FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES OF KETOROLAC TROMETHAMINE

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ABSTRACT : ***The aim of the study was to prepare a transdermal drug delivery device, which may be of an active or a passive design. It is a device that provides an alternative route for administering medication. The skin barrier allows to diver of the drug from the transdermal device. Inside a patch, a high dosage of the drug is applied, which is worn on the skin for an extended period. The drug enters the bloodstream directly through the skin by a diffusion process. Since there is a high concentration on the patch and a low concentration in the blood, the drug will keep diffusing into the blood for a long period, the blood flow was maintained by the constant concentration of drugs in the blood flow. 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.***

Keywords: Transdermal, ERL, HPMC, ERS, Patches, and Ketorolac Tromethamine.

I.INTRODUCTION

Ketorolac Tromethamine is the tromethamine salt of ketorolac, is a non-steroidal anti-inflammatory drug (NSAID), analgesic, and antipyretic properties. Transdermal patches are topically administered medicament with systemic effect at a predetermined and controlled rate. The active and passive design of transdermal drug delivery device, which provides an alternative route for administering medication. Skin barrier allows pharmaceutical medicament from these devices. From the patch, the high dosage of the drug, which is worn on the skin for an extended period. Through the diffusion process, the drug enters the bloodstream directly through the skin. Since there is a high concentration on the patch and a low concentration in the blood, the drug will keep diffusing into the blood for a long period, the blood flow was maintained by the constant concentration of drugs in the blood flow.

II.MATERIALS AND METHODS

2.1 Materials

Ketorolac Tromethamine (Chandra Labs, Hyd), HPMC E15 (S.S. Pharma, Warangal), Eudragit RS 100 (Degussa, Germany), Eudragit RL 100 (Degussa, Germany), Oleic acid (Merck Ltd, Mumba), Dichloromethane AR (Merck Ltd, Mumbai), Methanol AR (Merck Ltd, Mumbai), and Propylene glycol (Qualigens Fine Chemicals, Mumbai).

2.2 Methodology

Preparation of patches: Matrix type transdermal patches containing Ketorolac were prepared by solvent evaporation technique, using different ratios of HPMC E15, ERL 100(KT1 to KT5), and HPMC E15, ERS 100 (KT6 to KT10). The polymers were weighed in requisite ratios and allowed for swelling for about 6 hrs. in the solvent mixture (1:1 ratio of dichloromethane, methanol). 15% v/w propylene glycol was incorporated as a plasticizer. Then the drug solution was added to the polymeric solution, cast onto an umbra Petri plate with a surface area of about 69.24sq.cm, allowed for air-drying overnight followed by vacuum drying for 8-10 hrs. The entire sheet was cut into small patches with an area of 6.9 cm2 i.e. with a diameter of 2.9 cm. About 7 patches were obtained from each sheet. All formulations carried 15% v/w polyethylene glycol as plasticizer and 12% oleic acid as a penetration enhancer

Physicochemical evaluation of patches

Drug-excipient compatibility study carried out by FTIR analysis of pure drug (Ketorolac), pure polymers (HPMC E15, ERL 100, ERS 100), and their physical mixtures as used in formulations to study the possible interaction between drug and polymer.

Weight variation: Results of the weight variation test indicated uniformity in the weight of patches, as evidenced by SD values, which were less than 2.0 for all formulations. In formulations F1 to F10, the weight of the patches decreased with the decrease in HPMC E15 concentration. The order of weight of patches is F8>F10>F4>F9>F7>F3>F6>F1>F2 the weights of the patches are almost in the same range.

Thickness: The thickness variation test was found to be uniform. The thickness increased with an increase in HPMC E15 concentration in A and B series formulations (order of thickness in A-series (F4>F3>F5>F2 >F1 and B series F6>F9>F7>F10>F8). The SD values were less than 2 for all formulations, an indication of more uniform patches.

Folding endurance Patches did not show any cracks even after folding more than 80 times. ERS 100 containing patches has in the range of 40 to 90, ERL 100 containing paths have in the range of 18 to 85 and for the formulations prepared with penetration, enhancers have in the range of 70 to 105. The folding endurance number gives the mechanical property of the patches, high folding endurance number indicates that has high mechanical property. The folding endurance number was increased with increasing HPMC E15 content. These results indicated that the patches would not break and would maintain their integrity with general skin folding when applied.

Estimation of drug content in polymeric Patches: it indicated that the drug uniformly dispersed in all transdermal patches as evidence by low SD values. The drug content is ranged from 7.72 to 9.3 mg per 6cm2 patch area. The drug content analysis of the prepared formulations had shown that the process shown employed to prepare patches in the study was capable of giving patches with a uniform drug content and minimum batch variability.

Moisture absorption and Moisture content: Moisture content in the patches was ranged from 3.21 to 5.3% and 3.3 to 5.63% (for formulation A-series and B-series respectively). The moisture absorption in the formulations is ranged from 3.18 to 9.63% and 5.85 to 10.1% (for formulation A-series and B-series respectively). The results revealed that the moisture absorption and moisture content was found to increase with increasing the concentration of hydrophilic polymer (HPMC E15). The small moisture content in the formulation helps them remain stable and from being completely dried and brittle form.

III. RESULTS AND DISCUSSION

Weights, thickness, and folding endurance of Ketorolac Tromethamine Transdermal patches			
Formulation	**Weight (mg)**	**Thickness (mm)**	**Folding endurance**
F1	100.4±0.17	0.28±0.25	85±7.64
F2	104.6±0.61	0.29±2.05	62.5±1.05
F3	97.8.4±1.23	0.32±1.45	56.31±3.83
F4	103.2±0.27	0.33±0.42	26.16±5.04
F5	103.2±0.84	0.32±0.29	28.33±2.58
F6	102.1±0.82	0.38±0.14	90±8.91
F7	105.3±0.96	0.35±2.17	70.83±2.15
F8	106.3±0.54	0.29±0.19	83.5±5.95
F9	100.2±1.67	0.36±1.63	44.5±3.90
F10	98.3±0.28	0.32±1.23	49.67±3.46

Weights, thickness, and folding endurance of Ketorolac Tromethamine Transdermal patches with penetration enhancers			
Formulation	**Weight (mg)**	**Thickness (mm)**	**Folding endurance**
C1	102±0.15	0.34±0.71	105.1±1.20
C2	103±1.53	0.36±0.42	88.21±0.78
C3	100±0.84	0.33±0.41	75.25±2.92
D1	98±0.94	0.36±0.70	85.25±0.56
D2	95±0.69	0.34±1.35	92.05±1.38
D3	991±0.44	0.37±0.24	78.75±1.6

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	3.2±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	53.95±0.05

Drug content, % Moisture content of Ketorolac Tromethamine Transdermal patches.

Drug content, % moisture absorbed and % moisture content of Ketorolac Tromethamine Transdermal patches with penetration enhancers, mean± S.D (n=3)			
Formulation	**Drug content (mg)**	**% moisture content**	**% moisture absorbed**
C1	14.28±0.82	8.5±0.16	5.6±0.75
C2	14.05±1.82	13.5±1.95	7.55±0.22
C3	14.52±0.84	8.25±1.47	4.22±1.22
D1	14.25±0.68	6.6±2.85	5.45±1.08
D2	14.57±1.07	6.75±3.36	5.82±0.68
D3	14.25±0.88	8.25±1.25	3.85±1.22

Mechanical properties of optimized formulation				
Formulation	**Tensile strength (kg/m2)**	**Elongation at break (%mm-2)**	**Elastic modulation**	**Strain**
F5	1.02±0.26	65.92±9.02	2.68±0.38	0.46±4.023
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

Invitro Drug Release Studies from Transdermal Patches: The patch formulated with HPMC alone showed 87% of the drug within 8 hrs. and followed first-order kinetics. This means that the patch was not suitable for the release of the drug for 24 hrs. to get a prolonged release of the drug, a copolymer that decreases the drug release rate is needed to be added. Therefore, the rate-controlling polymers ERL 100 and ERS 100 were cast to achieve controlled release of the drug. The cumulative amount of drug released from A and B series patches are shown in table 12 and 13. The results indicate that there was an increase in the amount of drug release with an increase in

HPMC E15. There is an increase of drug release from F1 to F5 (F5>F4>F3>F2>F1) and F6 to F10 (F9>F10>F8>F6>F7).Formulations F5 and F9 exhibited the greatest (71.08±0.41 respectively) percentage of drug release values which are significantly different compared to the lowest values observed with the formulations containing ERL 100 and ERS 100 (36.07±1.98 % and 35.25±0.62 respectively). In the present study it was observed that as the concentration of hydrophilic polymer (HPMC) increased in the formulations, the drug release rate increased substantially.

Cumulative percent release of ketorolac Tromthamine from Transdermal Patches (Series –A)					
Time (hrs)	**Cumulative % drug release, 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±0.73	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

Cumulative percent release of ketorolac Tromthamine from Transdermal Patches (Series-B)					
Time (hrs)	**Cumulative % drug release, Mean ±S.D. (n=3)**				
	F6	**F7**	**F8**	**F9**	**F10**
0	0	0	0	0	0
1	4.9±1.43	3.9±0.61	5.75±1.61	5.34±0.68	5.13±1.80
2	6.72±1.74	5.25±1.08	8.1±1.30	9.5±1.18	10.12±1.42
3	9.63±1.50	6.6±1.14	11.5±2.61	15.5±1.07	18.43±0.63
4	11.92±2.49	7.13±0.45	12.5±1.41	18.01±0.21	23.21±0.32
5	13.8±2.54	10.43±1.67	16.36±1.67	20.05±1.65	24.53±3.70
6	18.5±1.36	13.22±1.40	19.08±1.43	23.2±1.56	27.41±0.46
8	22.5±0.57	17.5±0.87	25.9±3.55	29.91±1.30	33.63±0.21
10	28.7±1.22	12.45±1.05	36.25±1.11	13.9±1.32	37.21±0.29
12	33.2±0.5	26.6±4.10	41.6±1.92	41.8±0.30	43.24±1.92
24	44.7±0.41	35.2±0.62	52.1±0.74	57.08±0.41	62.31±1.87A

Ex-VIVO PERMEATION

Ex-vivo permeation, cumulative %release of ketorolac Tromthamine from Transdermal Patches					
Time (hrs)	**Cumulative % drug release, Mean ±S.D. (n=3)**				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	3.3±1.43	2.01±1.76	3.08±1.78	3.2±1.09	4.3±1.45
2	5.3±2.22	4.88±1.92	5.01±2.37	4.1±2.07	5.7±1.90
3	6.9±2.10	5.4±0.92	6.5±2.0.3	7.3±1.55	9.9±2.08
4	9.8±1.20	7.01±0.89	9.8±2.18	9.4±1.87	13.1±2.78
5	11.3±0.92	9.5±1.25	11.0±1.35	13.8±0.98	17.3±1.67
6	13.5±1.25	13.9±1.84	14.9±1.11	19.9±0.99	21.2±0.56
8	14.1±1.73	15.8±1.11	16.3±1.90	21.4±1.89	26.4±1.23
10	15.5±0.83	17.01±0.92	19.1±0.98	23.1±1.45	31.02±1.09

12	16.8±0.98	19.9±0.89	22.1±1.12	25.4±2.90	36.1±2.01
24	20.1±1.25	25.4±1.56	28.3±2.07	33.2±2.34	42.08±1.45

Ex-vivo permeation cumulative percent release of ketorolac Tromthamine from Transdermal Patches (Series-B)					
Time (hrs)	Cumulative % drug release, Mean ±S.D. (n=3)				
	F6	F7	F8	F9	F10
0	0	0	0	0	0
1	2.99±1.92	2.51±1.22	3.91±0.99	3.6±2.09	3.3±1.86
2	3.5±0.78	3.9±2.66	5.51±0.78	5.02±1.79	5.9±2.35
3	4.9±0.45	4.4±2.02	7.2±1.77	7.7±1.90	8.08±0.09
4	5.6±1.23	5.9±1.23	9.8±1.44	11.91±2.45	11.08±1.58
5	8.5±1.99	6.6±1.99	12.96±1.56	15.02±2.45	17.7±1.20
6	9.9±1.67	8.1±1.45	15.3±2.19	19.9±1.89	19.9±0.85
8	13.5±0.89	11.8±2.09	17.9±2.30	22.5±1.59	23.01±0.84
10	16.3±0.99	13.9±2.66	9.5±1.22	26.1±1.01	25.2±0.47
12	19.5±1.99	17.10±1.22	21.941.24	29.9±0.901	27.8±1.94
24	24.5±2.08	21.01±1.90	29.3±1.89	36.08±1.46	32.2±1.36

Time (hrs)	**Cumulative % drug release, Mean ±S.D. (n=3)**		
	C1	C2	C3
0	0	0	0
1	5.3±1.89	8.8±1.34	9.1±1.17
2	7.01±2.23	12.9±0.97	12.8±1.90
3	9.9±2.12	16.1±1.34	15.6±2.01
4	12.5±1.45	20.5±1.23	20.8±1.45
5	14.9±1.67	23.4±0.67	28.1±1.11
6	17.8±1.90	26..6±0.55	33.8±1.23
8	23.09±1.99	33.3±0.97	41.9±0.35
10	31.8±2.89	42.6±1.67	52.8±0.93
12	40.3±0.98	51.8±1.23	21.09±1.23
24	53.1±1.56	62.8±1.11	73.1±1.75

Time (hrs)	**Cumulative % drug release, Mean ±S.D. (n=3)**		
	D1	**D2**	**D3**
0	0	0	0
1	6.6±1.01	8.8±0.78	9.8±1.11
2	9.9±0.97	11.9±1.20	11.6±1.23
3	11.8±1.22	15.1±1.01	14.1±0,97
4	13.3±2.01	18.8±0,99	17.9±1.98
5	16.6±1.62	22.2±0.96	21.8±2.02
6	20.01±0.92	27.6±0.89	27.7±2.34
8	26.8±1.11	35.5±1.54	38.3±1.89
10	33.1±1.93	42.1±1.76	49.9±0.99
12	42.8±1.34	50.9±1.09	58.6±0.35
24	51.1±0.87	60.5±1.97	69.9±1.67

Formulation	Zero-order	First-order	Higuchi Model	Peppas Model	"n" value (Peppas model)
F5	0.845	0.876	0.939	0.956	0.822
C3	0.873	0.946	0.945	0.966	0.746
D3	0.884	0.935	0.926	0.941	0.731

***In vivo* permeation studies through rat abdominal skin from transdermal patches:**

The results of ex vivo skin permeation of ketorolac Tromethamine from patches of F5 and F9 an (area of 6.9 cm2) exhibited the greatest cumulative amounts of drug permeation, which were significantly different compared to the lowest values observed with the formulations containing ERL (F1) and ERS F7) in 24 hrs.

As the proportion of HPMC increased in all the formulations, increased drug release and permeation in both series were observed. Initial rapid dissolution of the hydrophilic polymer occurs when the patch in the skin surface and thus leading to saturation of the skin with drug molecules at all times.

The flux obtained with formulation F5 was found to be maximum. But with these formulations, the required flux was not obtained. Literature study gave an idea of using permeation enhancers to improve the drug through the skin. Oleic acid and d-limonene were used as permeation enhancers.

The results of ex vivo skin permeation of Ketorolac Tromethamine from patches prepared with permeation enhancers. The formulations C3 (containing 12% D-limonene), D3 (containing 12% oleic acid) exhibited the required flux. The fluxes obtained for formulations C3 and D3 are 128.6 µg/cm³/ hrs respectively which are in agreement with the target flux.

The ex vivo permeation results of optimized formulations F5, C3, and D3 were fitted into various kinetic models (zero-order, first-order, and Higuchi model, and Peppas model). The R^2 values reveal that the permeation of Ketorolac Tromethamine from the transdermal Patches followed the first order and diffusion rate-controlled mechanism.

According to the Peppas model, a value of slope (n) between 0.45 and 1 indicates an anomalous behavior (non-fickian). The n values of formulations F5, C3, and D3 are 0.822, 0.746, and 0.731. It indicates optimized formulation follows Non-Fickian diffusion.

IV. CONCLUSION

Different polymeric containing Ketorolac Tromethamine 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 ERS 100 and HPMC E15. The release rate was increased with an increase in HPMC E15 content. Ketorolac Tromethamine 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%), Oleic acid (12%) were found to meet the required flux. FTIR studies showed no drug and polymer interactions. The release Kinetics of the optimized zero-order and release mechanism was a non-fickian diffusion rate-controlled mechanism.

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