that the fitting is complicated by the fact that A_{1B} is also dependent on k_{1E}, although far less markedly than A_{EB}.

We have chosen not to attempt such pharmacokinetic modeling at the present time, not only because of the incompleteness of our data but because additional analyses of the effects of nonuniform bile flow rate should be undertaken. It certainly appears that the primary effect of nonuniform bile flow rates is on k_{1E} and that our treatment of this effect describes the data. However, there are secondary effects which should also be addressed.

One example would be the effect of bile flow rate on the thickness of the diffusion layer adjacent to the bile canalicular membrane, which represents an additional barrier to the transport between the hepatocyte and intrahepatic bile. The diffusion layer thickness within a cylindrical tube is discussed by Levich (11) and it can be shown that $\delta \alpha v_0^{-1/3}$ (9), where δ is the diffusion layer thickness and v_0 is the maximum flow velocity at the axis of the tube. For a nonelastic tube of constant radius, v_0 is directly proportional to the flow rate, Q_B. Thus, passive diffusion between the hepatocyte and the canaliculi would proceed at a rate proportional to $Q_B^{1/3}$.

Nonuniform bile flow rates result in nonuniform hydrostatic pressure within the canaliculi (12), which, in turn, could affect the effective diameter of any pores existing in the canalicular membrane. If the transport between hepatocyte and intrahepatic bile involves pore filtration (12), then this secondary effect of nonuniform bile flow rates could become important. The relationship between pore size and pore filtration rate is discussed by Lakshminarayanaiah (13).

Lightfoot (14) discusses flow through elastic ducts and indirectly indicates the effect that flow rate might have on the rate of transport across the duct wall. It could also be pointed out that the elution approach discussed above is quantitatively correct only if there is perfect mixing within the intrahepatic bile compartment.

All of the secondary points mentioned above suggest that further analysis is required before biliary excretion data can be used to accurately describe a model for hepatobiliary uptake and elimination. However, if the objective is merely to use biliary excretion data to support a crude model which could be used for predictive (*i.e.*, dosing) purposes, then our treatment of nonuniform bile flow rate should be of some value.

Lastly, it should be noted that the elution approach discussed above could possibly be applied to other flow rate-dependent physiological processes. Whereas the effects of blood flow rate have received considerable attention in the pharmacokinetic literature, the effects of nonuniform flow rates on elimination *via* urine, milk, saliva, lacrimal fluid, *etc.* should account for some of the fluctuation or scatter frequently observed in that type of data.

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Radiotelemetric Method for Evaluating Enteric Coatings *In Vivo*

J. B. DRESSMAN *x and G. L. AMIDON *

Received April 4, 1983, from *INTERx, Merck Sharp & Dohme Research Laboratories, Lawrence, KS 66044.* Accepted for publication July 20, 1983. *Present address: College of Pharmacy, University of Michigan, Ann Arbor, MI 48109.

Abstract □ A radiotelemetric method for the *in vivo* evaluation of enteric coating performance is described, and its advantages and disadvantages are compared with those of other available methods. Hydroxypropyl methylcellulose phthalate was used as the test enteric coating. Four dogs were administered several batches of enteric-coated tablets containing buffers. Tablet disintegration was determined by radiotelemetric detection of the pH drop in the upper intestine due to release of the buffer. Premature rupture of the coating in the stomach was detected by a rise and then a fall in gastric pH prior to gastric emptying. The average gastric emptying time was 80 ± 18 min (*SEM*), while the average time for a tablet to disintegrate in the upper intestine was 14.2 ± 2 min. The average disintegration time was not affected by a change in the batch (for a given tablet core pH) or the dog used, suggesting that the method yielded readily reproducible results. Although there was little correlation with *in vitro* disintegration times, the method gave results similar to those reported in the literature for the same enteric coating in a human study. Of the formulations tested, it was concluded that buffering the core to pH 4 was most suitable for studying enteric coating performance.

Keyphrases □ Enteric coating—*in vivo* disintegration, radiotelemetry, hydroxypropyl methylcellulose phthalate □ Hydroxypropyl methylcellulose phthalate—*in vivo* disintegration, tablet coating, radiotelemetry □ Radiotelemetry—*in vivo* disintegration, hydroxypropyl methylcellulose phthalate tablet coating

Enteric coating of dosage forms has been used in several ways to improve drug delivery. For example, the bioavailability of acid-labile drugs such as erythromycin can be improved by avoiding exposure of the drug to the gastric contents (1). A second reason for using an enteric coating is to avoid gastric irritation caused by drugs such as aspirin (2). Enteric coating has also been used to delay the release of a drug taken at bedtime with the aim of ensuring therapeutic blood levels when the patient awakes (3).

Several methods are available for evaluating enteric coatings. A widely used *in vitro* test is the USP disintegration test for enteric-coated tablets (4). *In vivo* methods of following the

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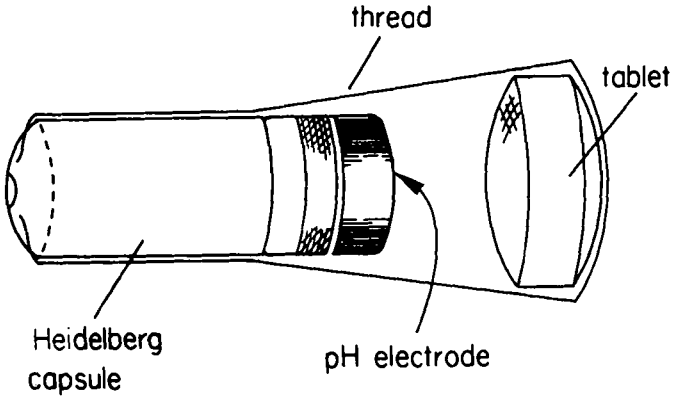

Figure 1—*Schematic for attachment of the enteric-coated tablet to the Heidelberg pH detector capsule.*

fate of dosage forms in the GI tract utilize techniques such as endoscopy (5), X-rays (3, 6), external scintigraphy (7-9), whole body scintillometry (10, 11), or a combination of these techniques (12). Pharmacokinetic data (13, 14) can also be used to estimate release times for enteric-coated products. The USP and similar *in vitro* tests have been compared with *in vivo* methods in several reports (3, 6, 15). Results indicate that *in vitro* tests tend to underestimate the disintegration time in the human GI tract. However, they provide an inexpensive and convenient way of screening the performance of the enteric coating. *In vivo* techniques have various advantages and disadvantages. The most obvious advantage is that the coating is tested under the actual conditions of use. Endoscopic, X-ray, and scintigraphic techniques have the added attraction of providing visual information. For endoscopy and X-ray techniques, data are collected at intervals rather than continuously, so exact gastric emptying and disintegration times cannot be obtained. With X-ray, scintillometry, and external scintigraphy, care must be taken to minimize exposure of the subject to radiation, although this is less of a problem in the latter cases. All the techniques for *in vivo* studies described above require either a skillful technical staff, expensive equipment, or both. Pharmacokinetic analyses of blood levels or urinary excretion data do not necessitate exposure to radiation, but there is the disadvantage of being unable to distinguish long gastric emptying times from slow enteric-coat dissolution times.

In the current report, a radiotelemetric method for the *in vivo* evaluation of enteric coatings is described, and its advantages and disadvantages are compared with those of other available methods.

EXPERIMENTAL SECTION

Tablets—Appropriate ratios of citric acid to citrate were chosen to formulate buffered tablet cores at pH 3, 4, and 5. The pH values were chosen so that disintegration/dissolution of the tablet in the upper intestine would produce an easily detectable pH drop (typically from pH ≥6 to the pH of the tablet buffers). In addition, if the coating failed, causing release of the buffers in the stomach, there would be a detectable upward shift in the gastric pH. The formula for pH 4 tablets is as follows: disodium citrate[1], 396 mg; citric acid[2], 144 mg; microcrystalline cellulose NF (PH 101)[3], 100 mg; modified cellulose gum[4], 64 mg; and lubricant[5], 14 mg.

After passing all the powders, except the lubricant, through a 40-mesh screen, they were mixed together and then wet granulated with a 50:50 mixture of ethanol–methylene chloride in a planetary blender[6]. The granules were dried at 55°C for 2 h, and the lubricant was added. Tablets weighing 720 mg were compressed using a single-punch tablet press[7]. The tablets were coated with hydroxypropyl methylcellulose phthalate[8] in a small laboratory pan coater. Other batches were prepared using the method outlined. To obtain a pH 3 buffering system, 192 mg of citric acid and 70 mg of sodium citrate[9] per tablet were used. For pH 5, the amounts were 64 mg and 290 mg, respectively. Coating weights varied from 20 to 34 mg per tablet, depending on the batch.

***In Vitro* Disintegration Test**—The USP disintegration test (4) for enteric-coated tablets was used to determine the *in vitro* disintegration time for each batch. Enzymes were omitted from the disintegration media; otherwise, the method was followed as described. Disintegration time was recorded as the time required, after transfer to simulated intestinal fluid, for all material to pass through the screen.

Animals—Four healthy male beagle dogs, ranging in weight from 10.6 to 17.3 kg, were selected for study. Before each experiment, the dogs were fasted for 24 h. Control GI pH profiles were obtained by administering a calibrated Heidelberg capsule[10] followed by 20 mL of water. The control profiles were used for comparison with profiles obtained after administering the enteric-coated tablets.

Radiotelemetric Technique—For each experiment, a Heidelberg capsule was calibrated using pH 1 and pH 7 standard buffer solutions. The enteric-coated tablet was then attached to the capsule with thread and acrylic glue (see Fig. 1). An antenna was strapped around the midriff of the dog to detect output from the Heidelberg capsule. The capsule–tablet combination was administered followed by 20 mL water, and the pH was continuously monitored using the radiotelemetric system[10] for a 6-h period. Important parameters such as baseline gastric pH, gastric emptying time, intestinal pH subsequent to gastric emptying, and time of onset of core disintegration were determined by analyzing the pH–time profile.

Statistical Analysis—The following statistical tests were applied to the data:

1. Linear regression to determine the degree of correlation between gastric emptying time and disintegration time, and between *in vivo* and *in vitro* disintegration time;
2. Analysis of variance to assess dog-to-dog, pH-to-pH, and batch-to-batch variation in the time of onset of disintegration *in vivo;*
3. Bartlett's test to analyze scatter differences between different groups of data in the *in vivo* tests.

Table I—Times for Onset of Disintegration of Enteric-Coated Buffered Tablets After Leaving the Stomach

Batch	Time for Onset, Min				
	Dog 62	Dog 72	Dog 73	Dog 74	Mean ± *SEM*
pH 3					
189/257	35	12 —[a]	—[b]	35	27.5 ± 7.5
194/080	20	10	13	11	13.5 ± 2.3
194/128	24	8	13	25	17.5 ± 4.2
pH 4					
189/096	6 18 —[a]	8 5	—[c] 5 10	40 8	12.5 ± 4.2
194/101	16	18	12	—[b]	15.3 ± 1.7
pH 5					
194/029	5	2	4	4	3.8 ± 0.6
Mean ± *SEM*	17.7 ± 3.9	9 ± 1.9	9.5 ± 1.6	20.5 ± 6.1	14.2 ± 2

Statistical Analysis		
Treatment	ANOVA	Bartlett's Test
Between dogs	NS	$p < 0.05$
Between pH values	$p < 0.05$	$p < 0.05$
Between batches at pH 3	NS	NS

[a] Failed in stomach. [b] Not tested. [c] Disintegration not observed.

RESULTS AND DISCUSSION

Performance of an enteric coating is evaluated by interpreting the pH profile generated by the radiotelemetric technique. Figure 2A shows a typical pH profile of the canine GI tract following administration of a Heidelberg capsule

[1] Fluka AG.
[2] Fisher Chemical Co.
[3] Avicel; FMC Corp.
[4] Type SD-711, Ac-Di-Sol; FMC Corp.
[5] Lubritab; Mendell.
[6] Model C100-T; Hobart Corp.
[7] Model 519-2; Stokes Equipment.
[8] HP-50; Shinetsu Chemical Co., Japan.
[9] Mallinckrodt.
[10] Telefunken, West Germany.

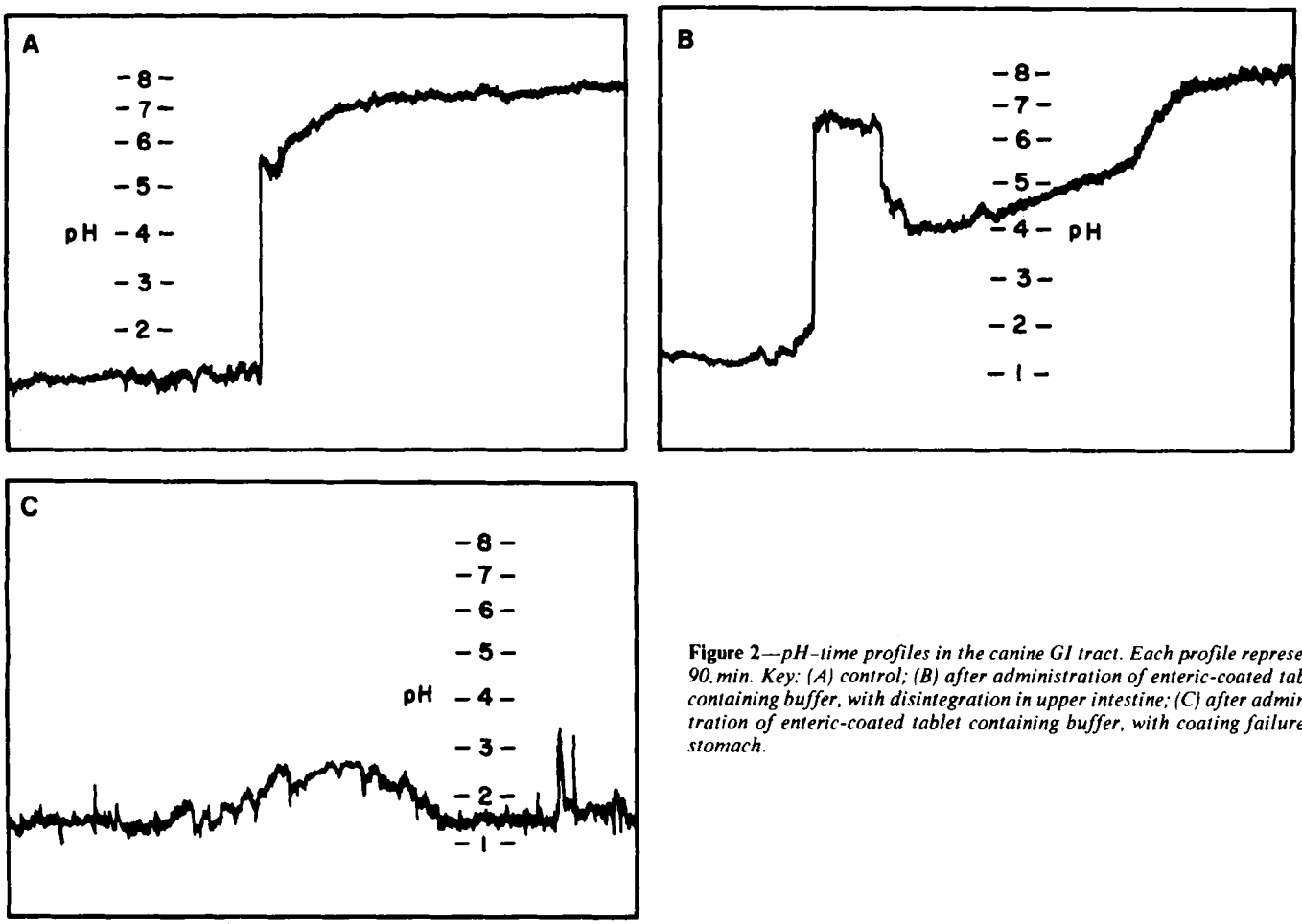

Figure 2—*pH-time profiles in the canine GI tract. Each profile represents 90 min. Key: (A) control; (B) after administration of enteric-coated tablet containing buffer, with disintegration in upper intestine; (C) after administration of enteric-coated tablet containing buffer, with coating failure in stomach.*

(control). In most cases, the gastric pH ranges from a pH slightly below pH 1 to ~2. Gastric emptying causes a sharp rise in pH to a value of 5.5–6.5, reflecting contact of the capsule with duodenal fluid. Thereafter, the pH rises gradually to ≥7.5. Note that the accurate measuring range of the Heidelberg capsule is pH 1–8, with a measuring error of ±0.5 pH units[11].

Unless the enteric coating ruptures prior to gastric emptying, the gastric pH after administration of an enteric-coated buffered tablet attached to a Heidelberg capsule is very similar to that observed in the control experiment. However, as shown in Fig. 2B, the pH profile in the upper intestine is altered distinctly when an enteric-coated buffered tablet is given. The pH rises at gastric emptying as in the control experiment, but when the coating dissolves the buffer materials are released and the pH drops rapidly. The time between gastric emptying and the start of the pH drop is designated as the time of onset of disintegration (t_{onset}). This method does not enable detection of completion of the core disintegration process. After the initial pH drop, there is a gradual rise in pH as the buffer materials are diluted and neutralized by secretion of bicarbonate ions until normal intestinal pH is recovered. Failure of the enteric coating to withstand gastric pH is detected by an increase in gastric pH from the baseline value, followed by a gradual return to the baseline value as shown in Fig. 2C.

A statistical analysis of the disintegration times for various formulations of enteric-coated buffered tablets in four dogs is presented in Table I. Twenty-nine tablets were administered: two failed in the stomach, one did not disintegrate within the observation period, and the rest disintegrated in the upper small intestine as expected. The mean disintegration time was 14.2 ± 2 min (*SEM*). Analysis of variance indicates that the mean disintegration time is not significantly different between dogs or between batches of tablets. However, there is a significant effect due to the tablet core pH ($p < 0.05$) with shorter mean disintegration time at pH 5 than at pH 3 or pH 4. Applying Bartlett's test to the results reveals that scatter in the disintegration time varies between dogs and between core pH values, but is not significantly affected (at a 95% confidence level) by the tablet batch. Overall, the statistical analysis suggests that the mean disintegration time is reproducible on both a dog-to-dog and batch-to-batch basis. Therefore, the radiotelemetric method is a reliable means of comparing enteric coating performance, provided tablet cores are formulated at the same pH. A convenient pH choice is pH 4, as in this case both gastric failure of the coat and disintegration of the coat in the upper intestine produce readily observable perturbations in pH.

The degree of correlation between *in vivo* and *in vitro* results can be judged by comparing the disintegration times presented in Table II. Linear regression analysis indicates that there is very little relationship between *in vivo* and *in vitro* disintegration test results ($r = -0.09$). The *in vivo* t_{onset} may be shorter, longer, or similar to the t_{disint} observed in the USP disintegration test for enteric-coated tablets; the times observed differed by as much as a factor of five. These results indicate that the USP test may not always be capable of predicting the *in vivo* performance of enteric coatings.

The extent of correlation between an *in vitro* test and results obtained *in vivo* depends on how closely the *in vitro* experimental conditions model the *in vivo* situation. Some specific differences between the USP test and the *in vivo* conditions encountered in this study include the following. The pH at which the hydroxypropyl methylcellulose phthalate coating used in this study begins to dissolve is pH 5.0[8]. The pH after gastric emptying in the dogs was typically between 5.5 and 6.5 (range 4.5–7.0), considerably lower than that of simulated intestinal fluid used in the *in vitro* test. This discrepancy in the *in vivo* and *in vitro* pH values, combined with the variation in the *in vivo* intestinal pH profile, may have contributed to the poor correlation in disintegration times for the coating studied. Another factor may have been the difference in the disintegration endpoints. *In vivo*, the t_{onset} was taken as the time

Table II—*In Vitro* and *In Vivo* Disintegration Times for Enteric-Coated Buffer Tablets[a]

Batch	pH	t_{disint} *in vitro*, s Mean ± *SEM*	*n*	t_{onset} *in vivo*, s Mean ± *SEM*	*n*
189/257	3	<600	3	1620 ± 456	3
194/080	3	3270 ± 118	6	810 ± 138	4
189/096	4	157 ± 10	6	750 ± 252	8
194/101	4	874 ± 102	6	918 ± 102	3
194/029	5	817 ± 71	6	225 ± 36	4

[a] Correlation coefficient = −0.09.

[11] Instruction Manual, Telefunken pH measurement system.

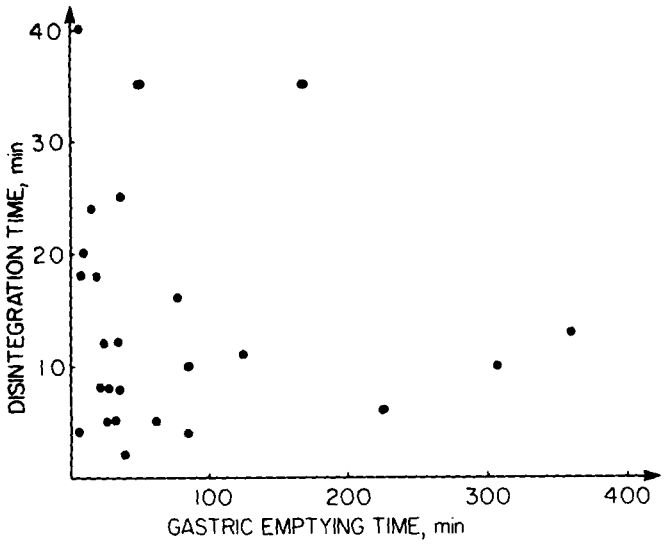

Figure 3—*Time of onset of disintegration of enteric-coated tablets in canine upper intestine* versus *gastric emptying time.*

when the pH first started to fall, whereas *in vitro* the time taken for complete disintegration was measured. Differences in other factors such as agitation and enzyme levels may also have played a role.

Two studies in the literature contain data which provide a comparison of disintegration times in humans with those observed in *in vitro* experiments (3, 14). In both cases the USP or similar test predicted shorter disintegration times than were observed *in vivo* [31 min *versus* >50 min (14), and <20 min *versus* 96 min mean disintegration time (3)]. A further study of *in vitro* and *in vivo* disintegration times of five batches of tablets in dogs (6) showed a variable ratio between *in vivo* and *in vitro* disintegration times, with up to a twofold difference in values. In that study, the batches were coated with different enteric coatings, so the variation between *in vivo* and *in vitro* results may have depended to some extent on the coating type. The value of *in vitro* disintegration tests has been further discussed by Aiache *et al.* (16).

In contrast to the poor *in vivo–in vitro* correlation, there appears to be some correlation between canine and human results. The data presented in this paper show that the average time for onset of disintegration in the canine upper intestine is 14.2 ± 2 min. This time compares closely with the time reported for disintegration in humans of tablets coated with hydroxypropyl methylcellulose phthalate. Using an endoscopic technique, Ehrhardt *et al.* (5) reported a disintegration time of 15 min after gastric emptying. This agreement suggests that use of the radiotelemetric technique in dogs gives a reasonable prediction of disintegration times in humans, at least for hydroxypropyl methylcellulose phthalate-coated tablets.

It has been proposed in the literature that the disintegration time may be dependent on the gastric emptying time. Blythe *et al.* (3) suggested that disintegration time is shorter for tablets which reside in the stomach for a long time than for those which are emptied quickly. In the current study, however, there was no significant correlation ($r = -0.08$) between gastric emptying time and disintegration time (Fig. 3).

The main advantage of the radiotelemetric method over other available methods is that the onset of disintegration of the enteric-coated tablet in the upper intestine can be accurately determined since the pH of the luminal contents is monitored continuously. It is also possible to pinpoint coating failures such as rupture in the stomach and nondisintegration in the intestine. The technique does not expose the subject or the investigators to radiation, as do other commonly used techniques. Because the dimensions of the Heidelberg capsule are fairly small (diameter, 7 mm; length, 20 mm) there is little chance of obstruction in the GI tract; no obstruction problems were encountered in the dogs studied. The Heidelberg capsule has little apparent effect on the gastric emptying of single-unit dosage forms; in the current study mean gastric-emptying time for the capsule-tablet combination was 80 ± 18 min (*SEM*) with a range of 5–360 min compared with a range of <30 min to >7 h (median 96 min) for tablets in the radiographic study by Blythe *et al.* (3).

The chief limitation of the method described in this report is that it is applicable only to monolithic dosage forms. A way of attaching more than one particle to the Heidelberg capsule must be devised, so that the method can be extended to evaluating enteric coat performance on multiparticulates. The fact that buffers must be incorporated into the test dosage form presents no more of a limitation than including barium in tablets to be evaluated by X-ray or γ-emitters in tablets studied by scintigraphic techniques. The advantages over pharmacokinetic methods lie in the greater accuracy with which the disintegration time can be determined and in avoiding blood or urine collection. The radiotelemetric technique requires less experimental expertise and less expensive equipment than other techniques and provides a facile and accurate means of evaluating enteric coating performance *in vivo.*

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