The Description of the Gastrointestinal Transit of Pellets Assessed by Gamma Scintigraphy Using Statistical Moments

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The gastrointestinal transit of multiple units (e.g., pellets), as determined by gamma scintigraphy, has been characterized by the application of statistical moments. Stomach emptying profiles can be described comprehensively by Mean Gastric Residence Time (MGRT) and Variance of Gastric Residence Time (VGRT) and caecum arrival data by Mean Caecum Arrival Time (MCAT) and Variance of Caecal Arrival Time (VCAT). This maximizes the data available, which is not the case when only described as 50% values. The statistical moments provide different information about the data observed compared to the classical descriptors, as there was only limited correlation between these two sets of parameters. Statistical moments therefore provide an important quantification of the process studied, and they can be used in any statistical test, where it is required to compare different experimental conditions.

KEY WORDS: gamma scintigraphy; gastrointestinal transit; mean caecum arrival time (MCAT); mean gastric residence time (MGRT); pellets; statistical moments.

INTRODUCTION

Gamma scintigraphy has widely been used to assess the position of dosage forms such as pellets (1), tablets (2), gels and suspensions (3), and food (4). In the case of a tablet an emptying time from the stomach or an arrival e.g. in the caecum can be determined as an event that happens between two measuring times of the radioactive signal. The accuracy with which this event can be described depends strongly on the time interval between the measurements taken. The monitoring of multiple solid dosage forms such as pellets or microcapsules, or that of semisolids such as gels, suspensions or food is more difficult, because these preparations are not transported as one unit through the gastrointestinal tract. The emptying of the stomach might take between a few minutes and several hours, and the arrival in the caecum also appears as an interval. Hence, reports of such data often include the complete scintigraphic profiles. Since the comparison of profiles as a whole is complicated, many authors use single numbers to characterize the average behaviour of emptying or arrival. The t_{50} value, where 50% of the test sample (e.g., pellets) has been emptied from the stomach or has arrived in the caecum, is often used. These values are taken from the graphical presentation of the percentage test sample remaining in the stomach or arriving in the caecum as a function of time. Again the frequency between the measuring time points is crucial for the accuracy of the values derived. Watts et al. (5) report a "Mean Residence Time (MRT)" for microparticles in the ascending colon. Although they give no mathematical explanation about how they have derived this value, a better description would be t_{50}, since they write "The mean residence time of 50% of the administered radioactivity . . .". The parameter MRT, however, has been clearly defined by Dost (6) and is based on statistical moments. With the exception of perfect zero-order kinetics, which does not apply to the gastrointestinal transit, the MRT never equals the time for exactly 50% of radioactivity to leave, and it is about 63% for a first-order process (7). The incorrect use of the abbreviation MRT for t_{50} causes confusion and should have been avoided.

The presentation of t_{50} values only has many disadvantages. First, it can be difficult to determine t_{50} because of irregular shaped profiles (see Fig. 1). It could be argued, that longer time intervals between the measurements smooth the scintigraphic curves, but they also involve the risk of missing sudden events such as a "housekeeper wave", which could empty a large quantity of the stomach content in a very short time interval. In such a case t_{50} becomes shifted to longer time values than actually occurred. Secondly, t_{50} does not contain any information about the distribution of emptying or arrival times. Hence, at least an interquartile range or other measure of spread should be calculated, but unfortunately, most authors fail to do so. Finally, t_{50} is in fact just based on two points of the scintigraphic profile, but a measure of an average emptying or arrival time should be based on a consideration of the whole process. With respect to that last remark, Grimes and Goddard (8) introduced the 'emptying index' to describe gastric emptying curves. The index was calculated from $[(1-f_T)/A]$, where f_T = fraction of the initial volume of radioactive labelled preparation remaining in the stomach at the last observation time, and A = area under the normalized emptying curve. Although this index considers all measuring points via A, there are some disadvantages in its use. The index is 1.0 regardless of the shape of the emptying profiles for a complete emptying, which is the aim of a good study. Mainly, however, the index is not an equivalent for an average emptying time. First, because it is a dimensionless number between 0 and 1, and secondly, because from a numerical point of view the index can have similar values for different values of A, if f_T changes proportionally, which occurs especially for fixed final observation times as used in (8).

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NOTATIONS: A, Area under the normalized emptying curve; AUC, Area Under Curve; ABC, Area Between Curve; I_{0-100}, Interval between start and finish of gastric emptying; MRT, Mean Residence Time; MGRT, Mean Gastric Residence Time; MCAT, Mean Caecum Arrival Time; P_{max}, maximal cumulative concentration in the target organ; P_t, percentage test preparation detected in the target organ at time t; VGRT, Variance of Gastric Residence Time; VCAT, Variance of Caecum Arrival Time; f_t, fraction of the initial volume of radioactive labelled preparation remaining in the stomach at t_{max}; r_s, rank correlation coefficient; t_{50}, time, where 50% of the test preparation has left or reached the target organ; t_{max}, last observation time.

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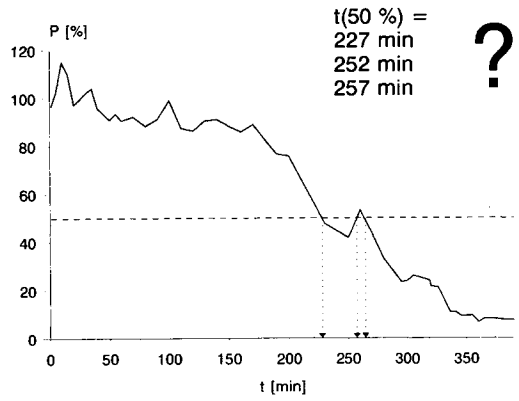

Fig. 1. Gastric emptying curve of Theophylline pellets and the deduction of a t_{50} value (data taken from Yuen et al. (1)).

Hence the following work investigates the possibility of describing the emptying or arrival of multiparticulate or semisolid/liquid test preparations based on statistical moments using data from a gamma scintigraphy study of Theophylline pellets, described in an earlier paper (1).

THEORY

Stomach emptying or caecum arrival results are usually presented as cumulative profiles. After normalization such profiles are an estimate of the distribution function F(t) of the time, in which one single unit of the test preparation has been emptied from or arrived at the target organ. Any such empirical distribution function can be described mathematically by the measures of central tendency and dispersion (9).

Usually the emptying process of a multiunit test preparation from the stomach is presented as amount of preparation retained at time t, whereas the caecum arrival is described as amount of preparation arrived at time t. Therefore, the central tendency of the two processes should be the Mean Gastric Residence Time (MGRT) of the test preparation in the stomach and the mean arrival time in the caecum ("Mean Caecum Arrival Time", MCAT). The MGRT has to be calculated from a Σ^--plot, whereas the MCAT results from a Σ^+-plot, and thus the mathematical development of both figures and their variances (VGRT and VCAT respectively) is slightly different. Figure 2 illustrates the important features on which the calculation is based.

The MGRT (see Fig. 2a) and VGRT (gastric emptying) can be obtained using simple trapezoidal rules (10):

$$MGRT = \frac{\int_0^{t_{max}} t \cdot P_t dt}{AUC} \quad (1)$$

$$VGRT = \frac{\int_0^{t_{max}} t^2 \cdot P_t dt}{AUC} - MGRT^2 \quad (2)$$

where AUC = area under the emptying curve, P_t = percentage test preparation remaining in the stomach at time t. The value of MCAT and VCAT (caecum arrival) can be calculated according to Brockmeier & von Hattingberg (11) and Voegele et al. (12):

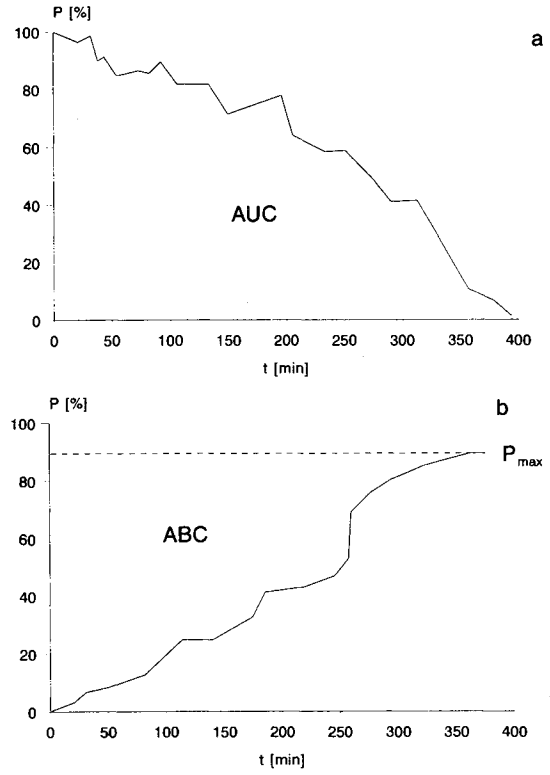

Fig. 2. Basics of the calculation of MGRT and MCAT 2a, Σ^--plot describing gastric emptying; 2b, Σ^+-plot, describing caecum arrival (simulated graphs) P, percentage of test preparation detected in the target organ, t, time, AUC, area under (emptying) curve, ABC, area between arrival curve and asymptotic maximum concentration, P_{max}, maximal cumulative concentration in the target organ (note, that P_{max} is not necessary 100%!).

$$MCAT = \frac{ABC}{P_{max}} = \int_0^{t_{max}} t \cdot f(t)\, dt \quad (3)$$

$$VCAT = \int_0^{t_{max}} t^2 \cdot f(t)\, dt - MCAT^2 \quad (4)$$

where $\int f(t)\, dt = \int d(F) = F(t)$.

RESULTS AND DISCUSSION

The gastrointestinal transit of Theophylline pellets has been studied using gamma scintigraphy by Yuen et al. (1). This particular study investigated the stomach emptying and the caecum arrival of the pellets when administered after a fasting period in comparison to the administration after a standard breakfast. The paper includes some of the gamma scintigraphy profiles, which represent the average behaviour of the pellet formulation, but all calculations in the current work have been made from the original observations. The authors of the previous paper used values of t_{50} and the time interval between start of emptying and completed emptying to characterize the stomach emptying numerically, and they used values of t_{50} for the caecum arrival of the pellets. Table I summarizes their results.

Table II lists the AUC, MGRT, VGRT, ABC, MCAT and VCAT values derived from the gamma scintigraphy measurements using eq. 1–4.

Table I. Stomach Emptying and Caecum Arrival Results for Theophylline Pellets Administered Under Fasted and Fed Conditions (data from Yuen *et al.* (1))

Volunteer	Stomach emptying t_{50} [min]	Stomach emptying I_{0-100} [min]	Caecum arrival t_{50} [min]
Fasted			
1	136	92	425
2	88	157	390
3	11	9	239
4	8	14	244
5	154	95	279
6	24	21	342
Fed			
7	176	180	454
8	246	220	503
9	183	79	318
10	179	170	413
11	183	150	388
12	118	106	412

Figure 3 compares the MGRT values with the t_{50} values of the stomach emptying phase. There is obvious correlation between the two measures, both in the fasted and in the fed state. A rank correlation test (13) was applied to quantify the relationship instead of using least-square correlation analysis, because the estimated t_{50} values are based on radioactivity counts, which possess Poisson distributed errors, while least-square algorithms require a normal distribution of the errors. Although the rank correlations between MGRT and t_{50} values are significant (r_s = 0.886 and 0.843, fasted and fed state respectively), there is not a 100% correlation. Considering the fact that MGRT values are based on the whole emptying process representing a statistical emptying value of all single units (pellets) administered with a normal distributed error, but t_{50} values are just taken from two measuring points during the emptying process, this should not be

Table II. Stomach Emptying and Caecum Arrival Results for Theophylline Pellets Administered Under Fasted and Fed Conditions Characterized Using Statistical Moments

Volunteer	Stomach emptying AUC [%min]	Stomach emptying MGRT [min]	Stomach emptying VGRT [min^2]	Caecum arrival ABC [%min]	Caecum arrival MCAT [min]	Caecum arrival VCAT [min^2]
Fasted						
1	12793.3	75.7	2719.9	26606.8	359.1	6980.2
2	10147.4	78.2	3653.4	37360.4	389.2	5032.3
3	1062.8	6.2	15.9	21109.0	250.1	2650.9
4	839.5	6.5	28.8	14265.8	206.8	1726.2
5	13229.0	79.8	2266.1	21748.5	271.9	4776.4
6	2848.9	17.9	179.1	28955.2	349.3	2445.7
Fed						
7	15254.8	99.2	4176.2	35088.0	455.7	3973.6
8	24158.7	141.4	8372.2	40422.5	491.8	777.6
9	17441.6	100.9	3950.4	32957.0	306.0	2130.6
10	16937.2	97.8	3843.0	29858.7	393.9	1958.3
11	16974.9	98.7	3850.4	42445.8	415.7	2899.4
12	10854.8	63.9	1830.5	30774.5	414.8	4922.8

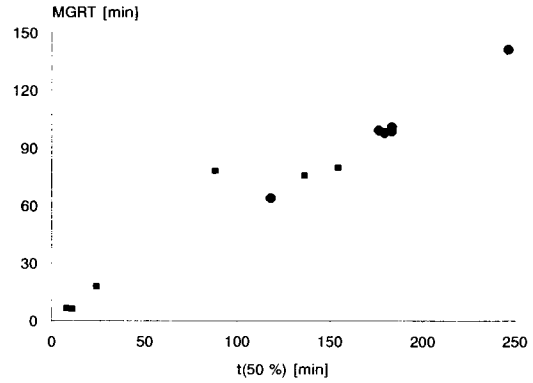

Fig. 3. Comparison between MGRT and t_{50} values reported by Yuen et al. (1) for fasted (■) and fed (●) volunteers.

surprising. Furthermore the MGRT values are smaller than the t_{50} values. Hence MGRT values give different information about the emptying process, which justifies the need for this more complex and less subjective method.

One argument against MGRT could be the fact that its calculation is based on the whole emptying profile measured, and thus a similar information could be obtained theoretically from the emptying interval. Therefore, the MGRT values were compared with the total emptying interval (see Fig. 4). However, again there is some rank correlation (r_s = 0.943 and 0.628, fasted and fed state respectively), but in particular the nonsignificant r_s value in the fed state experiment indicates, the MGRT and total emptying intervals provide different information. This is supported by the fact that 4 MGRT values of the fed state study and 3 MGRT values of the fasted state are similar for completely different total emptying intervals (see Fig. 4).

The rank correlation between the VGRT and both t_{50} and the total emptying interval ($r_s(t_{50}$, fasted) = 0.714, $r_s(t_{50}$, fed) = 0.643, $r_s(I_{0-100}$, fasted) = 0.943, $r_s(I_{0-100}$, fed) = 0.600) is limited. There is only one significant relationship (I_{0-100}, fasted), compared to 3 nonsignificant r_s values. Any variance, although influenced by the two tails of the distribution function, cannot be directly related to the total width of the distribution (9). Hence VCAT and the total emptying interval supply different information about the system under investigation.

Finally, Figure 5 compares the MCAT and the t_{50} values

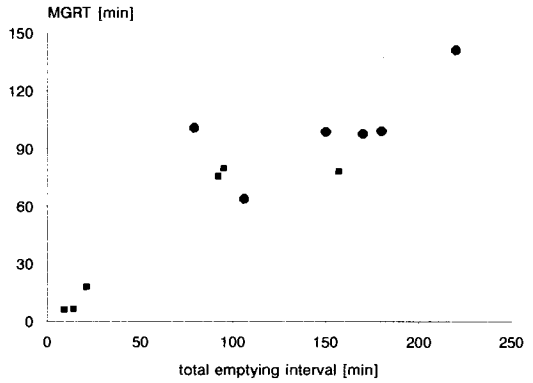

Fig. 4. Comparison between MGRT and emptying interval reported by Yuen et al. (1) for fasted (■) and fed (●) volunteers.

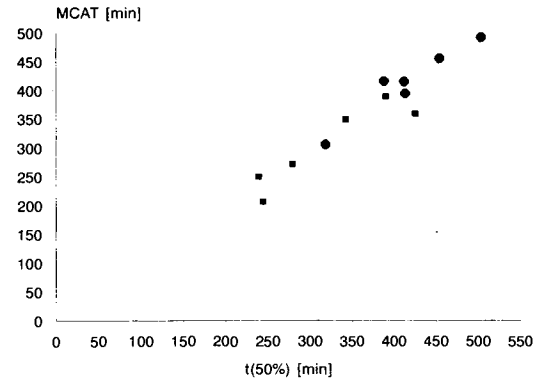

Fig. 5. Comparison between MCAT and t_{50} values reported by Yuen et al. (1) for fasted (■) and fed (●) volunteers.

for caecum arrival. Although there is again a tendency for MCAT to be related to t_{50} (r_s = 0.886 and 0.771, fasted and fed state respectively), the two sets of values obviously differ and in particular in the fed state the relationship is not significant, supporting the statements made above.

Statistical moments can be used in any statistical investigation which considers different results in experiments. This is also the case for t_{50} or interval values. Table III summarizes the statistical comparison between the fasted and fed state experiments using the statistical moments calculated. All 3 emptying parameters (AUC, MGRT, VGRT) are significantly different for fasted and fed experiments, suggesting both delayed emptying due to food and induced changes in stomach motility, because the VCAT values indicate different widths of the emptying distributions.

The caecum arrival of the pellets is also significantly different (ABC, MCAT), but the motility of the transport organ (small intestine) appears not to be effected by the intake of food (VCAT not significantly different). In this respect the statistical results agree with those reported by Yuen et al. (1), who analyzed the results in terms of t_{50} and total emptying interval.

Table III. Statistical Comparison Between Pellet Transport Through the Gastrointestinal Tract in Fasted and Fed State Experiments, Based on Statistical Moments ($\bar{x} \pm s$, n = 6) t_{indep}, t-value (independent t-test); $t_{10;P=0.05} = 2.23$ (tabulated value)

Parameter	Fasted	Fed	t_{indep}
Stomach emptying			
AUC	6820.2 ± 5873.8	16937.0 ± 4294.9	3.41
MGRT	44.0 ± 37.3	100.3 ± 24.6	3.09
VGRT	1477.2 ± 1601.3	4337.0 ± 2155.2	2.61
Caecum arrival			
ABC	25007.6 ± 7898.6	35257.8 ± 5155.9	2.66
MCAT	304.4 ± 71.7	413.0 ± 63.0	2.79
VCAT	3935.3 ± 1996.5	2777.0 ± 1492.4	1.14

It can be concluded that the application of statistical moments to gamma scintigraphy data in terms of characterizing the emptying or arrival of a test sample from or in a target organ is a possibility to improve the interpretation of such data. Statistical moments allow a comprehensive description of the data observed, and they can be used as a basis of statistical tests to compare gamma scintigraphy curves.

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