JPP Journal of Pharmacy and Pharmacology

JPP 2007, 59: 941–945

Received January 21, 2007
Accepted March 12, 2007
DOI 10.1211/jpp.59.7.0005
ISSN 0022-3573

Gastrointestinal transit of model mini-tablet controlled release oral dosage forms in fasted human volunteers

F. Podczeck, N. Course, J. M. Newton and M. B. Short

Abstract

The aim of this study was to compare the gastrointestinal transit of multiple unit, small diameter (3.2 mm), non-disintegrating tablets of differing densities with results previously reported in the same volunteers in the fasted state for larger diameter (6.6 and 12.2 mm) tablets. The gastrointestinal transit was observed with gamma-scintigraphy at various intervals over a 9-h period to give an accurate assessment of the transit characteristics. The value for the median emptying time of the first light tablet was significantly shorter than that for the dense tablet, but the total emptying time and the time for the last tablet to empty for both sets of tablets were not statistically different. The value of the median time for initial and final emptying of the small tablets from the stomach was significantly longer than that for the larger diameter tablets. The 9-h time limit of the observations limited the estimation of the time taken to enter the caecum and consequently the small intestine transit times. There was clear evidence that for the dense tablets of all sizes, the value for the small intestine transit time was longer than the 3–4 h reported in the literature. The only tablet system to enter the caecum within the time limit of the study was the normal density 12.2-mm tablets.

Introduction

The data reported by Course (1992) has recently been reanalysed to evaluate the influence of size and density on the gastric emptying in the fasted state of single unit tablets (Podczeck et al 2007). The differences identified could have implications for the performance of controlled release dosage forms, where the tablet stays intact during transit through the gastrointestinal tract. Single unit controlled systems have been criticized in the pharmaceutical literature. In fact, the European Agency for the Evaluation of Medicinal Products (EMEA) in their Note for Guidance on Quality of Modified Release Products states that "the development of single unit non-disintegrating dosage forms is discouraged since their residence time in the stomach is unpredictable and in general longer than disintegrating dosage forms with multiple units of pellets" (EMEA 1999). In the same study by Course (1992), data is available on the gastric emptying of small tablets, 3.2 mm in diameter. These could be considered as mini-tablets and representing multiple units, which are used in such products as Nutizym. The in-vitro and in-vivo performance of such systems has been described by Munday et al (1991a, b). The protocol in the experiment by Course (1992) was designed to ensure that the smaller tablets were administered to provide weights that were equivalent to the weight of a larger tablet (6.6 mm in diameter) of equal density (six for the heavy tablets and five for the light tablets) in associated studies. Therefore, such a system differs from the usual pellet multiple dose systems, which usually consist of between 100 and 300 pellets but could still be considered to provide a multi-unit system. To use the simple time for 50% of the pellets to empty from the stomach or the mean gastric residence time approach (Podczeck et al 1995) does not seem to be appropriate for this limited number of units. The gastrointestinal transit characterization appears to be preferable to the system proposed by Podczeck et al (1999) for single units if the time for the first and last tablet to empty from the stomach is used in the analysis. The results for the 3.2-mm tablets are considered together with those for the same volunteers previously reported by Podczeck et al (1999, 2007). The results for the arrival at the caecum for the different tablet sizes, available in the study by Course (1992), are also considered.

School of Health, Natural and Social Sciences, Pasteur Building, Sunderland University, City Centre Campus, Warncliffe Street, Sunderland SR1 3SD, UK

F. Podczeck

School of Pharmacy, University of London, Brunswick Square, London WC1N 1AX, UK

N. Course, J. M. Newton

Department of Medical Physics, University College London, Gower Street, London WC2E 6AD, UK

M. B. Short†

Correspondence: J. M. Newton, School of Pharmacy, University of London, Brunswick Square, London WC1N 1AX, UK. E-mail: michael.newton@pharmacy.ac.uk

Acknowledgement: The authors wish to thank Nordmark GmbH, Lübeck, Germany for the preparation of the 3.0-mm diameter tablets used in the study.

†Deceased

Materials and Methods

As with the previous study (Podczeck et al 2007), this study was undertaken before EU requirements that materials for use in human biological trials should be manufactured under GMP conditions. The materials for this study were prepared with the same care as employed previously and again under the supervision of a qualified person (JMN).

Tablet preparation

The light (1.38 g cm^{-3}) and dense (2.86 g cm^{-3}) tablets were prepared from the same materials (lactose or barium sulfate with polyvinyl pyrrolidone and magnesium stearate, plus the ion-exchange resins Amberlite CG400 or Dowex 50W-8H) of the same quality and using the same processes (mixing, granulation and compression) as described by Podczeck et al (2007) except that the tablets were prepared by Nordmark GmbH, Lübeck, Germany with 3.0-mm diameter punches under GMP conditions. To be able to produce uniform tablets, it was necessary to remove the granules greater than 0.7 mm in size by sieving and add 0.5% Aerosil 200 (Degussa, Frankfurt am Main, Germany) to the mixture. The tablets were coated as described previously (Podczeck et al 2007) with ethyl cellulose (N50), polyethylene glycol 4000 and diethyl phthalate, which resulted in tablets with a diameter of 3.2 mm. The density of the tablets was determined from the weight and dimensions.

The tablets were able to retain their structure when subjected to soaking and addition of the radioactive label (^{99m}Tc for the dense tablets and ^{111}In for the light tablets) and also remained intact when tested for disintegration, with no leaching out of the radioactivity in-vitro after 24 h.

Gamma-scintigraphy

The study was carried out as described by Podczeck et al (2007) with the approval of the same committees, the same pre-treatment of the volunteers, the same gamma-camera procedures and the same statistical procedures to evaluate the data. To provide a comparison with the 6.6-mm tablets, the same weight of the 3.2-mm tablets was administered. Thus, six dense tablets and five light tablets were administered. As with the previous study (Podczeck et al 2007), images of the two isotopes were obtained sequentially at 30-s intervals with both heads of the gamma camera. The levels of activity of ^{99m}Tc and ^{111}In were measured at 140 and 208 keV, respectively. All values were corrected for down-scatter 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 outside the stomach to the nearest minute. Once all the tablets were out of the stomach, the timing of the imaging was approximately every 15 min until 9 h. This procedure was also followed in the previous studies (Podczeck et al 1999, 2007) but only the results for gastric emptying were reported. The same volunteers were involved in all the studies, so an approved interval between the administration of the radioactivity was allowed.

Study comparisons

This study was the third in a series of studies undertaken as a PhD thesis (Course 1992). The results for the gastric emptying of a single 12.2- or 6.6-mm tablet have been reported previously (Podczeck et al 1999, 2007). As the volunteers were the same in each study, statistical comparisons are possible. In addition to the gastric emptying results reported previously (Podczeck et al 1999, 2007), the thesis (Course 1992) also contains some data for the arrival of the tablets in the caecum. These results are also considered here.

Statistical analysis

Bernoulli event statistics as described previously (Podczeck et al 1999) were used to determine the emptying times of the tablets. The emptying times of tablets were compared using the Wilcoxon signed ranks test (the test values are identified in the text as Z and the error probabilities as P) using double-sided error probability (SPSS 15.0; SPSS Inc., Woking, UK).

Results and Discussion

For these systems, the image for the multi-unit tablets was rather more confused than that for the previous studies (Podczeck et al 1999, 2007) with single tablets. As the resolution of the camera was only 10 mm at the surface of the individual (Devereux 1987), it was not considered appropriate to try and identify each tablet at every time interval. It was possible, however, to clearly identify when the first and last tablets left the stomach to the nearest 1-min interval, which allowed the application of the Bernoulli distribution function as described by Podczeck et al (1999) to these parameters. The individual results, the median and interquartile range, and the interval over which the emptying took place are presented in Table 1. The emptying times for the first light tablet were significantly shorter ($Z=-2.524$; $P=0.012$) compared with those for the first dense tablet. This agrees with the findings for the two

Table 1 Gastric emptying characteristics of 3.2-mm tablets in fasted volunteers

Volunteer	Time of first emptying (min)		Time of final emptying (min)		Emptying period (min)	
	Dense	Light	Dense	Light	Dense	Light
A	73	157	113	242	85	40
B	98	101	111	111	10	13
C	177	181	226	226	45	49
D	23	38	50	50	12	27
E	156	163	341	540	178	185
F	133	155	170	231	76	37
G	71	75	92	79	4	21
H	90	218	218	226	8	128
Distribution						
Median	156	94	226	141	28	38
Interquartile range	95	79	152	127	74	86

larger diameter tablets (Podczeck et al 1999, 2007). However, neither the emptying times nor the emptying period for the final light and dense tablets were statistically different. Comparison of the value for the median time for the initial or final tablet emptying with the values of the median emptying time obtained on different occasions in the same volunteers with 6.6- and 12.2-mm diameter tablets (Podczeck et al 1999, 2007), using the same statistical procedure, indicated that the value for the smaller tablets was significantly longer. The gastric emptying of the largest unit appeared to be the shortest and showed lower levels of variability. This does not agree with the statement of the EMEA guidelines (EMEA 1999). Nor does it agree with the results of Khosla & Davis (1989) who administered five tablets to fasted volunteers, or Khosla et al (1989) who administered 10 tablets of each of the diameters 3, 4, 5, 6 and 7 mm, the same number of 3, 4 and 5 mm diameter on another occasion, and 5, 6 and 7 mm diameter on a further occasion to fed volunteers. Their comments about the increasing variability of emptying with tablet size appear to be related to the variability in the emptying of the multiple units as opposed to the variability of a single unit.

While gastric emptying is considered to be an important variable in gastrointestinal transit, it is only one stage in the process involved in absorption of drugs from oral controlled release dosage forms. Yuen et al (1993) found that for a multiparticulate controlled release formulation of theophylline, the majority of the absorption took place when the pellets were in the small intestine and the colon. Nevertheless, the time spent in the stomach before reaching these areas will obviously have an influence on the performance of the dosage form. Equally, the time spent in the small intestine may be very important. The times for the first 3.2-mm diameter tablets to arrive at the ileo-caecal junction are presented in Table 2. For all the subjects, at least one tablet could be identified as arriving at this junction. The data can be analysed as before to provide a median and interquartile range. There was no statistically significant difference between light and dense tablets. That dosage forms often spend time at this junction before entering the caecum has been reported (e.g. Khosla & Davis 1989). This was observed here and, unfortunately, the restriction of the period of the study to a limit of 9 h prevented identification of the time at which all the tablets had entered the caecum in all subjects. Because the tablets where spread out along the gastrointestinal tract, it was possible to identify the position of each tablet, even with the limited resolution of the camera. Also recorded in Table 2 are the values for the percentage of tablets that had entered the caecum at 9 h. For the light tablets, in six of the eight volunteers, all the tablets were in the caecum, whereas with the dense tablets, only in one volunteer had all the tablets entered the caecum (again it must be remembered that there were six dense tablets as opposed to five light tablets). As a comparison, the values for the arrival of the 6.6- and 12.2-mm diameter tablets at the ileo-caecal junction and entry into the caecum are presented in Tables 3 and 4 (data taken from Course 1992). Again the time limit of 9 h restricted the data analysis to the identification of a median time for the caecal arrival and caecum entry. Because of the 9-h time limit, it was not possible to give a value for the

Table 2 Time taken for the first 3.2-mm tablets to arrive at the ileo-caecal junction and % of tablets in the caecum at 9 h

Volunteer	Caecum arrival time (min)		Tablets in the caecum at 9 h (%)	
	Dense	Light	Dense	Light
A	466	391	33	100
B	240	291	33	80
C	371	371	50	100
D	391	391	50	100
E	492	325	50	80
F	381	311	50	100
G	386	326	100	100
H	360	360	66	100
Distribution				
Median	384	343		
Interquartile range	84	72		

Table 3 Time taken for the 6.6-mm tablets to arrive at the ileo-caecal junction and to enter the caecum (data from Course 1992)

Volunteers	Caecum arrival time (min)		Caecum entry time (min)		Lag time (min)	
	Dense	Light	Dense	Light	Dense	Light
A	>540	>540	>540	>540	–	–
B	>540	259	>540	311	–	52
C	>540	379	>540	438	–	59
D	440	440	477	500	37	60
E	284	258	284	284	0	26
F	347	302	367	347	20	45
G	334	248	472	308	138	60
H	>540	>540	>540	>540	–	–
Distribution						
Median	>440	340	>477	392	–	52 (six subjects)

Table 4 Time taken for the 12.2-mm tablets to arrive at the ileo-caecal junction and to enter the caecum (data from Course 1992)

Volunteers	Caecum arrival time (min)		Caecum entry time (min)		Lag time (min)	
	Dense	Light	Dense	Light	Dense	Light
A	>480	200	>480	345	–	145
B	>480	208	>480	323	–	115
C	>480	292	>480	366	–	74
D	202	202	468	307	266	105
E	390	241	470	391	80	150
F	294	193	399	294	31	101
G	292	226	368	292	76	66
H	>480	246	>480	311	–	65
Distribution						
Median	>390	217	>470	317	16	103
Interquartile range		46		72	80	81

caecum arrival time of tablets except for the light 12.2-mm diameter tablets: median value of 217, interquartile range 46 min for the junction arrival time and median value of 317, interquartile range 72 min for the caecum entry time. These light tablets are the most likely to conform to a typical controlled release dosage form in terms of density. All that can be derived for the dense 12.2-mm diameter tablets and both types of 6.6-mm tablets are estimates of minimum values for the junction arrival and caecum entry times. Difficulties in identifying a time when the dosage forms enter the caecum make estimation of the small intestinal transit (SIT) time difficult. The only value that could be reliably identified as the difference between the median gastric emptying time and the median caecum arrival time was that for the light 12.2-mm diameter tablets, where a value of 302 min was derived. This seems rather longer than the value of 3–4 h quoted in the review by Wilding et al (2001), but with the addition of the standard deviation of 1 h they suggest, it is acceptably close. The values for the other systems tested, however, were all in excess of 6 h, which is very different. We have no obvious explanation for the extended values for the SIT time in our studies. Wilding et al (2001) claim that the SIT values reported are independent of the type of dosage form and whether the volunteers were in the fed or fasted state. Several of the studies used extended intervals between observations of the position of the dosage form and poorly defined identification of the actual time used from the interval data. Podczeck et al (1999) demonstrated the need to take samples at appropriate time intervals and the need to employ the correct statistical tests to measurements of this type. It must be emphasised that these studies were undertaken with the volunteers in the fasted state. Although this may not be the normal condition when patients are treated with the dosage forms, it is the more usual condition used when the formulations are being assessed for their pharmacokinetic performance and are not therefore totally artificial. On the intake of food, the stomach changes shape considerably (Standring 2005). There is dilation to accommodate the food, which results in the loss of the "folds", and there is emphasis of the "J" shape, which would provide the possibility for the dosage forms to fall to the lower part of the stomach, requiring considerable upward movement to expel it from the stomach. The presence of food also results in closure of the pylorus and changes the phase of the migrating motor complex. Course (1992) did undertake a further study with l2.2-mm diameter tablets in the same volunteers in the fed state. Analysis of the results by the method of Podczeck et al (1999) provides values for the median gastric emptying of 360 and 478 min, with interquartile range values of 178 and 318 min, for the light and dense tablets, respectively. With such extended gastric emptying times (previously 14.8 and 24.6 min in the fasted state) it is not surprising that only two of the light tablets and none of the dense tablets arrived in the caecum within the 9 h study period.

Conclusion

The gastric emptying of multiple mini-tablets (3.2 mm in diameter) in fasted volunteers, as assessed by the approach of Podczeck et al (1999), in terms of the time for the first tablet to empty from the stomach was found to be longer for the dense than the light tablets, in agreement with the previous findings (Podczeck et al 1999, 2007). The time for all the tablets to empty or the period over which emptying of the tablets occurred was found not to differ between the two sets of tablets. The time for the first small tablet to empty and for all the small tablets to empty occurred at a later time and took place over a longer period of time than for the single unit dosage form of 6.6- and 12.2-mm diameter tablets, contrary to previous literature reports. The 9-h period of observation meant that it was only possible to assess the arrival of the first small tablets at the ileo-cecal junction and not the entry into the caecum within the time span of the experiment. Even with this limitation, this observation is at variance with the perception of the lack of the effect of dimensions on the gastric emptying of solid dosage forms. Due to the 9-h time limit, it was only possible to obtain a reliable value for the median caecum arrival time, and hence the SIT time, for the light 12.2-mm diameter tablets. This was just within the reported range of literature values for the SIT time of dosage forms. Estimates of the SIT times for the other dosage forms were greater than those usually reported. There was no evidence that the large single unit tablets were more variable in their gastrointestinal transit than the multiple unit tablet system.

References

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

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

Devereux, J. E. (1987) *Gastrointestinal transit of multiple unit dosage forms*. PhD Thesis, University of London, London, UK

EMEA (1999) *Note for guidance on quality of modified release products*. Available at: http://www.emea.europa.eu/pdfs/human/qwp/060496en.pdf

Khosla, R., Davis, S. S. (1998) Gastric emptying and small and large bowel transit of non-disintegrating tablets in fasted subjects. *Int. J. Pharm*. **52**: 1–10

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

Munday, D. L., Fassihi, A. R., de Villiers, C. (1991a) Multiple dose in vivo evaluation of oral controlled release capsule of theophylline containing film-coated mini-tablets in beagle dogs. *Int. J. Pharm*. **73**: 89–93

Munday, D. L., Fassihi, A. R., de Villiers, C. (1991b) Bioavailability study of oral theophylline controlled release capsule containing film-coated mini-tablets in beagle dogs. *Int. J. Pharm*. **69**: 123–127

Podczeck, F., Newton, J. M., Yuen, K. H. (1995) The description of the gastrointestinal transit of pellets assessed by gamma scintigraphy using statistical moments. *Pharm. Res*. **12**: 376–379

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

Podczeck, F., Course, N. C., Newton, J. M., Short, M. B. (2007) The influence of non-disintegrating tablet dimensions and density on their gastric emptying in fasted volunteers. *J. Pharm. Pharmacol.* **59**: 23–27

Standring, S. (2005) In: Standring, S. (ed.) *Gray's anatomy: the anatomical basis of clinical practice*, 39th edn. Elsevier Ltd, Edinburgh

Yuen, K. H., Desmukh, A. A., Newton, J. M., Short, M. B., Melchor, R. (1993) Gastrointestinal transit and absorption of theophylline from multiparticulate controlled release formulation. *Int. J. Pharm.* **97**: 61–77

Wilding, I. R., Coupe, A. J., Davis, S. S. (2001) The role of gamma scintigraphy in oral drug delivery. *Adv. Drug Deliv. Res.* **46**: 103–124