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Design and evaluation of Keterolac Tromethamine impregnated Hydroxy Propyl Methyl Cellulose films

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ABSTRACT

The novel approach of using a transdermal drug delivery system through intact skin has time again been recognized as a important mode of administration of several systemically active drugs. Many drugs with short biological half-life and prone to first pass effect are reported to be good candidates for transdermal drug delivery. In recent years, crescendo of transder material, is encouraging. Therefore, in this work an attempt is made in developing transdermal patches of HPMC containing Keterolac for extended duration of action. This work is aimed at studying the release profiles of Keterolac , from HPMC matrix. The effect of various co-polymers, Cellulose acetate & Ethyl cellulose, each in different promal drug delivery has fallen to best of its share, in using hydrophillic polymer matrix containing drug, because of its patient compliance and avoidance of first pass metabolism. Keterolac tromethamine is a non-steroidal anti-inflammatory drug, reported to be potent analgesic and anti-inflammatory agent, has a short biological half life of 4-6 hrs. In this work, Keterolac is chosen as a suitable drug candidate to explore its potentiality in being delivered through skin. Previous research on HPMC, a hydrophillic, polymeric matrix portions 8:1, 4:1, 2:1 and 1:1 of HPMC (w/w) and the effect of different plasticizers/penetrating enhancers like, glycerol and DBP both in 20%, 30% & 40% w/w of HPMC, on the physical characteristics & In-vitro release profiles will be studied. Further, Pharmaco dynamic studies on suitable patches will be conducted. Also, stability studies at different temperatures and %RH will be undertaken.

Keywords: Keterolac tromethamine, HPMC, Cellulose acetate & Ethyl cellulose.

INTRODUCTION

The conventional dosage forms like tablets, capsules, ointments etc., used for the control of infection, pain and fertility may cause side effects like nausea, vomiting, gastric irritation and toxicity if they are consumed for long duration. This type of dosage forms are necessary to take several times a day. Administration of drugs in conventional dosage forms often results in fluctuations of drug concentration in systemic circulation and tissue compartments, the magnitude of these fluctuations depends on the rates of absorption, distribution and elimination and dosing intervals. Continuous I.V. infusion at a programmed rate has been recognized as a superior mode of drug delivery to by pass the hepatic first-pass elimination. Amongst all types of administration to maintain a constant, prolonged and therapeutically effective drug level in the body, intravenous administration can provide the advantages like direct entry of drug into the systemic circulation, and control of circulating drug levels. But, this type of drug delivery have certain disadvantages, which would require hospitalization of the patients and close medical supervision of the medication.[1]
The novel drug delivery system, has brought renaissance into the pharmaceutical industry for controlled drug delivery. The novel drug delivery system includes Transdermal drug delivery system, Mucoadhesive drug delivery system ,Nasal drug delivery system etc.

The transdermal route of drug delivery are gaining accolade with the demonstration of the percutaneous absorption of a large number of drugs. This type of drug delivery systems have been developed for controlled drug delivery with the intention of maintaining constant plasma levels, zero-order drug input and serves as a constant I.V.infusion. Several transdermal drug delivery systems (TDDS) have recently been developed, aiming to achieve the objective of systemic medication through topical application to the intact skin surface.

The intensity of interests in the potential bio-medical application of transdermal controlled drug administration is demonstrated in the increasing research activities in a number of health care institutions in the development of various types of transdermal therapeutic systems (TTS) for long-term continuous infusion of therapeutic agents, including antihypertensive, antianginal, antihistamine, anti-inflammatory, analgesic drugs etc.,.

Transdermal drug delivery systems are adhesive, drug containing devices of defined surface area that deliver a pre-determined amount of drug to the surface of intact skin at a pre-programmed rate. These systems provide drug systemically at a predictable rate and maintain the rate for extended periods of time.[2]

The skin acts as a formidable barrier to the penetration of drugs and other chemicals, it does have certain advantages which make it an alternative route for systemic delivery of drugs. Transdermal drug delivery systems involves the passage of substances from the skin surface through the skin layers, into the systemic circulation. The skin has been commonly used as the site for topical administration of drugs, when the skin serves as a port for administration of systemically active drugs. The drug applied topically is distributed, following absorption, first into the systemic circulation and then transported to the target tissue which can be relatively remote from the site of drug application, to achieve its therapeutic action.

The skin site for transdermal drug administration:
The skin is one of the most extensive and readily accessible organ of the human body. The skin of an average adult body covers a surface area of approximately $2m^2$ and receives about one-third of the blood circulating through the body[3].It is elastic, rugged and under normal physiological conditions, self regenerating with a thickness of 2.97±0.28mm. It separates the underlying blood circulation network and viable organs from the outside environment. It serves as a barrier against physical and chemical attacks and shields the body from invasion by microorganisms.

Different Transdermal drug delivery systems : Over a decade of intensive research and development efforts, several rate controlled TDDS have been successfully developed and commercialized. They can be classified into four basic approaches.[7]

A) Polymer membrane permeation controlled-TDDS
B) Polymer matrix diffusion controlled-TDDS
C) Drug reservoir gradient controlled-TDDS
D) Micro reservoir dissolution controlled- TDDS

A) **Polymer membrane permeation controlled-TDDS :**In this system the drug reservoir is sand witched between a drug-impermeable backing laminate and a rate controlling polymeric membrane. The drug molecules are permitted to release only through the rate controlling polymeric membrane. In the drug reservoir compartment the drug solids are dispersed homogeneously in a solid polymer matrix, suspended in a unreachable, viscous liquid medium to form a paste like suspension, or dissolved in a releasable solvent to form a clear drug solution. The rate controlling membrane can be either micro porous or a non porous polymeric membrane e.g., ethylene-vinyl acetate copolymer with a specific drug permeability on the external surface of the polymeric membrane a thin layer of dry-compatible, hypoallergenic pressure-sensitive adhesive polymer, e.g., silicone adhesive, may be applied to provide intimate contact of the TDDS with the skin surface. The rate of drug release from this transdermal drug delivery system can be tailored varying the composition of the drug reservoir formulation and the permeability coefficient and/or thickness of rate controlling membrane. Eg:Transderm-Nitro system, Transderm -Scop system etc.

B) **Polymer matrix diffusion controlled-TDDS :**The drug reservoir is formed by homogeneously dispersing the drug solids in a hydrophilic or lipophilic polymer matrix, and the medicated polymer formed is then molded into medicated discs with a defined surface area and controlled thickness. This drug reservoir-containing polymer disc is then mounted onto an occlusive base plate in a compartment fabricated from a drug impermeable plastic backing. The adhesive polymer is applied along the circumference of the patch to form a strip of adhesive rim surrounding the medicated disc. Eg:Nitro-Dur system.

Alternatively, the polymer matrix drug dispersion type TDDS can be fabricated by directly dispersing the drug in a pressure sensitive adhesive polymer and then coating the drug dispersed adhesive polymer by solvent casting or hot melt on to a flat sheet of a drug impermeable backing laminate to form a single layer of drug reservoir. Eg:Nitro glycerin-releasing TDDS and Nitro-Dur II System.

C) **Drug reservoir gradiednt controlled TDDS:**Polymer matrix drug dispersion type TDDS can be modified to have the drug loading level varied in an incremental manner, forming a gradient drug reservoir along the diffusion path across the multi-laminate adhesive layers.

D) **Micro reservoir dissolution controlled TDDS:**It is a hybrid of the reservoir and matrix type drug delivery systems. In this drug reservoir is formed by first suspending the drug solids in an aqueous solution of water miscible drug solubiliser and homogenously dispersing the drug suspension with controlled aqueous solubility, in a lipophillic polymer by high shear mechanical force, to form thousands of unleachable microscopic drug reservoirs. This thermodynamically unstable dispersion is quickly stabilized by immediately cross-linking the polymer chains in situ, which produces a medicated polymer disc with a constant surface area and a fixed thickness. A transdermal drug delivery system is then produced by mounting the medicated disc at the centre of an adhesive pad. Eg. Nitro- disc.With diffusion controlled devices two fundamentally different methodologies can be used;

1) release of active agent from monolithic devices and
2) release of active agent from reservoir devices.

Monolithic devices:

In a monolithic device the therapeutic agent is intimately mixed in a rate-controlling polymer and release occurs by diffusion of the agent from the device. It is necessary to consider two types of devices.

a) The active agent is dissolved in the polymer and
b) The active agent is dispersed in the polymer.

When the active agent is dispersed in the polymer, release kinetics follows Higuchi equation.

$$dm_t / dt = A/2 (2 D Cs Co / t)^{1/2}$$

Where, m_t =amount released at time 't', a = Area, Cs= Solubility of the active agent in the matrix(polymer), Co= total concentration in the matrix (dissolved plus dispersed), D= diffusion coefficient.

Unlike the slab with dissolved active agent in which the rate is proportional to $t^{1/2}$ only during the early portion of the release curve, slabs with dispersed active agent maintain a $t^{1/2}$ dependence over the major portion of the release curve and deviate from this dependence only when the concentration of the active agent remaining in the matrix falls below the saturation value. Because of $t^{1/2}$ dependence, a plot of cumulative agent release versus $t^{1/2}$ will yield a straight line.Although active release from monolithic systems does not proceed by zero-order kinetics, it is the simplest and most convenient way to achieve prolonged release of an active agent. Such devices can be conveniently prepared by using simple polymer fabrication techniques involving a physical blending of the active agent with a polymer matrix, followed by compression molding, injection molding , extrusion solvent casting.[8]

Advantages of transdermal drug delivery systems[9,10]: Avoids the risks and inconveniences of intravenous therapy. Bypass the variation in the absorption and metabolism associated with the oral administration. Permit continuous drug administration and the use of drugs with a short biological half-life. Increase the bio-availability and efficacy of drugs through the by pass of

hepatic first-pass elimination. Treatment can be continued or discontinued according to the desire of the physician. Most of the time lower doses are sufficient. Greater patient compliance due to the elimination of multiple dosing schedules. Permit a rapid termination of the medication, if needed, by simply removing the TDDS from the skin surface. However, there are some limitations too, the most prominent amongst which is the realization that only a small percentage of the drugs can be delivered transdermally because of three limitations, viz; difficulty of permeation through human skin, skin irritations and clinical need.

Selection of drug candidate for transdermal drug delivery[11,12]: Judicious choice of drug substance is the most important decision in the successful development of a transdermal product. The effective concentration (dose) of the drug should be low. A drug with short biological half-life is much better candidate for transdermal delivery. The drug should have reasonably wide therapeutic index to that enter individual variability in skin absorption would not pose too much a problem for dosage adjustment. The drug should have an extensive pre-systemic metabolism. The drug as well as other additives should be essentially free from skin irritation. More will be molecular weight, less will be the diffusion rate, hence low molecular weight, water soluble drugs are preferable. The drug should not be irreversibly bound in the subcutaneous tissue. A lipid/water partition co-efficient of 1 or greater, is generally required for optimal transdermal permeability. The free acid or base should be chosen, so that partitioning into the skin is optimized. Otherwise, ionized drug generally penetrates the skin poorly where as unionized form penetrates rapidly.

Kinetics of Drug release: It is generally understood that the release of drug from films can be considered as mass transport phenomena involving diffusion of drug molecules from a region of high concentration to a region of low concentration in the surrounding environment. Attempts to model drug release from the films have been reported and in the treatment of their data it was assured that the drug release was confined to any of the order such as zero order or first order process. One indication of the mechanism can be obtained using a plot of log cumulative percentage drug remaining in the matrix against time.

A first order release would be linear as predicted by the following equation:

$$\log Wo = kt/2.303 + \log W$$

Where

W = amount of the drug left in the matrix
Wo = initial amount of drug in the matrix
K = first order rate constant
t = time either in days or hours or minutes.

When a log cumulative percentage drug retained vs time is plotted the curve obtained would be linear indicating first order release. The slope of the curve will be equal to –K/2.303 or K= slope X 2.303.Fick's law states that quantity of solute (dq) diffusion through a unit cross section (s) of a barrier in unit time (dt) is called as flux (J). J = dq/dt X 1/s

Flux is proportional to the concentration gradient (dc/dt) in the plane of the barrier. Therefore, when dq X 1/s is plotted against time (dt), the resultant curve is linear whose slope is equal to the

Flux (J).Consider a barrier with cross sectional area 's' that separates two compartments (donor and a receptor). Let the thickness of the barrier be 'h', the concentration in the donor compartment be C1 and in the receptor compartment be C2

Applying Fick's law,

$J = dq/s \cdot dt$ (or) $dq/dt = sJ$ (or) $J.dt = dq/s$

$dq/dt = S.D \times (C_1-C_2)/h$

Slope of the straightline passing through origin = J, the flux

(Where $J = D \times dc/dx$ or $dc/dx = (C_1-C_2)/h$)

The concentration within the barrier is assumed to be constant for a quari-stationary state. C1 and C2 may be replaced by the partition co-efficient (K) and is given by:

$K=C1/Cd = C2/Cr$ (or)

$K.Cd=C1$ & $K.Cr=C2$

Sink conditions are provided for the receptor compartment Cr=0

Then, $dq/dt = D.S.K.Cd/h$ (or)

$dq/dt=P.S.Cd.$

When D.K/h=P (Permeability coefficient), since it is not possible to determine D,K and h independently, it is usualy to combine these membrane factors into a single constant P, permeability coefficient.Rearranging, dq = P.S.Cd.dt for a finite diffusion q=P.S.Cd.dt

$P.dt = dq \times 1/s \times Cd$

Slope of the straight line passing through origin is equal to 'p', permeability coefficient or

dq = P.S.Cd.dt rearranging

$dq/dt \times 1/s = P.Cd$, therefore $dq/dt \times 1/s = J$

$J = P.Cd$

Hence, $P= J/Cd$

Where, J = flux

dq = amount permeated in the receptor sink.

dt = time.

S = surface area of the film exposed to medium.

P = permeability coefficiesnt.

Cd = donor concentration.

It is relatively simple to obtain surface area 's' donor concentration Cd, and the amount of permeate 'q' in the receptor sink, 'P' can be obtained from the slope of linear plot of q vs t.

Keterolac: Keterolac is a potent analgesic but only moderately effective anti-inflammatory drug. Chemical Name: (±) 5-benzoyl-2,3-dihydro-1*H*-pyrolizine-1-carboxylic acid. Molecular Formula: $C_{15}H_{13}NO_3$, Molecular Weight: 255.27, MP: 154-156^{0}C, Pka:3.49±0.02.

Keterolac is a white colorless crystalline powder. It is freely soluble in water, ethanol and methanol. Sparingly soluble in denatured alcohol and tetra hydro furan. Insoluble in toluene, dichloromethane, chloroform, acetonitrile and carbon tetra chloride.

Pharmacological Profile[30]: Keterolac is a new alpha substituted aryl acetic acid derivative. It is an NSAID with pronounced analgesic, anti inflammatory and anti-pyretic action. However, it produces greater systemic analgesic activity than anti-inflammatory activity. In standard animal models for screening analgesic activity, Keterolac was found to be 800 times more potent than that of aspirin. In all assays, Keterolac was found to be more potent analgesic than that of many well known analgesics like naproxen, indomethacin etc., Keterolac has been demonstrated to produce anti-pyretic activity greater than that of aspirin and almost equivalent to that of naproxen. Keterolac, unlike narcotic analgesics does not depress respiratory centre. There would be in-significant increase in end tidal PCo_2 as compared to Morphine 6-12mg, pethidine 500 mg, 100mg, and pentazoline 30mg. Multiple dose studies showed that the Keterolac 10mg/kg/day for 15 days has produced analgesia almost equivalent to that of Morphine 10mg.

Mechanism of action[31]: Keterolac is a non-narcotic, non-steroidal anti-inflammatory drug (NSAID). It inhibits the activity of enzyme cycloxygenase and thereby leading to the decreased formation of precursors of prostaglandin and thromboxanes from arachidonic acid.Keterolac produces analgesia probably due to its peripheral action, in which blockade of pain impulse generation results from decreased prostaglandin activity. However, inhibition of the synthesis of actions of other substances that sensitize pain receptor to mechanical or chemical stimulation may also contribute to the analgesic effect. Keterolac is rapidly absorbed when given orally or intramuscularly, achieving peak plasma concentration in 30-50min. Oral bioavailability of Keterolac is about 80% almost totally bound to plasma proteins. It is excreted with an elimination half life of 4-6hours, Urinary excretion accounts for about 90% of eliminated drug, with about 60% excreted unchanged and the remaining as a glucoronitated conjugate. The rate of elimination is reduced in the elderly and in patients with renal failure. The minimum effective plasma concentration of Keterolac is 0.1 to 0.3 g/ml.

Dosage : Starting dose of Keterolac should be 10 mg with subsequent dose of 10-30mg for every 4-6 hours as required. The total daily dose of 90 mg non-elderly and 60mg for the elderly should not be exceeded. Maximum duration of treatment through intramuscular route is 2 days and 7 days through oral route.

Adverse effects : Adverse effects include somnolence, dizziness, headache, G.I. pain, dyspepsia, nausea, diarrhoea, constipation, nervousness, dryness of mouth, abnormal dreams, hyperkinesia, myalgia, asthma and pain at the site of injection.

Contraindications: Keterolac is contra indicated in patients of asthma, patients with full anti-coagulant therapy, patients with hemorrhage diathesis, and patients who are hypersensitive to Keterolac[31].

Therapeutic uses: Keterolac is used for post-operative pain as an alternative to opoid agents.Oral Keterolac has been used for treatment of chronic pain states, for which it appears to be superior to aspirin. Topical Keterolac may be useful for inflammatory conditions in the eye and is approved for the treatment of seasonal allergic conjunctivitis. Acute muscular skeletal painful conditions like acute strain and sprain, dislocation, fracture and soft tissue injury.Dental pain including pain after oral surgery, postpartum pain.Other pain states like cancer pain, sciatica, chronic pain states and as an adjuvant in renal colic and biliary colic.[31]

Analytical methods: Keterolac was dissolved in distilled water and scanned for maximum absorbance in Hitachi U-2000 Spectrophotometer (Double beam) in U.V.range i.e., from 190 to 380 nm. Keterolac has showed the maximum absorbance at 321.6nm.In the present work, spectrophotometric method was adopted using double beam U.V. Spectrophotometer (Hitachi U-2000, Japan)**.**Accurately weighed quantities of sodium chloride (8gms), disodium hydrogen phosphate (1.38 gms) and potassium dihydrogen ortho phosphate (0.19gms) were dissolved in 1000 ml of distilled water. The final solution of phosphate buffer gave a pH of 7.4.

Preparation of standard solution : 100mg of Keterolac was accurately weighed and dissolved in 75 ml of phosphate buffer of pH 7.4 and the volume is adjusted to 100ml with pH 7.4 Phosphate buffer. The prepared standard solution of Keterolac was subsequently diluted with pH 7.4 phosphate buffer to get 2, 4, 6, 8 and 10 gms of Keterolac per ml of the final solution.Then the absorbance was measured by spectrophotometric method at 321.6 nm using phosphate buffer of pH7.4 as a blank in Hitachi U-2000 Spectrophotometer. The concentrations of Keterolac solutions and their corresponding absorbance at 321.6 nm were in the table No. 1

Table No. 1

S.No.	Concentrations in µg/ml	Absorbance
1	0	0
2	2	0.103
3	4	0.208
4	6	0.309
5	8	0.413
6	10	0.515

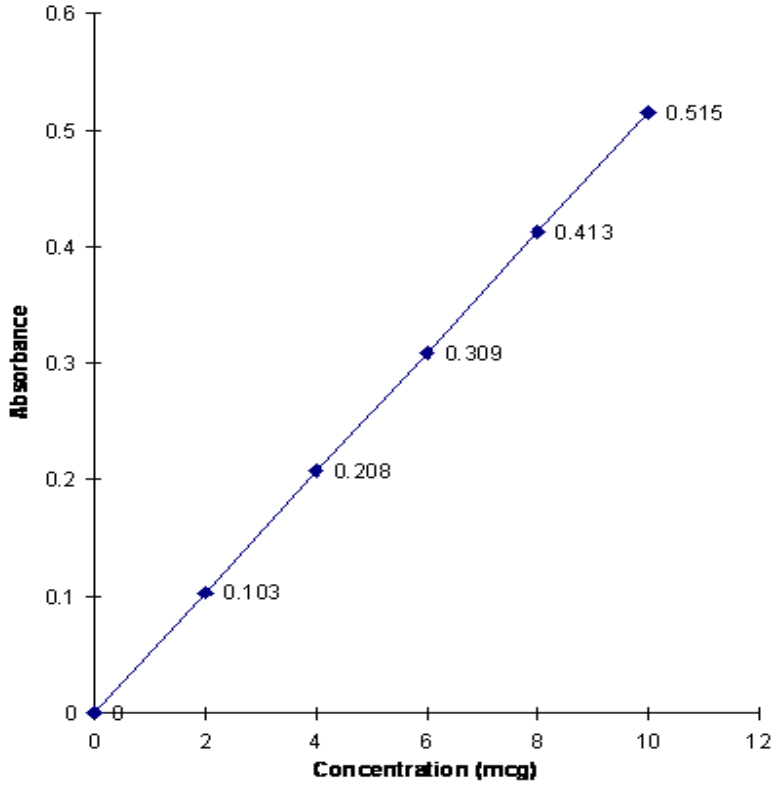
The absorbances were plotted against concentrations in µg/ml of Keterolac was shown in Fig. No. 1

Method of Preparation of Transdermal drug delivery films : The patches were fabricated from aqueous solution of Hydroxy propyl methyl cellulose (HPMC) with different co-polymers like cellulose acetate (CA), ethyl cellulose (EC); both in the ratios of 8:1, 4:1, 2:1, 1:1 dry weight of HPMC was used. Further, containing different plasticizers/ penetration enhancers, glycerol and dibutyl phthalate (DBP), both 20%, 30%, 40% weight of HPMC respectively were included. Totally nineteen formulations were planned and prepared. Initially, films containing only the drug and polymers were fabricated but, these films were observed to be brittle. Hence in all the formulations, plasticizer Glycerol was incorporated at 20% weight of HPMC in the formulations R_1 to R_9. In all the films Drug : HPMC ratio was kept at 1:3.

Method of preparation : Suitable glass rings of 5.5 cm diameter were taken and placed over a petri dish containing mercury substrate[13,42] Initially the volume required was calculated, and exactly the same volume, 5 ml was transferred with a pipette into the rings, for all formulations. The films of HPMC containing Keterolac were prepared, with co-polymers& plasticizers. In all the films drug : polymer ratio was kept at 1:3 (50mg. drug and 150mg HPMC)[43]. HPMC and Keterolac were dissolved in a minimum quantity of water and to this ethanol, as a solubilizer and evaporating agent, was included and mixed thoroughly for 10 minutes. An inverted funnel

was placed over the Petri dishes, for constant drying. The films were dried at room temperature for 48 hours and all the formulations were stored in a tightly closed desiccators.

Fig No. 1 Calibration curve for the estimation of Keteroloac tromethamine



The formulations R_2 and R_5 contains HPMC polymer matrix and drug (3:1), the cellulose acetate as a co-polymer, cellulose acetate was solubilised in acetone. HPMC and drug were dissolved in alcohol.1ml of Dichloromethane was added to obtain clear solution and glycerin as plasticizer (0.03Gms), the weight of HPMC was added.

Formulations R_6 to R_9 contains HPMC polymer matrix and drug (3:1), the ethyl cellulose as a co-polymer. Drug and polymer are mixed with alcohol, clear solution was obtained by incorporating Dichloromethane (1 ml). The glycerin was included as a plasticizer at 20% w/w of weight of HPMC.

Evaluation : The films were evaluated for the following parameters:

Weight variation: Six patches of each formulation were weighed. The weight of each film was noted, by weighing in an electrical balance. Mean weight, standard deviation and percentage coefficient of variation was calculated.

Uniformity of film : The thickness of each film was determined by using a screw guage at 10 different places of the film. Then mean thickness, standard deviation and percent coefficient of variation was calculated.

Area of the film : The area of the films were determined by using vernier calipers.

Density of film : From the above found weight and thickness, the density of films were calculated by the relationship, Density = mass/volume (Volume= area X thickness)

Water vapour transmission studies (WVT) : 1 gm of calcium chloride was accurately weighed and placed in dried empty vials having equal diameter. The polymer films were pasted over the brim with the help of an adhesive, then the vials were weighed and placed over a mesh in desiccators. Containing 200 ml of saturated sodium bromide and saturated potassium chloride solutions. The desiccators were tightly closed & the humidity inside the desiccators was measured by using a hygrometer and was found to be 56% RH and 84% RH respectively. Then the vials were weighed after 1^{st} day, 2^{nd} day, 3^{rd} day…….7^{th} day. The results were tabulated and a graph of cumulative amount water vapour transmitted vs time was plotted.

Water vapour absorption studies (WVA) : Accurately weighed films were placed on to a dry glass slide, which was kept in a desiccators containing 200 ml of saturated sodium bromide and saturated potassium chloride solutions. The desiccators were tightly closed and the humidity inside the dessicator was measured by using a hygrometer and was found to be 56% RH and 84% RH respectively. The films were weighed after 1^{st} day, 2^{nd} day, 3^{rd} day…….7^{th} day. The results were tabulated and a graph of cumulative percent water vapour absorbed vs time was plotted.

Drug content : A film of area 0.7539 sq.cm. was placed in a volumetric flask containing 50 ml of phosphate buffer of pH 7.4 and kept aside for some time to release the total drug present in the film and the volume was made upto 100 ml with the same buffer. Then the absorbance of this solution was measured after suitable dilution at 321.6 nm against phosphate buffer of pH 7.4 as blank. The content of Keterolac was calculated using standard graph.

***In-vitro* evaluation :** In-vitro diffusion studies were performed in Keshary-chien diffusion cell for all the nineteen films. Films of 0.7539 sq.cm. area were used from each patch formulation.

The sigma dialysis membrane was previously hydrated by soaking it in distilled water for 15 minutes, after which it was fixed to the donor compartment. The film was placed over the dialysis membrane, in the donor compartment. The receptor compartment was filled with phosphate buffer of pH 7.4. A teflon coated magnetic bead was placed in the receptor compartment and the whole assembly was placed on a magnetic stirrer and temperature maintained at $37^0 \pm 0.5^0$ C. Buffer was stirred at 50 rpm for all formulations. Samples of 2 ml were withdrawn at regular intervals of 5,10,15,30,45,60,120, ……. & so on. And were suitably diluted and the absorbance measured at 321.6 nm. The volume of the receptor compartment was maintained constant by replacing equal volume of buffer. The results were tabulated .

Stability Studies:

The stability experiments were conducted to investigate the influence of different temperatures and different relative humidity's on the drug content in different film formulations. For both the studies R-5 and R-9 formulations were selected.

Effect of temperature: R-5 and R-9 formulations were exposed to two different temperatures maintained at 30 ± 1°C and at 70 ± 1°C in two different Hot air ovens. The films were removed from the oven at the end of every 24 hours, for seven days, and were analyzed for drug content every day. Average of triplicate readings were taken. The observations were tabulated .

Effect of relative humidity : R-5 and R-9 formulations were exposed to two different relative humidity's of 56% RH and 84% RH respectively. Saturated solutions of sodium bromide and potassium chloride were kept in different desiccators and the humidity inside the desiccators was determined using a hygrometer and the percentage RH computed from a psychometric chart; humidity were found to be 56%RH and 84% RH respectively. The film samples were kept inside the desiccators and at the end of every 24 hours, every day for next 7 days, films were taken out and immediately analyzed for drug content. The results were tabulated.

RESULTS AND DISCUSSION

The aim of the work was to investigate feasibility of hydroxy propyl methyl cellulose to release Keterolac and to develop a suitable transdermal drug delivery patch/film formulation for the delivery of Keterolac.

Several formulations were prepared to study: The effect of various co-polymers, Cellulose acetate and Ethyl cellulose each in different proportions viz., 8:1, 4:1, 2:1 and 1:1 of the dry weight of HPMC, on the release kinetics of drug and on the physical characteristics of the film. The effect of different plasticizers/penetration enhancers like glycerol and dibutyl phthalate, both at 20%, 30% and 40% the weight of HPMC on the release rate of Keterolac and on physical characteristics of the film.

The work plane was divided into five sets
(A) Formulation R-1 :The formulation R-1 contains HPMC polymer matrix and drug Keterolac (Drug:polymer 1:3), was prepared to study the feasibility of HPMC to release the drug. Glycerol, 20% of dry weight of HPMC was included as a plasticizer.

(B) Formulations R-2, R-3, R-4 and R-5: These films were prepared to study the influence of different proportions of cellulose acetate on release rate of drug from HPMC monolithic matrix. Drug: polymer ratio was kept at 1:3; and HPMC:CA at 8:1 (R_2), 4:1 (R_3), 2:1(R_4) and 1:1 (R_5), 20% w/w of Glycerol to the dry weight of HPMC was included as plasticizer

(C) Formulations R-6, R-7, R-8 and R-9:These films were prepared to study the influence of different proportions of ethyl cellulose on release rate of drug from HPMC matrix. The drug: polymer ratio was kept at 1:3 and HPMC:EC at 8:1 (R_6), 4:1 (R_7), 2:1 (R_8) and 1:1 (R_9) was used. 20% w/w of glycerol to the dry weight of HPMC was included as plasticizer.

(D) Formulations R-5, R-10, R-11;R-9, R-12 and R-13:These films were prepared to study the influence of plasticizers/ penetrating enhancers like glycerol 20%, 30% and 40% the dry weight of polymer , on the release rate of drug. Drug: HPMC ratio was kept at 1:3, HPMC:CA (1:1), and HPMC:EC (1:1) .

(E) Formulations R-5, R-14, R-15, R-16; R-9, R-17, R-18 & R-19: These films were prepared to study the influence of plasticizer/penetrating enhancer Dibutyl phthalate 20%, 30% and 40% the dry weight of polymer. On the release rate of drug containing E.C. & C.A. both as co-polymers. Drug: HPMC ratios were kept at 1:3, HPMC:CA at 1:1 and HPMC:EC at 1:1 .

Water vapour transmission at 56% RH : The percent WVT studies reveal that all the 19 films transmit water vapour when exposed to 56% RH . The results indicate that, WVT through all the 19 film formulations follow zero order kinetics. Regression analysis was done. The slope values computed from the respective curves, their corresponding 'R' values are shown in table No.2

Table No. 2

Formula	Slope	Regression Value
R_1	7.955713 X 10^{-2}	0.9968198
R_2	6.702855 X 10^{-2}	0.9933797
R_3	6.702499 X 10^{-2}	0.9835222
R_4	6.218214 X 10^{-2}	0.9805911
R_5	5.769286 X 10^{-2}	0.9812291
R_6	6.742145 X 10^{-2}	0.9958675
R_7	6.667499 X 10^{-2}	0.9926159
R_8	6.522142 X 10^{-2}	0.9926338
R_9	6.428571 X 10^{-2}	0.9892595
R_{10}	7.210357 X 10^{-2}	0.9964998
R_{11}	6.996071 X 10^{-2}	0.9961596
R_{12}	6.618573 X 10^{-2}	0.9977341
R_{13}	6.446786 X 10^{-2}	0.9969000
R_{14}	6.174643 X 10^{-2}	0.9908139
R_{15}	5.992857 X 10^{-2}	0.9882668
R_{16}	5.871429 X 10^{-2}	0.9835341
R_{17}	6.783930 X 10^{-2}	0.9948825
R_{18}	6.550001 X 10^{-2}	0.9957113
R_{19}	6.370001 X 10^{-2}	0.9966210

The order of WVT for different sets are as under , Set A: R-1>R-2>R-3>R-4>R-5,Set B: R-6>R-7>R-8>R-9,Set C: R-10>R-11>R-12>R-13,Set D: R-14>R-15>R-16 & R-17>R-18>R-19

Water vapour transmission at 84% RH: The percentage WVT studies revealed that all the 19 films transmit water vapour when exposed at 84% RH. The results indicate that, WVT through all the 19 film formulations follows zero order kinetics. Regression values computed from the respective curves, their corresponding 'R' values are shown in table no.3

Water vapour absorption at 56% RH :WVA studies indicates that all the 19 films absorb water vapour when exposed to 56%RH. From the results it is clearly seen in general, that all the films absorb water vapour till a critical value is reached and then attain equilibrium when, further exposure to the same RH would not increase moisture content of the film. It is also observed that, as the co-polymers both CA and EC proportion is increased, the maximum % water vapour absorbed correspondingly decreases viz., 8:1> 4:1> 2:1> 1:1.In the films containing varying proportions of glycerol as plasticizer, maximum %water vapour absorbed increases from 20% to 30%. But further increase in glycerol concentration does not significantly increase the %WVA.

This is observed with films containing both the copolymers CA & EC (R-5, R-10, R-11 & R-9, R-12, R-13 respectively).Where as in the films containing varying proportions of dibutyl phthalate as plasticizer (20%, 30% and 40% w/w of HPMC), increasing the concentration of DBP, decreases the maximum %WVA with both CA & EC as copolymers (films R-14, R-15 & R-16 and R-17, R-18 & R-19 respectively).

Table No. 3

Formula	Slope	Regression Value
R_1	8.793929 X 10^{-2}	0.9916898
R_2	7.821429 X 10^{-2}	0.9986770
R_3	7.145713 X 10^{-2}	0.9947597
R_4	6.929284 X 10^{-2}	0.9877474
R_5	6.805714 X 10^{-2}	0.9773311
R_6	8. 448572 X 10^{-2}	0.9992819
R_7	7.465357 X 10^{-2}	0.9968190
R_8	7.160357 X 10^{-2}	0.9912627
R_9	7.225000 X 10^{-2}	0.9769200
R_{10}	7.595001 X 10^{-2}	0.9969550
R_{11}	7.665359 X 10^{-2}	0.9956977
R_{12}	7.778215 X 10^{-2}	0.9927195
R_{13}	7.794641 X 10^{-2}	0.9908204
R_{14}	6.792499 X 10^{-2}	0.9967582
R_{15}	6.567858 X 10^{-2}	0.9945051
R_{16}	6.342857 X 10^{-2}	0.9893919
R_{17}	7.568215 X 10^{-2}	0.9978104
R_{18}	7.488214 X 10^{-2}	0.9974434
R_{19}	7.138217 X 10^{-2}	0.9941837

The order of WVT for different sets as under,Set A: R-1>R-2>R-3>R-4>R-5,Set B: R-6>R-7>R-8>R-9

Set C: R-10>R-11>R-12>R-13,Set D: R-14>R-15>R-16 & R-17>R-18>R-19

Water vapour absorption at 84% RH :WVA studies indicates that all the 19 films absorb water vapour when exposed to 84%RH. From the results it is clearly seen in general, that all the films absorb water vapour till a critical value is reached and then attain equilibrium when, further exposure to the same RH would not increase moisture content of the film. It is also observed that, as the co-polymers both CA and EC proportion is increased, the maximum % water vapour absorbed correspondingly decreases viz., 8:1> 4:1> 2:1> 1:1.In the films containing varying proportions of glycerol as plasticizer, maximum %water vapour absorbed increases from 20% to 30%. But further increase in glycerol concentration does not significantly increase the %WVA. This is observed with films containing both the copolymers CA & EC (R-5, R-10, R-11 & R-9, R-12, R-13 respectively).Where as in the films containing varying proportions of dibutyl phthalate as plasticizer (20%, 30% and 40% w/w of HPMC), increasing the concentration of

DBP, decreases the maximum %WVA with both CA & EC as copolymers (films R-14, R-15 & R-16 and R-17, R-18 & R-19 respectively)

***In-vitro* Release Studies:**

In this investigation totally nineteen transdermal patch formulations containing different co-polymers, in various proportions and different plasticizers/penetration enhance in various proportions were studied. The drug: polymer ratio was kept constant, at 1:3 for all nineteen films. First patch formulation i.e., R-1 contains only polymer HPMC and drug Keterolac. Glycerol was included in this formulation at 20% the dry weight of HPMC to improve plasticity of the film. Different co-polymers viz., Cellulose acetate and Ethyl cellulose were included in further formulations, each at 8:1, 4:1, 2:1, 1:1 the weight of HPMC. The study was taken up to understand the influence of co-polymers in different ratios, on the release kinetics of drug. All the films contained plasticizer as included at different ratios (20%, 30% & 40% the weight of HPMC).The total area of each patch is 26.4313 sq.cm. from which the required area of 0.7539 sq.cm. cut from the patch. This cut film was used for in-vitro studies. Each of the above films were subjected to in-vitro diffusion studies using sigma dialysis sac, (12000 daltons) as a support to films, in Keshary-chien diffusion cells.

Formulation R-1 : R-1 film was prepared as per the formula , Drug to polymer ratio was kept at 1:3 initially. Formulation prepared polymer alone was fragile, hence 20%w/w of glycerol to the dry weight of HPMC was included to improve the plasticity of the film. The basic in-vitro data obtained was tabulated . It is clearly seen that 88.01% of drug was released within two hours and then the release is slow and gradual till eight hours when a maximum of 98.4130% of the drug is released. The patch formulation R-1 was found to follow first order release .with a rate constant of 7.6622031×10^{-3}. The regress ional value R being -0.9191966 indicating the curve is fairly linear. The diffusion data (dq x 1/s) was plotted against time as shown in figure No.28 Flux (J) and permeation coefficient (P) were obtained from the slope of the curve, which were found to be 1.26666×10^{-2} and 7.7908×10^{-3} respectively. The films were found to be permeable to water vapour at 56% RH and at 84% RH respectively. The films were found to be smooth, transparent and flexible.

In-vitro release studies of Keterolac From formulation R-1

Time in min	Cumulative amount released in mg.	dq X 1/s	Cumulative percentage released	Cumulative percentage retained	Log cumulative percentage retained
0	0.0000	0.0000	0.0000	100.000	2.000
5	0.2755	0.3654	16.9455	83.0545	1.9193
10	0.5346	0.7091	32.8822	67.1178	1.8268
15	0.7466	0.9903	45.9220	54.0780	1.7330
30	1.0009	1.3276	61.5635	38.4365	1.5847
45	1.1152	1.4792	68.5939	31.4061	1.4970
60	1.1910	1.5797	73.2562	26.7438	1.4272
120	1.4309	1.8979	88.0120	11.9880	1.0787
180	1.4794	1.9623	90.9952	9.0048	0.9544
240	1.5234	2.0206	93.7015	6.2985	0.7992
300	1.5626	2.0726	96.1126	3.8880	0.5897
360	1.5785	2.0937	97.0927	2.9073	0.4635
420	1.5900	2.1090	97.8002	2.1998	0.3424
480	1.6000	2.1222	98.4130	1.5870	0.2005

Formulations R-2, R-3, R-4 & R-5 : These Films were prepared to study the influence of different proportions of cellulose acetate on release rate of drug from HPMC monolithic matrix. Drug : polymer ratio was kept at 1:3; and HPMC : CA at 8:1 (R-2), 4:1 (R-3), 2:1 (R-4) and 1:1 (R-5), 20% w/w of glycerol to the dry weight of HPMC was included as plasticizer. The data indicates that, the release of drug from R-2,R-3,R-4 & R-5 are 98.1712% within nine hours; 97.8501% within 11 hours; 98.8005% within 12 hours; and 95.2447% within 13 hours respectively. All these films were found to follow first order release kinetics . Linear regress ional analysis was performed. The rate constant 'k' were obtained from the linear portion of the curve, determined by first using all the points and then successively removing the early points and repeating the regression analysis[46] The 'k' values and the corresponding 'R' values are presented in the following table below. Regression values (R) indicate that all the curves are fairly linear.

From the slope of the diffusion data, Flux 'J' and permeation coefficient 'P' were obtained. The slope was computed by taking slopes at different lines on the same curve, and average was calculated instead of taking best fit line on the curve or drawing tangents, to calculate the slope .

Formula Code	Frist order 'k' Value	First Order regression Value 'R'	Flux 'J'	Permeation Coeffiecient 'P'
R_2	3.0237077×10^{-3}	-0.954523	5.51666×10^{-2}	2.82601×10^{-2}
R_3	3.3838301×10^{-3}	-0.9245903	3.191660×10^{-2}	1.90070×10^{-2}
R_4	5.4700280×10^{-3}	-0.9537832	2.433330×10^{-2}	1.35750×10^{-2}
R_5	3.5268280×10^{-3}	-0.9312671	9.777700×10^{-3}	4.88390×10^{-3}

From the above results, the following conclusions were made: *The film of HPMC : CA are found to follow first order kinetics. Increasing the proportion of CA in to HPMC matrix does not significantly increase the amount of drug release but, definitely increases the duration of release. Also, it is seen that, the duration of release gradually increases with increase in CA proportion, as compared to that of HPMC matrix. All these films were found to be permeable to water vapour of 56%RH and 84%RH and the films were found to be smooth, transparent and flexible.*

Since, R-5 shows longer release than any other films in this study (Cmax 95. 2447% in 13 hours), it was selected for further investigation on the influence of plasticizer/penetration enhancer on the release rate of dry HPMC matrix.

C. Formulation R-6, R-7, R-8 and R-9 :

The films/patches were prepared to study the influence of different proportions of ethyl cellulose on release rate of drug from HPMC matrix. Drug : polymer ratio was kept at 1:3 and HPMC: EC at 8 : 1(R-6); 4:1 (R-7); 2:1 (R-8) & 1:1 (R-9) was used. Glycerol at 20% w/w the weight of HPMC was included as plasticizer. The data indicates that the release of drug from R-6, R-7, R-8 & R-9 are 95.3007% in 9 hours; 95.4627% in 10 hours; 96.3362% in 12 hours; and 98.7185% in 14 hours, respectively. All these films were found to follow first order release kinetics. Regression analysis was performed. The release constants 'k' were obtained from the linear portion of the curve - determined by first using all the points and successively removing the early points and repeating the analysis[46]. The 'k' values and their corresponding 'R' values are presented in the following table. Regression data indicate all the curves are fairly linear.

From the slope of diffusion data, flux, 'J' and permeation coefficient 'P' were obtained . The slope was calculated by taking slopes on different lines on the same curve, and the average was computed instead of going for best fit line or drawing tangents to calculate the slope.

Formula Code	Frist order 'k' Value	First Order regression Value 'R'	Flux 'J'	Permeation Coefficient 'P'
R_6	4.5215352 X 10^{-3}	-0.9466058	1.560 X 10^{-2}	7.3464 X 10^{-3}
R_7	4.6404690 X 10^{-3}	-0.9817684	2.22466 X 10^{-1}	3.1026 X 10^{-3}
R_8	1.7612561 X 10^{-3}	-0.9220982	8.6666 X 10^{-2}	5.33658 X 10^{-2}
R_9	2.8593380 X 10^{-3}	-0.9110796	6.39999 X 10^{-2}	1.04281 X 10^{-2}

From the above results following conclusions were made: *The films of HPMC : EC in different proportions, were found to follow first order kinetics release. Increasing the proportion of EC in HPMC matrix, does not significantly increase the amount of drug release but definitely increases the duration of release. Also, it is seen that the duration of release gradually increases with increase in EC proportion, as compared to that of HPMC. All these films were found to be permeable to Water vapour at 56% RH & 84% RH and the films were found to be smooth, transparent and flexible.*

Formulation R-9 was selected from this set for further studies to determine the influence of plasticizer/ penetration enhancer, since, this film shows maximum percentage release and for longest duration of time amongst the four films studied with HPMC.

Formulations R-5, R-10, R-11, R-9, R-12 & R-13 : These films were fabricated to study the influence of plasticizer/penetration enhancer Glycerol 20%w/w, 30%w/w and 40%w/w the dry weight of polymer on the release rate of drug. Drug : HPMC ratio was kept at 1:3, HPMC : CA (1:1), and HPMC : EC (1:1), i.e. R-5 and R-9 were selected from previous studies, in which the influence of Glycerol included in 30% w/w & 40% w/w the weight of polymer, on the release rate of drug was studied. The formulation prepared so, were coded as :

Formulation Code	Polymer Ratio (1:1)	% W/W Glycerol
R_5	HPMC : CA	20%
R_{10}	HPMC : CA	30%
R_{11}	HPMC : CA	40%
R_9	HPMC : EC	20%
R_{12}	HPMC : EC	30%
R_{13}	HPMC : EC	40%

The basic in-vitro data obtained were tabulated as shown in table No.42 to 45 for R-5, R-10, R-11, R-9, R-12 and R-13 respectively. The data shows that the release of drug from R-5, R-10, R-11, R-9, R-12 and R-13 are 95.2447% in 13 hours; 96.8955% in 11 hours; 98.2650% in 11 hours; 98.7185% in 14 hours; 98.9240% in 12 hours; and 98.4530 in 11 hours respectively.

The data was graphed as log cumulative percentage retained vs time, for first order release kinetics. Regression analysis was performed. The rate constant k' were obtained from the linear portion of the curve – determined by first using all the points and then successively removing the earlier points and repeating the analysis. The k' values and the corresponding R' values are presented . High regression values 'R' were obtained indicating curves are fairly linear .From

the slope of diffusion data, flux 'J' and permeation coefficient 'P' were obtained which are as shown in the following table. The slope was calculated by taking slopes on different lines of the same curve, and the average was computed instead of going for best fit line or drawing tangents to calculate the slope[46].

Formula Code	Frist order 'k' Value	First Order regression Value 'R'	Flux 'J'	Permeation Coefficient 'P'
R_5	3.5268280×10^{-3}	-0.9312671	9.77770×10^{-3}	4.88390×10^{-3}
R_{10}	4.8246440×10^{-3}	-0.9352409	2.83333×10^{-2}	1.43256×10^{-2}
R_{11}	5.7065392×10^{-3}	-0.9572384	8.16666×10^{-3}	4.70720×10^{-3}
R_9	2.8593380×10^{-3}	-0.9110796	6.39999×10^{-2}	1.04280×10^{-2}
R_{12}	1.6132270×10^{-3}	-0.9059429	2.10416×10^{-2}	1.26315×10^{-2}
R_{13}	4.6429539×10^{-3}	-0.9132587	2.46666×10^{-2}	1.55743×10^{-2}

From the above results following conclusions were made. The drug release from the films follow first order release kinetics. In HPMC:CA (R-5, R-10 & R-11) as the glycerol proportion is increased there is no significant increase in amount of drug release but rather with increasing glycerol content the duration of release is decreased from 13 hours for 20% w/w glycerol, to 11 hrs for both 30% & 40% glycerol w/w. Therefore, 20% glycerol concentration would be sufficient for maximum drug release & longer duration of release in HPMC:CA (1:1) films. Similarly in HPMC : EC (1:1) films, increasing the concentration of glycerol, does not increase the amount of drug release but rather, decreases the duration of release from 14 hours for 20% w/w glycerol to 12 hrs for 30% w/w glycerol to 11 hrs for 40% w/w glycerol. Therefore, 20%w/w of glycerol concentration would be sufficient for maximum drug release and longer duration of action in HPMC : EC (1:1) films All these films were found to be having permeation to water vapour at 56% RH & 84% RH and the files were found to be smooth, transparent and flexible.

Formulations R-14, R-15, R-16, R-17, R-18 and R-19 : These films were prepared as detailed to study the influence of plasticizer/ penetration enhancer Dibutylphthate 20% w/w, 30%w/w and 40%w/w, the dry weight of polymer, on the release rate of drug. Drug : HPMC was kept at 1:3 HPMC : CA (1:1), and HPMC : EC (1:1) into which DBP in different proportions was included in the above concentrations. The formulations were coded as ;

Formulation Code	Polymer Ratio (1:1)	% W/W DBP
R_{14}	HPMC : CA	20%
R_{15}	HPMC : CA	30%
R_{16}	HPMC : CA	40%
R_{17}	HPMC : EC	20%
R_{18}	HPMC : EC	30%
R_{19}	HPMC : EC	40%

The basic in-vitro data obtained were tabulated as table No. 45 to51, R-14 to R-19 respectively. The data shows that, the release of drug from R-14, R-15, R-16, R-17, R-18 & R-19 are 97.9041% in 12 hours; 97.0567 in 11 hours; 98.7985% in 11 hours; 98.1681% in 13 hours; 98.6789% in 12 hours and 98.6413% in 11 hours respectively. The data was graphed as log cumulative % retained vs time, for first order release kinetics. Regression analysis was performed. The release constant 'k' were obtained from the linear portion of the curve -

determined by first using all the points and successively removing the early points and repeating the analysis[46]. The 'k' values and their corresponding 'R' values are presented . Regression data indicates all the curves are fairly linear.From the slope of diffusion data, flux 'J' and permeation coefficient 'P' were obtained which are as shown in the following table. The slope was calculated by taking slopes on different lines on the same curve and the average was computed, instead of going for best fit line or drawing tangent to calculate the slope [46].

Formula Code	Frist order 'k' Value	First Order regression Value 'R'	Flux 'J'	Permeation Coeffiecient 'P'
R_{14}	4.256195 X 10^{-3}	-0.945181	2.6500 X 10^{-2}	1.15227 X 10^{-2}
R_{15}	3.939421 X 10^{-3}	-0.9262965	2.39999 X 10^{-2}	1.06865 X 10^{-2}
R_{16}	6.111908 X 10^{-3}	-0.9586232	1.43333 X 10^{-2}	8.4412 X 10^{-3}
R_{17}	3.134021 X 10^{-3}	-0.9298043	3.38333 X 10^{-2}	1.90696 X 10^{-2}
R_{18}	4.833817 X 10^{-3}	-0.9876471	3.96111 X 10^{-2}	1.73846 X 10^{-2}
R_{19}	5.250683 X 10^{-3}	-0.9651231	7.21111 X 10^{-2}	3.34389 X 10^{-2}

From the above results following conclusions were made: The drug release from the films follow first order kinetics. In the films of HPMC : CA (1:1), (R-14, R-15 & R-16) as the DBP proportion is increased there is no significant increase in amount of drug release but rather, with increasing DBP concentration, the duration of release is decreased from 12 hours for 20% DBP to 11 hours for both 30% and 40% DBP. Therefore, 20% w/w DBP concentration would be sufficient for maximum drug release and for longer duration of release in HPMC : CA (1:1) films. Similarly, in HPMC:EC (1:1) films, increasing the concentration of DBP does not significantly increase the amount of drug release but instead decreases the duration of release , from 13 hours for R-17, 12 hours for R-18 and 11 hours for R-19. Therefore, 20% DBP would be sufficient for maximum drug Release and longer duration of release in HPMC : EC (1:1) films. All the films were found to permeate to water vapour at 56% RH and 84% RH. The films were found to be smooth, transparent and flexible.

"When the influence of glycerol and DBP were compared vis-à-vis on HPMC:CA (1:1) and HPMC:EC (1:1), generally it was observed that, formulations containing 30% & 40% of either glycerol or DBP, duration of release is same for both. Albeit 20% glycerol releases the drug for an extended 1 hour than 20% DBP."

Stability studies: The stability experiments were conducted to investigate the influence of different temperatures and different relative humidity's on the drug content in different film formulations. For both the studies, R-5 and R-9 formulations were selected.

At 30^0C Temperature:

Formula		**TIME IN DAYS**							
		0	1	2	3	4	5	6	7
R_5	% D.C. *	100.00	99.88	99.40	99.16	97.96	97.00	95.69	94.26
R_9	% D.C. *	100.00	99.90	99.79	99.59	98.79	97.59	96.29	95.19

** % D.C. = Percentage of Drug Content * Average Values of Triplicate readings*

i) Effect of temperature : R-5 and R-9 formulations were exposed to two different temperatures maintained at 30±1^{o}C and at 70±1^{o}C in two different hot air ovens. The films were

removed from the oven at the end of every 24 hours, for seven days, and were analyzed for drug content every day. Average of triplicate readings were taken. The observation were tabulated .

At 70^0 C Temperature:

Formula		TIME IN DAYS							
		0	1	2	3	4	5	6	7
R_5	% D.C.*	100.00	94.97	89.84	83.87	78.01	71.80	65.23	59.49
R_9	% D.C.*	100.00	96.09	93.08	89.78	84.66	73.14	67.63	62.22

** % D.C. = Percentage of Drug Content * Average Values of Triplicate readings*

It is clearly seen that, drug content in both R-5 and R-9 films are less affected at 30^{o}C where as at higher temperatures of 70^{o}C both are significantly affected. Further, at higher temperatures the R-5 (HPMC:CA; 1:1) is comparatively more affected at 70^{o}C, than R-9 (HPMC:EC; 1:1).

ii) Effect of relative humidity : R-5 & R-9 formulations were exposed to two different relative humidity's of 56% RH and 84% RH respectively. Saturated solutions of Sodium bromide and Potassium chloride were kept in different desiccators, and the humidity inside the desiccators was determined using a hygrometer and the %RH computed using a psychrometric chart; humidity were found to be 56% RH and 84% RH respectively. The film samples were kept inside the desiccators and at the end of every 24 hours, every day for next seven days, films were taken out and immediately analyzed for drug contents. The results were tabulated.

Relative Humidity at 56%

Formula		TIME IN DAYS							
		0	1	2	3	4	5	6	7
R_5	% D.C. *	100.00	99.16	98.32	97.96	97.61	97.48	97.24	96.89
R_9	% D.C. *	100.00	99.79	99.40	99.20	98.90	98.59	98.19	97.89

** % D.C. = Percentage of Drug Content * Average Values of Triplicate readings*

Relative Humidity at 84%

Formula		TIME IN DAYS							
		0	1	2	3	4	5	6	7
R_5	% D.C. *	100.00	98.08	97.24	95.34	90.91	89.36	86.02	85.06
R_9	% D.C. *	100.00	99.09	97.39	96.19	95.09	92.18	91.48	89.67

** % D.C. = Percentage of Drug Content * Average Values of Triplicate readings*

The results indicate that, the drug content in both R-5 and R-9 were not affected significantly at 56% RH where as, at higher humidity i.e.84% RH both the formulations were significantly affected. *Therefore, from the above experiments it could be concluded that HPMC films containing Keterolac should be stored at 30^{o}C or less and at 56% RH or less.*

SUMMARY AND CONCLUSION

The development of transdermal therapeutic systems has set a landmark in pharmaceutical industry, in delivering the drug directly into systemic circulation through the skin as port of entry. First pass metabolism and G.I. disturbances can be avoided and hence patient compliance

can be improved. Current literature reveals that, HPMC possesses excellent film forming properties and can be used as a matrix carrier of drug. Several drugs, oxazepam, diltiazem.Hcl, terbutaline sulphate and Keterolac , have been successfully tried in HPMC matrices. This information was encouraging and therefore, this project was taken up to develop HPMC films containing Keterolac . In this work, an attempt is made to understand the influence of Cellulose acetate and Ethyl cellulose both as co-polymers included in 8:1, 4:1, 2:1 and 1:1 proportions of HPMC (w/w), on the release kinetics of drug. Further, effect of including plasticizers, glycerol and DBP both in 20% w/w, 30% w/w and 40% w/w of HPMC, on the release rate of drug is studied. Totally, 19 formulations were planned and prepared. The physical characteristics of the films, like thickness, weight variation, suraface area, density, surface pH, WVT and WVA were evaluated by standard techniques. In-vitro diffusion studies were carried out in Keshary-chien diffusion cells at 50 rpm and at 37 ± 0.5^{o}C. The data was analysed as detailed and graphed according to first order release plot. Flux and permeability coefficient were obtained from different graphs. Regressional analysis was performed. Stability studies at different temperatures and different % RH was also carried out. The results so far obtained during this investigation encouraged us to derive the following conclusions;

All of the 19 formulations were found to be smooth, flexible and transparent.Thickness and weight variation, remained uniform as indicated by low percent coefficient of variation.The surface pH of all 19 film formulations remained same i.e., pH 7.4.All the films were found to transmit water vapour at both 56% RH and 84% RH. It was found to follow zero order kinetics.All the 19 films were found to absorb water vapour, and after few days of storage attained equilibrium at both 56% RH and 84% RH.In-vitro release studies revealed all the formulations follow first order kinetics. The co-polymers Cellulose acetate and Ethyl cellulose in all proportions (i.e. 8:1, 4:1, 2:1 and 1:1 of HPMC) influence the rate of drug release and also the physical characteristics of the films. Also, with increasing proportions of either of the co-polymer extends duration of release in their respective formulation set. Diffusion data reveals enough flux of drug and also permeability through the film.Plasticizer make the films flexible and inclusion of DBP decreases duration of release as compared with glycerol.

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