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Formulation and evaluation of transdermal patches for the treatment of arthritis

Agrawal Rashi[1*], Dr. Azharuddin[1]

[1*]Research scholars, Sunrise University, Alwar, Rajasthan
[1]Associate Professor, Sunrise University, Alwar, Rajasthan

ABSTRACT

The most common side effects of Leflunomide are such as dyspepsia, nausea, abdominal pain, and oral ulceration. The benefits of transdermal patches include increased permeability of drug good skin penetration, avoidance of first pass metabolism. Increase drug delivery of leflunomide which result in increased concentration of drug at the site of action. The objective of making is formulation is to ensure that the drug remains on the inflamed tissue for a long time so that the drug can have better action

Keywords- Arthritis, leflunomide, transdermal patches, HPMC, EC, permeation enhancer

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease. Leflunomide is one of the more recent oral agents, classified as a disease-modifying antirheumatic drug (DMARD). It has a different mechanism of action than other existing DMARDs.[1] Leflunomide is a selective inhibitor of de novo pyrimidine synthesis. In phase II and III clinical trials of active rheumatoid arthritis, leflunomide was shown to improve primary and secondary outcome measures with a satisfactory safety profile.[2] Oral administration of leflunomide has some side effects like burning feeling in the chest or stomach, diarrhea, indigestion, stomach pain etc. Topical formulation eliminates the gastrointestinal related toxicities associated with oral administration. Transdermal patches of Leflunomide were formulated and evaluated for its efficacy and safety. This study aims to prepare prolonged-release Leflunomide transdermal patches.

MATERIALS AND METHOD:

Leflunomide was obtained from Torrent pharmaceuticals, Ahmedabad. HPMC, EC, DBP was purchased from loba chemie. All the chemicals are of analytical grades.

Transdermal patches of Leflunomide were prepared by a solvent casting technique. At different concentrations, the polymers HPMC EC were employed in the fabrication of transdermal patches as rate-controlling polymers. The weighed polymers (HPMC and EC) were then dissolved in 15mL ethanol separately. The solution was continuously stirred for a time period of 30 min using a magnetic stirrer set at 500 rpm. Transfer the HPMC solution into EC solution and add 1ml of DBP to the mixture. A specified amount of Leflunomide was added to the polymer solution with continuous stirring for uniform mixing and distribution.

A magnetic stirrer (500 rpm) was employed for the final dispersion process. In order to remove the entrapped air bubbles, the solution was placed in a Sonicator for 15 min and then poured into glass petri dishes. The glass petri dishes were placed in an oven at 40 °C for 12 h. The dried patches were removed from the glass petri dishes carefully. The patches were folded into aluminum foil and placed in a desiccator until further study.

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Formulation Code	Drug (in mg)	HPMC (in mg)	EC (in mg)	DBP (in ml)
1	20	200	150	0.5
2	20	200	150	1.5
3	20	400	150	0.5
4	20	400	50	0.5
5	20	200	50	0.5
6	20	200	50	1.5
7	20	300	100	1

Evaluation of patches

Folding endurance: The patches were sliced into required dimension (4 cm X 2 cm). Then they were folded at the same location repeatedly until it breaks. The number of times the film is folded without cracking or breaking is calculated.[3]

Tensile strength: The strip was clamped at the static end and was attached to the movable rod on a railing with the help of a clip. The weights were gradually added to the pan to increase the pull force till the film was cut. The elongation was determined simultaneously by noting the distance travelled by the pointer, before break of the film, on the graph paper. The weight required to break the film was noted as the break force.

The tensile strength was calculated using Allen's formula

$$\text{Tensile Strength} = \frac{\text{Break Force}}{a \times b} \times \frac{(1 + \Delta L)}{L}$$

Thickness: The thickness was measured at six different places using a Vernier Caliper and the mean Value was calculated.

Drug content: A formulated patch having 15.21 cm2 area was cut into small pieces and transferred into a graduated glass stoppered flask, which contained 100 mL of mixture of chloroform and methanol in the ratio of 1:1, maintained at 45-50˚C. It was closed and shaked vigorously for 24 hours period in a shaker. The solution was filtered and the amount of drug present in the filterate was determined by using Shimadzu uv-1700 spectrophotometer at 241 nm. Similarly, blank solution was prepared using a dummy patch. The procedure was carried out in duplicate to determine the drug content. The following procedure was carried out induplicate to determine the drug content.

Percentage moisture uptake: The weighed films kept in a desiccator at room temperature for 24 hours was taken out and exposed to 75% relative humidity (a saturated solution of sodium chloride) in a desiccator until a constant weight for the film was calculated as the difference between final and initial weight with respect to initial weight.

Percentage moisture uptake = (final weight- initial weight)/ final weight

Swelling index: The swelling index of the patches was determined by immersing pre-weighed patch of size 2 × 2 cm2 in 50 mL water. The strips were taken out carefully at 5,10,30,and 60 minutes intervals, blotted with filter paper, and weighed accurately; the average swelling index of all patches was determined. [4]

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Percentage moisture content: Moisture content can influence the mechanical strength and drug release behaviour of the transdermal therapeutic systems and therefore, in the present study determination of the moisture of the formulated patch was estimated by keeping the patch under vacuum desiccation until constant weights were obtained. The percentage moisture content of the patch was calculated by the following formula.[5]

Percentage moisture content = (Initial weight- Final weight) /Initial weight

***In vitro* drug release studies:** The prepared films were attached onto the dialysis membrane and further adhered to the Franz diffusion cell. Consequently, the surface from where the drug permeates having 0.785 cm2 area was facing towards receptor compartment. The receptor compartment contains phosphate buffer of 7.4 pH maintained at 37 ℃ which is magnetically swirled. At programmed timings, 5 mL samples were taken out and equal volume of fresh buffer was replaced. The samples withdrawn were diluted with ethanol and then analysed spectrophotometrically at 260 nm.

RESULTS AND DISCUSSION:

Formulation with high concentration of HPMC, as the glass transition temperature decreases, increase in tensile strength occurs. literature reveals that Ethyle cellulose increases the toughness of film but not elongation which in turn is improved by increase in the concentration of plasticizer and hydrophilic polymer to some extent. DBP is also reported in literature to increase the drug release by modifying the hydrophilicity of the film. Percent drug release ranged between 66.7% and 86.4% in patches containing DBP while maximum drug content was found to be 98.9 of F7 formulation. It was revealed that the release of drug decreases as concentration of EC (hydrophobic polymer) increases. Swelling index ranged between 21.4 and 24.8 in patches. As the concentration of HPMC increases, i.e., hydrophilic part of polymer blend, swelling properties of the patch were augmented. The formulation number 3 containing high concentration of HPMC i.e., 400mg shows high swelling index.

Folding endurance ranges from 11.3 to 13.6, while results of tensile strength shows 0.348 to 0.380. Thickness of formulations found to be 0.17-0.19.

Formu-lation Code	Drug Release	Swelling Index	Folding endurance ± SD	Tensile strength ± SD	Thickness ± SD	Drug content ± SD	% Moisture content ± SD	% Moisture uptake ± SD
1	69.7	24.1 ± 0.4	12.2 ± 0.5	0.354 ± 0.03	0.17± 0.3	97.3 ± 0.3	2.5 ± 0.5	21.32 ± 0.5
2	70.9	22.7 ± 0.6	13.6± 0.7	0.356 ± 0.05	0.18± 0.2	96.4 ± 0.7	2.3 ± 0.3	18.52 ± 0.4
3	73.4	24.8 ± 0.4	11.6 ± 0.9	0.359 ± 0.03	0.19± 0.3	96.9 ± 0.3	3.8 ± 0.7	16.84 ± 0.3
4	75.4	22.6 ± 0.6	13.4± 1.0	0.348 ± 0.07	0.18± 0.2	95.9 ± 0.7	2.5 ± 0.5	18.68 ± 0.4
5	78.8	21.8 ± 0.4	11.5 ± 0.5	0.369 ± 0.03	0.17± 0.2	96.9 ± 0.7	3.5 ± 0.7	21.48 ± 0.4
6	78.5	21.4 ± 0.8	11.4 ± 0.3	0.380 ± 0.05	0.19± 0.3	99.5 ± 0.5	3.8 ± 0.4	21.56 ± 0.4
7	86.4	24.1 ± 0.6	11.3 ± 0.2	0.367 ± 0.03	0.18± 0.2	98.9 ± 0.3	2.6 ± 0.5	18.31 ± 0.5

CONCLUSION:

Formulation F7 was found to be best based on drug content and drug release. Topically applied leflunomide can be delivered through topical route allowing better compliance in rheumatoid arthritis patients by

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avoiding leflunomide's side effects when given orally.

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