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Formulation strategies designed to maintain the biphasic release characteristics of liquid-filled capsules

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Abstract

Formulation strategies have been developed to prevent the intermixing and consequent loss of biphasic release characteristics during prolonged storage of a drug delivery system (HALO™) comprising liquid-filled capsules containing a rapid-release phase of oleic acid and propranolol base, and a sustained-release phase of an erodible matrix of the above. In one approach, a hydrophilic Gelucire® phase barrier was inserted between the rapid and sustained-release formulation components, while in an alternative approach, a hydrophobic Gelucire® was added to the rapid-release phase, solidifying it at temperatures below 37°C. Maintenance of the biphasic dissolution characteristics at pH 6.8, and acid resistance of the enteric coat were monitored by sensitive and discriminating dissolution methods at a variety of storage temperatures for up to 2 years. The importance of retaining the biphasic release characteristics of the formulation to ensure the greatly enhanced bioavailability of lipophilic drugs administered using the HALO™ delivery system is discussed.

Keywords: Liquid-filled capsules; Biphasic release; Propranolol; HALO™ drug delivery system; Enteric coating; Dissolution testing; Phase barrier

1. Introduction

The importance of biphasic oleic acid delivery in enhancing the oral bioavailability of lipophilic drugs, exemplified by propranolol, has been

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demonstrated in human volunteers (Barnwell et al., 1996). Concomitant delivery of fatty acids has also been shown to increase substantially the oral bioavailability of propranolol in animals (Aungst and Hussain, 1992).

In the case of HALO™-propranolol capsules, biphasic oleic acid and propranolol delivery has been achieved on commercial-scale manufacturing equipment by the sequential liquid filling of capsules with a sustained-release erodible thermosoftening matrix containing Gelucires®, followed by a liquid rapid-release phase consisting of oleic acid and propranolol base (Burns et al., 1995). The effective enteric coating of HALO™-propranolol capsules, discussed by Burns et al. (1994), has been shown to improve further the bioavailability performance of HALO™-propranolol capsules evidenced by comparing the results observed by Barnwell et al. (1993, 1994) with the later study of Barnwell et al. (1996).

A sensitive and discriminating in vitro dissolution method for assessing the biphasic release characteristics of HALO™-propranolol capsules, and other floating dosage forms has been developed (Burns et al., 1995), enabling the long-term stability of biphasic release formulations to be determined. The present study was carried out to test the technical feasibility of multi-component liquid-filling of capsules on production-scale manufacturing equipment and investigates formulation strategies for maintaining the long term stability of their biphasic release characteristics.

2. Materials and methods

2.1. Materials

Size 0 and size 1 clear hard gelatin capsules suitable for liquid filling were obtained from either Capsugel (Bornem, Belgium) or RP Scherer (Swindon, UK). Gelucires® (saturated polyglycolysed glycerides FrP) and propranolol base were supplied by Alfa Chemicals (Preston, UK). The enteric coating material, methacrylic acid copolymer type A USP/NF (Eudragit®, L100), was supplied by Dumas (UK) (Tunbridge Wells). Diacetylated monoglyclerides USP/NF (Myvacet® 9-45-K), used as a plasticiser, was obtained from Honeywill and Stein (Sutton, UK). Other components of the enteric coat, talcum EP, magnesium stearate EP, purified water EP and ethanol 96% BP were of an appropriate quality. Oleic acid BP was supplied by H. Foster (Leeds, UK). Cremophor® RH40 (polyethoxylated castor oil USP/NF) and Aerosil® 200 (colloidal silicon dioxide EP) were purchased from BASF (Stockport, UK) and Degussa (Wilmslow, UK) respectively. 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-μm high density polyethylene (HDPE) and 1.2-μm cellulose acetate filters fitted to the dissolution vessel sample probes were purchased from Sartorious (Epsom, UK).

2.2. Manufacturing methods

Liquid-filled 80-mg HALO™-propranolol capsules were manufactured by M.W. Encap (Livingston, West Lothian, UK) using standard production-scale, liquid-filling apparatus (Bosch H&K GKF 1500L), and sealed by gelatin banding with a Qualiseal S100 machine. In some cases up to 100 000 capsules were manufactured to test the full-scale production feasibility of the manufacturing method. Small-scale batches of capsules were manufactured by the method described by Burns et al. (1995). The sustained-release component of HALO™- propranolol capsules contained Gelucire®, Cremophor RH40®, Aerosil® 200, oleic acid and propranolol base, and was prepared by mixing these materials at a temperature above their melting point, until a homogeneous mixture was formed. This mix was then filled into capsules.

2.2.1. Biphasic capsules with liquid rapid-release phase

The rapid-release component of the formulation was manufactured by mixing propranolol base with oleic acid until completely dissolved to form a clear solution and stored at room temperature until required for capsule filling. Filling of the rapid-release phase was carried out immedi-

ately after the sustained-release component, using the dual pump facility of the Bosch H&K GKF 1500L liquid-filling machine. Alternatively, capsule caps were returned to the pre-lock position, after filling only the sustained-release phase, enabling partially filled capsules to be reloaded into the machine and subsequent phases to be filled.

2.2.2. Biphasic capsules with liquid rapid-release phase and phase barrier

Capsules were filled with the sustained-release component, reloaded into the capsule filling machine and then filled with a phase barrier, consisting of approximately 150 mg of Gelucire® 44/14, before subsequently also filling with the liquid rapid-release phase described above (Barnwell et al., 1995). The choice of a 150-mg phase barrier was based on preliminary studies which showed that this quantity of Gelucire® 44/14 was required to ensure complete phase separation across the entire interface.

2.2.3. Biphasic capsules with solid rapid-release phase

As an alternative to the liquid rapid-release phase formulation strategy described above, a rapid-release phase was prepared, containing oleic acid, propranolol base and Gelucire® 33/01, which was solid at 30°C but was completely liquid at 37°C (Burns et al., 1996). This formulation approach could be carried out either by sequential filling using the dual pump facility of the Bosch H&K GKF 1500 L, or by reloading partially filled (with sustained-release phase) capsules reclosed to the pre-lock position.

2.2.4. Enteric coating of biphasic capsules

Enteric-coating of the capsules was carried out by Pharma Vinci A/S (Denmark) on a production-scale Aeromatic 'Combi-Coata' fluidised-bed spray-coating machine using an aqueous-ethanolic enteric-coating solution containing the enteric polymer Eudragit® L100, the plasticiser Myvacet® 9-45K, magnesium stearate and talcum. The coating level of polymer used was 10 mg/cm^2 in line with the recommendations of Burns et al. (1994).

2.3. Dissolution testing

Dissolution testing of HALO™-propranolol capsules was carried out using a modification of the British Pharmacopoeia (1993)/ US Pharmacopeia (1990) dissolution method for tablets and capsules, the paddles set to the surface of the dissolution medium to allow sufficient erosion and dispersion of the floating capsule components in either a Hanson SR2 or 72R dissolution apparatus. A paddle rotation speed of 75 rpm, calibrated as described in the US Pharmacopeia (1990) for method 2 at 37 ± 0.2°C was used in accordance with the method of Burns et al. (1995). Each test was carried out in 900 ml of dissolution medium which contained 5.84 g/l disodium hydrogen orthophosphate, 4.61 g/l potassium dihydrogen orthophosphate, 2.00 g/l sodium cholate and 1.00 g/l sodium deoxycholate, adjusted to pH 6.8. The release of propranolol from HALO™-propranolol capsules was determined using 5-ml samples of dissolution medium removed for analysis through a 10-μm HDPE filter attached to the tip of the sample probe, followed by in-line filtration using a 1.2-μm cellulose acetate filter, at specified intervals (e.g. 15, 30, 60, 120 min) for up to 300 min. In each case the volume taken was replaced by 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 of 5 mm.

2.4. Acid challenge of enteric-coated capsules

Enteric-coated 80-mg HALO™-propranolol capsules were subjected to acid challenge in 0.1 M HCl for 4 h as described by Burns et al. (1994) using the apparatus configuration described above.

2.5. Stability testing

Enteric-coated and non-enteric-coated biphasic HALO™-propranolol capsules containing the solid sustained-release component with either liquid rapid-release phase, liquid rapid-release phase

with phase barrier, or solid rapid-release phase, were subjected to stability testing under a variety of storage conditions (e.g. 4, 25, 30, 30°C and 75% relative humidity, 37°C) for up to 2 years. Samples of capsules were taken at specific intervals and subjected to dissolution testing, acid challenge and visual inspection. In all cases capsules were stored in securitainers.

3. Results

3.1. An assessment of the long-term stability of biphasic capsules with a liquid rapid-release phase and no phase barrier

Dissolution testing of biphasic HALO™-propranolol capsules with a liquid rapid-release phase was carried out for up to 12 months following storage at 4°C, ambient dark, ambient light, 30°C and 75% relative humidity, and 37°C (see Fig. 1). Only the capsules stored at 4°C maintained the biphasic dissolution profile at 12 months. Capsules stored under these conditions for 3 months were used in the bioavailability study described by Barnwell et al. (1993, 1994). Fig. 1 shows that there is a progressive decline in biphasic release characteristics with increasing storage temperature. This decline is typified by the loss of the initial rapid-release component of the dissolution profile over the initial 60 min together with a reduction in the total extent of propranolol release at 300 min. For example, capsules stored at 37°C for 12 months released only 6.3% at 60 min and 20.8% of propranolol at 300 min, compared with values of 56.2% and 91.4%, respectively, for freshly manufactured capsules. Low levels of propranolol release were often accompanied by the appearance of a residual non-erodible plug of formulation components in the dissolution vessel. The photographs in Fig. 2(A) and (B), of non-enteric-coated capsules stored under similar conditions to the enteric-coated capsules subjected to dissolution testing, demonstrate a visible intermixing between the rapid and sustained-release phases accompanied by an orange/brown colouration and a decrease in the volume of the rapid-release phase, which became more apparent with time and elevated storage temperatures. This phenomenon was also observed with enteric-coated capsules from which the enteric coat had been removed with a scalpel. Non-enteric-coated capsules undergo a decline in biphasic release characteristics similar to that of enteric-coated capsules stored under identical conditions (see Fig. 3).

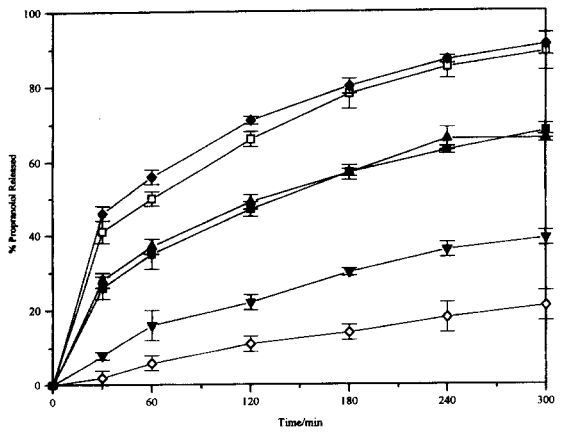

Fig. 1. Dissolution characteristics of enteric-coated HALO™-propranolol capsules with liquid rapid-release phase, freshly manufactured (◆) and stored for 12 months at 4°C (□), ambient light (▲), ambient dark (■), 30°C and 75% relative humidity (▼), and 37°C (◇).

3.2. An assessment of the long-term stability of biphasic capsules with a liquid rapid-release phase and solid Gelucire® 44/14 phase barrier

Dissolution testing of biphasic HALO™-propranolol capsules with a liquid rapid-release phase and a solid Gelucire® 44/14 phase barrier was carried out for up to 2 years following storage at 4, 25, 30, 37°C, and 30°C with 75% relative humidity. Fig. 4 shows that the dissolution profile of biphasic HALO™-propranolol capsules is maintained for at least 18 months at storage temperatures of 25°C and below. At the higher storage temperatures of 30 and 37°C there was, however, a loss in biphasic dissolution characteristics after 18 months storage (see Fig. 4). The photographs in Fig. 2(C) and (D) show that non-enteric-coated capsules stored at 25°C for 12 months maintain distinct phase separation between the rapid and sustained-release phases,

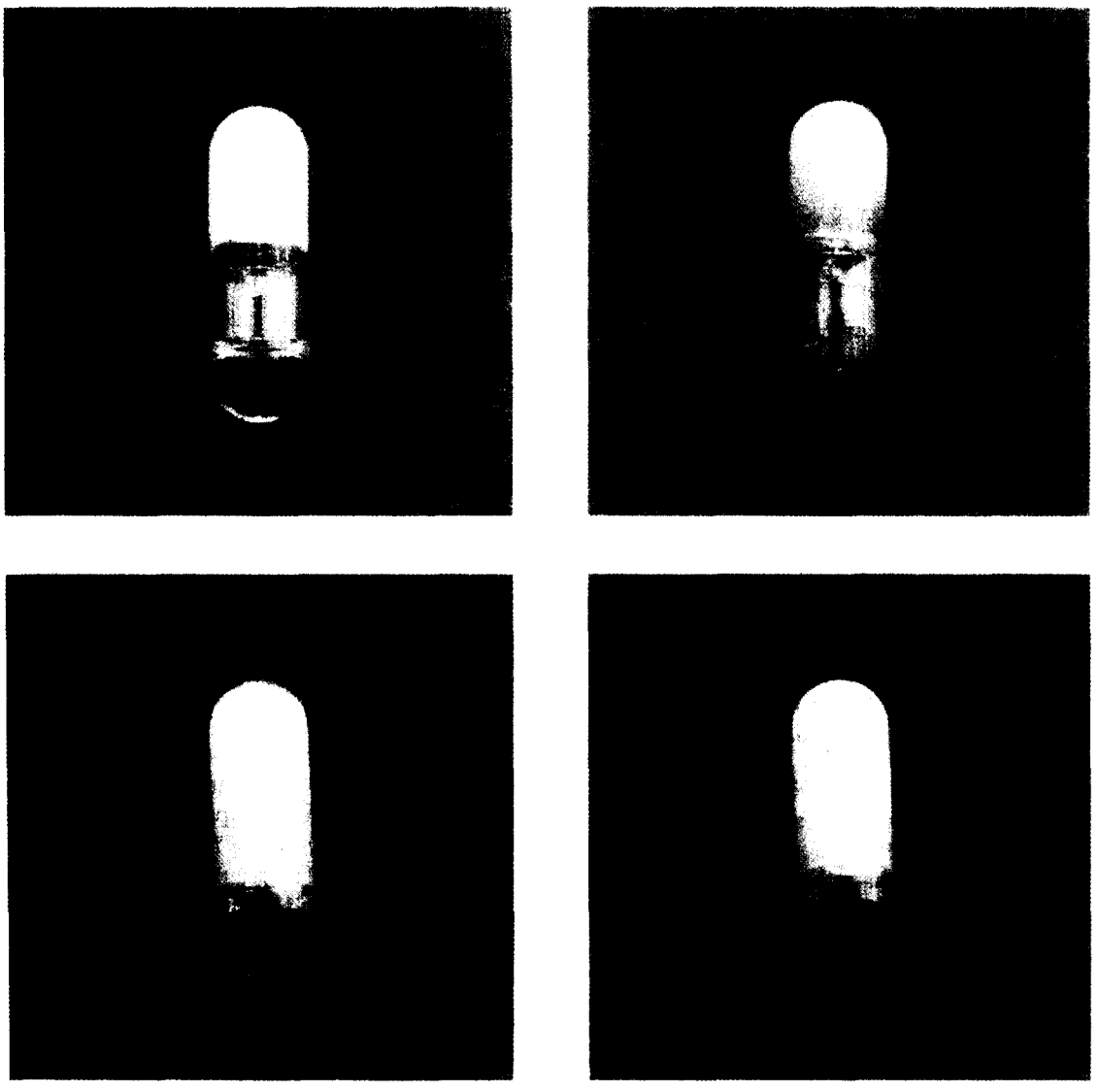

Fig. 2. Photographs of non-enteric-coated HALO™-propranolol capsules. Capsules without phase barrier, freshly manufactured (A) and after 12 months storage at 25°C (B). Capsules with phase barrier, freshly manufactured (C) and after 12 months storage at 25°C (D).

while at the same time maintaining biphasic dissolution characteristics (see Fig. 4). Visible intermixing within capsules containing a phase barrier was only observed at the higher storage temperatures after prolonged storage and coincided with a loss of biphasic dissolution characteristics. Enteric-coated capsules stored under identical conditions had a similar appearance upon the removal of the enteric coat with a scalpel. Enteric-coated HALO™-propranolol capsules stored under ambient conditions were used for the bioavailability study described by Barnwell et al. (1996) within 3 months of manufacture.

3.3. An assessment of the long-term stability of biphasic capsules with a solid rapid-release phase

Dissolution testing of biphasic HALO™-pro-

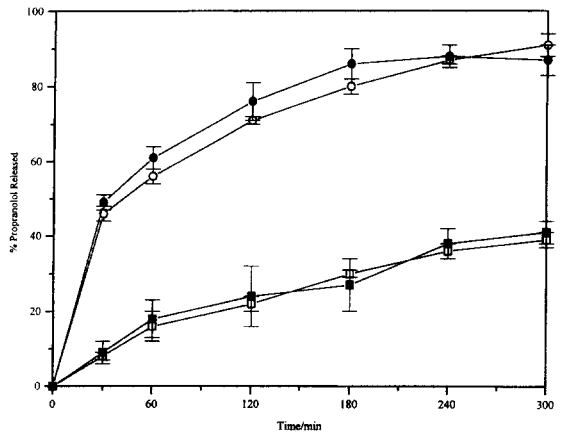

Fig. 3. Dissolution characteristics of HALO™-propranolol capsules with liquid rapid-release phase and no phase barrier, freshly manufactured (○) and after storage for 12 months at 30°C (□). Open symbols denote enteric-coated capsules, closed symbols denote non-enteric-coated capsules.

pranolol capsules with a solid rapid-release phase was carried out after storage at 25 and 30°C for up to 12 months. Fig. 5 shows that capsules stored at both temperatures maintained their biphasic dissolution profile.

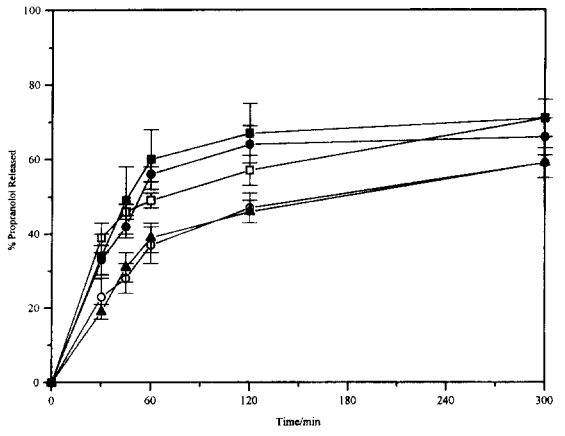

Fig. 4. Dissolution characteristics of enteric-coated HALO™-propranolol capsules with liquid rapid-release phase and Gelucire® 44/14 phase barrier, freshly manufactured (□) and stored for 18 months at 4°C (■), 25°C (●), 30°C (○) and 37°C (▲). The dissolution characteristics of capsules stored at 30°C and 75% relative humidity were similar to those of capsules stored at 30°C.

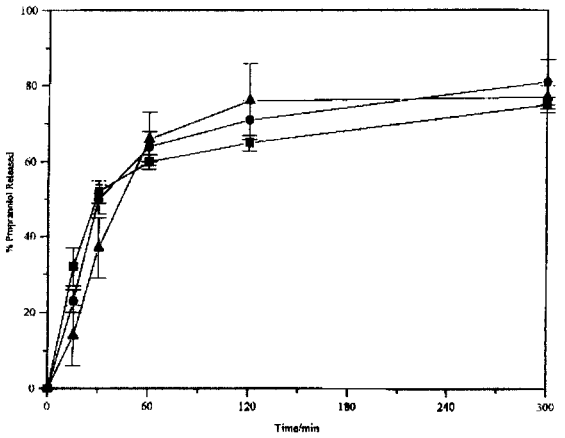

Fig. 5. Dissolution characteristics of non-enteric-coated HALO™-propranolol capsules with solid rapid-release phase, freshly manufactured (■), and stored for 12 months at 25°C (●) and 30°C (▲).

3.4. An assessment of the long-term stability of enteric-coated HALO™-propranolol capsules to acid challenge

The long-term stability of the enteric coat applied to HALO™-propranolol capsules was assessed by carrying out a 4-hour acid challenge test on capsules stored for up to 2 years following storage at 4, 25, 30 and 37°C, and 30°C with 75% relative humidity. The results showed that none of the capsules released significant amounts of propranolol during stability testing.

4. Discussion

The present study has demonstrated the technical feasibility of large-scale production of multi-component liquid-filled capsules. Two alternative formulation strategies are described which have the capability of maintaining the long-term stability of multi-component liquid-filled capsules formulated with biphasic release characteristics. Long-term viability and likely maintenance of enhanced in vivo bioavailability of biphasic HALO™-propranolol capsules is further supported by the continued integrity of the improved enteric-coating described by Burns et al. (1994).

Given the importance of biphasic oleic acid release from the HALO™ delivery system in en-

hancing the bioavailability of propranolol (Barnwell, 1992, 1995a,b; Barnwell et al., 1993, 1994, 1996; Tucker, 1993), it is essential that the beneficial release characteristics of this formulation are maintained in the long term to enable commercial exploitation to take place. Stability studies using biphasic HALO™-propranolol capsules with a liquid rapid-release phase demonstrated a decline in phase integrity and corresponding biphasic release characteristics at elevated storage temperatures. The most likely explanation for this phenomenon was the solubilisation of low-melting-point Gelucire® components from the sustained-release phase by the oleic acid present in the liquid rapid-release phase, penetration being enhanced by channels formed by colloidal silicon dioxide and the presence of surfactants. Two formulation strategies are described in the present study which overcome the problem of phase intermixing and therefore maintain the long-term stability of biphasic HALO™-propranolol capsules. A phase barrier technique involving an additional Gelucire® 44/14 liquid-filling step maintains biphasic release characteristics and phase integrity of HALO™-propranolol capsules for up to 2 years under standard storage conditions. The hydrophilic Gelucire® 44/14 probably maintains phase separation by resisting solubilisation by the hydrophobic liquid rapid-release phase and therefore preventing its contact with the hydrophobic sustained-release phase below (Barnwell et al., 1995).

A further approach to maintaining the long-term stability of the biphasic release characteristics of HALO™-propranolol capsules is to solidify the rapid-release phase with Gelcuire® 33/01 (Barnwell et al., 1995). This formulation strategy has also been used to prevent the leakage of formulation components from liquid-filled Capill® potato starch capsules (Burns et al., 1996). Providing the storage temperature remains below the melting point of the modified rapid-release phase (approximately 30–35°C) then phase integrity and dissolution performance are maintained. At storage temperatures above the melting point of the rapid-release phase, unrestricted phase intermixing can take place with a corresponding decline in dissolution performance.

In conclusion, the present study describes formulation and manufacturing strategies capable of maintaining the long-term stability of liquid-filled capsules with biphasic release characteristics. It is believed that this, together with the acid-resistance properties of the enteric coat, will enable the enhanced oral bioavailability of HALO™-propranolol capsules observed by Barnwell et al. (1996) to be reproduced after long storage periods.

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