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Research Article

Preparation, Characterization and Optimization of Ibuprofen Ointment Intended for Topical and Systemic Delivery

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Abstract

Purpose*: To develop an ibuprofen ointment with a potential for both topical and systemic delivery of the drug.*
Method: *A co-solvency technique with a trial and error approach was used to develop a 10% ibioprofen ointment in petrolatum base, with the entire drug dissolved in the base. An insertion cell was used to evaluate drug release from the formulations. Further, factorial design multiple regression (FDMRA) analysis, a statistical optimization technique, was used in the optimization of the final formulation.*
Result: *The desired ibuprofen ointments were developed. Release depended on vehicle and proportion of co-solvents. Best fit equations for optimization purposes including various fluxes (initial, steady-state and total) and diffusion coefficient as dependent variables and the concentrations of co-solvents as independent variables were obtained using SAS programme. Dependent variables strongly depended ($p<0.05$) on the independent variables and followed the polynomial equations generated.*
Conclusion*: The ointments consisting of petrolatum base (80%), PEG 400 (6%) and propylene glycol (4%) and ibuprofen (10%) and that consisting of petrolatum base (75%), PEG 400 (6%), propylene glycol (4%), menthol (5%) and ibuprofen (10%) can be used for topical and systemic delivery of the active, ingredient respectively.*

Key words: *ibuprofen, co-solvent, ointment, membrane permeability, optimization, SAS programme.*

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INTRODUCTION

The delivery of drug through the skin has long been a promising concept because of the ease of access, large surface area, vast exposure to the circulatory and lymphatic networks, and non-invasive nature of the treatment[1], This is true whether the bioavailability desired is systemic or local.

A 5% ibuprofen cream and a 5% gel are available in the market. Recently, a 10% ibuprofen gel and a 15% ibuprofen cream have been introduced, with the advantage of quicker release. However, as a result of the aqueous nature of the base, ibuprofen precipitation may occur in the gels. Also, it cannot be used on open wounds. It is for these reasons that we developed a petrolatum ointment of ibuprofen Manufacturers produce high quality, petrolatum, hence the choice of petrolatum is the vehicle in this study. Besides, petrolatum as occlussive and has been found to increase the skin permeability of several drugs[1]. Interestingly, ibuprofen can be conveniently solubilized in the petrolatum, which could be a constraint with gels and creams. In this study, we aimed at improving therapy by enhancing the local and systemic delivery of ibuprofen, a non-steroidal anti-inflammatory drug (NSAID) using an ointment preparation. NSAIDS are commonly used as topical analgesic/antirheumatic agents[2, 3] because of the decrease in the incidence of side-effects associated with systemic delivery. Literature data clearly indicates that ibuprofen can conveniently reach systemic circulation after topical application[4] but therapeutic blood levels of the drug may not be achieved at the low drug concentration of 5%w/w in the ointment.

The objectives of the study is two-fold, First, to develop a 10% ibuprofen ointment with a high skin permeability of the drug. Second, to develop a theoretical relationship that may be used to optimize the ointment formulation.

MATERIALS AND METHODS

Ibuprofen was obtained from Boots India Ltd., Mumbai. White beeswax and hard paraffin were purchased from Loba Chemic, Mumbai. White soft paraffin was purchased from Burgoyn Urbidges & Co., Mumbai. Polyethylene glycol 400, propylene glycol and menthol were obtained from S.D. Fine Chemicals, Bombay. Methanol was procured from Ranbaxy Chemicals, Delhi. To conduct release studies, magnetic stirrers from Remi Equipments Pvt. Limited and a dialysis membrane -70 obtained from Himedia was used. An SL 164 Elico Double Beam UV-Vis Spectrophotometer was used to analyze the samples. A diffusion cell (designed in our laboratory) was used for drug release study. Excel and SAS applications used in the studies were obtained from Microsoft (Redmond, WA, USA) and SAS Institute (Cary, NC, USA), respectively.

Preparation of the ointments

Paraffin ointment was prepared by melting together white bees wax, hard paraffin, polyethylene glycol or propylene glycol or menthol on a hot plate/stirrer (at 70ºC). Drug was added to this molten base while stirring. The entire mixture was stirred while cooling to form Ibuprofen ointment. Various compositions of the ointments were prepared for evaluation.

Estimation of drug solubility

To determine the solubility of the drug in the ointment base, a new technique based on microscopic evaluation was developed in our laboratory. According to this method, an ointment base was selected and the drug in the increasing concentrations was dissolved in the base. At the end of ointment preparation, a small aliquot was placed on to a glass slide with a cover slip and the number of crystals remaining in one field was determined. Readings from at least 10 fields was considered. A plot of concentration against the number of crystals. Resulted in a straight line. The solubility of the drug in the ointment base was considered as the intercept on the concentration axis.

Influence of PEG and propylene glycol on ibuprofen solubility

Petrolatum bases containing varying proportions of PEG 400 and propylene glycol were made. The solubility of ibuprofen in these ointment

Table 1: Compositions used in the study to prepare ointments

Composition/ Formulation	Form 1	2	3	4	5	6	7	8	9
Ibuprofen	10	10	10	10	10	10	10	10	10
Propylene Glycol	3	3	3	4	4	4	5	5	5
PEG 300	6	6	6	6	6	6	6	6	6
Menthol	3	4	5	3	4	5	3	4	5
Petrolatum, to	100	100	100	100	100	100	100	100	100

Table 2 SAS Program used in the optimization

```
DATA REGRESSN;
  INPUT X1 X2 Y;
  X11=X1**2; X22=X2**2;X12=X1*X2;
DATALINES;
3 3 y1
3 4 y2
3 5 y3
4 3 y4
4 4 y5
4 5 y6
5 3 y7
5 4 y8
5 5 y9
;
PROC REG DATA=REGRESSN;
  TITLE 'DRUG RELEASE';
  MODEL Y = X1 X2 X12 X11 X22 / P R; ….(2)
RUN;
QUIT;
```

Note: In the above data lines, y1, y2……y9 are the numbers associated with the dependent variable. For each of the dependent variable, the same program as mentioned above is written and the output was obtained by running the program.

bases was determined using the solubility method described in the preceding section.

Membrane permeability measurement

Drug release measurements were carried out in a diffusion cell designed in our laboratory. An inverted cylindrical test tube cut to a height of 8 cm was used as a donor cell. The receptor chamber cell consisted of a beaker containing 100 ml of water. A dialysis membrane soaked in warm water for 30 minutes was placed at the lower end of the cylindrical portion. 500 mg of ointment was placed in this chamber and this was inserted into the receptor chamber such that the height was sufficient for the drug to be released into the receptor. The receptor chamber was placed on a magnetic stirrer and mixed at a uniform speed. Samples were drawn

at predetermined time intervals. The samples were assayed for drug content spectrophotometer at λmax–nm. Cumulative amount of drug permeated vs. time (zero order plot) and vs the square root of time (Higuchi plot) were constructed. The Higuchi plot fitted more and hence was used in the calculation of the diffusion coefficients applying the Higuchi equation[5].

$$Q = 2C_0(Dt/\pi)^{1/2} \quad \text{…… eqn 1}$$

Where C_0 is the initial drug concentration in the donor, 'Q' is the cumulative amount of drug released at time 't' and 'D' is the diffusion coefficient.

Optimization of drug release

In the present study, the amount of propylene glycol and menthol in the ointments were selected as independent variables, whereas initial flux, steady state flux, total flux and diffusion coefficients were selected as dependent variables. These factors are known to influence the topical and systemic bioavailability of drugs from topical preparations. The factors were selected in a 3^2 factorial design, giving a total of nine different ointment formulations designed forms to Ibuprofen concentration in all the ointments was kept at 10% while the concentration of PEG 400 was also kept constant at 6% (see Table 1).

The initial and the steady state fluxes were calculated using the cumulative amount released vs time plot. When the plot of amount released vs square root of time gave a straight line, then diffusion coefficient was calculated using the Higuchi equation. Factorial design – multiple regression analysis (FD-MRA) was performed using SAS programme. The SAS programme selected gave the regression equation (Eq. 2), R-value and F-value along with the predicted numbers for the dependent variables. Surface contours were plotted with Excel software using the predicted numbers. The SAS Programme for the assessment of the relationship between dependent and independent variables is shown in Table 2.

RESULTS

As the concentration of propylene glycol and PEG 400 increased, there was an increase in the solubility of the drug in the ointment. Ibuprofen solubility in Forms 1, 2, 3, 4, and 5 were (%w/v): 5.8, 6.5, 6.75, 7.6 and 10.5, respectively. Form 5 was, therefore, the final topical ointment base and contained 10% drug in the soluble form, 6% PEG 400, 4% propylene glycol and the rest, petrolatum base. Formulations with high menthol content, up to 10%, can be used for systemic delivery of the drug, as menthol is a known skin permeation enhancer. The ointments were characterized for the drug release. (Fig 1)**.** The Higuchi plot yielded a straight line for all the ointment formulations. The diffusion coefficients of the drug from the various ointment bases was determined using the Higulchi model and the values are presented in Fig 2. The SAS output of the FD-MRA gave several statistics which could be used in the interpretation of the model. The analysis further gave predicted numbers for the experimental numbers. From the SAS output, a high drug release was associated with both the concentration of propylene glycol (X1) and menthol (X2). All the dependent variables namely, initial flux, steady state flux, flux and the diffusion coefficients produced strong correlation. The model used in the SAS programme gave good results (SAS output not presented here). Two-dimensional contour plots were established with predicted numbers using Excel. SAS was used to generated best fit equations for the initial flux, steady state flux, flux and the diffusion coefficients. The common equation for the dependent variable is as shown in Eq 3.

$$Y = A_0 + A_1X1 + A_2X2 + A_3X1^2 + A_4X2^2 + A_5X1X2 \quad \text{…….(3)}$$

The coefficients, R-2 values, F-value and p value are shown in Table 3.

DISCUSSION

In this study, we aimed firstly at the development of a 10% ibuprofen ointment with a potential for enhanced transdermal delivery. The estimated concentrations after epidermal applications of NSAID can be related to their flux across the epidermis from an applied vehicle[6], flux being

Table 3: Optimization parameters obtained using SAS Programme

	A_0	A_1	A_2	A_3	A_4	A_5	R_2	Fvalue	Pr>F
I. Flux	1195	561	-934	21	-76	109	0.95	11.49	0.036
S. Flux	-412	453	-106	-14	-47	19	0.98	36.10	0.007
Flux	-193	499	-250	-11	-54	36	0.98	37	0.007
$Dx10^{-7}$	-3.22	5.64	-3.12	-0.086	-0.63	0.44	1.00	181	0.006

I.Flux = initial flux; S. Flux= steady-state flux, D= diffusion coefficient

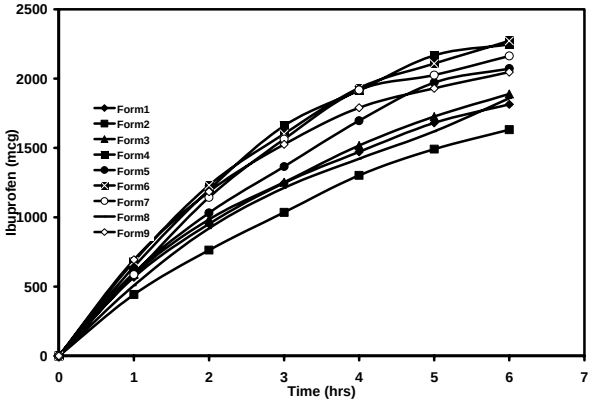

Figure 1: Cumulative drug released from various formulations

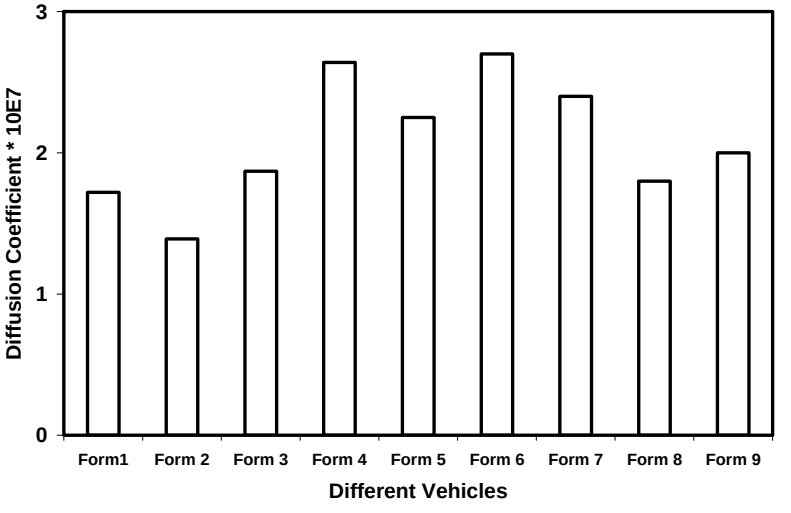

Figure 2: Diffusion coefficient of the ibuprofen from various ointment bases

directly proportional to the tissue concentration

of the drug[6]. Our preliminary study with 5% and 10% ibuprofen in petrolatum base gave similar results. The high drug release from the formulation containing 10% of the drug is therefore, an indication that the topical application of this formulation will achieve high tissue concentrations of the drug. The basis being that high drug release from the ointment base is associated with high skin permeability, provided that drug partitioning into the skin is not a problem. Enhanced release of drugs has also been achieved by supersaturation of the ointment base. In this study, we successfully employed a co-solvency technique to achieve the same results.

The second aim of this investigation was to statistically optimize the formulation. The FD-MRA technique has been used previously to statistically optimize the formation of ointments. The two factors evaluated were the concentrations of propylene glycol and menthol. It has also been shown that the four different dependent variables have strong influence on topical and systemic effects[8] are the initial flux, steady-state flux, flux and diffusion coefficient. The outcome of this study was consistent with the previous finding. All the equations fit into the SAS programme and demonstrated statistical strength ($p<0.05$). Thus, the response surface based optimisation scheme could be used for the evaluation of direction of formulation development. This type of optimisation approach has also been applied to liposome formulation[9].

CONCLUSION

The results of the study clearly indicate that transdermal formulations of ibuprofen (ointment/patch) are possible. Using a co-solvency technique, the soluble drug concentration in the ointment can be enhanced to 10%. The addition of a penetration enhancer, menthol, in the ointment will be expected to improve the skin permeability of the drug.

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