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COMMUNICATIONS

The influence of density on the gastrointestinal transit of pellets

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Abstract—The gastric emptying, intestinal transit and caecum arrival times of 1 mm pellets of density 1·5 and 2·8 g cm^{-3} have been assessed in fed and fasted volunteers by means of gamma-scintigraphy. The pellets were prepared by extrusion/spheronisation, coated with ethylcellulose and labelled with technetium-99m. The position of the pellets in the gastro-intestinal tract was followed by a double-headed gamma camera to allow detailed information over a period of up to 10 h. Analysis of variance established that there was a highly significant difference in the time for 50% of the pellets to empty from the stomach both in fed and fasted states. The 2·8 g cm^{-3} pellets had an extended resident time in both the fed and fasted states. The gastric emptying time was prolonged in the fed state. There was no significant difference in intestinal transit time between the two formulations nor whether the volunteers were fed or fasted. The caecum arrival time was therefore modified only by the gastric emptying time.

There is conflicting evidence as to the influence of high density material on gastrointestinal transit. Conventional solid dosage forms have densities in the region of > 1·5 g cm^{-3} but to date there is no clear evidence as to the effect of density levels greater than this.

Bechgaard & Ladefoged (1978) reported that an increase in density from 1·0 to 1·6 g cm^{-3} significantly delayed average transit time of pellets in ileostomy subjects. Bogentoft et al (1981, 1982) failed to confirm these differences in normal subjects with pellets of density 1·2 and 1·8 g cm^{-3} and Bechgaard et al (1985) found no difference between pellets of densities of 0·94 and 1·96 g cm^{-3}. Kaus et al (1984) administered single units of specific gravity 1·03 and 1·61 and observed no differences in rates of travel. Similarly, Davis et al (1986) found that the mean gastric emptying rates of pellets of densities 0·94 and 1·96 g cm^{-3} were not significantly different. Kaniwa et al (1988) administered units ranging in density from 1·29 to 1·92 g cm^{-3}, but did not observe any differences in gastric emptying rates. Gruber et al (1987) examined the gastric emptying of units of a much wider density range (0·5 to 2·9 g cm^{-3}) in the fasted dog. They concluded that gastric emptying appeared to be independent of density. Sangekar et al (1987) compared the gastric retention of floating (specific gravity 0·96) and non-floating (specific gravity 1·59) dosage forms. They reported that density did not influence gastric retention whereas the presence of food did in both cases.

Materials and methods

In the current study the gastrointestinal transit of pellets of density 2·8 g cm^{-3} and pellets of density 1·5 g cm^{-3} has been compared using a double-headed gamma camera (Siemens Rota). Pellets were prepared by the process of extrusion/spheronisation from formulations containing microcrystalline cellulose (Avicel PH101) with either lactose or barium sulphate and water. The pellets also contained 5% of an ion exchange resin (amberlite CG400(Cl)), and were coated with a layer of ethylcellulose (N50) to provide a product which was similar in all aspects to a standard pharmaceutical formulation. The pellets were labelled with technetium-99m (^{99m}Tc) (approximately 3·7 MBq) by soaking for 5 h in 1–2 mL solution of sodium pertechnetate. After rinsing, the pellets were allowed to dry overnight before filling into size 0 hard gelatin capsules. The release of technetium-99m into solution, 2 h in simulated gastric juice (USP XX 1980) pH 1·2 and 8 + 24 h in simulated intestinal buffer (USP XX 1980) pH 7·5 but with enzymes omitted was assessed in-vitro. The maximum technetium-99m level in solution after 24 h was 12·4% but was usually less than 10%. Hence it was considered that insignificant amounts would be available for absorption and would not interfere with the imaging. The final densities of two sets of pellets of diameter 1–1·4 mm was 1·5 (light) and 2·8 (heavy) g cm^{-3} as determined by air pycnometry.

After overnight fasting, eight male volunteers each took a single capsule with 200 mL of orange juice both with and (on a separate occasion) without a standard breakfast (23 g cornflakes with 25 mL semi-skimmed milk, two pieces of white toasted bread (78 g) spread with 15 g butter and 20 g marmalade; total = 535 kcal). The transit of the preparation was monitored through the gastrointestinal tract, continuously for the first 90 min, and at appropriate intervals thereafter. Subjects were provided with 200 mL of coffee after 90 min. At 200 min a standard lunch (MacDonald's Quarterpounder hamburger, french fries, an apple and a coffee, total 879 kcal) was provided. At 390 min 200 mL of tea was consumed.

A sealed source of 0·6 MBq ^{99m}Tc taped to the abdominal skin at the right lower costal margin was used to position the subject in an upright position reproducibly between the heads of the gamma camera. The images were stored on a computer until required. The experiments were repeated such that each volunteer took capsules containing pellets of both densities when both fed and fasted.

On completion of the study (when the pellets had reached the caecum), regions of interest were drawn on the screen of the VDU to represent the stomach and the caecum. These areas were designated by viewing all the images available before the assignment. The counts recorded for anterior and posterior heads, for each area of interest, were calculated from each image. The values were normalized for counting interval, corrected for background and radioactive decay. The geometric mean counts were expressed as percentages of the total counts recorded in the first frame attributable to the administered dosage form.

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Table 1. Times for
(a) 50% of 1·5 g cm^{-3} (light) and 2·8 g cm^{-3} (heavy pellets) to empty from the stomach (G50)
(b) the pellets to transit through the small intestine (I)
(c) 50% of the pellets to arrive at the caecum (C50) when administered to fasted and fed volunteers.

	Light pellets						Heavy pellets					
	Fasted			Fed			Fasted			Fed		
Time (min)	G50	I	C50	G50	I	C50	G50	I	C50	G50	I	C50
Subject												
1	64	406	470	214	169	383	185	267	452	319	279	598
2	82	161	243	203	296	499	258	268	526	213	122	335
3	166	221	387	106	178	285	206	335	541	217	210	427
4	197	271	468	133	418	551	195	280	475	221	407	628
5	211	379	590	218	301	519	219	319	538	568	341	568
6	71	153	224	164	280	444	221	266	487	216	436	652
7	111	179	290	205	146	351	139	236	375	191	195	386
8	95	154	249	201	174	375	211	166	377	205	133	338
Mean	125	241	365	181	245	426	204	267	471	269	265	492
Standard deviation	58·4	84·4	134·9	41·6	94·1	92·7	34·1	51·6	21·0	127·0	120·2	133·6

Results and discussion

The results from both types of pellets, when administered to 8 volunteers fed and fasted, are given in Table 1.

The results are also presented in Table 2 as mean values for the time for:

(a) 50% of the pellets to empty from the stomach G50
(b) the pellets to transmit through the small intestine I
(c) 50% of the pellets to arrive at the caecum C50.

In all cases, two-way analyses of variance established that there was no interaction between the factors of food and density. Hence for greater accuracy a pooled standard error can be used to assess the significance of the effects (Snedecor & Cochran 1980). Such an approach, however, provides a common standard error for each individual effect (light, heavy, fed and fasted) and another common standard error for the effects of food states and density of pellets. (See Table 2.)

Analysis of variance of the data in Table 1 clearly established that there was a highly statistically significant difference ($P<0·01$) in time for 50% of the pellets to empty from the stomach between the two densities of pellets (Table 2). There was also a highly statistically significant difference ($P<0·01$) between the fed and fasted state for the two types of pellets as would be expected from previous studies. It was clear, however, that the heavier pellets were retained in the stomach for a longer time than the light pellets, both in the fasted and fed states. There was no statistical difference in the small intestine transit time (Table 2). The time for 50% of the pellets to arrive at the caecum was modified only by the gastric emptying time (Table 2) the difference being highly statistically significant ($P<0·01$).

These findings clearly show density can influence gastric emptying and hence have important implications for the formulation of controlled release forms.

Table 2. Mean times (min) and standard errors of the time for 50% of the pellets to leave the stomach (G50), intestinal transit time (I) and time for 50% of the pellets to arrive in the caecum (C50), as a function of pellet density and food status.

	Light pellets	Heavy pellets	Pooled
Gastric emptying time (G50)			
Fasted	125 ± 25	204 ± 25	164 ± 17
Fed	181 ± 25	269 ± 25	225 ± 17
Pooled	153 ± 17	237 ± 17	
Intestinal transit time (I)			
Fasted	241 ± 27	267 ± 27	254 ± 19
Fed	245 ± 27	265 ± 27	255 ± 19
Pooled	243 ± 19	266 ± 19	
Caecal arrival time (C50)			
Fasted	365 ± 32	471 ± 32	418 ± 22
Fed	426 ± 32	492 ± 32	459 ± 22
Pooled	395 ± 22	481 ± 22	

References

Bechgaard, H., Ladefoged, K. (1978) Distribution of pellets in the gastrointestinal tract. The influence on transit time exerted by the density and diameter of pellets. J. Pharm. Pharmacol. 30: 690–692

Bechgaard, H., Christensen, F. N., Davis, S. S., Hardy, J. G., Taylor, M. J., Whalley, D. R., Wilson, C. G. (1985) Gastrointestinal transit of pellet systems in ileostomy subjects and the effect of density. Ibid. 37: 718–721

Bogentoft, C., Appelgren, C., Jonnson, W. E., Sjögren, J. (1981) Annual Meeting of the Swedish Pharmaceutical Society, Stockholm, p. 109

Bogentoft, C., Appelgren, C., Jonnson, W. E., Sjögren, J., Alpsten, M. (1982) Intestinal transit time of ^{51}Cr labelled pellets of different densities. In: Wilson, C. G., Hardy, J. G., Frier, M., Davies, S. S. (eds) Radionuclide Imaging in Drug Research, Croom Helm London pp 294–296

Davis, S. S., Stockwell, A. F., Taylor, M. J., Hardy, J. G., Whalley, D. R., Wilson, C. G., Bechgaard, H., Chrisensen, F. N. (1986) The effect of density on the gastric emptying of single and multiple unit dosage forms. Pharm. Research 3: 208–213

Gruber, P., Rubinstein, A., Li, V. H., Bass, P., Robinson, J. R. (1987) Gastric emptying of nondigestible solids in the fasted dog. J. Pharm. Sci. 76: 117–122

Kaniwa, N., Aoyagi, N., Ogata, H., Ejima, A., Motoyama, H., Yasumi, H. (1988) Gastric emptying rates of drug preparations. II. Effects of size and density of enteric-coated drug preparations and food on gastric emptying rates in humans. J. Pharmacobio. Dyn. 11: 571—575

Kaus, L. C., Fell, J. T., Sharma, H., Taylor, D. C. (1984) On the intestinal transit of a single non-disintegrating object. Int. J. Pharm. 20: 315–323

Sangekar, W., Vadino, W. A., Chaudry, I., Parr, A., Beihn, R., Digenis, G. (1987) Evaluation of the effect of food and specific gravity of tablets on gastric retention time. Ibid. 35: 187–191

Snedecor, G. W., Cochran, W. G. (1980) Statistical Methods, 7th Edition, The Iowa State University, Ames, Iowa, USA p. 255