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Research paper

Development of an enteric coating formulation and process for tablets primarily composed of a highly water-soluble, organic acid

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Abstract

The purpose of this study was to define coating conditions for the enteric coating of a highly water soluble, acidic tablet core. Acidic tablet cores containing a marker drug were separated into three groups and seal coated to coverage levels of 0% (uncoated, white), 1% (yellow), and 3% (tan) weight gains. By employing a 'color coding' scheme, the different seal coated tablets could be coated simultaneously to reduce the number of experiments and eliminate potential differences that may exist during separate coating processes. In addition, an allotment of each coded tablet type was sequentially numbered with a marker pen, weighed, and recorded in order to identify the precise level of enteric coating as well as to monitor the variability of a given coating operation. The tablets were coated with five Eudragit® L30D-based enteric formulations containing different amounts of plasticizer (10–20 parts) and talc (10–50 parts). During each enteric coating process, a predetermined amount of labeled tablets were removed after attaining 6, 8, and 10% weight gains. The labeled tablets were re-weighed, sorted, and then tested using USP disintegration and dissolution methods. Weight gain measurements of individual tablets indicated low coating variability (6.2% RSD) during the enteric coating processes. Dissolution results revealed that all enteric coat formulations inhibited drug release for 2 h in 0.1 N HCl. In contrast, it was found that tablets without a seal coat failed the USP disintegration test. In addition, seal coated tablets exhibited ca. 1.5–5 fold greater drug release at most intermediate sampling time points in phosphate buffer, pH 6.8, than tablets without a seal coat, suggesting that the dissolution of the latter was delayed by the generation of an acidic microenvironment at the interface of the enteric coat/acidic tablet core. Prior to enteric coating an acidic, highly water soluble substrate, a seal coat barrier should be applied to prevent retardation in drug release. A simple strategy utilizing color coding and tablet marking can be employed to test the effect of a seal coat, evaluate enteric coating formulations and process with minimal experimentation and analyses.

Keywords: Acidic core, Dissolution, Enteric coat, Organic acid, Seal coat

1. Introduction

Site-specific, drug delivery of a therapeutic agent to the intestinal region can be readily accomplished by the application of an enteric coating on a solid dosage form [1]. Commercially available polymers commonly employed for enteric coating consist of cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, copolymers of methacrylic acid and acrylic acid esters, and polyvinylacetate phthalate. In general, these substances are anionic polymers or copolymers which are insoluble in acidic media but acquire water solubility at near neutral pH values due to ionization of functional groups along the polymer chain [2,3].

It has previously been shown that the tablet core pH can affect the disintegration time of enteric coated tablets [4]. Specifically, enteric coated tablets with a core pH adjusted to 3 had a significantly longer in vitro disintegration time than similar tablets with a core pH of 5. More importantly, radiotelemetric measurements established that the in vivo disintegration times of enteric coated tablets with a core pH value of 3 was considerably longer than tablets with a core pH of five. This finding has been primarily attributed to a delay in dissolution of the enteric coat due to the suppression of ionization of the enteric polymers by the acidic core. As a result, tablets with a high proportion of an acidic therapeutic agent or acidic excipients would probably exhibit a retardation in dissolution if directly enteric coated. It is anticipated that the influence of the core pH on the dissolution of the enteric film could be overcome by the application of a polymer film barrier, i.e. seal coat, between the core and enteric coat. So far, the effect of the pre-application of a seal coat on both the disintegration time and dissolution profile of enteric coated tablets containing a large quantity of a highly acidic excipient has not been examined in detail.

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The primary objectives of the present study are: (1) to examine the role of a seal coat on the functionality of an enteric coat with a highly acidic tablet core, and (2) to optimize an enteric coat formulation composed of a plasticizer, detackifier, and enteric polymer for these tablets. A highly practical, systematic approach to accomplish these objectives is presented.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose NF/EP (Avicel® PH 101 and Avicel®PH 102) and croscarmellose sodium (Ac-Di-Sol®) were purchased from FMC Co., Philadelphia, PA. Mutchler Chemical Co., Inc., Westwood, NJ, supplied citric acid USP anhydrous powder. Povidone USP/EP K28-30 was obtained from BASF, Mt. Olive, NJ, and magnesium stearate of non-bovine origin was purchased from Mallinckrodt. CI-960 HCl, a Parke–Davis investigational anti-infective drug with a solubility of 97 and 0.60 mg/ml in 0.1 N HCl and pH 7.5 phosphate buffer (37°C), respectively, was utilized as a marker compound to facilitate evaluation of the coated tablets. Opadry® was obtained from Colorcon, West Point, PA. The components of the enteric coat formulation including Eudragit® L30D-55 30% aqueous dispersion, triethyl citrate, and talc USP (Altalc®400) were purchased from Röhm America, Inc., Somerset, NJ, Morflex, Inc., Greensboro, NC, and Luzenac America, Engelwood, CO, respectively.

2.2. Methods

2.2.1. Preparation of tablets

A Parke–Davis investigational drug, CI-960, microcrystalline cellulose and a large amount of citric acid (87% w/w) were granulated in a fluid bed (Glatt GPCG-3, Glatt Air Techniques, Inc., Ramsey, NJ) using povidone as a binder. The dry granulation was sized using a Comil (Quadro Engineering, Inc., Ontario Canada). The milled granulation was blended for 5 min with microcrystalline cellulose, croscarmellose sodium, and magnesium stearate in a V-blender (Patterson–Kelley 16 l blender, East Stroudsburg, PA). Approximately 770 mg of the final blend was compressed into caplets containing 20 mg CI-960 with a crushing strength of 10–13 kP (Schleuniger Pharmatron hardness tester, Inc., Manchester, NH) using a rotary press (Manesty B3B, BWI Manesty, Liverpool). The friability of the tablet cores was less than 0.5% after 4 min of tumbling in a Roche type friabilator.

2.2.2. Seal coating, labeling, and enteric coating of tablets

A Freund Hi-Coater (Model HCT-30, Vector Corp., Marion, IA) with a 750 g initial pan bed charge was used for all coating operations. Tablets were seal coated using Opadry®, a complete coating system consisting of hydroxypropylmethylcellulose (HPMC), plasticizer, and pigments that is commercially available in different colors and identical compositions. A 12% w/w aqueous dispersion of Opadry® yellow and tan applied at coverage levels of 1 and 3%, respectively. Prior to an enteric coating process, 50 of each seal coated tablets at 0% (white, uncoated), 1% (yellow), and 3% (tan) weight gains (150 total) were sequentially numbered with a marker pen and weighed in order to identify the precise level of enteric coat and weight gain variability among the tablets. The three groups of labeled tablets for analysis were mixed with a sufficient quantity of readily identifiable 'bulking' placebo tablet cores of the same shape, size, and mass to obtain a total 750 g pan charge. Labeled tablets comprised approximately 16% of the total tablet bed. Tablets were coated with five different (2×2 factorial design with centerpoint) Eudragit® L30D-based enteric formulations containing 100 parts Eudragit L30D (dry polymer weight) with different amounts of plasticizer (10–20 parts) and talc (10–50 parts), as listed in Table 1. Enteric coating dispersions containing a total of 20% w/w solids content were prepared [5]. The polymer was equilibrated with the plasticizer for at least 30 min prior to application of the enteric coating dispersion. The tendency for talc to sediment and alter the coating composition was reduced by continuously stirring the dispersion and by minimizing the transit time of the coating dispersion within the pumping apparatus. During each enteric coating process, 10–15 tablets of each seal coating level were removed after attaining 6 and 8% weight gains, without adding replacement tablets. Coating was halted when a 10% gain in mass was detected.

2.2.3. Evaluation of tablets

Tablets were evaluated in triplicate using USP 23 disintegration and dissolution test procedures for enteric coated tablets. Accordingly, tablets were tested without disks in a USP disintegration apparatus using 900 ml of simulated gastric fluid (SGF), without enzymes maintained at 37 ± 0.5°C. At the end of 1 h, the tablets were visually inspected for any evidence of enteric coat failure. Thereafter, tablet disintegration was completed by transferring the tablets into 900 ml simulated intestinal fluid (SIF), without enzymes maintained at 37 ± 0.5°C. Dissolution testing was carried out using a USP Apparatus 2 (Distek Dissolution System 2100A) set at 75 rev/min. Tablets were placed into 900 ml of 0.1 N HCl (37 ± 0.5°C) for 2 h then transferred into

Table 1
Enteric coat formulations (Dispersed Solids Content (parts)[a])

Formulation	Eudragit L30D[b]	Triethyl citrate (TEC)	Talc
I	100	10	50
II	100	10	10
III	100	20	50
IV	100	20	10
V	100	15	30

[a] All enteric coating dispersions contained 20% w/w solids.
[b] Value based on mass of dry polymer.

900 ml of pH 6.8, 0.05 M phosphate buffer (37 ± 0.5°C). Samples of the dissolution media were taken without replacement at the end of 2 h of acid exposure and every 15 min thereafter while in the phosphate buffer for a total of 4 h. Sink conditions were maintained throughout the dissolution procedure. All samples were analyzed using UV spectroscopy at 344 nm.

3. Results and discussion

Fig. 1 shows the general experimental scheme to define the enteric coating conditions of a highly water soluble, acidic tablet core. The experimental design employs an efficient, practical, systematic strategy to optimize an enteric coat composition and assess the variability of a given coating operation. In addition, the role of a seal coat on the functionality of the enteric coat is examined. The investigation of the aforementioned parameters can not only be cumbersome due to the large number of experiments involved but can also confound data analysis and interpretation, due in part, to variabilities associated with the coating operations. The intention of the experimental design is to integrate many separate coating experiments into a single study and thereby eliminate potential differences that may exist between separate coating processes. As a direct result, data comparison and interpretation is facilitated. In this study, identical tablet cores with three different seal coating levels of 0% (uncoated, white), 1% (Opadry® yellow), and 3% (Opadry® tan) weight gains were combined and simultaneously enteric coated. Furthermore, during each enteric coating trial, a predetermined amount of tablets were removed upon attaining theoretical coverage levels of 6, 8, and 10%, thus resulting in a combined nine-fold reduction in the number of enteric coating experiments.

All enteric coating processes utilized Eudragit® L30D, an aqueous dispersion of copolymers derived from methacrylic acid and acrylic acid esters, as the enteric coating material. In most applications, Eudragit® L30D dispersions require the addition of a suitable plasticizer and detackifier such as triethyl citrate and talc, respectively, for proper film forming properties and characteristics as well as processability [5]. In practice, the most suitable quantities of plasticizer and detackifier should be determined experimentally for a particular application since these values can depend on factors including the core substrate, operating conditions, and process equipment and scale. Table 1 lists the composition of five enteric coat formulations. It can be seen that the polymer level is fixed at 100 parts (based on dry polymer weight) whereas the plasticizer and talc levels vary from 10–20 parts and 10–50 parts, respectively.

An important consideration for the accurate comparison of different enteric formulations is that the final tested tablets should have as close to the desired level of enteric coat as possible. However, selecting individual tablets with the precise coating level can be problematic due, in part, to differences in the starting weight of the uncoated tablet cores and variations in the amount of applied coating materials. In order to select tablets which possess the desired level of enteric coat, a portion (50 tablets) of each seal coated tablet type was sequentially numbered with a marker pen, weighed,

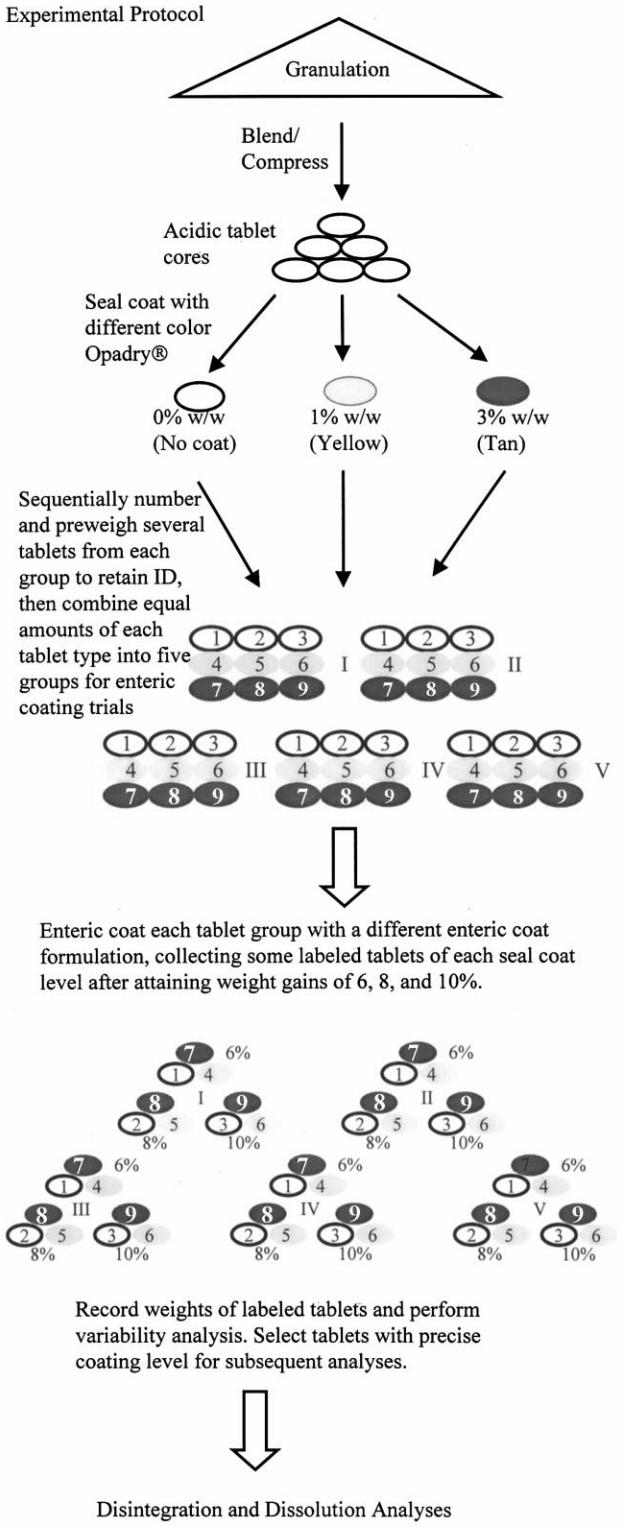

Fig. 1. General experimental scheme.

and recorded prior to enteric coating, as illustrated in Fig. 1. Quantification of the weight gain permits the selection of the most suitable labeled tablets for analytical testing. In addition, the variability of a given coating operation can be readily calculated by weight analysis of the labeled tablets. Analysis of the final tablets selected for dissolution studies indicate that the enteric coating levels were on target (6, 8, or 10% w/w). Overall, it was found that the enteric coating process results in uniform tablets with respect to coverage level with a 6.2% RSD, as tabulated in Table 2.

Table 2 summarizes the enteric coating and disintegration results of seal coated and non-seal coated tablets coated using formulations I–V. Disintegration analysis was employed as a tool to evaluate the functional qualities of the enteric coat during exposure to simulated gastric fluid (SGF). Immediately after SGF exposure, each tablet was visually inspected for any evidence which would indicate improper function of the enteric coat then transferred to a phosphate buffer media with a disk placed on top of the each tablet as described in the methods section. It can be seen in Table 2 that the high levels of talc present in formulations I and III (50 parts) reduced the tablet disintegration times. It has been reported that an increase in talc concentration tends to augment the internal stress of a polymer film and reduce the ability of a polymer film to deform under stress [6]. During the disintegration analysis procedure, the enteric films of formulation I and III probably fractured under the repeated impact of the disk on the tablet surface instead of deforming, leading to more rapid disintegration time. In addition, it was found that the disintegration time of tablets increases as the coverage level of the enteric coat increases. For example, tablets with a 3% w/w seal coat that were subsequently enteric coated to 6, 8, or 10% w/w weight gain using formulation I disintegrated completely in approximately 10, 15, and 17 min, respectively. Moreover, the disintegration time of non-seal coated tablets is typically shorter than the corresponding seal coated tablet. More importantly, it was observed that all non-seal coated tablets exhibited blistering and swelling of the enteric coat during the acidic medium exposure phase, suggesting that a small amount of SGF could penetrate the enteric coat and initiate tablet dissolution. Although the precise cause of the blistering of non-seal coated tablets is not known for certain, it was speculated that some of the citric acid migrated into the enteric coat during the coating operation, resulting in an increase in film permeability and subsequent failure. It was therefore postulated that a seal coat could improve the functionality of the enteric coat by inhibiting the core materials from leaching into the enteric film. As predicted, all enteric coat formulations with a 3% w/w seal coat passed the USP disintegration criteria, as listed in Table 2. These findings provide support for the premise that enteric coat defects resulted from the migration of the citric acid into the film.

Table 2
Disintegration results and coating level variability of enteric coated tablets

Enteric coat formulations	Enteric coat solids, parts			Seal coat (%w/w)	Enteric coat (%w/w)	Coating level (% RSD)	Disintergration result	Disintergration time (min:s)
	Eudragit	TEC	Talc					
I	100	10	50	0	6	8.2	Fail	6:30
				0	10	5.0	Fail	16:35
				3	6	6.2	Pass	10:20
				3	8	8.9	Pass	15:20
				3	10	5.6	Pass	16:40
II	100	10	10	0	6	–[a]	–	–
				0	10	–[a]	–	–
				3	6	6.6	Pass	13.45
				3	10	4.9	Pass	21.00
III	100	20	50	0	6	6.1	Fail	11:10
				0	10	6.0	Fail	15:00
				3	6	6.0	Pass	11:25
				3	10	5.0	Pass	17:00
IV	100	20	10	0	6	8.1	Fail	12:35
				0	10	5.2	Fail	18:55
				1	6	4.8	Pass	11:25
				1	10	5.7	Pass	19:25
				3	6	8.3	Pass	15:00
				3	10	5.4	Pass	19:10
V	100	15	30	0	6	4.7	Fail	11:45
				0	10	7.5	Fail	19:05
				1	6	9.1	Fail	14:25
				1	8	4.1	Pass	17:35
				1	10	5.3	Pass	17:35
				3	6	8.9	Pass	14:10
				3	10	4.1	Pass	19:40

[a] Enteric coating process failed.

It can be seen in Table 2 that the application of enteric coating formulation II onto uncoated tablet cores results in failure of the process. In this case, it was observed that the enteric coating did not adhere to the uncoated core. In sharp contrast, during the same coating operation, the enteric coating could be applied onto both 1 and 3% w/w seal coated tablets with no apparent defects. These findings provide additional support for the hypothesis that citric acid could migrate into the enteric coating of non-seal coated tablets and affect the film forming properties of the coating. It is important to note, however, that formulations I, III, IV, and V could be directly applied onto identical uncoated tablet cores with no apparent defects. As listed in Table 1, formulation II encompasses the lowest levels of both plasticizer and talc among the tested formulations (ten parts each), thus, the observed failure suggests that formulation II is not optimal for this particular coating application.

Disintegration analyses were conducted to determine whether a reduction of the seal coat level from 3 to 1% w/w could prevent defects from developing in the enteric coat. Test results of tablets with a 1% w/w seal coat and enteric coated to a 6 or 10% w/w level using formulations IV and V are listed in Table 2. It can be seen that both tablets (6 and 10% w/w) coated using formulation IV passed the test whereas tablets coated using formulation V to a 6% w/w level failed as evidenced by blisters in the film. Visual inspection of the 1% seal coated tablets revealed that this level afforded only a minimal film layer, suggesting that the inhibition of core leaching may be variable at this level of coating. For this reason, tablets possessing a 1% w/w seal coat were not tested in further studies.

Dissolution analysis was employed to assess the effect of the enteric coat composition and coverage levels on the release of the marker drug. The impact of a 3% seal coat on drug release was evaluated by using non-seal coated tablets as a comparison. In general, it was found that all enteric coat formulations effectively inhibit drug release during the acid exposure phase of the dissolution procedure regardless of whether a seal coat was applied. Dissolution analysis reveals that non-seal coated tablets which were enteric coated with formulations I–V exhibit a retardation in the release when compared to the corresponding seal coated tablet, ranging from ca. 1.5–5 fold lower at most intermediate sampling time points. Fig. 2 shows the dissolution profile in the phosphate buffer of tablets with and without a seal coat that were enteric coated to a 10% w/w level using formulation V. In this case, the amount of the marker drug which was released from the tablet with a seal coat is approximately five fold greater than from the tablet without a seal coat after 45 min in the buffer. The delayed release of non-seal coated tablets can most likely be attributed to the migration and/or diffusion of citric acid at the tablet core/enteric coat interface. A saturated citric acid solution has recently been reported to have a pH value of approximately 0.4 [7]; thus, it is expected that the citric acid could suppress the ionization of the enteric polymer functional groups and delay dissolution. A seal coat, therefore, functions as a barrier, both inhibiting the migration of the citric acid during the enteric coating operation and allowing the enteric coat to dissolve sufficiently prior to dissolution of the tablet core. The delayed dissolution of the enteric coat, governed by the low pK_a of the tablet core, is consistent with the model proposed by Dressman et al. [8].

Fig. 3 shows the effect of the enteric coat composition on the release of the marker drug from tablets with a 3% w/w seal coat and a 6% w/w enteric coat. Drug release in the

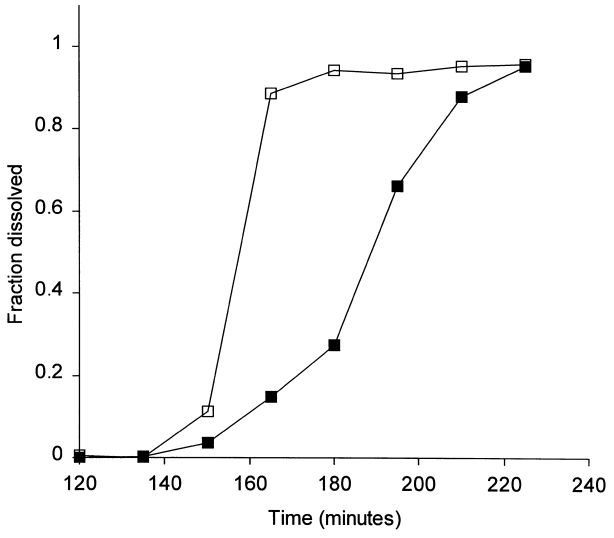

Fig. 2. Effect of a seal coat on marker dissolution with 10% enteric coat and 0% or 3% seal coat. Formulation V, no seal coat (■); formulation V, with seal coat (□); Data shown are the mean with $n \geq 3$.

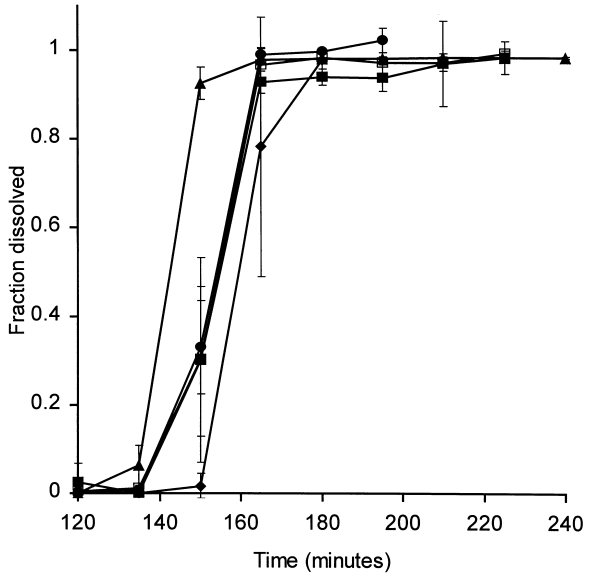

Fig. 3. Effect of enteric coat formulation on marker dissolution with 6% enteric coat and 3% seal coat. Formulation I (◆); formulation II (■); formulation III (▲); formulation IV (●) formulation V (□). Data shown are the mean with $n \geq 3$; error bars represent one standard deviation.

phosphate buffer is quite rapid and comparable, especially for enteric coat formulations II, IV, and V. It can be seen that the delay in the onset of tablet dissolution shown in Fig. 3 can differ from the disintegration pattern listed in Table 2. For example, tablet cores with a 3% w/w seal coat which are enteric coated using formulation I exhibit the slowest dissolution rate but disintegrate before the other tested formulations. As indicated previously, the disintegration procedure may have fractured this enteric coat whereas the coat could dissolve without fracture during dissolution analysis. As expected, increasing the enteric coat coverage level from 6 to 10% w/w (Fig. 4) on tablets containing a 3% w/w seal coat extends the onset of dissolution. Once again, enteric coat formulations II, IV, and V exhibit similar release rates in the phosphate buffer. It should be mentioned, however, that formulations containing lower levels of talc (II and IV) (ten parts) were easier to process at this scale due to a reduced tendency for the talc to settle out and obstruct the spray gun and pumping apparatus. Using several criteria including ease of processing, consistent, robust coating properties, and good predictability, enteric coat formulation IV (20 parts plasticizer and 10 parts talc) with a 3% seal coat was identified for further study.

Fig. 5 shows the impact of enteric coat level on the drug release profile when using formulation IV. As anticipated, higher levels of enteric coating extend the lag time of drug release. Although Fig. 5 shows that a 10% w/w enteric coat did not meet the level B_1 dissolution acceptance criteria for enteric coated tablets (each unit not less than Q of 75 + 5%) [9], it can be mentioned that this criteria was not critical for the development of this particular product. In a related study, the marker compound was replaced by a different investigational Parke–Davis compound and enteric coated at two

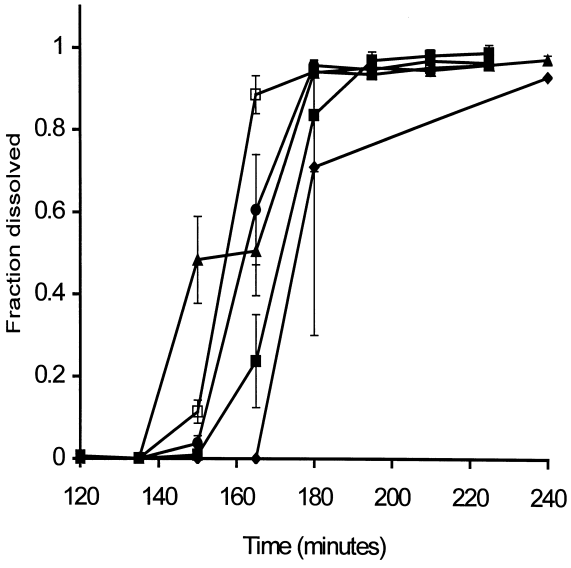

Fig. 4. Effect of enteric coat formulation on marker dissolution with 10% enteric coat and 3% seal coat. Formulation I (◆); formulation II (■); formulation III (▲); formulation IV (●); formulation V (□). Data shown are the mean with $n \geq 3$; error bars represent one standard deviation.

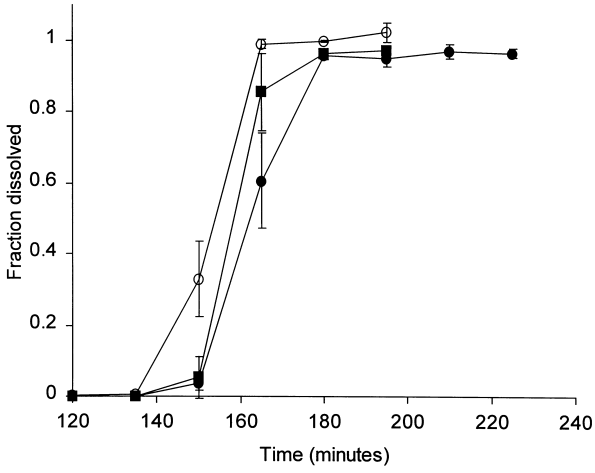

Fig. 5. Effect of enteric coat coverage level on marker dissolution using formulation IV and 3% seal coat. (●) 10% enteric coat; (■) 8% enteric coat; (○) 6% enteric coat. Data shown are the mean with $n \geq 3$; error bars represent one standard deviation.

different levels with the prior application of a 3% w/w seal coat. In an in vivo study using a dog model, the T_{max} values of tablets with a 7 and 10% enteric coat levels were 108 ± 51 and 140 ± 31 min, respectively. Although details of the study cannot be revealed, bioavailability results suggest that the application of a thicker enteric coat could improve drug absorption. In summary, prior to enteric coating an acidic, highly water soluble substrate, a seal coat barrier should be applied to prevent retardation in drug release. A simple strategy utilizing color coding and tablet marking can be successfully employed to test the effect of a seal coat, identify an enteric coat formulation, and evaluate the coating process with minimal experimentation and analyses.

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