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Effect of drug solubility on the *in vitro* availability rate from suppositories with lipophilic excipients

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The factors involved in mechanisms of availability of different drugs from suppositories with lipophilic excipients were studied by using an *in vitro* model of the rectal compartment with a porous membrane simulating the rectal barrier. The solubility in water of drugs was found to be the fundamental factor influencing the release rate from suppositories. In fact, following the melting of the suppository at body temperature the drug particles can migrate to the interface with the small volume of rectal secretion where they dissolve. Drug molecules can so diffuse until they come into contact with the rectal barrier through which the drug is absorbed. Drug concentration in the intrarectal aqueous phase produces the gradient against the large volume of the plasma phase. This gradient regulates the diffusion rate through the barrier. A drug with a low water solubility saturates the intrarectal phase at low concentration hindering the subsequent dissolution of the drug particles remaining in the melted excipient. This fact maintains the viscosity of the melted suppository at a ligh level, which slows the migration of the particles. On the other hand, a drug with high water solubility quickly leaves the excipient, producing a high concentration in the intrarectal phase which supports a high diffusion rate across the barrier. The results obtained indicate that drugs with low solubility in water result in low availability, while drugs with good solubility can give an intense and rapid drug supply for a rapid and intense therapeutic response with the dose administered almost completely utilised.

1. Introduction

The intrarectal route of drug administration to give a systemic effect is commonly used. Most suppository formulations use lipophilic excipients comprising a mixture of glycerides, combined, if necessary, with other types of lipophilic components. Most rectally administered drugs are insoluble or only slightly soluble in this type of excipient. Drug availability for absorption is the result of a series of successive steps [1]. Following melting of the suppository at body temperature, drug particles can migrate to the interface between the melted excipient and aqueous rectal secretion, where they form a solution. In this way drug molecules can diffuse until they come into contact with the rectal barrier through which the drug is absorbed. A series of factors influence the speed of these steps: melting point of the excipient, on which the melting rate of the suppository depends, viscosity of the melted suppository and drug solubility [2–7].

Using a lipophilic excipient, which is insoluble in water, the drug release rate from a melted suppository can be evaluated by simply placing the suppository in contact with the appropriate volume of aqueous liquid at body temperature and determining the time-course of the drug concentration in the solution [8–10].

However, this system does not take into consideration the actual conditions in the rectal compartment. In fact in the physiological situation the drug released by the suppository can pass into solution only in the small volume (3–5 ml) of rectal secretion; thereafter it is transferred through the mucous barrier to the large volume of circulating blood. Keeping these considerations in mind, a useful model for evaluating *in vitro* drug availability could consist of two aqueous phases at 37 °C: one of a small volume simulating the intrarectal phase where the suppository enters in direct contact, and the other of a larger volume simulating the plasma phase, with a porous membrane placed in-between representing the rectal barrier through which the drug can diffuse [11, 12].

Using this type of model we aimed to check the influence, that factors including excipient type, viscosity of the molten mass of suppository, and water solubility of the drug could have on mechanisms which govern the availability of different types of drugs administered in the form of suppositories with a lipophilic excipient.

Table: Solubilities in water and in buffer solution (pH 7.4) of different drugs at 20 and 37 °C

Drug	Solubility (mg/ml)			
	In water		In buffer (pH 7.4)	
	20 °C	37 °C	20 °C	37 °C
Naproxen	0.10	0.11	4.30	4.80
Propyphenazone	2.85	3.00	2.60	2.60
Paracetamol	16.00	18.50	13.90	16.80
Guaifenesine	37.00	446.00	37.70	247.00
Aminophenazone	52.50	55.00	47.90	47.50
Aminophylline	218.00	231.00	134.00	221.00

The solubility of a drug in water would be expected to be of fundamental importance bearing in mind how a drug administered as a suppository in the rectal cavity is absorbed and passes into circulation to produce a systemic effect. In fact, given that absorption through the rectal mucous membrane takes place mainly by passive diffusion, drug concentration in the intrarectal aqueous phase takes on a determining role. Thus, the greater the drug concentration in this phase, the greater the concentration gradient will be in respect to the plasma phase on the other side of the rectal barrier and therefore the drug absorption rate should be faster.

The drug dissolution rate in the intrarectal aqueous phase is, in turn, influenced by parameters relating to the molten suppository mass. The viscosity of the molten suppository is fundamental depending to both on the composition of the excipient and on the quantity of drug in suspension – viscosity increasing with the number of particles [2, 13].

This rate of drug particle migration in the molten suppository mass should increase progressively during release. In fact, as drug particles leave the suppository mass their number in the mass reduces, loosening the internal structure and therefore producing a progressive reduction in viscosity, an effect which should facilitate release.

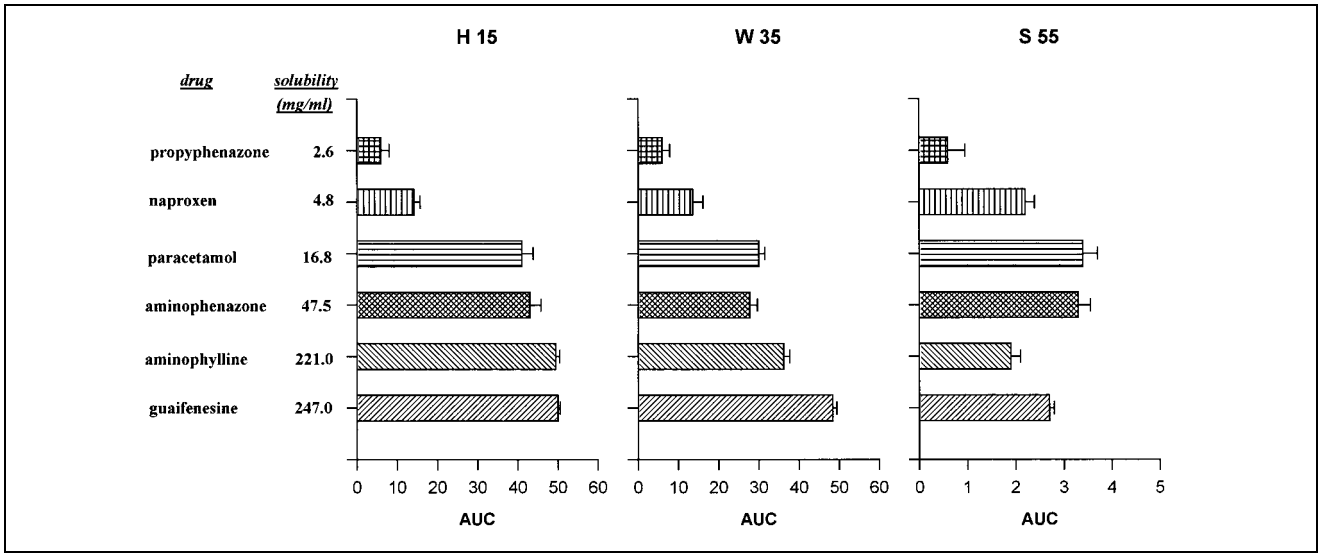

Fig. 1: Values of AUC (±SD) calculated for the dissolution curves of the drugs studied from suppositories with different lipophilic excipients in order of drug solubility at 37 °C

2. Investigations and results

2.1. Water solubility of drugs under rectal conditions

Solubility in water, at normal room temperature, was known for only some of the six drugs used in the test. The effect of pH on solubility at rectal temperature, by convention 37 °C, was not known. Solubility values in water and pH 7.4 buffer found experimentally at temperatures of 20 °C and 37 °C are compared in the Table.
For some drugs (propyphenazone, paracetamol, aminophenazone) solubility in water and buffer solution were very similar. The difference between 20 °C and 37 °C appeared to be negligible. For other drugs (naproxen, aminophylline) the differences between solubility in water and buffer solution were significant. A significant difference between 20 °C and 37 °C was observed for aminophylline only at pH 7.4. On the other hand, the solubility of guaifenesine appeared much higher with increasing temperature from 20 °C to 37 °C. At 20 °C, solubility in water and buffer solution was almost equal, however, at 37 °C, the solubility of the latter was almost half that in water.

2.2. Suppository drug release rate

The drug release rate from suppositories in contact with the aqueous phase was evaluated using three different types of lipophilic excipient (Witepsol H15, W35 and S55); a pH 7.4 buffer solution was used. The results obtained, expressed as area under the dissolution curve, are shown in Fig. 1 in the order of drug solubility at 37 °C. It can be clearly seen how release rate is influenced by type of excipient (in relation to migration speed of drug particles in the molten mass depending on both viscosity and affinity of the drug for the excipient). Further, it can be seen how with each excipient, release rate is generally related to drug solubility, except for the two drugs more soluble with Witepsol S55, an excipient of complex composition based on glycerides associated with surfactants.

2.3. In vitro drug availability

The same batches of suppositories of six different drugs in three different excipients were tested for drug availability with the simplified model of the rectal compartment

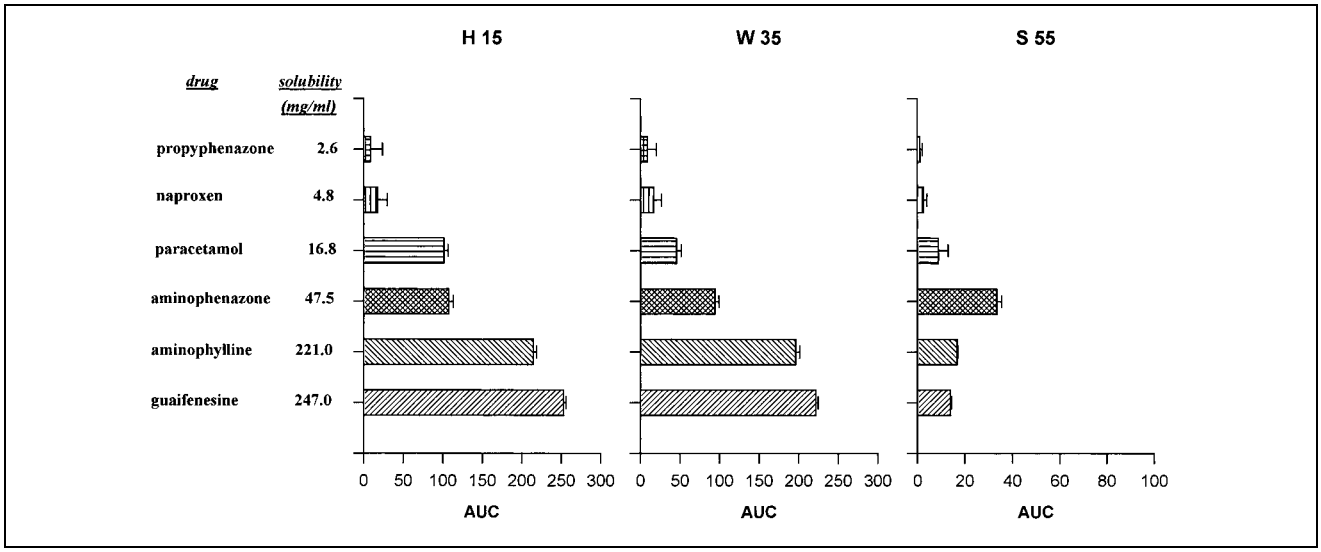

Fig. 2: Values of AUC (±SD) calculated for the release curves of the drugs studied from suppositories with different lipophilic excipients in order of drug solubility at 37 °C

using a porous membrane. The results obtained, expressed as values of area under the release curve, are compared in Fig. 2 for each excipient in order of solubility at 37 °C, similar to the above-mentioned test of dissolution rate. In this case also, drug solubility in water generally appeared to govern drug availability. This therefore demonstrates how the first step of the availability cycle (the dissolution of the drug from the melted suppository into the intrarectal aqueous phase) becomes a limiting factor in the entire cycle leading to the drug passing into the circulation.

In fact, having regard to the structure of the *in vitro* model used, drug released from the suppository reaches a concentration, in the small volume of intrarectal phase, in direct relation to its solubility. Therefore in this phase a less soluble drug, such as propyphenazone and naproxen, will reach a low concentration which will sustain a correspondingly low concentration gradient in respect to the plasma phase of large volume, in which the drug disperses. The diffusion rate will remain low. On the other hand in the small volume of intrarectal phase a highly soluble drug, such as aminophylline or guaifenisene, could reach concentrations high enough to sustain correspondingly high concentration gradients in respect to the plasma phase. This ensures an increased diffusion rate through the membrane simulating the rectal barrier.

2.4. Progress of the in vitro release test

Considering the successive steps by which the drug is mobilised within the suppository, transfers to in the intrarectal phase and diffuses through the rectal barrier into the plasma phase, the different factors involved have a combined effect and interact with one another.

The first factor involved is the viscosity of the molten mass of the suppository. This depends on the viscosity of the excipient melted at rectal temperature and the structural viscosity produced by the drug particles. The higher the drug dose and therefore the greater the number of particles the greater the viscosity [2, 13]. As the drug particles leave the molten suppository, the internal structure loosens allowing a freer movement of particles. At the same time the drug released from the suppository goes into solution in the intrarectal phase. This triggers diffusion through the membrane into the plasma phase in relation to the concentration gradient reached between the two phases, and this depends in turn on drug solubility.

Following the method adopted in previous research [14] drug concentration both in the intrarectal and in the plasma phases and viscosity of the suppository at different time intervals during the *in vitro* release test were determined. The same batches of suppositories with 500 mg doses of different drugs in Witepsol H15 were used for the test.

In Fig. 3, concentrations of propyphenazone and naproxen in the intrarectal and plasma phases are compared alongside the resulting changes in suppository viscosity compared with suppositories of excipient only. It was observed that drug concentration in the rectal phase, although quite less as a consequence of the relatively low solubility of the drug in water, remained at a higher level than in the plasma phase. This ensures an almost constant concentration gradient permitting the steady progress of the test although limiting the overall availability of the drug dose to 10% for propyphenazone and 19% for naproxen. The slow release of the drug from the suppository, resulting from saturation of the intrarectal phase which is no longer receptive to further quantities from the supposi-

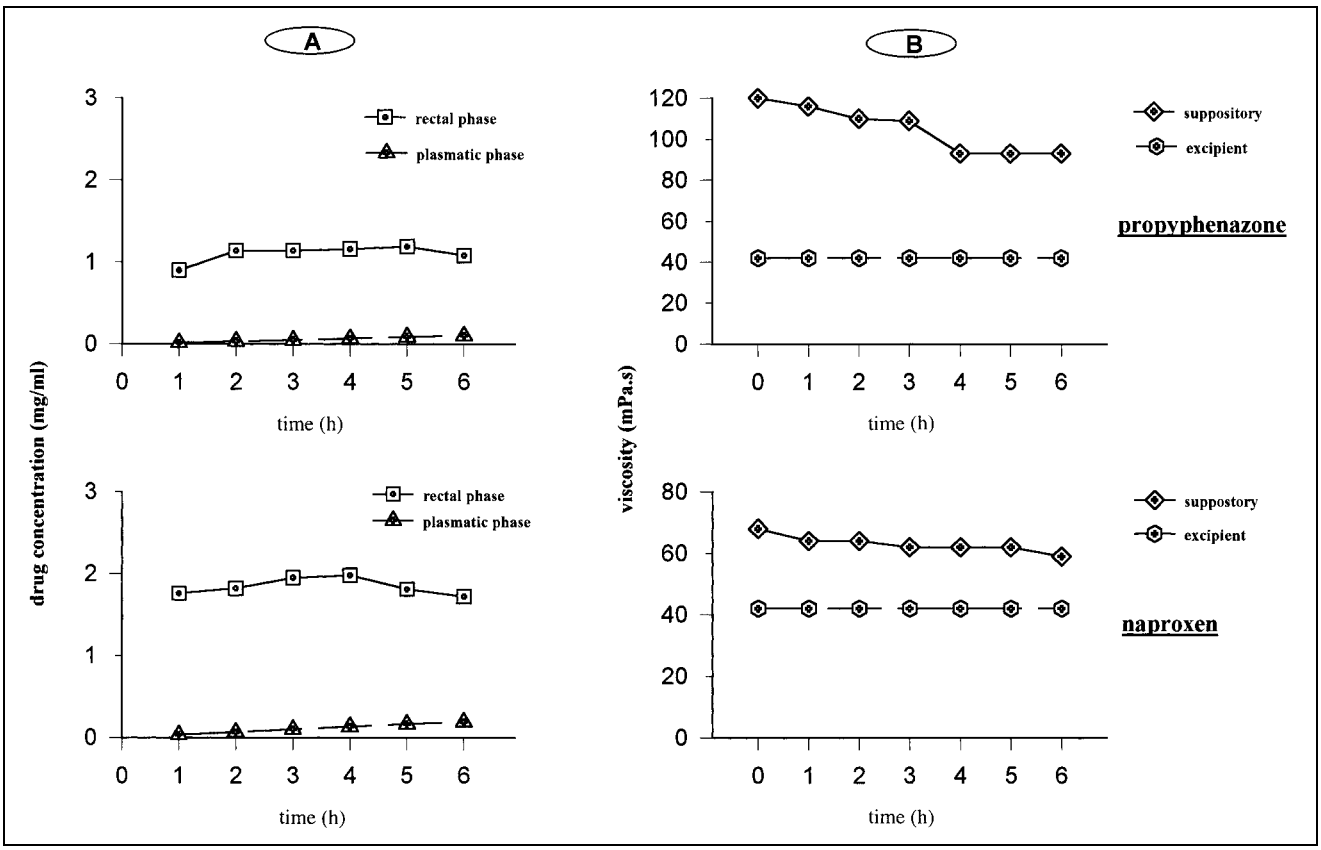

Fig. 3: Time-course of the concentration (A) of propyphenazone and naproxen in both the rectal and plasma phases compared with the time-course of the viscosity (B) of the suppositories at 37 °C during the release test

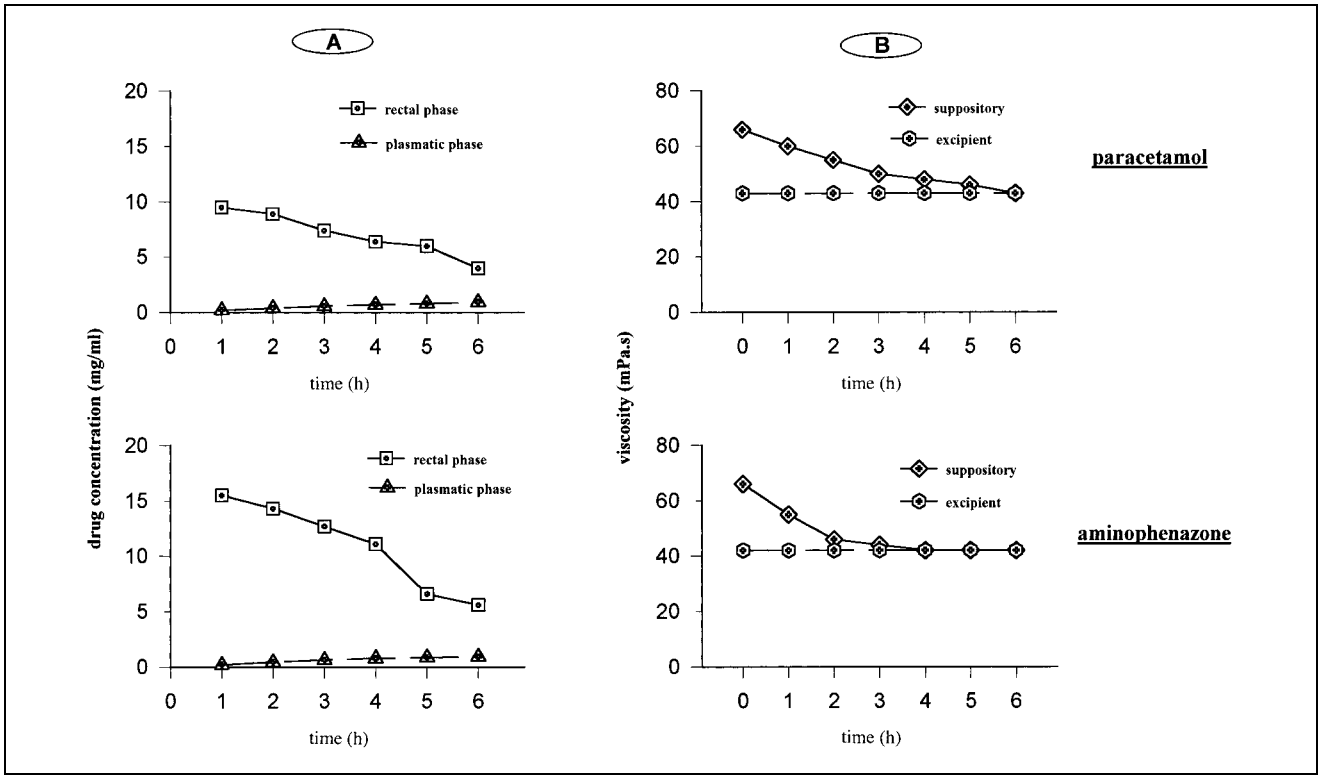

Fig. 4: Time-course of the concentration (A) of paracetamol and aminophenazone in both the rectal and plasma phases compared with the time-course of the viscosity (B) of the suppositories at 37 °C during the release test

tories, can be seen by the viscosity of the molten suppository which remained high, very different from the viscosity of the excipient alone. This confirms how most drug particles, hindered from entering solution in the rectal phase owing to saturation, remain within the suppository mass and contribute to maintaining its structure which maintains high viscosity even after some hours in the rectal cavity.

Paracetamol and aminophenazone which are more soluble in water and therefore shows greater availability from sup-

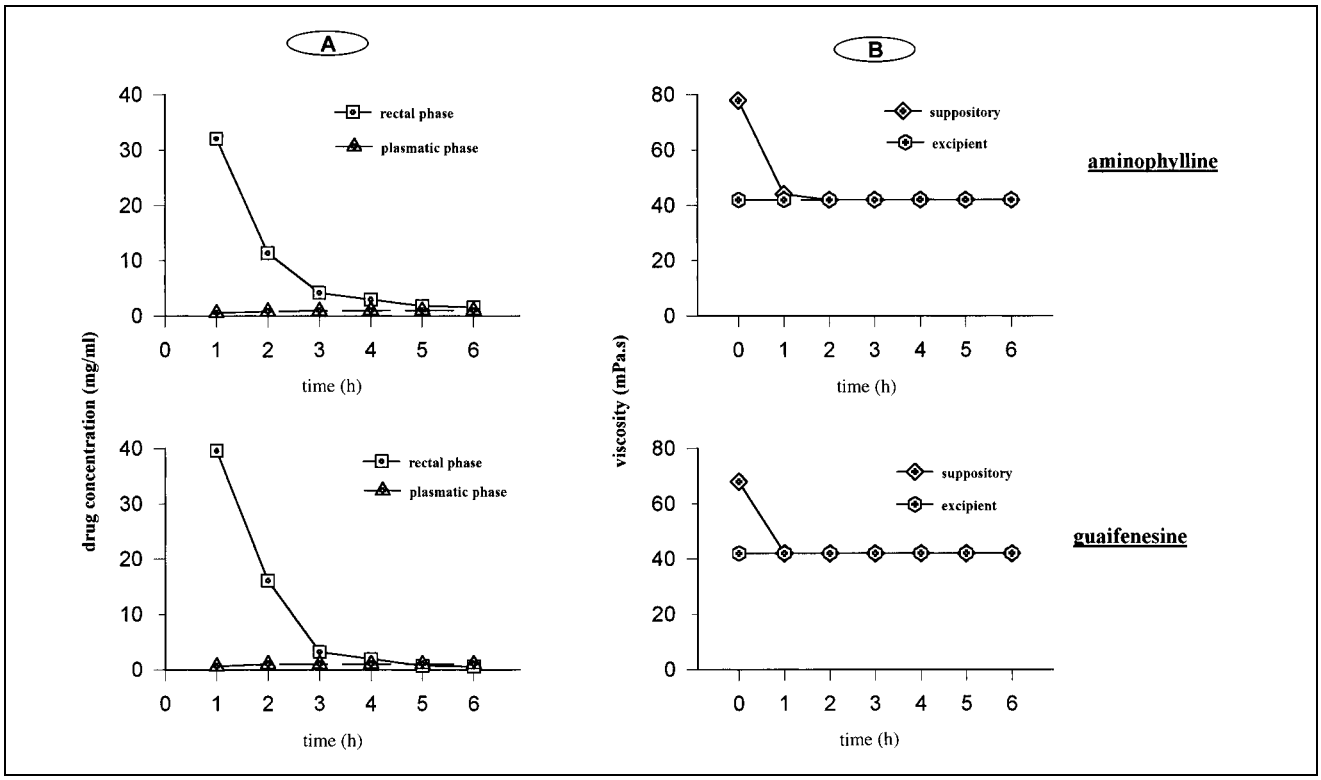

Fig. 5: Time-course of the concentration (A) of aminophylline and guaifenesine in both the rectal and plasma phases compared with the time-course of the viscosity (B) of the suppositories at 37 °C during the release test

positories, had a faster release rate, reaching high concentrations in the intrarectal phase after just 1 h, as seen in Fig. 4. The greater concentration gradient favoured a greater diffusion rate and therefore rapid drug transfer into the plasma phase. The progressive reduction in concentration in the rectal phase indicates the progressive consumption of the drug reserve in the suppository which leads to a progressive reduction in drug release rate from the molten mass of excipient. This is confirmed by the viscosity: as drug particles dissolve in the intrarectal phase the internal structure of the molten suppository loosens, and therefore viscosity decreases until it reaches the value of the excipient alone at the end of the test.

The higher availability from suppositories of the two drugs which are very soluble in water (aminophylline and guaifenesine) is confirmed by their concentration in the two phases during the test and the consequent viscosity (Fig. 5). The high suppository availability rate is sustained by high drug concentration in the intrarectal phase after 1 h. The rapid fall in concentration was evidence of a high diffusion rate through the membrane until the entire reserve of drug is consumed, reaching the same concentration in both phases when diffusion stops. Similar trends are seen in viscosity. The rapid release of the drug particles from the suppository is confirmed by the viscosity which quickly falls to levels which are comparable to the excipient alone after just 1 h.

3. Discussion

From the study, the strict relation between the solubility of a drug in water and its availability from suppositories with lipophilic excipients was first demonstrated. Using a simplified model of the rectal compartment, comprising a dialysis tube simulating the rectal barrier, and two aqueous phases simulating, in turn, the small volume of intrarectal phase and large volume of circulating plasma, some factors emerged on which the various stages in the process of availability of a drug from a suppository may depend.

The fundamental limiting factor appears to be the abovementioned drug solubility in water in rectal conditions of temperature and pH. In fact this solubility of the drug appears to depend on its concentration in the intrarectal aqueous phase, which conditions both drug release from the suppositories and the concentration gradient which controls diffusion rate through the barrier. As a result all the various stages of the entire cycle of suppository availability depend on this. It becomes clear that the kinetic of drug availability from suppositories depends on its solubility.

The graphs in Fig. 6 represent the amount of drug available at successive times. It can be seen that a less water soluble drug can only produce a low amount, even if over a prolonged time, and does not seem capable of allowing adequate utilisation of the dose administered. On the other hand, a very soluble drug is able to produce an intense and rapid drug supply, giving an equally rapid and intense therapeutic response with the possibility of almost complete utilisation of the dose administered. Drugs of average solubility can also be appropriate for sufficient supply. They can give an initial dose producing the required therapeutic response, followed by a lower supply prolonged over time, to maintain the same response. In turn the kinetics of drug availability can be modulated by choosing an excipient which, because of the characteristics of its compositions, influences the release rate of drug particles from the suppository.

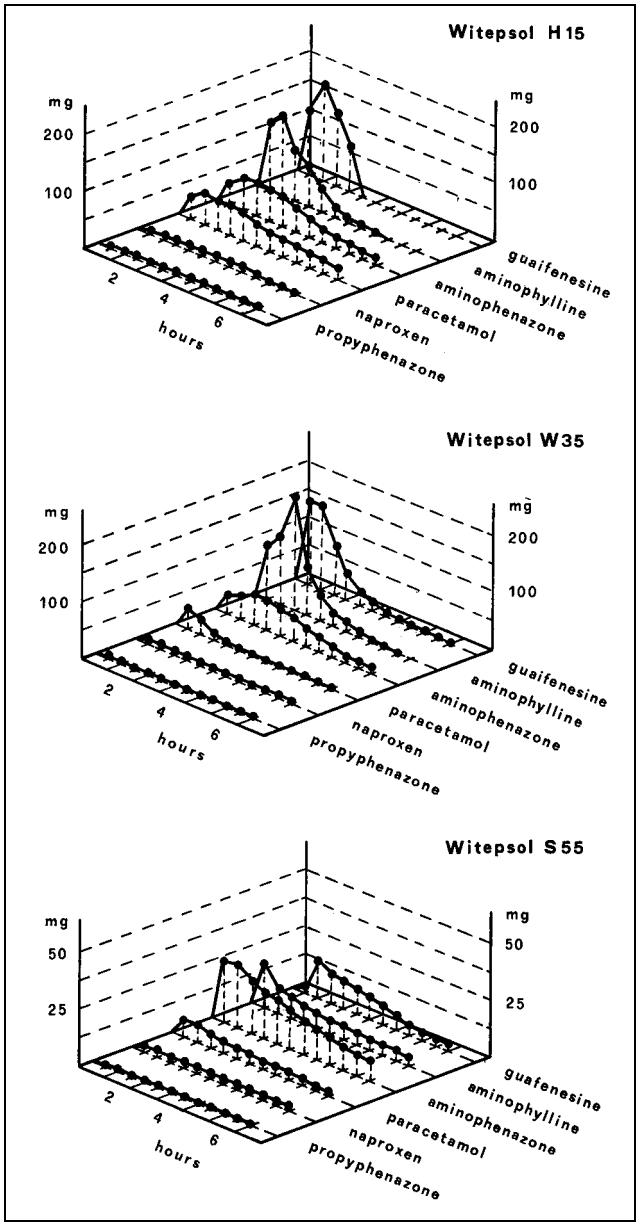

Fig. 6: Amounts (mg) of the drugs having different solubility in water available over time from suppositories with different lipophilic excipients

It is clear from the various results of the study that the administration of a drug rectally can be justified only when its adequate availability from the suppository is ensured.

4. Experimental

4.1. Materials

Paracetamol, aminophenazone, propyphenazone, aminophylline and guaifenesine were purchased from ACEF (Fiorenzuola d'Arda, Piacenza, Italy) and naproxen from Alfa Wassermann S.p.A. (Milano, Italy). Witepsol H15, W35 and S55 were used as excipients for the preparation of suppositories (Hüls AG, Werk Witten, Witten, Germany).

4.2. Methods

4.2.1. Determination of drug solubility

An excess of drug was introduced into 50 ml of water or phosphate buffer solution 1/15 M, pH 7.4, and shaken in a water bath at 20 or 37 $\pm$ 0.5 °C until the concentration remained constant under the following analytical conditions: after filtration and suitable dilution, the drug concentration (mg/ml) was determined spectrophotometrically at wavelengths of 267 nm

for propyphenazone; 262 nm for naproxen; 242 nm for paracetamol; 260 nm for aminophenazone; 271 nm for aminophylline and 222 nm for guaifenesine.

4.2.2. Preparation of suppositories

Suppositories of 3 ml were prepared with each drug tested at the same standard dose of 500 mg. The excipient was melted at 40 °C and the drug in fine powder form was uniformly dispersed by a Silverson turbomixer (Waterside, Chesham, U.K.). The melted mass was then poured into disposable PVC moulds and cooled to solidification at room temperature (18–20 °C). After 24 hrs the suppositories were refrigerated (5–10 °C) until their use in the different tests.

4.2.3. Determination of rheological characteristics of suppositories

A Rotovisco RV12 viscometer (Haake, Karlsruhe, Germany) with a PG142 programmer and NV measuring system was used. Determinations were carried out at a shear rates from 0 to 700 s^{-1} on a mass obtained by warming six suppositories for 20 hrs at 37 °C.

4.2.4. Drug dissolution rate from excipients

Each suppository was put into a glass cylinder, length 7 cm and internal diameter 5 cm, open at both ends and submerged for 3 cm in 500 ml of phosphate buffer 1/15 M, pH 7.4, at 37 °C, with stirring at 100 rpm. Every 15 min a sample of diffusion fluid was collected and replaced with the same amount of buffer solution. The amount of drug released was spectrophotometrically determined after suitable dilution at the above mentioned wavelengths. The test was repeated for six suppositories of the same batch.

4.2.5. Determination of in vitro drug availability

Each suppository from the tested batches was placed in a piece of dialysis tube (Visking Tubing, London, U.K.) 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 phosphate buffer solution 1/15 M, pH 7.4, the tube was closed at the other end; care was taken not to leave any air bubbles inside. The two ends of each tube were held by a Perspex 1.5×3 cm clamp with stainless steel screws. Each tube was placed horizontally in a 1 l beaker containing 500 ml of the same buffer solution thermostated al 37 ± 0.5 °C and stirred at 100 rpm by a 5-cm blade stirrer. Every 15 min a 2 ml sample of the diffusion fluid was collected and replaced with the same amount of buffer. Drug concentration was determined spectrophotometrically at the above-mentioned wavelengths. The test was carried out simultaneously on six suppositories.

4.2.6. Contemporary determination of drug availability and suppository viscosity during the test

Each suppository was placed in a piece of dialysis tube under the same conditions described above for the drug availability test. Six suppositories were placed horizontally and radially 3 cm from the bottom of a cylindrical basin (25 cm in diameter and 10 cm deep) containing 3 l of buffer solution thermostated at 37 ± 0.5 °C, and stirred constantly at 100 rpm by a 10 cm blade stirrer. The release test was carried out simultaneously with six basins for each suppository batch, 36 suppositories in total.
Every 15 min 2 ml samples of diffusion fluid were collected from each basin and replaced with the same amount of water. The total amount of drug released from suppositories in each basin during the time course was determined spectrophotometrically after suitable dilution with buffer solution at the above-mentioned wavelengths.
After 1 hr the test was stopped for the first of the six basins. Tubes containing the suppositories were placed on a plate (care was taken not to mix the contents) and cooled to +5 °C to solidify the suppository mass. The tubes were then opened and both the aqueous phase and the solidified mass were collected. The latter was carefully dried with filter paper. This operation was repeated hourly for the other five basins. In each aqueous phase collected the drug concentration was determined spectrophotometrically. The suppository masses were incubated at 37 °C for 20 h and then tested rheologically under the above-mentioned conditions.

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Received July 29, 1999
Accepted October 1, 1999

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