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BIOPHARMACEUTICAL STUDIES OF FATTY SUSPENSION SUPPOSITORIES I. SPREADING IN SITU

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SUMMARY

In the present publication an investigation is described about the qualitative and quantitative determination of the spreading of suppository vehicles and compounds suspended in suppositories in situ in the rat. The influence of variables such as particle size, particle concentration and solubility of the suspended compound are studied. Next to these parameters, factors such as the pressure of the rectum wall and the viscosity of the suppository vehicle at body temperature seem to be important for the spreading behaviour of the suppositories. Therefore, on theoretical grounds the spreading of the suppositories in vivo cannot be predicted.

GENERAL INTRODUCTION

The bioavailability of rectally administered drugs has been the subject of a good many investigations. Nevertheless many questions remain unanswered, even leaving room for questioning the route of administration per se. Bevernage and Polderman (1973), in their review of the subject, proposed a more systematic approach and ordered the many variables into groups according to their nature, i.e. physiological, related to the vehicle and related to the drug substance. This line has been extended recently in discussing the rationales underlying the design of rectal and vaginal delivery forms (de Blaey and Polderman, 1978). In between, a model for the mechanism of drug release from fatty suspension suppositories was proposed (de Blaey et al., 1976) in which three steps are discerned:

(1) transport of the suspended particle through the melted and spread vehicle to the interface with the rectal fluid;

(2) transport through that interface; and

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(3) dissolution in the rectal fluid.

This seems more appropriate than the treatment of release in analogy to the release from ointments (Higuchi, 1961), which has sometimes been proposed (Ritschel, 1973). The main consideration lies in relatively low viscosity of melted suppositories, resulting in an unstable system with respect to particle position in the vehicle. This mechanism of release has been the subject of investigation in our laboratory and preliminary results have been presented on several occasions (Bevernage et al., 1973; Kingma et al., 1975; Kingma and Breimer, 1975; Rutten-Kingma et al., 1977).

In this paper results will be presented on the spreading in situ, while in subsequent papers we will report on the influence of particle size and concentration on the release in vitro, in rats and in man.

SPREADING OF SUPPOSITORIES

After insertion a fatty suppository will start to melt and spread through the rectum. The time required to melt will mainly determine the onset of absorption, and until recently has not been considered of great importance as soon as a proper vehicle had been selected. It remains to be found out, however, whether this is also true in particular for aminophylline suppositories which, at least in vitro, show a marked reduction in melting behaviour and in release rate (de Blaey and Rutten-Kingma, 1976, 1977). Too little in vivo data are available as yet to permit conclusions (de Blaey and de Boer, 1976; Krowczynski et al., 1977). The extent of spreading and also the time involved are of direct consequence for the bioavailability, since they determine directly the area available for release and for absorption and thus the absorption rate. Besides, the suggested avoidance of first pass metabolism is also related to the spreading area, since this would require presence in lower parts of the rectum whose venous blood flow mainly leads into the vena cava, while higher parts lead to the vena porta. Recently data have been obtained on salicylamide (de Boer et al., 1977) and thiazinamium (Jonkman, 1977), but these investigations gave no information about the extent of spreading in connection with the first pass effect. Earlier Quevauviller and Jund (1951) had tried to determine the extent of the spreading of suppositories by using radiopaques. Volunteers were given suppositories containing 3 g of barium sulphate. Already after a few minutes this substance was detected in a wide area of the rectum, suggesting, in their opinion, the spreading of the cocoa butter suppositories. No differences were found between volunteers who were in an upright or in a horizontal position after the suppository was administered.

Hennig (1959) studied the spreading of cocoa butter and Witepsol suppositories. He used a smaller dose of barium sulphate ($\rho \simeq 4.3\ g \cdot cm^{-3}$) and, furthermore, Perabrodil ($\rho \simeq 1.5\ g \cdot cm^{-3}$) as radiopaques, and found a pronounced difference between those two agents. Whereas barium sulphate did not show spreading, Perabrodil did, indicating that the latter could be more representative for the spreading of suppositories in the rectum. Cocoa butter, which is the more rapidly melting vehicle, ended up higher in the rectum than Witepsol H15. Yet the question remained unanswered whether in all cases the contrast agent is representative for the suppository as a whole, i.e. whether the suspended contrast agent and the vehicle spread through the rectum at the same pace and to the same extent. Dissolution of the contrast agents in the rectal fluid and consecutive

transport in dissolved form had not been excluded.

Because of these uncertainties, and since the scant information on the physiological situation permits no predictions on theoretical grounds, we decided to investigate these phenomena in more detail. For this purpose we developed methods to follow the spreading in situ, using rats, permitting the evaluation of factors such as particle size and concentration and of a compound dissolved in the vehicle, on the spreading of suppository vehicles and drugs through the rectum.

MATERIALS AND METHODS

Two essentially different methods were developed. At first a *qualitative* one giving information about the presence of suppository vehicle and the dissolved or suspended compound in the intestine of rats. Secondly, a *quantitative* one by which the amount of vehicle and compound could be determined in various parts of the intestine at different times after administration.

The suppository mass was prepared by thoroughly mixing the vehicle and the particular compound manually at about 37°C. After cooling to around 34°C the mass was brought in a hypodermic syringe and either pressed in a mould, giving 180 mg suppositories, or extruded in the air as a bar. After solidifying this bar was cut in pieces, giving suppositories of about 50 mg.

These suppositories were administered to unanaesthetized male Wistar rats weighing between 150 and 300 g, who had fasted for at least 2 days. In order to prevent too much body loss, the rats had free access to a 5% glucose solution. Later on, in the quantitative experiments, the glucose solution was replaced with a solution of Vivonex, a chemically defined elemental diet which produces low residues. After insertion of the suppository to a depth of about 2.5 cm the anus was closed by two small clips, which prevented expulsion of the suppository. At 15, 30 or 45 min the rats were anaesthetized by the aid or ether vapour, after which the situation in the intestine was immediately fixed by freezing the whole rate at −70°C in a mixture of acetone and solid carbon dioxide.

In the *qualitative* method whole body slices of approximately 45 µm were made with the aid of a microtome knife at −15°C. The slices were dried at the same temperature. In order to enable detection of the vehicle in these slices fluoranthene (1,2-benzacenaphthene), a fat-soluble compound fluorescing at 366 nm, had been dissolved in it. Thus very small quantities of the vehicle could be detected visually. Using this method we have studied cocoa butter and Witepsol H5 with and without suspended particles. For this methylene blue (7.5% m/m in both vehicles), quinine sulphate (7.5% m/m in Witepsol H5) and ^{14}C-labelled barium carbonate (1% m/m in Witepsol H5) were used. They were detectable by their colour or fluorescence and, in the case of barium carbonate, through thin layer scanning of the slices. The location of each of them permits certain conclusions on the spreading of the vehicle and the suspended particles and their interrelation.

In the *quantitative* method the whole intestine and stomach were prepared after the rats had been defrosted and cut in some 13 parts. In each of these the vehicle and compound added were determined quantitatively. The compounds used were lithium sulphate, an organic one as free base and hydrochloride (Org. GC-94: 1,3,4,14b-tetrahydro-2,7-dimethyl-2H-dibenzo(b,f)pyrazino(1,2-d)(1,4)oxazepine) and ^{14}C-labelled

TABLE 1

Mean content ($\bar{x}$) and standard error (S.E.) of the model compound in the suppositories expressed as nCi for the radioactively labelled compounds or as % m/m for the non-labelled compound.

Suppository vehicle		Witepsol H_5			
Conc. model compound		5%		20%	
Particle size		<30 μm	~100 μm	<30 μm	~100 μm
GC-94 base	$\bar{x}$ (nCi)		328.4		324.1
	S.E. (nCi)		1.8		5.8
[^{3}H]GC-94 · HCl	$\bar{x}$ (nCi)	281.0	294.7	236.9	265.9
	S.E. (nCi)	6.2	81.9	6.4	10.3
1% [^{14}C]naphthalene	$\bar{x}$ (nCi)	28.0	22.0	20.8	19.8
	S.E. (nCi)	1.2	4.7	2.2	1.7
^{14}C-labelled $BaCO_3$	$\bar{x}$ (nCi)	271.1	a	311.4	a
	S.E. (nCi)	14.7		14.8	
$Li_2SO_4 \cdot H_2O$	$\bar{x}$ (%)	5.4	5.7	21.3	21.9
	S.E. (%)	0.1	0.1	0.4	0.3

[a] Not available.

barium carbonate. The water-soluble ones were investigated in 5 and 20% m/m concentration and as particles of <30 μm and approximately 100 μm. To some series [^{14}C]-naphthalene was added (1% m/m). The content of the suppositories is given in Table 1.

Lithium was extracted from the intestinal parts at 40°C with 100 ml of a solution of 3000 ppm cesium chloride and 8% butanol in distilled water. After filtration the proteins were precipitated with 10 drops of 50% trichloroacetic acid and the solution centrifuged. Lithium was then assayed by flame ionization in the limpid supernatant. Org. GC-94, being labeled with tritium, was assayed after oxidizing the intestinal parts in a Packard Sample Oxidizer model 306. This was equally so for [^{14}C]naphthalene, when present, by collecting $^{14}CO_2$ and $^{3}H_2O$ separately. Liquid scintillation counting was performed in 30 ml of Instagel (Packard Instr., Benelux). For reasons discussed later, it proved necessary to assess the bile excretion of Org. GC-94. The biliary duct was cannulated just before the experiments. The rats were anaesthetized in this case with 50 mg pentobarbital sodium per kg body weight and during the experiment with an additional 20 mg/kg in the abdominal lumen. Bile was collected at 40, 80, 120, 160 and 180 min.

RESULTS AND DISCUSSION

(a) Qualtitative method

In Fig. 1 an example of a slice of a rat is shown. The bright spots, caused by the fluorescence of the added amount of fluoranthene, represent the location of the suppository base. The addition of fluoranthene was justified, because no influence on the interfacial tension of the suppository base could be measured. The place of insertion of the suppository is marked by 1 and is 2.5 cm from the anus. The picture shows clearly a displacement of the suppository through the gut. Along the wall of the whole intestine fluorescence was detected. For ease of survey the conclusions which could be drawn from the pictures of all the experiments are combined and reproduced schematically in Table 2.

The results will be discussed following the table. In the case of the suppositories of

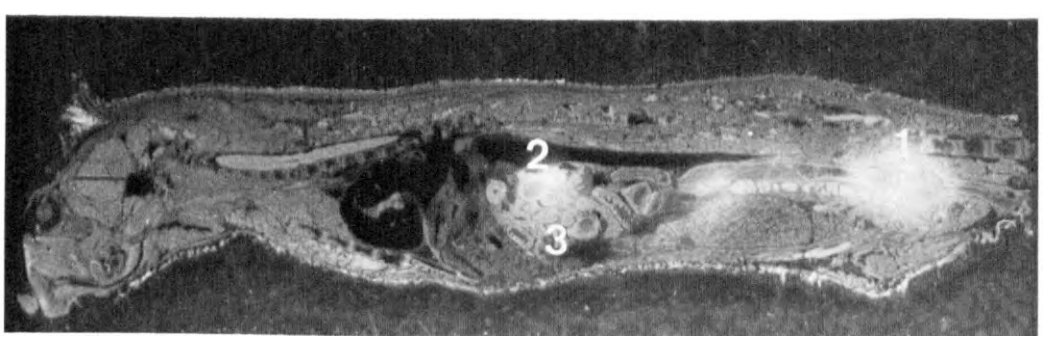

Fig. 1. An example of a picture of a slice of a rat. The bright spots show the availability of suppository vehicle. 1 = Place of insertion of suppository; 2 = colon located at the end of the small intestine; 3 = small intestine.

TABLE 2

Schematical representation of the location of the suppository vehicle (————) and suspended particles (– – – – – –) 15, 30 and 45 min after administration of the suppositories. The lines represent only the presence of the substance, no quantitative difference between amounts has been made.

	min.	± 15 cm Rectum/colon	Caecum	1–1½ m Small intestine	Stomach
(A) Witepsol H_5	15	———	———	———	
± 180 mg	30	———	———	———	———
	45	faeces ———	———		
(B) Witepsol H_5	15	———	——		
± 60 mg	30	———	———	———	
	45	———	———		
(C) Cocoa butter	15	faeces ———			
± 180 mg	30	faeces ———			
	45	———	——		
(D) Cocoa butter	15	faeces ———			
± 60 mg	30	———			
	45	———			
(E) Methylene blue	15	═══			
+ Witepsol H_5	30	═══	═══	═══	
± 60 mg	45	═══	═══	═══	
(F) Methylene blue	15	═══			
+ Cocoa butter	30	═══			
± 60 mg	45	═══			
(G) Quinine sulphate	15	———			
+ Witepsol H_5	30	———	———		
± 60 mg	45	———	———	———	
(H) $Ba^{14}CO_3$	15	═══			
+ Witepsol H_5	30	═══	———	———	
± 60 mg	45	═══ faeces			

180 mg (group A), the Witepsol H5 suppository vehicle was found spread throughout the gut. Even after 15 min the suppository vehicle could be detected in the small intestine and in the caecum; after 30 min it was even detected in the stomach. From these experiments it could be concluded that a displacement of the suppository against the normal peristaltic movement of the intestine seems to be possible. For the smaller suppositories (60 mg, group B) the extent of the spreading was much smaller, although the same rapid displacement through the distal part of the intestine was observed. An explanation for the difference in the results of the small and large suppositories may be an induced pressure of the rectum wall by the relatively large volume of the 180 mg suppositories. Because of this reason suppositories of about 50 mg have been chosen for all the absorption studies.

By comparing Witepsol H5 and cocoa butter suppositories (groups A and B versus C and D) the same rapid spreading was observed, but the Witepsol suppositories spread further through the gut. For neither kind of suppository could equal distribution of suppository mass be concluded, since lumps of suppository mass were detected in the rectum-colon part of the intestine. It was clearly observed that the presence of faeces can be a determining factor for the spreading, since in all the cases where faeces was present in the distal part of the intestine, only limited spreading was found. An example of this phenomena can be the spreading of Witepsol H5 (group A) after 30 min and 45 min. In the latter case faeces was present and the spreading was more limited than in the first case, where no faeces was observed. No influence of suspended particles on the spreading has been observed, neither in the case of a water-soluble compound (group E versus group

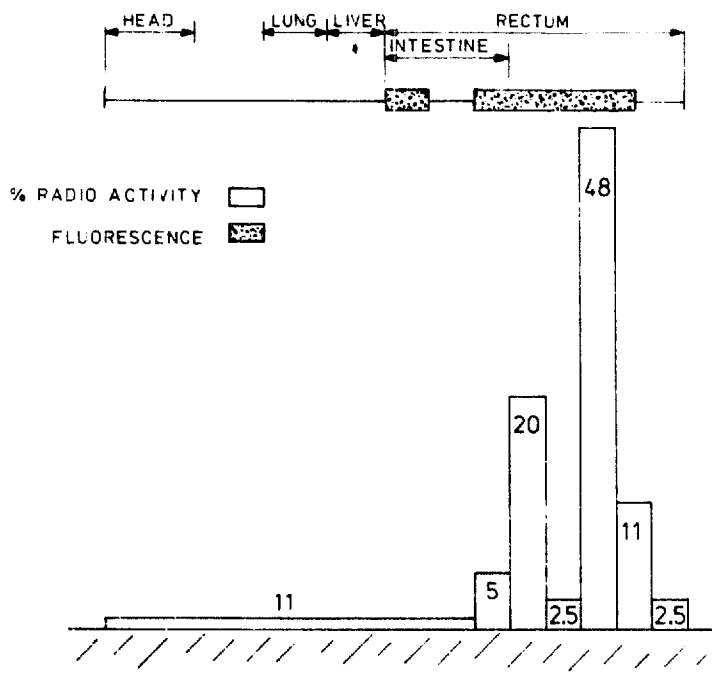

Fig. 2. Schematic representation of the availability of suppository vehicle and barium carbonate particles through the rectum/colon of a rat as found in one single slice of the rat.

B) nor in the case of a water-insoluble compound (groups G and H versus group B). The extent of the spreading of the suppository vehicle is the same for the suppositories with suspended particles as for suppositories without such particles.

As is shown in group H of the table, the suppository vehicle was found over a greater extent than the suspended barium carbonate particles. In Fig. 2 is shown the location of suppository mass and barium carbonate particles in one slice of a rat who received such a suppository and which slice is thought to be representative for these experiments. While most of the suspended particles are found in the very distal part of the intestine, the suppository mass was found over a much greater area. Because of the technique used the whole intestine was not represented in the slice, which caused the interruption in the base for the fluorescence. Still no radioactivity was found in the spot where fluorescence was observed clearly. So it could be concluded that for very heavy particles the spreading for the suppository mass and suspended particles will not necessarily be homogenous.

(b) Quantitative method

In the quantitative experiments factors which might be of influence were studied, such as the concentration of a dissolved or suspended compound (5% versus 20%), particle size (<30 μm versus ± 100 μm) and the density of the particles (GC-94 · HCl versus $Ba^{14}CO_3$).

In Table 3 the results of the experiments with suppositories with 5% and 20% dissolved [^{3}H]GC-94 are shown. The percentages of the totally administered amount of radioactivity determined per part of the gut are summarized. The bulk amount of the radioactivity was found in most cases around the place of insertion of the suppository, i.e. the three distal parts of the intestine. In these experiments the extent of spreading was found to be small, in contrast to the results of the qualitative experiments.

So we can conclude that the suppository base, influenced by GC-94, will not spread throughout the intestine. No clear difference in spreading was observed between the 5% and 20% series. The situation after 15 min was just the same as after 30 and 45 min, suggesting rapid spreading of the suppositories. The amount of radioactivity detected in the stomach or in the first parts of the small intestine will not have reached these parts by spreading because no radioactivity was found in the parts in between the distal parts of the rectum/colon and the first parts of the small intestine. A more likely explanation might be secretion by the bile liquid of the organic compound and of its metabolites. This will be discussed further below.

In Tables 4 and 5 the results of the suppositories containing particles of an average size of 100 μm and <30 μm, respectively, are summarized. [^{14}C]Naphthalene was added to these suppositories in order to differentiate between the vehicle and the suspended compound. The bulk of both, naphthalene and GC-94 · HCl was found in the colon/rectum. Although only small amounts of radioactivity were detected in the other parts, the fact that in each part radioactivity was located suggests somewhat more spreading of the suppository vehicle and the suspended particles than in the series with the dissolved GC-94 base. No differences between milled and unmilled particles were observed. The extent of the spreading was irregular in both series. No obvious differences existed between the 20% and 5% series; however, the extent of the spreading tended to be somewhat smaller

TABLE 3

THE AMOUNT OF GC-94 BASE DETERMINED PER PART OF THE INTESTINE EXPRESSED AS PERCENTAGES OF THE ADMINISTERED AMOUNT. FOR THE RECTAL PARTS THE DISTANCE FROM THE SPHINCTER ANI IS GIVEN IN cm.

	5% GC-94						20% GC-94					
minutes	15		30		45		15		30		45	
Stomach	0.1	–	–	–	–	0.2	–	–	0.1	–	–	–
Intestine	1.0	0.9	1.5	0.8	1.2	1.9	0.8	0.5	1.8	1.8	1.8	1.3
Caecum	–	–	0.1	–	0.3	–	–	–	–	–	0.2	–
Rectum (10–12.5)	–	–	–	–	0.1	–	–	–	–	–	0.1	–
Rectum (7.5–10)	–	–	–	–	0.1	–	–	–	19.8	0.1	–	–
Rectum (5–7.5)	5.3	28.6	0.1	1.4	–	–	–	7.6	5.6	42.2	0.2	0.6
Rectum (2.5–5)	1.1	40.4	37.7	77.8	15.1	0.6	–	45.8	47.8	17.7	37.4	16.5
Rectum (0–2.5)	8.5	6.2	22.1	5.4	56.0	82.5	15.0	33.4	9.5	20.9	12.5	10.6
Recovery	16.0	76.0	61.4	85.4	72.8	85.1	15.7	87.3	84.6	82.6	52.1	29.1
Absorbed	a	24.0	38.6	14.6	27.2	14.9	a	12.7	15.4	17.4	47.9	a

[a] Leaked.

TABLE 4

THE AMOUNT OF [^{3}H]GC-94 · HCl DETERMINED PER PART OF THE INTESTINE IN TWO EXPERIMENTS, EXPRESSED AS PERCENTAGES OF THE ADMINISTERED AMOUNT; SIMILARLY THE AMOUNT OF [^{14}C]NAPHTHALENE. FOR THE RECTAL PARTS THE DISTANCE FROM THE SPHINCTER ANI IS GIVEN IN cm.

	GC-94 · HCl, 20%, <30 μm						GC-94 · HCl, 20%, ~100 μm					
	15 min		30 min		45 min		15 min		30 min		45 min	
	^{14}C	^{3}H	^{14}C	^{3}H	^{14}C	^{3}H	^{14}C	^{3}H	^{14}C	^{3}H	^{14}C	^{3}H
Stomach	0.1	0.2	0.1	0.3	0.1	0.3	0.1	0.1	0.1	0.3	0.2	0.2
	0.0	0.1	0.2	0.2	0.1	0.2	0.1	0.1	0.1	0.5	0.2	0.2
Intestine	0.8	4.8	1.2	3.4	2.5	7.7	0.8	1.3	1.2	2.9	2.1	7.1
	0.4	2.3	2.7	7.0	1.2	4.4	0.9	1.7	0.8	3.4	2.0	6.0
Caecum	0.1	0.2	0.4	1.4	3.2	1.5	0.2	0.2	0.5	0.3	0.5	0.5
	0.1	0.1	12.4	9.7	0.4	1.0	0.3	0.1	0.1	0.5	0.4	0.8
Rectum	0.0	1.3	0.1	0.1	0.1	0.1	0.0	0.0	0.4	0.3	0.1	0.1
(10–12.5)	0.0	0.0	23.6	17.7	0.0	0.1	0.1	0.0	0.1	0.2	0.2	0.2
Rectum	14.3	13.3	1.7	1.8	37.0	33.4	0.1	0.2	0.3	0.3	0.8	1.5
(7.5–10)	0.2	0.6	7.6	8.4	0.1	0.2	41.8	18.6	5.3	4.5	8.5	8.4
Rectum	29.3	30.7	42.6	35.5	5.0	12.4	16.8	18.4	32.6	2.9	30.1	21.1
(5–7.5)	0.8	2.3	1.8	2.5	11.5	2.1	2.1	3.5	7.4	7.4	25.2	24.3
Rectum	2.2	9.3	4.8	15.9	1.7	5.4	0.7	3.1	33.3	22.6	1.7	8.3
(2.5–5)	0.8	3.3	2.6	11.4	1.1	2.2	1.1	2.4	2.8	6.1	2.3	4.7
Rectum	1.9	11.7	2.1	9.1	2.2	9.6	8.1	33.0	3.3	6.5	2.2	15.7
(0–2.5)	7.2	30.9	2.4	13.7	23.8	40.9	1.9	5.1	34.2	40.7	2.5	15.7
Total	48.4	71.5	53.0	67.5	51.5	70.4	26.8	56.3	41.6	36.3	37.6	54.6
	9.5	39.7	53.5	70.6	38.1	51.0	48.3	31.6	50.8	63.1	41.3	60.2
Until		5.0		3.8		8.0		1.4		3.2		7.4
caecum		2.4		7.2		4.5		1.8		3.9		6.2
Disappeared		33.5		36.2		37.6		45.1		67.1		52.8
		a		36.6		53.6		70.3		40.8		46.0

[a] Leaked.

TABLE 5

THE AMOUNT OF [^{3}H]GC-94 · HCl DETERMINED PER PART OF THE INTESTINE IN TWO EXPERIMENTS, EXPRESSED AS PERCENTAGES OF THE ADMINISTERED AMOUNT; SIMILARLY THE AMOUNT OF [^{14}C]NAPHTHALENE. FOR THE RECTAL PARTS THE DISTANCE FROM THE SPHINCTER ANI IS GIVEN IN cm.

	GC-94 · HCl, 5%, <30 μm						GC-94 · HCl, 5%, ~100 μm					
	15 min		30 min		45 min		15 min		30 min		45 min	
	^{14}C	^{3}H	^{14}C	^{3}H	^{14}C	^{3}H	^{14}C	^{3}H	^{14}C	^{3}H	^{14}C	^{3}H
Stomach	0.1	0.1	0.4	0.2	0.2	0.2	0.1	0.1	0.9	0.2	0.4	0.3
	0.0	0.0	0.1	0.1	0.6	0.2	0.4	0.1	1.5	0.1	0.6	0.3
Intestine	0.6	2.5	1.6	6.4	3.2	4.3	1.7	3.3	4.2	3.2	3.8	8.2
	0.8	1.7	1.2	5.3	1.6	2.8	1.3	2.5	4.0	6.5	3.8	8.6
Caecum	0.1	0.1	0.5	0.5	1.7	0.3	1.3	0.2	1.8	0.2	0.6	0.6
	0.1	0.1	0.1	0.3	0.5	0.2	0.3	0.2	1.0	0.3	0.8	0.8
Rectum	0.0	0.0	0.1	0.1	0.2	0.0	0.2	0.0	1.0	0.2	0.1	0.0
(12–15)	0.0	0.0	0.1	0.1	0.5	0.1	0.2	0.0	0.6	0.0	0.2	0.1
Rectum	0.0	0.0	0.1	0.4	0.1	0.1	0.1	0.3	0.4	0.1	0.3	0.2
(9–12)	0.0	0.0	0.1	0.0	0.4	0.1	0.2	0.0	0.7	0.1	0.2	0.3
Rectum	0.7	4.4	0.1	0.3	0.9	4.2	3.1	26.2	0.7	3.6	0.9	3.4
(6–9)	0.0	0.1	0.1	0.1	1.6	7.5	19.0	33.7	0.4	0.6	13.2	15.8
Rectum	13.0	31.6	0.9	4.2	50.8	79.3	55.6	60.2	14.5	41.2	11.4	30.7
(3–6)	47.6	68.4	40.6	65.5	25.9	64.7	3.7	16.3	8.9	24.9	5.2	19.9
Rectum	14.1	39.1	5.7	23.1	0.6	2.0	0.6	2.6	15.4	13.5	35.5	42.5
(0–3)	0.9	2.6	2.7	6.4	2.1	4.0	23.4	41.6	27.8	35.1	8.7	25.3
Total	28.8	77.8	9.4 [a]	35.2 [a]	57.7	90.3	62.1	92.9	38.9	63.0	53.0	85.8
	49.5	73.0	45.0	77.7	33.2	79.4	48.6	94.3	44.9	67.6	32.6	71.0
Until		2.6		6.6		4.5		3.4		3.4		8.5
caecum		1.7		5.4		3.0		2.6		6.6		8.9
Disappeared		24.7		a		14.2		10.6		41.4		22.9
		28.8		27.6		23.6		8.3		39.0		37.8

[a] Leaked.

TABLE 6

THE AMOUNT OF BARIUM CARBONATE DETERMINED PER PART OF THE INTESTINE EXPRESSED AS PERCENTAGE OF THE ADMINISTERED AMOUNT. FOR THE RECTAL PARTS THE DISTANCE FROM THE SPHINCTER ANI IS GIVEN IN cm.

	5% $BaCO_3$						20% $BaCO_3$					
	15 min		30 min		45 min		15 min		30 min		45 min	
Stomach	b	0.1	0.2	b	b	0.1	b	b	b	b	b	b
Intestine	0.4	0.4	0.4	b	b	0.2	0.1	b	b	b	b	b
Caecum	0.1	0.1	0.2	b	b	b	b	b	b	b	b	b
Rectum (12–15)	0.02	0.02	0.01	b	b	b	b	b	b	b	b	b
Rectum (9–12)	0.02	0.08	0.01	b	b	b	b	b	b	b	b	0.04
Rectum (6–9)	0.03	0.02	b	b	42.2	65.8	b	b	b	b	b	4.8
Rectum (3–6)	73.6	33.4	0.5	71.5	16.0	3.3	0.5	b	0.2	63.1	0.4	2.4
Rectum (0–3)	12.5	44.0	72.6	1.9	20.5	7.8	90.2	93.0	92.1	27.3	85.8	4.7
Recovery	86.7	78.1	73.9	73.4	78.7	77.2	90.8	93.0	92.3	90.4	86.2	40.9 [a]

[a] Leaked; [b] not detectable.

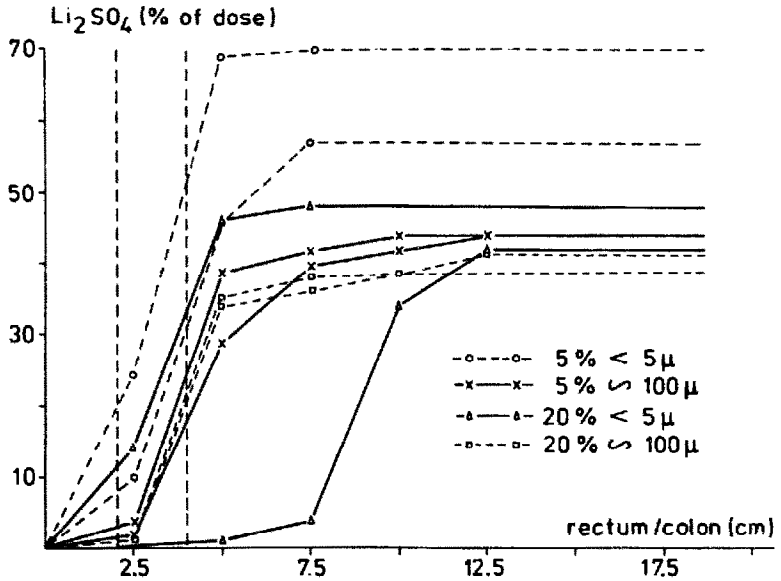

Fig. 3. The cumulative amount of lithium per part of the rectum/colon calculated from the sphincter ani (0 cm) to the caecum (15 cm), expressed as percentages of the total amount, 5 min after administration of four different suppositories.

in the 5% series (average ∿ 5 cm against ∿ 8 cm) than in the 20% series.

Almost 50% of the added amount of naphthalene was not determined in the intestine, so we have to be careful with the conclusion, but because of the fact that relatively high amounts of naphthalene and GC-94 · HCl are located in the same parts of the intestine it is most likely that the suspended particles and the suppository vehicle have spread homogenously.

The results of the experiments with the suppositories containing ^{14}C-labelled barium carbonate are summarized in Table 6. At a concentration of 20% the bulk of radioactivity was found in the most distal part of the intestine. Since only the suspended particles were radioactively marked, these results suggest that the suspended particles are not dragged along with the suppository vehicle. At a concentration of 5% very small quantities are spread through the gut; however, the bulk substance was found in the 2 or 3 most distal parts of the colon/rectum.

Thus far organic compound with a relative low density, and an inorganic compound with a relatively high density, were examined. Because the density of lithium sulphate is ∿2.2, less than the density of barium carbonate (4.3) which was not dragged along with the suppository vehicle, but more than the density of the organic compound (∿1.2) which seemed to be evenly distributed with the suppository vehicle, the next experiments were performed with this substance.

Because of the rapid absorption of lithium sulphate the situation in the intestine of the rat was fixed already 5 min after insertion of the suppositories with lithium sulphate.

In Fig. 3 the cumulative amounts of lithium sulphate determined in the rectum/colon parts from the anus to the caecum are presented. Already large quantities are absorbed

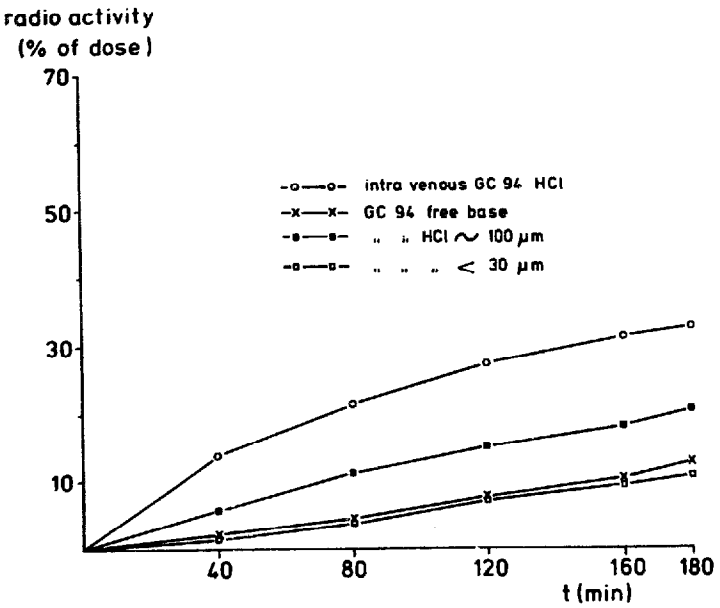

Fig. 4. The mean cumulative amount of radioactivity secreted through the bile, after administration of different dosage forms with GC-94 · HCl, expressed as the percentage of the dosage.

even after 5 min. The spreading of the lithium sulphate particles was very irregular, too, the same as in the other experiments. Neither the concentration of the suspended particles nor the particle size had an influence on the spreading since no differences could be observed when varying these parameters. It seems logical to suppose that the pressure of the colon wall is a more determining factor for the spreading of the suppositories.

As mentioned before, the possibility of secretion of the organic compound and/or its metabolites with the bile liquid had to be investigated. The results of the experiments with the cannulation of the biliary duct are summarized in Fig. 4, where the mean cumulative amounts secreted, calculated as percentages of the dose, are plotted versus time.

Besides an intravenous injection three kinds of suppositories were used: suppositories with 5% GC-94 free base and GC-94 · HCl with 5% of both milled and unmilled particles. From the results it was discovered that part of the GC-94 absorbed from the different dosage forms is secreted in the small intestine by the bile as the original compound or as its metabolites. In Fig. 4 we can see that after administration of the injection the amount of radioactivity secreted in the bile was high compared to the amount secreted after administration of the suppositories. In the case of the suppositories with the small-sized particles of the water-soluble compound, the relative amount secreted with the bile was small in comparison with the suppositories with the unmilled particles. Thus, from these experiments it was learned that the active compound could be secreted with the bile and that the absorption of the active compound was better from the suppositories with the unmilled particles than from the suppositories with the small particles or from the suppositories with the dissolved compound as its free base.

In conclusion, from these experiments it was learned that the spreading of the suppository after insertion can be quite irregular, due to many factors; as possible factors the pressure of the rectum wall and the viscosity of the suppository vehicle at 37°C can be suggested. Suspended particles are dragged along with the suppository vehicle since the density of the suspended compound is not too high, as can be concluded from the results of the experiments with barium carbonate. The influence of variables such as particle size and concentration seems not to be determining for the spreading behaviour of the suppositories.

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