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Gastrointestinal transit of ^{99m}Tc-labelled oral dosage forms of sucralfate in healthy volunteers

M. Vidgren [a], P. Paronen [a], P. Vainio [b], K. Bergström [b] and P. Pikkarainen [c]

Departments of [a] Pharmaceutical Technology, [b] Clinical Physiology and [c] Gastroenterology, University of Kuopio, P.O. Box 6, SF-70211 Kuopio (Finland)

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Summary

In this study the deposition and gastrointestinal transit of a conventional uncoated tablet, a chewable tablet, as well as an effervescent preparation containing 1 g of ^{99m}Tc-labelled sucralfate were evaluated over 180 min using a gamma camera. Each preparation was administered by five healthy volunteers after 10 h fasting. The conventional tablet and the effervescent preparation seemed to distribute immediately in the whole stomach area. With the chewable tablet, the initial deposition of sucralfate in the mouth and oesophagus was also detected. The transit of sucralfate into the intestinal area was noted for the conventional tablet and for the effervescent preparation as early as after 10 min, whereas the increase in sucralfate concentration in the intestinal area after administration of chewable tablets was observed after 30 min. After 60 min the amount of sucralfate remaining in the stomach was about 40% for the conventional tablet, about 20% for the effervescent preparation and about 80% for the chewable tablet. Thus, the effervescent preparation of sucralfate, administered as a suspension, was transported more rapidly into the intestine than the solid oral dosage forms. After 180 min almost all of the sucralfate liberated from the conventional and effervescent formulations was transported from the stomach into the intestine, whereas 21% of that liberated from chewable tablets was still present in the stomach. The dosage form of sucralfate seemed to have a significant effect on the gastrointestinal distribution and transit of sucralfate.

Introduction

Sucralfate is administered via the oral route in the treatment of gastrointestinal disorders (Brogden et al., 1984). Due to the acidity of the human gastric juice, sucralfate molecules are dissociated forming a viscous gel (Nagashima and Yoshida, 1979). The dissociated, negatively charged sucralfate molecules are prone to form polyvalent bridges with positively charged proteins, e.g., albumin, which usually exist at high concentrations on the surface of mucosal lesions (Nagashima et al., 1980). Thus, the affinity of sucralfate for protecting the mucosal layer of the human stomach is mainly explained by the vis-

Correspondence to: M. Vidgren, Department of Pharmaceutical Technology, University of Kuopio, P.O. Box 6, SF-70211 Kuopio, Finland.

cous adhesiviness of this drug substance on the surface of the disorders, e.g., gastric ulcer (Moshal et al., 1980). In addition, sucralfate molecules have a slight buffering effect on the acidity of the stomach and also absorb the bile salts as well as inhibit the action of gastric pepsin (Marks, 1987). To achieve these therapeutical effects of sucralfate the oral dosage forms should effectively distribute into the whole stomach area.

Sucralfate is a very hygroscopic drug substance which can rapidly bind gastric juice and thus form a gel on the surface of the tablet. This phenomenon can prevent the disintegration of the preparation and therefore it is important that the oral dosage forms of sucralfate are formulated in such a way that very rapid disintegration can be achieved. In order to overcome this drawback of disintegration, chewable and effervescent tablets of sucralfate have recently been developed. Using these dosage forms sucralfate can be dispersed effectively before ingestion.

The therapeutical efficacy of pharmaceutical dosage forms of sucralfate is usually studied during clinical trials. The results of a number of double-blind, controlled clinical studies indicate that sucralfate therapy is more effective than either placebo or antacid therapy in the treatment of peptic ulcer diseases (Mayberry et al., 1978; McHardy, 1979; Hollander, 1981). In addition, sucralfate has been found to be as effective as H_2-receptor antagonists in the treatment of gastric and duodenal ulcers (Marks et al., 1980; Martin et al., 1982). These clinical trials are usually based on the gastroscopia before and after the treatment. In addition, the changes in the subjective feelings of the patients during the treatment have been monitored. Radiolabelled sucralfate has been used for diagnostic purposes. However, the above-mentioned studies do not provide accurate information on the real deposition and gastrointestinal transit of oral sucralfate preparations.

In this study, the gastrointestinal deposition and transit of the conventional, uncoated tablet, as well as the chewable tablet and the effervescent preparation containing 1 g of sucralfate labelled with ^{99m}Tc were evaluated. Gastrointestinal transit was monitored using a gamma camera.

Materials and Methods

Sucralfate (Fermion, Finland) was first labelled according to the modified direct stannous reduction method (Grouls et al., 1988). 5 g of sucralfate was suspended in water and 3.0 mg of stannous chloride ($SnCl_2 \cdot 2H_2O$) in 0.1 M hydrochloric acid solution was added to the suspension of sucralfate and mixed. Radioactive technetium as the pertechnetate in a physiological sodium chloride solution was added and the mixture was incubated for 5 min. The total amount of radioactivity added was about 200 MBq. The pH value of the solution was 5.5. After centrifugation of the product the supernatant was separated and the solid ^{99m}Tc-labelled sucralfate was dried under IR radiation until the content of water in sucralfate was under 5%. The effectiveness of the labelling procedure was calculated by measuring the radioactivity of the sucralfate and supernatant.

Uncoated sucralfate and chewable tablets with the same compositions as Alsucral® 1 g tablets (Orion Pharmaceutica, Finland) were compressed using 1 g of dried sucralfate with suitable additives. The compressional force was adjusted to produce sucralfate tablets with the same breaking strength (7–8 kp, Schleuniger 2E, Switzerland) and disintegration time in water (< 2 min; Ph.Eur. method with discs) as those of Alsucral® 1 g tablets. In addition, 1 g of ^{99m}Tc-labelled sucralfate and the same additives as used in the Alsucral® effervescent tablets (Orion Pharmaceutica, Finland) were mixed and dosed. Each preparation contained radioactivity of about 40 MBq, which was determined to be suitable for measuring the gastrointestinal deposition and transport of the swallowed dosage forms of sucralfate.

Five fully informed healthy volunteers participated in the in vivo study. The study protocol was accepted by the Ethics Committee of the Kuopio University Hospital, Kuopio, Finland. The mean age of the volunteers was 27.2 years (range 22–32 years), the mean height was 179.2 cm (range 172–181 cm), and the mean weight was 76.1 kg (range 69–82 kg). Each subject was administered one radioactive sucralfate dosage form on each test day after a fasting period of at least 10 h. The

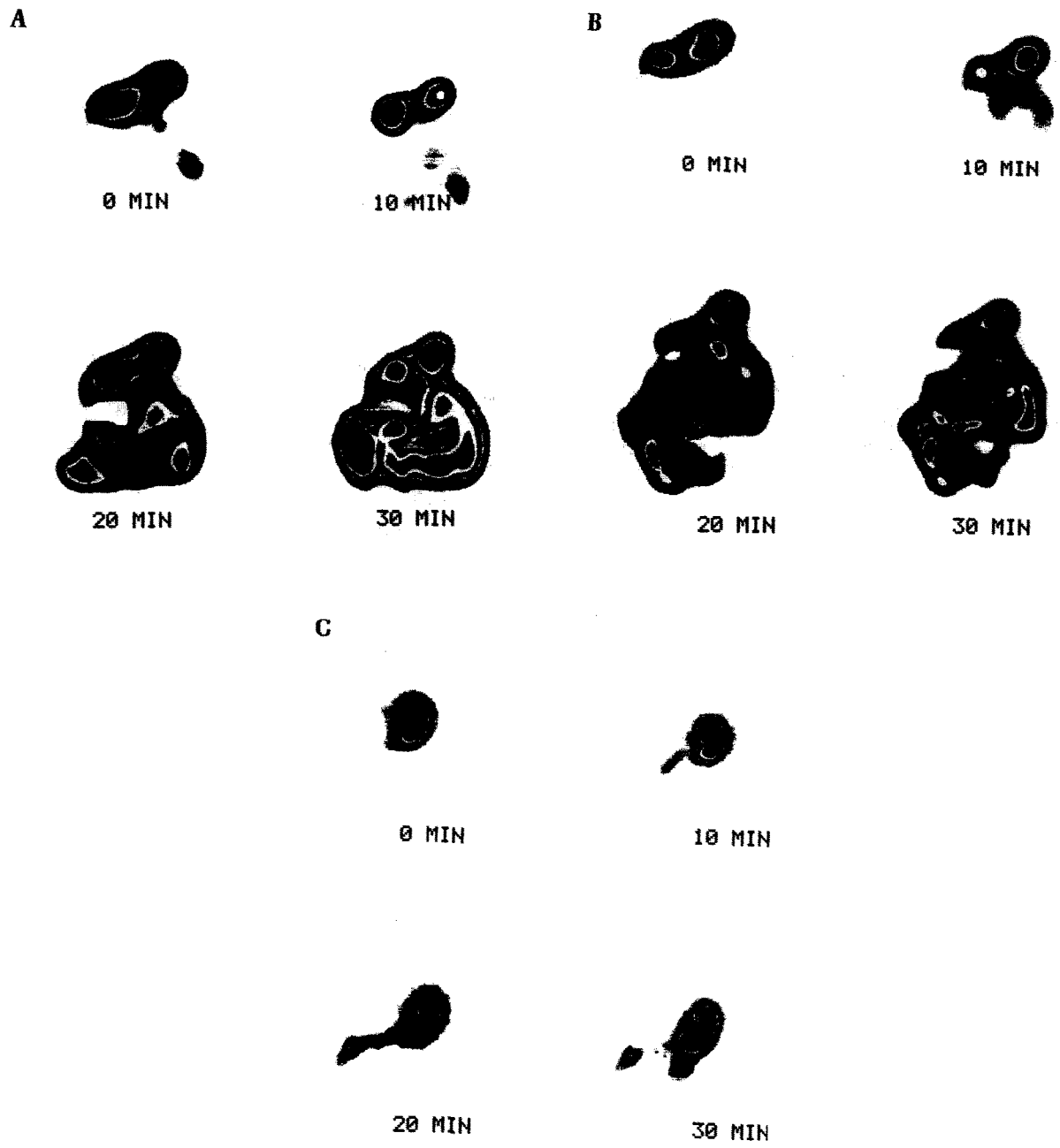

Fig. 1. Typical distribution patterns of ^{99m}Tc-labelled sucralfate in the gastrointestinal tract after the administration of conventional (A), effervescent (B) and chewable (C) formulations as a function of time (0–30 min).

conventional tablet and the disintegrated effervescent preparation were swallowed with 200 ml of tapwater, whereas the chewable tablet was ingested without water. The gamma camera study was performed at the same time on each test day.

Deposition and gastrointestinal transit of the swallowed sucralfate dosage forms were followed using a gamma camera (GE 400 T General Electric, WI, U.S.A.) having a 40 cm field of view and equipped with a low energy parallel hole collima-

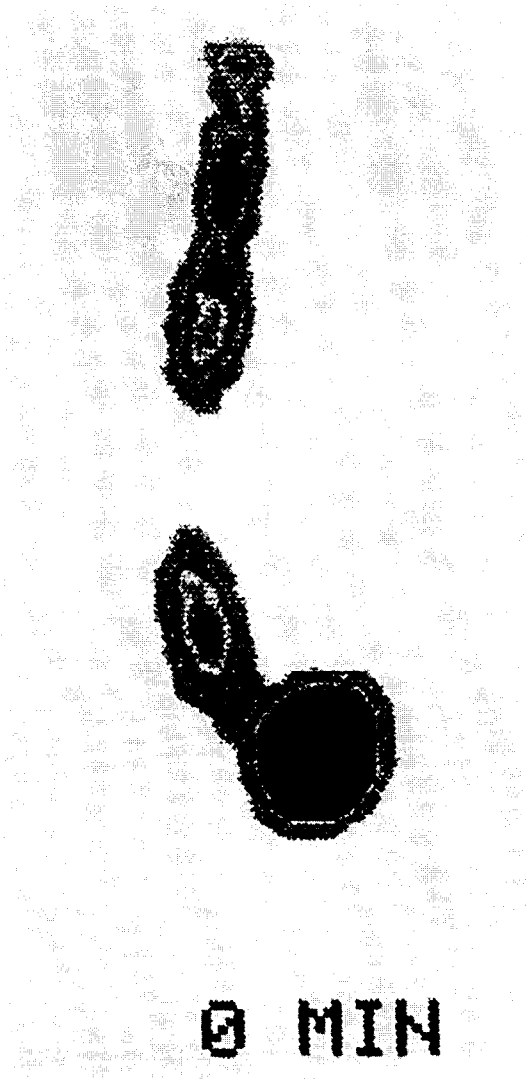

Fig. 2. Initial deposition of ^{99m}Tc-labelled sucralfate after administration of chewable tablet.

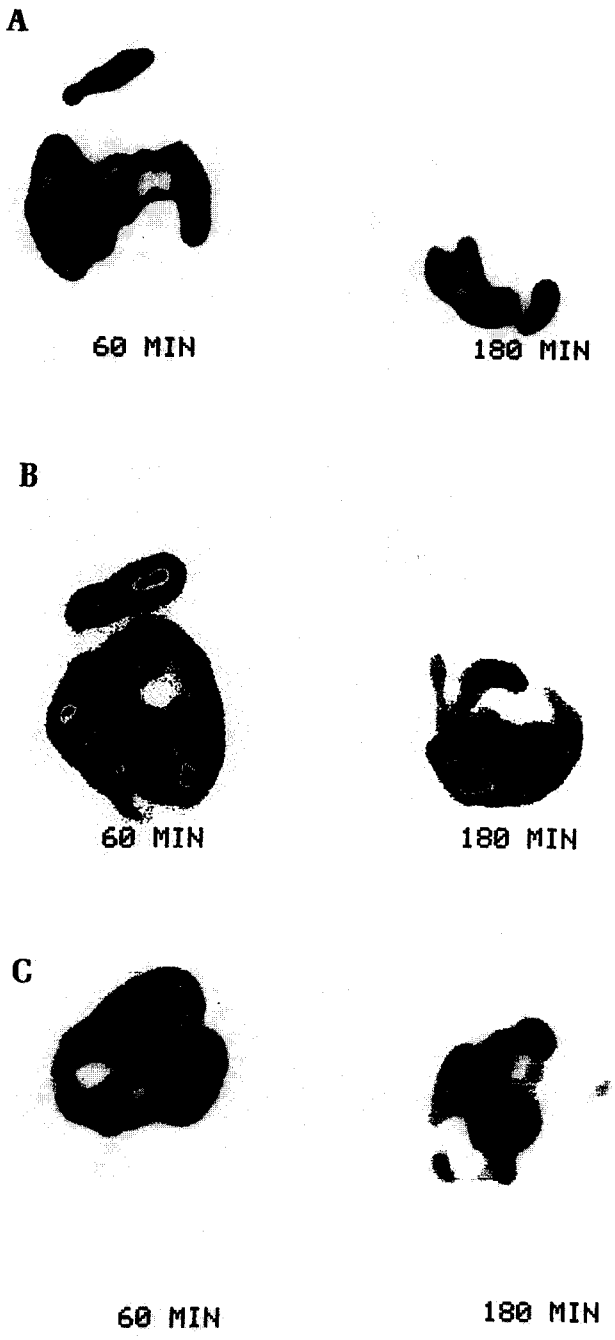

Fig. 3. Typical distribution pattern of ^{99m}Tc-labelled sucralfate in the gastrointestinal tract after the administration of conventional (A), effervescent (B) and chewable (C) formulations as a function of time (60 and 180 min).

tor. Anterior images were taken continuously during the first 30 min (each of 60 s) and two additional images (500 000 counts on each) were obtained 60 and 180 min after the administration of the radioactive tablet of sucralfate. The images were recorded using a Gamma-11 computer system (Digital Equipment Corp., MA, U.S.A.) and stored for subsequent analysis. The activity was quantified and corrected for background activity and radioactive decay.

Results and Discussion

Radioisotope techniques have been used to study the deposition and gastrointestinal transit of pharmaceutical dosage forms (Davis, 1986). Commonly, in these studies a suitable pure gamma radiator, e.g., technetium (^{99m}Tc) or indium (^{111}In) is bound to the insoluble resins which are subsequently incorporated into the pharmaceutical oral dosage form. Thus, it has been possible to monitor the swallowed preparation within the gastrointestinal tract with a gamma camera.

Sucralfate has previously been gamma labelled using human serum albumin (HSA), diethylenetriaminepentaacetic acid (DTPA) or selenium (^{75}Se) as a mediator between a sucralfate molecule and a radiotracer (Centi Colella and Sckopinaro, 1985; Vasquez et al., 1987; Knight et al., 1988). The direct stannous reduction method to label sucralfate molecules with ^{99m}Tc has also been introduced (Grouls et al., 1988). Nevertheless, the use of these labelling methods has been limited to the diagnostic purposes of gastrointestinal disorders. Thus, radiolabelled sucralfate has not been used in in vivo studies of gastrointestinal disintegration, or deposition and transit studies of the oral pharmaceutical dosage forms of sucralfate.

The results of this study indicate that the direct gamma labelling of sucralfate via the stannous reduction method enables the detection of the gastrointestinal transit of swallowed oral dosage forms of sucralfate with a gamma camera. The amount of radioactivity associated with sucralfate was determined to be 98.0–99.1% (n = 10) by measuring the activity of the supernatant and the sucralfate pellet. Additional washing of the product with purified water decreased the amount of radioactivity of solid sucralfate by only 1–2%. Grouls et al. (1988) have also reported that ^{99m}Tc-labelled sucralfate is stable at pH 3, 7 and 10 for 4 h and that only 5–8% of the radioalabel is released in 24 h. Thus, ^{99m}Tc was bound firmly enough to sucralfate to accomplish the deposition studies of oral dosage forms of sucralfate.

The conventional sucralfate tablets disintegrated almost immediately after administration and the released sucralfate distributed into the whole stomach area as effectively as chewable and effervescent preparations (Fig. 1A–C). No difference between deposition in the area of the pylorus and fundus could be detected for the dosage forms tested. Therefore, the conventional, uncoated sucralfate tablets were also succesfully formulated in such a way that immediate disintegration in the stomach could be achieved.

With the chewable tablets the initial deposition of sucralfate in the mouth and oesophagus was also detected (Fig. 2). Thus, with this dosage form the protective effect of sucralfate in refluxive aesophagite might also be achieved.

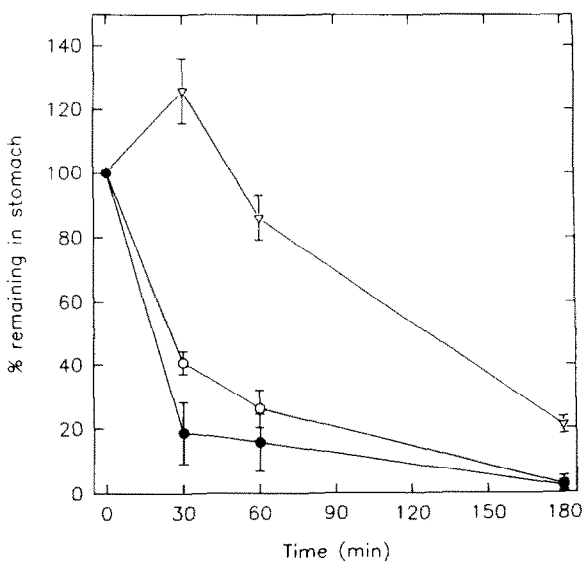

Fig. 4. Gastric emptying of the ^{99m}Tc-labelled sucralfate after the administration of conventional (○), effervescent (●) and chewable (▽) tablets as a function of time (0–180 min).

The gastrointestinal transit of sucralfate into the intestinal area of fasted subjects was observed for the conventional and effervescent tablets as soon as after 10 min (Figs 1A–C and 4). Thus, these preparations which were administered with water to fasted subjects followed the typical gastrointestinal transit of liquid dosage forms. These results are supported by the work of Davies (1986) who documented that solutions are more rapidly transported into the intestine than solid oral dosage forms. With the chewable tablets the increase in sucralfate concentration in the stomach was still achieved 30 min after administration. This was due to the fact that chewable tablets were administered without water and thus the sucralfate was also swallowed during gamma camera detection into the stomach. However, after 20 min the intestinal area appeared to be widely covered by sucralfate (Fig. 1A–C).

After the 60 min measuring period the amount of sucralfate remaining in the stomach area was about 20% for the conventional tablet, about 40% for the efferevescent preparation and about 80% for the chewable tablet (Figs 3A–C and 4). Thus, the effervescent preparation of sucralfate, administered as a suspension, was transported more rapidly into the intestine than sucralfate which was liberated from the solid oral dosage forms. In addition, the chewable tablets, which were administered without water, again remained much longer in the stomach.

After 180 min, on average only 5% of sucralfate from the conventional tablet, on average 4% from the effervescent tablet and on average 21% from the chewable tablet had been retained in the stomach (Fig. 4).

In conclusion, the gamma labelling of sucralfate via the stannous reduction method enables one to perform in vivo studies of oral dosage forms of sucralfate. The results of this study indicate that both the mode of administration and the formulation have an effect on the distribution and gastrointestinal transit of oral sucralfate preparations. However, in order to ascertain the significance of these biopharmaceutical differences with respect to the therapeutical effects of the dosage forms further clinical studies are needed.

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