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THE EFFECT OF BASES AND FORMULATION ON THE RELEASE OF INDOMETHACIN FROM SUPPOSITORIES.

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ABSTRACT

The in vitro release characteristics of indomethacin from different suppository formulations were investigated using a dialysis method. Suppositories containing 100 mg of indomethacin were prepared by the fusion method in a variety of Witepsol and Novata bases with different hydroxyl values. The rate of release of indomethacin was found to be unexpectedly higher from oily bases with low hydroxyl values.

Furthermore, the effect of surface active agents and some excipients commonly used in suppository formulations on the release properties of indomethacin was determined. Colloidal silicon dioxide, sodium lauryl sulphate and cetyl alcohol had a slight effect on the

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release of indomethacin, whereas dioctyl sodium sulphosuccinate significantly increased the amount of indomethacin released. White beeswax and Tween-80, however, resulted in a marked decrease in the release of indomethacin.

The in vitro release of indomethacin from five commercially available preparations was also determined using the same method. Suppositories formulated in PEG bases gave better release properties than those in oily bases.

INTRODUCTION

Indomethacin, like other analgesic and antiinflammatory agents carries the risk of GI irritations. The oral dosage forms have led to peptic ulcerations and anorexia (1-3), nausea, vomiting, dyspepsia and diarrhoea (4). Consequently, rectal administration offers a useful route for administering indomethacin to avoid GI side effects. Furthermore, drugs are administered rectally when the oral route is not convenient as in infants and elderly patients.

The absorption of a drug from its suppository base initially involves its release from vehicle and then the diffusion through rectal mucosa. Suppository bases which release the drug fastest to the surrounding medium should theoretically afford more rapid absorption by the body, since evidence indicates that the limiting factor in

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rectal absorption is the diffusion of the drug to the absorption sites (5).

The release of the drug from the suppository bases into the rectal environment depends on the relative solubilities of the drug in the vehicle and rectal fluid. Eckert (6) demonstrated that low affinity between drug and vehicle and solubility of drug in aqueous mucous favour release of drug and its availability for subsequent diffusion through mucous membranes.

In vitro studies (7) indicated that a suppository base of macrogol gave the highest rate of release of indomethacin. Also, Vidras et al. (8) found that the bioavailability of indomethacin after rectal administration was greater with macrogol bases and a significant correlation was obtained during the first 45 minutes between the *in vitro* release using the dialysis tubing method and the *in vivo* bioavailability. Moreover, pharmacokinetic studies involving the ractal administration of indomethacin have shown the drug to be absorbed satisfactorily and the average serum concentration after a 100 mg dose was 75% of that when given by mouth (9). Peak plasma concentrations were reached in 2-3 hours (10).

Several studies (11-13) have also shown that drug release from suppository bases is influenced by the inclusion of surface active agents and other additives in the formulation and may result in an increase or a

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decrease in the rate of release depending on the nature and concentration of excipients.

In this study, the in vitro release of indomethacin from different suppository bases and the effect of some excipients commonly used in suppository formulations on the drug release were investigated.

EXPERIMENTAL

Materials: Products were used as received from the manufacturer or distributor with no further purification. Indomethacin complied with the requirement of the British Pharmacopoeia and was purchased from Pharmatex Italia (Milano, Italy). Witepsol H15, H35,S55 and W35 were obtained from Dynamit Nobel (Triosdorf, West Germany). Novata C and BCF and sodium lauryl sulphate were obtained from Henkel (Dusseldorf, West Germany). Polyethylene glycol, dioctyl sodium sulphosuccinate, Tween 80, white beeswax and cetyl alcohol were all supplied by E. Merck (Darmstadt, W. Germany). Colloidal silicon dioxide from Biochemie (Vienna, Austria). Dialyzing cellophane tubing (300 x 35 mm) were purchased from Sigma Chemical Co. Ltd. (Dorset, England).

Preparation of Suppositories: The displacement value of indomethacin was first determined in the suppository bases (Witepsol H15, H35, S55 and W35 and Novata C and BCF).

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All suppositories containing 100 mg of indomethacin were prepared by the fusion method using stainless steel moulds.

Suppositories containing surface active agents or other pharmaceutical excipients were formulated using the following concentrations of additives:

Dioctyl sodium sulphosuccinate.....0.5%
Sodium lauryl sulphate.....0.1%
Tween 80 .....0.5%
Cetyl alcohol.....2.0%
White beeswax.....1.0%
Colloidal silicon dioxide.....1.0%

The suppositories were stored at 5° for 3 days and were then left at room temperature for 24 hours before testing. They were satisfactory in appearance and showed no evidence of cracking.

Release of Indomethacin from Suppository Bases: The release of indomethacin from suppository formulations was determined by a modification of the dialysis method of Flaxco et al. (12). Dialyzing bags were prepared from dialyzing cellophane tubing (100 x 35 mm) tied with cotton thread and soaked overnight in phosphate buffer solution (pH8). The bags were rinsed twice and filled with 20 ml of phosphate buffer and then suspended in a 500 ml wide-mouth bottle containing 400 ml of the phosphate buffer solution. The bottle was placed in a constant temperature water bath at 37° and stirred with a magnetic stirrer at

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a slow and constant speed. One suppository was placed in each bag. At certain time intervals, a 5 ml sample was withdrawn from the bottle for analysis. The dissolution fluid in the bottle was kept constant by addition of phosphate buffer after each sample had been taken. The amount of indomethacin released was assayed spectrophotometrically at 318 nm and the concentration determined from a standard calibration curve.

RESULTS AND DISCUSSION

The *in vitro* release characteristics of indomethacin from the different suppository formulations used in this work were evaluated in terms of the apparent dialytic rate constants of the drug. The equation derived by Davis (14) for the calculation of the apparent dialytic rate constant was used:

$$\log\left[V_o A_t - (V_o + V_i)\, A_o\right] = -\left[\frac{V_o + V_i}{2.3\, V_i V_o}\right] Kt + \log\,(V_o A_t)$$

where, V_i is the volume of the test medium in the dialysis bag; V_o, the volume of the test medium outside the dialysis bag; A_o, the amount of the drug dialyzed; A_t, the total amount of drug in the test sample; t, the time and K, the apparent dialytic rate constant. When the term $\log\left[V_o A_t - (V_o + V_i)\, A_o\right]$, which represents the amount of the drug remaining in the dialysis bag, was plotted against time, straight line relationships were obtained from samples formulated in lipid bases (Figures

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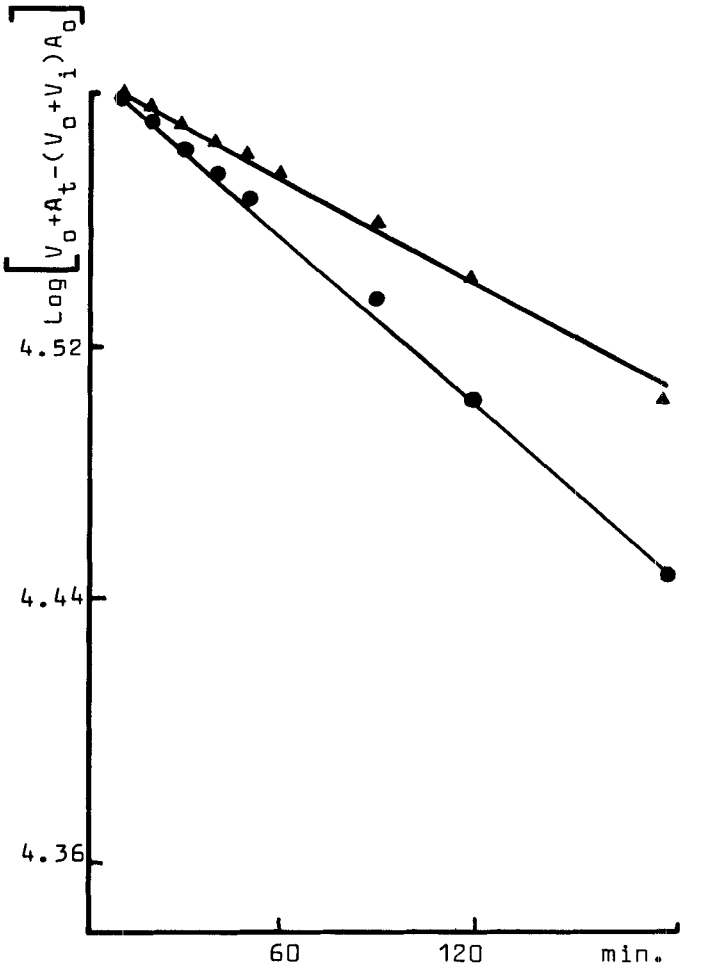

FIGURE 1

Release of Indomethacin from Suppository Bases.
Witepsol H15 (▲); Witepsol H35 (●).

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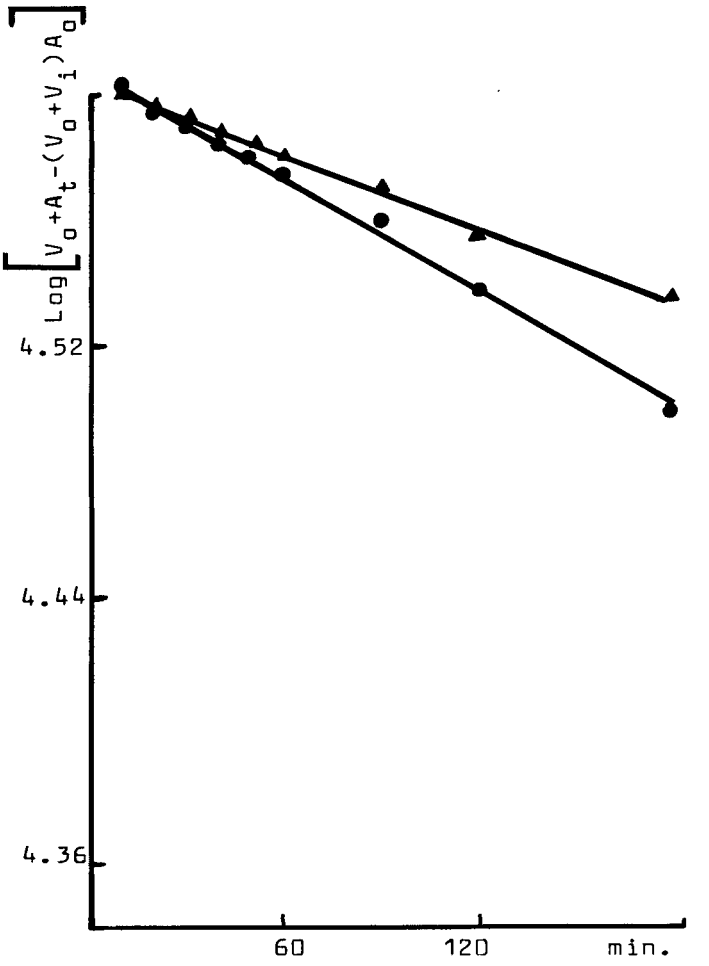

FIGURE 2

Release of Indomethacin from Suppository Bases.
Witepsol S55 (▲); Witepsol W35 (●).

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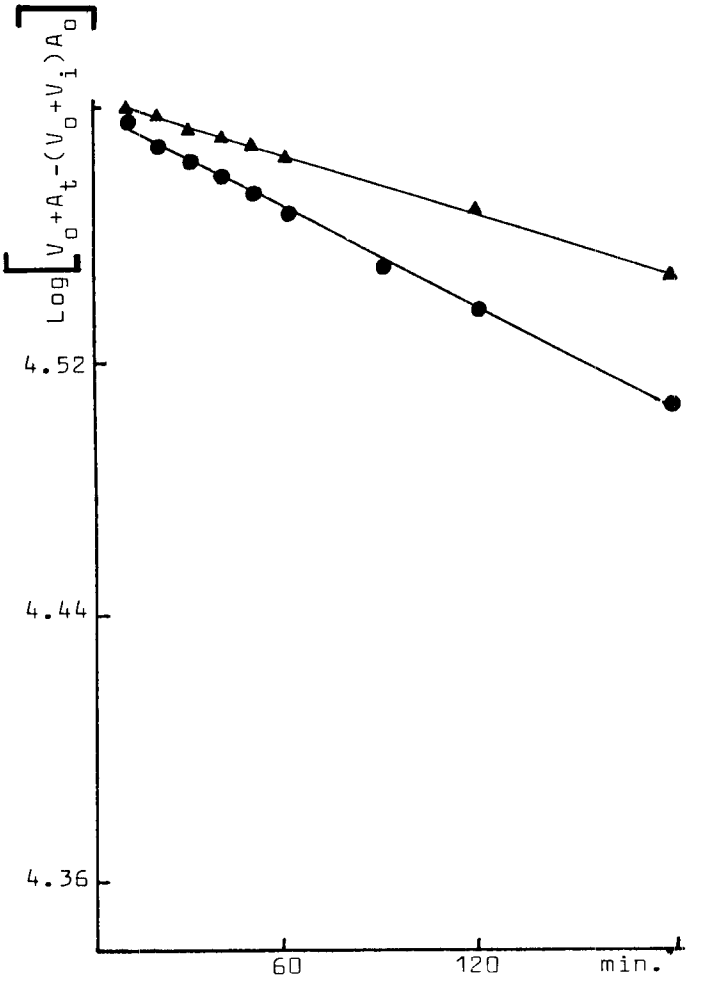

FIGURE 3

Release of Indomethacin from Suppository Bases.

Novata BCF (▲); Novata E (●).

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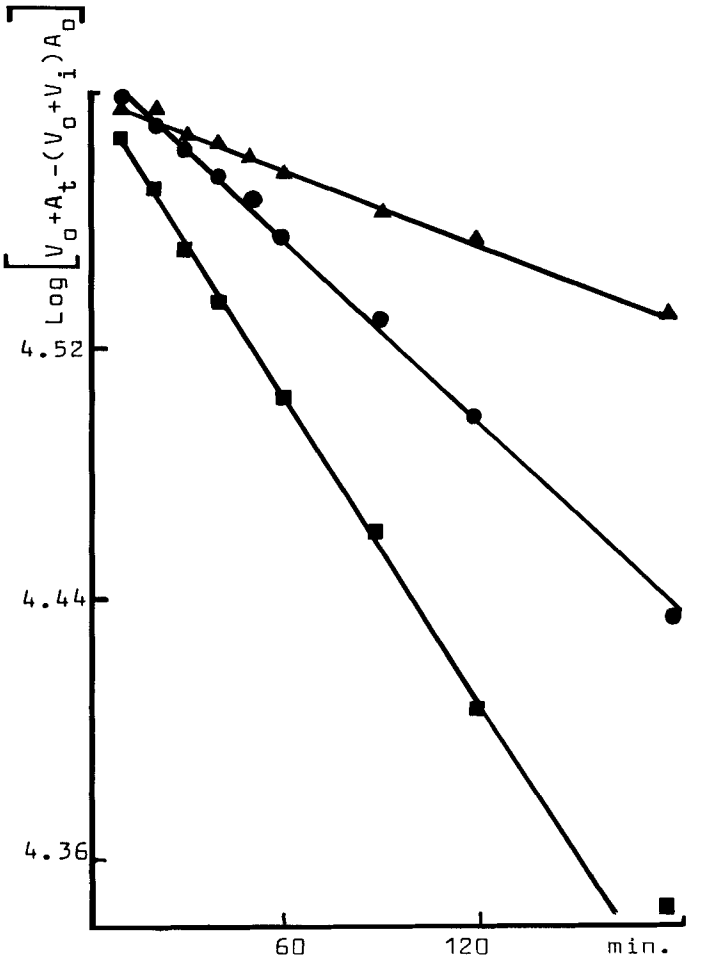

FIGURE 4

Effect of Surfactants on the Release of Indomethacin from Witepsol H35. Tween-80 (▲); Sodium Lauryl Sulphate (●); Dioctyl Sodium Sulphosuccinate (■).

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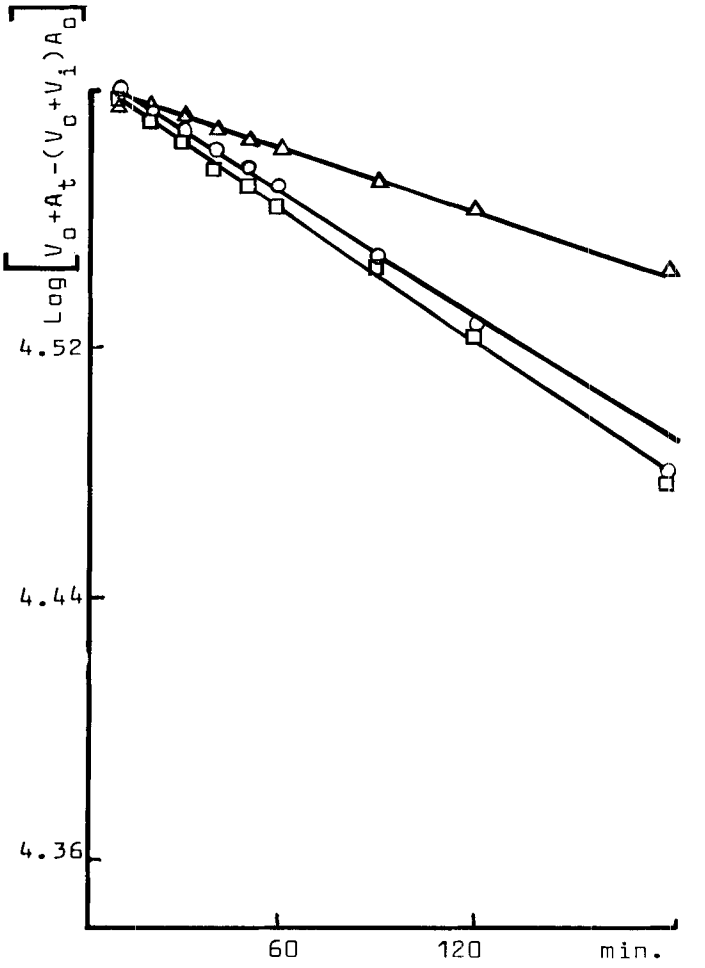

FIGURE 5

Effect of Pharmaceutical Additives on the Release of Indomethacin from Witepsol H35. White Beeswax (△); Cetyl Alcohol (○); Colloidal Silicon Dioxide (□).

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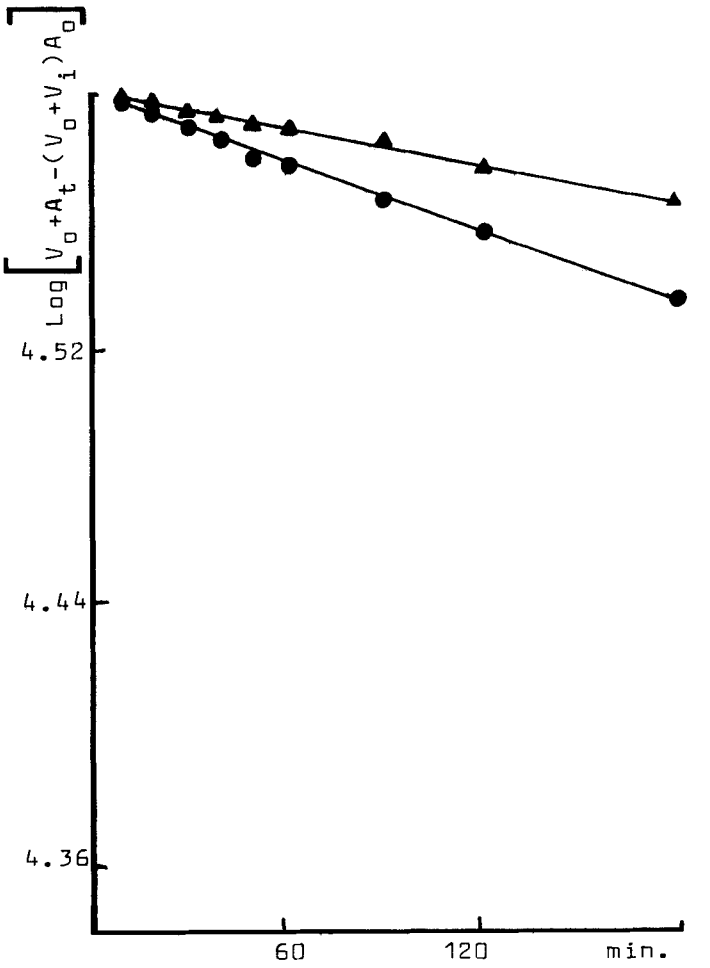

FIGURE 6

Release of Indomethacin from Commercial Suppositories.
Brand D (▲); Brand E (●).

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1-6). The apparent dialytic rate constant, K, was calculated as follows:

$$K = \frac{-(\text{slope})(2.3)(V_i V_o)}{V_i + V_o}$$

(See Table 1)

Results obtained from samples formulated in water soluble bases, viz. polyethylene glycol (PEG), were only

TABLE 1

Calculated Dialytic Rate Constants of Indomethacin Suppository Formulations.

	Suppository Formulation	Dialytic Rate Constant K ($min.^{-1}$) x 10^{-2}
1	Witepsol H35	3.83
2	Witepsol H15	2.39
3	Witepsol W35	2.50
4	Witepsol S55	1.69
5	Novata E	2.26
6	Novata BCF	1.35
7	Witepsol H35 + Tween-80	1.69
8	Witepsol H35 + SLS	4.09
9	Witepsol H35 + DSS	7.01
10	Witepsol H35 + W8W	1.46
11	Witepsol H35 + SiO_2	2.93
12	Witepsol H35 +Cetyl alcohol	2.92
13	Brand A	2.64*
14	Brand B	2.72*
15	Brand C	2.79*
16	Brand D	0.80
17	Brand E	1.64

*Calculated over the first hour.

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TABLE 2

Release of Indomethacin from Suppositories Formulated in Water Soluble Bases.

Time (min.)	$\log (V_o A_t - (V_o + V_i) A_o)$		
	Brand A	Brand B	Brand C
10	4.593	4.594	4.595
20	4.587	4.589	4.588
30	4.582	4.581	4.582
40	4.576	4.575	4.576
50	4.571	4.570	4.570
60	4.565	4.563	4.563
90	4.540	4.540	4.539
120	4.512	4.502	4.509
180	4.436	4.440	4.425

linear over the first hour and are presented in table form (Table 2).

The amounts of indomethacin released from Witepsol and Novata bases are depicted in figures 1 to 3. No clear conclusion could be arrived at from the examination of these results. However, two factors were apparently found to be of some significance; these are the hydroxyl values and the solidification points of the suppository bases (Table 3). The synthetic suppository bases are mixtures of fatty acid esters with certain amount of glycerides and their hydroxyl values represent the presence of mono- and diglycerides and therefore the availability of free hydroxyl groups in the bases.

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TABLE 3

Hydroxyl Values and Solidification Points of Witepsol and Novata Bases.

Base	Hydroxyl Value	Solidification Point °C
Witepsol H15	< 15	32.5 - 34.5
Witepsol H35	< 3	32.0 - 35.0
Witepsol W35	40 - 50	27.0 - 32.0
Witepsol S55	50 - 65	28.0 - 33.0
Novata BCF	20 - 30	30.0 - 32.0
Novata E	45 - 60	29.0 - 31.0

Unexpectedly, drug release from bases with low hydroxyl values (Witepsol H35 and Witepsol H15) was shown to be faster than from Witepsol S55 which has a higher hydroxyl value. Witepsol H35 (hydroxyl value < 3) showed the highest rate of release. A similar finding was also obtained by Becirevic et al. (11) in their work on the release of meclozine from different suppository bases. These results could not be accounted for on the basis of simple partitioning of the drug between lipid and aqueous phases since indomethacin would be expected to exhibit higher affinity for the lipid base than for the aqueous environment.

However, the fact that the pH of the aqueous medium used in these sets of experiments was 8.0 may account for the higher release of indomethacin (pKa = 4.5) from bases

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with a low hydroxyl value into the aqueous medium since the drug would be over 99.9% ionized at this pH. In contrast, the partitioning of the drug, when using bases with high hydroxyl values, appears to favour the lipid phase which is indicated by the lower rate of release observed with these bases. Also, the Witepsol S series comprises special grades and contain surface active agents which could act to enhance or retard drug release as shown later in this work and confirmed by other workers (11, 12).

Consideration of hydroxyl values could not account alone for the apparent dialytic rates observed in all bases used in this study, since Witepsol W35, despite having a higher hydroxyl value than Witepsol H15, showed a slightly higher rate of release. Examination of the solidification points shows Witepsol W35 to have a lower point than Witepsol H15, which could result in a faster release of the drug. This observation is in accordance with the finding of Eckert and Muhlemann (15) in their work on the effect of temperature and melting points on the release of drugs from fatty bases. In this case,the solidification point appears to play, at least in part, a greater role in release. This point may also be exemplified by the faster release of the drug from Novata E compared with Novata BCF. Novata E has a higher hydroxyl value but a lower solidification point than Novata BCF. However, Novata E is an emulsion type

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base which would introduce a further complicating factor in the mechanism of drug release.

On examining the effect of surface active agents on the release characteristics of indomethacin from Witepsol H35, conflicting results were observed (Figure 4). Inclusion of dioctyl sodium sulphosuccinate (DSS) in the suppository formulation exhibited the most pronounced effect on the rate of release of the drug and resulted in over 80% increase in the dialytic rate constant (Table 1). In contrast,the use of Tween 80 resulted in around 55% decrease in the release of indomethacin, while sodium lauryl sulphate (SLS) showed no apparently significant effect on the release profile.

These results could be interpreted in terms of micellar solubilization of the drug with surface active agents. The addition of a surfactant to a suppository formulation affects drug release from the suppository and the drug diffusion through the semipermeable membrane. The membrane would not be expected to be permeable to the micellar solubilized drug and only an unsolubilized form of the drug can diffuse through the membrane.

The addition of cetyl alcohol, white beeswax (WBW) or colloidal silicon dioxide to the suppository base (Witepsol H35) was found to decrease the rate of release of indomethacin (Figure 5). White beeswax exhibited the highest retarding effect on the release of the drug, and

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resulted in over 60% decrease in the dialytic rate constant. This could partly be explained in terms of these substances effect on the melting point of suppository bases, since such additives are known to increase the melting point and therefore decrease the rate of release.

Determination of drug release from a number of commercial products containing indomethacin in water soluble bases (Table 1 and 2) or lipid bases (Figure 6 and Table 1) revealed that release of indomethacin was highest from PEG-based formulations. This would suggest the better suitability of PEG bases for use in indomethacin suppositories. However, the inclusion of DSS in lipid bases may offer an alternative formulation with good release properties.

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