NATURALISTA CAMPANO
ISSN: 1827-7160
Volume 28 Issue 1, 2024

Formulation, Optimization, and Characterization of Transdermal Patches Leflunomide by Quality by Design Approach

Agrawal Rashi[1*], Dr. Azharuddin[2]

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

Abstract: Dyspepsia, nausea, abdominal pain, and oral ulceration are the most common side effects of Leflunomide. Transdermal patches reduce the risk of first-pass metabolism and improve drug penetration through the skin. Leflunomide can be delivered more efficiently, resulting in a higher drug concentration at the site of action. The formulation's goal is to make sure that the drug stays on the inflamed tissue for a long time so that it can work better. Transdermal patches were formulated using Design expert software following Box Behnken design. HPMC and EC were selected as hydrophilic and hydrophobic polymers. DBP was used as permeation enhancer. Swelling index and *in-vitro* drug release were selected as evaluation response.

Keywords: Arthritis, leflunomide, transdermal patches, HPMC, EC, permeation enhancer.

1. Introduction

Rheumatoid joint inflammation (RA) is an ongoing incendiary joint illness. One of the more recent oral medications, leflunomide, is a DMARD (disease-modifying antirheumatic drug). Leflunomide is a selective inhibitor of de novo pyrimidine synthesis, which sets it apart from other DMARDs currently in use.[1] Leflunomide improved primary and secondary outcome measures with a satisfactory safety profile in phase II and III clinical trials of active rheumatoid arthritis.[2] Oral administration of leflunomide can cause diarrhea, indigestion, stomach pain, and other side effects. Effective plan kills the gastrointestinal related poison levels related with oral organization. Leflunomide transdermal patches were developed and tested for safety and efficacy. This study plans to get sustained release Leflunomide transdermal patches.

2. 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.
Using a solvent casting method, Leflunomide transdermal patches were prepared. The polymers HPMC EC were utilized as rate-controlling polymers in the formulation of transdermal patches at various concentrations. The weighed polymers, HPMC and EC, were then separately dissolved in 15 millilitres of ethanol. A 500-rpm speed at magnetic stirrer was used to continuously stir the solution for 30 minutes. Add 1 millilitre of DBP to the mixture after transferring the HPMC solution into the EC solution. To ensure uniform mixing and distribution, Leflunomide added to the polymer solution and was continuously stirred. For the final dispersion step, a 500-rpm magnetic stirrer was used. To eliminate the captured air bubbles, the arrangement was put in a Sonicator for 15 min and afterward filled glass petri dishes. For 12 hours, the glass petri dishes were baked at 40 °C. The glass petri dishes with the dried patches were carefully removed. For the time being, the patches were dried out in a desiccator after being folded into aluminium foil. [3]

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]
***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. [5]

Quality by Design: Input variables and responses, design of experiment, carrying out experiment along with statistical analysis and formulation optimization are the critical parameters of statistical design. Collective impact of process variables i.e. concentration of polymers; HPMC and EC along with DBP on percent elongation and drug release; dependent variables were analysed by Box Behnken design.

3. Results and Discussion:

Factors

Factor	Name	Units	Type	Minimum	Maximum	Coded Low	Coded High	Mean	Std. Dev.
A	HPMC	mg	Numeric	131.82	468.18	-1 ↔ 200.00	+1 ↔ 400.00	300.00	92.39
B	EC	mg	Numeric	15.91	184.09	-1 ↔ 50.00	+1 ↔ 150.00	100.00	46.19

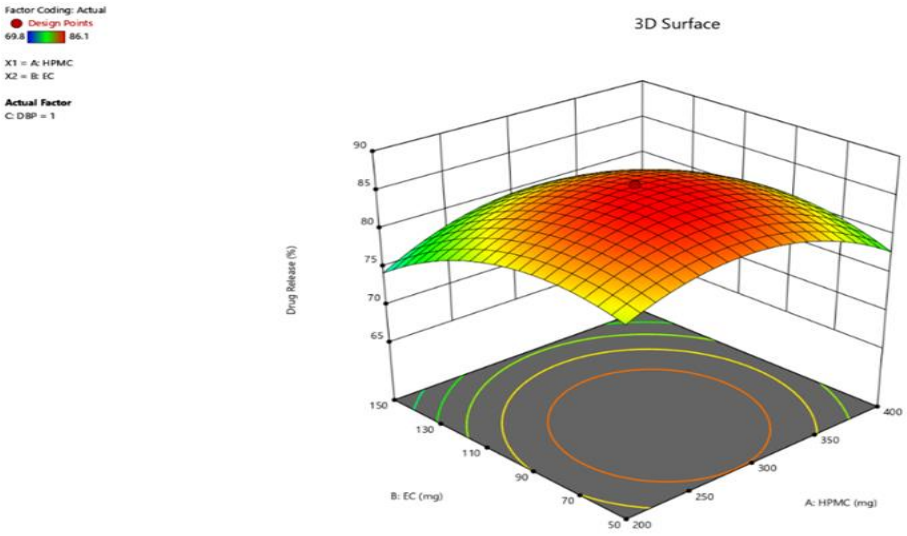
Run	Factor A:HPMC (in mg)	Factor 2 B:EC (in mg)	Factor 3 C:DBP (in ml)	Response1 Drug Release	Response2 Swelling Index
1	468.179	100	1	71.3	23.2 ± 0.5
2	200	50	0.5	78.8	21.8 ± 0.4
3	300	184.09	1	69.8	24.3 ± 0.2
4	400	150	0.5	73.4	25.4 ± 0.4
5	300	100	1	86.1	24.1 ± 0.6
6	300	100	1.8409	68.9	24.3 ± 0.4
7	300	100	1	86.1	24.1 ± 0.6
8	300	15.9104	1	77.4	20.6 ± 1.7
9	200	50	1.5	78.5	21.4 ± 0.8
10	400	50	0.5	75.4	22.6 ± 0.6
11	300	100	0.159104	65.9	23.2 ± 1.5
12	200	150	0.5	69.7	24.1 ± 0.4
13	200	150	1.5	70.9	22.7 ± 0.6
14	400	50	1.5	72.3	25.3 ± 0.7
15	400	150	1.5	73.2	24.4 ± 0.5
16	131.821	100	1	63.9	21.2 ± 0.7
17	300	100	1	86.1	24.1 ± 0.6

C	DBP	ml	Numeric	0.1591	1.84	-1 ↔ 0.50	+1 ↔ 1.50	1.00	0.4619

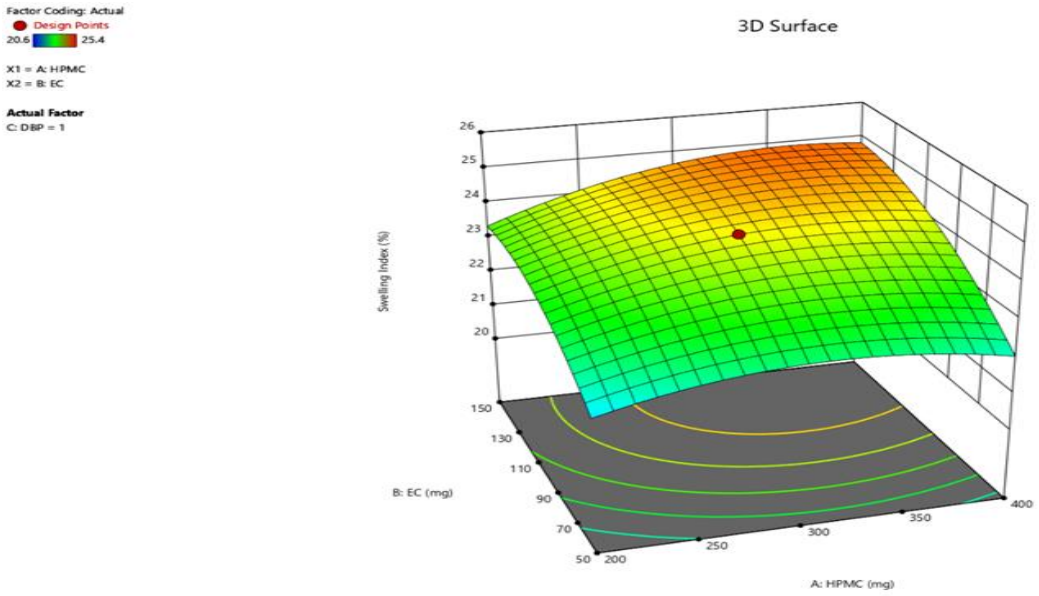
Responses

Response	Name	Units	Observations	Analysis	Minimum	Maximum	Mean	Std. Dev.	Ratio	Transform	Model
R1	Drug Release	%	17	Polynomial	69.8	86.1	75.54	5.58	1.23	None	Quadratic
R2	Swelling Index	%	17	Polynomial	20.6	25.4	23.1	1.39	1.23	None	Quadratic

Drug Release= 26.29112+ 0.249316HPMC+0.179892EC + 32.99982DBP + 0.000247HPMC*EC-0.00325 HPMC*DBP+0.0235 EC*DBP- 0.00046HPMC^2-0.0016EC^2-17.7209DBP^2



Swelling Index = 13.34484 +0.031087 HPMC+ 0.075383 EC+ 1.73076 DBP + 0.000056 HPMC * EC + 0.00365 HPMC * DBP - 0.0223 EC * DBP - 0.00006 HPMC^2 - 0.00024 EC^2 - 0.56474 DBP^2



Solution Found

Factor	Name	Level	Low Level	High Level	Std. Dev.	Coding
A	HPMC	202.54	200.00	400.00	0.4239	Actual
B	EC	96.36	50.00	150.00	0.4173	Actual
C	DBP	1.07	0.5000	1.50	0.2356	Actual

Optimum Formula Prediction and Verification

The desirability value is used as an important indicator in determining the optimum mixture. A desirability value close to 1 signifies closeness to the predicted value. The optimum formula is obtained after the analysis of the suggested model. The optimum formula is obtained by determining each component's priority level, either the independent variable as a factor or response. The model obtained from the factorial design experiment was used to predict an optimum mixture composition in the process of Leflunomide patch formulation. The optimum polymer mixture consists of a HPMC concentration of 328.84% and 109.9% EC with a desirability value of 0.890.

Optimized formula

HPMC	EC	DBP
328.843	109.914	1.0051

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 analyzed spectrophotometrically at 416 nm. The average was determined. The swelling index of the optimised patches were carried out 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.

Results of drug release and swelling index

Drug Release	Swelling Index
85.727	24.322

85.1	24.593
84.989	24.877

4. Conclusion:

The developed formulation of Leflunomide is expected to improve the patient compliance, form better dosage regimen and provide maintenance therapy to patients suffering from inflammation and allergy. These promising results showed the feasibility of delivering Leflunomide through transdermal patch. The developed transdermal patches of Leflunomide may prove to be a better alternative to conventional dosage forms in allergy.

5. References

1. Rozman B. Clinical pharmacokinetics of leflunomide. Clinical pharmacokinetics. 2002 May; 41:421-30.
2. Breedveld FC, Dayer JM. Leflunomide: mode of action in the treatment of rheumatoid arthritis. Annals of the rheumatic diseases. 2000 Nov 1;59(11):841-9.
3. Prabhakara P, Koland M, Vijaynarayana K, Harish NM, Shankar G, Ahmed MG, Narayana C, Satyanarayana D. Preparation and evaluation of Transdermal patches of Papaverine hydrochloride. Int J Res Pharm Sci. 2010;1(3):259-66.
4. Al Hanbali OA, Khan HM, Sarfraz M, Arafat M, Ijaz S, Hameed A. Transdermal patches: Design and current approaches to painless drug delivery. Acta Pharmaceutica. 2019 Jun 30;69(2):197-215.
5. Kriplani P, Guarve K, Baghel US. Formulation optimization and characterization of transdermal film of curcumin by response surface methodology. Chinese Herbal Medicines. 2021 Apr 1;13(2):274-85.