



Optimization of Transdermal Patches Formulation of Leflunomide for Drug Release and Swelling Index Using Box-Behnken Statistical Design

Rashi Agrawal^{*1}, Deepak Birla²

^{*1} Research Scholars, Research scholars, Sunrise University, Alwar, Rajasthan

²Professor, Sunrise University, Alwar, Rajasthan

Abstract:

The study investigates the effects of varying concentrations of Hydroxypropyl Methylcellulose (HPMC), Ethylcellulose (EC), and Dibutyl Phthalate (DBP) on the drug release profile and swelling index of film formulations. A Box-Behnken design was employed to evaluate the interaction of these formulation factors. The results indicate that the concentration of HPMC, EC, and DBP significantly influences both the mechanical properties and the drug release characteristics of the films. These findings provide insight into the optimization of film formulations for controlled drug delivery applications.

Keywords: Box-Behnken design, HPMC, EC, DBP, drug release, swelling index, film formulation.

1. Introduction

Controlled drug delivery systems, particularly in the form of films, provide sustained and targeted release of therapeutic agents. The selection of polymeric materials, such as Hydroxypropyl Methylcellulose (HPMC) and Ethylcellulose (EC), and the incorporation of permeation enhancers like Dibutyl Phthalate (DBP) can significantly influence the drug release rate and the mechanical properties of the film.

In this study, the formulation of drug-loaded films was optimized using a Box-Behnken statistical design to investigate the impact of HPMC, EC, and DBP on two key responses: drug release and swelling index. By understanding these relationships, the study aims to develop a formulation that ensures effective and controlled drug delivery.

2. Materials and Methods

2.1 Materials

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

2.2 Formulation Preparation



Films were prepared using solvent casting. The required amounts of HPMC, EC, and DBP were dissolved in a suitable solvent, followed by the addition of the active pharmaceutical ingredient. The mixture was cast into a mold and allowed to dry at room temperature.

2.3 Box-Behnken Design

A Box-Behnken statistical design was employed to examine the effect of three formulation factors (HPMC concentration, EC concentration, and DBP concentration) on two responses: drug release and swelling index. The design consisted of 17 experimental runs, with three factors at three levels each.

The experimental factors and their respective levels are as follows:

Factor	Low Level (A)	Medium Level (B)	High Level (C)
HPMC (mg)	200	300	400
EC (mg)	50	100	150
DBP (ml)	0.5	1	1.5

2.4 Evaluation of Film Properties

Drug Release: The drug release rate was measured using a USP dissolution apparatus. The percentage of drug released at different time intervals was determined and analyzed.

Swelling Index: The films were immersed in phosphate buffer solution, and the swelling index was calculated by measuring the increase in film weight over time.

3. Results and Discussion

3.1 Effect of Formulation Factors on Drug Release

The drug release profiles from the films showed significant variations depending on the concentrations of HPMC, EC, and DBP. From the data (see Table 1), the following observations can be made:

- HPMC concentration played a crucial role in controlling drug release. Higher HPMC concentrations (e.g., 400 mg) tended to slow the drug release, likely due to the increased viscosity and slower diffusion of the drug through the film matrix.
- EC concentration also impacted the release rate. Films containing higher levels of EC (150 mg) exhibited slower drug release, possibly due to the more rigid structure of the EC polymer.
- DBP concentration affected the release rate by acting as a plasticizer, which increased the film flexibility and promoted faster drug release at higher concentrations (e.g., 1.5 ml).



A regression analysis of the data showed significant interactions between these factors, with the optimal formulation yielding a balanced release profile.

3.2 Effect of Formulation Factors on Swelling Index

Swelling index is a critical parameter that influences the mechanical strength and bioavailability of drug-loaded films. The swelling index results indicated:

- HPMC contributed to higher swelling indices due to its hydrophilic nature, which enhanced water uptake.
- EC, being hydrophobic, reduced the swelling tendency, especially at higher concentrations.
- DBP at higher concentrations (1.5 ml) increased the swelling index due to its plasticizing effect, which made the film more flexible.

Films with balanced HPMC and EC concentrations, in combination with optimal DBP levels, exhibited favorable swelling properties for controlled drug release.

Run	Factor 1 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



3.3 Statistical Analysis and Optimization

Using the Box-Behnken design, a second-order polynomial model was developed to predict the response variables. Analysis of variance (ANOVA) was performed, and significant terms were identified. The optimal levels for HPMC, EC, and DBP were determined to maximize drug release while maintaining an acceptable swelling index.

ANOVA for Quadratic model

Response 1: Drug Release

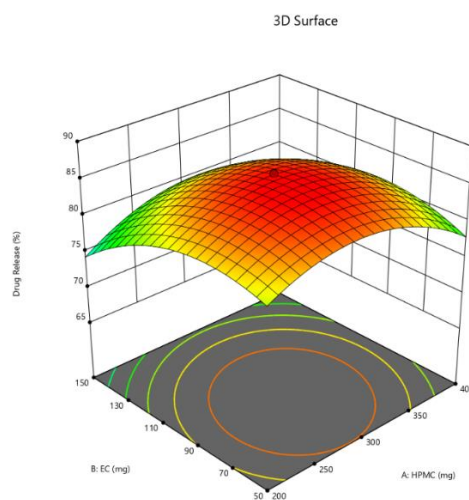
Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	485.88	9	53.99	32.31	< 0.0001	significant
A-HPMC	1.66	1	1.66	0.9924	0.3523	
B-EC	62.65	1	62.65	37.49	0.0005	
C-DBP	3.89	1	3.89	2.33	0.1710	
AB	12.25	1	12.25	7.33	0.0303	
AC	0.2112	1	0.2112	0.1264	0.7326	
BC	2.76	1	2.76	1.65	0.2395	
A ²	235.62	1	235.62	141.00	< 0.0001	
B ²	180.91	1	180.91	108.27	< 0.0001	
C ²	221.26	1	221.26	132.41	< 0.0001	
Residual	11.70	7	1.67			
Lack of Fit	11.70	5	2.34			Non-significant
Pure Error	0.0000	2	0.0000			
Cor Total	497.58	16				

Final Equation in Terms of Actual Factors

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



Factor Coding: Actual
 Design Points
 69.4 96.1
 X1 = A: HPMC
 X2 = B: EC
 Actual Factor
 C: DBP = 1



Response 2: Swelling Index

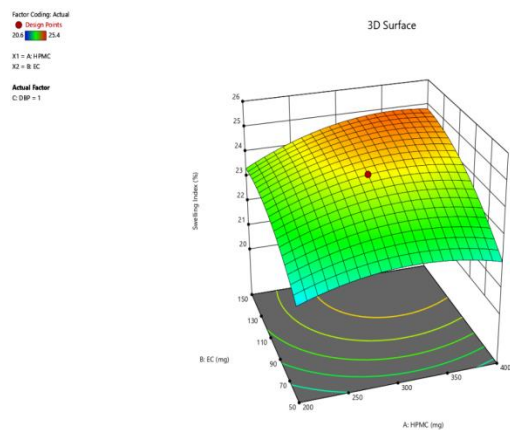
Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	30.53	9	3.39	140.67	< 0.0001	significant
A-HPMC	2.83	1	2.83	117.27	< 0.0001	
B-EC	16.91	1	16.91	701.04	< 0.0001	
C-DBP	0.9726	1	0.9726	40.33	0.0004	
AB	0.6384	1	0.6384	26.48	0.0013	
AC	0.2664	1	0.2664	11.05	0.0127	
BC	2.49	1	2.49	103.11	< 0.0001	
A ²	4.02	1	4.02	166.77	< 0.0001	
B ²	4.02	1	4.02	166.77	< 0.0001	
C ²	0.2247	1	0.2247	9.32	0.0185	
Residual	0.1688	7	0.0241			
Lack of Fit	0.1688	5	0.0338			Non-significant
Pure Error	0.0000	2	0.0000			



Cor Total	30.70	16				
-----------	-------	----	--	--	--	--

Final Equation in Terms of Actual Factors

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 HPMC² - 0.00024 EC² - 0.56474 DBP²



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 a key indicator for identifying the optimal mixture. A desirability value nearing 1 indicates that the result is close to the predicted value. The optimal formula is derived from analyzing the proposed model. This involves determining the priority level of each component, whether as an independent variable, factor, or response. Using the model from the factorial design experiment, the optimum mixture composition for the Leflunomide patch formulation was predicted. The ideal polymer mixture includes 328.84% HPMC and 109.9% EC, with a desirability value of 0.890.



Solution 1 of 100 Response	Predict ed Mean	Predict ed Median	Observed	Std Dev	SE Mean	95% CI low for Mean	95% CI high for Mean	95% TI low for 99% Pop	95% TI high for 99% Pop
Drug Release	82.0592	82.0592		1.2926 8	0.66756 3	80.48 06	83.63 77	74.81 04	89.30 79
Swelling Index	23.0362	23.0362		0.1552 88	0.08019 36	22.84 66	23.22 59	22.16 55	23.90 7

Optimized formula #1

HPMC	EC	DBP
328.843	109.914	1.0051

Drug Release	Swelling Index
85.727	24.322
85.1	24.593
84.989	24.877

4. Conclusion

The study demonstrated the effectiveness of a Box-Behnken statistical design in optimizing the formulation of leflunomide-loaded Transdermal patches. The concentration of HPMC, EC, and DBP significantly influenced both the drug release and swelling index. By carefully adjusting these parameters, an optimal formulation was achieved, providing a basis for further research in controlled drug delivery systems.

References

1. Shah S. Transdermal Drug Delivery Technology Revisited Recent advances: Pharm info net. 2008 March; 6(5): 98-106.
2. Joseph S D. Transdermal Patches: An Innovative Drug Delivery System That Has Raised Serious Safety Concerns. News Inferno.2006.
3. Lionberger R., Lee S., Raw A., Quality by design: concepts of ANDAs.2017



4. Mohtashamian S., Bodedohi S., Preparation and optimization of self-assembled chondroitin sulfate-nisin nanogel based on quality by design concept.2018.
5. Mamatha, T., Rao, V. J., Mukkanti, K., & Ramesh, G. (2010). Development of matrix type transdermal patches of lercanidipine hydrochloride: Physicochemical and in-vitro characterization. *Daru*, 18(1), 9–16.
6. Munoz, M. D., Castan, H., Ruiz, M. A., & Morales, M. E. (2017). Design, development and characterization of transdermal patch of methadone. *Journal of Drug Delivery Science and Technology*, 42, 255–260.
7. Rajesh, N., Siddaramaiah, H., & Gowda, D. V. (2010). Formulation and evaluation of biopolymer based transdermal drug delivery. *International Journal of Pharmacy and Pharmaceutical Sciences*, 2, 142–147.