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International Journal of Pharmaceutics 148 (1997) 155–163

international journal of pharmaceutics

Layered excipient suppositories: the possibility of modulating drug availability

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Received 20 September 1996; accepted 11 December 1996

Abstract

The release rate of a drug dose from suppositories is affected by characteristics of the excipient (melting temperature and rate, viscosity at rectal temperature, hydro-lipophilic characteristics). Release kinetics from excipients commonly available do not always respond to clinical requirements, even after the introduction of auxiliary agents. Release curves which were differentiated and adaptable to therapeutic conditions were obtained by vehicling a drug in suppositories of two superimposed layers of lipophilic excipients with different characteristics and hence with a difference in drug availability. The two distinct excipient layers release the drug from these suppositories contemporaneously but independently. The amount of drug released in the time course is the sum of the single amounts individually released by the two suppository layers. By previously mixing the two excipients, release rate becomes uniform in the suppository body overall and is conditioned only by the assumed characteristics of the mixture. The release mechanism for superimposed layer suppositories is confirmed by the good agreement between experimental and calculated curves. By using a pair of excipients with different characteristics in superimposed layers between which the drug is distributed, it is possible to modulate drug release kinetics by regulating the reciprocal ratio between the two suppository fractions. © 1997 Elsevier Science B.V.

Keywords: Suppository; Double layer excipients; Release modulation

1. Introduction

Drug availability from suppositories with lipophilic excipient is the result of a series of steps (Moës, 1989). The process starts with the fusion of the suppository at rectal temperature which allows drug particles to migrate and be transferred into the rectal acqueous secretion, in which they can be solubilized, in order to achieve the necessary condition of contact with rectal mucous membrane through which they can be absorbed. Since rectal absorption is fundamentally by diffusion, drug release rate from suppository affects its

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PII S0378-5173(96)04841-7

own concentration in the aqueous rectal phase and hence the absorption rate. Drug release rate from the suppository is mainly conditioned by excipient characteristics: temperature and fusion rate, viscosity, hydro-lipophilic characteristics (Van Bosch et al., 1976; Bornschein et al., 1980; Moës, 1980; Tukker et al., 1983; Möller, 1984; Ragazzi et al., 1984; Tukker and De Blaey, 1984). The same drug dose is therefore able to produce a different therapeutic responses when vehicled in excipients with different characteristics.

With the aim of changing drug release rate, the introduction of different auxiliary agents such as glycerides (Baichwal and Lohit, 1970; Bornschein et al., 1976), silica gel (Regdon and Kedvessy, 1968; Moës, 1976; Ragazzi et al., 1984; Tukker and De Blaey, 1984; Dal Zotto et al., 1991a), insoluble powders (Dal Zotto et al., 1991b), carbomers (Dal Zotto et al., 1991c), cellulose derivatives (Dal Zotto et al., 1991d), surfactants (Minkov et al., 1984; Regdon et al., 1984; Minkov et al., 1985; Singh and Jayaswal, 1985) into lipophilic excipient, has been suggested without affecting release kinetics.

The possibility of modulating release kinetics of some drugs in suppositories according to clinical requirements was studied, using pairs of layered lipophilic excipients.

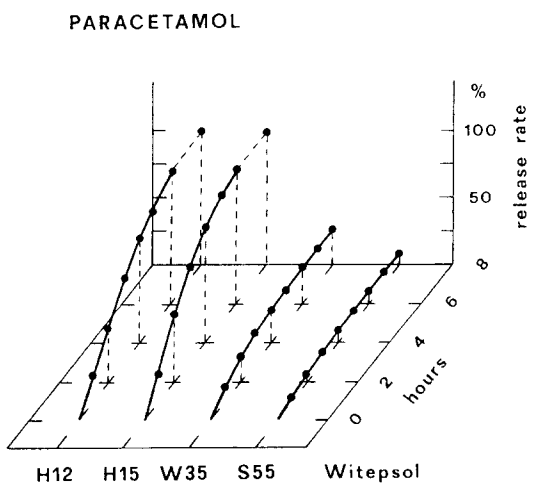

Fig. 1. Release curves for paracetamol from suppositories prepared with the four different types of Witepsol tested.

2. Experimental

2.1. Materials

Paracetamol (Chimifarm, Verona Italy); aminophenazone, aminophylline, (ACEF, Fiorenzuola D'Arda Italy); Witepsol H12, H15, S55, W35 (Hüls, Werk Witten, Germany).

2.2. Suppository batches preparation

Batches of 3-ml suppositories containing the same 500-mg dose of the three drugs tested were prepared with each of the types of Witepsol used.

After melting the excipient at 40°C, a Silverson turbomixer (Waterside, Chesham, UK) was used to disperse uniformly the drug in fine powder. The melted mass was then poured into disposable PVC moulds and cooled to room temperature (18–20°C).

To obtain layered suppositories in different volumetric ratios, two distinct masses with each of the two selected excipients containing the same drug concentration (500 mg in 3 ml) were prepared. A first fraction of the mass containing the first of the two excipients (0.75, 1.5, 2.25 ml equal to 25, 50, 75% of suppository volume, respectively) was poured into the mould and cooled to room temperature. Then, suppositories were made up to the volume of 3 ml by pouring the second fraction of the mass containing the second of the two tested excipients into the same moulds and cooling them again to room temperature.

For suppositories with two mixed excipients, mixtures in ratios of 25:75, 50:50, 25:75 were prepared and melted at 40–42°C. Each of the three tested drugs at the same unitary dose of 500 mg per 3 ml suppository were dispersed in the masses obtained.

The different batches of suppositories, after 24 h at room temperature, were refrigerated (5–10°C) until required for the different tests.

2.3. Determination of the drug release (Dal Zotto et al., 1991a)

Each suppository from the tested batches was put in a piece of dialysis tube (Visking Tubing,

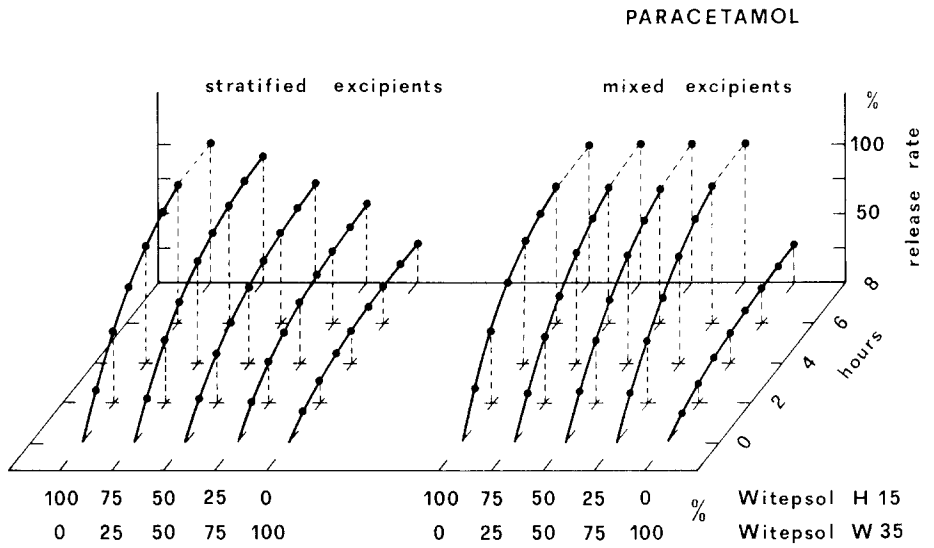

Fig. 2. Release curves for paracetamol in suppositories with superimposed layers of the two excipients, Witepsol H15 and W35, in different volume ratios, compared with release curves for suppositories prepared with only two excipients and previously mixed in the same ratios.

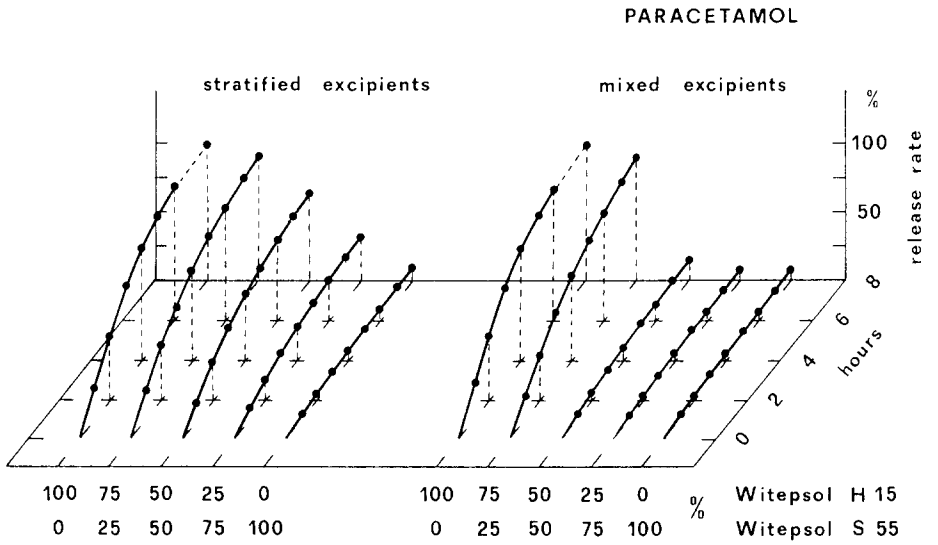

Fig. 3. Release curves for paracetamol in suppositories with superimposed layers of the two excipients, Witepsol H15 and S55, in different volume ratios, compared with release curves from suppositories prepared with only two excipients and previously mixed in the same ratios.

London, UK) 10 cm long, 25 mm diameter, closed at one end, which had previously been soaked in water overnight at room temperature. After the addition of 5 ml of water, the tube was closed at the other end, so as not to leave any air bubbles inside. Both ends of each tube were held by a perspex 1.5 × 3 cm clamp with stainless screws. Six suppositories were placed horizontally and radially 3 cm from the bottom of a cylindrical basin, 25 cm diameter and 10 cm deep, containing

3 l of water thermostated at 37 ± 0.5°C, stirred constantly at 100 revs./min by a 10-cm blade stirrer.

Every 15 min, six 2-ml samples of diffusion fluid were collected from the basin and replaced with the same amount of water. The total amount of drug released in the time course from suppositories in the basin was spectrophotometrically determined after a suitable dilution with water (paracetamol at 242 nm, aminophenazone at 260 nm, aminophylline at 271 nm).

3. Results

Paracetamol, dispersed in four excipients in the Witepsol series tested in the same doses per suppository (500 mg) gave the release curves reported in Fig. 1. The two types, H12 and H15, both of solid glycerides with a low hydroxyl value, had different melting temperatures (32–33.5°C for H12; 33.5–35.5°C for H15). They allowed a fast drug release rate, practically complete after 5–6 h. The W35 with a high number of mono-diglycerides and the S55, containing surfactants, but with the same melting temperature as the H15, have given slower drug availability.

The same paracetamol dose was vehicled in suppositories obtained by superimposing layers of

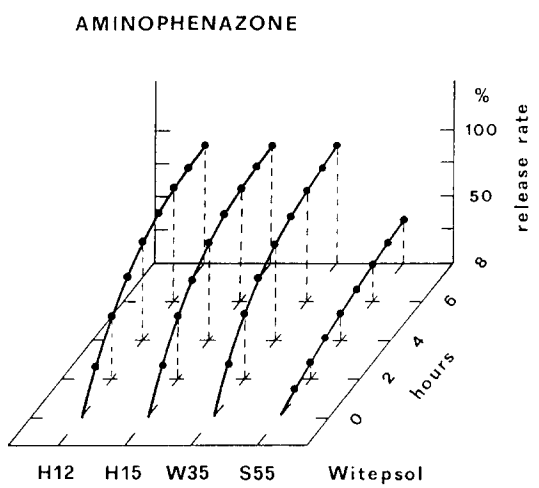

Fig. 4. Release curves for aminophenazone in suppositories prepared with the four different types of Witepsol tested.

the two excipients which showed different release curves, Witepsol H15 and W35, in three different ratios of 75:25, 50:50 and 25:75. The resulting release curves were between the curves obtained for the two excipients alone, with a tendency related to the reciprocal ratio between the two layers. In Fig. 2 the curves, obtained for the two excipients alone, are compared with the curves for suppositories prepared with the same two excipients in the same reciprocal ratios, but mixed in the melted state, from which the drug release rate resulted practically the same as Witepsol H15.

Similar results were obtained by coupling Witepsol H15 and S55 in superimposed layers. As Fig. 3 shows, release curves were between those of the two excipients alone, different from suppositories obtained by mixing in the same ratio, the two excipients in the melted state which gave a release rate similar only to H15. At higher ratios the release rate was similar to S55.

Aminophenazone, vehicled in the same four excipients of the Witepsol series at the same unitary dose of 500 mg, gave release curves which are compared in Fig. 4. The release rate was practically equal from three of the excipients. Only S55 was different.

At the same unitary dose, the drug was vehicled in suppositories consisting of two superimposed layers of two of the excipients which produced different release rates.

By superimposing the two excipients H12 and S55 in the three volume ratios above mentioned, the release curves reported in Fig. 5 showed a gradual drug availability related to the reciprocal ratio between the two excipients. From the same two excipients in the same volume ratios, but previously mixed in the melted state, the release rate was different and affected by the prevalence of one of the two excipients in the mixture.

Analogous results were obtained with the pair of excipients, W35 and S55, in suppositories with superimposed layers in the same volume ratios (Fig. 6). In this case too, release rate was different for suppositories prepared with mixed excipients and it was even more conditioned by the prevalence of one of the two tested excipients in the mixture.

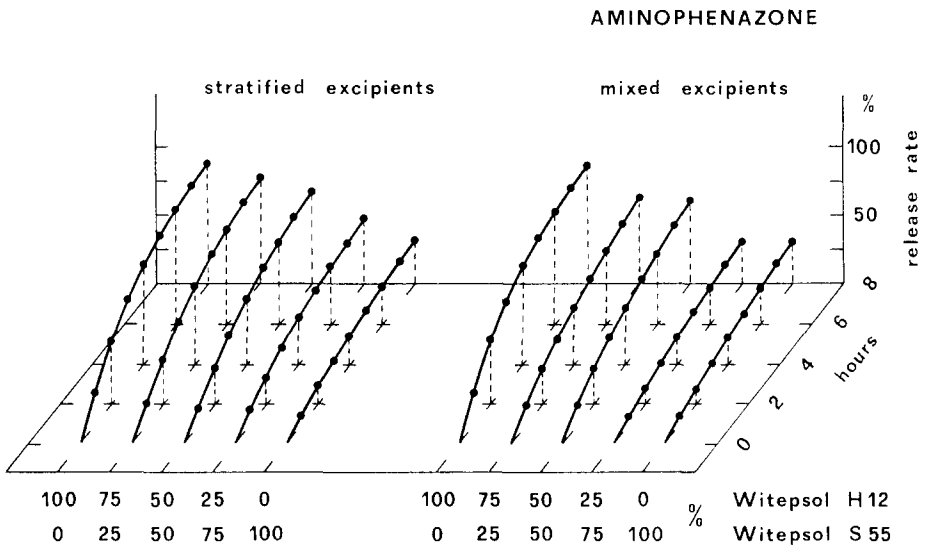

Fig. 5. Release curves for aminophenazone in suppositories with superimposed layers of the two excipients, Witepsol H12 and S55, in different volume ratios, compared with release curves for suppositories prepared with only two excipients and previously mixed in the same ratios.

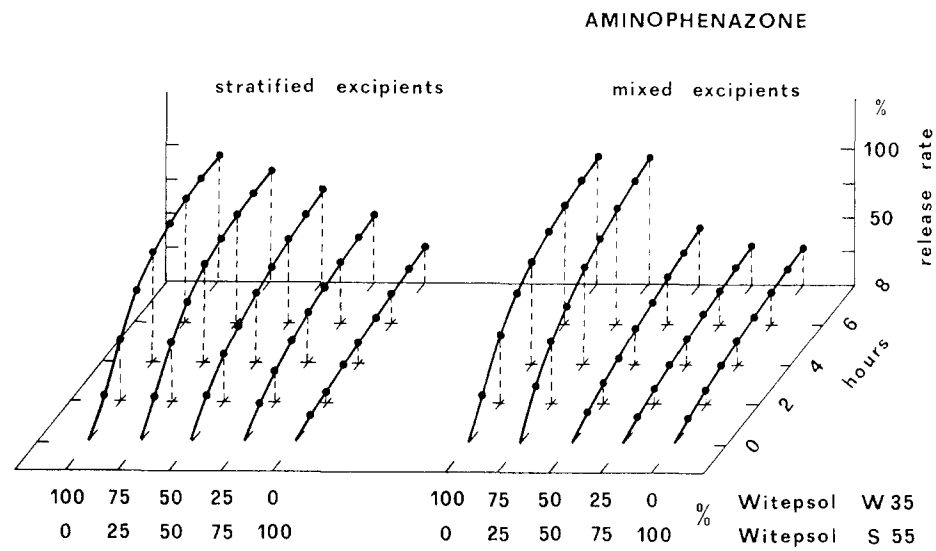

Fig. 6. Release curves for aminophenazone in suppositories with superimposed layers of the two excipients, Witepsol W35 and S55, in different volume ratios, compared with release curves for suppositories prepared with only two excipients and previously mixed in the same ratios.

At the same unitary dose of 500 mg, aminphylline gave release rates different from the four tested excipients of the Witepsol series. As shown by the curves reported in Fig. 7, drug availability from the H12 and H15 types was fast. The first, with a lower melting temperature, allowed a faster release. Lower, but likewise satisfactory, was the availability from W35, while the release from S55 was remarkably slower in this case too.

At the same unitary dose of 500 mg, aminophylline was introduced into suppositories with two excipients with different release rates in

superimposed layers. By using Witepsol H12 coupled to S55 in the same volume ratios mentioned above, release curves with different gradients related to the ratio between the two superimposed fractions of excipients were obtained (Fig. 8). Completely different results were obtained with the two excipients previously mixed in the same ratios, as in the previous case of aminophenazone.

Similar results were obtained with the pair W35 and S55, as shown in Fig. 9. Also in this case the release from the same two excipients mixed in the melted state in the same volume ratios was confirmed to be clearly different.

4. Discussion

Differences in release curves between suppositories with superimposed excipients in different volume ratios and the same two excipients mixed led to consideration that the two drug amounts were contemporaneously but independently released by the two distinct excipient layers. The amount of drug released at subsequent time intervals was thus the sum of the amounts released by the two fractions of the suppository individually. As drug release rate is a function of the nature and composition of each excipient, it follows that in double-layer suppositories the overall drug release rate could be regulated as a function of the reciprocal volume ratio between the two suppository fractions obtained from excipients with different characteristics.

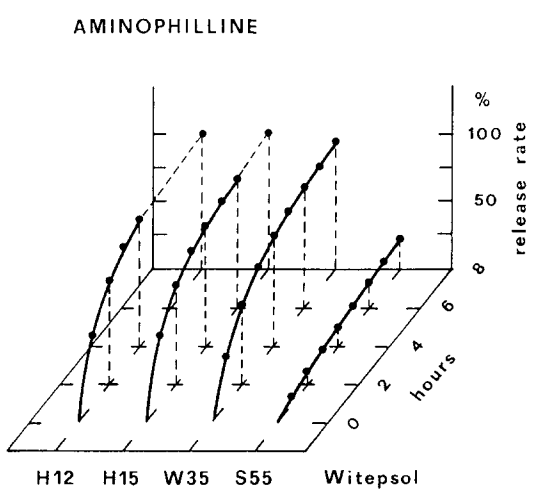

Fig. 7. Release curves for aminophylline in suppositories prepared with the four different types of Witepsol tested.

On the other hand, in the case of the two excipients previously mixed in the melted state, drug release rate was uniform in the body of suppository. It was regulated by the composition of the mixture itself and was not directly related to the reciprocal ratio between the two excipients.

In fact in layered suppositories, with an equal ratio of the two excipients, release kinetics were different from suppositories with mixed excipients. By expressing drug amount released as a function of the square root of time according to a first order process, the value of regression coefficient was significantly lower for layered suppositories than for suppositories of only one excipient or a mixture of excipients, confirming that the release curve was the result of two distinct contemporary kinetics. Fig. 10, shows calculated values for paracetamol suppositories with the two excipients Witepsol H15 and S55.

Supposing that in layered suppositories drug release was independent of the two excipient fractions, the amount of drug released at subsequent time intervals as a result of the two contemporary kinetics could be represented by the expression:

$$Q(t) = \frac{Q_A(t) \cdot x + Q_B(t) \cdot y}{100}$$

where: $Q(t)$ is the amount of drug available from suppository at time t; $Q_A(t)$ is the amount of drug released from a suppository with the excipient A only at time t; $Q_B(t)$ is the amount of drug released from a suppository with the excipient B only at time t; x is the volume percent of excipient A; y is the volume percent of excipient B.

Release curves for superimposed layer suppositories with different excipients employed in different volume ratios were calculated on the basis of the quantities, of the three drugs tested, released at different time intervals from suppositories prepared with single excipients. Fig. 11 shows release curves for the three drugs from layered suppositories compared with those calculated by means of the above expression. The good agreement between the values confirmed the above-mentioned contemporaneous and independent release mecha-

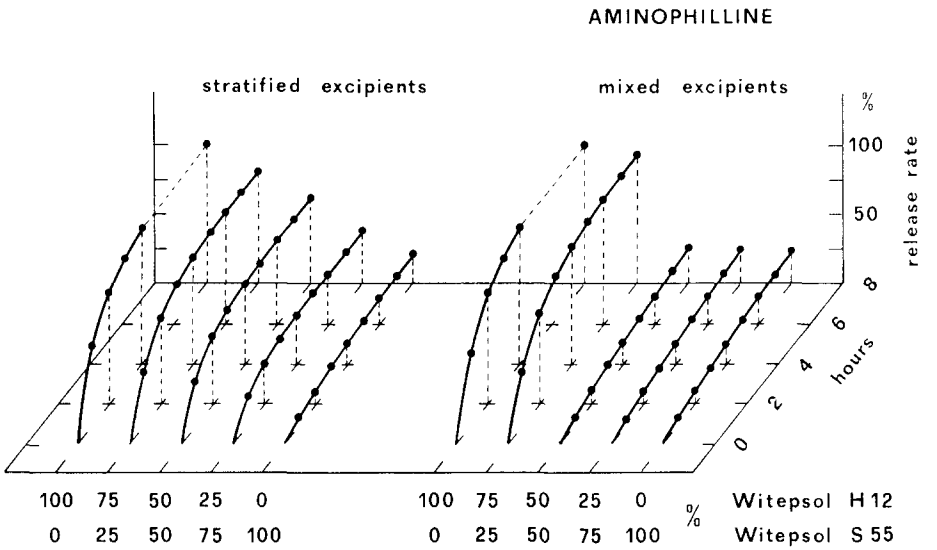

Fig. 8. Release curves for aminophylline in suppositories with superimposed layers of the two excipients, Witepsol H12 and S55, in different volume ratios, compared with release curves from suppositories prepared with only two excipients and previously mixed in the same ratios.

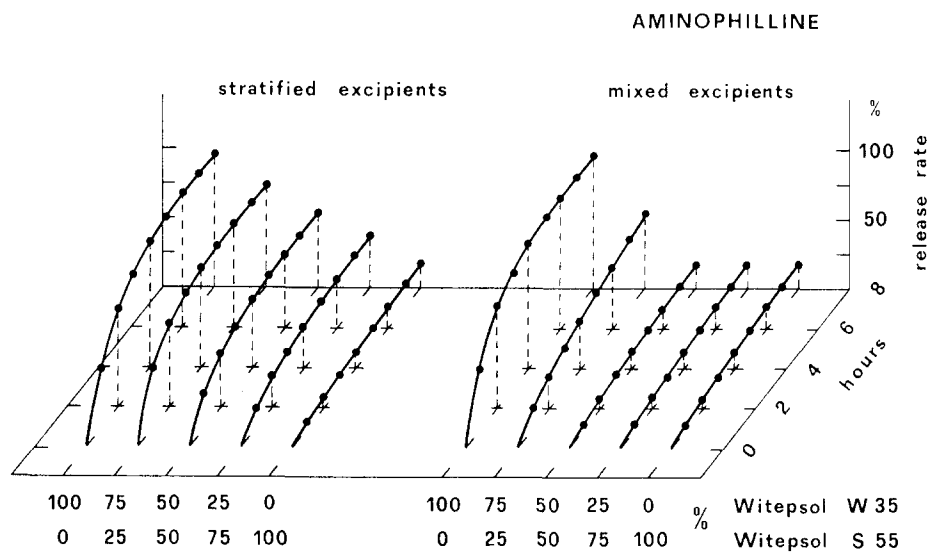

Fig. 9. Release curves for aminophylline in suppositories with superimposed layers of the two excipients, Witepsol W35 and S55, in different volume ratios, compared with release curves from suppositories prepared with two only excipients and previously mixed in the same ratios.

nism of the two drug fractions distributed in two distinct suppository layers. For the overall results, no significant differences between calculated values and those found appeared at Student's t-test for coupled values ($P < 0.05$).

It was therefore confirmed that by using in different ratios two excipients with different characteristics in superimposed layers, it was possible to modulate drug release kinetics in relation to the required therapeutic response.

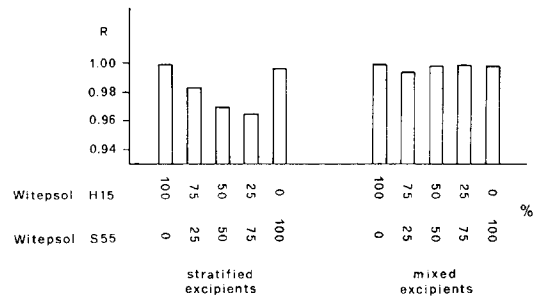

Fig. 10. Values of the regression coefficient of the release curves of paracetamol in suppositories prepared with the two excipients Witepsol H15 and S55, both stratified and mixed.

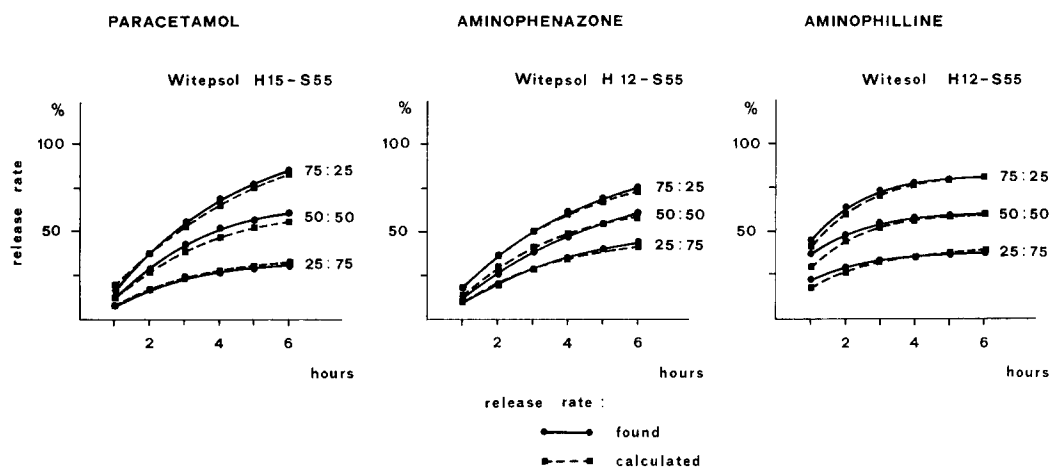

Fig. 11. Release curves of the three drugs tested in stratified suppositories compared with the corresponding curves calculated.

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