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A study of enteric-coated liquid-filled hard gelatin capsules with biphasic release characteristics

S.J. Burns [a], S. Higginbottom [a], D. Corness [a], G. Hay [a], I. Whelan [a], D. Attwood [b], S.G. Barnwell [a,*]

[a] *Cortecs Ltd, Research and Development Division, Techbase 1, Newtech Square, Deeside Industrial Park, Deeside, Clwyd CH5 2NT, UK*

[b] *University of Manchester, Pharmacy Dept, Manchester M13 9PL, UK*

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Abstract

Studies were carried out using enteric-coated, liquid-filled hard gelatin capsules with biphasic rapid and sustained release characteristics, containing 80 mg of propranolol in a novel HALO^{TM} drug delivery formulation designed to avoid hepatic first-pass metabolism. The disintegration at pH 1.0 of HALO^{TM}-propranolol capsules, coated with different levels (3–12 mg/cm^2) of enteric polymer (methacrylic acid copolymer, type A USP/NF) was visually assessed using the disintegration test for enteric-coated capsules described in the BP 1988. Quantification of propranolol release, at pH 1.0, from enteric-coated capsules was carried out using a dissolution procedure based on the USP XXII method. The results of the study showed that significant release of propranolol (> 10%) could take place at low coating levels (3 mg/cm^2) without visible breakdown of the enteric coat. In a further study, enteric-coated HALO^{TM}-propranolol capsules coated with 4 mg/cm^2 of enteric polymer were stored under a variety of conditions for up to 18 months. Dissolution and disintegration studies showed that under conditions of low temperature storage (4°C) HALO^{TM}-propranolol capsules released significant amounts (> 10%) of propranolol at pH 1.0 without visible breakdown of the enteric coat. Dissolution studies carried out at pH 6.8 following acid challenge demonstrated that inadequate enteric protection greatly affected the subsequent sustained-release dissolution profile of HALO^{TM}-propranolol capsules. The present investigation demonstrates the importance of ensuring a sufficient enteric-coating level for oral dosage vehicles to maintain post gastric dissolution characteristics and illustrates the need for a reliable means of assessing enteric coat performance in vitro.

Key words: Enteric coating; Hard gelatin capsule; Biphasic release; Propranolol; HALO^{TM} drug delivery system

1. Introduction

The HALO^{TM} drug delivery system is designed to improve the systemic bioavailability of drugs which undergo high first-pass metabolism exemplified by propranolol (Barnwell et al., 1992, 1993, 1994; Tucker, 1993). The HALO^{TM} delivery system consists of a biphasic rapid and sustained release formulation containing oleic acid and dissolved drug. The sustained release component is a solid erodible matrix, at 37°C, containing Gelu-

* Corresponding author.

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cire® while the rapid release phase is a liquid. To maintain the performance of the biphasic delivery system in vitro and in vivo it is necessary to use an enteric-coated dosage form.

In the present study HALO™-propranolol hard gelatin capsules, enteric-coated with methacrylic acid copolymer, type A USP/NF (Eudragit® L100), were assessed using the disintegration test for enteric-coated capsules (BP, 1988) and a dissolution test based on that described in USP XXII (Apparatus 2) (USP, 1990). The aim of the study was to assess the importance of making a quantitative determination of drug release as a measure of enteric-coat performance, rather than a subjective visual assessment of enteric-coat integrity.

2. Materials and methods

2.1. Materials

The enteric coating material, methacrylic acid copolymer type A USP/NF (Eudragit L100) was supplied by Dumas (U.K.) Ltd, (Tunbridge Wells, U.K.). Diacetylated monoglycerides USP/NF (Myvacet 9-45-K), used as a plasticiser was obtained from Honeywill and Stein (Sutton, U.K.). Other components of the enteric coat, talcum E.P., magnesium stearate E.P., purified water E.P., and ethanol 96% B.P. were obtained from reputable sources and were of an appropriate quality. Size 0 or size 1 clear hard gelatin Licaps®, Snaplock® or Starlock® capsules were obtained from Capsugel (Bornem, Belgium), or R.P. Scherer Ltd (Swindon, U.K.). The bile acids used in the dissolution media, cholic acid (sodium salt) and deoxycholic acid (sodium salt), were obtained from either Sigma (Poole, U.K.) or Fluka (Gillingham, U.K.).

2.2. Manufacturing methods

Liquid-filled 80 mg HALO™-propranolol capsules were manufactured by MW Encap Ltd (Livingstone, W. Lothian) using standard production scale, liquid-filling apparatus (Bosch H8K GKF 1500L), and sealed by gelatin banding with an Elanco Qualiseal S100 machine. Capsules were enteric-coated by Pharma Vinci A/S, (Denmark) in a 'Combi-Coata' production scale fluidised-bed spray-coating machine using an aqueous-ethanolic enteric coating solution containing the enteric polymer methacrylic acid copolymer type A USP/NF (Eudragit L100), diacetyled monoglycerides (Myvacet 9-45-K) as plasticiser, magnesium stearate and talcum. The level of enteric coat applied to the hard gelatin capsules varied from 3 to 12 mg/cm^2.

2.3. Dissolution and disintegration testing

Disintegration testing of enteric-coated 80 mg HALO™-propranolol capsules was carried out in accordance with the BP monograph for enteric-coated capsules.

Dissolution testing of 80 mg HALO™-propranolol capsules was carried out in 900 ml of dissolution buffer at either pH 1.0, using 0.1 M HCl as the dissolution medium, or at pH 6.8. The pH 6.8 dissolution medium contained 5.84 g l^{-1} disodium hydrogen orthophosphate, 4.61 g l^{-1} potassium dihydrogen orthophosphate, 2.00 g l^{-1} sodium cholate and 1.00 g l^{-1} sodium deoxycholate. Dissolution testing was carried out using a modification of the BP 1988/USP XXII dissolution method for tablets and capsules, the paddles set to the surface of the dissolution medium to allow sufficient agitation of the floating HALO™-propranolol formulation to enable erosion to take place. The paddle rotation speed used was 70 rpm. The dissolution medium was dearated by sonication and maintained at 37 ± 0.2°C throughout the test period. To determine the release of propranolol from the HALO™-propranolol capsules, 5 ml samples of dissolution medium were removed for analysis through a 10 μm HDPE filter, attached to the tip of the sample probe, followed by a 1.2 μm cellulose acetate filter fitted to the top of the probe, and subsequently replaced with fresh dissolution medium. The propranolol content of dissolution samples was determined spectrophotometrically, at 290 nm, within 10 min of sample collection, and quantified by comparison with authentic standards. Excipient interference was found to be less

than 2% at 290 nm when compared with 100% formulation dissolution using drug-free capsules.

3. Results

3.1. Dissolution testing of non-enteric-coated HALO™-propranolol capsules at pH 1.0 and 6.8

The dissolution characteristics of HALO™-propranolol capsules were initially determined using freshly manufactured non-enteric-coated capsules at pH 6.8 and 1.0. The results in Table 1 show that at pH 6.8, HALO™-propranolol capsules exhibit a biphasic rapid/sustained release dissolution profile with more than 50% propranolol release occurring after 60 min, from the liquid component of the capsule, followed by sustained release from the solid erodible plug. It was observed during this study that the floating capsules rapidly opened within 3 min to release the oily rapid release phase into solution resulting in a progressive hazing of the dissolution medium, subsequently leaving a floating erodible plug at the dissolution medium surface. Release of propranolol from the formulation reached 71% after 5 h. The dissolution of non-enteric-coated HALO™-propranolol capsules in pH 1.0 was rapid and complete within 15 min forming a thick cloudy dispersion of the formulation components.

Table 1
Dissolution testing of non-enteric-coated capsules at pH 1.0 and 6.8

Time (min)	% propranolol released	
	pH 1.0	pH 6.8
15	complete dissolution	31.6 ± 6.5
30	complete dissolution	43.8 ± 7.5
60	complete dissolution	52.8 ± 7.8
120	complete dissolution	59.0 ± 5.9
300	complete dissolution	71.3 ± 4.1

Values represent means of six determinations ± S.D. In a separate experiment, greater than 90% release of propranolol was observed after a 22 h dissolution test at pH 6.8. Capsules were tested within 3 months of manufacture.

Table 2
Dissolution testing of enteric-coated and non-enteric-coated capsules at pH 6.8

Time (min)	% propranolol released	
	Enteric coated	Non-enteric coated
15	N.D.	31.6 ± 6.5
30	28.9 ± 5.7	43.8 ± 7.5
45	48.6 ± 4.5	N.D.
60	N.D.	52.8 ± 7.8
75	55.7 ± 4.9	N.D.
120	62.6 ± 4.7	59.0 ± 5.9
300	75.8 ± 3.0	71.3 ± 4.1

Values represent means ± S.D. of six determinations. Capsules used for the test were either uncoated or coated with 10 mg/cm^2 of enteric polymer and tested within 3 months of manufacture.

3.2. Effect of enteric coating on the dissolution of HALO™-propranolol capsules at pH 6.8

Table 2 compares the dissolution profiles at pH 6.8 for newly manufactured HALO™-propranolol capsules, coated with 10 mg/cm^2 of enteric polymer, and non-enteric-coated HALO™-propranolol capsules. The amount of propranolol released at 30 min from the enteric-coated capsules was less than that from non-enteric-coated capsules (29 vs 44%) because of the time taken for the enteric coat to be removed from the capsule. Time to enteric-coated capsule rupture using the BP disintegration test at pH 6.8 was 13 min; complete coat removal occurred after 17 min.

3.3. Dissolution and disintegration testing of HALO™-propranolol capsules coated with different levels of enteric polymer

Table 3 compares the results of dissolution and disintegration tests carried out on HALO™-propranolol capsules coated with 3–12 mg/cm^2 of enteric polymer. Determinations carried out using the standard BP disintegration test for enteric-coated capsules, at pH 1.0, indicated that the enteric coat on the HALO™-proprano-

Table 3
Effect of coating level on dissolution and disintegration of capsules at pH 1.0

Coating level (mg/cm^2)	Time (min)	% propranolol released					
		1	2	3	4	5	6
3	120	27.7	13.0	24.9	20.8	16.6	22.9
	240	33.5	22.3	46.0	31.7	23.6	26.7
8	120	0	0	0	0	0	0
	240	0 [a]	0	0	0	0	0
12	120	0	0	0	0	0	0
	240	0	0	0	0	0	0

Dissolution results at 120 and 240 min represent % propranolol released from individual capsules.
[a] Capsule failed USP dissolution test after 270 min releasing greater than 10% of its propranolol content; all capsules passed the BP disintegration test for enteric-coated capsules at 120 min. Capsules were tested within 3 months of manufacture.

lol capsules remained visibly intact on all capsules at coating levels of 3, 8 and 12 mg/cm^2. In contrast, however, a dissolution test involving a quantitative determination of propranolol release from enteric-coated HALO™-propranolol capsules demonstrated that, at the lowest coating level of 3 mg/cm^2, between 13 and 28% of the propranolol content had been released from the capsules after 120 min, increasing to between 22 and 46% after 240 min. No release of propranolol from capsules coated with 8 and 12 mg/cm^2 of enteric polymer was observed after 240 min, although the enteric coat on one 8 mg/cm^2 capsule failed after 270 min.

3.4. Effect of storage on the dissolution of enteric-coated HALO™-propranolol capsules at pH 1.0

HALO™-propranolol capsules were coated with 4 mg/cm^2 of enteric polymer and stored for up to 18 months at 4°C; ambient temperature in both light and dark; 30°C with 75% relative humidity; and 37°C. Table 4 shows the results of dissolution and disintegration tests carried out on enteric-coated HALO™-propranolol capsules after 12 months storage. After this period of storage at 4°C, a significant release (> 10%) of propranolol was observed from four of six capsules undergoing dissolution testing at pH 1.0 without visible breakdown of the enteric coat. Only one other capsule tested at 12 months, stored at ambient temperature in the light, was found to release significant amounts of propranolol. Similar results were observed after 18 months storage.

3.5. Effect of acid challenge on the dissolution profile of HALO™-propranolol capsules at pH 6.8

The dissolution of propranolol from enteric-coated capsules, stored at 4°C for 12 months, was examined at pH 6.8 for capsules which had been subjected to acid challenge, and compared to non acid challenged capsules. The results in Table 5 show that the mean dissolution of propranolol after 60 min had been reduced from 50 to 33% by acid challenge, a result which was accompanied

Table 4
Assessment of enteric-coated capsules after 12 months storage

Test	4°C	Ambient dark	Ambient light	30°C 75% RH	37°C
Propranolol (%)	15.1 ± 12.0	0.1 ± 0.2	3.6 ± 4.4	0.5 ± 0.1	1.6 ± 1.8
USP test pass	2/6	6/6	5/6	3/3	3/3
BP test pass	6/6	6/6	6/6	3/3	3/3

Results show mean propranolol release as a percentage of total capsule drug content ±SD of either three or six individual determinations. Also recorded are the number of individual capsules releasing greater than 10% of propranolol content (USP test) and visual integrity of the enteric coat on each capsule after 120 min (BP test).

Table 5
Effect of acid challenge on pH 6.8 dissolution of enteric-coated capsules stored for 12 months at 4°C

pH	Time (min)	% propranolol released						Mean ± S.D.
		1	2	3	4	5	6	
Acid challenged capsules								
1.0	120	−0.1	22.9	22.4	23.1	−0.8	23.0	15.1 ± 12.0
6.8	15	15.1	2.6	4.5	−1.7	19.0	1.9	6.9 ± 8.2
	30	33.9	12.9	14.5	14.2	33.2	12.1	20.1 ± 10.4
	60	47.9	26.6	25.1	23.4	47.3	24.4	32.5 ± 11.8
	120	65.7	44.8	41.7	42.7	64.8	45.4	50.9 ± 11.2
	180	77.5	56.8	51.8	52.4	69.9	54.1	60.4 ± 10.7
	240	83.9	62.5	59.8	60.1	75.5	61.6	67.2 ± 10.2
	300	105.7	86.0	83.2	81.2	95.4	81.9	88.9 ± 9.7
Non acid challenged capsules								
6.8	15	38.4	35.2	37.1	29.7	30.8	27.5	33.1 ± 4.4
	30	40.3	41.2	41.6	45.1	35.9	41.9	41.0 ± 3.0
	60	50.7	48.6	50.2	46.9	48.9	52.6	49.7 ± 2.0
	120	64.6	65.3	64.5	64.6	67.8	70.1	66.2 ± 2.3
	180	73.9	78.7	76.7	79.5	73.7	83.3	77.6 ± 3.7
	240	81.9	84.1	82.6	84.2	88.2	88.2	84.9 ± 2.7
	300	94.2	87.9	87.6	89.5	80.1	93.2	88.8 ± 5.0

Values are percent propranolol release expressed as individual capsule dissolution studies for enteric-coated acid challenged and non acid challenged capsules with means and standard deviation after storage for 12 months at 4°C.

by a greater inter-capsule variability in dissolution performance as illustrated by an increase in standard deviation from ±2.0 to ±12%. Examination of the dissolution characteristics of individual acid challenged capsules in Table 5 shows that capsules releasing greater than 10% (USP limit) of their total propranolol content at pH 1.0 after 120 min, capsules 2–4 and 6, released between 23 and 27% of their remaining propranolol content after 60 min at pH 6.8. Interestingly, however, capsules 1 and 5 which did not show significant propranolol release during acid challenge had initially slower propranolol release at 15 min, 15 and 19%, respectively, compared with a mean of 33% for non-challenged capsules at pH 6.8.

4. Discussion

The present study has evaluated the performance of enteric-coated, liquid-filled, hard gelatin capsules during long-term storage. Also investigated was the amount of enteric polymer required to maintain gastric protection and the methods used to assess enteric-coated products.

In the case of the HALO™ delivery system, the need to maintain enteric protection during the entire period of gastric retention is illustrated by: (i) the acid dissolution study (Table 1) which showed that non-enteric-coated HALO™-propranolol capsules undergo complete dissolution within 15 min, therefore losing their sustained release properties; and (ii) the results in Table 5, which showed that inadequate enteric protection of HALO™-propranolol capsules stored at 4°C for 12 months results in either partial loss of capsule contents at pH 1.0 and/or an adverse effect on ideal dissolution rate exemplified by non acid challenged capsules. Adverse changes in dissolution performance compared with non acid challenged capsules appeared to be caused by acid penetration into the capsule interior, in some cases without significant propranolol leakage at pH 1.0.

A number of studies have shown that the

gastric retention of single unit dosage forms, exemplified by enteric-coated hard gelatin capsules, may be considerably longer than the 120 min period specified in the current tests for enteric products described in the BP 1988 and USP XXII, particularly when taken with food (Davis et al., 1986; Khosla and Davis 1990; Coupe et al., 1991). For this reason the studies designed to assess optimal levels of enteric polymer reported here included an extension of the acid dissolution test to 240 min and a measurement of actual drug release. To pass this more stringent requirement for enteric protection it was shown to be necessary to increase the level of enteric polymer applied to HALO^{TM}-propranolol capsules to at least 8 mg/cm^2. Capsules coated with 3 mg/cm^2 of enteric polymer released significant amounts of propranolol (> 10%) after 120 min without visible degradation of the enteric coat (Table 3), therefore passing the BP disintegration test for enteric-coated capsules but failing the USP XXII dissolution test for enteric-coated capsules.

The influence of storage conditions was examined in the stability study performed on HALO^{TM}-propranolol capsules coated with a level of enteric coat generally believed to provide adequate enteric protection (4 mg/cm^2). All enteric-coated capsules remained visibly intact during disintegration testing and therefore passed the BP test for enteric-coated capsules. However, measurement of the propranolol released from the capsules after 120 min during the dissolution test at pH 1.0 indicated that the majority of capsules stored at 4°C released > 10% of their propranolol content and therefore failed the USP XXII test for enteric-coated capsules.

The present study illustrates the need for an adequate means of assessing enteric protection using an actual measurement of drug release from enteric-coated dosage forms and also indicates the importance of assessing the effects of acid exposure of the formulation on subsequent dissolution performance at normal duodenal pH. The results show that enteric coatings applied to hard gelatin capsules may be unstable under conditions of prolonged low temperature storage, possibly because of thermal contraction and expansion when capsules are transferred from cold storage. Finally, this investigation indicates that a greater level of enteric coating of oral dosage forms may be required if adequate enteric protection is to be maintained during prolonged periods of gastric retention.

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