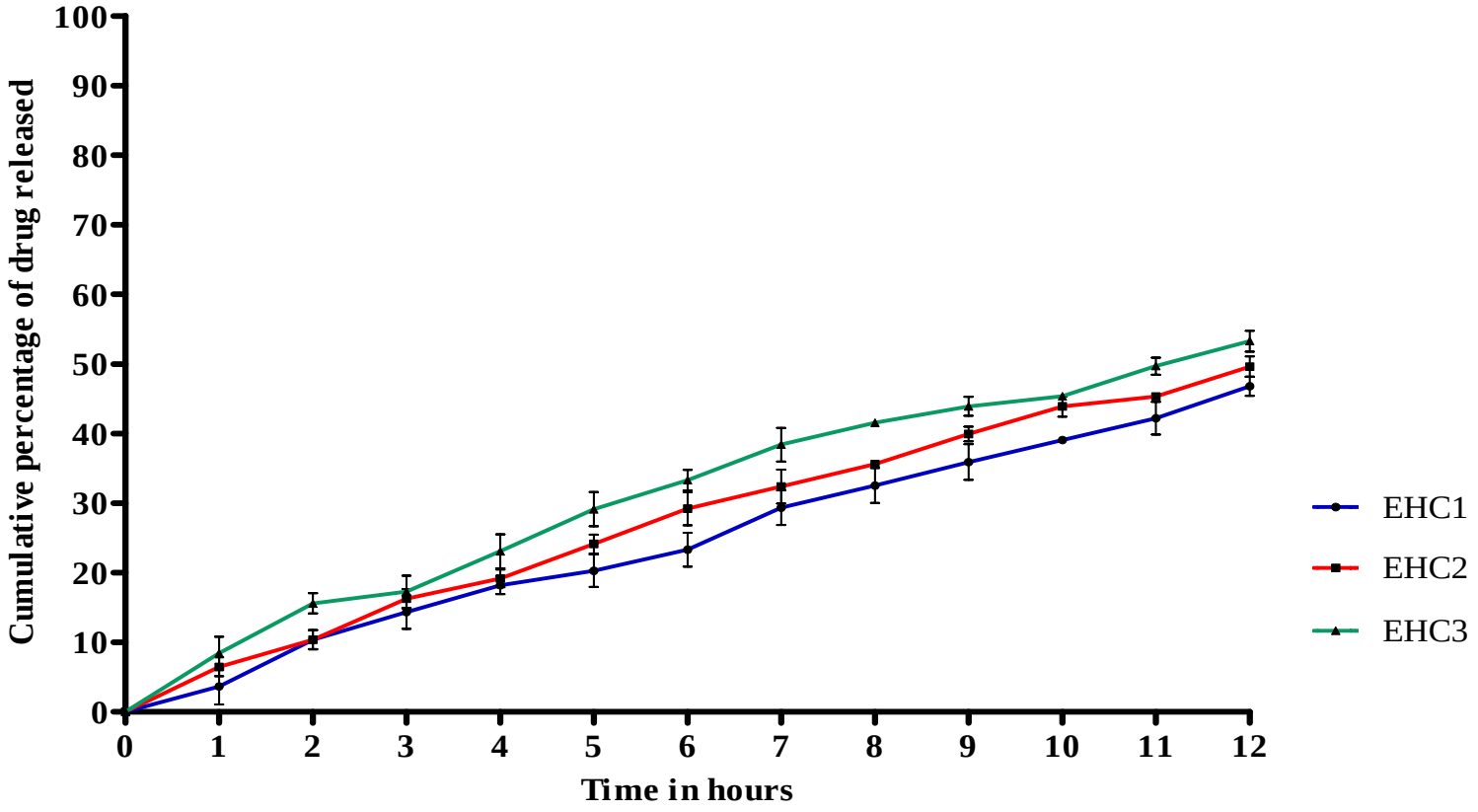


Fig - 15 In-vitro permeation studies of EPA3, EPB3 and EPC1

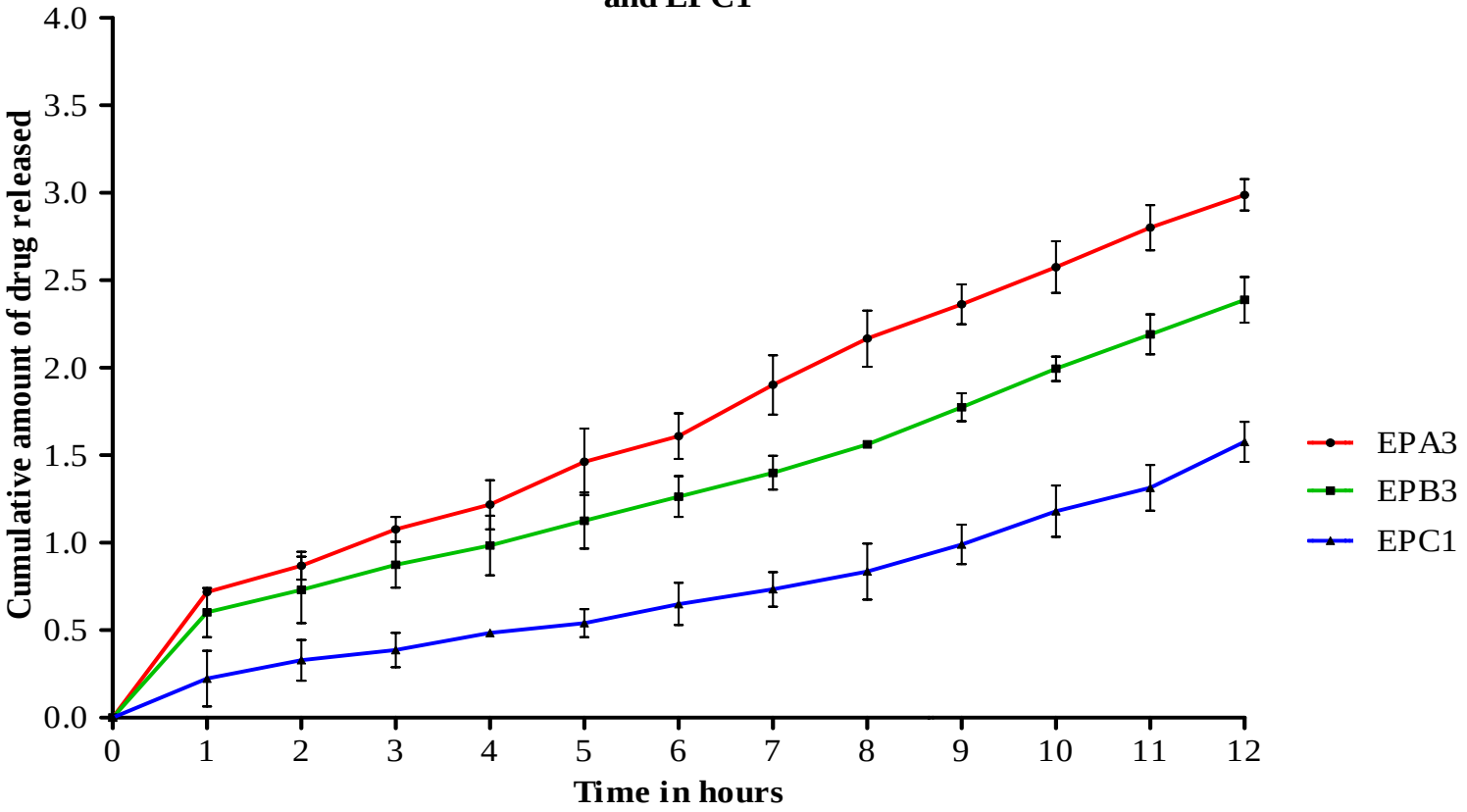
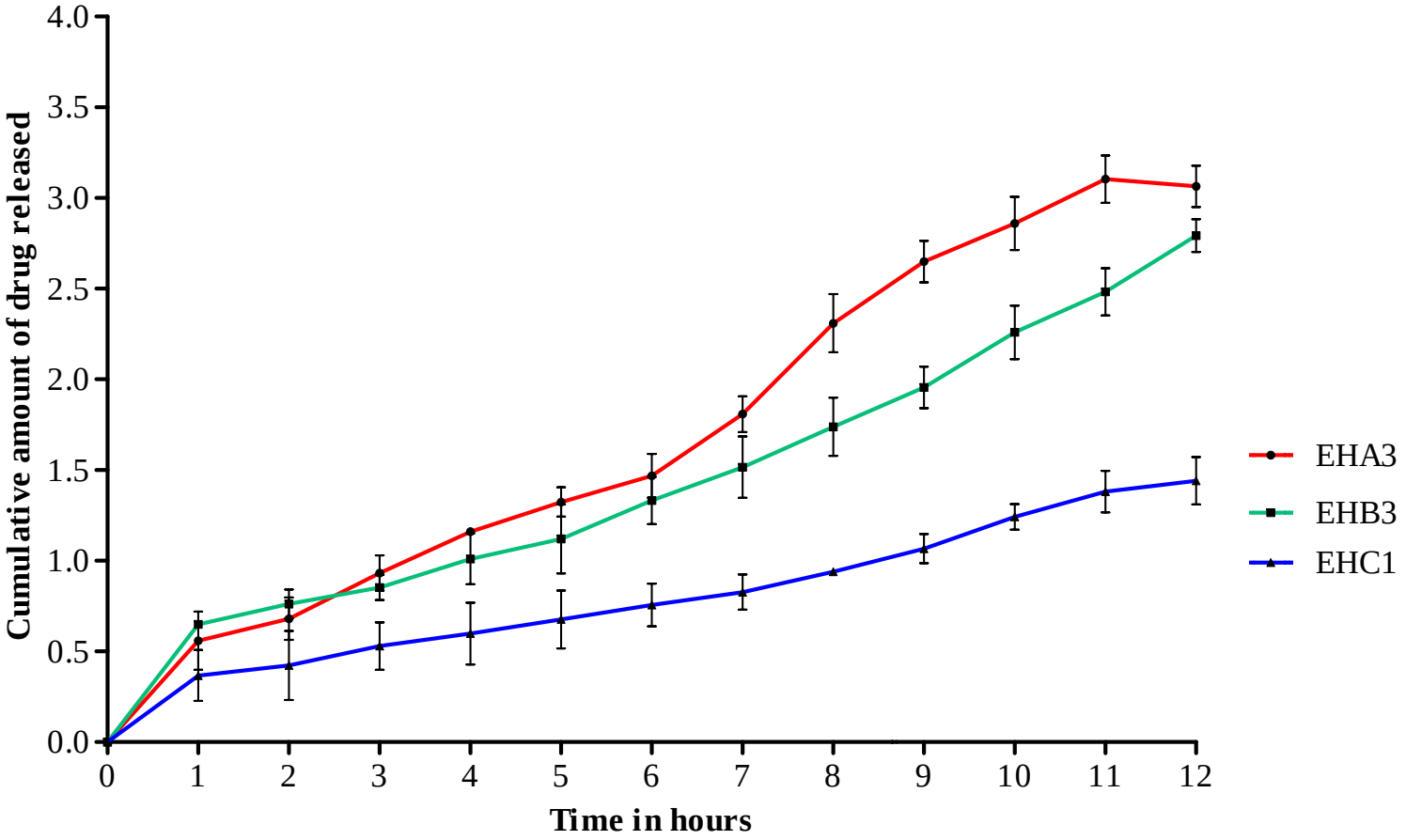


Fig - 16 In-vitro permeation studies of EHA3, EHB3 and EHC1



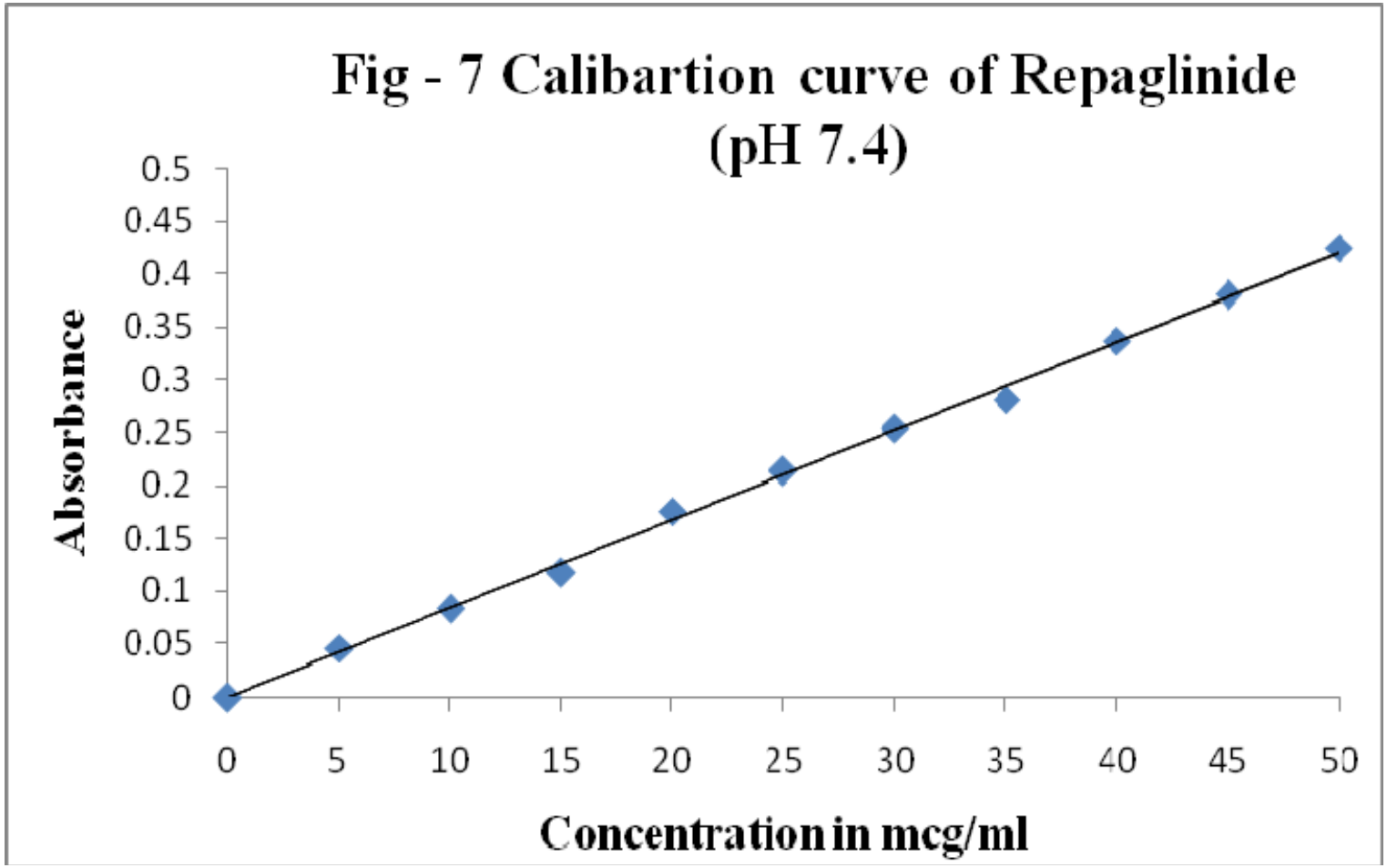


Fig - 7 Calibartion curve of Repaglinide (pH 7.4)
Absorbance
0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
0
5
10
15
20
25
30
35
40
45
50
Concentration in mcg/ml

Figure - 23

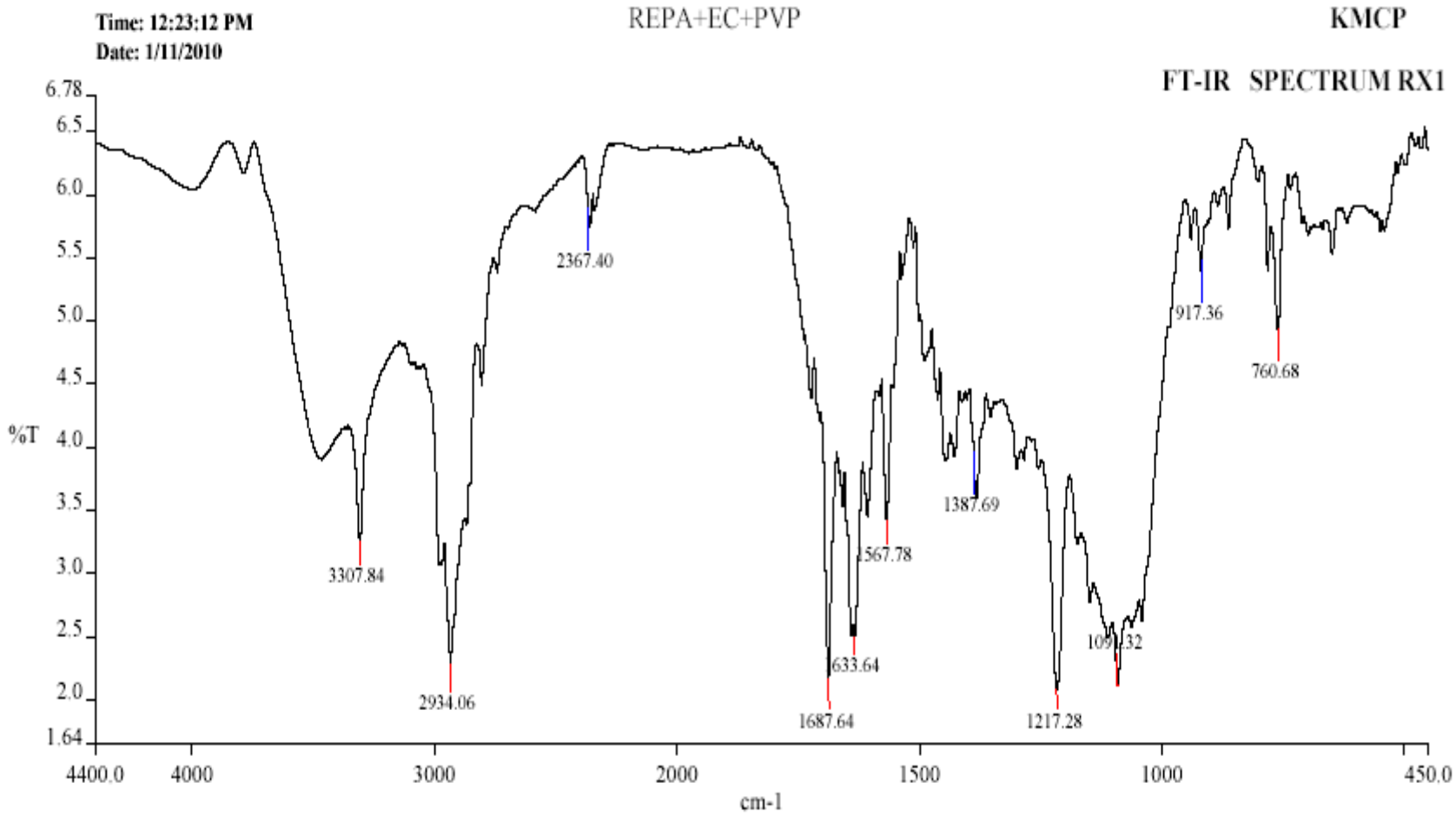

Time: 12:23:12 PM
Date: 1/11/2010
REPA+EC+PVP
KMCP
FT-IR SPECTRUM RX1
%T
6.78
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.64
3307.84
2934.06
2367.40
1687.64
1633.64
1567.78
1387.69
1217.28
1091.32
917.36
760.68
4400.0
4000
3000
2000
1500
1000
450.0
cm-1

Figure - 24

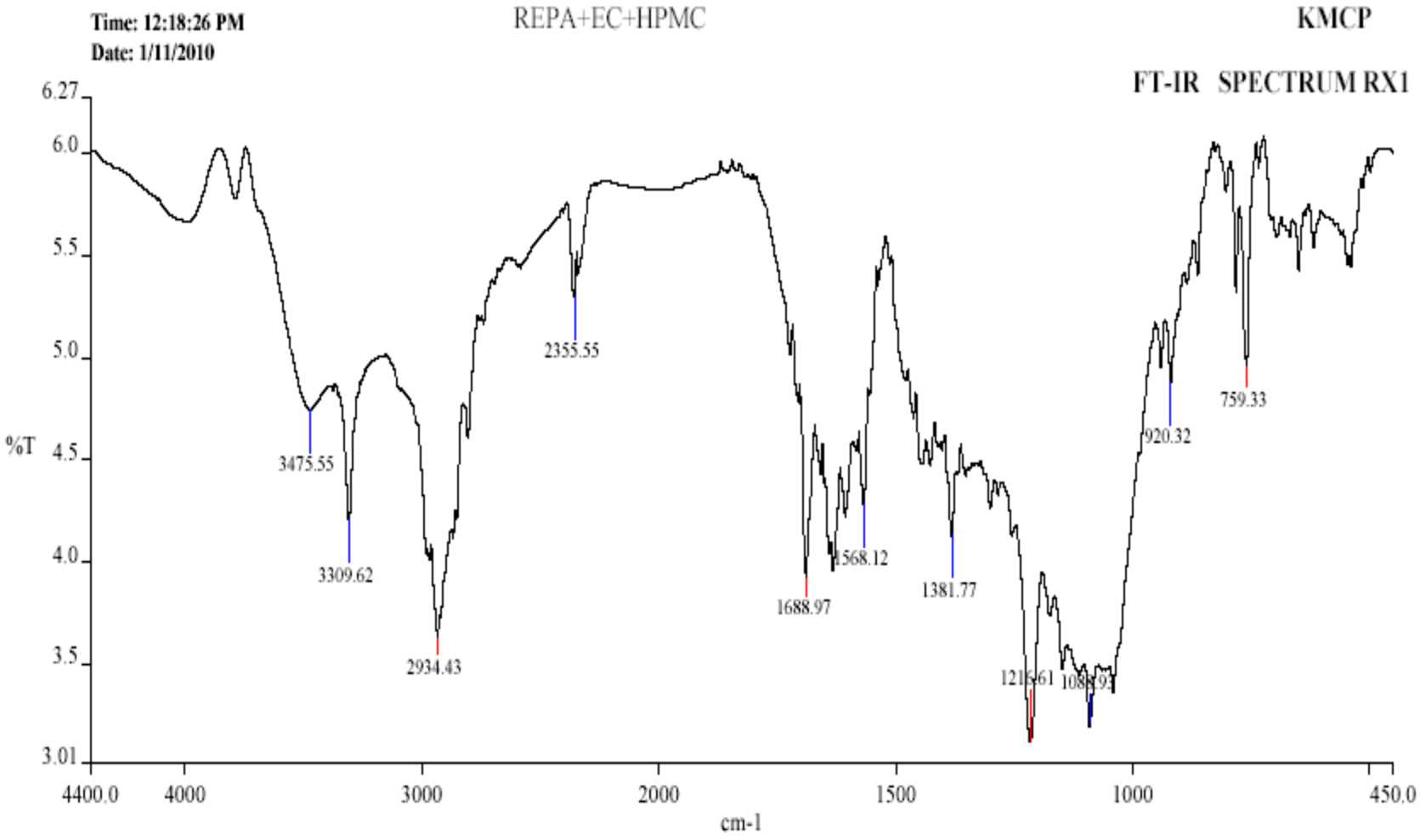

Time: 12:18:26 PM
Date: 1/11/2010
REPA+EC+HPMC
KMCP
FT-IR SPECTRUM RX1
%T
6.27
6.0
5.5
5.0
4.5
4.0
3.5
3.01
3475.55
3309.62
2934.43
2355.55
1688.97
1568.12
1381.77
1215.61
1088.93
920.32
759.33
4400.0
4000
3000
2000
1500
1000
450.0
cm-1

Figure - 22

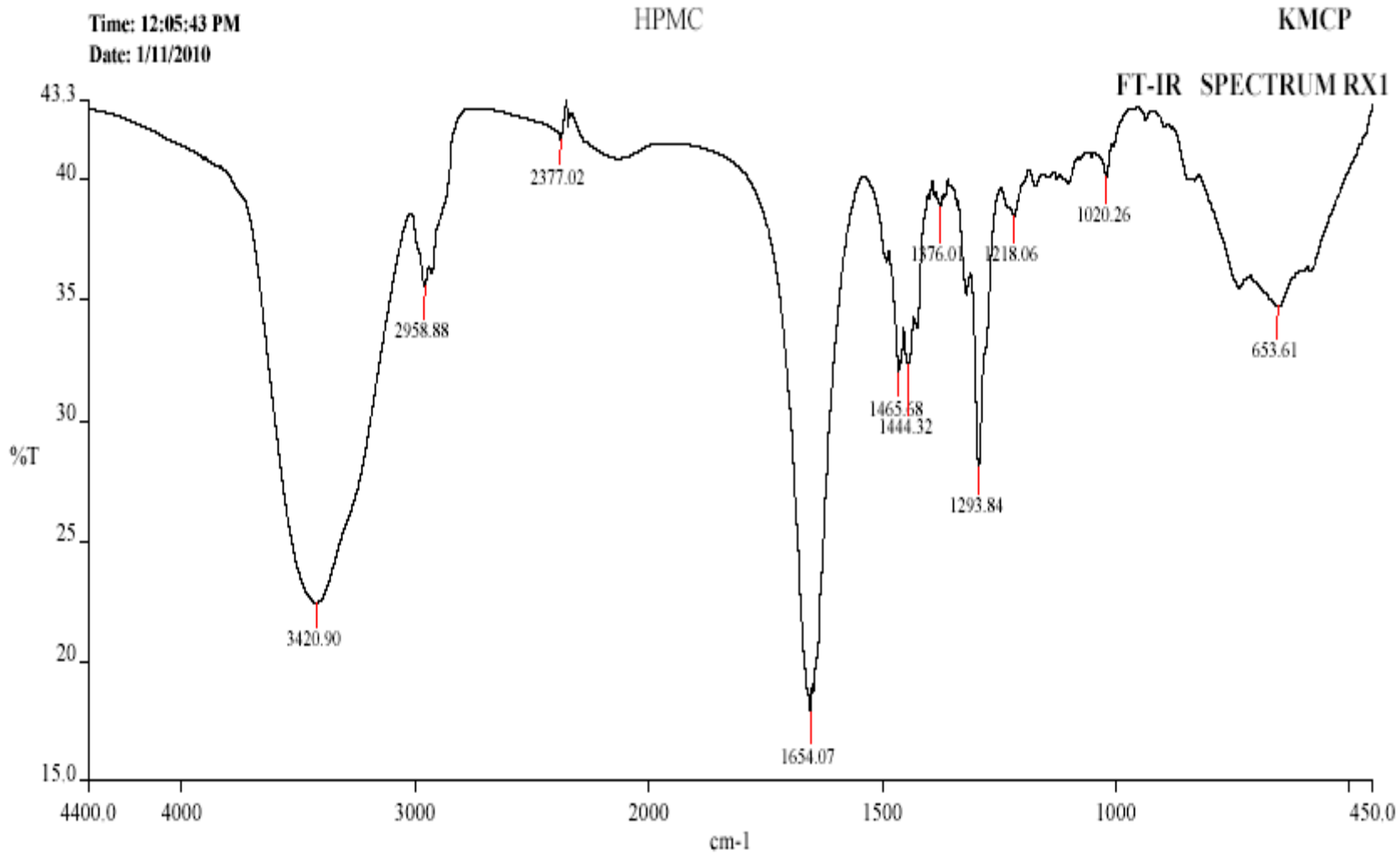

Time: 12:05:43 PM
Date: 1/11/2010
HPMC
KMCP
FT-IR SPECTRUM RX1
43.3
40
35
30
25
20
15.0
%T
3420.90
2958.88
2377.02
1654.07
1465.68
1444.32
1376.01
1293.84
1218.06
1020.26
653.61
4400.0
4000
3000
2000
1500
1000
450.0
cm-1

Figure - 19

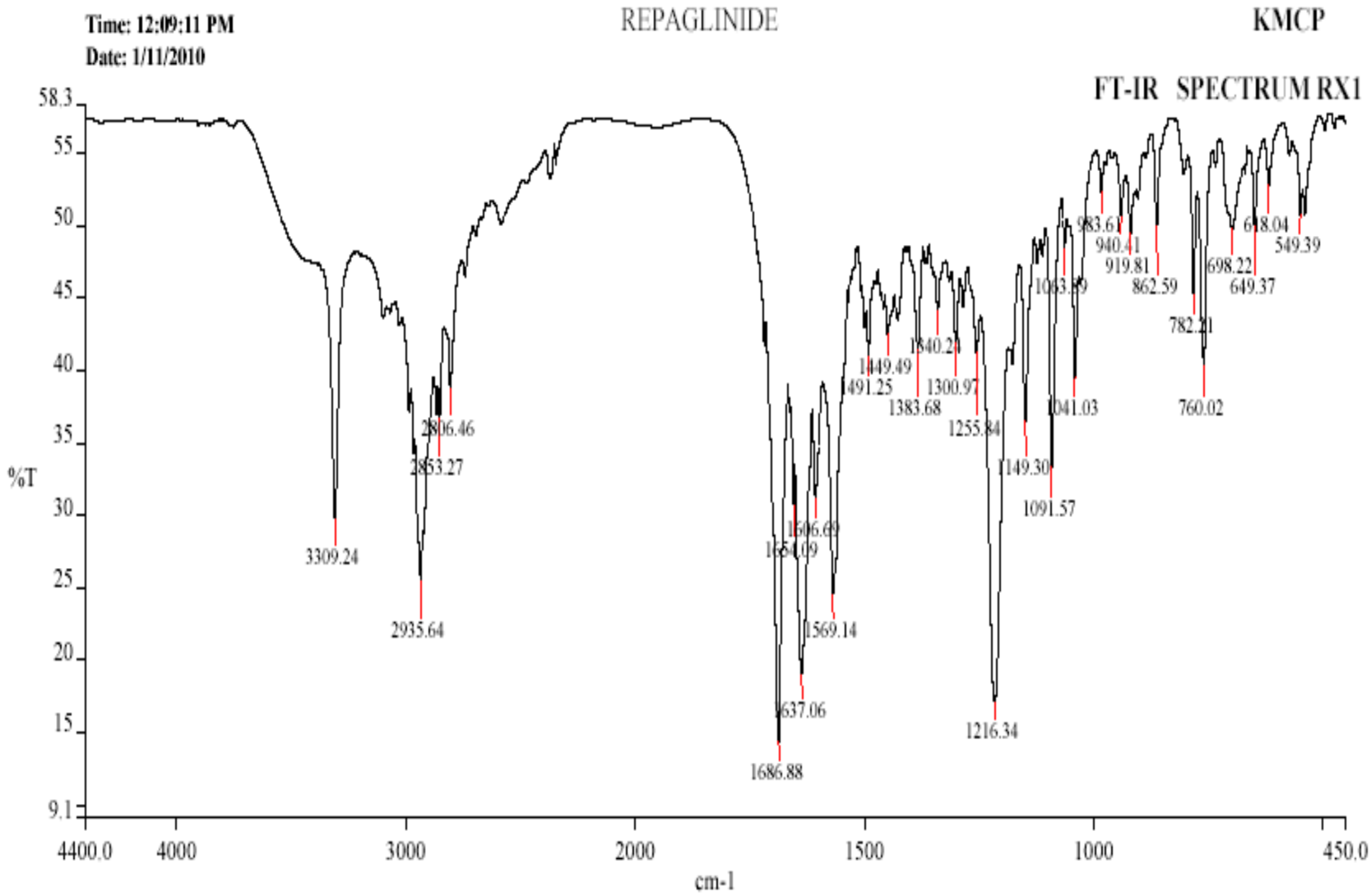

Time: 12:09:11 PM
Date: 1/11/2010
REPAGLINIDE
KMCP
FT-IR SPECTRUM RX1
%T
58.3
55
50
45
40
35
30
25
20
15
9.1
4400.0
4000
3000
2000
1500
1000
450.0
cm-1
3309.24
2935.64
2853.27
2806.46
1686.88
1637.06
1606.69
1569.14
1491.25
1449.49
1383.68
1300.97
1255.84
1216.34
1149.30
1091.57
1041.03
983.61
940.41
919.81
862.59
782.21
760.02
698.22
649.37
618.04
549.39

Figure - 20

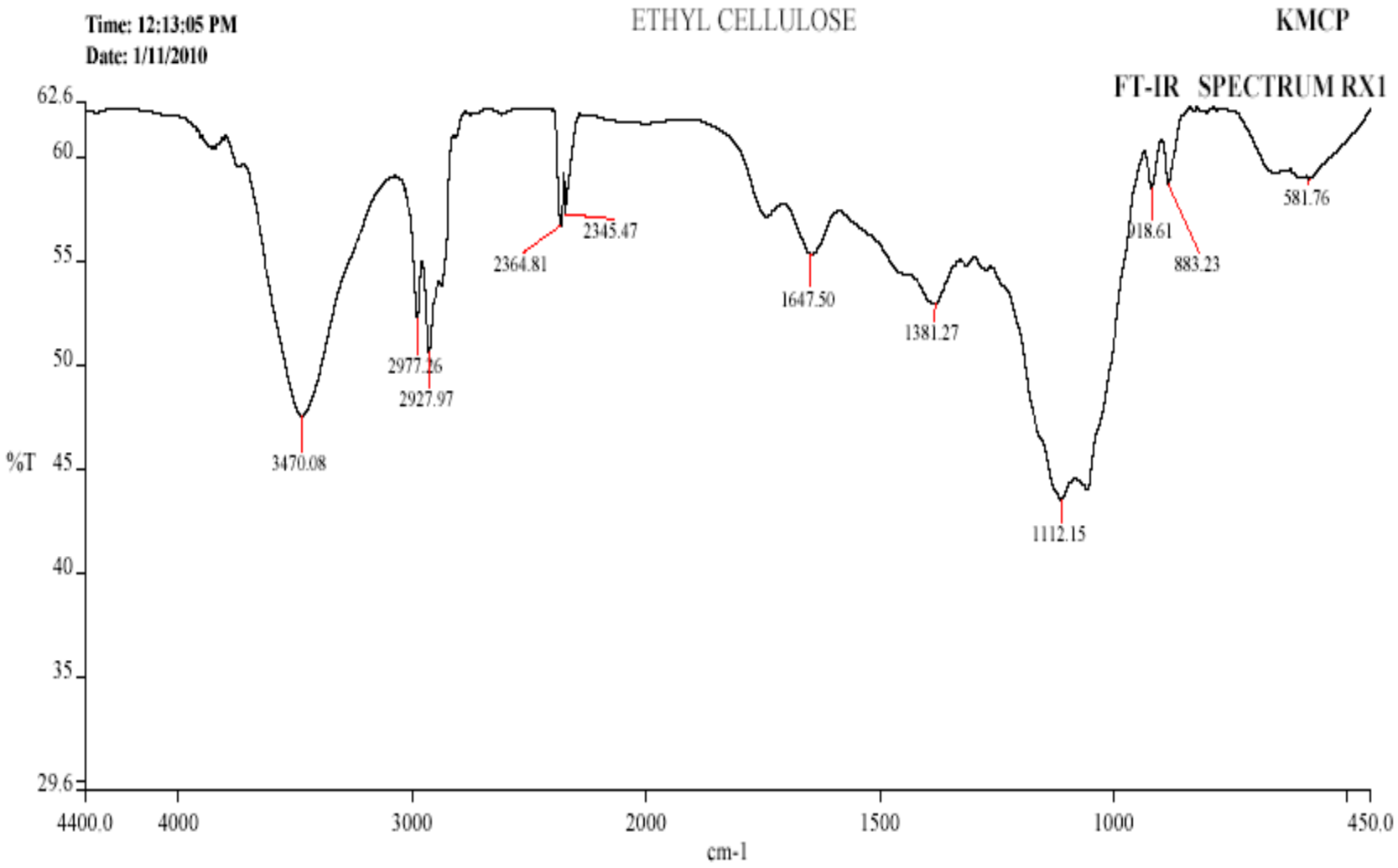

Time: 12:13:05 PM
Date: 1/11/2010
ETHYL CELLULOSE
KMCP
FT-IR SPECTRUM RX1
62.6
60
55
50
%T 45
40
35
29.6
3470.08
2977.26
2927.97
2364.81
2345.47
1647.50
1381.27
1112.15
918.61
883.23
581.76
4400.0
4000
3000
2000
1500
1000
450.0
cm-1

Figure - 21

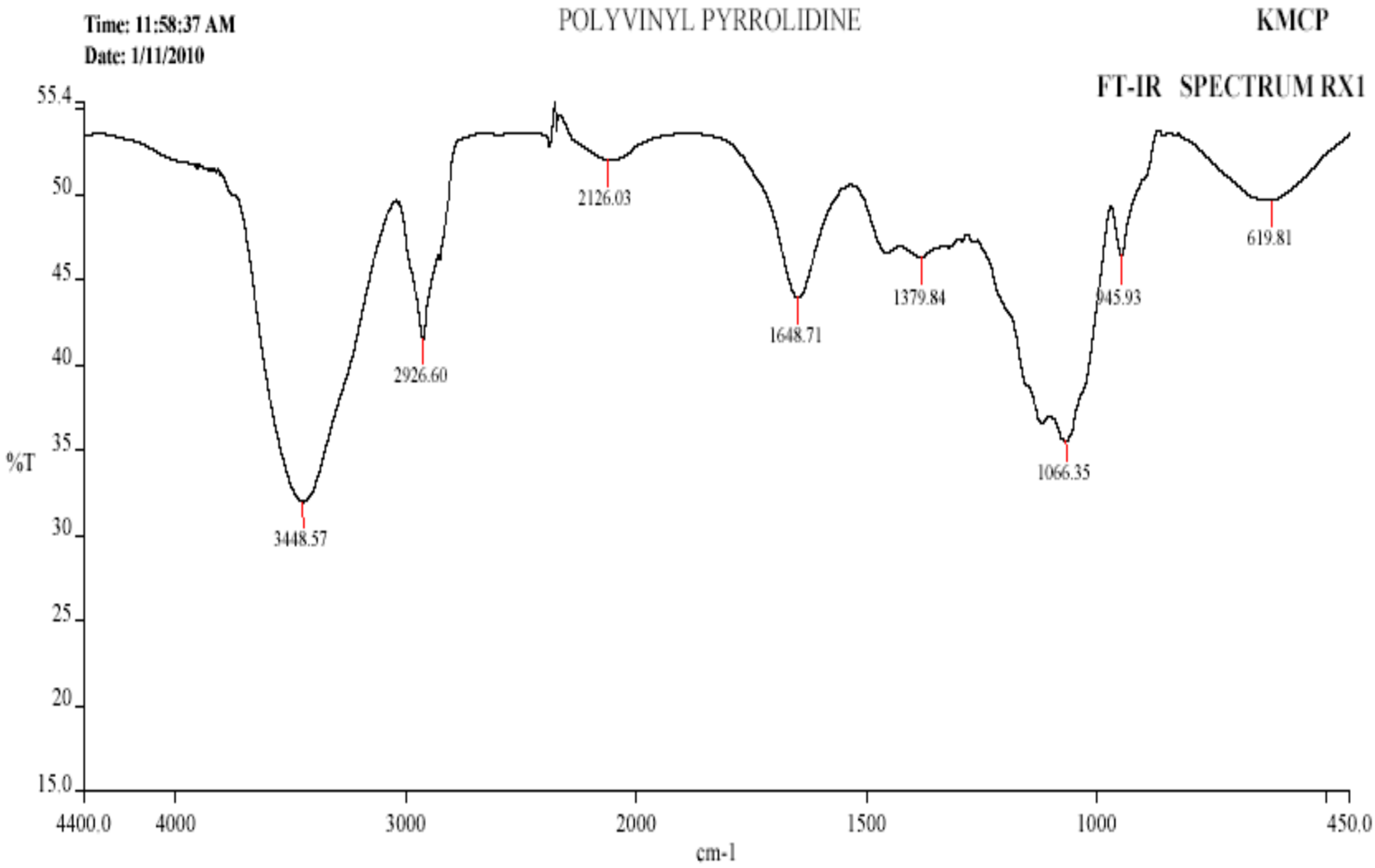

Time: 11:58:37 AM
Date: 1/11/2010
POLYVINYL PYRROLIDINE
KMCP
FT-IR SPECTRUM RX1
55.4
50
45
40
35
30
25
20
15.0
%T
3448.57
2926.60
2126.03
1648.71
1379.84
1066.35
945.93
619.81
4400.0
4000
3000
2000
1500
1000
450.0
cm-1

Figure – 17

SEM Photograph of Repaglinide Transdermal patch (EPC1) before permeation studies

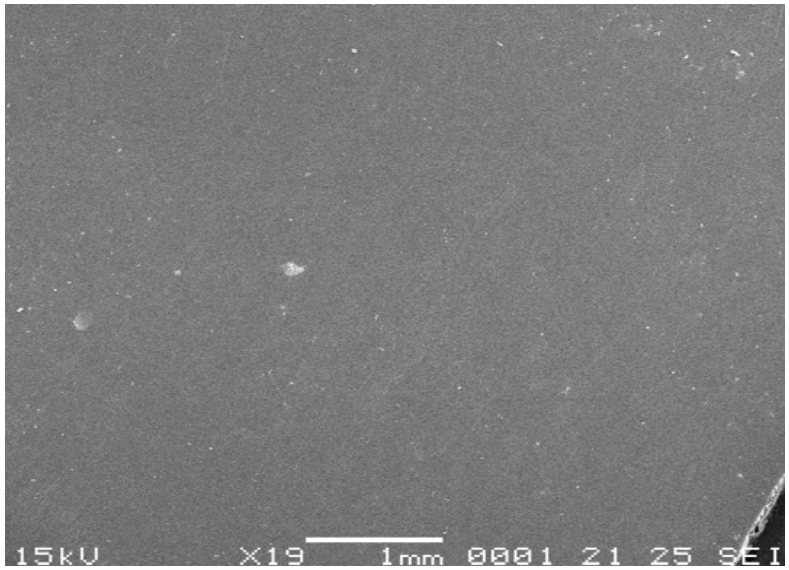
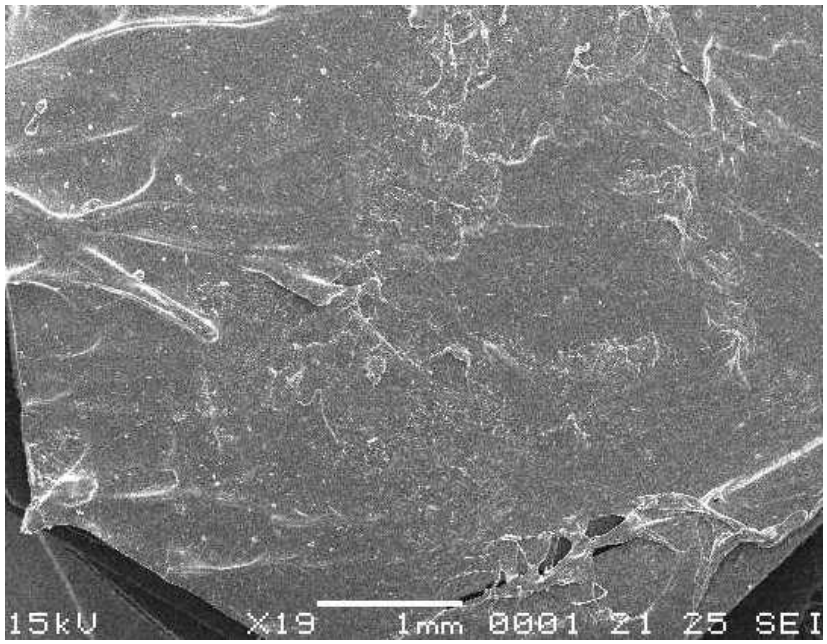


Figure – 18

SEM Photograph of Repaglinide Transdermal patch (EPC1) After permeation studies.



REFERENCES

1. **Vasant V. Ranade ,Mannfred A**. **Hollinger,** 'Drug delivery systems' 2004 CRC press New York, second edition, chapter 6, page no – 1 to 2.
2. **Vyas, S**.P., " Controlled drug delivery concepts and advances", III rd edition, CBS – publishers, New Delhi, 2002,1-10, 477 -502.
3. **Vyas .S.P. and Khar.R.K**. "Controlled drug delivery concepts and advances", vallabh Prakashan, Ist edition., page no -1 to 7
4. **Chien Y.W.,** "Novel drug delivery systems", marcel dekker, II nd edition revised and expanded, Newyork, page no – 1 to 2.
5. **Ashok K.Tiwari, Bharti sapra and Subheet jain,** " Innovations in Transdermal Drug delivery : Formulations and techniques", Recent patents on drug delivery & Formulation, 2007, page no – 23 to 36.
6. **www.wikipedia.com.**
7. **Tanner.T and Marks.R.,** " Delivering drugs by the transdermal route: review and comment", Skin Research and Technology, 2008, 14,page no 249 to 260.
8. **Ritesh kumar and Philip .,** " Modified transdermal technologies: Breaking the barriers of drug permeation via the skin" Tropical journal of pharmaceutical research, March 2007, 6 (1), page no – 633 to 644.
9. **Nanda. A, Nanda.S and Khan Ghilzai .,** " Current developments using emerging transdermal technologies in physical enhancement methods", Current drug delivery, 2006, 3, page no – 233 to 242.
10. **Jain .N.K.,** "Controlled and novel drug delivery" CBS publishers, New delhi, page no-100.

11. **Barry.B.W.,** "Novel mechanisms and devices to enable successful transdermal drug delivery" European journal of pharmaceutical sciences, 14, 2001, page no -101 to 114.
12. **Rama padmanaban, Robert M.Gale, J.Bradely Phipps.,** "Modified Release Drug Delivery Technology" Marcel dekker, inc., 2003, page no 481 to 498.
13. **Heather A.E. Benson.,** "Transdermal Drug Delivery: Penetration Enhancement Techniques" Current Drug Delivery, 2005, 2, page no 23 to 33.
14. **Dinesh L.Dhamecha, Amit A Rathi, Maria Saifee,** "Drug vehicle based approaches of penetration enhancement" International journal of pharmacy and pharmaceutical sciences, 2009, volume 1, Issue1, page no 24 to 46.
15. **Keith AD.** "Polymer matrix considerations for transdermal devices, Drug Delivery and Industrial Pharmacy", 1983, 9, 605.
16. **Guy RH.** "Current status and future prospects of transdermal drug delivery", Pharma Research, 1996, 13, 1765-1769.
17. **Guy RH, Hadgraft J, Bucks DA.** "Transdermal drug delivery and cutaneous metabolism", Xenobiotica 1987, 7, 325-343.
18. **Gordon RA, Peterson TA.** "Four myths about transdermal drug delivery", Drug Delivery Technology 2003, 3, 1-7.
19. **Williams AC, Barry BW**. "Penetration enhancers",Advanced drug delivery reviews 2004, 56, 603-618.
20. **Godbey KJ.** "Improving patient comfort with nonocclusive transdermal backings", American Association of Pharmaceutical Scientists 1996, 1-2.

21. **Gondaliya D, Pundarikakshudu K.** "Studies in formulation and pharmacotechnical evaluation of controlled release transdermal delivery system of bupropion", AAPS PharmSciTech 2003, 4, Article3.
22. **Costa P, Ferreria DC , Morgado R, Sousa Lobo JM.** "Design and evaluation of a lorazepam transdermal delivery system", Drug Delivery and Industrial Pharmacy 1997, 23, 939-944
23. **Lewis S, Pandey S, Udupa N.** "Design and evaluation of matrix type and membrane controlled transdermal delivery systems of nicotine suitable for use in smoking cessation", Indian journal of Pharmacuetical Sciences 2006, 68, 179-184.
24. **Raju.R.Thenge*, Krodhi. G. Mahajan, Harigopal. S.Sawarkar, Vaibhav.S.Adhao, Purushottam.S.Gangane,** "Formulation and evaluation of transdermal drug delivery system for lercanidipine hydrochloride" International Journal of PharmTech Research, Jan-Mar 2010, Vol.2, No.1, pp 253-258,
25. **Satyanarayan Pattnaik, Kalpana Swain, Parthagan Choudhury, Pradeepta K. Acharya, Subrata Mallick,** "Alfuzosin Hydrochloride Transdermal Films: Evaluation of Physicochemical, In Vitro Human Cadaver Skin Permeation and Thermodynamic Parameters" International Braz J Urol, November - December, 2009, Vol. 35 (6): 716-729,
26. **Kevin C. garala, Anil J. shinde, Pratik H. shah,** "Formulation and *in-vitro* characterization of monolithic matrix transdermal systems using Hpmc/Eudragit S 100 polymer blends" International journal of pharmacy and pharmaceutical sciences, 2009, volume 1, 109 to 116.

27. **Ting Li, Changshun Ren, Manli Wang, Ligang Zhao, Ximeng Wang, Liang Fang**., "Optimized preparation and evaluation of indomethacin transdermal patch", Asian Journal of Pharmaceutical Sciences 2007, 2 (6): 249-259.
28. **Mutalik.S, Udupa.N**, "Glibenclamide Transdermal Patches: Physicochemical, Pharmacodynamic, and Pharmacokinetic Evaluations", Journal of pharmaceutical sciences, June 2004, Vol. 93, no. 6, Page no 1577–1594.
29. **Ammar.H.O, Ghorab .M , El-Nahhas .S.A , Kamel . R.,** "Design of a transdermal delivery system for aspirin as an antithrombotic drug", International Journal of Pharmaceutics, 2006, 327, Page no 81 to 88.
30. **Yun-Seok Rhee, Seok-Young Kwon, Chun-Woong Park, Na-Young Choi, Woo-Jin Byun, Sang-Cheol Chi, and Eun-Seok Park,** "Characterization of Monolithic Matrix Patch System Containing Tulobuterol", Arch Pharm Res, 2008 Vol 31, No 8, Page no 1029-1034.
31. **Mohd. Aqil, Asgar Ali, Yasmin Sultana, Kiran Dubey.,** " In-Vivo Characterisation of Monolithic Matrix Type Transdermal Drug Delivery Systems of Pinacidil Monohydrate: A Technical Note", AAPS PharmasciTech, 2006, 7 (1) article 6, page no E1 to E5.
32. **Ramesh Panchagnula ., Ranadeep Bokalial, Puneet Sharma, Sateesh Khandavilli.,** "Transdermal delivery of naloxone: skin permeation, pharmacokinetic, irritancy and stability studies", International Journal of Pharmaceutics, 2005, vol.293, Page no 213–223.
33. **Olivier J.C., Rabouan . S , Couet .W.,** "In vitro comparative studies of two marketed transdermal nicotine delivery systems: Nicopatch® and Nicorette®", International Journal of Pharmaceutics , 2003, 252 , Page no133–140

34. **Soodabeh Davaran, Mohammad R. Rashidi, Reza Khandaghi, Mahdi Hashemi**., "Development of a novel prolonged-release nicotine transdermal patch", Pharmacological Research, 2005, 51, Page no- 233–237.
35. **Nicoli . S, Penna .E, Padula .C, Colombo .P, Santi .P .,** "New transdermal bioadhesive film containing oxybutynin : In vitro permeation across rabbit ear skin", International Journal of Pharmaceutics, 2006, 325, page no 2–7.
36. **Mohd. Aqil, Asgar Ali.,** "Monolithic matrix type transdermal drug delivery systems of pinacidil monohydrate: in vitro characterization", European Journal of Pharmaceutics and Biopharmaceutics, 2002, 54, page no 161–164.
37. **Christopher W. Jeans, Charles M. Heard.,** "A therapeutic dose of primaquine can be delivered across excised human skin from simple transdermal patches", International Journal of Pharmaceutics, 1999, 189, page no 1–6.
38. **Guyot .M , Fawaz .F.,** "Design and in vitro evaluation of adhesive matrix for transdermal delivery of propranolol", International Journal of Pharmaceutics, 2000, 204 , page no 171–182.
39. **Chomchan Amnuaikit ,, Itsue Ikeuchi, Ken-ichi Ogawaraa, Kazutaka Higakia, Toshikiro Kimura,.** "Skin permeation of propranolol from polymeric film containing terpene enhancers for transdermal use", International Journal of Pharmaceutics, 2005, 289, page no 167–178.
40. **Ayman El-Kattan, Charles S. Asbill and Sam Haidar.,** "Transdermal testing: practical aspects and methods", PSTT, December 2000, Vol. 3, No. 12, Page no 426 to 430.

41. **Mi-Kyeong Kim, Hong Zhao, Chi-Ho Lee, Dae-Duk Kim**., "Formulation of a reservoir-type testosterone transdermal delivery system", International Journal of Pharmaceutics, 2001, 219 ,page no 51–59.
42. **Paula Chedgzoy, Gareth Winckle, Charles M. Heard.,** "Triclosan: release from transdermal adhesive formulations and in vitro permeation across human epidermal membranes", International Journal of Pharmaceutics, 2002, 235, page no 229–236.
43. **Girish K. Jain, A.K. Sharma , S.S. Agrawal .,** "Transdermal controlled administration of verapamil-enhancement of skin permeability" International Journal of Pharmaceutics, 1996, 130, page no 169—177.
44. **Janardhanan Bagyalakshmi, Ramachandra Purapu Vamsikrishna, Rajappan Manavalan, Thengungal Kochupappy Ravi, and Probal Kumar Manna**. "Formulation Development and In Vitro and In Vivo Evaluation of Membrane-Moderated Transdermal Systems of Ampicillin Sodium in Ethanol: pH 4.7 Buffer Solvent System", AAPS PharmSciTech 2007, 8 (1) Article 7, page no E1 - E6.
45. **Udhumansha Ubaidulla, Molugu V.S. Reddy, Kumaresan Ruckmani, Farhan J. Ahmad, and Roop K. Khar.,** "Transdermal Therapeutic System of Carvedilol: Effect of Hydrophilic and Hydrophobic Matrix on In Vitro and In Vivo Characteristics", AAPS PharmSciTech, 2007, 8 (1) Article, Page no E1 – E8.
46. **Narasimha Murthy. S and Shobha Rani R. Hiremath.,** "Physical and Chemical Permeation Enhancers in Transdermal Delivery of Terbutaline Sulphate", AAPS PharmSciTech, 2001, 2 (1), page no 1 to 5.

47. **Jamakandi. V. G, Mulla. J. S, Vinay .B.L, Shivakumar . H.N.,** "Formulation, Characterization and Evaluation of Matrix-type Transdermal Patches of a Model Antihypertensive Drug", Asian journal of Pharmaceutics, 2009, page no 59 – 65.
48. **Krzysztof Cal, Stanislaw Janicki, Malgorzata Sznitowska.,** "In vitro studies on penetration of terpenes from matrix-type transdermal systems through human skin", International Journal of Pharmaceutics, 2001, 224, page no 81–88.
49. **Stanley Scheindlin. "**Transdermal drug delivery: past, present, future".Mol. Int 2004; Volume 4, Issue 6: page no 308-312.
50. **www.novonordisk-us.com.**
51. **www.Rxlist.com.**
52. **www.drugbank.com**
53. **Laurence L. Brunton, Keith L. Parker,** "Goodman and Gilman's manual of Pharmacology and Therapeutics" McGraw Hill publications, 2008, page no – 1053.
54. **AFHS, Drug information,** "American Society of Health System Pharmacists" 2004, page no – 68:20.16 to 68:20.20.
55. **cims**
56. **Raymond C Rowe,** "Handbook of Pharmaceutical Excipients", PHP pharmaceutical press, London, fifth edition page no – 369 to 371.
57. **Sateesh Kandavilli, Vinod Nair, Ramesh Panchagnula**, "Polymers in Transdermal drug delivery systems", Pharmaceutical Technology, May 2002, page no 62 to 80.
58. **Karen A. Coppens, Mark J. Hall, Shawn A. Mitchell, and Michael D. Read,** "Hypromellose, Ethyl cellulose and Polyethylene Oxide Use in Hot Melt Extrusion", Pharmaceutical technology, January 2006, page no 1 – 6.

59. Indian pharmacopoeia.
60. Wagh M.P, David H, Bagal .M, “Formulation and Evaluation of Transdermal Drug Delivery System for Simvastatin”, Indian Drugs, March 2009, 46 (3), page no 221 - 225
61. **Mohamed aqil, Yasmin sultana, Agsar Ali,** “Matrix type transdermal drug delivery systems of metoprolol tartrate: In-vitro characterization”, Acta pharm, 2003, 53, page no 119 – 125.
62. **The United States pharmacopoeia,** 23rd edition, US Pharmacopoeial Convention Rockvile 1999, page no 1796 – 1799.
63. **www.Labhut.com**
64. **Nashwa A. El-Gendy, Nirmeen A.Sabry, Mai El-Attar, Emad Omar, Manal Mahmoud**, “Transdermal patch incorporating Salbutamol sulphate: *In-vitro* and clinical characterization” Drug Discovery Theory, 2008, 2(4), page no 219 – 228.
65. **Shinde Anil kumar. J, Garala C Kevin, More Harinath,** “Formulation and Evaluation of Transdermal patches of Metoprolol Tartrate”, The Indian Pharmacist, June 2009, page no 69-74.