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RESEARCH PAPER

Effects of Silicium Dioxide on Drug Release from Suppositories

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ABSTRACT

Silica gel is frequently introduced into lipophilic excipients for suppositories as a viscosity agent, to prevent drug sedimentation in the melted mass, and to decrease release rate. The effect of silica gel (Aerosil 200) concentration on the availability of some drugs frequently used in suppositories in different unitary doses was studied. When silica gel concentration in the excipient was increased, a decrease in aminophylline and aminophenazone release rate was observed. Paracetamol in small unitary doses has shown a tendency to increase release rate at higher silica gel concentrations. This behavior was even more evident in suppositories containing promethazine hydrochloride, while for those containing benzydamine hydrochloride the increase in release rate with increasing silica gel concentration was evident for all drug doses. However, the behavior was a consequence of the trend of suppository viscosity during drug release. As a consequence of both the drug and silica gel being discharged, the viscosity progressively decreased with an increased silica gel concentration. The effect on drug availability was conditioned by silica gel concentration, as well as the type and dose of the drug, which could act on the shape of the suppository inner structure that is responsible for viscosity and mobility of drug particles.

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INTRODUCTION

The introduction of silica gel into lipophilic excipients for suppositories produces an increase in viscosity of the melted mass (1–5). Such an effect is useful in practice to reduce sedimentation of the suspended drug, ensuring homogeneity of the melted mass when pouring into molds and uniformity of drug distribution in suppositories until solidification, particularly when the drug is in unitary doses of few milligrams. Increase in viscosity of suppositories at rectal temperature nevertheless involves a reduction in drug release rate (4,6–8).

In a previous study we observed that the release rate of paracetamol from suppositories based on glycerides decreased progressively when the concentration of both hydrophilic (Aerosil 200) and lipophilic (Aerosil R972) silica gel increased (9). With small doses of benzydamine hydrochloride in suppositories with the same type of excipient, (10) it was observed instead that increasing hydrophilic silica gel concentration led to a decrease in release rate at the lowest concentrations, followed by a progressive increase at the highest concentrations. This was ascribed to the drop in viscosity of suppositories during release, to which the discharge of silica gel from melted suppositories contributed. Such behavior did not occur, however, with suppositories containing lipophilic silica gel, the drug release rate of which decreased progressively with the increase in additive concentration.

The aim of this study was to assess whether the different behavior observed regarding hydrophilic silica gel with the two above-mentioned drugs should be ascribed to the different type and different physicochemical characteristics of the drugs or their different dosage. Suppositories with a lipophilic excipient, generally used with drugs for common rectal application, having different chemical and physical-chemical characteristics in different unitary doses, were prepared varying the concentration of a hydrophilic silica gel (Aerosil 200).

MATERIALS AND METHODS

Materials

Paracetamol (Chimifarm, Verona, Italy); aminophenazone, aminophylline, promethazine hydrochloride, benzydamine hydrochloride (ACEF, Fiorenzuola D'Arda, Italy); Aerosil 200 hydrophilic silica gel (Degussa, Frankfurt, Germany); Miglyol 812, and Witepsol H15 (Hüls AG, Werk Witten, Germany) were used.

Suppository Batch Preparation

Batches of suppositories of 2 ml were prepared with each of the drugs tested at the four unitary doses of 25, 50, 100, and 250 mg. Witepsol H15 added to Miglyol 812 (10% w/w) was used as excipient (11). Batches of suppositories containing different concentrations of Aerosil 200 (0.5, 1.0, 1.5, and 2.0% w/w) were prepared for each unitary drug dose.

After the excipient had been melted at 40°C, silica gel and then the drug in fine powder form were uniformly dispersed by a Silverson turbomixer (Waterside, Chesham, UK). The melted mass was then poured into disposable PVC molds and cooled to solidification at room temperature (18–20°C).

To evaluate the effect of silica gel on the viscosity of the excipient, batches of suppositories with the same concentration of Aerosil 200, without the drug, were also prepared.

After 24 hr at room temperature, the batches were refrigerated until their use in different tests.

Weight and content uniformity of each suppository batch were checked according to the Italian Pharmacopoeia (F.U.I. IX, II Supp., pp. 69 and 72). Content uniformity was checked by dissolving a sample of six suppositories in 50 ml of *n*-hexane, extracting the drug in water, filtering the aqueous extract on a Millipore membrane (type HA, pore size 0.45 μm), and determining the drug content spectrophotometrically as in determination of release rate.

Determination of Rheological Characteristics of Suppositories

A Rotovisco RV 12 viscometer (Haake, Karlsruhe, Germany) with a PG 142 programmer was used, utilizing NV measurement equipment.

Determinations were carried out on a mass obtained by incubating six suppositories for 20 hr at 37°C, at shear rates ranging from 0 to 700 sec^{-1}.

Contemporary Determination of Drug Release Rate and Suppository Viscosity During Release Rate (10, 12)

Each suppository from the tested batches was placed in a piece of dialysis tube (Visking Tubing, 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; 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. 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 liters of water 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 three basins for each suppository batch, 18 suppositories in total.

Every 15 min six 2-ml samples of the 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 spectrophotometrically determined after suitable dilution with water (paracetamol at 242 nm, aminophenazone at 260 nm, aminophylline at 271 nm, promethazine hydrochloride at 249 nm, and benzydamine hydrochloride at 306 nm).

After 1 hr the test was stopped for the first of the three basins. The six 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 to collect the solidified mass, which was carefully dried with filter paper. This operation was repeated after 2 and 3 hr for the other two basins. The masses from each basin were incubated at 37 ± 0.5°C for 20 hr and then rheologically tested in the above-mentioned conditions.

RESULTS AND DISCUSSION

Most drugs vehicled into suppositories are insoluble or barely soluble in lipophilic excipient and thus the drug is dispersed in fine particles. At rectal temperature, the drug is made available by fusion of the suppository. As a consequence, drug particles are able to migrate from within the mass toward the interface with the rectal aqueous phase. Drug transfer in this phase is the indispensable condition for its absorption related to the concentration reached as a consequence of its solubility and dissolution rate (13, 14). Hence, the migration rate of drug particles in the melted suppository mass is conditioned by excipient viscosity and the type of "structure" produced within the suppository by dispersed particles. The structure is more compact the higher the number of particles. Consequently, the same unitary dose of drug in each suppository can affect its release rate. In fact, the higher the drug dose, the greater the number of particles and hence the more complex and compact is the structure produced inside the suppository. Such a structure can hinder the migration of drug particles outside the suppository and consequently the release rate decreases (9, 10, 15).

Thus, different unitary doses of drugs frequently used for rectal administration were vehicled in 2-ml suppositories using a common glyceride excipient, Witepsol H15.

The viscosity of suppositories at 37°C showed a significant increase, with an increase in dose of the different drugs (Table 1). In spite of this, drug availability generally did not undergo significant changes at low doses (Fig. 1). Only at the higher doses (100 and 250 mg) was an initial decrease in release rate observed. This rate increased progressively at the subsequent time intervals up to the end of test when practically equivalent values were reached. In fact, during the release test a progressive drop in viscosity of the melted suppositories' mass was observed until reaching, after a time interval depending on the drug, the same values of the excipient alone. This indicated that while the drug particles were being discharged, their progressively decreasing number within the suppository rendered the structure produced by them progressively more expanded, allowing an increasing mobility of particles, consequently producing greater drug availability. The initial slope of the release curve at the highest drug concentrations appeared in reality as low as the drop in suppository viscosity over time.

The only exception was for aminophenazone, the particles of which showed low mobility. The mobility rose with the increase in dose and hence with the increase of the number of particles in the suppository. Although contributing to produce the inner structure, the increased number of particles could have exerted progressively higher pressure on the base of the layer of particles, forcing them to migrate through the interface of the excipient with the rectal aqueous phase, a mechanism assisted by good drug solubility. In this way it is possible to explain the progressive increase in release rate, which at the highest dose of 250 mg followed the same trend as the other drugs tested.

Silica gel contributes to producing a structure inside lipophilic liquid mass, increasing viscosity up to a gel system. Its effect on viscosity has often been exploited in the production of suppositories (1–5), particularly when the unitary dose is low. The viscosity produced in the melted excipient mass contributes to reducing the migration rate of drug particles up to immobilization, involving them in the formation of the structure. In this

Table 1

Time Course of Suppository Viscosity at 37°C During the Release Test of Five Tested Drugs in Different Unitary Doses

	Viscosity (mPa·sec) In Suppositories Containing																			
Drugs	Paracetamol				Aminophenazone				Aminophylline				Benzydamine Hydrochloride				Promethazin Hydrochloride			
Unitary Doses (mg)	25	50	100	250	25	50	100	250	25	50	100	250	25	50	100	250	25	50	100	250
Test time (hr)																				
0	39	39	45	53	38	40	41	47	39	40	43	56	38	39	43	57	39	39	44	69
1	38	38	42	52	37	38	41	39	37	38	38	38	37	37	38	38	37	37	39	42
2	37	37	39	44	37	37	38	38	37	37	37	37	37	37	38	38	37	37	38	41
3	37	37	38	41	37	37	37	37	37	37	37	37	37	37	37	37	37	37	37	40

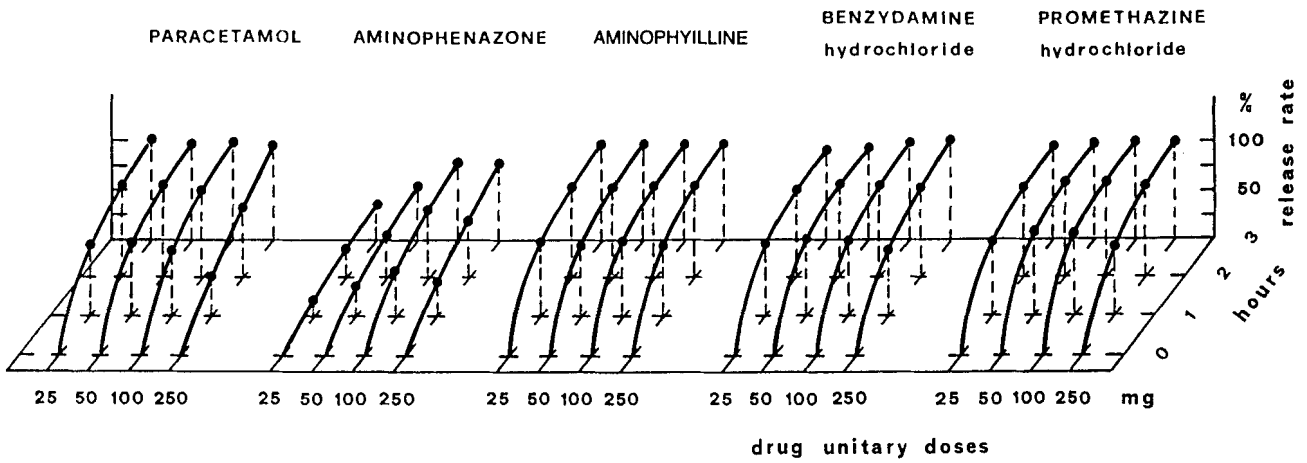

Figure 1. Release curves of five tested drugs in different unitary doses in suppositories prepared with Witepsol H15.

way, homogeneous distribution of the drug in the melted mass when the suppositories are poured into molds can be guaranteed. Moreover, during the interval between pouring and solidification, a homogeneous distribution of small drug doses (10–50 mg) in the body of the suppository is guaranteed, without an accumulation toward the head due to sedimentation.

Increased viscosity of the suppository can decrease drug release rate. In a previous study (9) we observed that with increasing paracetamol dose and concentration of silica gel, the hydrophilic (Aerosil 200) and the lipophilic (Aerosil R972) type, release rate progressively decreased until it almost stopped completely. Using benzydamine hydrochloride, vehicled in suppositories of 100-mg doses, it was possible to observe (10) that with an increase in the concentration of lipophilic silica gel, the release rate of drug decreased, without changes in suppository viscosity at 37°C during in vitro release test. Otherwise, using hydrophilic silica gel in suppositories, at doses equal to the unitary drug dose, it was possible to observe a sharp drop in drug availability at the lowest gel concentrations, followed by a progressive increase at the highest gel concentrations. At the same time, a drop in suppository viscosity during the test was observed. This pointed to the direct involvement of hydrophilic silica gel in the behavior.

The different behaviors of the two drugs in the presence of silica gel led us to check the effect of silica gel concentration and unitary drug dose on the drug release rate from suppositories with lipophilic excipient in other drugs.

Suppositories were prepared using the same glyceride excipient (Witepsol H15), with four unitary doses (25, 50, 100, and 250 mg) of five different drugs with silica gel concentrations between 0.5 and 2% (w/w).

The conditions adopted for the in vitro release test allowed the progress of the viscosity of suppositories to be followed contemporaneously. In this way it was possible to indicate that the effect of the presence and concentration of the hydrophilic silica gel, such as Aerosil 200, in the complex mechanism of the release from the excipient was related to the different nature and hence to the different characteristics of drug and also the drug dose in the suppositories.

Aminophylline

The effect of silica gel concentration on release was more significant at the lower the unitary drug dose. At the highest dose tested (250 mg), the introduction of just 0.5% of Aerosil 200 produced a clear decrease in availability (Fig. 2). It was related to the increased viscosity of suppositories at 37°C (Table 2). When silica gel concentration was 1%, in spite of a further increase in viscosity, the release rate (which was low in the first hour of test) increased to values comparable with those of suppositories without silica gel. This behavior was repeated at the higher concentrations, up to 2% silica gel, after which the mass could no longer be poured into molds. The viscosity of suppositories, being higher with greater concentrations of viscogenic agent, showed a sharp drop after the first hour. This allowed greater mobility of particles and hence greater drug release rate.

Reducing the unitary dose to 100 mg and increasing silica gel concentration produced a progressive decrease in drug availability. The initial values of suppository

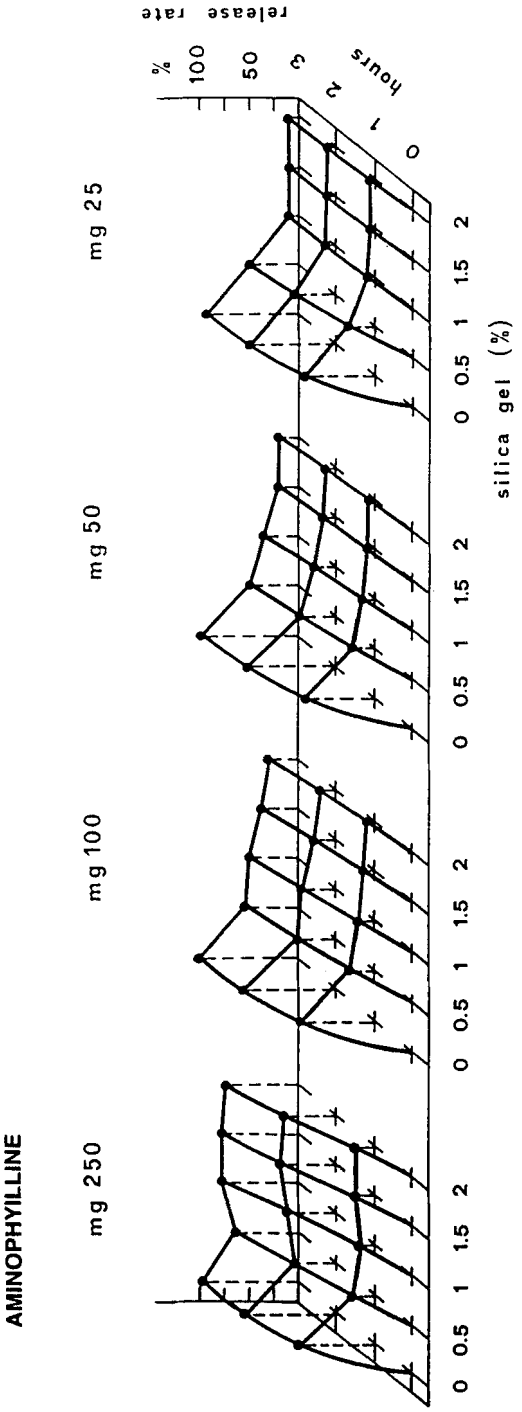

Figure 2. Release curves of aminophylline in different unitary doses prepared with Witepsol H15 alone and with the addition of increasing percentages of Aerosil 200.

Table 2

Time Course of Suppository Viscosity at 37°C During the Release Test of Aminophylline in Different Unitary Doses

	Viscosity (mPa·sec) in Suppositories Containing Aminophylline																			
Unitary Doses	250 mg					100 mg					50 mg					25 mg				
Silica Gel (%)	0	0.5	1	1.5	2	0	0.5	1	1.5	2	0	0.5	1	1.5	2	0	0.5	1	1.5	2
Test time (hr)																				
0	56	75	97	124	161	43	55	73	94	118	40	48	60	78	97	39	46	57	71	84
1	38	54	55	58	64	38	47	56	57	70	38	43	52	60	68	37	42	57	71	78
2	37	45	48	57	64	37	41	50	57	69	37	41	46	55	66	37	39	53	70	75
3	37	39	46	56	62	37	41	41	53	62	37	39	44	53	61	37	39	53	66	70

viscosity, which were lower than in the previous series, underwent less change, remaining at relatively high values until the end of the test.

At even lower unitary doses, such as 50 and 25 mg, the effect of silica gel concentration was more significant until release stopped at the highest concentrations. The initial viscosity levels, which when compared with silica gel concentration were lower with a lower drug dose as a result of the fewer particles dispersed in the suppository mass, decreased by few units during the test then remained practically constant.

This permits explanation of how the structure produced in the system by silica gel, which is capable of trapping drug particles and so hindering their migration inside the suppository, was conditioned by the very number of such particles. The more numerous the drug particles, interposing between silica gel particles, the more they were a hindrance to formation of an organized structure, allowing a freer flow of drug particles, the passage of which into the aqueous phase was made easier by their high water solubility. However, the significant drop in viscosity remained an indication of the structure's disorganization. The lower their number and unitary dose, the lower the influence by drug particles on the structure. At the lowest unitary doses, drug particles were trapped in the increasingly organized silica gel structure and their availability was totally insufficient.

Aminophenazone

The introduction of increasing concentrations of silica gel in the suppository mass produced a progressive decrease in drug release rate at the highest tested doses of 250 and 100 mg (Fig. 3). The lower the drug availability, the lower the drop in suppository viscosity during the test (Table 3), enough to recognize the formation of a compact structure to which both gel and drug particles contributed to block particle mobility completely.

Compared with suppositories without silica gel, the effect of concentration of the viscogenic agent was insignificant at the two lowest unitary doses of 50 and 25 mg. Conversely, at the highest silica gel concentration, a sharp increase in drug release rate took place and the higher drug mobility was related to the sharp drop in suppository viscosity during the test course.

Paracetamol

The effect of the presence and concentration of silica gel at 250 mg drug dose was intense with high viscosity values during the test (Table 4).

At the highest silica gel concentrations it became more evident that drug availability tended to increase progressively, like for aminophenazone, as the unitary dose decreased (Fig. 4). This increase was always accompanied by a decreasing trend in viscosity of suppositories during the test.

However, the introduction of silica gel produced increases in viscosity compatible with a satisfactory drug availability only at low unitary doses and low silica gel concentrations.

Promethazine Hydrochloride

The effect above observed with paracetamol was more evident with promethazine hydrochloride (Fig. 5 and Table 5). At the two highest doses (250 and 100 mg) silica gel produced a distinct decrease in release independent of its concentration. In spite of the high viscosity level, during the test it quickly decreased helping the migration of drug particles after just 1 hr. It was observed that with the two lower doses of 50 and 25 mg, release rate tended to increase at the highest silica gel concentration, corresponding exactly to the higher initial viscosity of suppositories. In this condition, compared with the other suppositories in the same series, the most intense drop in viscosity was observed.

Benzydamine Hydrochloride

The effect of the release rate increase at higher silica gel concentrations was shown with all drug unitary doses and was more marked the lower the dose (Fig. 6). This effect was evident from the first hour of the test, corresponding to a drastic drop in suppository viscosity (Table 6). The turbidity of the aqueous phase around the suppository in the model of the rectal compartment adopted showed how a quantity of silica gel migrated out of the suppository, justifying the drop in viscosity.

However, the results obtained in the previous study on suppositories containing benzydamine hydrochloride with a lipophilic excipient of silica gel added (10) were confirmed as a characteristic behavior of the drug.

Behavior of Suppositories with Silica Gel Only

A series of suppositories were prepared with the same glyceride excipient Witepsol H15 containing only silica gel at the same concentrations as those tested with the different drugs. Suppositories were tested under the same operative conditions as the drug release test. At the same time intervals (1, 2, and 3 hr) samples of suppositories were taken to measure viscosity at 37°C.

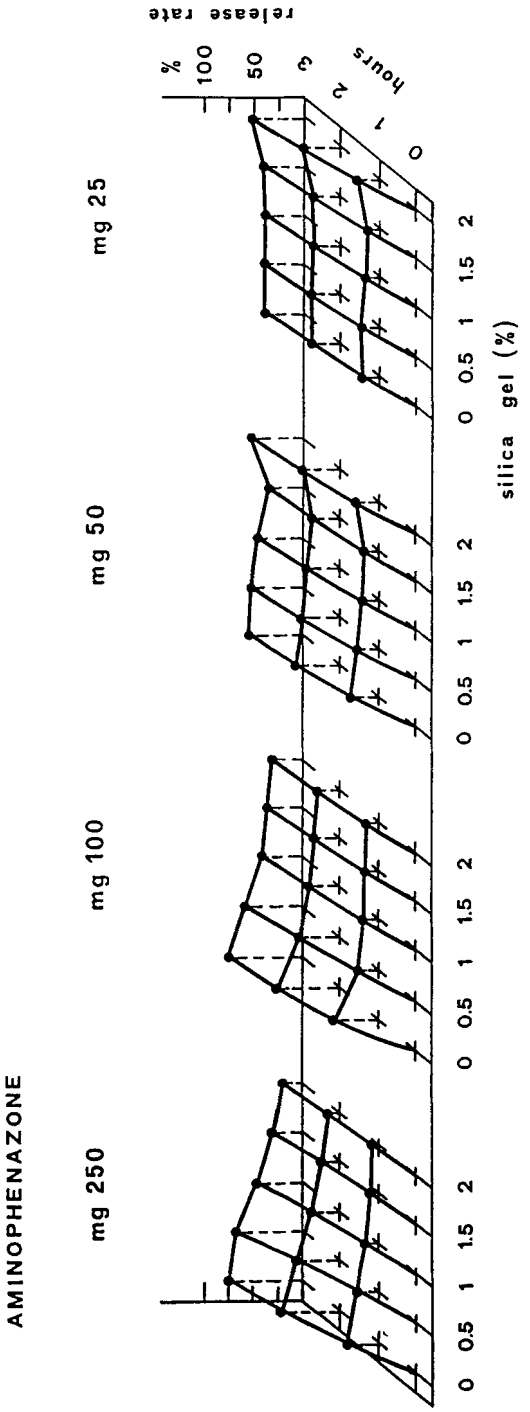

Figure 3. Release curves of aminophenazone in different unitary doses, prepared with Witepsol H15 alone and with the addition of increasing percentages of Aerosil 200.

Table 3

Time Course of Suppository Viscosity at 37°C During the Release Test of Aminophenazone in Different Unitary Doses

	Viscosity (mPa·sec) in Suppositories Containing Aminophenazone																			
Unitary doses	250 mg					100 mg					50 mg					25 mg				
Silica Gel (%)	0	0.5	1	1.5	2	0	0.5	1	1.5	2	0	0.5	1	1.5	2	0	0.5	1	1.5	2
Test time (hr)																				
0	47	55	66	79	98	41	44	52	64	77	40	42	50	60	69	38	42	48	56	64
1	39	41	56	77	91	41	38	46	58	73	38	38	41	54	55	37	38	40	44	50
2	38	38	51	66	90	38	38	46	54	62	37	38	39	53	44	37	38	38	39	44
3	37	38	39	56	90	37	38	42	51	55	37	38	38	51	40	37	38	38	39	40

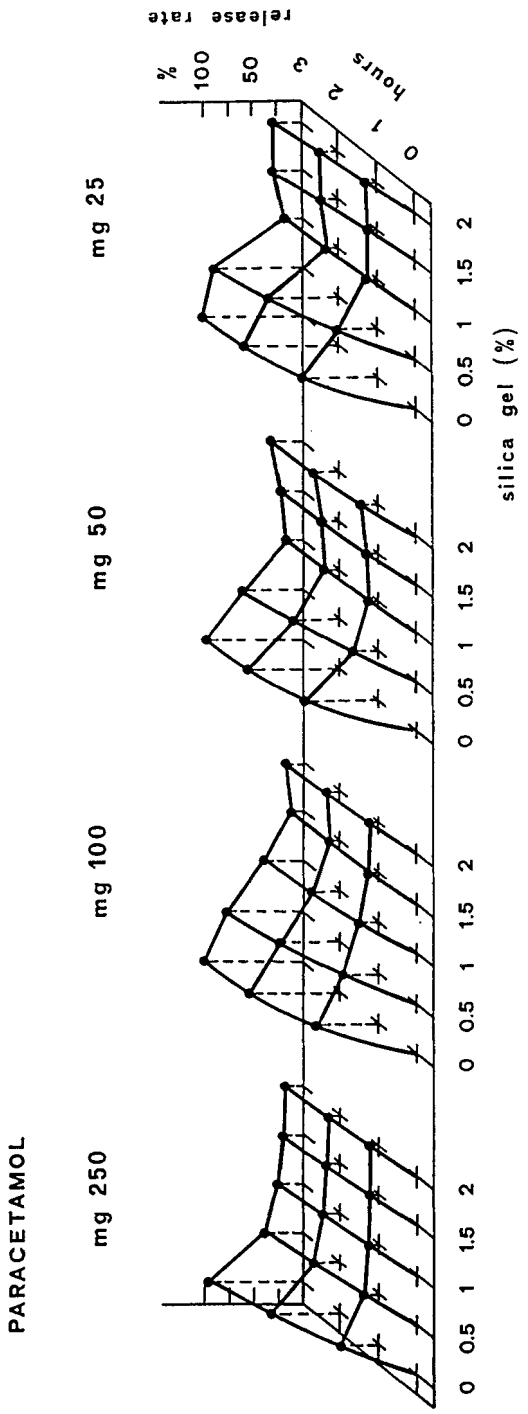

Figure 4. Release curves of paracetamol in different unitary doses, prepared with Witepsol H15 alone and with the addition of increasing percentages of Aerosil 200.

Table 4

Time Course of Suppository Viscosity at 37°C During the Release Test of Paracetamol in Different Unitary Doses

	Viscosity (mPa·sec) in Suppositories Containing Paracetamol																			
Unitary Doses	250 mg					100 mg					50 mg					25 mg				
Silica Gel (%)	0	0.5	1	1.5	2	0	0.5	1	1.5	2	0	0.5	1	1.5	2	0	0.5	1	1.5	2
Test time (h)																				
0	53	64	78	93	110	45	50	60	74	88	39	46	55	64	75	39	44	51	58	66
1	52	62	73	86	100	42	44	59	70	80	38	44	54	62	73	38	40	50	58	66
2	44	56	71	84	94	39	43	53	67	78	37	42	52	60	68	37	38	50	56	65
3	41	55	66	70	73	38	39	51	67	75	37	39	48	60	65	37	37	50	56	64

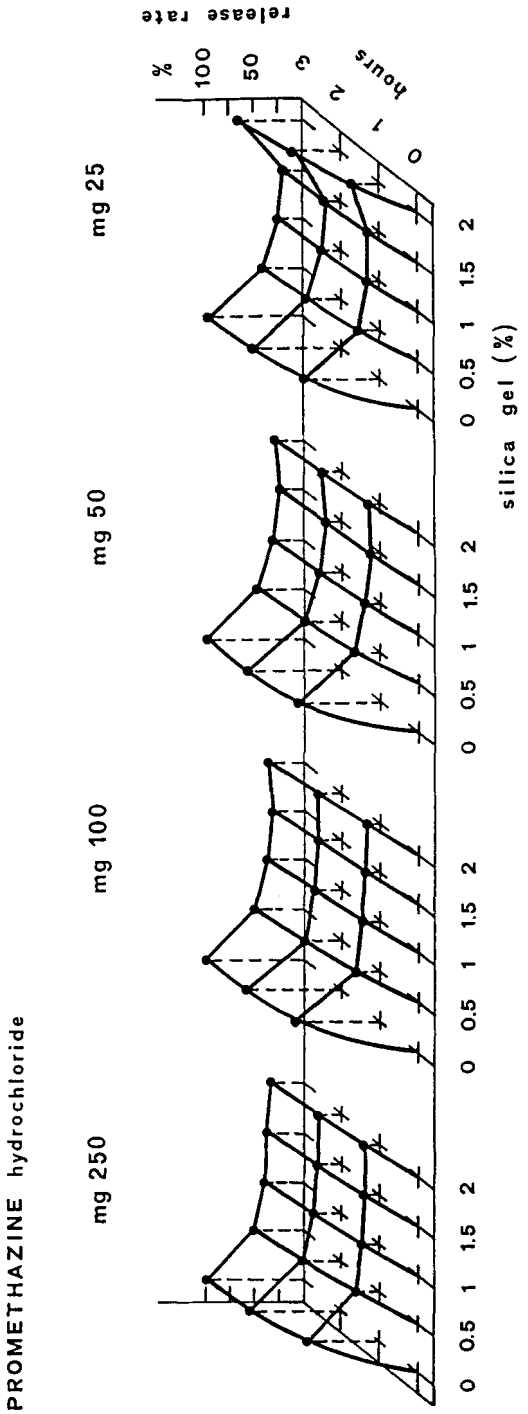

Figure 5. Release curves of promethazine hydrochloride in different unitary doses, prepared with Witepsol H15 alone and with the addition of increasing percentages of Aerosil 200.

Table 5

Time Course of Suppository Viscosity at 37°C During the Release Test of Promethazine Hydrochloride in Different Unitary Doses

	Viscosity (mPa·sec) in Suppositories Containing Promethazine Hydrochloride																			
Unitary Doses	250 mg					100 mg					50 mg					25 mg				
Silica Gel (%)	0	0.5	1	1.5	2	0	0.5	1	1.5	2	0	0.5	1	1.5	2	0	0.5	1	1.5	2
Test time (hr)																				
0	69	75	88	107	134	44	52	63	78	101	39	46	54	66	85	39	44	52	60	77
1	42	70	72	75	79	39	46	53	61	77	38	42	50	62	83	37	41	50	58	59
2	41	57	60	64	75	38	42	52	57	72	37	41	46	61	74	37	41	48	57	52
3	38	50	58	61	69	37	42	50	55	68	37	41	44	61	64	37	41	44	56	47

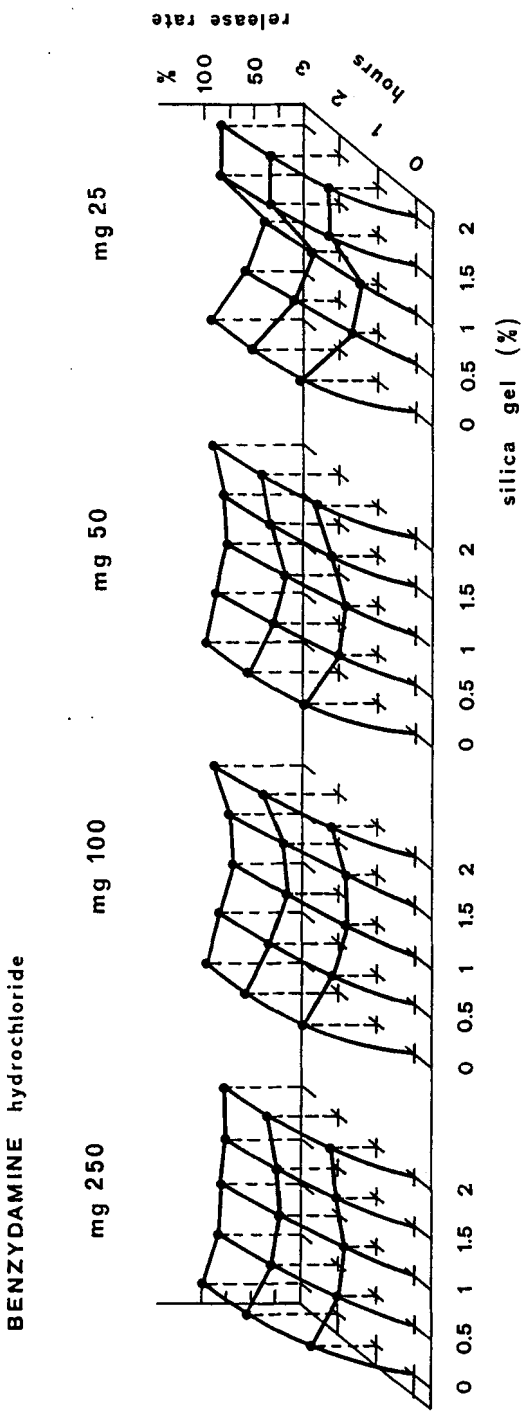

Figure 6. Release curves of benzydamine hydrochloride in different unitary doses, prepared with Witepsol H15 alone and with the addition of increasing percentages of Aerosil 200.

Table 6

Time Course of Suppository Viscosity at 37°C During the Release Test of Benzydamine Hydrochloride in Different Unitary Doses

	Viscosity (mPa·sec) in Suppositories Containing Benzydamine Hydrochloride																			
Unitary Doses	250 mg					100 mg					50 mg					25 mg				
Silica Gel (%)	0	0.5	1	1.5	2	0	0.5	1	1.5	2	0	0.5	1	1.5	2	0	0.5	1	1.5	2
Test time (h)																				
0	57	64	75	91	113	43	51	60	73	88	39	46	53	65	78	38	45	52	61	74
1	38	38	43	41	38	38	41	47	48	42	37	40	45	43	43	37	42	47	42	42
2	38	38	38	38	39	38	39	42	44	40	37	39	43	39	39	37	41	44	39	41
3	37	38	38	38	39	37	38	41	42	39	37	38	42	41	38	37	41	42	38	39

Table 7

Time Course of Viscosity at 37°C of Witepsol H15 Suppositories Containing Different Percentages of Aerosil 200 During Drug Release Test

	Viscosity (mPa·sec) of Witepsol H15 Containing Aerosil 200				
Test Time (hr)	0%	0.5%	1%	1.5%	2%
0	37	42	51	59	71
1	37	39	44	54	67
2	37	38	39	49	66
3	37	38	39	49	60

Results reported in Table 7 showed a drop in viscosity of the suppository mass until it reached steady values after the second hour of testing. This behavior was a result of the turbidity of the aqueous phase surrounding the suppository in the rectal compartment model adopted. This effect demonstrated that hydrophilic silica gel particles were able to migrate outside the suppository, progressively expanding the structure previously produced within the suppository, with a consequent decrease in mass structural viscosity.

Drug particles, each with their own characteristics, mixing with silica gel and aiding the formation of the above-mentioned structure, necessarily produced an increase in viscosity. Nevertheless, drug particles are able to influence the structure shape, also forming links with silica gel particles. In this way it is possible to explain the different behavior of suppositories with a change in the type of drug and its unitary dose in suppositories.

CONCLUSION

The introduction of hydrophilic silica gel, such as the Aerosil 200 tested, into suppositories with lipophilic excipient produced an increase in the viscosity of the melted mass proportional to its own concentration. The effect is in some circumstances particularly pursued to guarantee a homogeneous dispersion of drug particles when the unitary dose is small.

The effect on drug availability is influenced both by the viscosity produced by silica gel concentration and the nature and dose of the drug, which could influence the structure produced by the viscogenic agent and finally its own mobility in the fused suppository.

According to the drug and its dose, silica gel concentration has to be evaluated with the aim of giving adequate viscosity to the suppository mass so that it can be poured into molds, and avoiding drug sedimentation without compromising drug availability.

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