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Effect of operating parameters on the *in vitro* drug availability test from suppositories

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An *in vitro* model of the rectal compartment widely used to evaluate drug availability from suppositories, is performed with a polymer membrane of dialysis tubing simulating the rectal barrier. This is placed between the small volume of aqueous phase simulating the intrarectal aqueous secretion and a second aqueous phase of a larger volume simulating the circulating plasma [1]. The methods based on this model use different volumes of intrarectal and plasmatic phase [1–5]. In a previous study [2] the rate of drug availability accumulating in the plasma phase of the above-mentioned model appeared to be related to the solubility of the drug in water and ambient rectal conditions. Since drug diffusion between the intrarectal and plasmatic phases is conditioned by the concentration gradient , and in turn by drug solubility [2], it was necessary to investigate the influence of volume of the phases on *in vitro* test results by using suppositories containing drugs of different solubilities in a lipophilic excipient.

Six drugs with different solubilities in water under intrarectal conditions, which are currently used in suppositories, were tested. Drug solubility at 37 °C in buffer solution of phosphate 1/15 M at pH 7.4 was determined in a previous study [2]. The availability test was carried out on suppositories with lipophilic excipient of each of the drugs tested by using the method described in the experimental section in two series of experiments:

- varying the volume of intrarectal phase between 0 and 20 ml and keeping the volume of plasmatic phase constant at 1 l;
- varying the volume of plasmatic phase between 500 and 2000 ml and keeping the volume of intrarectal phase constant at 5 ml.

The availability of the different drugs to the outer compartment was calculated by evaluating the area under the curves (% drug released versus time) as obtained in a 6-h *in vitro* test.

The Fig. shows that in the conditions described above in the first point the availability of the two least soluble drugs (propyphenazone and naproxen), although remaining constantly low, was significantly greater ($p < 0.05$) in the absence an intrarectal phase. This may be explained by considering the melted suppository in direct contact with the large volume of plasmatic phase connected through the capillary pores of the membrane filled with the same phase. In contrast, in the presence of a defined volume of intrarectal phase in which the drug goes into solution, the phase rapidly reaches saturation and appears only slightly receptive to further quantities of drug from the suppository. The constantly low drug concentration keeps the concentration gradient with the plasmatic phase low and therefore the drug availability through the membrane is also low.

The two drugs of intermediated solubility (paracetamol and aminophenazone) show significantly less ($p < 0.05$) availability in the absence of intrarectal phase. However, from 2.5 ml of intrarectal phase, the availability remains constant.

For the two drugs with greatest solubility (aminophylline and guaifenesine), the availability appears to be related to the volume of intrarectal phase. As the latter increases there is an increase in amount of drug in solution and thus an increase in availability. With volumes greater than 10 ml of intrarectal phase, drug concentrations decrease because a progressively lower concentration gradient is created compared to the plasmatic phase.

A volume of between 5 and 10 ml of intrarectal phase appears compatible with the different types of drug.

In the conditions described above in the second point the same suppositories of the six drugs were tested for availability by maintaining the volume of intrarectal phase constant at 5 ml and modifying the volume of plasmatic phase. No significant differences ($p < 0.05$) were observed between these results and the previous ones. Thus it is assumed that "sink" conditions are guaranteed by the volumes used.

Experimental

1. Materials

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

2. Preparation of suppositories

Suppositories of 3 ml were prepared with each of the drugs tested at the same unitary dose of 500 mg by using disposable PVC moulds. After 24 h suppositories were refrigerated (5–10 °C) until their use in the different tests.

3. 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 overnight in water at room temperature. After the addition of phosphate buffer solution 1/15 M, pH 7.4 (from 0 to 20 ml), the tube was closed at the other end; care was taken to remove all air bubbles. 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 2 l beaker containing the same buffer solution (from 500 to 2000 ml) thermostated at 37 ± 0.5 °C and stirred at 100 rpm by a 5-cm blade stirrer. Every 15 min, a 2 ml sample of diffusion fluid was collected and replaced with the same amount of buffer. The concentration of drug was spectrophotometrically determined 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. The test was carried out simultaneously on six suppositories.

Data are the arithmetic mean ± standard error of mean (SEM). Comparisons were performed by ANOVA, followed by Duncan's test. Significance was tested at the 0.05 level of probability.

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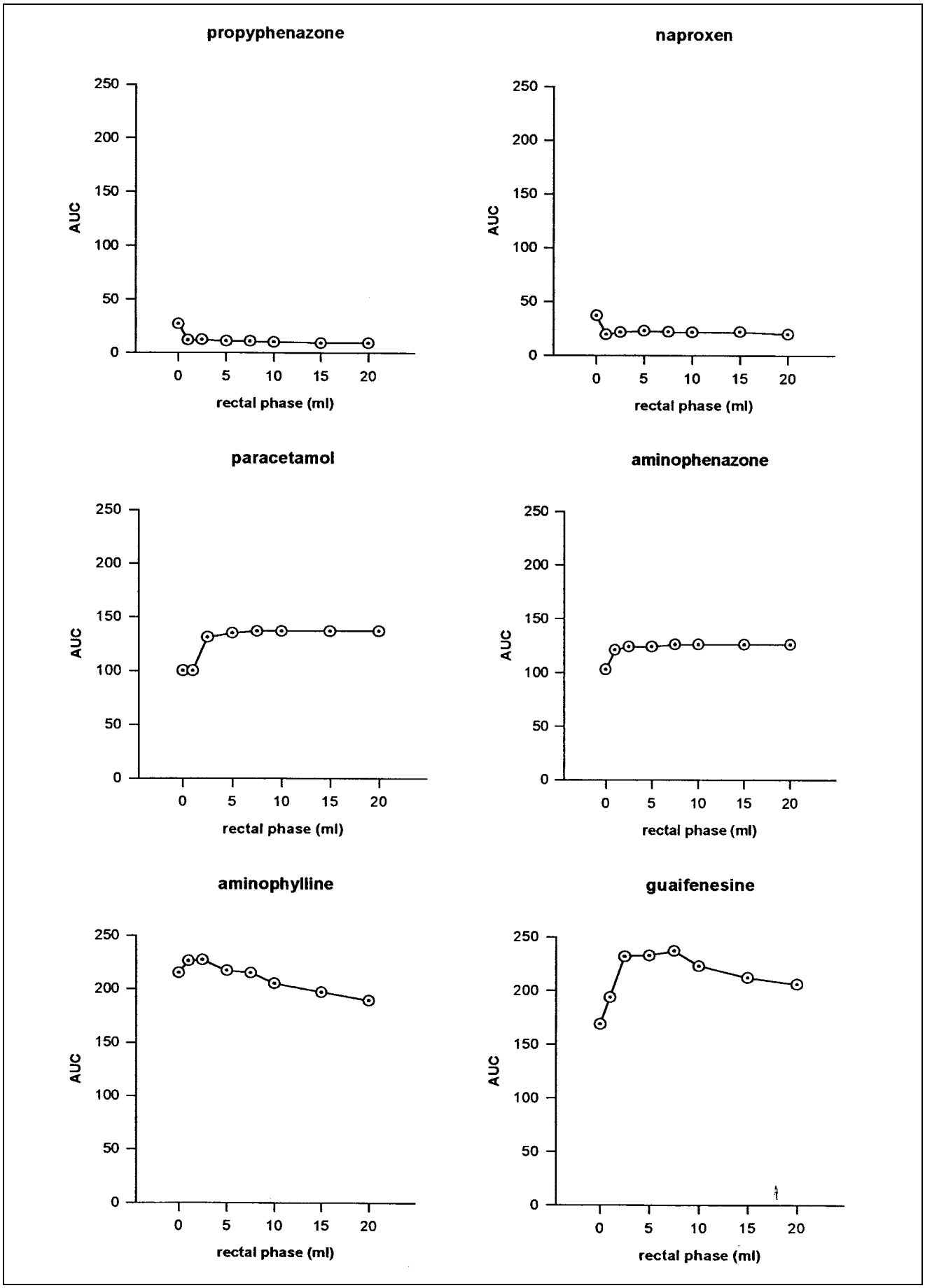

Fig.: Trend of AUC values (% of drug released × time) of the six drugs with different solubilities experimented by adopting different intrarectal phase volumes in the *in vitro* availability test.