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DESIGN AND IN-VITRO CHARACTERIZATION OF KETROLAC TRANSDERMAL PATCHES

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ABSTRACT

Different polymeric Patches containing Ketorolac were prepared and evaluated for physicochemical, in vitro drug release and permeation characteristics. Transdermal patches with ERL 100 and HPMC E15 showed better release than patches with ERS 100 and HPMC E15. The release rate was increased with an increase in HPMC E15 content. Ketorolac transdermal Patches with penetration enhancers d-limonene, oleic acid in 4%, 8% and 12% v/w concentrations were prepared and evaluated for physicochemical and permeation characteristics. The release kinetics of the optimized formulations followed zero order and release mechanism was Non-fickian diffusion rate-controlled mechanism. The transdermal patches of Ketorolac with required flux could be prepared with suitable mechanical properties, further studies are recommended to find their therapeutic utility in humans by pharmacokinetic and pharmacodynamic studies. Immediate release tablets of ketorolac were formulated by direct compression method using menthol as subliming agent, Microcrystalline cellulose as diluent, CCS as super disintegrant, Magnesium stearate as lubricant. Friability values are found to be less than 1% in all the cases and considered to be satisfactory. The total weight of each formulation was maintained constant, and the weight variation of the tablets was within limits.

Keywords: Ketorolac, transdermal patches, direct compression method

INTRODUCTION

Controlled Drug Delivery Systems

Controlled drug delivery systems have been developed which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue[1].

Controlled drug delivery or modified drug delivery systems are conveniently divided into four categories.

- Delayed release
- Sustained release
- Site-specific targeting
- Receptor targeting

More precisely, Controlled delivery can be defined as[2]: -

- Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects.
- Localized drug action by spatial placement of a controlled release system adjacent to or in the diseased tissue.

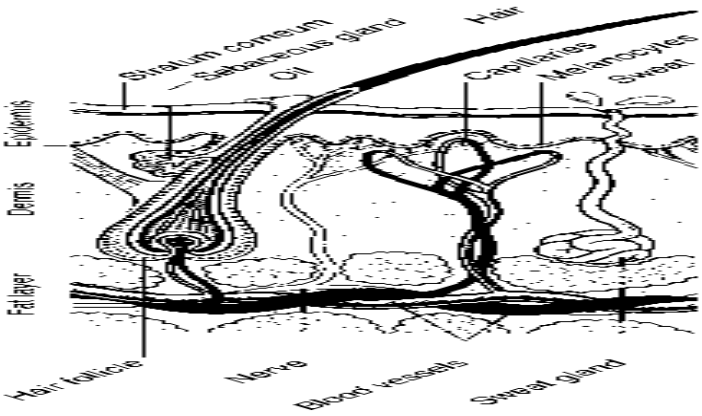


Fig 1: Structure of human skin

2. REVIEW OF LITERATURE

R. Panner selvam et al.,(2010) reported a review on transdermal drug delivery systems for antihypertensive drugs. They mentioned that transdermal delivery of antihypertensives enhancing the bioavailability as well as improoving the patient compliance. This review reported that various antihypertensives like timolol maleate, nicardapine HCL, captopril, atenlol, metoprolol, clonidine, labetolol, pinacidil, verapamil HCL, niterndipine, nifedapine, carvedilol were formulated into transdermal delivery systems[5]

Jitendra Banweer et al., (2010) reported formulation, optimization and evaluation of matrix type transdermal system of lisinopril dihydrate using penetration enhancers. The patches were prepared employing HPMC and PVA in1:1 ratio using glycerol as plasticizer in 6% concentration. Isopropyl alcohol and oleic acid were added as penetration enhancers individually and in blend in different concentrations and ratios.

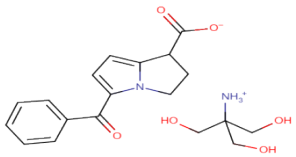
Pravin. Gavali et al., (2010) reported design and development of HPMC based polymeric films of enalapril maleate. Patches were prepared using different concentrations and grades of HPMC (K4M, K15M,K100M) and evaluated for their physico chemical characterization.

3. AIM AND OBJECTIVE

The present study was designed to develop suitable matrix type transdermal drug delivery systems of Ketorolac using two different polymeric combinations, E RL100 with HPMC E 15; E RS 100 with HPMC E 15. E RL100 and E RS 100 are acrylic acid matrices which have been used to make drug-polymer matrix patches for transdermal delivery systems which are reported to be compatible with many drugs.

4. DRUG PROFILE

Ketorolac Tromethamine



STRUCTURE

Molecular Formula: $C_{19}H_{24}N_2O_6$

Molecular Weight: 376.41

Chemical Name: 5-benzoyl-2, 3-dihydro-1H-pyrrolizone-1-carboxylic acid 2- amino-2 -(hydroxymethyl)-1, 3-propanediol.

Melting Point: About 163° C with decomposition.

5. MATERIALS AND EQUIPMENT

Materials

Nitroglycerin	Chandra Labs, Hyderabad.
HPMC E15	S.S. Pharma, Warangal.
Eudragit RS 100	Degussa, Germany
Eudragit RL 100	Degussa, Germany
Oleic acid	Merck Ltd., Mumbai
Dichloromethane AR	Merck Ltd., Mumbai
Methanol AR	Merck Ltd., Mumbai
Propylene glycol	Qualigens Fine Chemicals., Mumbai

Equipment

EQUIPMENTS	MANUFACTURER
Digital weigh balance	Shimadzu, Japan
Glass ware	Borosil
Magnetic Stirrer	Remi equipments, Mumbai
pH Meter	Elico limited, Hyderabad
UV-Vis Spectrophotometer	Shimadzu, Japan

6. METHODOLOGY

6.1 Construction of standard graph of Ketorolac

Construction of standard graph of Ketorolac in phosphate buffer pH 6.8.

The calibration curve is obtained by dissolving 50 mg of Ketorolac in 50 ml of volumetric flask and then make up with pH 6.8 phosphate buffer. From this stock-I solution 1ml solution was taken and made up to 10 ml with pH 6.8 phosphate buffer and this was stock- II.

Drug-Excipient Compatibility study

This was carried out by FTIR analysis of pure drug (Ketorolac), pure polymers (HPMC E 15, ERL 100 and ERS 100) and their physical mixtures as used in formulations to study the possible interaction between drug and polymers.

Preparation of Ketorolac Transdermal Patches

Matrix type transdermal patches containing Ketorolac were prepared by solvent evaporation technique, using different ratios of HPMC E 15, ERL100 (KT1 to KT5) and HPMC E 15, ERS100 (KT6 to KT10). The polymers were weighed in requisite ratios by and allowed for swelling for about 6 hrs in solvent mixture.

Table 1: Composition of Ketorolac transdermal patches

Formulation code	Drug (mg)	HPMC E15 (mg)	ERL 100 (mg)	ERS 100 (mg)
KT1	60	60	750	-
KT 2	60	120	600	-
KT 3	60	180	450	-
KT 4	60	240	300	-
KT 5	60	300	150	-
KT 6	60	120	-	240
KT 7	60	240	-	120
KT 8	60	180	-	180
KT 9	60	300	-	60
KT 10	60	60	-	300

6.2 Characterization of Ketorolac Transdermal Patches[24]

Physicochemical properties

The Patches prepared by general procedure were evaluated for the following properties

Thickness

The thickness of the film was measured at ten different points on one film using vernier calipers. For each formulation three selected Patches were used and average thickness was recorded.

Weight variation

Six Patches from each batch of an area of 6 cm^2 were weighed individually and the average weight was calculated.

Folding endurance

Folding endurance of the patch was determined manually by repeatedly folding a small strip of the medicated patch at the same place until broke. The number of times the strip could be folded at the same place without breaking gave the folding endurance number.

Estimation of drug content in polymeric Patches

The formulated polymeric patches were assayed for drug content in each case. Three polymeric patches from each formulation were assayed for content of drug.

Procedure

Patches from each formulation were taken, cut into small pieces and was allowed to dissolve in a 100 ml solution containing 50 ml of methanol and 50 ml of dichloromethane. The solution was diluted suitably and the absorbance of the solution was measured using UV-Vis spectrophotometer at a wavelength of 322 nm against methanol dichloromethane mixture (1:1) as blank.

Moisture Content Determination

The patches were weighed accurately and placed in a desicator containing calcium chloride at 40°C for 24hr. Then the final weight was noted when there was no further change in the weight of individual patch. The percentage of moisture loss was calculated as difference between initial and final weight with respect to final weight.

$$\% \text{ Moisture Content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

In vitro Release Studies

The drug release studies from Ketorolac transdermal patches were performed using Franz diffusion cell. The drug containing patches was kept between donor and receptor compartments, separated from these compartments by gelatin membrane. The receptor compartment containing diffusion medium was stirred with magnetic bead operated by magnetic stirrer, to prevent the formation of concentrated drug solution layer below the dialysis membrane. 3ml of sample was collected from the receptor compartment at appropriate time intervals and replaced with phosphate buffer pH 6.8.

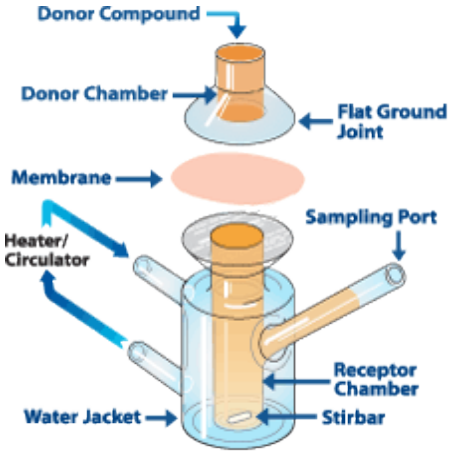


Fig 1: Franz diffusion cell

7. RESULTS AND DISCUSSION

Construction of standard graph of Ketorolac

The standard graphs of Ketorolac in pH 6.8 phosphate buffer constructed and The standard graphs of Ketorolac in pH 6.8 buffer have shown good linearity over a concentration range of 2 to 12µg/ml with R^2 of 0.9978 respectively.

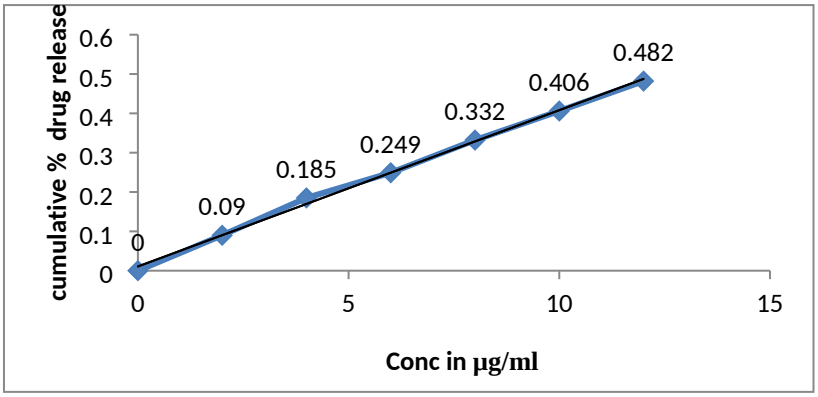


Fig 2: Standard graph of ketorolac in pH 6.8 phosphate buffer

Patches were formulated with E RS 100, E RL 100 and HPMC E15. Many experiments were performed by varying the concentrations of polymer. The experiment was initiated by taking 460 mg of polymer and as the polymer concentration increased the patch could accommodate more amount of Nitroglycerine.

Table 2: Drug content, % Moisture absorbed and % Moisture content of Nitroglycerine transdermal patches, mean ± S.D (n=3)

Formulation	Drug content (mg)	% Moisture content
F1	14.35±0.64	5.3±0.24
F2	14.08±0.56	4.3±0.46
F3	14.72±0.55	4.08±0.88
F4	14.15±0.95	3.21±0.80
F5	**14.82±0.07**	**3.98±0.60**
F6	14.30±0.86	3.3±0.52
F7	14.45±0.29	4.88±0.57
F8	14.62±0.03	5.63±0.45
F9	14.34±0.06	4.9±0.66
F10	14.33±0.64	3.95±0.05

Table 3: Mechanical properties of optimized formulations

Formulation Code	Tensile strength(kg/m^2)	Elongationbreak (%mm^{-2})	Elastic modulus (kg/mm^2)	Strain
F5	1.02±0.26	65.92±2.02	2.68±0.38	0.46±0.023
C3	1.09±0.31	69.7±1.06	2.09±0.41	0.52±0.018
D3	1.06±0.11	72.16±1.89	2.84±0.50	0.49±0.037

In vitro *Drug Release Studies from Transdermal Patches*

The patch formulated with HPMC alone showed 87% of drug within 8 hrs and followed first order kinetics. This means that the patch was not suitable for the release of drug for 24 hrs to get a prolonged release of drug, copolymer that decreases the drug release rate is needed to be added. Therefore, rate controlling polymers ERL 100 and ERS100 were cast with the aim to achieve controlled release of drug.

Table 4: Cumulative percent release of Nitroglycerine from transdermal patches

Time (hrs)	Cumulative % of drug released, mean ± S.D (n=3)				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	6±0.06	4.5±2.67	6±1.30	5.7±1.88	6.4±0.62
2	9±1.09	5.9±0.02	10±1.03	8.13±1.09	7.2±1.08
3	9.9±1.78	9.01±0.17	13±1.70	12.42±0.56	9.52±0.37
4	14.9±0.43	13.13±1.19	18±2.50	14.06±1.09	13.7±1.21
5	19±0.10	17±1.08	22.1±1.3	19.05±1.99	16.05±1.05
6	21±0.80	19±1.60	28±0.62	24.38±1.80	20.12±1.96
8	29±0.56	23±0.85	33±1.38	28.3±1.16	34.93±1.39
10	36±1.08	32±1.31	38±1.05	38.5±0.30	43.53±1.38
12	41±0.43	36±1.90	41±3.52	44.8±1.39	56.03±0.30
24	75±1.98	73±1.07	53±0.80	59.1±1.03	73.08±0.41

Drug- Excipient Compatibility Study

The IR spectral analysis of Nitroglycerine showed that the principal peaks and for the mixture of Nitroglycerine, ERS 100 and HPMC E15 additional to the principal peaks, some additional peaks were observed with physical mixtures, which could be due to the presence of polymers. The presence of all the characteristic bands due to functional groups in polymer mixtures suggest that there is no interaction between the drug and polymers used in the present study.

8. VALIDATION

Construction of standard graph of Ketorolac

The standard graphs of Ketorolac in pH 6.8 phosphate buffer constructed. The standard graphs of Ketorolac in pH 6.8 buffer have shown good linearity over a concentration range of 2 to 12µg/ml with R^2 of 0.9978 respectively.

Characterization of Ketorolac Transdermal Patches

Physicochemical properties

The Patches prepared by general procedure were evaluated for the following properties:

Weight Variation Test

The results of weight variation test for various transdermal Patches Results of weight variation test indicated uniformity in weight of patches, as evidenced by SD values, which were less than 2.0 for all formulations. In formulations KT1 to KT10 the weight of the patches decreased with decrease in HPMC E15 concentration .

Thickness Variation Test

The results of thickness variation test for various transdermal Patches In thickness variation test, the thickness was found to be uniform.

Folding endurance number

The folding endurance numbers of formulations are presented in the Tables. patches did not show any cracks even after folding for more than 80 times.ERS 100 containing patches has in the range of 40 to 90, ERL 100 containing patches has in the range of 18 to 85

Estimation of drug content in polymeric Patches

The results of drug content for various transdermal Patches. The results of content uniformity indicated that the drug was uniformly dispersed in all transdermal patches as evidenced by low SD values. The drug content analysis of the prepared formulations had shown that the process shown employed to prepare patches

Moisture Content study

The results revealed that the moisture content was found to increase with increasing the concentration of hydrophilic polymer (HPMC E15). The small moisture content in the formulations help them to remain stable and from being a completely dried and brittle film.

Table 5: Weight, thickness and folding endurance of Ketorolac transdermal patches

Formulation	Weight (mg)	Thickness (mm)	Folding endurance
KT1	100.1±0.02	0.28±0.25	75±7.64
KT2	101.6±0.45	0.29±2.05	82.5±1.05
KT3	102.8±0.02	0.32±0.45	86.31±3.83
KT4	103.2±0.07	0.33±0.42	86.16±5.04
KT5	103.2±0.08	0.33±0.29	88.33±2.58
KT6	102.1±0.82	0.38±0.14	90±8.91
KT7	104.3±0.96	0.35±2.17	80.83±2.15
KT8	106.3±0.54	0.29±0.19	83.5±5.95
KT9	102.2±1.67	0.36±1.63	84.5±3.90
KT10	98.3±0.28	0.32±1.23	69.67±3.46

Table 6: Drug content and % Moisture content of ketorolac transdermal patches, mean ± S.D (n=3)

Formulation	Drug content (mg)	% Moisture content
KT1	58.3±0.05	5.3±0.24
KT2	58.2±0.21	4.3±0.46
KT3	60.4±0.45	4.08±0.88
KT4	59.2±0.05	3.21±0.80
KT5	56.1±0.24	3.98±0.60
KT6	59.4±0.22	3.3±0.52
KT7	58.1±0.10	4.88±0.57
KT8	56.1±0.45	5.63±0.45
KT9	59.7±0.25	4.9±0.66
KT10	56.3±0.98	3.9505

In vitro Release Studies

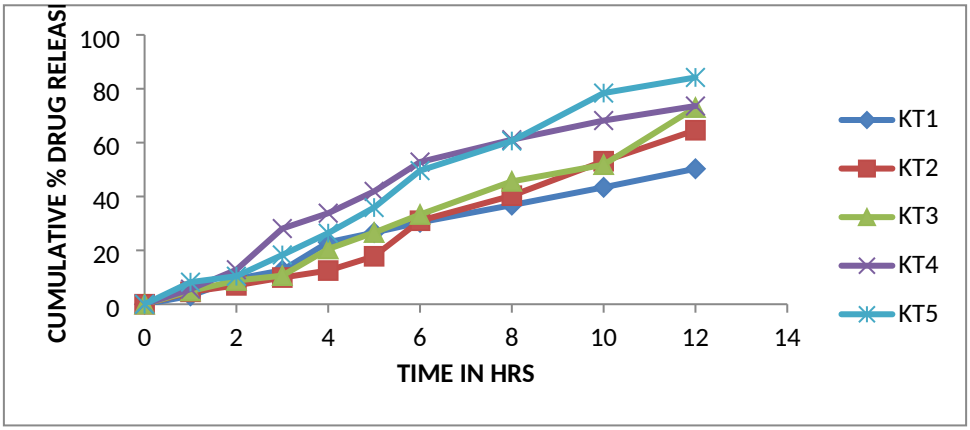


Fig 3: Cumulative percent release of Ketorolac from transdermal patches KT1-KT5

9. CONCLUSION

Different polymeric Patches containing Nitroglycerine were prepared and evaluated for physicochemical, in vitro drug release and permeation characteristics. Transdermal patches with ERL 100 and HPMC E15 showed better release than patches with ERS 100 and HPMC E15. The release rate was increased with an increase in HPMC E15 content. Nitroglycerine transdermal Patches with penetration enhancers d-limonene, oleic acid in 4%, 8% and 12% v/w concentrations were prepared and evaluated for physicochemical and permeation characteristics. The formulations containing d-limonene (12%), 0leic acid (12%) were found to meet the required flux.

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