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The application of γ-scintigraphy for the evaluation of the relative spreading of suppository bases in rectal hard gelatin capsules

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Summary

The relative spreading of suppository base and incorporated suspension in the rectum of human subjects has been followed using the technique of γ-scintigraphy. Suppositories formulated from a surfactant system, Labrafil WL2514, and a standard triglyceride base, Witepsol H15, did not spread to a particularly great extent. When spreading did occur the movement of the base did not necessarily lead to a similar spreading of the suspended material. Such separation of suspended material from the base was greater for the surfactant system than for the simple triglyceride system.

Introduction

The rectal route of delivery has some advantages over more conventional oral therapy, particularly with regard to drugs with a high first-pass metabolism and for patients who are unable to ingest dosage forms. Recently attention has been focused on rectal delivery for the absorption of "difficult" drugs such as antibiotics and various polypeptides. In some cases absorption enhancers have been shown to increase bioavailability significantly both in animals and human subjects (Davis et al., 1985).

Suppositories can be formulated with classical excipients such as gelatin and the various triglycerides. Polyethylene glycols and surfactant systems have also been employed in order to improve the absorption of the drug into the systemic circulation or the spreading characteristics of the delivery system (Hagenlocher et al., 1986a).

A less common rectal dosage form is the rectal capsule which generally are similar to soft gelatin capsules except that they usually have a lubricating coat to aid gliding during administration. Before absorption of the dispersed or dissolved drug substance can take place it is necessary that the product be released from the suppository mass usually by a melting and distribution of the suppository base in the rectum. The requirement is thus that the base melts at a temperature between 30 and 37 °C. In countries where the temperature frequently exceeds this range, special storage conditions are necessary.

The development of excipients to enable hard gelatin capsules to be filled with semi-solids now

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means that this capsule can be considered as a rectal dosage form when filled with a suppository type base. A subsequent sealing of the capsule (Cadé et al., 1987) to prevent the contents from leaking allows a greater flexibility in the choice of excipients.

Hagenlocher (1986b) has compared the absorption of paracetamol from hard gelatin capsules formulated with amphiphilic and lipophilic excipients with that from a hard fat suppository. He found that the amphiphilic filled hard gelatin capsule gave a faster absorption of paracetamol than the lipophilic capsule and the hard fat suppository.

The non-invasive evaluation of suppository formulations in man has been carried out using X-ray methods and more recently by the technique of γ-scintigraphy (Hay, 1982; Jay et al., 1985). In such studies either the suppository base or a dispersed material (such as an ion-exchange resin) have been used to follow the melting and movement of the suppository and the spreading tendency. In vitro studies conducted in the Netherlands have indicated that sedimentation of suspended drug can occur so that the spreading of the labelled base may not indicate the position of the drug (Schoonen et al., 1979, 1980; Fokkens and De Blaey, 1984).

This study in human subjects with two different types of suppository bases, Witepsol (saturated triglyceride) and Labrafil (ethoxylated saturated glycerides), filled into hard gelatin capsules has been undertaken in an attempt to investigate the mechanism of the increased absorption from the amphiphilic capsule. The relative movements of the base and suspended material have been evaluated on a concurrent basis using γ-scintigraphy. The bases were labelled with iodine-123 and suspended particulate material was labelled with indium-111. In so doing the relative movements of the base and suspended material could be evaluated on a concurrent basis.

Materials and Methods

Labelling of suppository bases

A dual labelling procedure was used to follow the spreading of dispersed "drug" and vehicle. It is not usually practicable to label drugs directly with a γ-emitting radionuclide and instead model labelled materials are used. Cation exchange resin (particle size < 30 μm in diameter) was labelled with indium-111 to provide a non-absorbed marker system. The resin was incorporated into the suppository base to give a disperse phase concentration of 10% w/v (equivalent to 100 mg in a 1-g dose).

The radiolabelling of the base was achieved using iodine-123 by iodination across the double bonds in the fatty acids. However, since the two chosen bases, Witepsol H15 and Labrafil WL2514, have low levels of unsaturation (low iodine values) they were labelled by the incorporation of small amounts (ca. 5%) of iodinated unsaturated compounds of similar structure; arachis oil and Labrafil WL2700 respectively. At the time of administration each suppository contained 1 MBq indium-111 and 2 MBq iodine-123.

Subjects

The study was conducted according to a cross-over design in 8 healthy male volunteers (age range 18–21 years, height range 1.68–1.88 m, and weight range 65–85 kg).

The study was conducted in accordance with the Declaration of Helsinki Guidelines for Ethics in Research and was approved by the Ethical Committee of the University of Nottingham. No restrictions were placed on diet. The subjects provided information on their normal bowel habits and the time of last defaecation before dosing. The two parts of the crossover study were separated by an interval of 7 days. No drug that could affect the results of the investigation (e.g. laxatives) were permitted 7 days prior to the start of the study.

Methods

Following a light breakfast each volunteer received a capsule filled with labelled suppository system of 1 g in size. To allow easy application of the capsules they were coated with a mixture of polyethylene glycols to improve gliding (Hannula et al., 1986).

Imaging was undertaken using a 40-cm-diame-

ter field of view γ-camera. The γ-camera was fitted with a medium-energy (300 keV maximum) parallel hole collimator. The camera was tuned to detect the 245 keV gamma radiation from indium-111 using a 20% energy window and the 159 keV radiation from iodine-123 with a 15% window. For the initial 4 h the subjects remained supine and subsequently they were in upright postures. Two hours after dosing each subject drank a cup of coffee and at 4 h consumed a meal comprising 1 cheese roll, 1 ham roll, 1 fruit yoghurt and 150 ml orange juice. Anterior and lateral static images of 1 min duration were recorded at approximately 15-min intervals during the first hour, half-hourly during the next 3 h and then hourly for a total of up to 10 h. All defaecations were noted. The study was repeated 7 days later with each subject being dosed with the alternative preparation.

Data analysis

Images were recorded by computer and the iodine images corrected for indium counts detected in the lower energy window. Left lateral images were viewed on a television monitor and a count rate contour defined at 20% of the maximum count rate in each image. Tracer spreading was expressed in terms of the dimensions of the contour. The 20% contour represented well the boundaries of the image of the preparation as displayed on a television monitor (Fig. 1). Counts detected beyond this contour were mainly due to scattered radiation. The width of the contour represents the diameter of the bowel and was relatively constant both along its length in each subject and for different individuals. Thus the length of the contour provided a reasonable measure of the extent of spread.

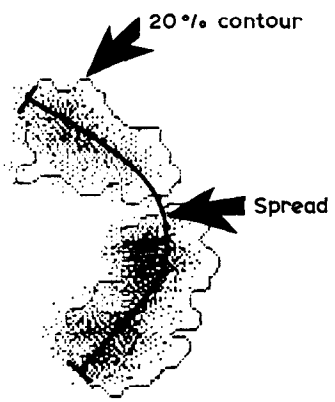

Fig. 1. Radionuclide image showing a contour plot and evaluation of spreading.

Results and Discussion

Examples of spreading data obtained from the analysis of the iodine and indium distribution contours are shown in Figs. 2–4 along with representative images. The examples illustrate respectively, both components generally moving together, little spreading of either component and greater spreading of the base in respect to the suspended material.

In general spreading observed for either of the two suppository systems was not particularly great and in most cases the base and resin remained

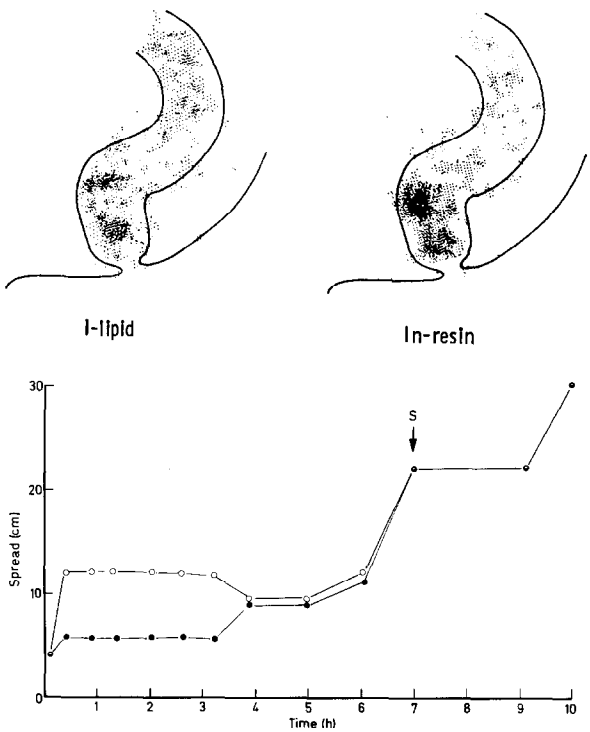

Fig. 2. Data from one subject showing movement of base (○) and resin (●) together after initial separation (Labrafil system); s, time of recording of images shown.

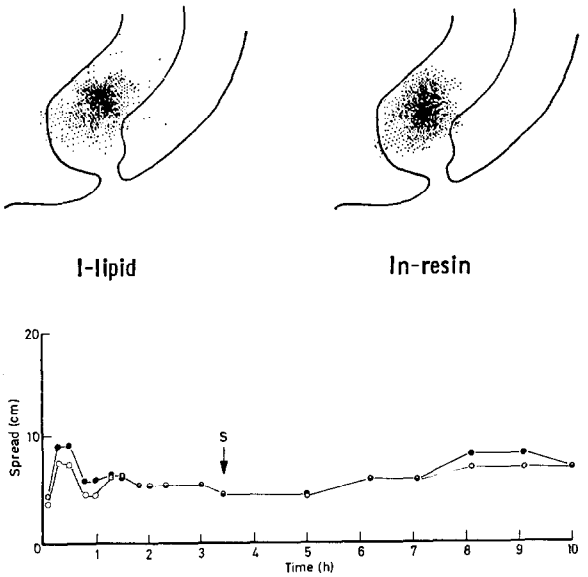

Fig. 3. Data from one subject showing little movement of base (○) and resin (●) (Witepsol system); s, time of recording of images shown.

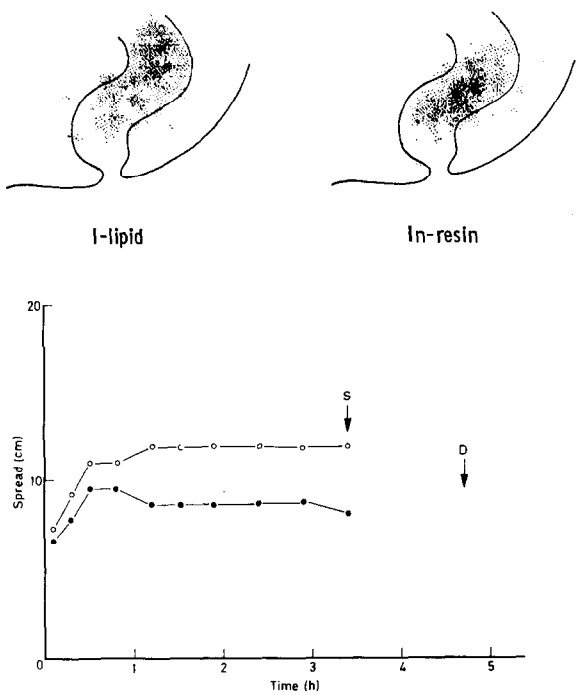

Fig. 4. Data from one subject showing separation of base (○) and resin (●); s, time of recording of images shown; D, defaecation (complete excretion of tracers).

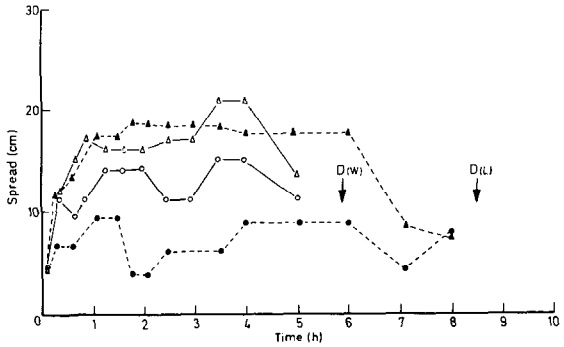

Fig. 5. Data from one individual showing separation of base and resin on two occasions. Witepsol: △, base; ○, resin; D_W, defaecation. Labrafil: ▲, base; ●, resin; D_L, defaecation.

together in the rectum. One subject demonstrated extensive spreading on both occasions. Interestingly, with the Labrafil WL2514 system (and to a lesser extent the Witepsol H15 system) there was definite separation of the base from the suspended resin as shown in Figs. 5 and 6.

As a general rule it would appear that spreading, if it occurred, was related more to the movement of the base than to the suspended material. Consequently, the spreading of the base does not necessarily result in the spreading of suspended material. These results are in agreement with various studies by Schoonen et al. (1979) who have discussed the importance of sedimentation of drug particles in molten suppository bases.

Statistical analysis (ANOVA) of the grouped data (Fig. 7) showed that there is no significant difference in the spreading of Labrafil and Witepsol. There was a trend to indicate that Labrafil WL2514 spreads more than Witepsol H15. Also, for the Labrafil WL2514 system, there is a clear suggestion of a greater separation of base and suspended particles than for the Witepsol H15 system. The data have been replotted to show this difference in spreading of base and suspended solid (Fig. 8).

Conclusions

Differences in absorption of paracetamol from different bases found by Hagenlocher (1986b) therefore probably cannot be attributed to differences in spreading. Hard gelatin capsules filled

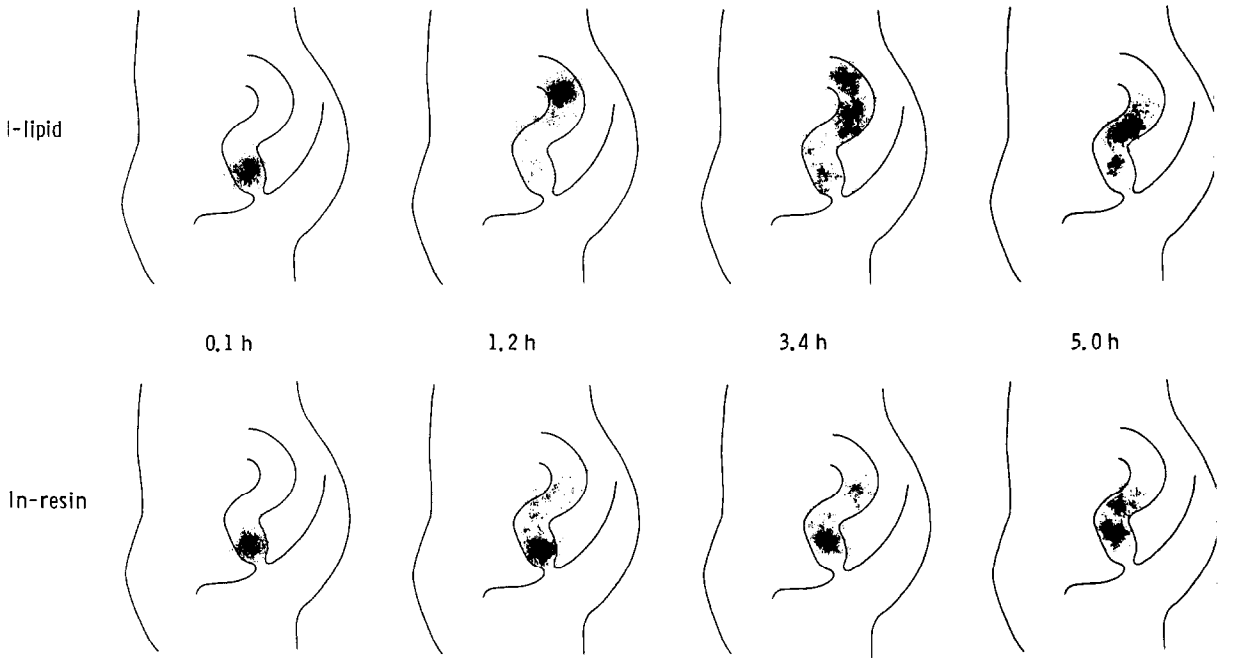

Fig. 6. Radionuclide images showing separation of base and resin (Witepsol system).

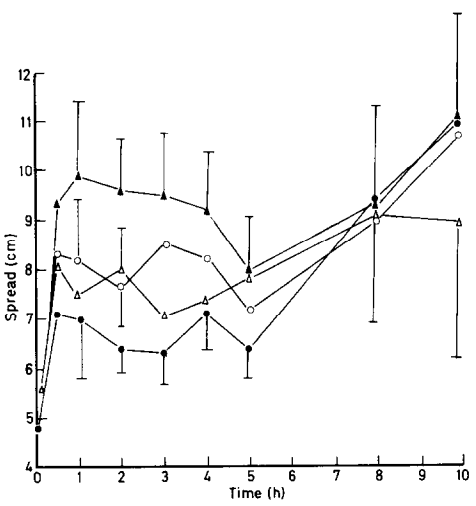

Fig. 7. Grouped data — spreading of base and resin for suppository systems (n = 8, ±S.E.M.). Witepsol: △, base; ○, resin. Labrafil: ▲, base; ●, resin.

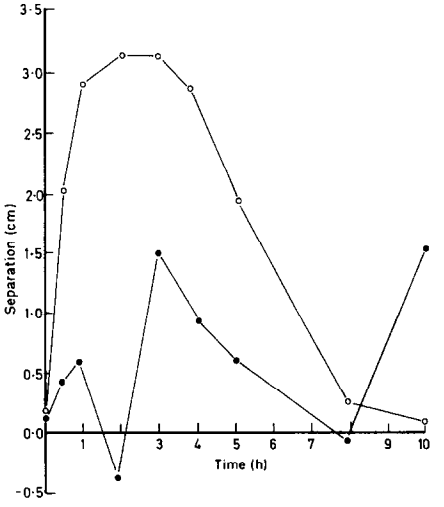

Fig. 8. Separation of base and resin for Witepsol (●) and Labrafil (○).

with Labrafil WL2514 and Witepsol H15 do not as a rule spread to any great extent beyond the rectum following administration. Most of the spreading occurs within an hour of dosing. There is no significant effect in the spreading behaviour that can be attributed to the nature of the base. Moreover, there is an indication that spreading of the base does not necessarily lead to a concom-

itant spreading of material suspended therein. The separation of suspended material from base was greater for Labrafil WL2514 than for Witepsol H15.

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References

Cadé, D., Cole, E.T., Mayer, J.-P. and Wittwer, F., Liquid filled and sealed hard gelatin capsules. *Pharm. Acta Technol.,* in press.

Davis, S.S., Burnham, W.R., Wilson, P. and O'Brien, J. The use of adjuvants to enhance the rectal absorption of cefoxitin in human volunteers. *Antimicrob. Agents Chemother.,* 28 (1985) 211–215.

Fokkens, J.G. and De Blaey, C.J., Drug release from non-aqueous suspensions. II. The release of methylxanthines from paraffin suspensions. *Int. J. Pharm.,* 18 (1984) 129–138.

Hagenlocher, M., Hannula, A.M., Wittwes, F., Soliva, M. and Speiser, P., Hard gelatin capsules for rectal delivery. *Proc. 4th Intern. Conf. Pharm. Tech. Paris,* 1 (1986a) 398–405.

Hagenlocher, M., *Hartgelatinekapseln als Arzneitrager fur die Rektale Applikation,* Thesis ETH Zurich, 1986b.

Hannula, A.M., Hagenlocher, M. and Speiser, P., Evaluation of a gliding coat for rectal hard gelatin capusles. *Acta Pharm. Tech.,* 32 (1986) 26–28.

Hay, D.J., Spreading characteristics of proprietary rectal steroid preparations. In Wilson, C.G., Hardy, J.G., Frier, M. and Davis, S.S. (Eds.), *Radionuclide Imaging in Drug Research,* Croom Helm, London, 1982, pp. 171–180.

Jay, M., Beihn, R.M., Digenis, G.A., DeLand, F.H., Caldwell, L., and Mlodozeniec, A.R., Disposition of radiolabelled suppositories in humans. *J. Pharm. Pharmacol.,* 37 (1985) 266–268.

Schoonen, A.J.M., Moolenaar, F. and Huizinga, T., Release of drugs from suppository bases. I. The release mechanisms. *Int. J. Pharm.,* 4 (1979) 141–152.

Schoonen, A.J.M., Moolenaar, F., Reuvers, K.A. and Huizinga, T., Release of drugs from suppository bases. II. A rate-limiting interfacial process. *Int. J. Pharm.,* 7 (1980) 29–43.