ELSEVIER

International Journal of Pharmaceutics 121 (1995) 37–44

international journal of pharmaceutics

Development and validation of an in vitro dissolution method for a floating dosage form with biphasic release characteristics

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

[a] *Cortecs Limited, Research and Development Division, Techbase 1, Newtech Square, Deeside Industrial Park, Deeside CH5 2NT, UK*
[b] *University of Manchester, Pharmacy Department, Manchester M13 9PL, UK*

Received 26 September 1994; accepted 15 December 1994

Abstract

The present study describes the development of a dissolution method for a floating dosage form using HALO™-propranolol capsules containing propranolol base dissolved in oleic acid. A modified paddle dissolution method in which the paddle blades were set to the surface of the dissolution medium was shown to be effective for assessing HALO™-propranolol capsules, characterised by having both rapid release and sustained release properties. The standard paddle or basket methods described in the British Pharmacopoeia (1993) were unable to provide either sufficient mixing of the dissolution medium to disperse the oily rapid release material or sufficient mechanical erosion of the sustained release component of the formulation. Further studies showed that the modified paddle method resulted in reproducible biphasic-release dissolution profiles when paddle speeds were increased from 70 to 100 rpm and the dissolution medium pH varied from pH 6.0 to 8.0. Dissolution performance was adversely affected by temperatures below 36.8° C but unaffected up to a temperature of 37.5° C. Increasing the bile acid concentration in the dissolution medium from 7 to 14 mM did not alter the dissolution profile. The physiological implications of these results are discussed.

Keywords: Liquid-filled hard gelatin capsule; Biphasic release; Propranolol; HALO™ drug delivery system; Dissolution testing; Floating dosage form

1. Introduction

Floating dosage forms have been investigated as a means of prolonging retention in the gastrointestinal tract in order to maintain sustained drug release particularly in the stomach over long periods. One problem identified by Desai and Bolton (1993) was poor correlation between in vitro dissolution performance of a floating dosage form and the results of in vivo bioavailability studies. The present study describes the development and validation of a dissolution method for a floating dosage form with biphasic release characteristics, as exemplified by the HALO™ drug delivery system, although in this case the func-

* Corresponding author. Cortecs Ltd, Techbase 1, Newtech Square, Deeside Industrial Park, Deeside, Clwyd CH5 2NT, UK.

SSDI 0378-5173(94)00431-5

tioning of the delivery system is not reliant upon the floating characteristics of the formulation.

The HALO™ delivery system consists of a biphasic rapid and sustained release formulation containing a lipophilic drug, exemplified by propranolol, dissolved in oleic acid. Initial rapid release of the drug-oleic acid solution is followed by the subsequent sustained release of these components from a solid erodible matrix containing a Gelucire® of low HLB and melting point above 37° C. In order to maintain biphasic release characteristics, in vivo and in vitro, and delay release of formulation components until the lipid absorption sites in the small intestine are reached, an enteric-coated dosage form is required. The importance of enteric protection for maintaining the performance of the HALO™ delivery system has been discussed previously (Burns et al., 1994).

The HALO™ drug delivery system is designed to improve the systemic bioavailability of lipophilic drugs with poor aqueous solubility and/or high first-pass metabolism. Human volunteer studies have shown that the HALO™ delivery system increases the bioavailability of propranolol by at least 2-fold, in terms of AUC and Cmax, compared with a standard commercial preparation, Half Inderal LA® (ICI) (Barnwell et al., 1993, 1994; Tucker, 1993).

The maintenance of the biphasic dissolution profile of the HALO™ delivery system is one of the essential features which determines improved bioavailability of HALO™ formulated drugs (Barnwell, 1992; Barnwell et al., 1993, 1994). The present study describes the process of selection, development and validation of a dissolution method for 80 mg HALO™-propranolol capsules to enable the generation of robust and discriminative data for studying possible inter-batch variation, and the effects of storage on the performance of floating dosage forms of this type.

2. Material and methods

2.1. Materials

The components of the enteric-coat were supplied from the sources described in Burns et al. (1994). Size 0 or size 1 clear hard gelatin Licaps®, or Starlock® capsules were obtained from Capsugel (Bornem, Belgium), or R.P. Scherer Ltd (Swindon, UK). Propranolol base and Gelucire® (diacetylated monoglycerides Fr.P.) were supplied by Alfa Chemicals Ltd (Preston, UK). Oleic acid B.P. grade was supplied by H. Foster & Co. (Leeds, UK). Cremophor® RH40 (polyethoxylated castor oil USP-NF) was supplied by BASF plc (Stockport, UK) and Aerosil® 200 (colloidal silicon dioxide E.P.) by Degussa (Wilmslow, UK). The bile acids used in the dissolution medium, cholic acid (sodium salt) and deoxycholic acid (sodium salt), were obtained from Sigma (Poole, UK) or Fluka (Gillingham, UK). All other chemicals used were of an appropriate grade and obtained from reputable suppliers. The 10 mm HDPE and 1.2 mm cellulose acetate filters fitted to the dissolution vessel sample probes were purchased from Sartorius (Epsom, UK).

2.2. Manufacturing methods

Biphasic liquid-filled 80 mg HALO™-propranolol capsules containing propranolol base, oleic acid, Gelucire®, Cremophor RH40®, and Aerosil® 200 were manufactured by mixing the sustained release formulation components at a temperature above their melting point until a clear solution was formed before filling into capsules. After solidification of the sustained-release component the rapid-release phase of the formulation was added, each phase contained 40 mg of propranolol. HALO™-propranolol capsules were manufactured on a bench scale using heated mixing vessels and positive displacement pipettes. Capsules were sealed using an Elanco Laboratory Model Capsule Sealing Machine. Intermediate and full-scale manufacture of HALO™-propranolol capsules was carried out by M.W. Encap Ltd (Livingstone, UK). Intermediate-scale capsule filling was performed using a Hibar capsule filling machine, while full-scale capsule filling was carried out with a Bosch H8K GKF 1500L, the capsules being sealed with an Elanco Qualiseal S100 capsule sealing machine. Capsules were enteric-coated by Pharma-Vinci A/S (Denmark) in an Aeromatic '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), diacylated monoglycerides (Myvacet® 9-45-K) as plasticiser, magnesium stearate and talcum. The coating level used was 10 mg/cm^2, as discussed by Burns et al. (1994).

2.3. Dissolution testing

Dissolution testing of 80 mg HALO^{TM}-propranolol capsules was carried out with either a Hanson SR2 or 72R dissolution apparatus at a paddle rotation speed of 75 rpm (unless otherwise stated in the text) calibrated as described in the USP 1990 for method 2 at 37 ± 0.2° C. Each test was carried out in 900 ml of dissolution medium which 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, adjusted to pH 6.8. To determine the release of propranolol from the HALO^{TM}-propranolol capsules, 5 ml samples of dissolution medium were removed for analysis through a 10 mm HDPE filter, attached to the tip of the sample probe followed by in-line filtration using a 1.2 μm cellulose acetate filter. Samples were removed at specific intervals (e.g., 15, 30, 60, 120 min) for up to 300 min, in each case the volume taken being replaced with fresh dissolution medium. The propranolol content of the samples was determined spectrophotometrically, at 290 nm, within 10 min of sample collection, and quantified by comparison with authentic standards using a light path length of 5 mm. Excipient interference was found to be less than 2%.

2.4. Disintegration testing

Disintegration testing of enteric-coated 80 mg HALO^{TM}-propranolol capsules was carried out in accordance with the British Pharmacopoeia (1993) monograph for enteric-coated capsules using a Pharmatest® PW30 disintegration apparatus. Testing was carried out both at pH 1.0 in 0.1 M HCl and with the medium described in section 2.3, adjusted to pH 5.0, 6.0, 6.8 and 8.0. The time taken for capsule rupture and for complete capsule disintegration were recorded.

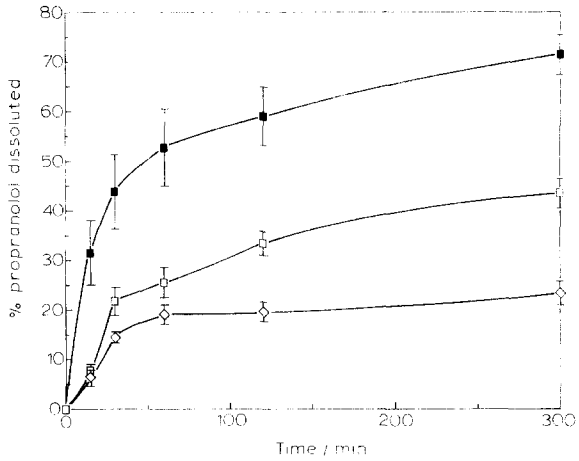

Fig. 1. Dissolution profiles of HALO^{TM}-propranolol capsules using basket (◇), paddle (□) and modified paddle (■) dissolution methods. Values are means ± SD of six determinations.

3. Results

3.1. Selection of dissolution method for HALO^{TM}-propranolol capsules

The dissolution performance of HALO^{TM}-propranolol capsules was compared using three dissolution methods; BP type 1 basket apparatus, BP type II paddle method and a modified paddle method in which the paddle blades were set to the surface of the dissolution medium. The results of this comparison are shown in Fig. 1. Using the BP type 1 basket apparatus, HALO^{TM}-propranolol capsules ruptured within 15 min releasing the rapid-release phase of the formulation into the dissolution medium, subsequently floating as droplets at the surface. After 300 min, the basket was removed and the contents examined. Although a small amount of the solid sustained-release component of the formulation had been squeezed into the mesh of the basket, most remained substantially intact. These observations were reflected in the dissolution profile (see Fig. 1) of propranolol, with only 19%

release taking place after 60 min and 23% after 300 min.

In the assessment of dissolution with the BP type II paddle method, the HALO™-propranolol capsules floated at the dissolution medium surface, rupture taking place within 15 min. A frequent observation was the adherence of the capsule and/or sustained-release component to the paddle shaft. After 300 min, the majority of the sustained-release formulation component remained intact. Similarly, the levels of propranolol measured in the dissolution medium showed that only 26% release had occurred after 60 min and 43% after 300 min (see Fig. 1).

In the modified paddle method, in which the paddles were set so that the top of the paddle blade was just breaking the surface film of the dissolution medium, capsule rupture again took place within 15 min, however, in this case the rapid-release phase was rapidly dispersed and the sustained-release component underwent substantial erosion leaving only a small residual wax plug after 300 min. In accordance with these observations 59% propranolol release occurred after 60 min, increasing to 72% after 300 min. The modified paddle method was thus the only one of the three methods investigated which was able to adequately demonstrate the biphasic release characteristics of the HALO™ delivery system (see Fig. 1).

3.2. Rotational speed selection

The selection of the ideal rotational speed of the paddles in the modified method was made on the basis of the ability to discriminate between 'acceptable' and 'unacceptable' HALO™-propranolol capsules. Acceptable capsules were represented by freshly manufactured biphasic HALO™-propranolol capsules, whereas unacceptable capsules were those which had been stored at elevated temperatures for at least 18 months, resulting in a melting of the sustained-release components and in the case of non-enteric coated capsules, a visible intermixing between the rapid and sustained-release formulation components. Dissolution studies on acceptable capsules were initially carried out at 25, 50, 70, 75 and 100 rpm with the modified paddle method described above. The results are shown in Fig. 2. At rotational speeds below 70 rpm the oily rapid-release formulation component collected at the surface of the dissolution medium resulting in sampling difficulties caused by the adherence of oil droplets to the sampling probe. At rotational speeds of 70–100 rpm there was little variation in the dissolution performance of HALO™-propranolol capsules, demonstrating that satisfactory sampling had been possible.

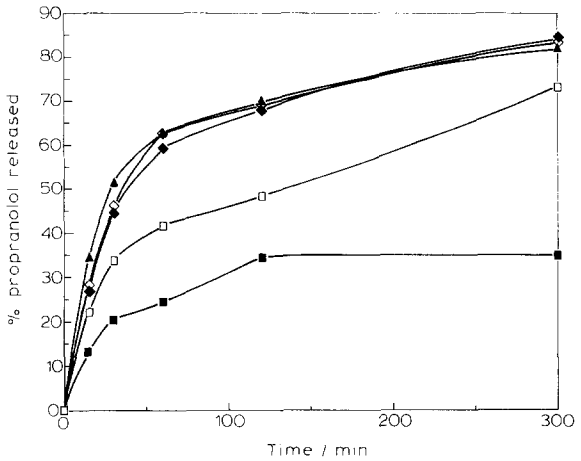

Fig. 2. Dissolution profiles of HALO™-propranolol capsules at 25 (■), 50 (□), 70 (◇), 75 (◆) and 100 (△) rpm. Values are means of six determinations.

A second series of studies were carried out using the unacceptable capsules. From the results in Table 1 it is evident that at paddle rotation speeds between 70 and 100 rpm the method

Table 1
Effect of paddle rotation speed on the dissolution of HALO™-propranolol capsules

Time (min)	% propranolol released					
	70 rpm		75 rpm		100 rpm	
	A	U	A	U	A	U
0	0	0	0	0	0	0
15	28±6	10±3	27±4	10±2	35±2	9±4
30	46±4	17±3	45±4	14±2	51±2	18±4
60	63±6	27±2	59±6	27±2	63±4	33±5
120	69±7	42±3	68±7	41±3	70±3	53±4
300	84±3	62±2	84±3	60±4	82±3	61±3

Values are means±SD of six determinations. A, acceptable capsules; U, unacceptable capsules as defined in section 3.2.

Table 2
Effect of pH on the disintegration of enteric-coated HALO™–propranolol capsules

	% propranolol released				
	pH 1.0	pH 5.0	pH 6.0	pH 6.8	pH 8.0
Coat rupture time (min)	NCR	NCR	66.7 ± 3.1	13.3 ± 0.8	9.1 ± 1.0
Capsule disintegration time (min)	NCR	NCR	87.6 ± 8.6	19.8 ± 1.2	18.9 ± 0.6

Values are means ± SD of six determinations using enteric-coated HALO™–propranolol capsules.
NCR represents no capsule rupture after 120 min.

indicated that the biphasic rapid and subsequent sustained-release profile of propranolol from the formulation had been lost compared with the acceptable capsules.

For example, values at 30 min are reduced to around 14–18% release for unacceptable capsules compared with 45–51% propranolol release for acceptable capsules. The fact that the dissolution profile of unacceptable capsules was similar for these paddle rotation speeds indicates that the effect of rotation speed is robust for both acceptable and unacceptable capsules. Paddle rotation speeds below 70 rpm were not suitable because of the sampling difficulties outlined above.

3.3. Effect of pH on the dissolution of HALO™-propranolol capsules

Prior to investigating the effect of pH on the dissolution performance of HALO™-propranolol capsules, disintegration testing was carried out to determine the pH at which the enteric-coat, made from methacrylic acid co-polymer (Eudragit L100®), released the contents of the HALO™-propranolol capsules. The results of this study are shown in Table 2. At pH 1.0 and pH 5.0 there was no visible rupture or release of capsule contents after 2 h. At pH 6.0 capsule rupture time was 66.7 min, decreasing to 9.1 min at pH 8.0. Capsule disintegration time was 87.6 min at pH 6.0 decreasing to 18.9 min at pH 8.0. These studies show that in order to investigate the effect of low pH on the dissolution of HALO™-propranolol capsules it is necessary to avoid the potential interference caused by the enteric coat. For this reason non-enteric coated HALO™-propranolol capsules were used to assess the effect of pH on dissolution performance, therefore avoiding potentially long periods for enteric coat removal at low pH. Table 3 shows the results of dissolution testing of non-enteric coated HALO™-propranolol capsules carried out at pH 5.0, 6.0, 6.75, 6.8 and 8.0. At pH 5.0 the oily rapid-release formulation components were visible at the surface of the dissolution medium and a largely intact sustained-release formulation component remained after 300 min. However, as can be seen from Table 3 the levels of propranolol released at this pH reached levels greater than 100% (e.g., 109% at 300 min). It is likely that these values are erroneous because of the cloudiness of the dissolution medium which probably results from the precipitation of bile acids at

Table 3
Effect of pH on the dissolution of HALO™–propranolol capsules

Time (min)	% propranolol released				
	pH 5.0	pH 6.0	pH 6.75	pH 6.8	pH 8.0
15	19.8 + 2.4	24.0 ± 4.3	35.0 ± 2.4	32.6 ± 4.5	36.2 ± 1.8
30	37.0 ± 6.3	66.3 ± 25.9	51.4 ± 4.2	47.0 ± 1.3	48.3 ± 3.1
60	62.3 ± 31.5	51.6 ± 5.2	54.3 ± 4.4	53.2 ± 3.3	51.9 ± 2.5
120	104.3 ± 33.2	62.9 ± 5.9	57.6 ± 1.0	59.6 ± 7.4	56.9 ± 2.3
300	109.0 ± 30.9	78.3 ± 6.2	71.6 ± 0.3	70.3 ± 4.3	67.4 ± 2.7

Values are means ± SD of six determinations using non-enteric coated HALO™–propranolol capsules.

pH 5.0. At pH 6.0 an erratic dissolution profile was observed, whereas at pH 6.75, 6.8 and 8.0 a reproducible biphasic dissolution profile was observed.

3.4. Effect of temperature on the dissolution of HALO^{TM}-propranolol capsules

The results of the dissolution studies carried out with HALO^{TM}-propranolol capsules at 36.5, 36.8, 37.0, 37.2 and 37.5° C are shown in Fig. 3. A comparison of the dissolution profiles indicates that at 36.5° C there was a considerable decrease in both initial release of propranolol (54% at 60 min compared with 63% at 37° C) and in the sustained-release of propranolol (73% compared with 84% at 300 min at 37° C). No apparent increase or decrease in rapid or sustained-release of propranolol was observed at temperatures above 36.8° C.

3.5. Effect of bile acid concentration on the dissolution of HALO^{TM}-propranolol capsules

A dissolution study was carried out using the modified paddle method in which the bile acids described in section 2 were omitted from the dissolution medium. Under these conditions the rapid-release component of the HALO^{TM}-propranolol formulation failed to disperse, floating as oily droplets at the surface of the dissolution medium. In addition, the sustained-release component of the formulation did not undergo extensive erosion.

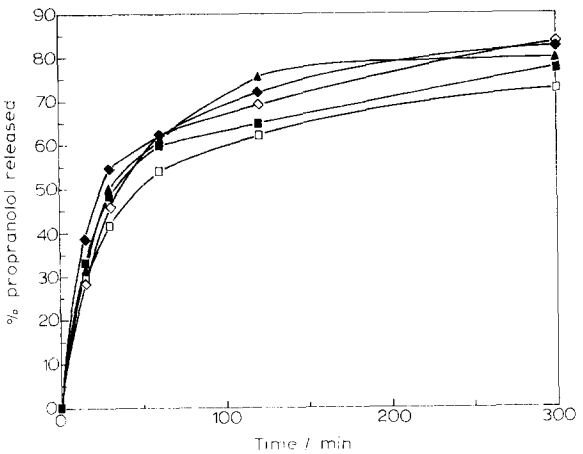

Fig. 3. Dissolution profiles of HALO^{TM}-propranolol capsules at 36.5 (□), 36.8 (■), 37.0 (◇), 37.2 (◆) and 37.5° C (▲).

Table 4
Effect of bile acid concentration on the dissolution of HALO^{TM}-propranolol capsules

Time (min)	% propranolol released	
	7 mM bile acids	14 mM bile acids
15	32.6±4.5	39.3±8.7
30	47.0±1.3	57.0±7.6
60	53.2±3.3	60.3±8.5
120	59.6±7.4	66.3±5.8
300	70.3±4.7	72.0±2.0

Values are means±SD of six determinations using non-enteric coated HALO^{TM}-propranolol capsules.

In a further series of experiments, the bile acid content of the dissolution medium was increased from 2.0 to 4.0 g l^{-1} and from 1.0 to 2.0 g l^{-1} for sodium cholate and sodium deoxycholate, respectively, corresponding to an increase in total bile acid concentration from approx. 7 to 14 mM. The results in Table 4 show that the dissolution profile of HALO^{TM}-propranolol capsules remains unchanged under conditions of elevated bile acid concentration.

4. Discussion

The HALO^{TM} drug delivery system enhances the bioavailability of lipophilic drugs (Barnwell et al., 1993, 1994; Tucker, 1993) by a mechanism which is believed to redirect drug absorption into the lymphatic system, raising the possibility of avoiding hepatic first-pass metabolism. It is well known that long-chain fatty acids, exemplified by oleic acid, are absorbed in large quantities, almost exclusively via the lymphatic system as chylomicron components (Bloom et al., 1951). Recently, oleic acid has been identified as a likely trigger for the synthesis and secretion of chylomicrons into the lymphatic system (Field et al., 1988; Dashti et al., 1990; Moberley et al., 1990). A major source of oleic acid and other unsaturated fatty acids containing 18 carbon atoms is biliary lecithin (Balint et al., 1965; Davidson et

al., 1986, 1988; Barnwell et al., 1987; Ichihashi et al., 1991a,b, 1992) suggesting that the appearance of bile-derived oleic acid in the intestine may initiate lipid absorption and lymph production by enterocytes. The explanation for improved propranolol bioavailability using the HALO™ delivery system is based on the hypothesis that oleic acid stimulates lymph flow and therefore lymphatic absorption of drugs. In an earlier study (Barnwell et al., 1992) it became apparent that the capacity for improved drug delivery using oleic acid may be limited, perhaps requiring sustained drug access to the lymphatic system while maintaining the potential triggering effect of a bolus release of oleic acid. These two criteria are met by using a biphasic rapid and sustained release format for oleic acid drug release, the assessment of which is the subject of the present study (Barnwell, 1992).

The rapid-release component of the biphasic HALO™-propranolol formulation contains propranolol base dissolved in oleic acid, and, the sustained-release of oleic acid and drug from the formulation is achieved by using polyglycolysed glycerides (Gelucires®). Gelucires® exist in many grades of varying melting point and HLB (hydrophile-lipophile balance), a particular grade or combination of grades of Gelucire® may be selected to give an appropriate in vitro/in vivo release profile. Further modifications to the release rate of oleic acid and drug may be achieved by the inclusion of the non-aqueous stiffening agent colloidal silicon dioxide (Aerosil® 200) and a non-ionic surfactant such as polyoxyl-40-hydrogenated castor oil (Cremophor® RH40). The sustained-release of oleic acid and drug from the Gelucire® matrix is by progressive surface erosion. This is demonstrated by the present study which compares propranolol release using standard basket, paddle and modified paddle dissolution methods and shows that significant release of the propranolol from the sustained-release phase could only be detected when surface erosion occurred with the modified paddle method. This dissolution method has the ability to discriminate clearly between acceptable and unacceptable capsules exemplified by the loss of the initial rapid-release of propranolol from the latter. The robustness of the dissolution method is clearly demonstrated for rotational speed and for physiological gastrointestinal pH values providing that the enteric-coat is removed. Of further interest is the lack of effect of increased bile acid concentration in the dissolution medium, suggesting dissolution of the HALO™ formulation is likely to be unaffected by the wide variations in bile acid concentration observed in the human small intestine (Carey and Cahalane, 1988). One area in which the present dissolution method for HALO™-propranolol capsules was found to lack robustness was in the effect of temperatures below 37° C. The effect of temperature on capsule dissolution in vivo is unlikely to be significant because body temperature is maintained within narrow limits, however, in vitro it is necessary to set tighter limits of temperature control of $\pm 0.2°$ C rather than the $\pm 0.5°$ C specified in the British Pharmacopoeia (1993).

In conclusion, investigation of the robustness of the present dissolution method would suggest that variations in gastrointestinal pH, bile acid concentration and mechanical erosion are unlikely to greatly affect the in vivo dissolution of HALO™-propranolol capsules. Furthermore, the present study describes a dissolution method for floating dosage forms which is able to discriminate between acceptable and unacceptable formulations.

Acknowledgements

The authors wish to express their thanks to Miss A. Hart and Mrs L. Minshull for preparing the manuscript. Cortecs Limited has been awarded a Supporting Products Under Research (SPUR) grant from the UK Department of Trade and Industry through the Welsh Office.

References

Balint, J.A., Kyriakides, E.C., Spitzer, H.L. and Morrison, E.S., Lecithin fatty acid composition in bile and plasma of man, dogs, rats and oxen. *J. Lipid Res.*, 6 (1965) 96–99.

Barnwell, S.G., Biphasic release formulations for lipophilic drugs. *International Patent Application WO92 / 06680*, 1992.

Barnwell, S.G., Gauci, L., Harris, R.J., Attwood, D., Littlewood, G., Guard, P., Pickup, M.E. and Barrington, P., Greatly enhanced oral bioavailability of propranolol using the HALO™ liver-bypass drug delivery system. *Capsule News*, 8 (1993) 2–3.

Barnwell, S.G., Gauci, L., Harris, R.J., Attwood, D., Littlewood, G., Guard, P., Pickup, M.E. and Barrington, P., Greatly enhanced oral bioavailability of propranolol using the HALO™ liver-bypass drug delivery system. *J. Controlled Release*, 28 (1994) 306–309.

Barnwell, S.G., Laudanski, T., Story, M.J., Mallinson, C.B., Harris, R.J., Cole, S.K., Keating, M. and Attwood, D., Improved oral bioavailability of propranolol in healthy human volunteers using a liver bypass drug delivery system containing oleic acid. *Int. J. Pharm.*, 88 (1992) 423–432.

Barnwell, S.G., Tuchweber, B., Yousef, I.M., Biliary lipid secretion in the rat during infusion of increasing doses of unconjugated bile acids. *Biochim. Biophys. Acta*, 922 (1987) 221–223.

Burns, S.J., Higginbottom, S., Corness, D., Hay, G., Whelan, I., Attwood, D. and Barnwell, S.G., A study of enteric-coated liquid-filled hard gelatin capsules with biphasic release characteristics. *Int. J. Pharm.*, 110 (1994) 291–296.

Bloom, B., Chaikoff, I.L., Reinhardt, W.O., Intestinal lymph as pathway for transport of absorbed fatty acids of different chain lengths. *Am. J. Physiol.*, 166 (1951) 451–455.

British Pharmacopoeia, HMSO, London, Appendix A160–A161, 1993.

Carey, M.C. and Cahalane, M.J., Enterohepatic circulation. In Arias, I.M., Jakoby, W.B., Popper, H., Schachter, D. and Shafritz, D.A. (Eds), *The Liver: Biology and Pathobiology*, Raven Press, New York, 1988, pp. 573–615.

Dashti, N., Smith, E.A. and Alanpovic, P., Increased production of apoprotein B and its lipoprotein by oleic acid in Caco2 cells. *J. Lipid Res.*, 31 (1990) 113–123.

Davidson, N.O., Drewek, M.J., Gordon, J.I. and Elovson, J., Rat intestinal apolipoprotein B gene expression. Evidence for integrated regulation in bile salt, fatty acid and phospholipid flux. *J. Clin. Invest.*, 82 (1988) 300–308.

Davidson, N.O., Kollmer, M.E. and Glickman, R.M., Apolipoprotein B synthesis in rat small intestine regulation by dietary triglyceride and biliary lipid. *J. Lipid Res.*, 27 (1986) 30–39.

Desai, S. and Bolton, S., A floating controlled-release drug delivery system: In vitro-in vivo evaluation. *Pharm. Res.*, 10 (1993) 1321–1325.

Field, F.J., Albright, E. and Mathur, S.N., Regulation of triglyceride-rich lipoprotein secretion by fatty acids in Caco2 cells. *J. Lipid Res.*, 29 (1988) 1427–1437.

Ichihashi, I., Kinoshita, H. and Yamada, H., Absorption and disposition of epithosteroids in rats: 2. Avoidance of first-pass metabolism of mepitiostane by lymphatic absorption. *Xenobiotica*, 21 (1991a) 873–880.

Ichihashi, I., Kinoshita, H., Takagishi, Y. and Yamada, H., Effect of bile on absorption of mepitiostane by the lymphatic system in rats. *J. Pharm. Pharmacol.*, 44 (1991b) 565–569.

Ichihashi, I., Kinoshita, H., Takagishi, Y. and Yamada, H., Effect of oily vehicles on absorption of mepitiostane by the lymphatic system in rats. *J. Pharm. Pharmacol.*, 44 (1992) 565–569.

Moberley, J.G., Cole, T.G., Alpers, D.H. and Schonfield, G., Oleic acid stimulation of apolipoprotein B secretion from HepG2 cells and Caco2 cells occurs post-transcriptionally. *Biochim. Biophys. Acta*, 1042 (1990) 70–80.

Tucker, G., Drug delivery: lymphing along? *Lancet*, 341 (1993) 1314–1315.