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Diffusion Studies of Ibuprofen from Ointment Bases

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The release of Ibuprofen from ointment bases through a dialysing cellulose membrane was studied. The drug release was greater from water soluble bases than other bases and was generally concentration dependent. The data obtained may be useful in the formulations of topical Ibuprofen products.

THE release of medication from a vehicle plays an important role in percutaneous absorption. One of the main functions of a semisolid dosage form base is the control it experts over the release and therapeutic activity of the drug.[1-3] The release of drug from a topical formulation, can be enhanced by effecting the barrier function of the epidermis or by altering diffusion of drug from the vehicle to the skin.[4] Various investigators[2,5,6] have used diffusion experiments to evaluate the release of drugs from semisolid dosage forms.

Ibuprofen (±) 2 - (p-isobutyl phenyl) propionic acid, an NSAID, is very slightly soluble in water and has poor wettability. Ibuprofen when given orally over long periods may cause gastric and intestinal ulceration. In the present investigation, Ibuprofen has been formulated in various ointment bases and evaluated for its usefulness on topical applications.

EXPERIMENTAL

Preparation of Ointments: Ten different ointment bases containing 4%, 5% and 6% w/w Ibuprofen were prepared **(Table 1).**

Method: Cylindrical glass tubes open at both ends[7] with an exposed surface area of 3.76 cm^2 were filled with 1 gm of ointment and one of the tube ends was covered with hydrated cellophane membrane secured with a rubber band. Ointments were spread uniformly over the membrane and all air at the interface between the ointment and the membrane was removed. This dialysis cell was inverted and immersed slightly in 150ml of buffer (ph 7.4) in a beaker and the system was maintained for 6 hours at 37.5 ± 0.5°C. The buffer was stirred with a magnetic paddle. Samples (1 ml) withdrawn at one hour interval for 6 hours were replenished with fresh buffer (1 ml). The Ibuprofen content of the samples was estimated spectrophotometrically at 221 nm.[8] The diffusion characteristics of all the ointments containing 4%, 5% and 6% w/w of Ibuprofen were studied in triplicate.

RESULTS AND DISCUSSION

From the data obtained, Diffusion rate, Diffusion rate constant, Percent drug released **(Table 2)** were calculated for all the sets of ten ointments and compared. Plots of percent drug released vs. time for different concentrations of drugs were linear. The percent drug released are different for each formulation. There is maximum release of drug from formulation no. 1 (about 40%) and least from formulation no.10 (about 30%). Thus the release of drug from an ointment can be modified simply by altering the composition of the vehicles.[9] The linearity of the plots are supported by the values of co-efficient of

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Table -1: Composition of the Ointment Bases

Formulation No. (F)	Type of base	Composition
1.	Water Soluble	PEG 4000/PEG 400/Tween 80 (40:59:1)
2.	Water Soluble	PEG 4000/PEG 400 (40:60)
3.	Water Soluble	PEG 4000/PEG 400/Cetyl Alcohol (47.5:47.5:5)
4.	Water Miscible	Cetostearyl Alcohol/ White beeswax/Span 60/ Tween 80/Purified water (15:2.5:7.5:5:70)
5.	Hydrophilic	Cholesterol/Cetyl Alcohol/ White beeswax/Yellow soft paraffin (3:3:8:86)
6.	Oleaginous	Wool fat/Hard paraffin/ Cetyl Alcohol/Yellow soft paraffin (5:5:5:85)
7.	W/O emulsion	Liquid paraffin/White beeswax/Wool fat/Borax/Water Sorbitan mono-oleate (45:10:2:8:41)
8.	O/W emulsion	White beeswax/Cetyl alcohol/ Propylene glycol/Tween 80/water (1:15:10:2:72)
9.	O/W emulsion	White beeswax/Cetyl Alcohol/ Propylene glycol/Sodium lauryl sulfate/Water (1:15:10:2:72)
10.	W/O emulsion	Wool fat/Purified Water (70:30)

correlation (r) which ranges from 0.973 to 0.998 (Table 2). A significant linear correlation $p < 0.001$ was found with $df = 4$, except in one case, where $p < 0.01$. As a result the slope of such a plot (Diffusion rate constant, determined from log percent unreleased vs. time) will quantitatively affect the drug release profile.

Data reveals that percent drug release was concentration- dependent. Similar observations have

Table -2: consolidated

Formulation No.	Concentration	% drug released (at the end of study)	Diffusion rate constant (K) ($1x10^{-3}$)	Coefficient of correlation + (r)	Level of Significance.
1.	4%	44.60±0.916	$1.31±5.77x10^{-5}$	0.979	*
	5%	47.60±0.346	1.40±0.012	0.987	*
	6%	49.00±0.346	$1.44±5.77x10^{-5}$	0.986	*
2.	4%	44.00±0.346	$1.43±5.77x10^{-5}$	0.981	*
	5%	45.80±0.346	1.50±0.00	0.979	*
	6%	47.20±0.346	$1.47±5.77x10^{-5}$	0.987	*
3.	4%	41.60±0.346	1.30±0.00	0.998	*
	5%	42.60±0.00	1.34±0.00	0.998	*
	6%	43.60±0.346	1.40±0.00	0.997	*
4.	4%	40.00±0.346	$1.33±5.77x10^{-5}$	0.993	*
	5%	40.80±0.6	$1.33±5.77x10^{-5}$	0.994	
	6%	41.20±0.346	$1.33±5.77x10^{-5}$	0.992	*
5.	4%	37.80±0.6	1.20±0.00	0.993	*
	5%	39.00±0.346	1.20±0.00	0.989	*
	6%	39.80±0.346	1.20±0.00	0.996	*
6.	4%	36.40±0.92	$1.27±5.77x10^{-5}$	0.973	**
	5%	37.20±0.60	$1.18±3.46x10^{-5}$	0.996	*
	6%	38.60±0.346	1.20±0.00	0.998	*
7.	4%	36.40±0.92	$1.20±4.04x10^{-5}$	0.995	*
	5%	37.60±0.92	1.20±0.00	0.997	*
	6%	39.00±0.60	$1.43±3.21x10^{-4}$	0.993	*
8.	4%	35.80±0.92	$1.17±4.61x10^{-5}$	0.994	*
	5%	36.40±0.92	$1.20±5.77x10^{-5}$	0.997	*
	6%	37.00±0.92	$1.23±5.77x10^{-5}$	0.996	*
9.	4%	30.80±0.92	$0.98±2.31x10^{-5}$	0.998	*
	5%	34.60±0.92	$1.17±5.77x10^{-5}$	0.996	*
	6%	35.20±0.35	$1.17±5.77x10^{-5}$	0.997	*
10.	4%	29.60±0.69	$1.04±6.80x10^{-5}$	0.994	*
	5%	32.00±0.916	$1.12±2.5x10^{-5}$	0.997	*
	6%	34.20±0.6	$1.17±4.6x10^{-5}$	0.996	*

*P < 0.001 ** P < 0.01 + log % unreleased VS time plot

been made with respect to the release of Benzocaine,[2] Sorbic acid[7], Salicylic acid[9] and Benzoic acid.[9] The diffusion rate was higher in the first one hour and thereafter it declined. The general rank of order of the drug release was found to be; Water soluble > Water miscible > Hydrophilic > Oleaginous and W/O emulsion base (F 7)> O/W emulsion base (F 8) > O/W emulsion base (F 9)> W/O emulsion base (F 10).

The high diffusion rate of Ibuprofen from the water soluble ointment bases may be due to the diffusion of media through the cellophane membrane and formation of solvent polyethylene glycol solution which increases the solubilities and thus the rate and extent of release of Ibuprofen.

Similar observations involving use of PEG based ointments have been made with respect to the release of salicyclic acids,[10] Benzocaine[2] and Methyl Salicyclate.[11] Water soluble bases containing 1% w/w Tween 80 show the maximum amount of drug released due to the wetting properties of Tween.

A general rule in an ointment formulation is that if the drug is held firmly by the vehicle, the rate of release of drug is slow.[2,12] The high affinity of Ibuprofen towards cetyl alcohol may explain the difference in the diffusion of Ibuprofen from PEG ointment base containing cetyl alcohol. A slow release of Ibuprofen has been observed from bases containing lipoidal excipients. This may be due to the high lipoidal affinity of the drug, which favours its retention in the base. The high release of drug from the W/O emulsion base (F 7) as compared to the O/W emulsion base (F 8) can be explained similarly.

The O/W emulsion base containing 2% Tween 80 gave significantly higher rates of release of Ibuprofen than O/W emulsion containing 2% Sodium lauryl sulphate. It is likely that release of drug is dependent on the HLB value of the surfactant, probably due to the difference in the solubilization capacities. The higher release of Ibuprofen from the O/W emulsion base (F 8 and F 9) than from W/O emulsion base (F 10) may be due to the formation of a continuum from the external phase of the O/W emulsion base with the media in the beaker.[13] A survey of literature concerned with the release of drugs from the vehicles leads to the conclusion that it is not possible to which base will release the drug better.

Data obtained was subjected to statistical evaluation. The ANOVA (F-ratio Test)[14] was applied using percent drug released and Diffusion rate constant data of formulations containing moderate (5% w/w) concentration of drug. It has been inferred that the ten sets of data differ significantly (**Table 3**). Therefore, the probability of these ten samples being drawn from the same population is less than 0.5. Further t-Test[14] was performed to find out whether the difference is significant or not. Using percent drug released data of all ten formulations containing 4%, 5% and 6% w/w of drug, 90% of the formulations showed significant difference and there exists an effect of concentration on the release of drug from ointment bases. However, from the diffusion rate constant data we can not infer that the release is concentration dependent. The t-Test data for 5% w/w Ibuprofen depicts that a highly significant differences exists in more than 50% formulations for df = 4 and P = 0.05 (Two tail). In some cases difference is not significant as clearly shown in **Table 4**, wherein ointment bases are compared with each other. Based on these statistical analysis we may rank our formulations in the following order:

1> 2> 3 = 4> 5> 6 = 7= 8 = 9> 10 (but 6> 9)

In conclusion, the present investigation clearly reveals the effect of base composition on the release of Ibuprofen. Further detailed studies shall help in formulating Ibuprofen ointments with appropriate bases and optimal drug concentrations.

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Table - 3: Analysis of Varience

	Sources of Variation	Degree of Freedom	Sum of square	Mean square	F Ratio	Level of Significance
A.	%Drug released at the end of Study:					
	Among regimens	t-1 = 9	645.372	71.708	149.39	$P < 0.01$
	Within regimens	$\sum ni\text{-}1^{=20}$	9.6	0.48		
B.	Diffusion rate constant:					
	Among regimens	t-1=9	$4x10^{-7}$	$4.45x10^{-8}$	3.42	$P < 0.025$
	Within regimens	$\sum ni\text{-}1^{=20}$	$2.6x10^{-7}$	$1.3x10^{-8}$		

Table - 4: Individual Comparison Mode

Base Type +	10	9	8	7	6	5	4	3	2
1.	*	*	*	*	*	*	*	*	*
2.	*	*	*	*	*	*	*	*	
3.	*	*	*	*	*	*	NS		
4.	*	*	*	*	*	*			
5.	*	*	*	*	*				
6.	*	*	NS	NS					
7.	*	NS	NS						
8.	*	NS							
9.	*								

* - Significant

NS - Not Significant.

+ - As stated in Table - 1.

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