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The influence of non-disintegrating tablet dimensions and density on their gastric emptying in fasted volunteers

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Abstract

The aim of this work was to identify the influence of tablet density on their gastric emptying in fasted subjects and to compare the findings with those of a previous study using the same subjects with tablets of a larger diameter. Tablets of 6.6 mm diameter and densities of 1.41 and 2.85 g cm^{-3} were labelled with ^{99m}Tc and ^{111}In. They were coated with ethyl cellulose to ensure that they remained intact within the gastrointestinal tract. Their position within the gastrointestinal tract of fasted healthy subjects was monitored with a double-headed gamma camera at 1-min time intervals. The median gastric emptying time and the interquartile range were derived from the Bernoulli random event distribution. It was found that the dense tablets had a significantly longer gastric emptying time than the light tablets. Comparison with the results from the previous study gave a clear indication that irrespective of tablet density, the 6.6-mm tablets had longer gastric emptying times than the 12.0-mm tablets.

Introduction

There have been numerous studies employing gamma scintigraphy on the gastric emptying of non-disintegrating objects, including tablets. As yet, however, it is not possible to give a definitive answer to the issue of whether or not the size and the density of the tablet do in fact have a significant effect on the emptying process. This is due to various reasons. In some cases the experiments were carried out with dogs as the test animal (Kelly 1981; Meyer et al 1985; Kaniwa et al 1988). In several instances the subjects were in the fed state (Mojaverian et al 1985; Khosla & Davis 1989; Khosla et al 1989; Agyilirah et al 1991; Abrahamsson et al 1996) and this was clearly identified as a factor that extended the gastric emptying time. In some instances the time interval between the observations of the tablet position is given but not the method used to identify the time at which the tablet empties from the stomach from this interval data (e.g. Ofori-Kwakye et al (2004)). As pointed out by Podczeck et al (1999), it is important to identify an appropriate time interval for the observation of the tablet and also to ensure that the position of the tablet in the gastrointestinal tract is clearly identified, to ensure a reliable estimate of the gastric emptying time. This procedure can have an important impact on the treatment of the results and the ability to identify whether there are statistically significant differences between different factors. With this in mind, therefore, this study was devised to determine whether the previous findings (Podczeck et al 1999), showing a significant difference between the gastric emptying of light (density 1.5 g cm^{-3}) and heavy (density 3.7 g cm^{-3}) tablets with a diameter of 12 mm, would also be observed with light (density 1.41 g cm^{-3}) and heavy (density 2.85 g cm^{-3}) tablets of 6.6 mm diameter, and whether the two tablet sizes differed in their gastric emptying properties.

Additional data to that which had been utilised in the paper by Podczeck et al (1999) was taken from the thesis presented by Course (1992) to check whether the differences between the gastric emptying of light (density 1.5 g cm^{-3}) and heavy (density 3.7 g cm^{-3}) tablets of a smaller diameter resulted in the same conclusions when analysed by this new approach. It would also be possible to check whether the two tablet sizes differed in their gastric emptying properties. Course (1992) had found a method of providing four different isotopes for the four different types of tablets to allow the effects of size and density to be

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compared on one occasion, but this would have resulted in a doubling of the dose of radioactivity received by the subjects. This was not acceptable to the Ethical Committee and therefore the two studies were carried out independently, separated by a period of one month in the administration to each individual. Using four different tablets on a single occasion would also have increased the time between the identification of the position of the individual tablets, which would have reduced the accuracy of identification of the gastric emptying time.

Materials and Methods

Materials

The dense tablets contained barium sulfate BP (grade HR10; Sachtleben Chemie GmbH, Duisburg, Germany) and the ion-exchange resin Amberlite CG400 (Aldrich Chemicals Co. Ltd, Gillingham, Kent, UK). The light tablets contained lactose monohydrate BP (Sheffield Products, Norwich, NJ) and the ion-exchange resin Dowex 50W-8H (BDH, Poole, UK). The ion-exchange resins were incorporated to hold the radioactive elements added to enable the tablets to be traced in the gamma-scintigraphy studies. Polyvinyl pyrrolidone BP (BDH, Poole, Dorset, UK) and 1% magnesium stearate BP (BDH, Poole, Dorset, UK) were used as binder and lubricant, respectively.

The coating solution applied to ensure that the tablets did not disintegrate as they passed through the gastrointestinal tract was prepared from ethyl cellulose BP (Grade N50; Colorcon, Dartford, Kent, UK) plus 1.2% diethyl phthalate BP (McCarthy's, Romford, Essex, UK) and 2.4% polyethylene glycol 4000 (pore former to allow the uptake of the radioactivity during the labelling process; Koch Light Laboratories, Berkshire, UK) in a 70:30 mixture of methylene chloride–methanol (both Analar grade, BDH, Poole, Dorset, UK).

Preparation of tablets

The study was undertaken before the EU requirement that materials for use in human biological trials should be manufactured under GMP conditions. All ingredients were of a grade suitable for administration to man. All the equipment was thoroughly cleaned before use and was housed in clean laboratories and the processes supervised by a Qualified Person (JMN) as defined by the Medicines Act.

The tablets were prepared employing wet granulation for both sets of tablets. The powders (90% of either barium sulfate or lactose with 5% of the appropriate ion-exchange resin and 5% of polyvinyl pyrrolidone, were blended with the appropriate quantity of water in a planetary mixer (Kenwood Chef, Kenwood, London, UK). The wet mass was pushed by hand through a 1.7-mm mesh screen and dried for 2 h at 60·C in a hot-air oven. Any fines were removed with a 0.25-mm screen. The granules were then blended with 1% magnesium stearate by tumbling in a round screw-capped jar on rollers. The tablets were compressed with 6.5-mm diameter normal concave punches at a fixed displacement setting on a rotary tablet machine (Type D; Manesty Machines, Liverpool, UK).

The coating was applied in a fluidised coater fitted with a Wurster column and bottom pneumatic spray (Aeromatic Strea-1; ACM Machinery, Tadley, Berkshire, UK) to give a tablet weight gain of 5%. The final diameter of both sets of tablets after coating was 6.6 mm; the weights were 298.6 mg and 128.2 mg and the final densities (derived from the weight and dimensions of the tablets) were 2.85 g cm^{-3} and 1.41 g cm^{-3}.

Radiolabelling of the tablets

The radiolabel was attached to the tablets by immersing them for 5h in either a solution of sodium pertechnetate ($Na^{+}TcO_4^{-}$) in 95% saline (dense tablets) or a 0.04 M hydrochloric acid solution of indium-111 (light tablets). After soaking, the excess solution was removed and the tablets washed with two separate 5-mL quantities of normal saline. They were further washed with 10 mL of normal saline for 1 h in an automatic shaker. The excess solution was removed and the tablets dried in a hot-air oven at 40·C overnight. The radioactivity of the tablets was measured with an isotope assay calibrator (Model 270; Pitman Instruments, Surrey, UK). The final activity provided on the day of the study was 7.4 MBq for the ^{99m}Tc and 2.6 MBq for the ^{111}In.

To test the retention of the radio-label, the tablets were placed in 20 mL of simulated gastric juice (USP 1980), omitting the pepsin, pH 1.3, in sealed tubes which were rotated in a shielded water bath at 37·C. After 2 h, a 2-mL sample was removed and the level of radioactivity measured with a sodium iodide probe connected to a multi-channel analyser (J&P Engineering, Reading, UK). The remaining fluid was removed from the sample container and replaced with 20 mL of simulated intestinal fluid (USP 1980), omitting the pancreatin, pH 7.5. Two 2-mL samples were tested after 8 and 24 h. The tests were run in duplicate for each tablet and isotope system. The counts were corrected for decay and, when expressed as a percentage of the original activity of the tablets, never exceeded 4.4%.

Gamma-camera study

The gamma-scintigraphy study was carried out using a protocol that had been approved by the University College Hospital Ethics Committee and that complied with the Declaration of Helsinki and the Administration of Radioactive Substances Act. Eight healthy male subjects, age range 22–56 (median age 24), took part in the study, having provided written consent. (These were in fact the same volunteers who took part in the previous study (Podczeck et al 1999) with the presence of one additional subject.) They were fasted overnight from 2000 h on the day before the study. At zero time the subjects swallowed a light and heavy tablet with 50 mL of water, while sitting between the heads of a double-headed gamma camera (Siemens Rota Camera; Siemens, Cambridge, UK) fitted with medium-energy collimators. Images of the two isotopes were obtained sequentially at 30-s intervals with both heads to give anterior and posterior images. The levels of activity of ^{99m}Tc and ^{111}In were measured at 140 and 208 keV, respectively. All the values for the level of radioactivity of ^{99m}Tc were corrected for downscatter from the ^{111}In and were the geometric mean of the anterior and posterior images.

With these levels of imaging, it was possible to define the time when the tablet first appeared out of the stomach to the nearest minute. Once the tablet had emptied from the stomach, images were taken at 15-min intervals until 9 h. A 0.5-MBq ^{99m}Tc point source was taped on the right side at the base of the ribs as a reference marker to allow position of the subject between the heads of the camera. The position of the stomach was defined before the study and after the standard lunch by the use of an ^{81m}Kr orange drink, as described by Course et al (1992). The standard lunch, consisting of a MacDonald's Quarter Pounder, French fries and an apple (3546 kJ), was consumed after 3.5 h.

Statistical data evaluation

The median and inter-quartile range values for the gastric emptying time, using the Bernoulli random event probability distribution approach, were determined using the method described by Podczeck et al (1999). The statistical comparisons between emptying times were undertaken with the Wilcoxon signed-rank test (e.g., see Snedecor & Cochran 1980) using SPSS 14.0 (SPSS Inc., Woking, UK).

Results and Discussion

In a recent review of gastric motility, Olsson & Holmgren (2001) found an extensive body of literature on gastric emptying and they concluded that "almost everything seems to affect the rate of emptying". They listed the most important factors, but these did not include those of dimensions or density of solid objects, which is perhaps not surprising as they were considering the gastric emptying of food, the composition of which is very important. Nevertheless, it does indicate the complexity of the situation and the potential for varying observations. Olsson & Holmgren (2001) clearly identified that the gastric emptying of food depends on the contractile state of the stomach, pyloric sphincter and the proximal part of the intestine, and the peristaltic waves over the stomach. One would therefore expect that, except for the proximal part of the intestine, the same factors would be involved in the gastric emptying of inert objects, such as coated tablets. The migrating motor/myoelectric complex (MMC) is the major source of contractile events in the fasted state. In contrast, peristalsis may occur only in the fed state (Spencer 2001). The MMC occurs cyclically about every two hours and is considered to act as a transport of waste material along the intestine. Such waves have not, however, been found always to be the source of the emptying of tablets from the stomach (Mitchell 1997).

The administration of the 50 mL of liquid to ensure the satisfactory swallowing of the tablets would not be expected to convert the stomach to the fed state. The anatomy of the fasted stomach, as described in Gray's Anatomy (2005), indicates that the surface of the stomach will consist of folds, or rugae, for which there is no particular pattern. The description presented suggests that the folds run longitudinally from the fundus to the pyloric antrum. Thus the tablets may interact with these folds and the smaller the diameter, the more likely they could be trapped between the folds. On the other hand, the larger the diameter of the tablets, the more likely they would stay on top of the folds. In addition, the illustrations of the fasted stomach clearly show that when fasted, the posterior/inferior surface will be less curved, with an axis that is nearly vertical. This will result in the tablets moving toward the pyloric antrum rather than becoming lodged in the lower portion of the 'J' shape, which develops as the stomach is distended when in the fed state. One must remember, however, that Moore & Dalley (2006) clearly say that "the shape and position of the stomach can vary markedly in persons of different body types and even in the same individual as a result of diaphragmatic movements during respiration".

The values for the time at which the tablet can be identified as being out of the stomach are given in Table 1. These values have been used to determine the median and inter-quartile range values for the gastric emptying time. The results are presented in Table 2, together with those for the 12.0-mm tablets reported in the study by Podczeck et al (1999). Comparison of the values for gastric emptying for the 6.6-mm tablets by the Wilcoxon test clearly illustrates that there was a significant difference between the values for the light and dense tablets ($Z = -2.521$, $P = 0.012$), confirming the previous observation (Podczeck et al 1999) for the 12.0-mm diameter tablets. Thus, it can be concluded that the median value for gastric emptying time was shorter for the light tablets than the dense tablets. The median values for the 6.6-mm tablets were considerably longer than those for the 12-mm tablets. Although the same subjects were involved with both studies, they were carried out on two entirely different occasions separated by one month in any one individual. Every effort was made to try and ensure that the conditions were the same on both occasions. However, we have observed, over

Table 1 Gastric emptying times of light and dense 6.6-mm tablets

Subject	Gastric emptying times (min)	
	Light tablets	Dense tablets
1	23	37
2	114	198
3	92	191
4	51	82
5	65	69
6	42	44
7	181	191
8	58	>540

Table 2 Median and inter-quartile range (IQR) of gastric emptying of light and dense 6.6- and 12-mm diameter tablets

	6.6-mm diameter tablets		12.0-mm diameter tablets[a]	
	Light	Dense	Light	Dense
Median	58.0	82.0	14.8	24.6
IQR	72.0	154.0	16.8	21.0

[a]Results from Podczeck et al (1999).

several studies, that there can be a difference in behaviour of the same individual on different occasions even for fasted conditions. Although the subjects were fasted, there is no guarantee that they were all in the same stage of the same phase of the migrating myoelectric complex (MMC) when the tablets were administered on the two different occasions.

Comparison between tablets of the different densities on a given occasion, however, should be possible in terms of the standardisation of the influence of the MMC. In fact, comparing values for light and dense tablets did show that on several occasions the tablets emptied at very similar times. Comparing the ranking of the gastric emptying values of the individuals for the two different densities of tablet, using the Spearman rank correlation coefficient (0.755 for the 6.6-mm tablets and 0.786 for the 12.0-mm tablets, with $P<0.05$ in both cases), does indicate that the ranking was statistically the same for both the light and dense tablets on each of the two occasions the tablets were administered. There is some indication that the emptying process is such that tablets of the different densities are emptied at approximately the same time. For example, subjects 5 and 6 of this study, and subjects 3 and 6 of the previous study had approximately the same emptying times, suggesting that contractions of the stomach are the dominant feature of the emptying process in these cases. On every occasion, however, the higher density tablet left the stomach after the light tablet.

The question of whether the tablet size influences the gastric emptying time is more difficult to answer. There was clearly a significant difference between the values for the gastric emptying time of both the light and dense 6.6- and 12.0-mm tablets ($Z=-2.028$, $P=0.043$ and $Z=-2.366$, $P=0.018$ for light and dense tablets, respectively) and the difference was larger for the 12-mm tablets. Due to the fact that the formulations of the 6.6-mm tablets included an ion-exchange resin, the densities of the tablets were lower than those used in the previous study. The difference in the values between the light tablets, which were 1.41 and 1.50 g cm^{-3} for the 6.6- and 12.0-mm diameter tablets, respectively (i.e. 0.09 g cm^{-3}), would not be expected to have an effect, if the studies with pellets reported by Clarke et al (1993, 1995) are considered. Here, pellets with densities up to 2.40 g cm^{-3} emptied in the same manner. Considering the findings that the light tablets emptied in a shorter time than the dense tablets, there is clear support for the more rapid emptying of the larger light tablets. The findings are at variance with those of Khosla & Davis (1989, 1990) and Khosla et al (1989). Two of these studies (Khosla & Davis 1989, 1990) involved subjects in the fed state and involved taking multiple tablets and using simple t_{50} values as a measure of gastric emptying, thus providing an entirely different estimate of the process of gastric emptying. The administration of the multiple number of tablets (up to ten) used in these studies is not the usual clinical use of tablets and therefore provides information that does not fit into a practical situation. The administration of single units of controlled-release tablets is nearer to the practical situation, except in the case of the use of mini tablets (those with diameters less than 3 mm), where greater numbers of tablets would be used. The 6.6-mm tablets have a density that exceeds the critical value of 2.60 g cm^{-3} for gastric retention suggested by Clarke et al (1993, 1995) for pellets in the size range 0.5–5 mm and the density values of 2.80 g cm^{-3} for 1.0-mm pellets reported by Devereux et al (1990). The 12.0-mm tablets have an even higher value for the density, 3.70 g cm^{-3}, which suggests that they should be well within the range of values where density does retard gastric emptying. As previously stated, the paper by Podczeck et al (1999) established that tablets of higher density do have a statistically significant longer gastric emptying time than lighter tablets. It would appear, therefore, that there is some justification for the conclusion that the 12.0-mm dense tablets do empty at a shorter time than the 6.6-mm dense tablets despite being of a higher density. It appears in this case, therefore, that the effect of size outweighs that of density. As subjects were in the fasted condition it would appear that the concept that the pyloric sphincter controls the dimensions of the object that leaves the stomach is not involved in any instance here as it is the larger dimension tablet that has the more rapid emptying. That the 12-mm tablet can empty from the stomach agrees with the observations of Munk et al (1978) that the mean resting diameter of the pylorus sphincter is 12.8 ± 8.7 mm.

The identification of the reasons for the events described above requires improved observation of the position of the tablets within the stomach and hence requires the development of a technique that is more sensitive than gamma scintigraphy.

Conclusions

The study has established that under fasted conditions, increasing the density of a 6.6-mm tablet from 1.41 to 2.85 g cm^{-3} extends the gastric emptying time of the tablet. Comparison of the results of a previous study (Podczeck et al 1999), which used the same group of subjects, supports these findings. There is clear evidence that, irrespective of tablet density, a 12.0-mm tablet has a shorter emptying time than a tablet of 6.6 mm.

References

Abrahamsson, B., Alpsten, M., Jonsson, U. E., Lundberg, P. J., Sandberg, A. Sundgren, M., Sveheden, A., Tolli, J. (1996) Gastrointestinal transit of a multiple-unit formulation (metoprolol CR/ZOK) and a non-disintegrating tablet with the emphasis on colon. *Int. J. Pharm.* **140**: 229–235

Agyilirah, G., Green, M., duCret, R., Banker, G. S. (1991) Evaluation of the gastric retention properties of coated tablets versus those of a non-disintegrating tablet. *Int. J. Pharm.* **75**: 241–247

Clarke, G. M., Newton, J. M., Short, M. D. (1993) Gastrointestinal transit of pellets of differing size and density. *Int. J. Pharm.* **100**: 81–92

Clarke, G. M., Newton, J. M., Short, M. D. (1995) Comparative gastrointestinal transit of pellet systems of varying density. *Int. J. Pharm.* **114**: 1–11

Course, N. C. (1992) *Gastrointestinal transit of tablets of different size and density*. PhD Thesis, University of London, UK

Course, N. C., Newton, J. M., Short, M. D. (1992) Stomach outline visualisation in gastrointestinal transit studies using scintigraphy. *J. Pharm. Pharmacol.* **44**: 127–129

Devereux, J. E., Newton, J. M., Short, M. B. (1990) The influence of density on the gastrointestinal transit of pellets. *J. Pharm. Pharmacol.* **42**: 500–501

Gray's anatomy (2005). 39th edn, Standing, S. (ed.), Elsevier Ltd, Edinburgh, pp 1143–1155

Kaniwa, N., Aoyago, N., Ogata, H., Ejima, A. (1988) Gastric emptying rates of drug preparations. I Effects of size of dosage forms, food and species on gastric emptying rates. *Pharmcobio-Dyn*. **11**: 563–570

Kelly, K. A. (1981) Motility of the stomach and gastroduodenal junction. In: Johnson, L. R. (ed.) *Physiology of the gastrointestinal tract*. Raven, New York, pp 393–410

Khosla, R., Davis, S. S. (1989) Gastric emptying and small and large bowel transit of non-disintegrating tablets in fasted subjects. *Int. J. Pharm*. **52**: 1–10

Khosla, F., Davis, S. S. (1990) The effect of tablet size on the gastric emptying of non-disintegrating tablets. *Int. J. Pharm*. **63**: R9–R11

Khosla, R., Feely, L. C., Davis, S. S. (1989) Gastrointestinal transit of non-disintegrating tablets in fed subjects. *Int. J. Pharm*. **53**: 107–117

Meyer, J. H., Dressman, J., Fink, A., Amidon, G. (1985) Effect of size and density on canine gastric emptying of non-disintegrating solids. *Gastroenterology* **89**: 805–813

Mitchell, C. L. (1997) *The relationship between motility and gastrointestinal transit of tablets*. PhD Thesis, University of London, UK

Mojaverian, P., Ferguson, R. K., Vlasses, P. H., Rocci, M. L., Oren, A. Fix, J. A. Caldwell, L. J. Gardener, C. (1985) Estimation of gastric residence time of the Heidelberg capsule in humans: effect of varying food composition. *Gastroenterology* **89**: 392–397

Moore, K. L., Dalley, A. R. (2006) *Clinically oriented anatomy*. 5th edn, Lippincott Williams & Wilkins, Philadelphia, USA, pp 248–259

Munk, J. F., Ganway, R. M., Hoare, M., Johnson, A. G. (1978) In: Duthie, H. L. (ed.) *Gastric motility in health and disease*. MTP Press, Lancaster, UK, pp 104–117

Ofori-Kwakye, K., Fell, J. T., Sharma, H. L., Smith, A.-M. (2004) Gamma scintigraphy evaluation of film-coated tablets intended for colonic or biphasic release. *Int. J. Pharm.* **270**: 307–313

Olsson, C., Holmgren, S. (2001) The control of gut motility. *Comp. Biochem. Physiol*. Part A **128**: 481–503

Podczeck, F., Course, N. C., Newton, J. M. (1999) Determination of the gastric emptying of solid dosage forms using gamma-scintigraphy: a problem of image timing and mathematical analysis. *Eur. J. Nucl. Med*. **26**: 373–378

Snedecor, G. W., Cochran, W. G. (1980) *Statistical methods*. 7th edn, The Iowa State University Press, Ames, Iowa, pp 141–143

Spencer, N. J. (2001) Control of migrating motor activity in the colon. *Curr. Opin. Physiol*. **1**: 604–610