Development And Characterization Of Ketoprofen Transdermal Patches

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ABSTRACT : ***The objective of present study was to develop matrix type transdermal therapeutic systems of Ketoprofen using various such as HPMC, ethylcellulose and eudragit polymers as matrix formers. Results revealed that prepared patches showed good physical characteristics, no drug-polymer interaction and no skin irritation was observed. The in vitro release study revealed that F2 formulation showed maximum release in 8hrs. Formulation F2 was subjected for accelerated stability studies. The F2 formulation was found to be stable as there was no drastic change in the Physico-chemical properties of the patches, which was also confirmed by FTIR. Thus conclusion can be made that stable transdermal patches of Ketoprofen has been developed. F2 formulation showed highest cumulative percentage drug release of 93.35% were obtained during in vitro drug release studies after 8 hrs. The release of Ketoprofen appears to be dependent on lipophilicity of the matrix. Moderately lipophillic matrices showed best release. The predominant release mechanism of drug through the fabricated matrices was believed to be by diffusion mechanism. Based upon the in vitro dissolution data the F2 formulation was concluded as optimized formulation.***

Key words: Ketoprofen, HPMC, Eudragit, ethylcellulose, solvent casting technique, in vitro drug release studies.

I.INTRODUCTION

Transdermal patches system medicated adhesive patches are prepared which deliver therapeutically effective amount of drug across the skin when it placed on skin. [1] Topical drug delivery methods have advantages over other delivery methods, one of which is to avoid the metabolism of the first pass effect on the liver. [2] Transdermal Drug Delivery System (TDDS) are defined as self contained, discrete dosage forms which are also known as "patches" [3,4] when patches are applied to the intact skin, deliver the drug through the skin at a controlled rate to the systemic circulation. [5] TDDS are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin.[6] Administration of Ketoprofen using transdermal system is an alternative which can be used to avoid the side effect. Many studies show that Ketoprofen is more effective than others NSAID (Non-Steroidal Anti Inflammantory Drug) such as Diclofenac and Ibuprofen. Effect of Ketoprofen as an analgesic is very good and fast. [7, 8]The problem of transdermal administration is a barrier provided by human skin for the drug to permeate.3-4 Enhancer is one of methode that can approach amount of drug permeation in the transdermal drug design.5-7 Beside that, polymer that used in formula also can affect drug release, permeability, elasticity and character of the formula. [9,10] Ketoprofen is a non-steroid anti-inflammatory drug with analgesic and antipyretic action. It inhibits cyclo- oxigenase activity with a reduction in the tissue production of prostaglandins such as PGE . The aim of present study is to formulate and evaluate transdermal drug delivery of ketoprofen[11]

II.MATERIALS AND METHODS

Ketoprofen was collected as a gift sample from Hetero labs, Hyderabad and various excipients like synthetic polymers and other excipients were purchased from AR chemicals, Hyderabad.

2.1 Methodology

Compatibility studies of drug and polymers:[12,13]

In the formulation of Ketoprofen patch formation , API and Excipient may interact as they are in close communication with each other, which could lead to the instability of drug. FT-IR spectroscopy was employed to ascertain the compatibility between Ketoprofen and the selected polymers. The pure drug and drug with excipients were scanned separately.

Formulation design[14]

Preparation of transdermal patches:

Transdermal patches containing Ketoprofen were prepared by the solvent casting evaporation technique. The drug Ketoprofen was dissolved in suitable solvent. Polymers HPMC, Ethylcellulose were taken in a boiling tube, to this add Ketoprofen drug which was previously dissolved in methanol. Polyethylene glycol was taken as a plasticizer, and added to the mixture and mixed well. It was set aside for 2 hours to exclude any entrapped air and was then transferred into a previously cleaned petri plate ($40cm^2$), drying of patches was carried out in vacuum oven at room temperature. Dried patches were packed in aluminium foil and stored in a desiccator for further evaluation.

Table-1: Formulation Design of Ketoprofen Transdermal Patches

S. No	Formulation code	Ingredients (gms)			
		Drug (mg)	HPMC	Ethyl cellulose	Eudragit
1	F1	100	500	-	-
2	F2	100	-	500	-
3	F3	100	250	-	500
4	F4	100	-	250	-
5	F5	100	-	-	250

Evaluation of transdermal formulation: [15,16,17]

Physical appearance: All the prepared transdermal films were observed for color, clarity, flexibility, and smoothness.

Folding endurance: Folding endurance of the patches was determined by repeatedly folding at the same place till it broke. The number of times the patch could be folded at the same place without breaking is the folding endurance. This was repeated on all the patches for three times and the mean values plus standard deviation was calculated.

Thickness of the film: The thickness of each film was measured by using screw gauze. The thickness was measured at three different places on each film and the average thickness of the film was taken as the thickness of the film.

Weight uniformity: The prepared patches are to be dried at 60^0C for 4hrs before testing. A specified area of 4.52 cm^2 of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

Drug content: The formulated transdermal films were assayed for drug content in each case. Three patches from each formulation were assayed for content of drug. Each formulation was casted in triplicate and one film from each was taken and assayed for content of drug.

Moisture absorption studies: The films were weighed accurately and placed in a desiccators containing aluminium chloride to maintain 79.50% RH. After 3 days, the films were taken out and weighed. The percentage of moisture uptake was calculated using the following formula.

$$\text{Perentage moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Moisture loss studies: Three films were weighed individually and kept in a desiccator containing calcium chloride at 37^0C for 24 hrs. Then the final weight was noted when there was no further change in the weight of the patch. The percentage of moisture loss was calculated using the following formula.

$$\text{Percentage moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

***In-vitro* Drug release studies:**[18] The *in-vitro* study of drug permeation through the Dialysis membrane was performed using a modified Franz type glass diffusion cell. The modified cell having higher capacity is (10 ml) is used to maintain sink condition. The samples were analyzed for drug content spectrophotometrically. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal.
Percentage of drug release was determined using the following formula.

$$\text{Perentage drug release} = \frac{Da}{Dt} \times 100$$

Where, Dt = Total amount of the drug in the patch
Da = The amount of drug released

Conditions:

Medium: Phosphate buffer pH 7.4
RPM: 200
Temperature: 37 ± 0.5^{0}C
Time intervals: 1, 2, 3, 4, 5, 6, 7, 8 hours

Stability studies:[19] Optimized medicated films were subjected to short term stability testing. The transdermal films were sealed in aluminium foils and kept in a humidity chamber maintained at 40 ± 2 ^{0}C and 75 ± 5% RH for 1 month as per ICH guidelines. Changes in the appearance and drug content of the stored films were investigated after storage at the end of every week.

III.RESULTS AND DISCUSSION

Drug - excipient compatability studies
Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied. The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components.

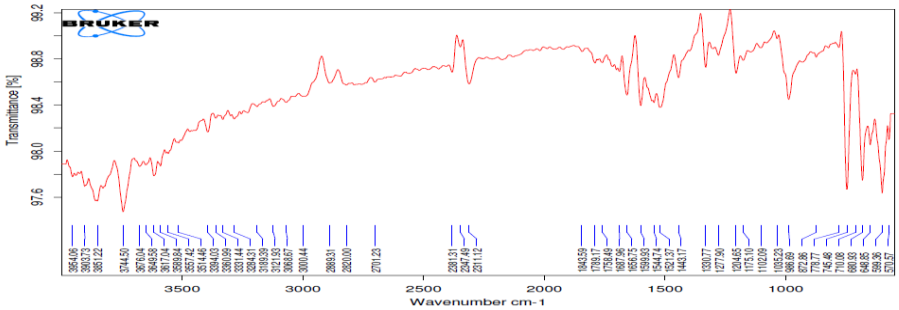

Fig-1: FTIR spectra of pure drug

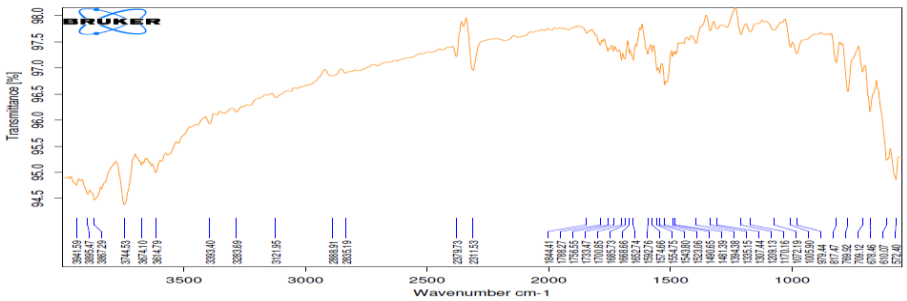

Fig-2: FTIR Spectra of optimaized formulation

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of Pure drug and physical mixture of drug and excipients were studied. The characteristic absorption of peaks were obtained as above and as they were in official limits (±100 cm^{-1}) the drug is compatible with excipients.

Evaluation of Transdermal formulation

Physical appearance:
The prepared patches were found to be uniform, smooth, flexible and homogenous.

Folding endurance:
The folding endurance numbers of all the Ketoprofen patches are 189 – 192. The folding endurance number gives the mechanical property of the patches, high folding endurance number indicate that has high mechanical property. The folding endurance number was increased with increasing the HPMC content. These results indicated that the patches would not break and maintain their integrity with general skin folding when applied.

Thickness of the film:
Thickness was changed from batch to batch in individual strips of medicated patch carry uniform thickness, which indicates that total medicated patch carry uniform thickness..

Weight uniformity:
The weights are in the range of 245-274. The F2 formulation patches showed maximum weight.

Drug content:

The drug content analysis of the prepared formulations have shown that the process employed to prepare the patches was capable of giving uniform drug content with minimum batch variability. All the patches were found to have drug content in the range of 90 – 101%. So the method employed i.e. solvent evaporation method is satisfactory for the preparation of Ketoprofen transdermal patches.

Table-2: Physicochemical evaluation of Ketoprofen patches

Formulation code	Weight (mg)	Thickness (mm)	Folding endurance	Drug content (%)	% moisture loss	% moisture absorption
F1	245.9	0.90	192	89.63	6.85	9.95
F2	265.4	0.96	190	99.85	9.20	10.20
F3	286.2	0.91	189	96.65	10.85	10.95
F4	274.7	0.95	191	94.42	9.85	11.85
F5	241.9	0.99	194	97.10	10.29	12.32

***In vitro* release study:**

Phosphate buffer pH 7.4 was used as medium for the release studies and good linearity was observed in the plotted standard graph with a correlation coefficient of 0.995. The drug release profiles of Ketoprofen patches containing different ratios of polymers HPMC, Ethylcellulose. It was cleared from the release profiles of formulations, that the drug release was governed by polymer nature and content.

Table-3: *In vitro* drug release profiles of Ketoprofen transdermal patch (F1-F5)

Time	F1	F2	F3	F4	F5

0	0	0	0	0	0
1	14.56	18.68	16.48	14.80	13.56
2	23.72	28.25	26.50	24.68	22.72
3	34.94	39.52	38.71	36.62	34.94
4	41.16	53.28	49.36	40.18	41.16
5	51.88	63.63	56.25	56.71	57.88
6	65.33	72.46	69.07	69.20	61.33
7	78.46	82.60	78.53	73.76	73.46
8	90.87	93.35	89.15	80.92	89.87

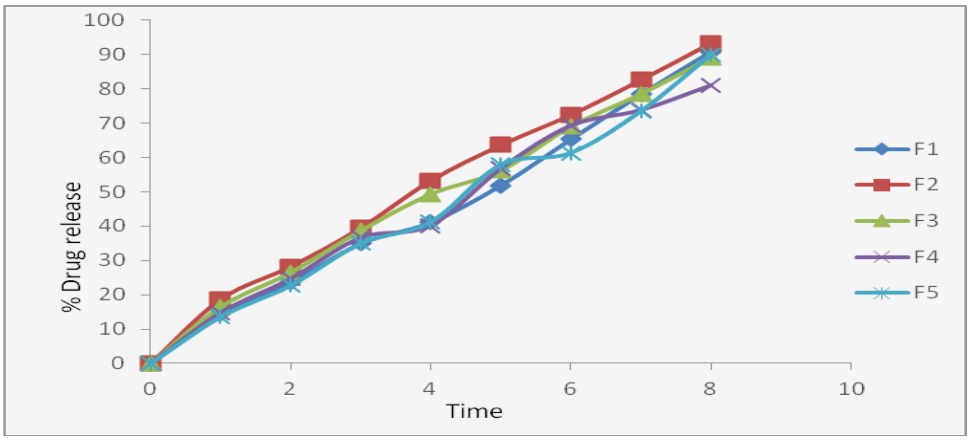

Fig-3: Drug release for all formulations

Stability studies:

Optimized formulations F2 was selected for accelerated stability studies as per ICH guidelines. The patches were observed for color, appearance and flexibility for a period of three months. The folding endurance, weight, drug content, % cumulative drug release of the formulation was found to be decreasing. This decrease may be attributed to the harsh environment (40^0C) maintained during the studies.

Table-4: Stability studies of optimized formulations at 40 ± 2 ^{0}C and 75 ± 5% RH for 1 month

Time in days	Drug content (%)	Physical appearance	% Cumulative drug release
0	99.85	No change in color	93.35
30	99.56	Slight yellowish color	93.29

IV. CONCLUSION

The following conclusions could be drawn from the results: Results revealed that prepared patches showed good physical characteristics, no drug-polymer interaction and no skin irritation was observed. The F2 formulation was

found to be stable as there was no drastic change in the Physico-chemical properties of the patches, which was also confirmed by FTIR. Thus conclusion can be made that stable transdermal patches of Ketoprofen has been developed. F2 formulations showed highest cumulative percentage drug release of 93.35%, were obtained during *in vitro* drug release studies after 8 hrs. The release of Ketoprofen appears to be dependent on lipophilicity of the matrix. Moderately lipophillic matrices showed best release. The predominant release mechanism of drug through the fabricated matrices was believed to be by diffusion mechanism. Based upon the *in vitro* dissolution data the F2 formulation was concluded as optimized formulation.

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