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FORMULATION AND IN VITRO EVALUATION OF TRANSDERMAL PATCHES OF KETOPROFEN USING TAMARIND KERNAL POWDER AS MUCO ADHESIVE POLYMER

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AIM: The aim of the work is to formulate and evaluate the transdermal patches of ketoprofen using different combinations of polymers and plasticizers.

OBJECTIVE: ·. Transdermal patches of ketoprofen were prepared to sustain the release and patient compliance. Different formulations were prepared by using different combinations of the polymers like HPMC E5 LV: Eudragit E 100. (1:1,1:2,1:3) and Ethyl cellulose and PVP ratio (1:1,1:2,1:3)by solvent casting method. Tamarind kernel powder is used as a mucoadhesive polymer. The prepared formulations were evaluated for various parameters like moisture content, moisture uptake, folding endurance , percentage drug content , In-vitro permeation using Franz diffusion cell, drug-excipient compatibility by FTIR studies. The diffusion data was fitted into various kinetic models (zero order, first order, Higuchi and Korsmeyer peppas model). The formulation containing the combination of Ethyl cellulose and PVP at a ratio of 1:3 using PEG 4000 as plasticiser was considered optimum batch and showed the drug release up to 8hrs ,91.78% and more similar to the marketed ketoprofen patch (30mg) and similarity factor was calculated as f2=60.78.

Key words: Tansdermal patch, ketoprofen, Ethyl cellulose, tamarind kernel powder, Franz Diffusion cell and controlled release

1.Introduction

Novel drug delivery systems include transdermal drug delivery systems that in drug therapy break many barriers like need of assistance, uncomfortable administration and intermediate dosing. Transdermal drug delivery systems are adventitious over conventional modes of drug delivery in that they avoid hepatic first pass metabolism, potentially decreased side effects and improved patient compliance. The transdermal route of drug delivery is an alternate to oral route and might enhance patients' compliance and tolerance by reducing drug-related side effects. Other than that, it also avoids the pain associated with IV and intramuscular (IM) routes[(1)]Topical nonsteroidal anti-inflammatory drugs (NSAIDs) are also available in this form and can be administered systemically in low concentration, thus avoiding upper gastrointestinal complications such as gastric and peptic ulcers and dyspepsia[(2)]. Oral therapy of NSAIDS for the treatment of rheumatoid arthritis causes gastric irritation and ulceration[(3)]. Ketoprofen has a half life of 1.5hours and the bioavailability of ketoprofen is 86%. The total daily dose of ketoprofen is 75 mg hence it requires frequent dosing. The purpose

of this research work was to formulate and evaluate the transdermal drug delivery system of Ketoprofen. The transdermal patches were evaluated for their physicochemical properties like thickness, weight variation, flatness, folding endurance, drug content, swellability, surface pH. In addition, interaction between drug & polymer was also evaluated. The patches were found to be free of any skin irritation. UV, FTIR studies showed no interaction between drug and polymer.

2.Materials and methods: Ketoprofen obtained as gift sample from Vasudha Pharmaceuticals,Visakhapatnam. the remaining excepients were purchased from yarrow chemicals,Mumbai.

2.1Preparation of Tamarind Kernel powder

Tamarind seeds were collected from the local market and were decorticated. The decorticated seeds were crushed using laboratory mixer and passed through the sieves to obtain fine powder and stored in a air tight container till further use

2.2 Preformulation Studies Of Tamarind Kernel Powder

2.2.1 Solubility of Tamarind kernel powder

Solubility of tamarind kernel powder was measured in different solvents like water, ethanol, chloroform, Hcl and NaOH. Identification tests were done according to the standard procedure.

2.2.2 FTIR studies:

The FT-IR study was performed using KBr equipped Shimadzu® Affinity-1 FT-IR instrument. The overlapping peaks were identified for the drug, excipients, polymers, and physical mixture. Any new product or major change in the spectra was reported. The peaks were expressed as cm−1 in the range of 4,000−400 cm−1

2.3.Construction of calibration curve of Ketoprofen

For the stock solution 50mg of Ketoprofen was dissolved in 50ml of Phosphate buffer pH 7.4. and was kept in ultrasonifier until the complete dissolution of drug. From the stock solution dilutions were made to get concentrations of 10, 20, 40, 60 and 100µg of Ketoprofen per ml of solution,which were analysed by U.V spectrophotometer at wavelength of 276nm and the results were given in table no1.the calibration curve was constructed.

2.4.Preparation of Ketoprofen Transdermal Patches using different polymers by solvent casting method :Matrix type transdermal patches containing Ketoprofen were prepared using varying concentrations of EC and PVP individually or in combination keeping drug concentration constant . The required amount of drug (30 mg) and polymer were dispersed in casting solvent (methanol and chloroform) and allowed to stir for 6h. Propylene glycol was incorporated as a plasticizer. Almond oil was used as a penetration enhancer. After mixing the drug and polymer, the solution was allowed to stand for 15 minutes to remove air bubbles and the resulting solution was poured on a glass petri dish. The petri dish was kept on a horizontal surface. The polymeric drug solution allowed evaporation for 24hr to achieve drug polymer matrix patch. The rate of evaporation was controlled by inverting a funnel over the petri dish. After drying the films were peeled from the petri dish, and films were cut to generate transdermal patch of 1.0 cm diameter and patches were wrapped in aluminium foil, and preserved in desiccators for further studies.

Formulation table:

Ingredients	KTP1	KTP2	KTP3	KTP4	KTP5	KTP6
Ketoprofen	30mg	30mg	30mg	30mg	30mg	30mg
HPMC E5LV: Eudragit E100	1:1	2:1	3:1	-	-	-
Ethyl cellulose: PVP	-	-	-	1:1	2:1	3:1
Tween80	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml
Propylene glycol	1ml	2ml	2.5ml	-	-	-
Almond oil	0.1ml	0.1ml	0.1ml	0.1ml	0.1ml	0.1ml
Methanol:Chloroform	1:1	1:1	1:1	-	-	-
PEG4000	-	-	-	1ml	1.5ml	2ml
Tamarind Kernel powder	50mg	50mg	50mg	50mg	50mg	50mg

2.5.Evaluation tests

● **Folding Endurance**:- A patch on the specific area was cut evenly and repeatedly folded at the same place until it was broken. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance.

● **Drug Content**:- A specified area of the patch is to be dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyse the drug content with the suitable method (UV or HPLC technique). Each value represents an average of three samples.

● **Moisture content**:- The prepared films weighed individually and kept in a desiccator containing calcium chloride at room temperature for 24 hr. The films are weighed again after a specified interval until they show a constant weight. The percent moisture content was calculated by the following formula. % Moisture content= [Initial weight – Final weight / Final weight] × 100

● **Moisture uptake**: Weighed films were kept in desiccators at room temperature for 24hr. These were taken out and exposed to 84% relative humidity using saturated solution of potassium chloride in a desiccator until a constant weight is achieved. % Moisture uptake= [Final weight – Initial weight / Initial weight] × 100

● **In vitro permeation studies**: In vitro permeation studies were performed on Franz diffusion cells with an effective sectional area of 3.14 cm2and 150 ml of receiver chamber capacity. The egg membrane was tightly secured between the donor and receptor compartments. The upper surface of the membrane was exposed to solution of drug formulation. The receptor compartment was filled with isotonic phosphate buffer pH 7.4. The whole assembly was kept on a magnetic stirrer and solution in the receptor compartment was constantly and continuously stirred using a magnetic bead. An aliquot of the sample was periodically withdrawn at the regular time intervals and an equal volume was replaced with fresh dissolution medium. Absorbance of these solutions was measured at 238 nm using UV-Visible spectrophotometer. The film was cut into 2x2 sq.cm and placed on the Franz diffusion cell.

The calculation for the amount of drug present in 2x2 sq.cm film is as follows,

Diameter of petri dish - 9.0 cm, Radius = 4.5 cm,

Area of petri dish = Πr 2 = 3.14x 4.5x 4.5 = 63.58 sq.cm.

63.58sqcm patch contain 30mg ketoprofen

Similarity Factor:

The prepared ketoprofen batches were subjected to diffusion studies and compared with Ketoplast-30mg and similarity factor was calculated from diffusion data using the formula

$f_2 = 50\log\{[1+1/n\sum^{n}_{t=1}(R_t-T_t)^2]^{-1/2}x100\}$

n=no of diffusion time points,R_t=Diffusion value of the reference drug product at time t

T_t=Diffusion value of the test drug product at time t

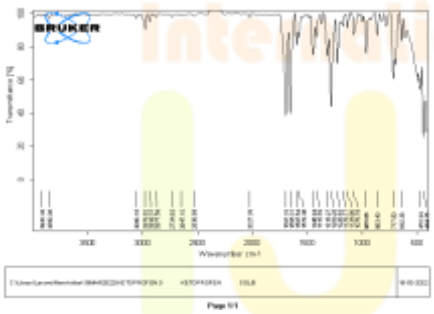
3.Results and Discussion

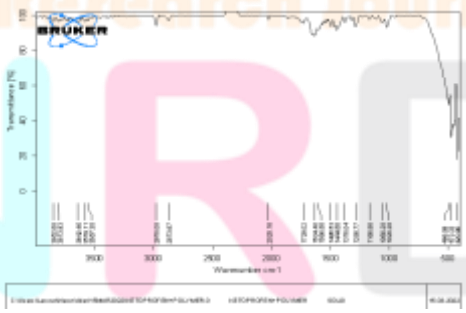
3.1.Preformulation studies of Tamarind kernel powder:

Identification tests

Test	Observation	inference
Molisch test: 2ml of sample solution (1%w/v) with 5 drops of Molisch's reagent in a test tube. Add gently through the side of test tube, about 2 ml of Conc. Sulphuric acid	Violet ring at the junction of two liquids was seen	Carbohydrate present
Solubility: Sample + Water	Sparingly soluble	Polysaccharide Present.
ConfirmationTest For glucose: 2 ml of test solution+5%NaoH Solution	Brown precipitate was observed	Glucose Confirm

3.2 FTIR studies for pure drug and in combination with polymer

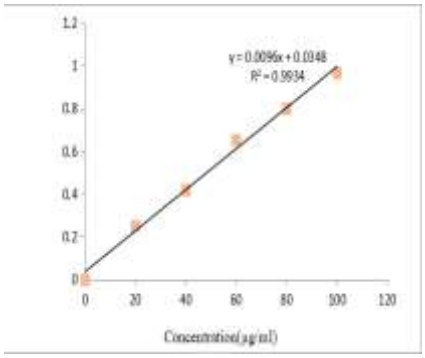




FTIR studies has shown that there is no significant interaction in between drug and polymers.

3.3.Calibration curve for Ketoprofen in pH 7.4 Phosphate buffer

S.No	Concentration (µg/ml)	Absorbance (nm)
1	0	0
2	2	0.25
3	4	0.4178
4	6	0.6521
5	8	0.797
6	10	0.9665



3.4Evaluation Tests for Ketoprofen Transdermal patches:

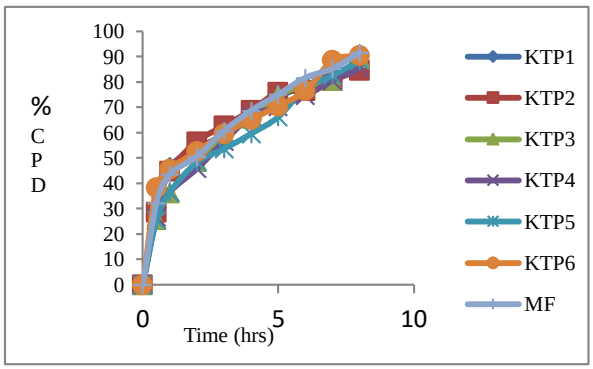
Evaluation tests	KTP1	KTP2	KTP3	KTP4	KTP5	KTP6
Folding endurance	171.89	184.5	198	211.5	238.5	252
Moisture uptake	1.74	2.143	3.75	2.946	2.54	1.34
Moisture content	3.38	4.06	6.7	5.43	4.74	2.7
Drug content	99.2	98.5	98.8	99.3	99.1	99.4

3.5.Results for In-vitro diffusion studies of transdermal patches:

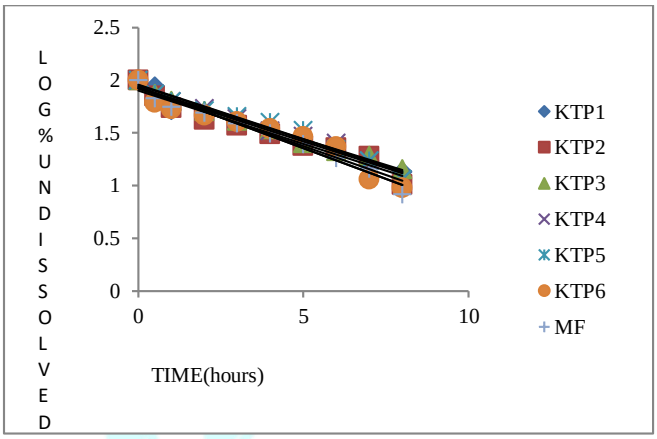
Time(hours)	KTP1	KTP2	KTP3	KTP4	KTP5	KTP6	MF
	Cumulative %drug relese						
0	0	0	0	0	0	0	0
0.5	30.58	28.59	25.64	26.64	25.45	38.26	32.26
1	46.51	44.89	36.24	36.58	36.58	45.64	43.58
2	53.78	56.48	48.64	45.85	48.28	52.64	50.56
3	59.59	62.68	58.64	56.79	53.64	59.64	60.68
4	68.68	68.79	65.69	66.64	59.64	65.28	68.69
5	74.25	75.96	74.64	70.28	66.28	70.58	75.02
6	78.61	76.68	78.56	74.64	77.78	76.56	81.64
7	82.31	80.68	80.56	80.68	82.63	88.53	85.26
8	86.48	84.68	89.68	85.64	88.53	90.44	91.56

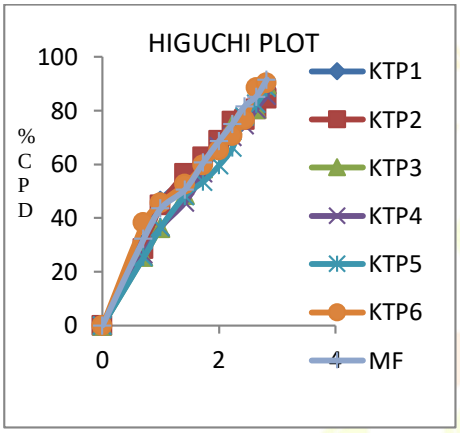
3.6.Fitting of diffusion data into various kinetic models

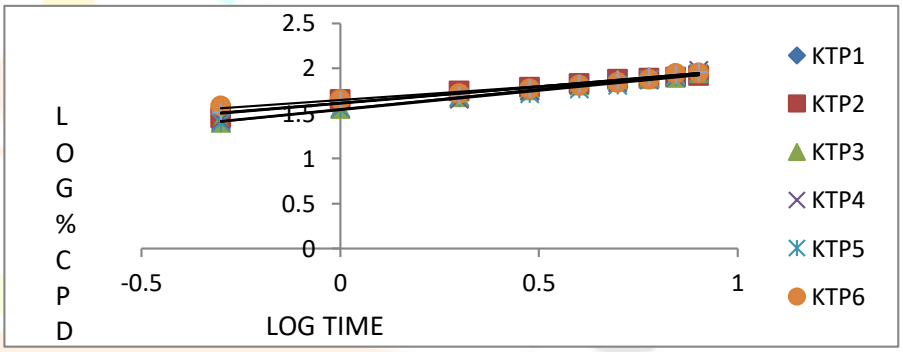
Zero order curve



First order curve







Koresemeyer peppas plot

Correlation coefficient values for diffusion data				
Formulation	Zero order	First order	Higuchi Graph	Korse-meyerGraph n-values
KTP1	0.907	0.969	0.968	0.468
KTP2	0.793	0.950	0.959	0.366
KTP3	0.886	0.985	0.993	0.446
KTP4	0.907	0.978	0.992	0.435
KTP5	0.907	0.976	0.990	0.426
KTP6	0.838	0.937	0.960	0.304
MF	0.864	0.976	0.984	0.367

- Based on R^2 values , the release follows first order, and diffusion followsHiguchi models.
- Based on 'n' values in Korsmeyer Peppas ($n<0.5$) indicating the combined mechanism (diffusion through matrix and partially through water-filled pores).

SUMMARY:- The transdermal patches of ketoprofen with polymer combination of HPMC E5LV and Eudragit E100 along with the plasticizer propylene glycol produced sticky and inferior quality films.Whereas the transdermal patch with combination of ethyl cellulose and PVP in the ratio of 1:1and PEG 400 as a plasticiser, almond oil as a permeation enhancer, by using chloroform as solvent has very good film properties the polymers used in the formulation produces transparents and flexible films which smooth appearance.Tamarind kernel powder used as a mucoadhesive polymer.when tween80 included in a formulation the mechanical properties of the film were improved.

CONCLUSION:-The present work based on drug release studies and other evaluation tests concluded that the transdermal patches of ketoprofen with combination of ethyl cellulose and PVP, using the PEG 4000 as a plasticizer has shown better control release. Tamarind kernel powder can be used as mucoadhesive polymer in controlled release formulation.

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