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COMMUNICATION

Cataplasm-Based Controlled Drug Delivery: Development and Optimization of a Novel Formulation

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ABSTRACT

The objective of the present study was to study the formulation variables involved in the development of a novel plasterlike preparation (cataplasm) and to optimize important formulation variables with an aim to maximize the in vitro release of the drug with minimum lag time. Cataplasm was prepared by dispersing a model drug (ibuprofen), humectant (glycerol), adhesive (Indopol H100®), polymer (Carbopol C934P®) with other formulation ingredients in a beaker with an open-blade impeller. The paste was cast on a nonocclusive backing membrane and dried overnight. The diffusion of the model drug was studied across a cellulosic membrane using Franz's diffusion cells. The amounts of three formulation variables, carbopol (X_1), glycerol (X_2), and indopol (X_3) were studied at three levels, and a face-centered cubic design was used to maximize the flux. An optimization procedure for maximum flux and minimum lag time predicted a flux of 97.22 mcg/cm^2/hr at X_1 (2% w/w), X_2 (11.75% w/w), and X_3 (6% w/w). An experimental patch prepared with the above concentrations yielded a flux of 90.7 mcg/cm^2/hr.

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INTRODUCTION

The incidence of external pain manifestations such as bruises, sprains, muscle pains, arthralgia, frostbite, shoulder pains, and burns is usually concentrated at one or more local site(s) on the body. The use of plasters for injuries (1), peri- and extra-articular rheumatological diseases (2), knee osteoarthritis (3), and localized inflammatory diseases (4) has been reported. A similar preparation, cataplasm, is a consistent pastelike substance containing the drug, a rate-controlling substance with a soothing agent, and an adhesive with nonocclusive backing membrane. The major advantages of a cataplasm patch meant for application at the local site are the combined benefit of local/systemic controlled delivery of drug, ease of application/removal, and reduced side effects. The flux studies of flurbiprofen cataplasm have been reported without the formulation aspects (5).

Ibuprofen, a nonsteroidal anti-inflammatory drug, has a plasma half-life of about 2–3 hr, and it is excreted completely and rapidly. The influence of certain vehicles on the transdermal flux of ibuprofen and the factors affecting the in vitro penetration of ibuprofen through human skin have been reported (6). The focus of the present study was to develop a prototype cataplasm adhesive patch for transdermal delivery of ibuprofen. A three-factor, three-level face-centered cubic design was used to optimize the formulation variables to maximize the flux with minimum lag time. Preliminary experiments provided the levels of the three formulation variables studied: Carbopol C-934P® (X_1), glycerol (X_2), and Indopol H100® (X_3). An orthogonal design was used so that the factor levels were evenly spaced and coded for low, medium, and high settings as −1, 0, and 1, respectively. The independent and dependent variables used in the design with their respective concentrations (%w/w) are shown in Table 1. The randomized experimental runs and the observed responses are shown in Table 2.

Table 1

Variables in the Face-Centered Cubic Design

	Levels (%w/w)		
Independent variables	−1	0	1
Carbopol C934P X_1	2	4	6
Glycerol X_2	8	16	24
Indopol H100 X_3	2	4	6
Dependent variables			
Lag time Y_1			
Cumulative amount released/ cm^2/hr Y_2			

Table 2

Experimental Runs and Observed Responses (Randomized)

	Controlled Factors			Measured Responses	
Run	X_1	X_2	X_3	Y_1	Y_2
1	6	24	2	54.62	47.05
2	4	16	4	61.06	35.44
3	4	16	4	33.56	41.37
4	4	16	4	45.45	35.20
5	4	16	6	14.33	68.93
6	6	8	6	45.27	32.14
7	2	16	4	49.77	86.80
8	2	8	6	33.86	93.23
9	6	24	6	35.80	31.41
10	4	16	2	45.34	40.91
11	2	24	6	43.95	83.64
12	6	16	4	42.84	36.29
13	4	24	4	71.08	49.59
14	4	8	4	61.11	43.00
15	2	8	2	92.98	57.83
16	6	8	2	77.35	27.64
17	2	24	2	35.06	75.79

MATERIALS AND METHODS

Materials

Ibuprofen, Carbopol C-934P NF, and Indopol H100 were gifts from Albemarle and Company, Baton Rouge, LA; B. F. Goodrich Company, Brecksville, OH; and Amoco Chemical Manufacturing Company, Chicago, IL, respectively. Glycerine was obtained from Spectrum Chemical Manufacturing Company, Gardena, CA; colloidal kaolin USP from Whittaker, Clarke, and Daniel, South Plainfield, NJ; titanium dioxide from Warner Jenkinson Company, South Plainfield, NJ; peppermint oil from Ruger Chemical Company, Irvington, NJ; and aluminum sulfate from Mathson, Coleman, and Bell Company, Norwood, OH. Silicon liners Nat 2.0 Pet Silox were a gift from Akrosil (Menesha, WI) and Spectro/por® 3 membranes were purchased from Spectrum Medical Industry, Incorporated, Houston, TX.

Methods

Formulation and Fabrication of Prototype Cataplasm Patches

Carbopol C-934P was dispersed in a mixture of water, glycerol, ibuprofen (5% w/w), and Indopol H100, stirring

at 800–1000 rpm using an open-blade impeller. This mixture was continuously stirred until a gel was formed. The dispersion was neutralized and made viscous by adding a 10% solution of Tris amino® dropwise. Peppermint oil (5% w/w) was added dropwise, following which kaolin was added (2.5% w/w) and mixed uniformly. After obtaining a smooth consistency, aluminum sulfate (10 mg) was added. Stirring was continued until a tacky polymer paste was formed. This was then cast immediately into molds (14.5 cm × 11 cm) containing backing membrane (nonwoven cotton fabric) and air dried for about 24 hr. Several cataplasm patches were obtained by varying the concentration of formulation variables such as glycerol, carbopol, and indopol according to the experimental design described. The concentrations of ibuprofen, kaolin, and aluminum sulfate were kept constant.

In Vitro Release Studies

Franz cells were used for diffusion studies at 37°C. A 1-inch diameter circular patch of cataplasm was cut with scissors and mounted along with a Spectro/por® 3 diffusional barrier between the donor and receiver compartments. The receiver compartment had 20 ml of pH 7.2 phosphate buffer. At predetermined intervals, 1.0 ml of receptor solution was withdrawn (which was replaced immediately with the same volume of pH 7.2 phosphate buffer) for a period of 12 hr. The amount of drug in the sample was analyzed using the high-performance liquid chromatography (HPLC) method described below. The cumulative amount of drug released Q was plotted against time t for all the experimental formulations.

Analytical Method

Ibuprofen was assayed by an HPLC procedure employing a Novapak C_{18}, 15 cm × 3.9 mm column. The HPLC apparatus was fitted with an ultraviolet (UV) detector (Waters, model 484), an ISCO isocratic pump (model 2350), an integrator (Shimadzu CR-501), an ISIS Autosampler, and an autoinjector with a valco valve. The mobile phase was a mixture of 4% chloroacetic acid and methanol in the ratio 38:62. The wavelength selected was 254 nm. The operating conditions were as follows: flow rate 0.75 ml/min, attenuation 5, injection volume 10 µl, detector sensitivity 2 AUFS. Flurbiprofen was used as an internal standard.

RESULTS AND DISCUSSION

A schematic representation of the cataplasm patch is shown in Fig. 1. Aluminum sulfate used in the formulation aids in cross-linking the carbopol polymer for increased viscosity. This cross-linked structure will not dissolve regardless of the solvent (7). The amount of aluminum sulfate added is critical for the formation of the paste. An excess amount leads to dramatic loss in viscosity, whereas a smaller amount does not cross-link the mucilage to form the paste. The tacky paste obtained

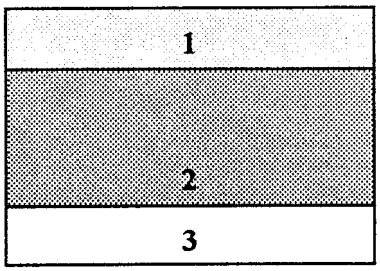

Figure 1. Model cataplasm patch: (1) nonocclusive backing membrane; (2) drug, polymer, and adhesive matrix; (3) silicon protective liner.

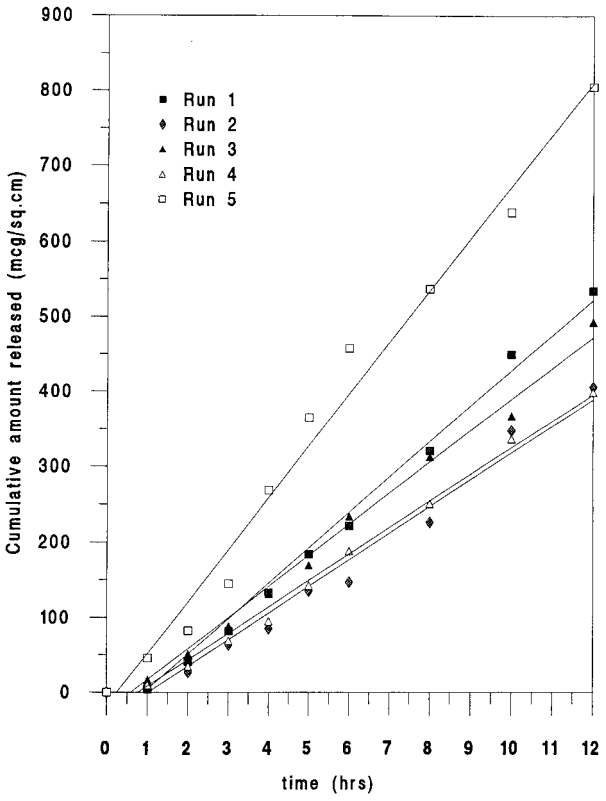

Figure 2. Release profiles of ibuprofen from experimental runs 1–5.

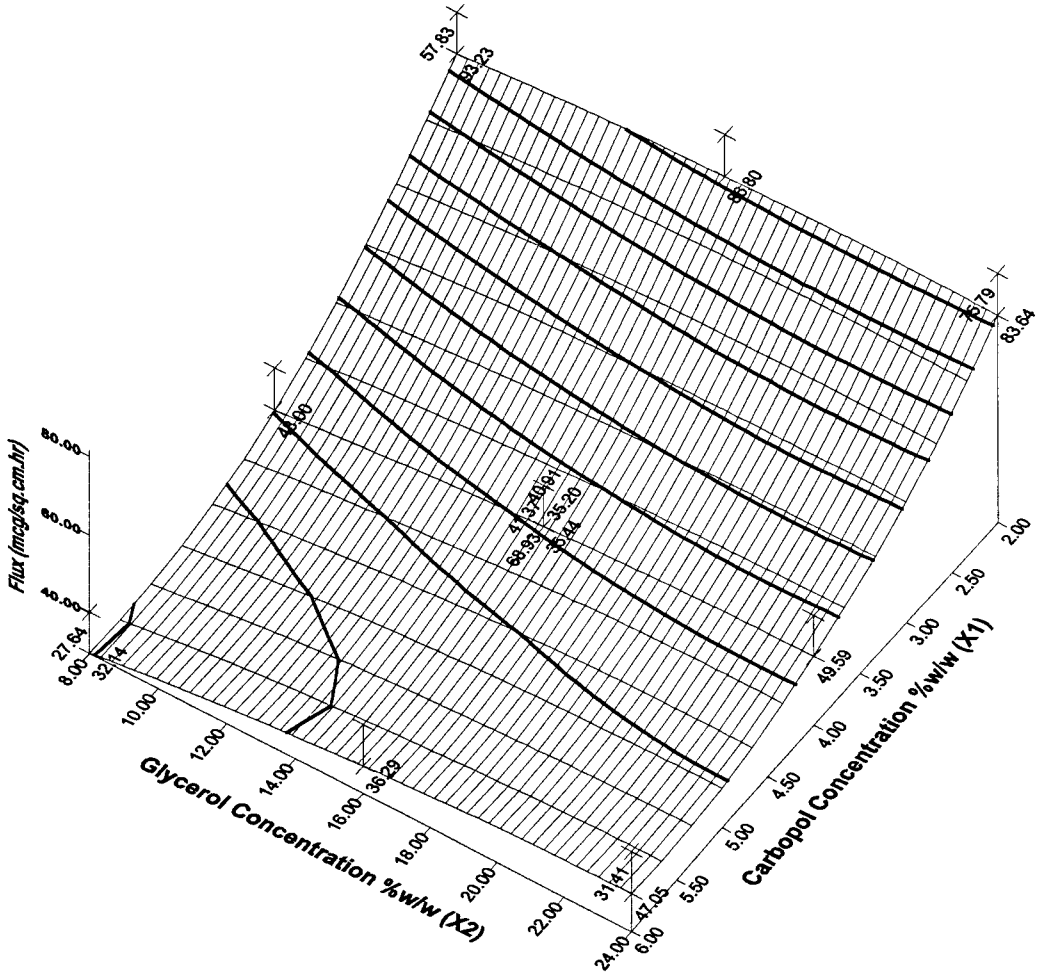

Figure 3. Response surface plot (three dimensional) showing the effect of carbopol concentration X_1 and glycerol concentration X_2 on the flux of ibuprofen.

has good spreading property, and it easily adheres to the nonwoven backing membrane. The diffusion profiles of all the 17 experimental runs were obtained, and as a representative example, Fig. 2 shows the profiles of runs 1–5.

Mathematical relationships between dependent and independent variables were generated using the statistics software X-Stat® 2.0 (8). The polynomial equation generated for the response is

$$Y_2 = 76.05 - 28.81\,X_1 - 3.42\,X_2 + 5.84\,X_3 + 0.08\,X_1X_2 - 0.37\,X_2X_3 - 1.70\,X_1X_3 + 2.90\,X_1^2 - 0.06\,X_2^2 + 1.24\,X_3^2$$

The values of the coefficients X_1–X_3 relate to the effects of these variables on the flux. Coefficients with more than one factor represent the interaction terms, and coefficients with higher order terms indicate the quadratic nature of the relationship.

The relationship between dependent and independent variables and the mixed effect of independent variables on the flux can be elucidated with contour and response surface plots (9). The effect of polymer concentration X_1 and glycerol concentration X_2 on flux Y_2 can be seen in Fig. 3. As shown in the figure, when polymer concentration increases, the flux value decreases irrespective of the change in concentration of glycerol. Further, it shows that

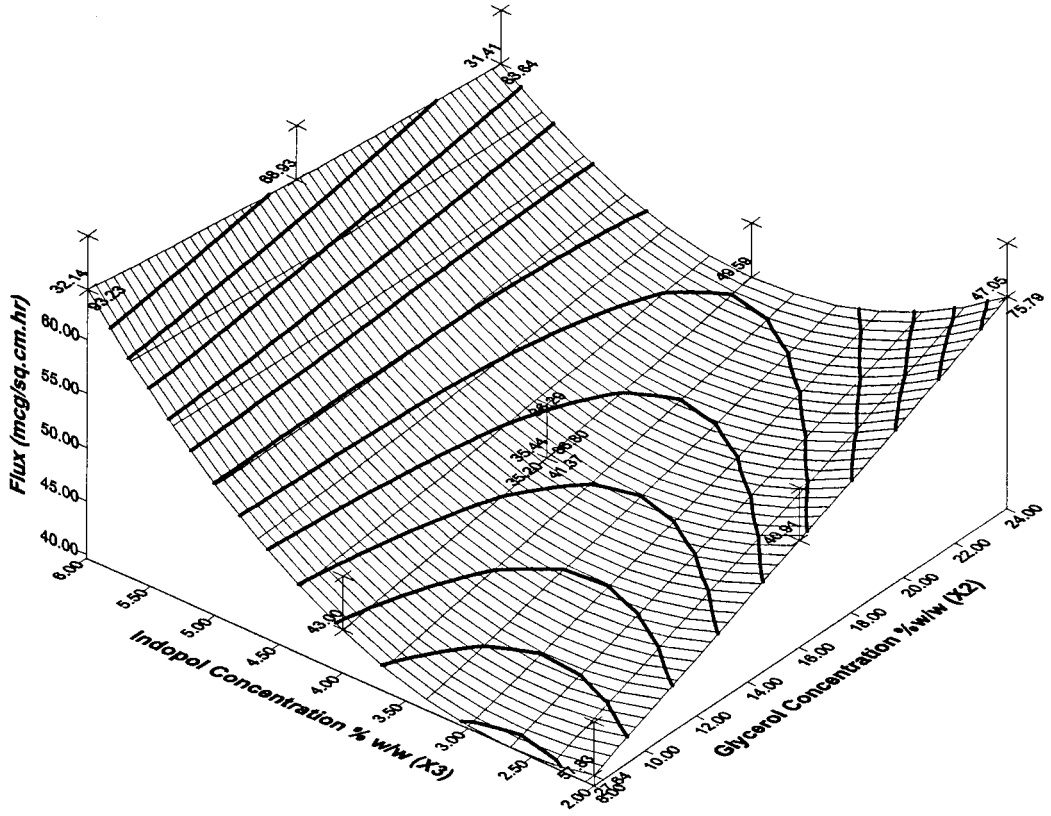

Figure 4. Response surface plot (three dimensional) showing the effect of glycerol concentration X_2 and indopol concentration X_3 on the flux of ibuprofen.

at constant adhesive concentration (2% w/w), for high levels of glycerol when the polymer content decreases, the flux increases from 47.05 to 75.79 ($\Delta F = 28.74$). At low levels of glycerol when the polymer content decreases, there is increase in flux from 27.64 to 57.83 ($\Delta F = 30.19$). This suggests that there is no significant interaction between carbopol and glycerol. Carbopol type polymers have rate-controlling characteristics, and glycerol is a plasticizer. Glycerol tends to soften the polymer particles in the patch. The lowest concentration used seems enough to keep the paste moist.

The effect of glycerol concentration X_2, indopol concentration X_3, and their interaction is shown in Fig. 4. As the concentration of glycerol increases, the flux increases at low and high levels of adhesive. The increase is greater at low levels of the adhesive compared to high levels of the adhesive. Keeping the polymer level constant (2% w/w), at a low concentration of adhesive (2% w/w), as the glycerol concentration is increased, the flux increases from 57.83 to 75.79 ($\Delta F = 17.96$). However, at a high concentration of the adhesive (6% w/w), when the glycerol concentration is increased, the flux decreases from 93.23 to 83.64 ($\Delta F = -9.59$). At a high concentration, the adhesive seems to interact with the glycerol by decreasing the permeation of the drug by acting as a barrier. Increased flux at low levels of indopol may be due to increased plasticization or wetting by increased glycerol levels.

The effect of polymer concentration X_1 and adhesive concentration X_3 on the flux Y_2 is shown in Fig. 5. It shows that, at low levels of the adhesive, the flux increases from 47.05 to 57.83 ($\Delta F = 10.78\%$) when the polymer concentration increases from 2% to 6%. However, at high levels of the adhesive, the flux increases from 32.14 to 93.23 ($\Delta F = 61.09\%$) for the same increase in polymer levels. This suggests that there is an interaction between the two factors, and the adhesive concentration should be on the higher side for flux to be maximum.

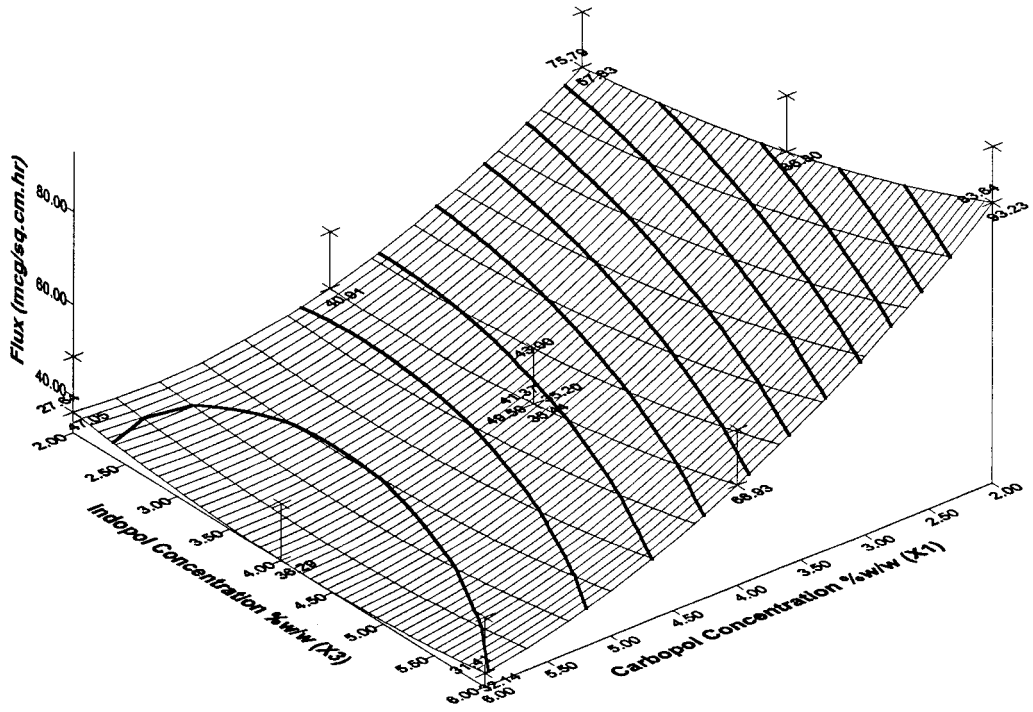

Figure 5. Response surface plot (three dimensional) showing the effect of carbopol concentration X_1 and indopol concentration X_3 on the flux of ibuprofen.

The computer optimization procedure for maximizing the flux with minimum lag time yielded carbopol (2% w/w), glycerine (11.75% w/w), and indopol (6% w/w) and a response of 97.22 mcg/cm^2/hr. A fresh patch was cast with these values. The average response of flux obtained was 90.21 mcg/cm^2/hr with a lag time of 7.3 min.

A kinetic investigation of the release profile revealed that the permeation of ibuprofen through the cellulosic membrane from different systems follows a linear Q versus t relationship, that is, a zero-order release. It appears that the release of the drug involves absorption of water into the hydrogel and simultaneous desorption of the drug by diffusion, as explained by Fick's law of diffusion by the equation

$$Q = [(DAK)/h]\, C_d t,$$

where Q is the amount permeated through the cellulosic membrane at time t; D and K correspond to the diffusivity coefficient and partition coefficient, respectively; A is the effective surface area of the membrane exposed; h is the thickness; and C_d is the concentration of the drug in the donor site.

CONCLUSIONS

A prototype cataplasm was successfully developed. All the formulation variables chosen for the experimental design affected the flux. The optimization procedure yielded flux values that could be closely related to the theoretical values. The optimized cataplasm had a flux value that was fairly close to the predicted value of the experimental design. The drug release followed zero-order kinetics.

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