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Assessment of a dissolution vessel designed for use with floating and erodible dosage forms

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Abstract

A standard dissolution vessel was modified for the purpose of assessing more reliably the performance of floating dosage forms, particularly those which rely on erosional mechanisms to control drug release rate. The floating dosage form was placed under a supported stainless steel mesh, situated 72 mm from the base of the vessel, and the dissolution test carried out with the paddles set 10 mm above the mesh. The performance of the modified dissolution vessel was explored using two different floating dosage forms; liquid-filled HALO™-propranolol capsules with biphasic rapid and sustained-release characteristics and a rapid-release only floating dosage form consisting of lipidic granule-filled Macrotonin™ capsules. In the case of HALO™-propranolol capsules, performance of the novel dissolution vessel was compared with an existing dissolution method for floating dosage forms in which the paddles are set to the surface of the dissolution medium in the vessel, and the use of wire sinkers. The results showed that the modified dissolution vessel provided a more reproducible dissolution profile, eliminated the risk of floating dosage forms adhering to the paddles and simplified sampling procedures, while retaining the ability to differentiate between acceptable and unacceptable dissolution performance. © 1998 Elsevier Science B.V.

Keywords: Dissolution testing; Modified dissolution vessel; Biphasic release; Floating dosage forms; Drug delivery; Propranolol; Calcitonin

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1. Introduction

Floating dosage forms may have a number of advantages in oral drug delivery because of their prolonged retention in the gastrointestinal tract, particularly the stomach. They may, for example, facilitate sustained drug release or function to maintain high concentrations of drug within the gastric mucosa, a property which may assist the antibiotic eradication of *Helicobacter pylori* (Blaser, 1992). Traditional in vitro dissolution methods have been shown to be poor predictors of in vivo performance for floating dosage forms (Desai and Bolton, 1993).

Burns et al. (1995) developed and validated a sensitive and discriminating in vitro dissolution method for floating dosage forms based on the standard British Pharmacopeia (1993)/ US Pharmacopeia (1990) apparatus 2 method, except that the paddle blades were positioned at the surface of the dissolution medium. The studies were carried out using enteric-coated HALO™-propranolol capsules containing biphasic rapid and sustained-release propranolol base dissolved in oleic acid. The maintenance of biphasic release characteristics and adequate enteric protection has been shown to be prerequisite in producing the greatly enhanced oral bioavailability performance of the HALO™ delivery system compared with standard commercial preparations of propranolol (Barnwell, 1992, 1995a,b; Barnwell et al., 1993, 1994, 1995, 1996; Burns et al., 1996a). (For a review of the form and function of the HALO™ delivery system see Barnwell and Attwood, 1996).

The present study describes a further improvement in the dissolution method for floating dosage forms described by Burns et al. (1994, 1995, 1996a,b), eliminating the need for the positioning of the paddle blades at the surface of the dissolution medium, thereby simplifying sampling, and preventing adhesion of dosage forms to the paddle blades. Comparative studies are undertaken to demonstrate the improved performance of the modified dissolution vessel using both biphasic HALO™-propranolol capsules and a rapid-release lipidic granule-filled capsule product containing salmon calcitonin.

2. Materials and methods

2.1. Materials

Clear glass dissolution vessels complying with British Pharmacopeia (1993)/ US Pharmacopeia (1990) specifications (Copley Instruments, Nottingham, UK) were modified by Chester Scientific Glass Blowing Services (Chester, UK). Stainless steel gauze, gauze size 2 mm, (Russel–Finex, Feltham, Middlesex, UK), was cut to size, and fixed with spot-welded stainless steel edging strips by Dieline — Rykel (Merseyside, UK). Size 0 or size 1 clear hard gelatin capsules (EP) were supplied by either Capsugel (Borenm, Belgium) or R.P. Scherer (Swindon, UK). Components of the HALO™ delivery system were supplied as described in Burns et al. (1995). 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).

Salmon calcitonin EP was supplied by Bachem (Torrance, CA) and an ELISA diagnostic kit suitable for the detection of salmon calcitonin in dissolution media supplied by Cortecs Diagnostics (Deeside, Flintshire, UK). All other chemicals used were of an appropriate grade and obtained from reputable suppliers. The 10-μm HDPE and 1.2-μm cellulose acetate filters fitted to the dissolution sample probes were purchased from Sartorius (Epsom, UK).

2.2. Manufacturing methods

Biphasic liquid-filled 80 mg HALO™-propranolol capsules were manufactured by MW Encap (Livingston, W. Lothian, UK) and enteric-coated by Pharma-Vinci (Denmark) as described by Burns et al. (1995, 1996c). The enteric coat level was at least 10 mg/cm^2 as discussed by Burns et al. (1994).

Macrotonin™-calcitonin capsules (potency 400 i.u. per capsule) were manufactured by spray granulation of a water-in-oil emulsion, containing phosphatidylcholine, oleic acid, nonionic surfactants and salmon calcitonin, onto a swelling hydrocolloid matrix consisting of

carboxymethylcellulose, alginic acid and gelatin. The lipidic granules were filled into hard gelatin capsules, gelatin banded and enteric-coated by a similar process to that described for HALO™-propranolol capsules.

2.3. Modified dissolution vessel

The modified dissolution vessel and insert is shown in Fig. 1 as a sectional view. The standard dissolution vessel was modified by the insertion of a moulded and indented continuous glass shoulder which runs around the entire internal circumference, 72 mm from the base, upon which a circular stainless-steel mesh insert, of similar diameter to the upper portion of the dissolution vessel may rest. This effectively divides the vessel into a lower portion, which represents approximately one-third of vessel volume, and an upper portion. A pharmaceutical dosage form undergoing testing is placed under the inserted mesh, where it is retained in the lower portion of the vessel and prevented from floating freely to the surface for the duration of the test. A standard USP paddle is rotated immediately above the mesh to cause agitation of the dosage form. The dissolution vessel described above and in Fig. 1 is subject to Unregistered Design Right and International Patent Applications (Burns et al., 1996b).

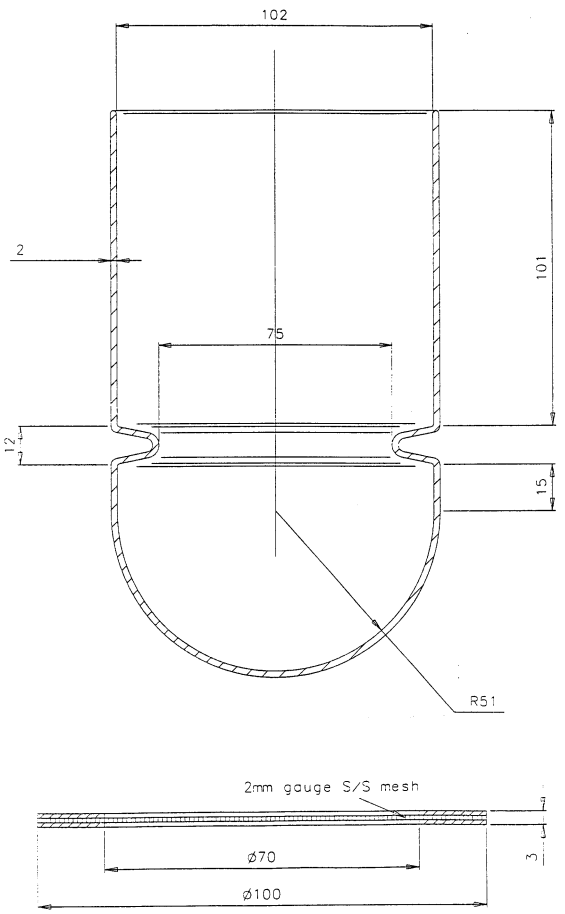

Fig. 1. A sectional view of the modified dissolution vessel. This vessel is subject to Unregistered Design Right belonging to Cortecs Ltd. and International Patent Applications (Burns et al., 1996b).

2.4. Dissolution testing

Testing of HALO™-propranolol capsules and Macrotonin™ capsules was carried out with either a Hanson SR2 or 72R dissolution apparatus at a paddle rotation speed of 75 rev./min or 100 rev./min for the modified vessel, calibrated as described in the US Pharmacopeia (1990) for method 2 at 37 ± 0.2°C.

Each test was performed in 900 ml of dissolution buffer at pH 6.8. The pH 6.8 dissolution medium contained 5.84 g/l disodium hydrogen orthophosphate, 4.62 g/l potassium dihydrogen orthophosphate, 2.00 g/l sodium cholate and 1.00 g/l sodium deoxycholate. Dissolution testing was carried out using a modification of the British Pharmacopeia (1993)/ US Pharmacopeia (1990) dissolution method for tablets and capsules, either using the modified dissolution vessel described in Section 2.3 or a standard vessel in which the paddle blades were set to the dissolution medium surface (see also Burns et al., 1994, 1995). To determine the release of propranolol from 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. The release of calcitonin was determined by removal of unfiltered 5-ml samples of dissolution medium. Particulate matter was removed from the samples by centrifugation, filtration having

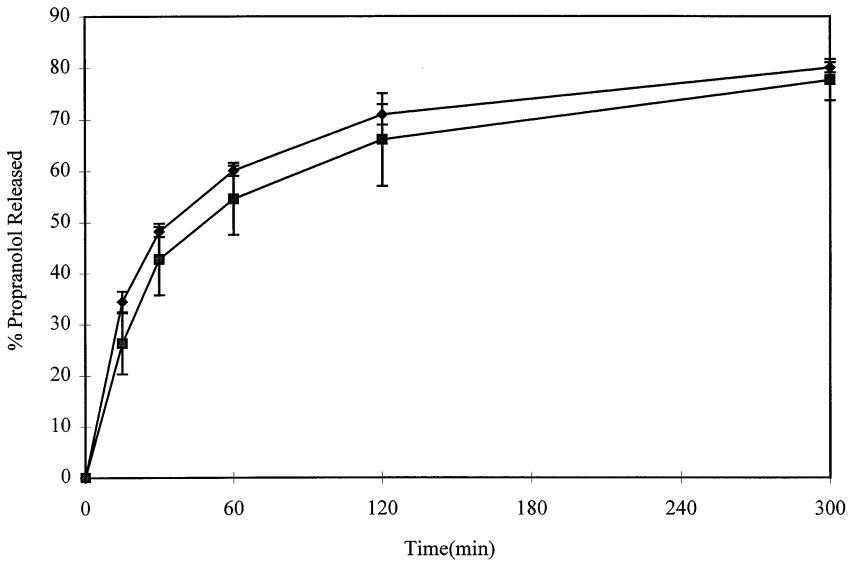

Fig. 2. Dissolution profiles of HALO™-propanolol capsules using standard (■) and modified (◆) dissolution vessels. Values represent means of six determinations with standard deviation.

proved unsuccessful due to absorption losses of drug on the filter membranes. Samples were removed at specific intervals (e.g. 15, 30, 45, 60 min) for up to 300 min, in each case a correction factor was applied to the drug concentration determined in the sample to allow for removal of medium and active. Propranolol release was determined spectrophotometrically at 290 nm, using a path length of 5 mm, and measured within 10 min of sample collection. Calcitonin was measured by a specific ELISA method following appropriate sample dilution.

3. Results

3.1. Dissolution testing of biphasic sustained-release HALO™-propranolol capsules at pH 6.8

The results in Fig. 2 show that the dissolution characteristics of biphasic HALO™-propranolol capsules were similar using both the modified and standard dissolution vessels. An observation made during the dissolution studies using the method in which the paddles were positioned at the surface was that approximately 1 in 15 capsules became attached to the paddles. This could not of course occur with the modified dissolution vessel as the capsules were retained below a mesh away from the paddle blades. Attempts were also made to use wire sinkers in conjunction with a standard dissolution technique for HALO™-propranolol capsules; however these were unsuccessful because either the capsule components adhered to the sinker preventing adequate erosion of the sustained-release matrix, or if a more loosely fitting sinker was used, the sustained-release matrix escaped to the buffer surface.

3.2. Dissolution testing of rapid-release Macrotonin™ capsules at pH 6.8

The results in Table 1 show the dissolution profiles of Macrotonin™ capsules using the standard and modified dissolution vessels. The extent and rate of calcitonin release was greater with the modified dissolution vessel; 90% after 30 min compared with 74% for the standard method. Use of the modified vessel also resulted in less variation in the dissolution data, as indicated by the generally lower coefficient of variance. Further-

more, subsequent testing of capsules with the standard dissolution arrangement resulted in a number of capsules failing the preliminary dissolution specification of 70% release after 45 min. Inspection of these capsules indicated that the non-erosional nature of the standard dissolution method had allowed the outer layers of the lipidic granules contained within Macrotonin™ capsules to swell preventing further ingression of dissolution medium. As a result some granules remained unmoistened at the end of the test. This was not observed with the modified dissolution vessel method.

4. Discussion

The present study describes the first use of a novel dissolution vessel specifically designed to assist in the in vitro evaluation of floating dosage forms and dosage forms in which erosional forces are important in determining drug release rate. Maintenance of the floating dosage form below a mesh retainer in the modified dissolution vessel allowed the paddle blades to be positioned within the body of the dissolution medium, rather than at the surface as described previously by Burns et al. (1995). This arrangement provided (i) sufficient erosion of the sustained-release component of the HALO™-propranolol formulation by allowing the Gelucire® matrix to abrade against the retaining mesh, and, (ii) adequate mixing of the dissolution medium to allow the efficient dispersion of the lipophilic components of both HALO™-propranolol and Macrotonin™ capsules. The dissolution profile produced with HALO™-propranolol capsules using a method in which the paddles were positioned at the surface and the modified dissolution vessel method was similar to the predicted in vivo dissolution of the dosage form. Deconvolution of previously published in vivo data (Barnwell et al., 1993, 1994, 1996) suggests that the rapid release phase of the HALO™-propranolol capsules is complete within 1 h of the dosage form entering the duodenum (enteric coat removal at pH 6.0). This is followed by an in vivo sustained release of drug which continues for at least 5 h. These deconvoluted in vivo release rates are comparable to those observed in vitro by both dissolution methods used to assess HALO™-propranolol capsules.

Table 1
Dissolution profiles of Macrotonin™ capsules at pH 6.8

Time (min)	% Calcitonin release	
	Standard method	Modified method
0	0	0
10	<2	<2
15	2.7 ± 5 (185)	22 ± 19 (86)
20	20 ± 27 (135)	54 ± 21 (39)
25	51 ± 32 (64)	82 ± 7 (9)
30	74 ± 24 (33)	90 ± 8 (9)

The values are means of $n = 6$ determinations ± standard deviation with coefficient of variance shown in parentheses.

It is believed that the success of these dissolution techniques in mimicking in vivo behaviour is due to the contribution of both erosional and diffusional dissolution forces applied to the dosage forms typical of those experienced within the gastrointestinal tract. The modified dissolution vessel also enabled easier access of the sampling probes, as the risk of contact with the paddle blades was reduced, while at the same time preventing the adherence of floating dosage forms to the paddle blades.

In conclusion, a modified dissolution vessel is described which is well suited to the assessment of complex floating dosage forms with erosional release characteristics without the complication of using polystyrene beads (see Aoki et al., 1992 and Khan, 1996). It is believed that this apparatus will contribute to the effective development of drug delivery systems of this type.

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