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INFLUENCE OF ADJUVANTS OF POLYETHYLENE GLYCOL SUPPOSITORIES ON THE PHYSICAL CHARACTERISTICS AND DRUG BIOAVAILABILITY IN RABBITS

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ABSTRACT

Theophylline suppositories were made by the fusion method, using a polyethylene glycol base. Formulations were prepared containing theophylline in the plain base, and in base with added sodium salicylate or lecithin-sodium deoxycholate as adjuvants. Changes in melting range over time were studied. Differential scanning calorimetry studies characterized the physical nature of the formulations as being brittle or elastic. These data were confirmed by concurrently measuring the initial slope of stress - strain curves obtained at constant strain rate during hardness determination. Release rates were determined with a modified dissolution basket containing glass beads and dialyzing membrane. It was found that drug release rate from plain suppository base > base containing lecithin-sodium deoxycholate > base with sodium salicylate. *In vivo* bioavailability of theophylline after rectal administration in rabbits showed that rectal absorption was not enhanced in the presence of adjuvants, and theophylline was

x Correspondence

completely absorbed. These methods may be used as both predictive and ongoing physical stability tests during development and evaluation of water soluble suppositories and formulas.

INTRODUCTION

Suppositories are indicated for systemic action when problems are associated with oral and parenteral administration. Such problems include drug inactivation in the upper GI tract or the liver; drug administration in infants, in patients who are comatose or who cannot tolerate oral medication due to emesis or pathological conditions of the gastrointestinal tract. There are conflicting opinions on the amount of drug to be given rectally as compared with the oral dose. Rectal delivery is also hampered by poor and inconsistent absorption of many drugs. Generally, suggested rectal doses range from one and a half times to twice the oral dose. Assuming constant physiological factors, the appropriate rectal dose would depend on the suppository formulation and physicochemical properties of the drug. Thus, pharmaceutical factors may be rate limiting and influence the bioavailability and dose of a drug administered.

Polyethylene glycols (PEG) are among the most widely used of the hydrophilic polymer suppository bases. Drug liberation occurs as a result of base dissolution into the aqueous environment of the rectum, differing radically from the lipophilic bases which melt at body temperature and act as a reservoir from which transport through the fat/water interface occurs prior to absorption. The use of PEG in some instances has produced plasma levels similar to equivalent oral doses[1-2]. Studies on drugs incorporated into a polyethylene glycol matrix include those on acetaminophen[3], iodoform[4], thiazinamium and indomethacin[5-6], chloramphenicol[7], sulfonamides[8], antipyrine and sodium barbital[9], diphenhydramine and its hydrochloride salt[10], oxytetracycline[11] and other antibiotics[12]. When selecting a suppository base, it

may be generally accepted that lipophilic drugs are best formulated in hydrophilic bases, and water soluble compounds are best formulated in lipophilic bases for rapid and complete release.

Recently much attention has been paid to the influence of absorption enhancers in the suppository formulation. Although the mechanisms of action of these absorption promoters are unknown, direct effects on the biological barrier (e.g. surfactants) is a distinct possibility. In addition, compounds with pharmacological activity involving alterations in cellular membrane function (e.g. phenothiazines) may also enhance drug transport across biological membranes. Both salicylate and cholate adjuvants enhance bioavailability of theophylline, sodium cefoxitin, lidocaine, levodopa[13-14] and insulin[15]. Furthermore, it has been found that rectal absorption of theophylline solution (having optimum ionic strength) in rats was facilitated by concurrent administration of sodium salicylate[13, 16].

The aims of this study were to elucidate the influence of adjuvants on the physical stability of synthetic suppository bases, and to evaluate those parameters relevant to in-process control during production. In addition, rectal absorption of theophylline from polyethylene glycol suppositories, as opposed to absorption from solutions of known ionic strength, in the presence and absence of sodium salicylate or a premicellar concentration of lecithin-sodium deoxycholate, was investigated.

EXPERIMENTAL

Materials

Theophylline anhydrous B.P. quality and sodium salicylate, sodium-deoxycholate and polyethylene glycol 1000-4000 (BDH-Chemical Ltd., Poole, England) were used. Ovolecithin was obtained from Merck, Darmstadt, W. Germany. Hanson dissolution drive control and multiple spindle drive (B. Braun Melsungen AG) and Beckman Model 25 spectrophotometer were used in dissolution studies and analyses. Male, white New Zealand rabbits weighing

between 2.8 and 3.5 kg were included in the studies. A Differential Scanning Calorimeter (DSC) Perkin Elmer DSG2 Model 3500 data station and aluminium DSC sample pans were used to obtain the thermograms. An Instron compression machine Model 4301 (Instron Ltd, England) was used for hardness determinations. Serum theophylline was measured using a TDX-analyser system (Abbott Laboratories).

METHODS

PREPARATION OF SUPPOSITORIES

Theophylline suppositories, 500 mg, containing 20 mg of drug, were prepared with polyethylene glycol 1540 (96% m/m) and PEG 4000 (4% m/m) as base. The displacement factor for the drug and adjuvants was determined as in equation 1:

$$F = XB/100(A-B) + XB \quad \text{..... eq. 1}$$

where F is displacement value of a drug, A is standard weight of unmedicated suppository (g), B is weight of suppository with theophylline or combination with adjuvants (g) and X is active ingredient per suppository (%).

All suppositories were prepared by the fusion method using a metal mold with 12 cavities. Various formulations were produced: (A) contained 20 mg theophylline and 20 mg sodium salicylate in PEG. (B) contained 20 mg theophylline and 1.5% lecithin-sodium deoxycholate in PEG. (C) contained 20 mg theophylline in plain PEG base. The filled mold was held at 5°C for 24 h. Suppositories were then removed and kept in screw cap bottles in the refrigerator until required. Disintegration times and content uniformity tests were determined following the B.P. 1980 procedure.

DESIGN OF BASKET AND BEAD BED

The USP dissolution basket was modified to provide better and more precise control over the interfacial area for drug

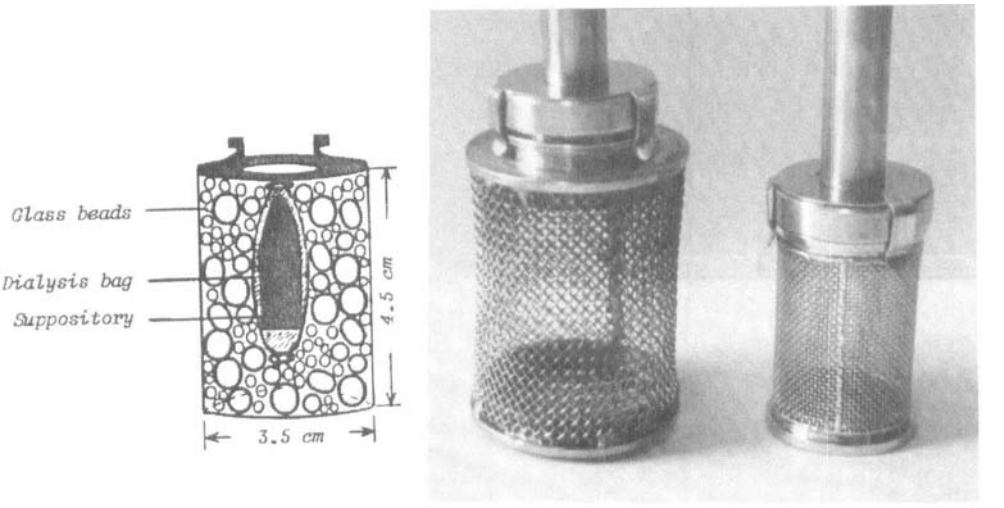

Figure 1

Modified dissolution basket, bead-bed and dialysis bag for supposity dissolution study.

dissolution and to maintain a constant hydrodynamic condition. In addition the modified basket could easily be mounted into a dissolution drive rod of the standard dissolution apparatuses. The basket consisted of a stainless steel screen (20 mesh), chemically resistant glass beads of 3 to 6 mm diameter, and a dialyzing membrane (Fig. 1).

IN VITRO RELEASE FROM SUPPOSITORIES

Cellophane dialyzing bags were soaked overnight in distilled water before use. After rinsing the bags, the suppository was placed into a dialysis bag (simulating the rectal mucosa) and 1.5 ml of deionised water was placed in each bag which was then placed in the test basket half-filled with glass beads. The remainder of the basket was filled with glass beads, mounted in

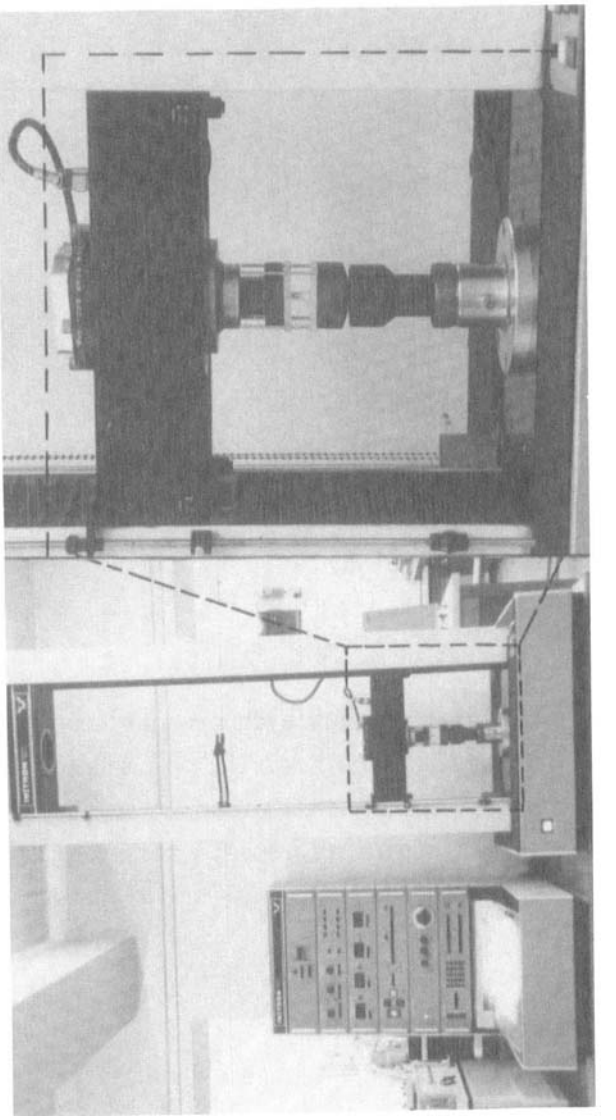

Figure 2

The Instron compression machine and the designed suppository holder unit used to obtain the force-time curves.

position and lowered into the 1 liter beaker containing 500 ml of distilled water maintained at 37 ± 0.5°C. Drug release was monitored with a UV spectrophotometer (272 nm) at a paddle speed of 50 rpm. The cumulative amount released was determined from the standard curve.

DIFFERENTIAL SCANNING CALORIMETRY (DSC) STUDIES

The melting property was investigated by the DSC technique to obtain the transition temperatures of different suppository formulations. The physicochemical status of theophylline-PEG preparations was investigated in the presence of various adjuvants over 6 months. In order to identify any changes in melting behaviour attributed to hardening of suppositories, and influencing the pharmacokinetic characteristics of the active ingredient, DSC measurements were conducted with a Perkin-Elmer DSC apparatus at a heating rate of 5°K min^{-1}.

BREAKING TEST (HARDNESS)

Hardness of PEG based suppositories is important for manageability as well as drug dissolution and release. Measurements were conducted using an Instron compression machine. Individual suppositories were placed in the sample holder (Fig. 2) and force-time curves were obtained for various formulations. Samples of identical geometry and size were compressed at a constant strain rate under reproducible temperature conditions. Suppositories were stored for at least 24 hours at the testing temperature (25°C ± 0.5°C) prior to the determination.

ADMINISTRATION AND BLOOD SAMPLING

Rabbits were fasted overnight with water available *ad libitum*. On the day of the experiment, the animals were anaesthetized with intraveneous pentobarbital, 35 mg/kg, and immediately thereafter one suppository was inserted per rectum. Nine rabbits were used in this study. Blood samples (2.5 to 3.0 ml) were drawn from the marginal ear vein at suitable time

intervals, and placed in heparinized tubes. They were centrifuged within two hours and the serum was separated and frozen at -20°C until analysis. Serum concentrations were measured by fluoresence polarization immunoassay.

RESULTS AND DISCUSSION

The definition of rectal suppositories as reported in USPXX pharmacopeia specifically states that "suppositories should usually melt, soften or dissolve at body temperature". However, these characteristics are of little value, unless the method of their determination is given. A precise and reproducible method for determining the melting range is thermal analysis, and knowledge of the melting transitions is useful in deciding whether a suppository is sufficiently firm to be introduced into the rectum or handled and stored at ordinary room temperature or in warm environments. Melting ranges were determined using the DSC techniques. Figures 3 and 4 show transition temperatures of different suppository formulations. In Fig. 3 the DSC thermograms of freshly prepared suppositories are shown, illustrating a narrow melting range for all formulations. The difference in thermal behaviour of samples from the bulk and from the surface of the suppositories was not significant. Figure 4 shows the physicochemical status of theophylline-PEG preparations in the presence of adjuvants within a storage period of 6 months. The thermogram of formulations containing lecithin-sodium deoxycholate as adjuvant appears to be unchanged, but slight alteration of the melting range is seen for other formulations. This hardening effect could be due to changes in the polymorphic transformation, interaction of the formulation components, or lattice defects introduced by the thermal treatment during production.

It is important for systemic action that disintegration or dissolution should take place quickly and quantitatively, and compositions should be designed to reflect this objective.

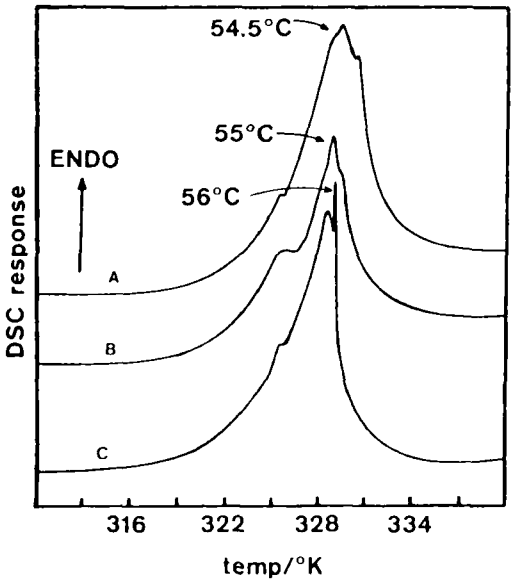

Figure 3

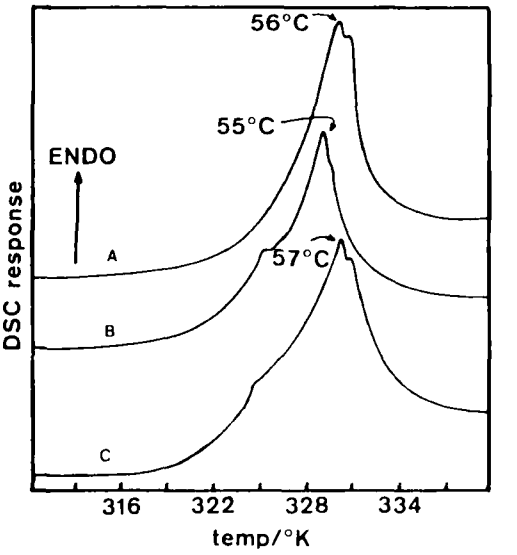

Figure 4

DSC thermograms of freshly prepared (figure 3) theophylline-PEG suppository formulations: A, with sodium salicylate; B, with lecithin-sodium deoxycholate; C, without adjuvants and after a storage period of 6 months (figure 4).

Results of disintegration times determined according to the B.P. procedure, and the content uniformity of suppositories, are given in Table 1. The theophylline content was 100 ± 2.5% of the calculated amount and disintegration times and content uniformity were unchanged after six months. These results indicate that the disintegration times of water soluble bases used in this study remained constant during the storage period. The blend of polyethylene glycols composed of 96% PEG 1540 and 4% PEG 4000 was selected as a suitable base.

The breaking test was designed to measure brittleness and fragility of suppositories. Breaking load of various formulations of theophylline suppositories as a function of time is shown in

TABLE 1

Disintegration time and theophylline content of suppositories

Formulation	Disintegration time (min)			Average time (min)	Theophylline[a] content (mg)
A	12	16	14	14	19.5 ± 0.81
B	17	19	21	19	20.3 ± 0.64
C	10	11	14	11.6	20.0 ± 0.82

[a] Results are reported as mean ± SD

Note: no significant differences were observed in disintegration times or drug content of the suppositories after a storage period of six months.

Fig. 5. The curves illustrate the degree of deformation and brittleness of suppositories. A steep curve (formulation C: plain base) indicates brittleness, whereas less steep curves with plateaus (formulations A and B) indicate greater elasticity of the suppository base containing sodium salicylate and lecithin-sodium deoxycholate. These physical characteristics could also be observed from the DSC thermograms of freshly prepared suppository formulations (Fig. 3). A sharp melting transition in the case of formulation C further confirms the brittle nature of this formulation, whereas a broader melting transition was obtained for more elastic types. However, these characteristics changed slighly after storage for six months at room temperature, as shown by dashed lines in Fig. 5. The mechanical strength of suppositories changes with interactions among many variables. Therefore, knowledge of the approximate molecular weight of polymers used, the storage conditions, breaking load and aging can serve as a useful composite guide for predicting physical characteristics of the base.

The release of theophylline from various formulations of polyethylene glycols using the USPXX paddle dissolution apparatus

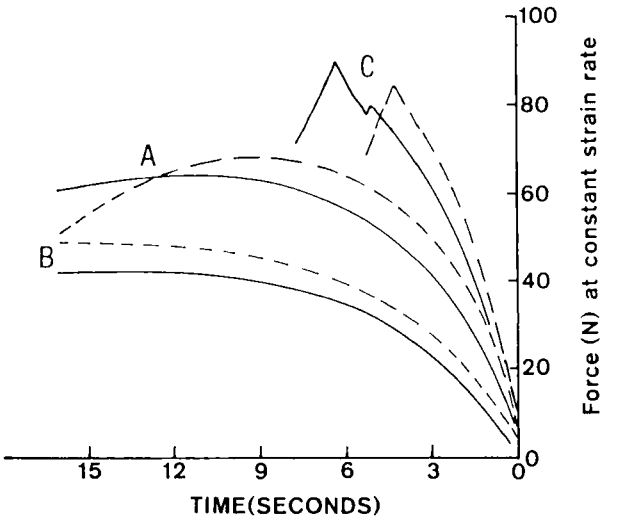

Figure 5

Force-time curves for various formulations of theophylline suppositories. Freshly prepared (——) and after six months storage period (----).

is shown in Fig. 6 (Insert). The data indicate that due to the water solubility of polyethylene glycol base, the influence of formulation parameters on drug release is masked. Therefore, the USP dissolution apparatus as such cannot be used for determination of the medicament release from water soluble bases. Membranes have been used to control the interfacial area on the assumption that when the suppository softens (in the case of fat-type bases) it would spread over the entire membrane, restricting the area exposed to the dissolution fluid[17]. However, the introduction of an additional physical process, i.e. membrane transport, complicates matters and may mask the release kinetics. Thus a continuous flow bead-bed dissolution apparatus was developed to provide greater constancy of the exposed suppository area for dissolution of fat-type suppository bases[17].

However, the inutility of the abovementioned method with water soluble bases led to the use of membrane, bead-bed and a

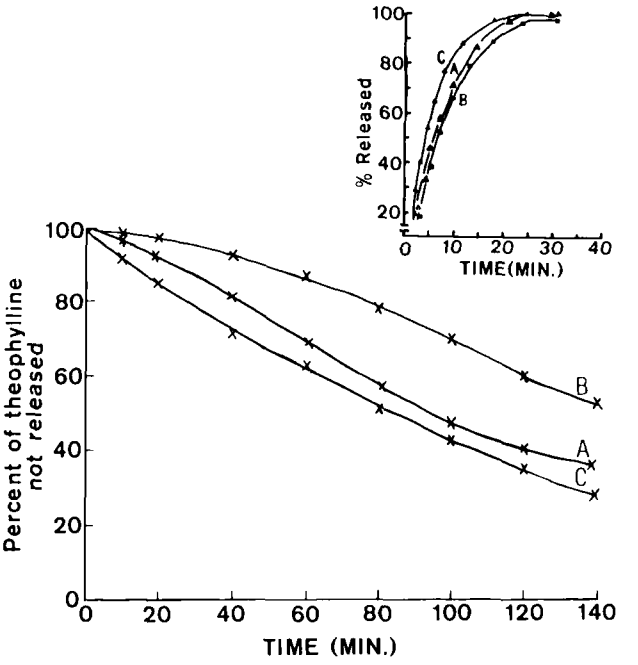

Figure 6

Percentage of theophylline not released from different suppository formulations versus the time (min) using the dialyzing tubing and bead-bed method. Insert: Percentage of theophylline released from different formulations versus time using the USPXX dissolution apparatus.

modified dissolution basket to control the dissolution process in the present report. The release of theophylline from several suppository formulations was measured in a modified dissolution basket with bead-bed and dialysis bag (see Methods). The suppositories were placed in a dialyzing membrane and bead-bed to ensure that the interfacial area and hydrodynamic conditions during dissolution were reproducible. The dissolution results indicate good reproducibility of drug release (Fig. 6). The release profiles of theophylline are shown in terms of percent of unreleased drug as a function of time from suppository formulations A, B and C. Each dissolution profile represents an

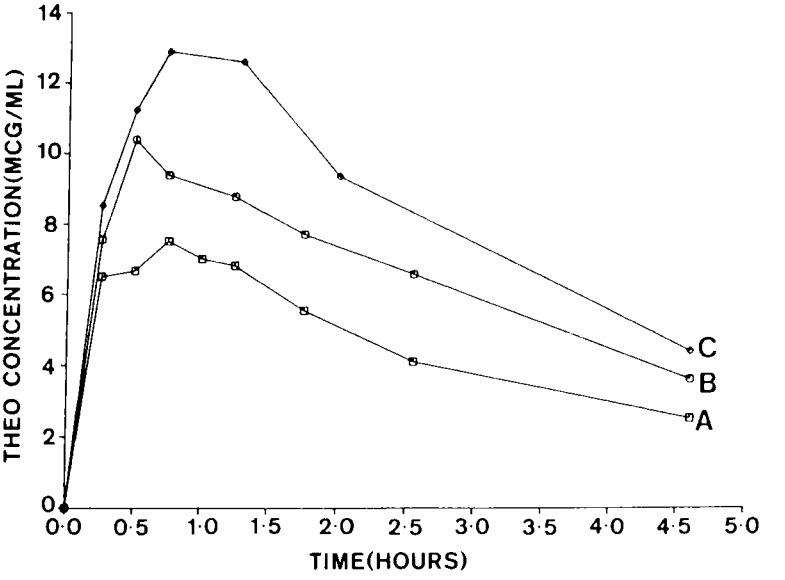

Figure 7

The influence of various suppository formulations on theophylline absorption. (Typical individual serum profiles for 3 rabbits).

average of three determinations. It appears that theophylline dissolves most rapidly when formulated with the plain base, followed by formulations containing lecithin-sodium deoxycholate and sodium salicylate respectively. Although a lag time of up to 20 minutes was observed for formulations A and B, the differences in release profiles between various formulations could be determined and further investigation is under way to optimize the technique.

The bioavailability of a drug after administration in a suppository is often incomplete and irregular. Causes of this irregular drug uptake from water soluble bases are, among other factors, variability in the dissolution and release of drug, and interactions between drug, formulation components and physiological agents. Figure 7 shows rectal bioavailability of theophylline. Bioavailability parameters are shown in Table 2.

TABLE 2

Summary comparison of pharmacokinetic parameters of the individual blood concentration-time curves after rectal administration in rabbits.

Suppository formulations	Dose (mg/kg)	C_{max} (µg/ml)	t_{max} (hr)	$AUC_{0-4.6}$ (µg/ml hr)	$AUC^{*}_{0-4.6}$ (µg/ml hr)	k_{el} (hr^{-1})	$t_{½}$ (hr)
A	6.21	7.5	0.75	21.300	27.260	0.294	2.357
B	5.51	10.38	0.50	30.105	38.275	0.266	2.605
C	7.05	12.87	0.75	38.199	37.710	0.311	2.228

*Dose normalized to 7 mg/kg

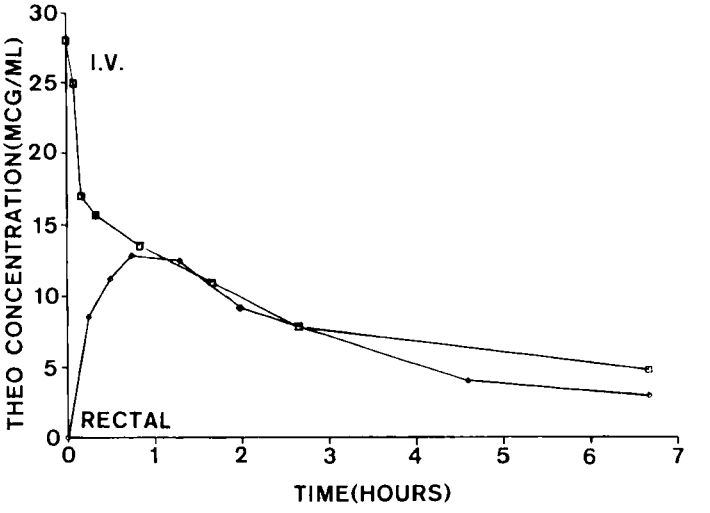

Figure 8

Comparative bioavailability of theophylline after rectal administration of plain suppository base and intravenous infusion (F=0.919).

These data clearly indicate that the systemic bioavailabilities of theophylline following rectal administration with or without adjuvants do not differ significantly. The results were comparable with those obtained upon intravenous infusion (Fig. 8), which reflects complete rectal absorption of theophylline and shows that it cannot be enhanced by the presence of adjuvants. Similar results have also been reported for theophylline solutions in the presence of sodium salicylate, with and without anaesthesia[16].

CONCLUSIONS

1. The DSC curves demonstrate the significance of formulation components on changes in melting transition during storage.
2. Force-time curves demonstrate the mechanical strength and resistance of various formulations to the applied load, and identify the physical characteristics of suppositories in terms of brittleness or elasticity.
3. A modified membrane-bead-basket gives greater constancy of the exposed suppository area for dissolution. This gives reasonable correlation with the in vivo data for the three suppository formulations studied. Investigation is underway to optimize the parameters involved in this technique.
4. The blood concentration-time curve after rectal administration suggests that the coadministration of sodium salicylate or lecithin-sodium deoxycholate does not increase the blood concentration of theophylline in comparison with adjuvant-free formulations. Theophylline is completely absorbed on rectal administration. In contrast to reports in the literature, results obtained in this study thus show that rectal absorption of theophylline is not enhanced with absorption promoters.
5. Polyethylene glycols appear to be good suppository bases for the rapid release of theophylline.

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