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Production and characterisation of enteric beads

H.C. Zaniboni, J.T. Fell *, J.H. Collett

Department of Pharmacy, University of Manchester, Manchester M13 9PL, UK

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Abstract

Enteric beads have been produced using a purely aqueous system. The method relies on the precipitation of the enteric polymer hydroxypropylmethylcellulose phthalate (HPMCP), when its solutions in an aqueous alkaline media are dropped into an acidic environment. Two compounds, riboflavin and riboflavin 5-phosphate, representing a poorly soluble and readily soluble compound respectively, have been successfully incorporated in the beads. Drug release studies show that the relatively insoluble compound is well protected in an acidic environment but rapid release occurs when the pH is raised. Solute migration during drying forms a high surface concentration with the soluble material allowing some release in acid.

Keywords: Enteric bead; Riboflavin; Drug release

1. Introduction

Enteric systems have several applications in pharmacy both for specific drugs and/or disease states. A number of enteric polymers are now available with the required pH sensitivity and these can be used as coatings or matrices. One problem with single unit enteric dosage forms is the highly variable gastric residence time. Prolonged residence times are particularly apparent in the fed condition. For example, Borin et al. (1990) found that in five out of eight fed subjects, an 800 mg sustained release ibuprofen tablet remained in the stomach for 7–12 h and in the remaining three subjects, gastric emptying took place in about 4 h. In contrast, the same tablets emptied in 10–16 min. in the fasted state (Parr et al., 1987). Prolonged residence puts an undue stress on the enteric system and can also lead to the problem of a tablet still being present in the stomach when a second one is taken later. Multiparticulate systems may go some way to overcoming these problems because, although still variable, the gastric emptying times are less extreme in range and are more reproducible (Bechgaard and Christensen, 1982).

Hydroxypropylmethylcellulose phthalate (HPMCP) is a polymer used in enteric coating applications. It is insoluble in gastric fluid but dissolves rapidly in media of pH equivalent to that of the upper small intestine. This paper describes the preparation of enteric beads of HPMCP by a simple pH change method and their evaluation.

* Corresponding author.

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2. Materials

Hydroxypropylmethylcellulose phthalate (HP-50) was obtained from Stancourt, Muir and Sons Ltd, Tunbridge Wells, UK. Sodium bicarbonate and citric acid were reagent grade (BDH, Poole, UK). Riboflavin and riboflavin-sodium-phosphate (both E. Merck, Darmstadt, Germany) were used as model drugs. All preparative procedures and characterisation involving these compounds in solution were carried out in subdued light.

2.1. Preparation of microspheres

The preparation procedure relies on the change in solubility of the HPMCP with pH. The change in pH when a solution of HPMCP in sodium bicarbonate is added dropwise to a citric acid solution is sufficient to precipitate the HPMCP causing the formation of beads. HPMCP solutions (200ml) were pumped using a peristaltic pump at 4.2 ml/min (Watson Marlow Type MHRE22C) to a square-ended needle located 10 cm above a dish containing 400 ml of citric acid solution. The citric acid solution was stirred continuously using a flat bladed paddle. The HPMCP solutions were continuously agitated with a magnetic stirrer during bead preparation to prevent settling of suspended drug particles. Preliminary experiments indicated that the following were satisfactory conditions for bead formation:

Temperature of HPMCP	Ambient
Temperature of citric acid solution	0°C
Concentration of HPMCP	5–15% w/v
Concentration of sodium bicarbonate	1.5–2% w/v
Concentration of citric acid	5–15% w/v

The beads were left in the citric acid solution for 2 h after which they were filtered through a nylon filter, washed with water and dried in an oven at 28°C for 72 h. The beads containing the two model compounds were prepared from 2% w/w solutions or suspensions in 2% w/w sodium bicarbonate and 14% HPMCP dropped into 10% citric acid. These conditions produced the most uniform, spherical beads.

2.2. Particle size analysis

This was carried out by sieving a 10 g sample of the beads for 10 min using a vibrating sieve shaker (Fritsch Analysette). Median particle sizes were derived from % oversize plots where appropriate. In cases where fractions were retained on only two sieves, the arithmetic mean of the sieve sizes was used.

2.3. Scanning electron microscopy

The morphology of the beads was examined by scanning electron microscopy using a Cambridge 360 S.E.M. (Cambridge Instruments, UK). The beads were coated with a 15–30 μm thick gold coat prior to observation.

2.4. Dissolution

This was carried out by using the B.P. (1993) apparatus II with the beads held at the top of a B.P. dissolution basket situated at the base of the dissolution vessel. (Timmermans, 1991). Studies were carried out on 200 mg of beads in 1 l of medium at 37°C stirred at 100 rpm. The dissolution medium was either pH 1.3 hydrochloric acid or pH 5 and 7.4 Sorensen's phosphate buffer. Analysis was performed continuously using a flow-through UV/Vis spectrophotometer at the wavelength of maximum absorption.

2.5. Drug loading

A known weight (200 mg) of beads was dissolved in pH 7.4 buffer and the resultant solution analysed for drug content spectrophotometrically.

3. Results and discussion

Preliminary experiments showed that beads could be produced within the range of conditions given earlier. The concentrations chosen to produce the riboflavin containing beads were those that produced consistent, uniformly shaped particles.

The influence of needle external diameter on the median particle size of the beads is given in Fig. 1. The liquid drop weight (Fig. 1) will change in proportion to the needle diameter and as the drop forms over the complete tip of the needle the external diameter is the important dimension. The final bead size reflects the amount of material in the original drop. In all cases, the size distribution of the beads was very narrow. A range of bead sizes can be produced by varying the needle size. However, the viscosity of the solutions and the presence of suspended particles precludes the production of very small beads by this method. It is likely that the final size of the beads is a complex function of several variables including needle size, pumping rate, drying conditions, temperature and reagent concentrations.

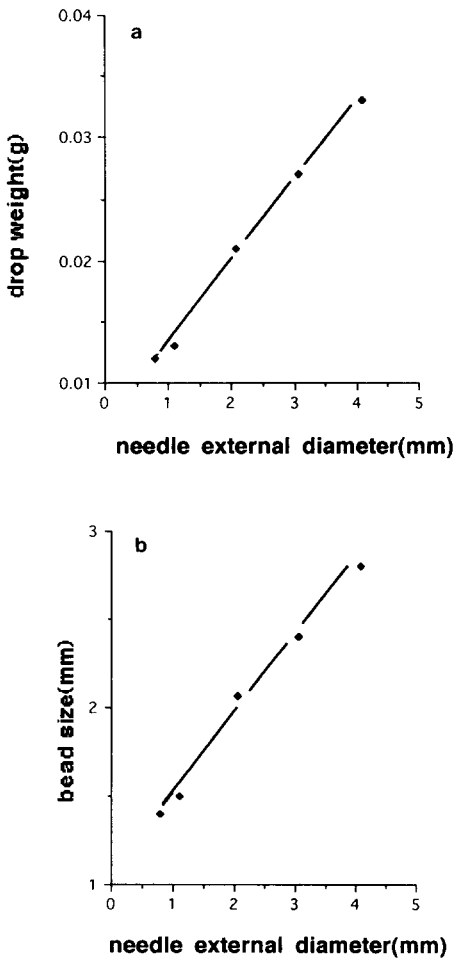

Fig. 1. Relation between needle external diameter and (a) drop weight and (b) bead size.

Scanning electron photomicrographs of the beads are shown in Fig. 2. The particles are spherical with a densely packed surface. The fracture surface of the spheres shows that some cavities exist within the particles but these do not connect to the surface. This structure is typical of a particle that has been dried directly from a droplet of solution or suspension. Movement of solvent to the surface to replace that lost by evaporation will carry with it dissolved or suspended solute forming the dense outer layer shown in Fig. 2. Evaporation of pure solvent left in the centre will create the hollow structure, although the lack of obvious connections between the hollow cavity and the surface implies that water was able to permeate to the surface readily. Drugs dissolved in the droplet will also migrate to the surface and crystallise as shown in Fig. 2. The process is somewhat analogous to the migration that occurs in the drying of granules (Ridgway and Rubinstein, 1971). The percentage of the theoretical amount of drug that was incorporated into the beads was 62% for the riboflavin and 34% for the riboflavin sodium phosphate. Losses for the relatively insoluble riboflavin may be due to sedimentation of the drug prior to drop formation, and some dissolution during the hardening process. The larger losses for the riboflavin sodium phosphate are most likely due to dissolution during hardening and washing. This may be reduced by both forming and washing the beads in a saturated solution of the drug.

The dissolution rates of riboflavin and riboflavin sodium phosphate from the beads are shown in Fig. 3–5. Riboflavin sodium phosphate represents a soluble drug, the beads being prepared from a solution of the drug. Riboflavin is relatively insoluble and the beads are prepared from a suspension.

At pH 1.3, approx. 40% of the incorporated riboflavin sodium phosphate is released in 2 h: thereafter, little further release occurs. The presence of a high concentration of drug at the surface, due to migration as discussed above, will explain this immediate release. Once this mate-

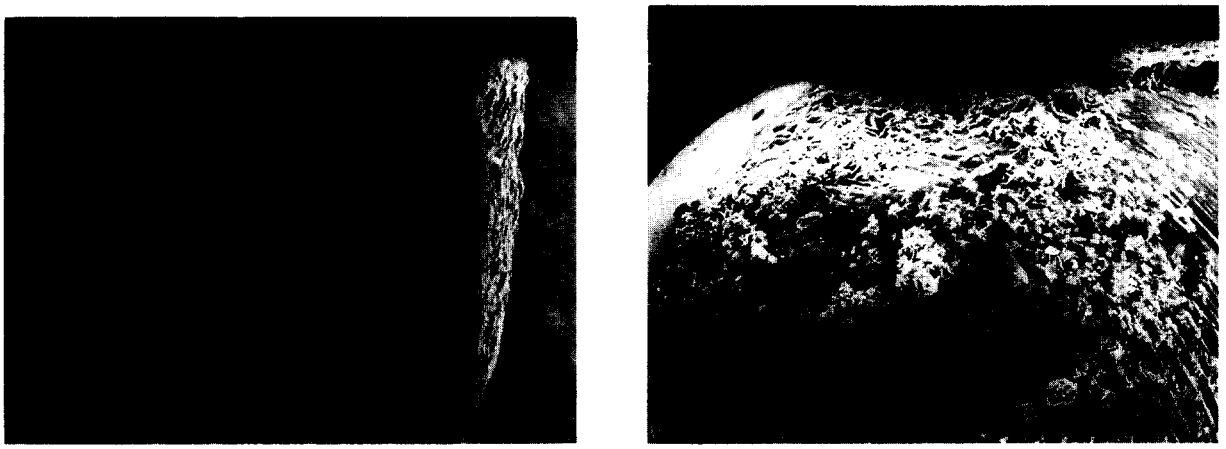

Fig. 2. Scanning electron photomicrographs of beads: (a) fractured bead; (b) surface view of bead containing riboflavin sodium phosphate.

rial is removed, the insoluble nature of the HPMCP prevents further drug dissolution. Very little release of the relatively insoluble riboflavin occurs at pH 1 confirming the enteric potential of this system for compounds of this type.

The HPMCP used in these studies is soluble at pH 5 and above. At pH 5 it is only slowly soluble and the relatively rapid release of the riboflavin sodium phosphate will be due to a combination of the surface effect discussed above and the solubility of the HPMCP.

The beads used in these studies are essentially monodispersed and spherical. The dissolution of

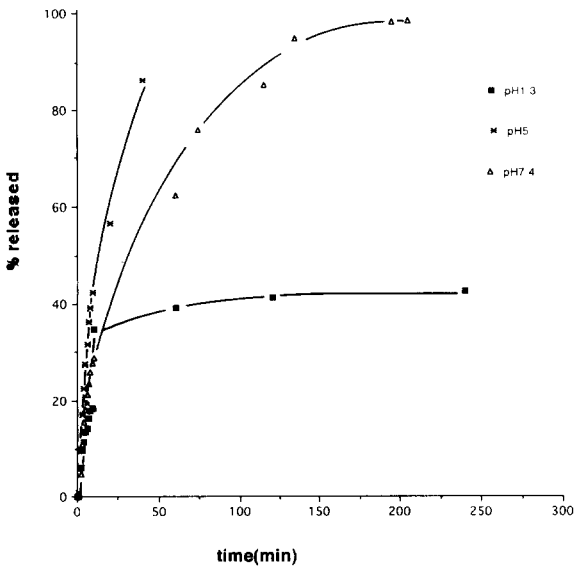

Fig. 3. Dissolution rates of riboflavin sodium phosphate at three pH values.

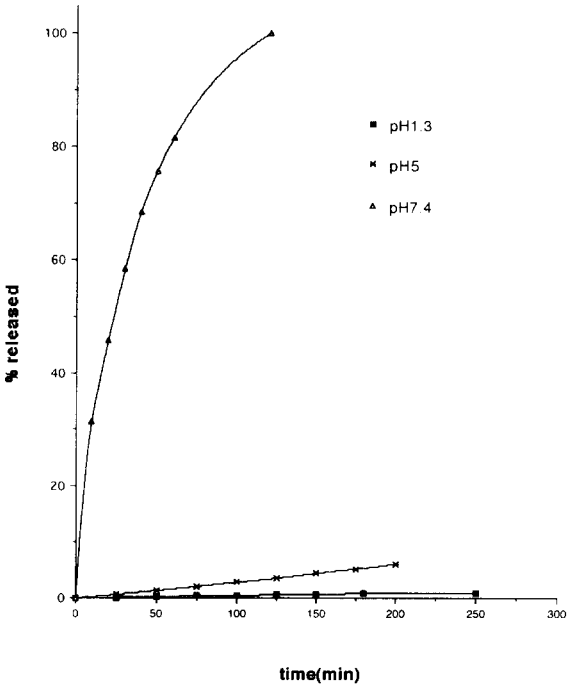

Fig. 4. Dissolution rates of riboflavin at three pH values.

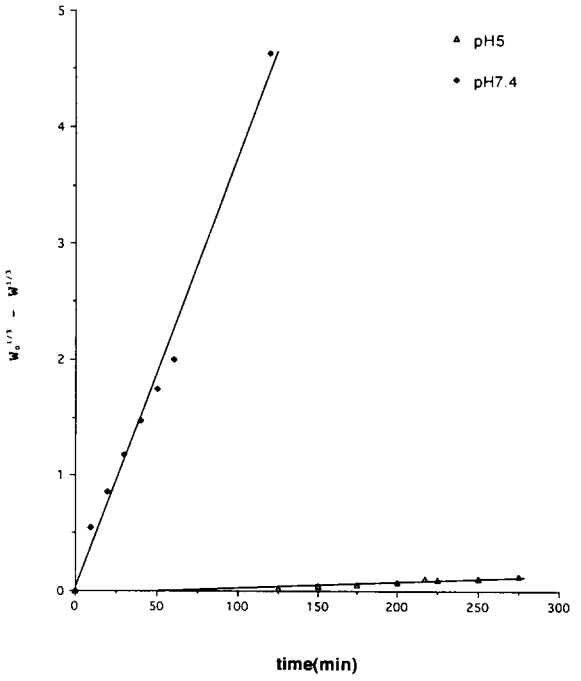

Fig. 5. Cube root dissolution rate plot for riboflavin at two pH values.

the spheres themselves should be described by the Hixson and Crowell equation (1931):

$$w_0^{1/3} - w^{1/3} = kt$$

where w_0 is the weight of material at time 0 and w is the weight at time, t. The release of riboflavin from the beads is plotted in this manner in Fig. 5. The fact that the release obeys the cube root law suggests that the release of riboflavin is governed by the dissolution of the beads. Similarly, this relationship is obeyed at pH 7 (Fig. 5) and the faster dissolution of the HPMCP at this pH is reflected in very similar release rates for the two riboflavins. The initial "burst" effect of the more soluble compound is effectively hidden at this pH because of the rapid dissolution of the beads themselves.

The method described provides a means of producing enteric microspheres from moderately insoluble compounds. More soluble materials can be incorporated into the microspheres but drug release at low pH occurs due to a high surface drug concentration formed during drying. Changes in the drying process to prevent migration, such as that suggested by Okano et al. (1990) may make the process equally suitable for soluble compounds.

Acknowledgement

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