

European versus United States Pharmacopeia Disintegration Testing Methods for Enteric-Coated Soft Gelatin Capsules

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ABSTRACT

The aim of this work was to investigate the differences between the disintegration testing methods specified by the *United States Pharmacopeia (USP)* and the *European Pharmacopoeia (Ph. Eur.)* for enteric-coated soft gelatin capsules. Disintegration of the coated capsules in the pH 6.8 buffer stage of the test was much faster under the conditions specified by *Ph. Eur.* than under the conditions specified by the *USP*. Further investigation showed that the differences are related to the different buffer capacities and the ionic strengths of the media specified by the two pharmacopeias. This shows the importance of harmonizing such tests among the different pharmacopeias and accounting for factors like buffer capacity and ionic strength when designing appropriate media for disintegration and dissolution tests.

KEYWORDS: Enteric-coated soft gelatin capsules; dissolution; disintegration.

INTRODUCTION

Enteric coatings have been used for decades to delay drug release from oral solid dosage forms until after gastric emptying either to protect the active ingredient from degradation by gastric acid or to protect the gastric mucosa from irritation caused by the active ingredient. These coatings are based on pH-sensitive film-formers that should prevent release under the acidic conditions in the stomach but allow it under the higher pH conditions in the small intestine. Therefore, for disintegration and dissolution testing, a two-stage testing approach was adopted by the different pharmacopeias for such products: a first stage done in an acidic medium where the coat should prevent disintegration and drug release, and a second stage in a higher pH buffer where the dosage form should disintegrate (1, 2).

However, that the employed testing conditions accurately simulate gastrointestinal (GI) conditions is questionable. For example, a study performed by Wagner et al. (3) more than 40 years ago provided an example where aminosalicic acid enteric-coated tablets passed the *USP* disintegration test but failed to release the drug in vivo. In addition, in a study by Wilding et al. (4), enteric-coated naproxen tablets took much longer to disintegrate after gastric emptying in vivo than in the buffer stage of the *BP 1988* disintegration test. Another study by Cole et al. (5) showed that the onset of release from enteric-coated HPMC capsules was appreciably earlier during the pH 6.8 buffer stage of in vitro dissolution testing than after gastric emptying in vivo.

For disintegration testing in particular, the picture is further complicated by the fact that different pharmacopeias specify different test conditions for enteric-coated products. Table 1 summarizes the differences between the disintegration testing conditions specified for enteric-coated soft gelatin capsules by *Ph. Eur.* and the *USP*. In this work, we studied the differences in the test results of the methods when performed on enteric-coated soft gelatin capsules manufactured in-house. The exact causes behind these differences were also investigated.

Table 1. Differences Between the Disintegration Testing Methods for Enteric-Coated Soft Gelatin Capsules According to *Ph. Eur.* and *USP*.

Characteristic		<i>Ph. Eur.</i>	<i>USP</i>
Acid Stage Medium		0.1 M HCl	0.084 M HCl 0.034 M NaCl 0.32% w/v pepsin
Acid Stage Duration		2 h	1 h
pH 6.8 Buffer-Stage Medium	Buffer-Forming Species (i.e., phosphate) Total Conc. (M)	0.154	0.05
	Ionic Strength (M)	0.463	0.094
	Counterions	Na ⁺	K ⁺ (0.05 M) Na ⁺ (0.022 M)
	Other Differences	Inclusion of enzymes not mandatory	Inclusion of enzymes mandatory

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MATERIALS AND METHODS

Materials

Uncoated size 4 oval placebo soft gelatin capsules were received as a gift from Catalent Pharma Solutions (Eberbach, Germany). Shellac aqueous solution (Aqualacca 25) was received as a gift from Chemacon (Bühl, Germany). HPMC (Pharmacoat 606) was received as a gift from HARKE (Mülheim an der Ruhr, Germany). All the other materials used were of analytical grade.

Coating of Soft Gelatin Capsules

Batches of soft gelatin capsules were coated to levels of 12, 15, and 18 mg solid/cm² with a coating formulation composed of shellac, HPMC, and glycerin (62.5:25.0:12.5 w/w/w) dissolved in water at a total concentration of 14.75% w/w coating solids. A Glatt GC-300 drum coater (Glatt, Germany) was used. The coating parameters were as follows: 900 g uncoated capsules batch weight; inlet and exhaust air preheated at 30 °C for 30 min; coating solution input rate of 5 g/min; air flow rate of 100 m³/h; coating inlet air temperature of 35 °C; exhaust air temperature of 30 °C; atomizing air pressure of 1.2 bar; and a rotational drum speed of 20 rpm.

Disintegration Testing

All batches were tested using both the *USP* and *Ph. Eur.* conditions. In addition, a series of disintegration tests was performed on the 15-mg/cm² batch, where in each test, some parameter of the *USP* test was changed to what is specified by *Ph. Eur.* In one test, it was the duration of the acid stage; in the second test, it was the absence of enzymes; in the third test, it was the ionic strength (adjusted using sodium and potassium chloride to maintain the potassium–sodium ratio) of the buffer; and in the fourth, it was both the total phosphate concentration (reflecting the buffer capacity) and the ionic strength of the buffer.

RESULTS

All the tested capsules withstood the acid stages. As for the buffer stages, large differences among the disintegration times obtained with the two methods were found as shown in Figure 1. The disintegration times were consistently longer in the *USP* medium than in the *Ph. Eur.* medium. These differences were large to the extent that all the three batches passed the *Ph. Eur.* test but failed the *USP* test.

An investigation of the causes behind these differences showed that the duration of the acid stage had only a small effect and the enzymes had almost no effect, but ionic strength and buffer capacity had large effects and were the major factors in play (Figure 2).

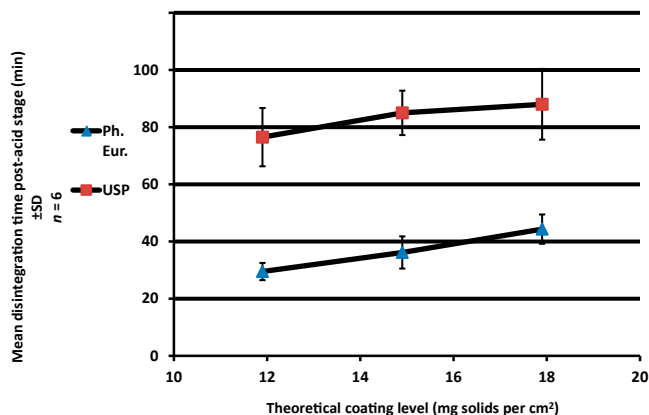


Figure 1. Differences in disintegration times between *Ph. Eur.* and *USP* methods.

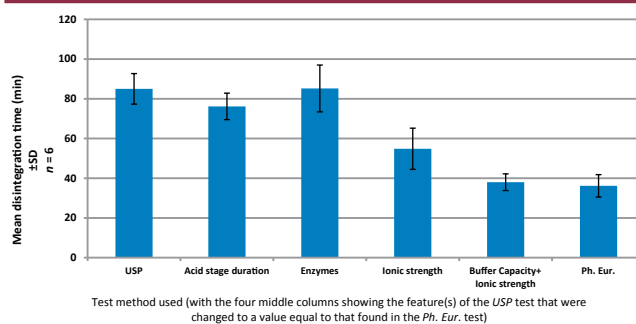


Figure 2. Investigations leading to the causes underlying the different disintegration times of enteric-coated soft gelatin capsules.

DISCUSSION

The buffer specified by *Ph. Eur.* for disintegration testing of enteric-coated products promotes faster disintegration than that specified by the *USP*. The differences in the results between the two methods were related to the different phosphate concentrations (and therefore buffer capacities) and ionic strengths of the two media. The higher buffer capacity of the *Ph. Eur.* medium (due to its higher phosphate molarity) results in a higher pH in the immediate vicinity of the shellac molecules within the coat. The acidic shellac molecules cause the pH within the coat to be lower than the bulk pH, and in a higher buffer capacity medium, this difference will be smaller, which will allow a greater degree of shellac ionization. In addition, the higher ionic strength of the *Ph. Eur.* medium will shift the mass balance between ionized and un-ionized shellac in the ionization-promoting direction because higher ionic strength will reduce the values of the activity coefficients of ionized shellac molecules. This will lead to further ionization of shellac to compensate the effect of

reduced activity coefficients on the activity values and maintain chemical equilibrium. These findings are in line with the findings of other groups (7–9) concerning the effects of changing buffer composition on the dissolution characteristics of enteric-coated tablets and pellets. For other enteric-coated products, the testing conditions for tablets are the same as those for capsules in *Ph. Eur.* In the *USP*, they are the same as those specified for soft gelatin capsules except for the fact that the use of disks is omitted for tablets. Therefore, larger differences than the ones observed in this study would not be surprising if the product studied was an enteric-coated tablet product. Questions will arise concerning which test conditions are more biorelevant, and thus more suitable to be adopted. Considering the fact that the buffers specified for this test by both pharmacopeias exhibit a buffer capacity much higher than that of intestinal fluid (with this difference being much bigger in the case of *Ph. Eur.*) and that the *Ph. Eur.* buffer also exhibits a much higher ionic strength (10), the *USP* buffer might be considered as potentially more biorelevant.

CONCLUSION

Disintegration testing conditions specified for enteric-coated products by the *USP* and *Ph. Eur.* can lead to different test results. This shows the importance of harmonizing such tests among the different pharmacopeias. In addition, the development of more physiologically relevant buffer systems for disintegration testing of enteric-coated dosage forms is needed since both the *Ph. Eur.* and the *USP* buffers show poor biorelevance. However, until this is achieved, the *USP* buffer can be used as the one that is potentially more biorelevant.

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