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Formulation, release characteristics and evaluation of ibuprofen suppositories

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Summary

Suppositories of ibuprofen were formulated using cocoa butter, witepsol E_{75} and polyethylene glycol (PEG) bases. Cocoa butter suppositories showed the best permeation of the drug (indicated by their k value being the highest) and the fastest dissolution rate. The four PEGs formulae and witepsol followed in order. Ibuprofen in cocoa butter and PEG 'A' was physiologically evaluated in albino rats using local vascular permeability and pain sensation as parameters. The results obtained from both methods revealed that cocoa butter was more efficient than PEG as a base for ibuprofen suppositories, in agreement with the in vitro release studies.

Introduction

The effect of different suppository bases on the in vitro release of drugs has been described in several papers (Fadel et al., 1979; Becirevic and Petricic, 1986; Othman and Muti, 1986; Young et al., 1987). Generally, drug release from a number of suppository bases depends on the drug solubility in the base, the chemical composition of the base and drug particle size.

Several studies (Ibrahim et al., 1980; Palmaieri, 1984; Nishimura et al., 1985; Singh and Jayaswal, 1985; Yata et al., 1985) have shown that drug release from suppository bases is influenced by the presence of other additives in the formulation and may result in an increase or decrease in the rate of release depending on the nature of the base and that of the additive and its concentration. There are reports describing attempts at enhancing the rate of release of the drug from different suppository bases by incorporation of surfactants (Ibrahim et al., 1980; Othman and Muti, 1986). This effect was correlated with the HLB of surfactants used, as well as their concentration. On the other hand, surfactants sometimes exerted an adverse effect on the rate of drug release from suppositories (Abd El-Gawad et al., 1985).

A survey of pharmaceutical literature revealed that no consideration has been given to the formulation of ibuprofen in the form of suppositories except for one report (Ghanem et al., 1988). In the article cited, a significant increase was observed in

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the release rate of ibuprofen in case of solid dispersions with surfactants relative to that of drug alone. Also, the maximum blood level was attained in vivo. The authors recommended that the formulation of ibuprofen in the form of suppositories could be used safely in the treatment of rheumatic disease.

In the present investigation, a trial was made to formulate ibuprofen in the form of suppositories using water-soluble as well as fatty bases. Also, the permeation patterns of the drug from the bases through cellophane membranes were studied. The effect of additives on the rate of drug dissolution from the suppository bases was also investigated. Since in vitro dissolution procedures are routinely used to compare drug release profiles from different bases, the experimental data show that the level of in vitro/in vivo correlation is often poor (Muller, 1984). For this reason, physiological evaluation of drug release from the most efficient bases was investigated in rats and considered as a useful measure for comparison in vivo.

Materials and Methods

Materials

Ibuprofen (Boots, U.K.), KH_2PO_4 (May & Baker, U.K.), NaOH (El-Naser, Egypt), polyethylene glycols 6000, 4000, 1540 and 1500 (Fluka, Switzerland), polyvinylpyrrolidone and Tween 20 (BDH, U.K.), cocoa butter (B.P. grade), witepsol E_{75} (Nobel Dynamite, Witten Werke, F.R.G.) and prostaglandin $F_{2\alpha}$ (Upjohn, U.K.) were obtained from the indicated sources.

Methods

Preparation of suppositories

In vitro studies. Accurately weighed quantities of the respective suppository bases (Table 1) were melted on a water bath. The finely divided drug powder (200 mg) and/or additive was incorporated into the melted base via thorough mixing. The melted mass was poured into the appropriate suppository mould (1 g capacity). The suppositories formed were then refrigerated; exposure to room temperature was carried out no longer than 24 h before use in in vitro release studies.

TABLE 1

Type and composition of the suppository bases

Base type	Composition
Polyethylene glycols (PEG)	
PEG A	PEG 1500:PEG 4000 3:1
PEG B	PEG 1500:PEG 4000 9:1
PEG C	PEG 1540:PEG 6000 7:3
PEG D	PEG 1540:PEG 6000 1:1
Cocoa butter	
Witepsol	

Physiologic evaluation. Ibuprofen (3.5 mg dose; calculated according to Ghosh and Schild, 1971) was mixed with melted suppository base and the mixture then poured into a special suppository mould (about 60 mg capacity).

For comparison, an aqueous solution of ibuprofen was prepared by dissolving 175 mg in 4 ml of 0.1 N NaOH plus 21 ml phosphate buffer, pH 7.4. This solution was used as an oral dosage form (3.5 mg/0.5 ml).

Permeation studies

A simple assembly was used for the release studies. The suppository to be tested was placed in an open-ended glass tube over one end of which a standard cellophane membrane (soaked overnight in buffer solution) was stretched and securely fastened with a rubber band. The tube was hung in a vertical position into a 250-ml beaker containing 100 ml phosphate buffer (pH 7.4 $\pm$ 0.1), such that the lower end of the tube was 3 cm from the bottom of the beaker. The beaker was then placed in a thermostatically controlled water bath (37 $\pm$ 0.1° C) and the solution agitated using a magnetic stirrer. Phosphate buffer (5 ml) was placed inside the tube over the suppository at the beginning of experiments. Samples of 5 ml each were withdrawn from the solution in the beaker at specified time intervals and were replaced by fresh buffer samples kept at the same temperature. Ibuprofen concentrations for these samples were determined spectrophotometrically at 264 nm.

Dissolution rate studies

The USP dissolution apparatus was used for evaluation of dissolution rates. The dissolution

medium was 250 ml phosphate buffer kept at $37 \pm 0.1°C$; the suppository was placed in the metal basket which was then spun at 50 rpm. Samples of 5 ml were withdrawn at specified time intervals for spectrophotometric estimation of ibuprofen concentration. Samples which had been withdrawn were replaced by fresh buffer solution. The materials used did not interfere with the assay procedure for the drug.

Physiologic evaluation of ibuprofen suppositories

Local vascular permeability. Four groups of adult female albino rats (average weight 181 g) were used, each comprising five animals. One group was treated with prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) to induce inflammation (Pearl and Willis, 1971; Williams and Peck, 1977), the other three being treated with ibuprofen oral solution, PEG 'A' and cocoa butter suppositories. Skin samples from each rat in group 1 were taken as control samples. The animals were anaesthetized with sodium barbiturate (40 mg/kg) intraperitoneally and their abdominal skin was shaved. Either PEG suppositories (average weight 73 mg) and that formulated in cocoa butter base (average weight 60 mg) or ibuprofen solution (dose used 3.5 mg) were administered to the three groups. After 1.5 h, pontamine sky blue dye (100 mg/kg) was injected intravenously into one of the tail veins of each rat (Psychoyos, 1961). After 20 min following injection of the dye, rats were treated with 0.1 ml containing 1 mg $PGF_{2\alpha}$ intradermal injection into the abdominal skin. At 10 min post-intradermal injection of $PGF_{2\alpha}$ to all rats, the animals were killed and the blue colour was examined from the underside of the dermal skin. The areas of the blue reaction sites were measured and the intensities determined.

Histological examination of the blue reaction sites on an area of 1 cm^2 was performed for determination of the number of blood capillaries and of their diameter.

Pain sensation. Three groups of adult female albino rats (average weight 181 g) were used, each group consisting of eight animals. The three groups were treated with ibuprofen in the form of solution and suppositories (PEG and cocoa butter).

The effect of ibuprofen on pain sensation was evaluated using the tail flick unit (Model-DS 20 Rocrel, Italy). The rat was placed on the upper panel of the instrument in such a way that its tail covered a flush-mounted photocell window. A pedal switch was depressed which starts a solid-state second counter. On experiencing pain, the rat flicks its tail which stops the second counter. The reaction time of each animal was thus determined before (control) and at 1 and 2 h post-medication.

Results and Discussion

Permeation patterns

The permeation patterns of ibuprofen from the six different suppository bases were studied (Fig. 1). It is obvious that permeation was most rapid

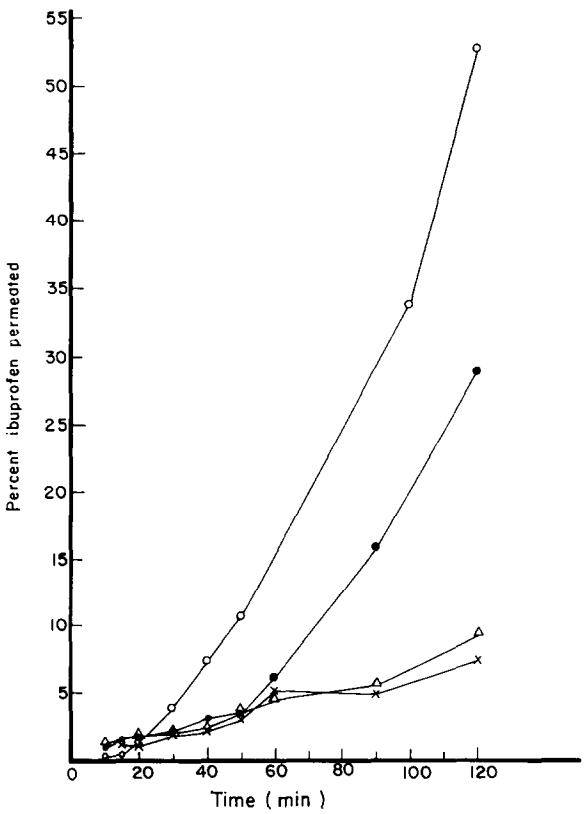

Fig. 1. Permeation patterns of ibuprofen from different suppository bases. (○) Cocoa butter, (△) Witepsol E_{75}, (●) PEG A, (×) PEG B.

TABLE 2

Calculated dialytic rate constant (k) of ibuprofen suppository formulations within 2 h

Suppository formulation	k (min^{-1}) ($\times 10$)	r
Cocoa butter	0.14847	0.98575 [a]
Witepsol E_{75}	0.040226	0.94059
Polyethylene glycols		
A	0.045155	0.90646 [a]
B	0.014445	0.91790
C	0.040716	0.99604
D	0.031766	0.98336

[a] Calculated for 1 h.

from cocoa butter base, followed by polyethylene glycol base A (PEG A). In comparison, permeation from Witepsol E_{75} and PEGs B–D was slower and similar in magnitude. For clarity's sake the lines corresponding to PEGs C and D have been omitted from Fig. 1 and are listed in Table 2. The permeation behaviour of ibuprofen from the above-mentioned bases was evaluated in terms of the apparent dialytic rate constant of the drug, calculated according to the following equation (Othman and Muti, 1986):

$$\log[V_0 A_t - (V_0 + V_i) A_0] = \frac{[V_0 + V_i]}{2.3 V_i V_0} kt + \log(V_0 A_t) \quad (1)$$

where V_i and V_0 denote the volume of the test medium within and outside the dialysis tube, respectively, A_0 and A_t are the amount dialyzed and the total amount of drug in the test sample, respectively, t, the time and, k, the apparent dialytic rate constant.

On plotting the term $\log[V_0 A_t - (V_0 + V_i) A_0]$ (which represents the amount of drug remaining in the dialysis tube) vs time, a linear relationship was obtained. The apparent dialytic rate constant k, was calculated as follows:

$$k = \frac{-(\text{slope}) 2.3 (V_i V_0)}{V_i + V_0} \quad (2)$$

For the values of the correlation coefficients obtained from samples formulated in cocoa butter and in PEG A, it was found that the lines were linear only over the first hour (Table 2). The magnitudes of the calculated dialytic rate constants ranked in the following sequence with respect to the base used: cocoa butter > PEG A > PEG C > Witepsol E_{75} > PEG D > PEG B.

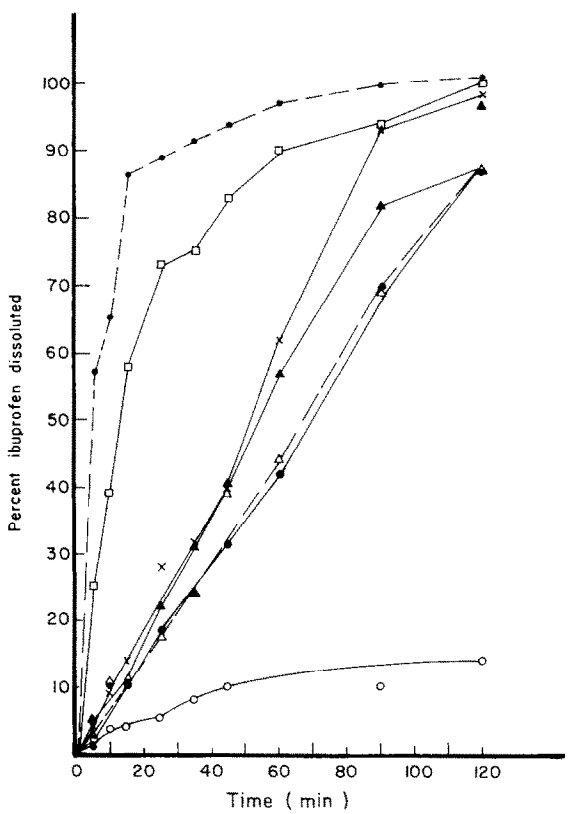

Fig. 2. Dissolution patterns of ibuprofen from different suppository bases. (— — —) Powder, (▲) PEG B, (□) cocoa butter, (○) Witepsol E_{75}, (●) PEG C, (△) PEG D, (×) PEG A.

TABLE 3

Effect of ibuprofen on capillary permeability in albino rats

Parameters	Control	Ibuprofen treatment		
		Oral solution	PEG A supp.	Cocoa butter supp.
Mean diameter of response site (mm) (±S.E.)	5.38 ± 0.32	3.63 ± 0.46 [a]	2.25 ± 0.37 [b]	0.5 ± 0.27 [b]
% change	–	32.53	58.18	90.71
Average number of blood capillaries (±S.E.)	16.61 ± 0.97	11.96 ± 0.60 [a]	9.61 ± 0.54 [b]	7.00 ± 0.38 [b]
% change	–	28.00	42.14	57.86
Average transverse diameter of blood capillary (μm) (±S.E.)	18.60 ± 0.99	10.80 ± 1.06 [b]	6.20 ± 0.45 [b]	5.80 ± 0.35 [b]
% change	–	41.94	66.67	68.82

[a] $P < 0.01$.
[b] $P < 0.001$.

Dissolution patterns

Dissolution patterns of the drug from different bases compared with drug powder are shown in Fig. 2. It is clear that cocoa butter base was the most efficient base for formulating ibuprofen suppositories, since dissolution amounted to approx. 90% after 1 h, followed by about 62% for PEG A whereas PEGs B–D showed less dissolution of the drug. On the other hand, drug release was lowest for witepsol E_{75}.

In spite of the hydrophobic nature of the drug and its high affinity for the fatty base (cocoa butter), the release rate from this base was high. This may be explained on the basis of (i) cocoa butter melted easily at 37 °C (melting range, 33.5–35 °C; Herbert and Joachim, 1970), thus readily dispersing the drug throughout the dissolution medium; (ii) drug partitioning was favoured into aqueous medium of pH 7.4 (indicated by the high dissolution rate for drug powder in this medium; Fig. 2). On the other hand, using the water-soluble polyethylene glycols, the base dissolved rapidly, leaving the drug which precipitated from the dissolution medium (as observed throughout).

The results obtained using witepsol E_{75} indicated that both the higher melting range (Herbert and Joachim, 1970) of this base as compared to that of cocoa butter (37–39 °C) and its chemical composition may exert an influence on the slow rate of release of the drug from witepsol E_{75}.

Attempts at increasing the dissolution rate of the drug from PEG D and cocoa butter using different additives were unsuccessful. The additives used were 2% carboxymethylcellulose and 5% PVP in the case of PEG D, as well as Tween 20 and 5% PVP for cocoa butter. However, there was a slight increase in dissolution rate on employing 10% PVP with PEG B, the effect being more pronounced on using PEG A with this additive.

Physiologic evaluation of ibuprofen suppositories

Local vascular permeability. Table 3 illustrates the effect of ibuprofen suppositories on vascular permeability in rats using the mean diameter of response site (mm). The average number of blood capillaries as well as the average transverse diameter (TD) of the blood capillary (μm) was also studied. From Table 3 it is apparent that these parameters were significantly reduced for the case of treatment of rats with ibuprofen suppositories as compared to oral solution ($P \leqslant 0.01$). The effect was more pronounced on using ibuprofen in cocoa butter ($P \leqslant 0.001$) and the above parameters were decreased by 90.70, 57.86 and 68.82%,

TABLE 4

Effect of ibuprofen on pain sensation (average reaction time, in s) (± S.E.) in rats

	Ibuprofen treatment		
	Oral solution	PEG A supp.	Cocoa butter supp.
Control	4.46 ± 0.89	3.5 ± 0.20	3.89 ± 0.44
After 1 h	6.80 ± 1.69 *	4.75 ± 0.73 *	8.78 ± 1.40 [b]
% change	52.47	35.71	125.70
After 2 h	8.64 ± 1.40 [a]	9.56 ± 1.32 [b]	11.23 ± 1.59 [c]
% change	93.72	173.1	188.69

[a] $P < 0.05$.
[b] $P < 0.01$.
[c] $P < 0.001$.
* No significant change.
Control: average reaction time for rats, before medication.

respectively, compared to controls. PEG A suppositories showed a less dramatic lowering effect than that of cocoa butter, the corresponding values being 58.18, 42.14 and 66.67%, respectively. The percentage decrease for oral solutions was 32.53, 28.00 and 41.94%, respectively.

The colour of the reaction site was monitored throughout the work. Ibuprofen generally decreased the intensity of extravasation of the blue dye compared with the control ($PEG_{2\alpha}$), which appeared as an intense blue ring. The shade of blue colour changed from dark to very pale blue with oral solution, PEG A and cocoa butter suppositories.

Effect of ibuprofen suppositories on pain sensation. Table 4 lists the effects of ibuprofen suppositories on pain sensation by rats, using the tail flick unit. Generally, reaction time was increased significantly ($P \leqslant 0.01$ and $P \leqslant 0.001$) with ibuprofen suppositories as compared to control especially at 2 h post-medication. As detailed in Table 4, the reaction time for treated animals increased by 188.69, 173.1 and 93.73% for the case of cocoa butter, PEG suppositories and oral ibuprofen solution, respectively.

Histological examination of transverse skin sections from treated animals indicated extensive narrowing of capillary blood vessels compared with control. This effect was more pronounced on treatment with cocoa butter suppositories. From the above results, it may be concluded that suppositories were more efficient than oral solution. Furthermore, cocoa butter base was more efficient than PEG A for formulating ibuprofen in the form of suppositories.

Moreover, in vitro release was demonstrated to correlate well with the in vivo situation. Ibuprofen in the form of suppositories is a recommended dosage form of the drug for counteracting its hazardous gastric effects, since previous histological examination (Ghanem et al., 1985) showed that it does not exert adverse effects on rectal tissues.

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