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An in vitro assessment of liquid-filled Capill® potato starch capsules with biphasic release characteristics

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Abstract

This paper describes the first use of liquid-filled Capill® potato starch capsules formulated for biphasic release and reports the development of dissolution methods suitable for assessment of drug release from this type of dosage vehicle. The liquid filling of Capill® capsules was made possible by overcoming the problem of incomplete sealing of the Capill® cap and body which initially resulted in leakage of liquid capsule contents. This was achieved by modification of the formulation to incorporate a thermosoftening agent which remained solid below 30°C, but melted at 37°C. The use of enteric-coated liquid-filled Capill® capsules formulated for biphasic release required further development of the dissolution method to incorporate a dissolution medium containing bile acids at a concentration of 14 mM to produce a similar release profile to that seen from enteric-coated hard gelatin capsules containing the same formulation. The concentration of bile salts used is in agreement with the acceptable range previously validated for use with enteric-coated hard gelatin capsules whilst also remaining within the physiological levels of bile acids found in vivo.

Keywords: Liquid-filled Capill® capsules; Biphasic release; Propranolol; HALO™ drug delivery system; Dissolution testing; Potato starch capsules

1. Introduction

Recent advances in injection moulding technology have resulted in the development of capsules

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made from potato starch (Capill®) as an alternative to hard gelatin capsules (Stepto and Tomka, 1987). Capill® capsules represent a robust dosage form with a reduced susceptibility to changes in storage conditions and which is readily suited to enteric coating (Kenyon et al., 1994). Scintigraphic techniques have shown that non-enteric coated and enteric coated Capill® capsules (Cole and Lentz, 1991; Doll et al., 1993) behave in a similar fashion in vivo to traditional hard gelatin capsules (Kenyon et al., 1994). However, in order to evaluate encapsulated formulations routinely it is important that an in vitro dissolution test can be applied which is indicative of the in vivo performance of the formulation.

If Capill® capsules are to be used reliably as an alternative to standard hard gelatin capsules then the capsule contents must not interfere with the dissolution profile of complex, as well as simple delivery systems. An example of a complex formulation is the HALO™ delivery system, which is able to enhance the oral bioavailability of lipophilic drugs, such as propranolol, subject to high hepatic first pass metabolism (Barnwell, 1995a,b; Barnwell et al., 1992, 1993, 1994, 1995, 1996; Tucker, 1993). The HALO™ delivery system consists of a drug-oleic acid solution from which drug is released at two distinct rates; an initial rapid release phase followed by sustained release from a solid erodible matrix. This biphasic formulation is encapsulated and subsequently enteric coated to obtain optimum performance in vivo (Burns et al., 1994). In another study (Burns et al., 1995), an in vitro dissolution method for an enteric coated HALO™-propian propranolol formulation was developed and validated using hard gelatin capsules as the means of encapsulation. The present study investigates the suitability of this dissolution method for assessing Capill® potato starch capsules containing the HALO™ delivery system modifying the dissolution method where appropriate. The implications of the results for predicting the in vivo dissolution performance of this complex formulation in Capill® capsules are discussed.

2. Materials and methods

2.1. Materials

Capill® potato starch and hard gelatin capsules were supplied by Capsugel (Bornem, Belgium). Propranolol base and Gelucire® (saturated polyglycolysed glycerides FrP) were obtained from Alfa Chemicals (Preston, UK). Oleic acid BP grade was supplied by H. Foster and Co. (Leeds, UK). Cremophor® RH40 (polyethoxylated castor oil USP-NF) was supplied by BASF plc (Stockport, UK) and Aerosil® 200 (colloidal silicon dioxide EP) by Degussa (Wilmslow, UK). The components of the enteric coat were obtained from the sources described in Burns et al. (1994). The bile acids and α-amylase (EC 3.2.1.1.) used in the dissolution medium were supplied by Sigma (Poole, UK) or Fluka (Gillingham, UK). The 10 μm HDPE probe tip filters were purchased from Pharmatest (Tredegar, UK) and the 1.2 μm cellulose acetate filters from Sartorius (Epsom, UK). All other chemicals used were of an appropriate grade and obtained from reputable suppliers.

2.2. Manufacturing methods

Biphasic, liquid-filled 80 mg HALO™-propranolol capsules were prepared in the following manner. A combination of oleic acid, Cremophor® RH40 and Gelucire® 50/02 were heated to 50°C and mixed. Propranolol base and Aerosil® 200 were blended into this slurry until a homogeneous mixture was produced. The resulting mixture was maintained at 50°C and filled by weight into size 0 Capill® and hard gelatin capsules and allowed to solidify upon cooling, forming the sustained release component of the formulation. The rapid release phase was formed by dissolving propranolol base in oleic acid. This solution was then dispensed by weight into capsules already containing the solid sustained release component. In a further series of studies, leakage of the formulation from Capill® capsules was prevented by solidification of the liquid rapid release phase with Gelucire® 33/01. Capsules were sealed using either an 80:20 (v/v) water:ethanol solution applied to the inside of the Capill® cap or by

gelatin banding in the case of hard gelatin capsules. The enteric coating was applied using an Aeromatic 'Combi-Coata' production scale fluidised bed coating machine using an aqueous-ethanolic coating solution containing methacrylic acid co-polymer type A USP-NF (Eudragit L100), diacetylated monoglycerides (Myvacet® 9–45 K), magnesium stearate and talcum. Where necessary placebo capsules of similar size and weight to the HALO™-propranolol capsules were used to provide sufficient bulk to allow the use of the full scale 'Combi-Coata'. The enteric coating level used on both Capill® and hard gelatin capsules was 10 mg/cm^2 as discussed by Burns et al. (1994). Manufacture of capsules at laboratory manufacture scale (batch size, 200 g) was carried out using heated magnetic stirrers and positive displacement pipettes, while pilot scale manufacture (batch size, 1 kg) was performed at MW Encap (W. Lothian, UK) using a Hibar-capsule filling machine and a Bonapace Capill® Benchtop sealing machine. Hard gelatin capsules were sealed using an Elanco Laboratory Model Capsule sealing machine.

2.3. Assessment of capsule leakage

To assess leakage of formulation components from capsules after sealing the following procedure was implemented. Individual capsules were weighed and any capsule with a gross weight 30 mg (equivalent to 20% of the rapid release phase) less than the target gross weight was deemed to have leaked. Leakage was confirmed by visual observation of capsules stored overnight on a sheet of absorbent paper.

2.4. Dissolution testing

Dissolution testing of HALO™-propranolol capsules was carried out using either Hanson SR2 or 72SR dissolution baths at a paddle rotational speed of 75 rev./min in accordance with the recommendations of Burns et al. (1995). All dissolution baths were calibrated as described in the USP XXII (apparatus suitability test). The dissolution method used was based on the BP 1993 type II apparatus, except that the paddle was raised so that the upper edge of the blade was flush with the surface of the dissolution medium, as described in Burns et al. (1995). The tests at pH 6.8 were carried out in 900 ml of phosphate buffer which contained 5.84 g l^{-1} disodium hydrogen orthophosphate, 4.61 g l^{-1} potassium dihydrogen orthophosphate, 4.6 mM sodium cholate, and 2.4 mM sodium deoxycholate (total bile acid concentration of 7 mM). Alternatively the bile salt concentration was increased to 4.8 mM and 9.2 mM for sodium deoxycholate and sodium cholate respectively (total bile acid concentration of 14 mM). These bile acid levels are in accordance with the limits determined by Burns et al. (1995). The release of propranolol from HALO™-propranolol capsules was determined by assaying 5-ml samples of dissolution medium removed at specified times through a 10-μm HDPE probe tip filter followed by an in line 1.2-μm cellulose acetate filter. Removed buffer was replaced at each of the time points to maintain a volume of 900 ml throughout the test. The propranolol content of the samples was evaluated by assessing their UV absorption at 290 nm, using a path length of 5 mm. Samples were measured within 10 min of sample collection and quantified by comparison with standard solutions.

3. Results

3.1. Assessment of formulation component leakage from Capill® HALO™-propranolol capsules

Examination of HALO™-propranolol Capill® capsules after filling and sealing, but before enteric coating revealed that 67 out of 100 capsules were identified as having leaked; this was confirmed by standing capsules on absorbent paper overnight. Reformulation of the liquid rapid release phase by incorporation of Gelucire® 33/01 resulted in a thermosoftening matrix which was liquid at 37°C but solid below 30°C. No leakage was observed from these reformulated capsules. Dissolution testing of this formulation indicated that the formulation modification did not affect the propranolol release profile com-

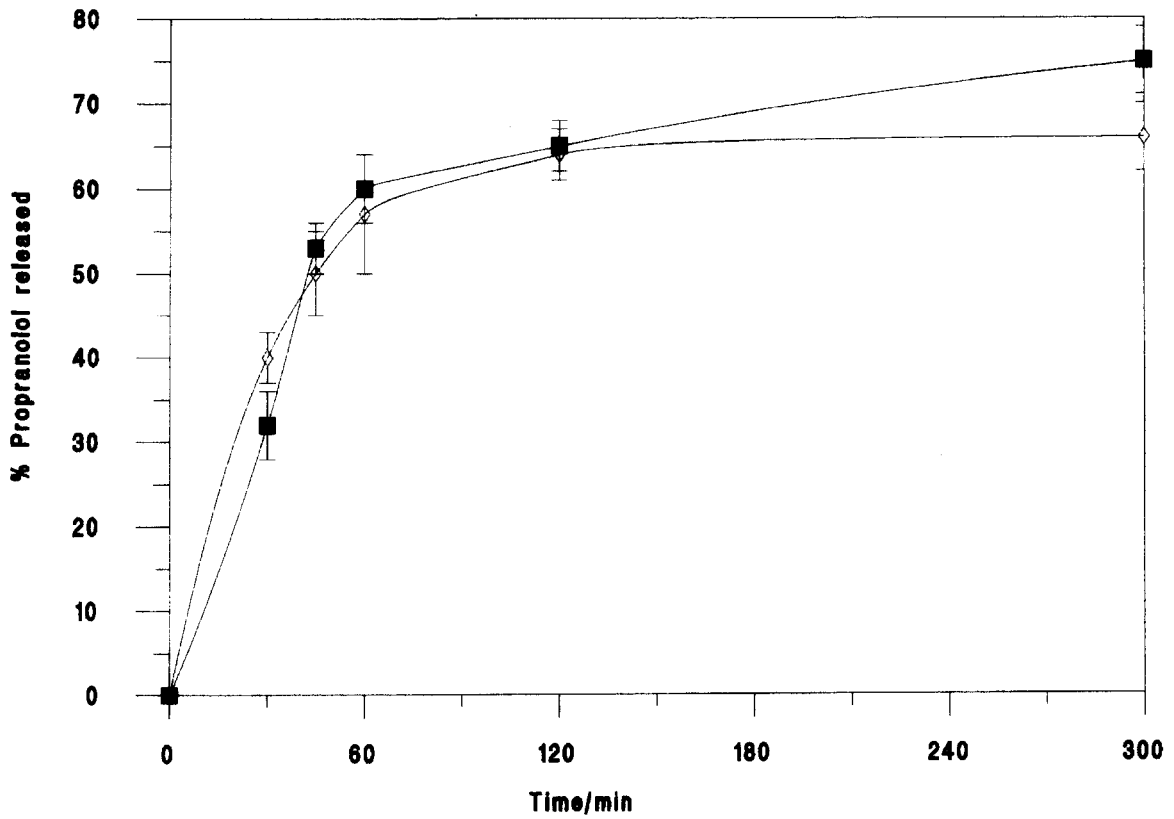

Fig. 1. Dissolution profiles of non-enteric coated HALO™-propranolol Capill® capsules formulated with liquid (◇) and thermosoftening (■) rapid release phases. Values are means ± S.D. of six determinations.

pared with capsules containing a liquid rapid-release phase (Fig. 1).

3.2. Dissolution profiles of non-enteric coated hard gelatin and Capill® potato starch HALO™-propranolol capsules

The dissolution profiles of non-enteric coated HALO™-propranolol formulations indicate similar biphasic release profiles from both hard gelatin and Capill® capsules (Table 1). The Capill® potato starch capsule showed a slightly slower release during the first 30 min of the test (23% compared with 32% release from the hard gelatin capsules). This difference was not apparent at 45 min and is therefore unlikely to be clinically significant. The sustained release phase (1–5 h) of the profile was similar for both types of capsule.

3.3. Dissolution profiles of enteric coated HALO™-propranolol hard gelatin and Capill® potato starch capsules

A comparison of the dissolution profiles of HALO™-propranolol Capill® and hard gelatin capsules enteric coated with methacrylic acid copolymer are shown in Fig. 2. It can be seen that the in vitro propranolol release was considerably slower from Capill® potato starch capsules when compared with the hard gelatin capsule formulation. The reduced release rate from the Capill® formulation was seen predominantly during the initial rapid release portion of the profile (0–75 min) where a release rate of 30 mg h^{-1} compared to 45 mg h^{-1} from the hard gelatin capsules was observed. Slower release of propranolol from the Capill® capsules was accompanied by the appear-

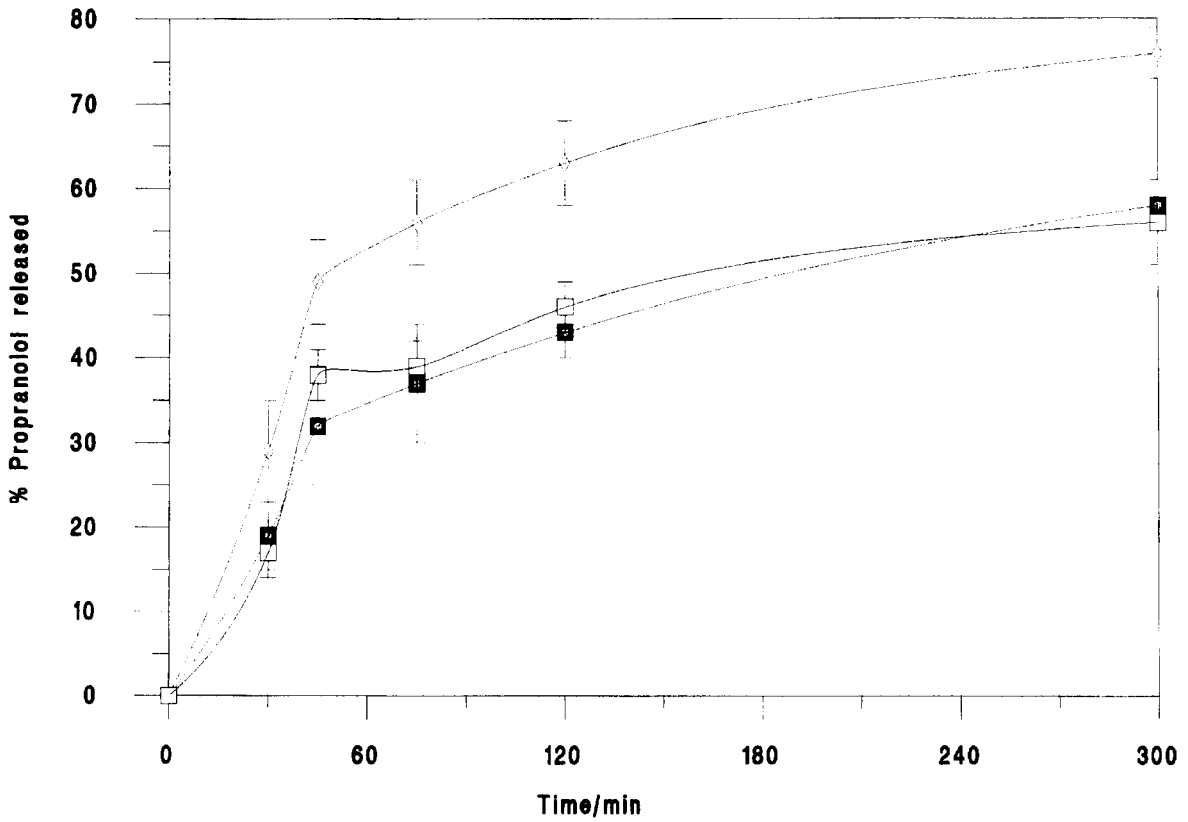

Fig. 2. Dissolution profiles of enteric coated HALO™-propranolol hard gelatin (◇), Capill® (■) capsules, and Capill® capsules in the presence of amylase (□). Values are means ± S.D. of six determinations.

ance of oily aggregates at the surface of the dissolution medium.

3.4. Effect of α-amylase on the dissolution of enteric coated HALO™-propranolol Capill® capsules

In an attempt to increase the rate of propranolol release from enteric-coated HALO™-propranolol Capill® capsules a 50-fold excess of α-amylase was added to the dissolution medium (sufficient to digest 50 times the mass of starch contained in one capsule in 3 min). The release profiles shown in Fig. 2 indicate that the release rate from the HALO™-propranolol Capill® capsules was unaffected by the addition of α-amylase, remaining considerably slower than from HALO™-propranolol hard gelatin capsules. As previously, oily aggregates were observed floating on the surface of the dissolution medium. It seems likely therefore that digestion of the starch with α-amylase does not improve the ability of the formulation components to disperse in the dissolution medium.

3.5. Dissolution profile of enteric coated hard gelatin and Capill® potato starch HALO™-propranolol capsules in the presence of increased bile acid concentrations

In a further series of studies the bile acid concentration of the dissolution medium was increased from 7 mM to 14 mM in an attempt to solubilise any lipophilic materials released from the enteric coated HALO™-propranolol Capill® capsules. The results in Fig. 3 clearly show that

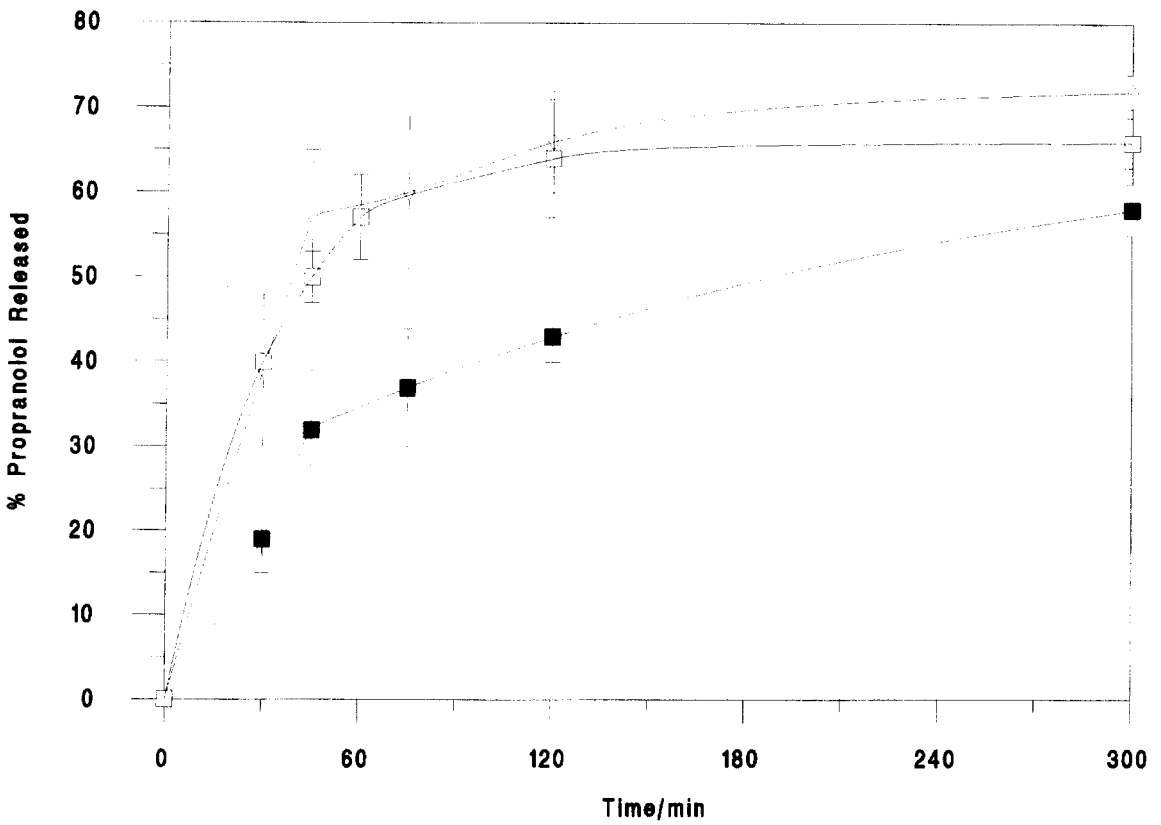

Fig. 3. Dissolution profiles of enteric coated HALO™-propranolol Capill® (◇) and hard gelatin (□) capsules with media containing bile acids at a concentration of 14 mM. Dissolution profile of enteric coated HALO™-propranolol Capill® capsules in media containing 7 mM bile acids (■) included for comparison.

the dissolution profiles of HALO™-propranolol Capill® and hard gelatin capsules were similar when the increased bile acid concentration was used in the dissolution medium, (release rate of 48 mg h^{-1} compared to 45 mg over the period 0–75 min). Furthermore, dissolution of enteric coated HALO™-propranolol Capill® capsules was achieved without the appearance of oily aggregates at the dissolution medium surface.

4. Discussion

The HALO™ drug delivery system is designed to enhance the bioavailability of lipophilic drugs particularly those liable to first pass metabolism exemplified by propranolol (Barnwell, 1995a,b; Barnwell et al., 1992, 1993, 1994, 1995, 1996; Tucker, 1993). Studies using propranolol as a model drug have shown that improved bioavailability is dependent upon the biphasic release of oleic acid (Barnwell et al., 1995; 1996). The importance of the biphasic delivery of fatty acids for enhancing the bioavailability of propranolol has also been demonstrated by Aungst and Hussain (1992). The contribution of an effective enteric coat may be demonstrated by comparing the two fold increase in propranolol bioavailability observed by Barnwell et al. (1993, 1994) with the three-fold increase seen in a more recent study (1996), the enteric coating level having been increased from 4 mg/cm^2 to 10 mg/cm^2 in accordance with the recommendations of Burns et al. (1994). Capill® potato

starch capsules have superior film adhesion properties to hard gelatin capsules making them particularly suitable for the enteric coating required by the HALO™ delivery system.

The non-enteric coated Capill® formulation released drug at a slower rate than the equivalent hard gelatin formulation during the first 30 min of dissolution testing. However, greater than 80% of the propranolol in the rapid release phase had been released by 45 min. Traditionally, dissolution of immediate release solid dosage preparations is said to be satisfactory if 70% of the drug is released within 45 min (British Pharmacopoeia, 1993). As the release of propranolol from the non-enteric coated Capill® capsules easily exceeds this requirement it is unlikely that the reduced release rate during the initial 45 min of the test is significant.

The application of an enteric coat to the Capill® formulation decreased the amount of propranolol released at all points during dissolution testing. However, the size of the sustained release plug remaining at the end of the test and the presence of oily aggregates in the dissolution medium indicated that although dissolution was proceeding as normal, the propranolol was not being solubilised, i.e. sink conditions in the dissolution medium were not being created. The results of the present investigation have shown that degradation of the starch from the Capill® capsule with α-amylase did not normalise the dissolution profile. This indicated that either starch was not the most significant factor in reducing the release rate from enteric coated Capill® formulations or that the limit dextrins produced by the enzymatic degradation of the starch affect the dissolution profile in a similar way to starch itself.

Increasing the bile acid concentration of the dissolution medium from 7 mM to 14 mM restored the propranolol release rate from enteric coated Capill® formulations to that observed with enteric-coated hard gelatin capsule formulations. The level of bile acids used was in accordance with the previous limits determined for enteric coated hard gelatin capsules by Burns et al. (1995) and probably represents levels encountered by the formulation in the gastrointestinal tract. In view of these results, it is likely therefore that the altered release profile of enteric coated Capill® HALO™-propranolol capsules is due predominantly to the presence of lipophilic components of the enteric coat and their interaction with the Capill® potato starch capsule rather than the capsule components per se.

The present study has described the first use of Capill® capsules for liquid filling, the problem of liquid leakage being overcome by the use of a solid rapid release phase. The solid rapid release phase becomes liquid at 37°C and as a result release of drug from this formulation proceeds in the same manner as drug release from the liquid formulation. This modification to the HALO™-propranolol delivery system will ensure that Capill® based formulations can be manufactured in the same manner as those using hard gelatin capsules as the means of encapsulation (Barnwell et al., 1995)

In conclusion, the modified dissolution method described in this study has shown that Capill® potato starch capsules represent an alternative dosage vehicle for complex formulations such as the HALO™ delivery system, particularly where reliable enteric coating is of prime importance.

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