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International Journal of Pharmaceutics 123 (1995) 145–147

international journal of pharmaceutics

Evaluation of the gastric behaviour of coevaporate particles under fasting and non-fasting conditions

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Received 10 October 1994; revised 13 February 1995; accepted 28 February 1995

Abstract

The gastric emptying half-times of Eudragit® S-^{111}In-oxinate coevaporate particles (fraction size, 0.10–0.50 mm; density, 1.36 g cm^{-3}) were determined by gamma scintigraphy in both fasted and fed healthy volunteers. The mean gastric emptying half-times ± SD under fasting and non-fasting conditions were 67 ± 15 and 308 ± 53 min, respectively, indicating that gastric emptying of coevaporate particles is delayed in the presence of food to a greater extent than most pellets of normal density.

Keywords: Coevaporate; Pellet; Gastric emptying; Gamma scintigraphy; ^{111}In-oxinate; Eudragit® S

In previous studies, the solid dispersion technique was proposed to prepare sustained-release oral dosage forms using enteric and insoluble acrylic polymers such as Eudragit® S, RS and RL (Hasegawa et al., 1986; Oth and Moës, 1989; Beten and Moës, 1994).

In order to determine the gastric emptying half-times of coevaporate particles in both fasted and fed volunteers, radiolabeled (^{111}In-oxinate) coevaporate of Eudragit® S was prepared by the solvent method (ethanol-dichloromethane 1:1) and the particle size fraction 0.10–0.50 mm was selected by sieving. The powder was then washed with 0.1 N HCl followed by distilled water in order to eliminate the amount of unbound radioactivity (approx. 30%) which was released rapidly (burst) into the liquid medium of an in vitro radioactivity release test.

After filtration and drying, 375 mg of the radiolabeled coevaporate powder (density, 1.36 g cm^{-3}; air comparison pycnometry) was filled into size 0 hard gelatin capsules.

The activity to be used for labeling the forms was calculated in order to obtain a resultant dose of 3.7–5.6 MBq at the time of administration.

Six male subjects (age range, 18–34 years; weight range, 60–96 kg) participated in this study after providing informed written consent. Each subject declared himself to be healthy and had no history of gastrointestinal disorders. The study protocol was approved by the University Erasme Hospital Ethics Committee.

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SSDI 0378-5173(95)00087-9

Table 1
Individual $T_{50\%}$ gastric emptying (min) of coevaporate particles under fasting and non-fasting conditions

Fasting		Non-fasting	
Subject no.	$T_{50\%}$	Subject no.	$T_{50\%}$
1	74	1	329
2	48	2	288
3	64	3	360
4	84	4	211
5	50	5	340
6	82	6	> 320
Mean	67	Mean	308
±SD	15.6	±SD	53.1
CV (%):	23.3	CV (%):	17.3

After an overnight fast, each subject swallowed a capsule containing the radiolabeled coevaporate with 150 ml tap water. The volunteers were imaged in the left anterior oblique (LAO) views (Ford et al., 1992) every 4 min for 90 min, in upright posture.

This technique was shown to be suitable for the determination of gastric emptying times of dosage forms under both fasting and non-fasting conditions.

At the end of the fasting session, the same volunteers received a light snack at 11 a.m. followed by a standardized lunch at 12.30 p.m. (1280 kcal), then they were given a labeled capsule at 1.30 p.m. with 150 ml tap water.

The volunteers were imaged in the LAO views every 5 min up to 6 h in upright posture. At the end of each session, delineation of the stomach was realized with 7.4 MBq [^{99m}Tc]pertechnetate administered with 150 ml tap water.

The individual gastric emptying half-times ($T_{50\%}$) measured under fasting and non-fasting conditions are listed in Table 1.

In fasted subjects, the emptying of coevaporate particles followed a two-stage process with a slow first phase corresponding to a lag period, followed by rapid emptying of the particles as a bolus.

The dispersion of the particles in the stomach started 5–15 min after ingestion of the capsule.

Under non-fasting conditions, the dispersion of coevaporate particles in the stomach contents was slow and incomplete despite the rapid dissolution of the capsule shell.

The particles remained in the upper part of the stomach for at least 1 h then gradually moved towards the antrum. They started to be emptied after widespread lag times ranging from 95 to 270 min.

A statistically significant difference was observed between the two sets of values ($p < 0.05$; independent t-test), indicating clearly that the gastric emptying of the coevaporate particles is significantly delayed in the presence of food.

Under fasting conditions, the gastric emptying $T_{50\%}$ values of coevaporate particles (0.1–0.5 mm)

Table 2
Mean gastric emptying half-times of pellets determined under non-fasting conditions

Mean $T_{50\%}$ (range) (min)	Size (mm)	Density (g cm^{-3})	Type of meal	References
79 (33–150)	0.8–1.1	1.2	breakfast	Davis et al. (1984a)
119 (80–190)	0.7–1.2	1.2	light breakfast	Davis et al. (1984b)
285 (150–420)	0.7–1.2	1.2	heavy breakfast	Davis et al. (1984b)
99 (61–124)	0.7–1.4	1.8	light breakfast	Christensen et al. (1985)
353 (270–450)	0.7–1.0	0.94 [a]	light breakfast	Davis et al. (1986)
325 (200–432)	0.7–1.0	1.96	light breakfast	Davis et al. (1986)
240	0.7–1.3	1.2	lunch 3800 kJ	O'Reilly et al. (1987)
132	2 × 5–6	1.46	light breakfast	Sugito et al. (1990)
181 (106–214)	1.0–1.4	1.5	2100 kJ	Devereux et al. (1990)
269 (191–568)	1.0–1.4	2.8 [b]	2100 kJ	Devereux et al. (1990)
181 (118–240)	1.2–1.4	–	2238 kJ	Yuen et al. (1993)
151 (66–330)	0.8–1.1	1.2	light breakfast	Coupe et al. (1993)

[a] At early times, these pellets tended to float toward the fundus.
[b] The gastric emptying of these heavy pellets was significantly delayed under both fed and fasting conditions.

were similar to those reported for pellets (0.5–1.8 mm), 67 and 72 min, respectively, by Hardy et al. (1985) but were much shorter than those reported by Clarke et al. (1993) for small pellets (0.5 mm) of normal density (1.5 g cm^{-3}): mean ± SD = 125 ± 52.8 min (range, 48–192 min).

Recently, the same authors confirmed their previous results for standard size pellets (1.18–1.40 mm) of density 1.5, 2.0 and 2.4 g cm^{-3} tested separately in healthy fasted male subjects (Clarke et al., 1995).

In the presence of food, however, a distinct lag phase was observed for coevaporate particles administered in hard gelatin capsules, and gastric emptying was delayed significantly and according to literature data, to a greater extent than most pellets of normal density (Table 2).

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