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Formulation of Fenbufen suppositories. II. Selection of a suppository base using dissolution studies and histological studies in rats

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Summary

The dissolution of fenbufen and ethanolamine fenbufen from Polyethylene glycol 1500, Witepsol H12 and Suppocire AP suppository bases was determined. The more soluble ethanolamine salt produced significantly faster dissolution than the parent drug, with the Witepsol H12 base giving the most rapid release. In vivo studies showed that the incorporation of ethanolamine fenbufen into Witepsol H12 increases the morphological change in the rectal tissue 1 h after insertion but there was no difference with the control tissue after 24 h. The data highlights the importance of parallel in vitro and in vivo studies in the development of rectal formulations.

Introduction

Rectal drug delivery is used to overcome problems of first-pass metabolism, gastrointestinal irritation or patient compliance that may be associated with oral administration of drugs. Suppository formulation can affect both the rate and the extent of drug absorption (Senior, 1974). Although in vitro dissolution procedures are used to compare drug release profiles from different bases, experimental data have shown that a poor in vitro/in vivo correlation is often obtained (Muller, 1984; Touitou and Yosselson-Superstine 1985). There are several possible physiological factors that may be responsible for this. One factor that is frequently overlooked is the possible interaction of the base and the base/drug complex with the rectal mucosa which could significantly alter the barrier to drug absorption.

Our preceding paper (Reid et al., 1987) has reported the interaction of a number of bases with the rectal mucosa. In this report the in vitro dissolution of fenbufen, a non-steroidal anti-inflammatory agent, and its ethanolamine salt, from a hydrophilic, hydrophobic and amphiphilic suppository base, namly Polyethylene glycol 1500 (PEG), Witepsol H12 and Suppocire AP respectively, was investigated. The morphology of the rectal tissue 1 and 24 h after rectal administration to rats of the ethanolamine salt in Witepsol H12 base was assessed.

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Materials and Methods

Materials

Fenbufen (melting point 186°C) and its ethanolamine salt (melting point 127°C) were provided by Cyanamid (U.K.). The 3 suppository bases, PEG 1500 (Hythe Chemicals, Hythe, U.K.), Witepsol H12 (Dynamit Nobel, Slough, U.K.) and Suppocire AP (Alfa Chemicals, Wokingham, U.K.) were used as received.

Methods

Suppositories (1 g) containing 225 mg fenbufen or the equivalent weight of the ethanolamine salt (280 mg) were prepared in each of the 3 bases, by heating the base over a water bath and dispersing the solid micronised drug into the molten base. With continuous stirring the melt was then poured into the suppository moulds and left to cool. After 10–15 min the suppositories were removed and left for at least 24 h prior to testing.

Dissolution study

The dissolution profile for each formulation was determined using a modified USP paddle dissolution apparatus. The length of the paddles was reduced to 21 cm in order to allow for a wire mesh stand (diameter 8 cm, height 4 cm, mesh 2 mm) to be placed at the bottom of each vessel in order to retain the suppository. The paddles were rotated at 50 rpm in a dissolution medium of pH 7.8 phosphate buffer. Filtered samples were assayed spectrophotometrically at 278 nm.

In vivo study

Suppositories (mean weight 69 mg) of ethanolamine fenbufen (1.4 mg) in Witepsol H12 and of Witepsol H12 alone, were prepared and administered to anaesthetised rats as described previously (Reid et al., 1987). Rectal tissue samples from rats either 1 or 24 h after treatment were analysed for morphological changes and compared to an untreated control as described in the previous paper.

TABLE 1

Time (min) for 50% dissolution of drugs from the bases (mean ± S.D. n = 6)

	Fenbufen	Fenbufen ethanolamine
PEG	23.26 ± 2.38 [d]	7.61 ± 0.84 [abd]
Witepsol H12	> 90	4.87 ± 0.89 [ac]
Suppocire	22.92 ± 12.17	15.42 ± 4.30 [bc]

For a vs a, b vs b, c vs c, d vs d, $P < 0.05$

Results

Dissolution study

The dissolution profiles for the different formulations are shown in Figs. 1 and 2. The times to 50% dissolution are given in Table 1; the data were compared using the Student's unpaired *t*-test. The semi-logarithmic plots of the data for the ethanolamine salt are shown in Fig. 3. The graph indicates that the dissolution from each base followed two first-order rate processes, although there are generally insufficient points in the second phase to characterise this fully. The rate constants (k) for the first rate process were 0.036, 0.083 and 0.021 min^{-1} for PEG, Witepsol H12 and Suppo-

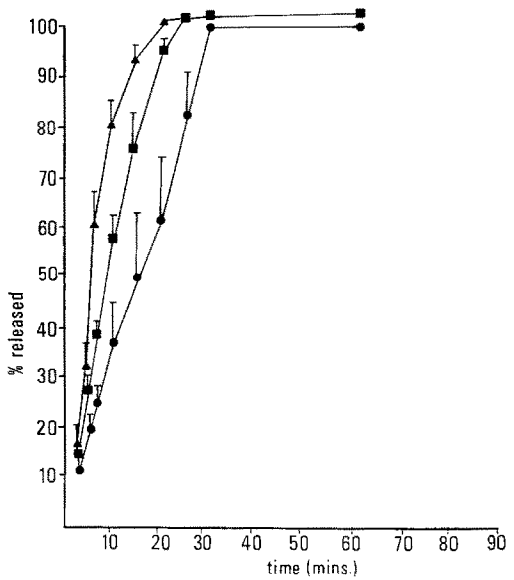

Fig. 1. Release profiles of fenbufen from suppositories containing the ethanolamine salt. ■, PEG; ▲, Witepsol H12; ●, Suppocire AP. Mean + S.D., $n = 6$.

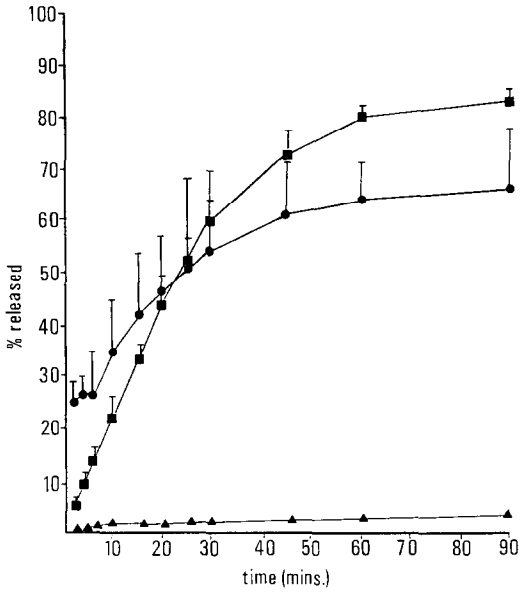

Fig. 2. Release profiles of fenbufen from suppositories containing the parent drug. ■, PEG; ▲, Witepsol H12; ●, Suppocire AP. Mean + S.D., $n = 6$.

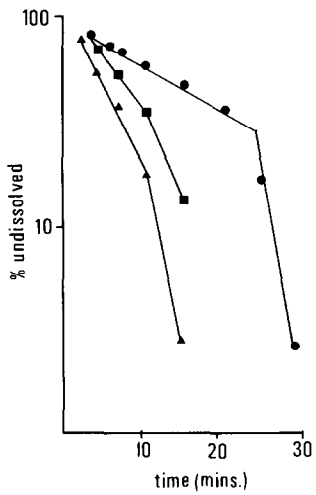

Fig. 3. Semilogarithmic plots of fenbufen ethanolamine release from suppositories of PEG (■), Witepsol H12 (▲) and Suppocire AP (●).

cire AP, respectively. Treating the dissolution of fenbufen in the PEG base similarly (first order rate process $k = 0.0126\ \text{min}^{-1}$) showed release was slower than with the ethanolamine salt.

In vivo study

The changes in tissue morphology observed are shown and described in Table 2. At 1 h Witepsol H12 induced a significant type 1 change compared to the control, but after 24 h this returned to control levels. The incorporation of ethanolamine

TABLE 2

Counts of the 3 types of changes observed in the rectal epithelium between the anorectal junction and the 100 gland interglandular site of the rat following suppository treatment (mean ± sem, n = 5)

Treatment	Type of change	Interglandular sites				
		1–20	21–40	41–60	61–80	81–100
Untreated control	1	1.4 ± 0.6	1.4 ± 0.3	1.2 ± 0.2	1.6 ± 0.4	0.9 ± 0.2
Witepsol H12	1	3.8 ± 0.8	4.5 ± 1.2	6.0 ± 1.3	5.8 ± 0.3	4.9 ± 1.4
	2	0.1 ± 0.1	0	0.2 ± 0.1	0.6 ± 0.2	0.3 ± 0.1
Witepsol H12 plus	1	2.2 ± 0.5	2.6 ± 0.5	4.1 ± 0.6	5.1 ± 0.3	4.2 ± 0.8
ethanolamine salt of	2	0.2 ± 0.2	0.3 ± 0.1	1.5 ± 0.6	2.0 ± 0.6	2.3 ± 0.7
Fenbufen	3	0.1 ± 0.1	0	0	0.6 ± 0.3	1.0 ± 0.6
Witepsol H12 24 h after	1	1.0 ± 0.4	1.0 ± 0.1	1.2 ± 0.4	1.1 ± 0.3	1.5 ± 0.6
treatment	2	0	0	0	0.1 ± 0.1	0.1 ± 0.1
Witepsol H12 plus	1	1.8 ± 0.4	1.7 ± 0.2	1.5 ± 0.6	1.7 ± 0.5	1.7 ± 0.6
ethanolamine salt of	2	0	0	0.1 ± 0.1	0.1 ± 0.1	0.2 ± 0.1
Fenbufen 24 h after	3	0	0	0	0	0.1 ± 0.1
treatment						

Type 1 change: cells detached from surface or in process of detachment. Type 2 change: epithelium reduced in height being composed of cuboidal and/or squamous cells. Type 3 change: complete epithelial desquamation and bare basal lamina.

fenbufen induced type 2 and type 3 changes in the tissue at 1 h, although after 24 h the tissue showed significant repair with data approaching control levels.

Discussion

The study demonstrates the importance of considering both the release characteristics of a drug from suppository formulations and the interaction of the drug base complex with rectal mucosa.

The release of the fenbufen ethanolamine salt was significantly faster than that of fenbufen from each of the suppository bases. This is probably due to the greater aqueous solubility of the salt (solubility fenbufen 0.88 mg/ml, fenbufen ethanolamine 5.70 mg/ml). Comparison of the *t* 50% values showed that overall the ethanolamine salt was released faster from the hydrophobic Witepsol H12 base than the hydrophilic PEG base and release was slowest from the Suppocire AP base. However, statistical analysis of the *t* 50% values appears of little utility in comparatively assessing drug dissolution from the suppository bases due to the mixed mechanisms for release involved.

The biphasic first-order release processes exhibited by the ethanolamine salt suggests that initially drug release is limited by the available surface area of the suppository and is controlled by the spreading or dissolution of the base. The second phase of the dissolution profile then corresponds to the dissolution of the drug from the base. Witepsol H12 has a melting point of 32–33° C and therefore melts rapidly and spreads on insertion or dissolution, producing a very rapid first phase dispersion process. Because of the very low partition of the salt into the hydrophobic base, dissolution occurs rapidly in the simulated rectal fluid (Grant et al., 1983). PEG bases liquify by absorption of water producing swelling and dissolution of the suppository. This leads to a dispersion process that is some 2–3 times slower than the melting point of the Witepsol base. Suppocire AP has a melting point of 35–37° C and therefore has a slower initial melting phase than the Witepsol base resulting in slower overall drug release.

In contrast to and irrespective of the preferable initial phase melting/spreading behaviour, dissolution of the parent drug, fenbufen, was minimal from Witepsol H12 base. Clearly the poor water solubility of the parent drug, the favourable partitioning into the hydrophobic base and the relatively high drug content prohibits rapid drug release. The formulation appears to require a hydrophilic base to promote efficient penetration of water into the base and the subsequent dissolution of the drug. This is demonstrated by the faster dissolution of fenbufen when formulated in the PEG and Suppocire AP bases.

The initial rapid drug release from the Suppocire AP base may result from efficient dispersion of the base caused by an orientation of hydrophilic component of the base to the outer layer of the suppository or from dissolution of fenbufen located at the surface. A slower more erratic release was then observed in comparison to the PEG base, which may have been due to the mixed nature of the base.

These in vitro data indicate that a greater drug bioavailability would be achieved with the ethanolamine salt in comparison to the parent drug and that either Witepsol or possibly PEG would be suitable suppository bases. The results of the previous investigation suggested that PEG bases are more likely to irritate the rectal mucosa than the Witepsol bases. The ethanolamine salt of fenbufen in Witepsol H12 base was therefore selected for the in vivo study.

The incorporation of ethanolamine fenbufen into Witepsol H12 increased the interaction of the suppository with the rectal tissue producing small but insignificant rectal irritation (Reid et al., 1987). Type 3 change to the tissue was not extensive as produced by pure PEG 1500 suppositories. The oral administration of non-steroidal anti-inflammatory agents is known to be associated with gastric irritancy. It is therefore not unexpected that incorporation of fenbufen into the Witepsol base increased the interaction of the formulation with the rectal mucosa. However, after 24 h a normal mucosa was restored.

The interaction of the ethanolamine fenbufen Witepsol H12 suppository with the rectal mucosa could alter the barrier to drug absorption, in turn

influencing the plasma drug profile. Variance from the predicted in vivo behaviour using in vitro dissolution data could result. Thus this study illustrates the value of parallel in vitro and in vivo investigations in the development of rectal formulations.

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