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Distribution of pellets in the gastrointestinal tract. The influence on transit time exerted by the density or diameter of pellets

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The influence on transit time exerted by the density or diameter of pellets has been established in six ileostomy subjects. An increase in density from 1·0 to 1·6 significantly increased the average transit time of pellets in the small intestine. The average transit time for the light and heavy pellets being 7 and 25 h respectively. The diameter of pellets is of minor significance. The findings suggest the use of density as a means of modifying the period of absorption of controlled-release pellets.

Oral controlled-release products can be formulated as single-unit or multiple-units doses (Bechgaard & Hegermann Nielsen, 1978). Single-unit preparations tend to follow food, which has a normal transit time through the small intestine of between 3 and 8 h (Prescott, 1974). Accordingly, 6–10 h are recommended by many authors as the maximum duration for *in vitro* release from depot formulations (Ritschel, 1973; Sjögren, 1975). However, there are instances where it is desirable to detain the drug depot in the upper gut, to ensure optimal absorption, or to additionally extend the absorption phase as with drugs with biological half-lives requiring an absorption period of more than 6–10 h for facilitating a lower dosage frequency (once daily). As the sub-units of the multiple-units formulations are distributed freely throughout the gastrointestinal tract, their transport is less affected than single-unit preparations by transit time of the food (Ekenved, Bogentoft & others, 1977), so they offer the possibility of achieving a longer-lasting and more reliable source of drug. Moreover a preliminary study, performed on four ileostomy subjects, indicated that size and density of pellets influenced their intestinal transit time (Bechgaard & Antonsen, 1977). We have examined the influence of size and density of pellets on intestinal transit time in a controlled trial in ileostomy subjects with the object of detaining a drug depot in the small intestine.

SUBJECTS AND METHODS

Six ileostomy out-patients, five females and one male, aged 25–50 years (median 30 years) participated with their informed consent. Three of the subjects had Crohn's disease and three ulcerative colitis. The small intestine was intact in four of the subjects, and part of the ileum, 20 cm and 50 cm respectively, resected in two with Crohn's disease. During the three months previous to the study the remaining small intestine of the patients appeared normal, as evaluated by X-ray, sedimentation rate and serum orosomucoid. The time elapsed from ileostomy ranged from 3 months to 5 years (median 2 years).

Gastrointestinal transit time, determined with carmine, showed an average of 5·8 h (range 3·5–9·0 h), estimated the day before the examination. Neither subject with ileal resection had the shortest transit-time. The subjects were allowed no medication during the 48-h of examination.

Heavy/small, heavy/large, light/small and light/large coated, non-toxic pellets were used. The light pellets which were coated white contained hard paraffin, the heavy pellets, coated black, contained barium sulphate; the densities were 1·0 and 1·6 respectively. Diameters ranged between 0·3–0·7 mm and 1·2–1·7 mm.

In the morning on the day of examination, after 12 h fast each subject was provided with a transparent ileostomy bag and was administered 250 pellets of each of the four kinds suspended in a standard solution consisting of 100 g Complan in 300 ml water. Otherwise the patient resumed his usual meal and locomotive routine. Total consumption of food and fluids was recorded. The ileostomy bag was emptied every 2 h during the first 14 h, and every 4 h during the 8 night hours. The pattern of emptying was repeated the next day, to complete a 48 h collection period. The contents

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of the bags were individually weighed, and stored at 4°.

Pellets were counted by removing them from thin layers of the visceral contents, spread on to dishes placed either on black or white pads, so that the four types of pellets could be distinguished from their coatings.

RESULTS

The total recovery of pellets from the bags averaged 90% (range 84–95%). Consumption of food was normal and uniform for the six subjects, according to the diet recordings but the intake of fluid was above normal for subject I, who drank 6900 ml, 5000 ml of which was beer. The average intake of fluid for the other subjects was 2900 ml (range 1900–4900 ml); beer was not included.

The percentage recovery of pellets in the bags during the first 18 h from 8 a.m. to 2 a.m., is shown in Table 1. The recoveries can be seen to correlate with density rather than with diameter. Though

Table 1. *Percent recovery*[1] *of pellets during the first 18 h.*

	Small		Large	
	light	heavy	heavy	light
I	91·9	77·0	68·8	99·2
II	100·0	17·2	10·9	99·1
III	100·0	6·3	4·4	99·6
IV	90·4	9·8	2·1	77·2
V	100·0	16·4	3·4	96·8
VI[2]	97·7	16·6	5·4	87·6
	$P < 0{\cdot}05$		$P < 0{\cdot}05$	
	$P < 0{\cdot}05$			
Average[3]	97·6	13·3	5·2	92·1
s.d.	4·2	4·9	3·4	9·6

1. Relative to total recovery of individual type of pellets.
2. Average of two replicate studies.
3. Subject I not included in the average, because of an atypical fluid intake (6900 ml, including 5000 ml beer).

the number of participants was limited, there was a statistically significant difference between the frequencies of the small/light and small/heavy, the large/light and large/heavy and the heavy/small and heavy/large pellets ($P < 0{\cdot}05$). The average percent recovery of light and heavy pellets in the first 18 h was 95 and 10%, respectively.

The inter and intra-subject variation in transit time ($t_{50\%}$), i.e. the time required for 50% of each type of pellets to appear in the ileostomy bag, is shown in Table 2. Here the difference in transit

Table 2. *Inter- and intra-subject variations in the period of time (h) required for 50% (median) of the recovered pellets to pass the small intestine.*

	Small		Large	
	light	heavy	heavy	light
I	6·6	7·6	7·8	7·0
II	4·6	22·9	23·2	4·7
III	4·5	23·0	23·5	4·6
IV	10·3	25·3	27·8	12·4
V	6·9	25·1	25·8	7·0
VI[1]	8·8	26·5	27·0	8·4
VI[1]	6·2	24·9	25·3	6·8
	$P < 0{\cdot}05$		$P < 0{\cdot}05$	
Average[2]	6·9	24·6	25·4	7·3
Range	4·5–10·3	22·9–26·5	23·2–27·8	4·6–12·4

1. The same subject at two replicate studies.
2. Subject I not included in the average, because of an atypical fluid intake (6900 ml, including 5000 ml beer).

time for the small/light and small/heavy, the large/light and large/heavy pellets was statistically significant ($P < 0{\cdot}05$). The average transit times ($t_{50\%}$) for the small/light and small/heavy pellets were 6·9 h (range 4·5–10·3 h) and 24·6 h (range 22·9–26·5 h), respectively (Table 2). Thus, a gap of about 18 h separated the $t_{50\%}$ values of the light and heavy pellets.

One subject (VI) repeated the study after a month and the transit times for all four types of pellets were displaced by about 2 h from the previous times (Table 2). The intra and inter-subject variations in transit times thus appear to be similar (Table 2).

DISCUSSION AND CONCLUSION

Thus in six ileostomy subjects pellets from multiple-units controlled-release products are dispersed throughout the small intestine and pass through the intestine at a rate that depends largely on their density rather than their diameter. The average transit times ($t_{50\%}$) were 7 and 25 h for light and heavy pellets, respectively, and differences were significant not only within but also between subjects.

Previously reported investigations in man, with solid particles or pellets having different sizes and densities, have been aimed either at a diagnostic procedure for the estimation of total gut transit time (mouth-to-anus) (e.g. Alvarez & Freedlander, 1924; Hinton, Lennard-Jones & Young, 1969; Kirwan & Smith, 1974), or at simulating the transit time of the dietary residue throughout the gut, e.g. Cummings, Jenkins & Wiggins (1976), Hoelzel (1930).

However, these reports dealing with the *total* intestinal transit time, are of limited bearing on the present topic, with the exception of that by Hinton & others (1969) which also concerns the transit time of pellets (density 1·1) in ten ileostomy subjects. The average transit time ($t_{50\%}$) of 4·8 h (range 2·3–8·0 h) reported by these authors is in accordance with the median transit time for the light pellets, 4·5 to 12·4 h (Table 2), observed in the present study.

Whether the intestinal transit time of pellets in ileostomy subjects is comparable to that of healthy subjects is open to question, but the reasons for ileostomy were different and subjects with a resection were not those showing the shortest transit times. The relative distribution of pellets is likely to be the same, but this, of course, requires confirmation by X-ray or absorption studies.

The results of the simultaneous administration of four types of pellets differing in diameter and density have shown, that the increase in density from 1·0 to 1·6 exerts a predominant influence on pellet distribution in the small intestine (Table 2) resulting in a shift of the transit time from the first to the second day. The diameter of pellets, increased from 0·5 to 1·5 mm, is of minor importance compared with the effect of density. It is not relevant to consider further increase in diameter of the pellets as a tool for increasing the prolongation of the average transit time, since a diameter of 1·5 mm must be regarded maximal for a true multiple-units formulation. Thus, the results of the study indicate the density of the pellets as the primary object for modification when multiple-units formulations are required to meet specific biopharmaceutical demands.

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REFERENCES

ALVAREZ, W. C. & FREEDLANDER, B. L. (1924). *J. Am. med. Ass.*, **83**, 576–80.

BECHGAARD, H. & ANTONSEN, O. (1977). Communication at 37th International Congress of Pharmaceutical Sciences, pp. 69. F.I.P. Hague.

BECHGAARD, H. & HEGERMANN NIELSEN, G. (1978). *Drug Develop. Ind. Pharm.*, **4**, 53–67.

CUMMINGS, J. H., JENKINS, D. J. A. & WIGGINS, H. S. (1976). *Gut*, **17**, 210–218.

EKENVED, G., BOGENTOFT, C., CARLSSON, I. & MAGNUSSON, A. (1977). Farmaceutiska Arskongres 1977, Apotekarsocieteten, Stockholm.

HINTON, J. M., LENNARD-JONES, J. E. & YOUNG, A. C. (1969). *Gut*, **10**, 842–847.

HOELZEL, F. (1930). *Am. J. Physiol.*, **92**, 466–97.

KIRWAN, W. O. & SMITH, A. N. (1974). *Scand. J. Gastroenterol.*, **9**, 763–66.

PRESCOTT, L. F. (1974). *Med. Clins N. Am.*, **58**, 907–16.

RITSCHEL, W. A. (1973). *Drug design*, Vol. 4, pp. 47–73. Editor: Ariens, E. J. New York and London: Academic Press.

SJÖGREN, J. (1975). *Farm. Tid.*, **85**, 1065–74.