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Research Article

Design and Development of Aceclofenac Transdermal Patch by Applying CCRD-RSM Methodology

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Abstract

Aceclofenac, a non-steroidal anti-inflammatory agent is frequently prescribed for the long term treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis.Aceclofenac transdermal patch were fabricated by solvent evaporation technique on mercury substrate and Centre composite rotable design response surface model (CCRD-RSM) was employed; three factors such as HPMC, EC concentration and Glycerine concentration were used. Optimised patch (F10) had drug content (%) was 99.88 ± 0.12 and % DR was (98.89 ± 0.15) respectively. In-vitro diffusion studies revealed that Aceclofenac transdermal patch (98.89 ± 0.15) had a significantly higher release compared to plain drug suspension (PDS) (52.23 ± 0.26). The corresponding plot of (log cumulative percent drug release vs log time) of the Korsmeyer-Peppa's equation release exponent (n) was found to be 0.83. It was found that the in-vitro drug release of transdermal patch containing Aceclofenac explained by First order model of Anomalous Non Fickian diffusion mechanism.This design, the best models such as linear model can be selected due to the analysis of variance (ANOVA) F-value and P value < 0.05 which is considered to be statistically significant.Response surface model (RSM) was used to determine interaction pattern of independent and dependent variables. All concentrations of independent variables shows significant effect on dependent variables.

Keywords: Aceclofenac, transdermal patch, CCRD-RSM, in vitro release, Anomalous.

Introduction

Aceclofenac is a non-steroidal anti-inflammatory drug (NSAIDs) widely used clinically to reduce inflammation and pain in conditions such as rheumatoid arthritis, menstrual pain, dysmenorrheal, fever, osteoarthritis or acute injury. It has a potent anti-inflammatory effect, but it does not penetrate well through skin and cannot reach the effective concentration at the site of action after transdermal application. For this reason, we wanted to suggest new, alternative dosage forms for transdermal application of Aceclofenac [1]. The objective of present study was conducted to develop a transdermal patch of Aceclofenac using hydroxyl propyl methylcellulose (HPMC), Ethyl cellulose (EC), Glycerine. Transdermal patch is prepared by solvent evaporation technique on mercury substrate method by usingCentre composite rotable design response surface model (CCRD-RSM). This design, the best models such as linear model can be selected due to the analysis of variance (ANOVA) F-value and P value < 0.05 which is considered to be statistically significant. The transdermal patch were evaluated for thickness, drug content, folding endurance and moisture content and in vitro drug release.In vitro drug release study explained by First order model of Anomalous Non Fickian diffusion mechanism. Polynomial Equation shows the relationship between independent variables and response variables such as drug content (X) and % DR (Y) respectively. The aim of present investigation was to develop Aceclofenac-transdermal patch by applying CCRD-RSM methodology [2].

Material and Methods

Materials

Aceclofenacwas obtained from obtained from Loba Chemie Ltd. (Mumbai, India). Hydroxyl propyl methyl cellulose (HPMC), Ethyl cellulose (EC), Glycerine was obtained from obtained from Loba Chemie Ltd. (Mumbai, India). All other reagents used were of analytical grade.

Methods

Experimental Design

To design the Aceclofenac transdermal patch, Preliminary experiments revealed that the independent variables like Hydroxyl propyl methyl cellulose (HPMC) concentration (A), Ethyl cellulose (EC) concentration (B), Glycerine (C) during preparation, were the main factors that affected the dependent variables such as, Drug content and % Drug release (% DR). CCRD–RSM (Design-Expert software, version 7, Stat-Ease, Inc., Minneapolis, Minnesota, USA) was applied to systemically investigate the influence of these three decisive independent variables on two dependent variables of the patch. All independent, coded and actual values of the variables of CCRD-RSM are given in (Table1). This design, the best models such as linear model can be selected due to the analysis of variance (ANOVA) F-value and P-value < 0.05 which is considered to be statistically significant[3].

Preparation of Transdermal Patch

The transdermal patch was prepared by solvent evaporation technique on mercury substrate. Polymer solution containg Aceclofenac (50 mg), HPMC (200 mg) and EC (125 mg), Glycerine (3 mL) was prepared in Methanol and chloroform (Q. S.). The solution was poured on glass rings placed on mercury surface and allowed to dry in air for 24 h. Circular patches of 2 cm diameter (3.14 cm2) were cut from semi-dried patches and placed in desiccator with 0% Relative Humidity (RH).

Drug Content

Aceclofenac from patch was extracted by dissolving small portion of patch in methanol. Aceclofenac content in the methanolic extract was analyzed spectrophotometrically (UV 1700, Shimadzu, Japan) at 277 nm [4].

Thickness

The thickness of Aceclofenac loaded patches was determine at three different places using a micrometre and mean values were calculated (mean ± SD, n = 3) [5].

Table 1: Independent variables along with their code, levels and respective drug content (%) and % DR (%) of different batches of Aceclofenac transdermal patch (n = 3). These results are mean ±standard deviation

Batch	HPMC (mg) (A)	EC (mg) (B)	Glycerine (mL) (C)	% Drug content (X)	% DR (Y)
1	200	125	3	99.88	98.89
2	150	100	1	99.44	98.55
3	200	125	3	99.88	98.55
4	250	150	1	99.55	98.23
5	200	125	0.363585661	99.55	98.77
6	200	125	3	99.88	98.54
7	200	125	6.363585661	97.44	96.41
8	250	150	5	98.44	97.55
9	200	125	3	99.88	98.89
10	200	125	3	99.88	98.89
11	250	100	5	98.22	97.85
12	150	150	5	99.33	98.52
13	115.9103585	125	3	99.55	98.24
14	150	100	5	99.22	97.52
15	284.0896415	125	3	98.55	97.26
16	200	125	3	99.88	98.89
17	150	150	1	99.74	98.41
18	200	82.9551792	3	99.22	98.23
19	250	100	1	99.55	98.46
20	200	167.044821	3	99.85	98.46

A = HPMC concentration in mg (high level-250, low level-150); B = EC concentration in mg (high level-150, low level-100) and C = Glycerine in mL (high level-5, low level-1)

Folding endurance

This was determined by folding capability as well as braking of patch. Many times the patchwas folded at the same place without breaking/cracking gave the value of folding endurance.

Percentage of moisture content

Patch was weighed individually and kept in a desiccators containing activated silica at room temperature for 24 h. Individual patch was weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight [6].

***In vitro* skin permeation studies**

In vitro diffusion study of Aceclofenac transdermal patch of optimized batch (10) is carried out by diffusion cell apparatus (Electrolab), Franz diffusion cell having 2.0 cm diameter and 25 ml capacity. Dialysis membrane (Himedia) used as diffusion membrane. Diffusion cell was filled with pH 5.4 phosphate buffer and dialysis membrane was mounted on cell. The temperature was maintained at 37 °C and patch is placedon donor chamber. Samples were periodically withdrawn from the receptor compartment for next 4 h and replaced with the same amount of fresh pH 5.4 phosphate buffer, and assayed by a UV at 277 nm [7].

Model fitting to drug release profile

To study the release kinetics of optimized patch (10), data obtained from in- vitro drug release studies were plotted in various kinetic models: zero order as cumulative amount of drug released vs. time, first order as log cumulative percentage of drug remaining vs. time, and Higuchi's model as cumulative percentage of drug released vs. square root of time. In Zero order: $C = K_0 t$ (K_0 is the zero-order rate constant expressed in units of concentration/time and t is the time in minutes. A graph of concentration vs. time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes), First order: $\text{Log } C = \text{Log } C_0 - Kt/2.303$ (C_0 is the initial concentration of drug, Kt is the first order constant and t is the time) andHiguchi:Qt = Kt½Qt is the amount of drug release in time t, K is the kinetic constant and t is the time in minutes) [8].

Mechanism of drug release

To evaluate the mechanism of drug release from Aceclofenac loaded transdermal patch, data for the drug release was plotted in Korsmeyer-Peppas equation as log cumulative percentage of drug released vs. log time. The release exponent n and K value was calculated through the slope of the straight line ($Mt/M\infty = Ktn$).

Results and Discussion

Experimental Design

Responses observed for twenty formulations prepared were fitted to various models using Design-Expert® software 7.0.1. CCRD-RSM methodology offers to investigate a high number of variables at different levels with limited number of experiments. To fit the data, a linear second-order polynomial model was chosen as the best model. Polynomial Equation shows the relationship between independent variables and response variables such as Drug Content (X), % drug release (% DR) (Y) respectively. All values of R2, SD and % coefficient of variation and ANOVA are depicted in (Table 2).

$X = +99.88 - 0.27*A + 0.12*B - 0.48*C.$

$Y = +98.89 - 3.75*A + 2.10*B - 0.22*C.$

Where, X= Drug Content (%), Y = % drug release (% DR), A =Hydroxyl propyl methyl cellulose (HPMC) concentration, B =Ethyl Cellulose (EC)concentration, C =Glycerine concentration.

Table 2: Summary of results of regression analysis for responses X and Y analysis of variance for drug content and % DR.

Parameters	DF	SS	MS	F	P value	R^2	SD	%CV
Drug Content (X)								
model	3	4.39	1.46	5.46	0.0089Significant	0.9996	0.52	0.52
Residual	16	4.29	0.27	-	-	-		
Total	19	8.68	-	-	-	-		
% DR (Y)								
model	3	3.31	1.10	5.46	0.0089Significant	0.9999	0.54	0.55
Residual	16	4.60	0.29	-	-	-		
Total	19	7.91	-	-	-	-		

DF, degrees of freedom; SS, sum of square; MS, mean sum of square; F, Fischer's ratio, p value, Probability value; SD, standard deviation; %CV, Coefficient of variation.

Response surface plots

A response surface plot was important three dimensional surface curves for studying the interaction patterns. Three dimensional response surface plots generated at different levels by the Design-Expert® software. Response surface plot showing effect of concentration HPMC and EC concentration on drug content (E) (Figure 1), response surface plot showing effect of concentration EC and Glycerine concentration on Drug content (F) (Figure 1) and response surface plot showing effect of concentration HPMC and Glycerine concentration on Drug content (G) (Figure 1). Response surface plot showing effect of concentration HPMC and EC concentration on % DR (H) (Figure 2), response surface plot showing effect of concentration EC and Glycerine concentration on % DR (I)(Figure 2) and response surface plot showing effect of concentration HPMC and Glycerine concentration on % DR (J) (Figure 2).

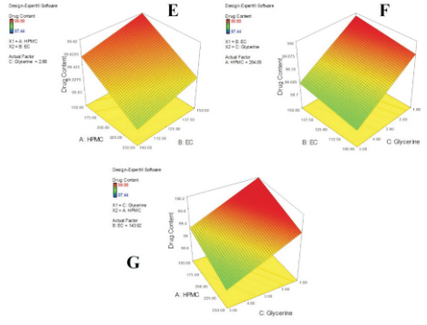

Figure 1: Response surface plots: for HPMC and EC concentration on drug content (E), for EC and Glycerine concentration on drug content (F), for HPMC and Glycerine concentration on drug content (G)

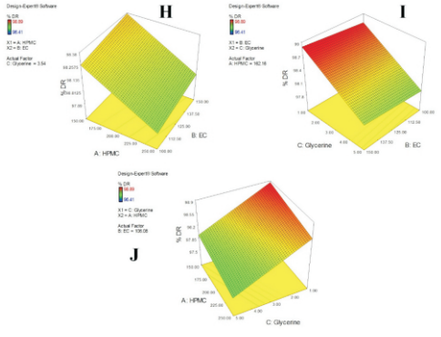

Figure 2: Response surface plots: for HPMC and EC concentration on % DR (H), for EC and Glycerine concentration on % DR (I), for HPMC and Glycerine concentration on % DR (J)

Effect of HPMC (A) and EC (B) concentration on Drug content (%)

In A concentration increases to increase drug content. In B concentration decreases to increase drug content. Concentration of A and B show significant effect on drug content (Figure 3).

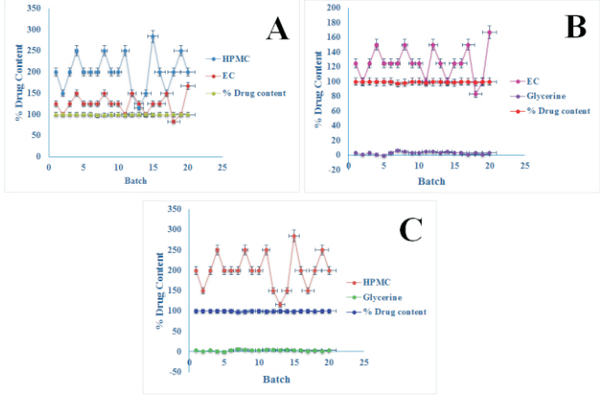

Figure 3: Effect of concentration HPMC and EC concentration on drug content (A), Effect of concentration EC and Glycerine concentration on drug content (B) and Effect of concentration HPMC and Glycerine concentration on drug content (C)

Effect of EC (B) and Glycerine (C) concentration on Drug content (%)

In B concentration increases to decrease drug content. In C concentration was increases to increases drug content. Concentration of B and C shows significant effect on drug content (Figure 3).

Effect of HPMC (A) and Glycerine (C) concentration on Drug content (%)

In A concentration increases to increase drug content. In C concentration increases to increase drug content. Concentration of A and C show significant effect on drug content (Figure 3).

Effect of HPMC (A) and EC (B) concentration on % DR

In A concentration was increases to increases % DR. In B concentration was increases to increases % DR. Concentration of A and B shows significant effect on % DR (Figure 4).

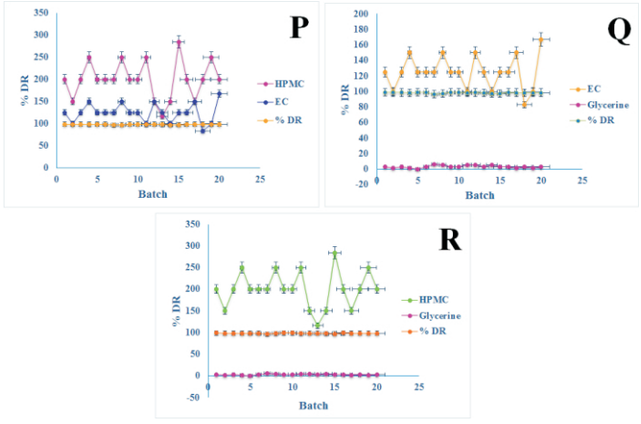

Figure 4: Effect of concentration HPMC and EC concentration on % DR (P), Effect of concentration EC and Glycerine concentration on % DR (Q) and effect of concentration HPMC and Glycerine concentration on % DR (R)

Effect of EC (B) and Glycerine (C) concentration on % DR

In B concentration was increases to increases % DR. In C concentration was increases to decreases % DR. Concentration of B and C shows significant effect on % DR (Figure 4).

Effect of HPMC (A) and Glycerine (C) concentration on % DR

In A concentration was increases to increases % DR. In C concentration was increases to decreases % DR. Concentration of A and C shows significant effect on % DR (Figure 4).

Drug Content (%)

Drug content of optimized batch (10) was found to 99.88 ± 0.12 for Aceclofenac transdermal patch (mean ± SD, n=3).

Thickness, Folding Endurance and Percentage of Moisture Content

The thickness of optimized batch (10) was found to be 116 ± 2.6 µm, which indicate that they are uniform in thickness. Folding endurance test (10) (216 ± 4.23) results indicated that the patches would not break and would maintain their integrity with general skin folding when applied. The moisture content of the prepared patch (10) (1.16 ± 0.12 %) was low, which could help the formulations remain stable and reduce brittleness during long term storage. The moisture uptake of the formulations was also low, which could protect the formulations from microbial contamination and reduce bulkiness.

***In vitro* skin permeation studies**

The release profile of Aceclofenac from optimized batches (10) of transdermal patch (98.89 ± 0.15 %) and plain drug suspension (PDS) (52.23 ± 0.26 %) through the dialysis membrane at pH 5.4 phosphate buffer showed in Figure 5. The release pattern of optimized transdermal patch appears to be fast release of drug as compared to PDS.

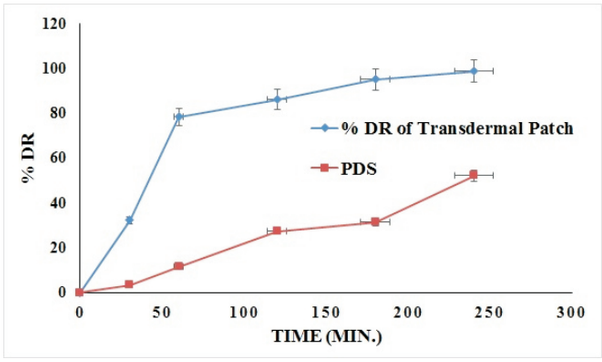

Figure 5: *In vitro* skin permeation studies

Model fitting to drug release profile

The release constant was calculated from the slope of the appropriate plots, and the regression coefficient (R^2) was determined. It was found that the *in-vitro* drug release of patch containing Aceclofenac explained by First order model (the model is concentration dependent) (the concentration was increases absorbance was increases) was best, as the plots showed the highest linearity (R^2 = 0.9999) (Figure 6 and Table 3).

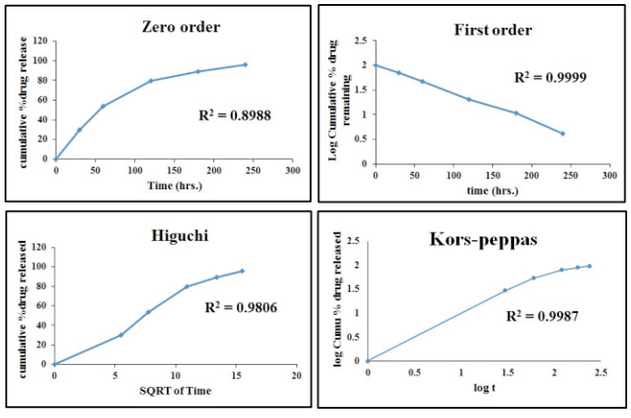

Figure 6: Release kinetics of transdermal patch containing Aceclofenac

Table 3: Model fitting of the release profile of Transdermal Patch

Drug	Optimize batch	Zero order (R^2)	First order (R^2)	Higuchi (R^2)	Korsmeyer peppas	
					R^2	n
Aceclofenac	10	0.8988	0.9999	0.9806	0.9987	0.83

Best fitted model: Anomalous Non Fickian;
Order of release: First order; **Release Mechanism:** Diffusion

Mechanism of drug release

The corresponding plot of (log cumulative percent drug release Vs log time) of the Korsmeyer-Peppa's equation indicated a good linearity of regression coefficient (R^2) 0.9987 for Aceclofenac. The release exponent (n) of Korsmeyer-Peppa's equation was found to be 0.83 shown in Figure 6 and Table 3). The *in-vitro* drug release of transdermal patch containing Aceclofenac explained by First order model of Anomalous Non Fickian diffusion mechanism.

Conclusion

The method of preparation of transdermal patches of Aceclofenac presented in this research work is simple. Aceclofenac loaded Transdermal patch was developed and formulated by using CCRD-RSM methodology. All formulation also showed good physicochemical properties like thickness, drug content, folding endurance and moisture content. The in-vitro release data showed that drug release from the patch formulation have been affected by types of polymer and concentration of polymer. These studies indicated that as the concentration of penetration enhancer increased drug permeation was increased. The in vitro studies revealed a significant increase in release of drug effects as compared with PDS. The release kinetics was also studies to identify the best possible release mechanism of the drug by different types of plot like Zero order plot, Higuchi plot, first order plot, Korsmeyer-Peppa's equation. The finding of this result revealed that the problems of Aceclofenac on oral administration like dissolution rate limited absorption, gastric side effects and first pass metabolism can be overcome by applying Aceclofenac topically in the form of transdermal patch.

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Conflicts of interest

The authors confirm that this article content has no conflict of interest.

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