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Amoxycillin release from a floating dosage form based on alginates

Lynne Whitehead, John H. Collett, John T. Fell *

School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester M13 9PL, UK

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Abstract

Floating alginate beads have been prepared from alginate solutions containing either dissolved or suspended amoxycillin. The beads were produced by the dropwise addition of the alginate into calcium chloride solution, followed by removal of the gel beads and freeze drying. Drug release studies showed that beads prepared with the drug in solution provided some sustained release characteristics and that these could be improved by the addition of amylose. In all cases, the drug release was consistent with release of a dissolved solute from a granular or porous matrix. The beads retained their buoyancy when amylose and amoxycillin were incorporated, exhibiting resultant weight values greater than zero after 20 h. Preparation of the beads from alginate solutions containing the drug in suspension allowed higher drug loadings, at the expense of faster release and lower buoyancy.

Keywords: Gastric retention; Floating dosage forms; Drug release; Amoxycillin

1. Introduction

Prolonging the gastric residence of a dosage form may be of therapeutic value. Amongst the methods available to achieve this, floating dosage forms show considerable promise (Moës, 1993). Recently, a method was described to produce a floating, multiparticulate system based on calcium alginate. This system was shown to exhibit considerable gastric retention compared to a similar, non-floating system when studied in human volunteers allowed normal food intake (Whitehead et al., 1998).

One reason for wishing to prolong the gastric retention of a dosage form is to achieve a local therapeutic effect. Although there is uncertainty as to whether the antibacterials used to eradicate *H. pylori* from the stomach act locally or systemically (Cooreman et al., 1993), there is evidence to show that prolonged local concentrations of antibacterials may be of value in achieving eradication.

This paper describes the incorporation of an agent known to be effective against *H. pylori*, amoxycillin, into calcium alginate beads and reports the release of the drug from the beads in an acidic environment.

* Corresponding author. Tel.: +44-161-2752365; fax: +44-161-2752396.

E-mail address: jfell@fs1.pa.man.ac.uk (J.T. Fell).

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2. Materials and methods.

2.1. Materials

Amoxycillin trihydate, ATH, (particle size ~ 250 μm) was a gift from Norton Healthcare. Sodium alginate (Manugel GMB) was a gift from Kelco International. Amylose (Corn, practical grade, Sigma), calcium chloride (BDH), hydrochloric acid (Fisons), potassium dihydrogen phosphate (BDH), disodium phosphate dihydrate (BDH) were standard laboratory reagents and used as received.

2.2. Bead preparation

Beads were prepared as detailed by Whitehead et al. (1998). Briefly, 2% w/w sodium alginate solutions were extruded through 21G needles into stirred 2% w/w calcium chloride solution containing 0.35% w/w ATH. The gel beads formed were left for 30 min in the solution prior to filtration and freeze drying as described previously (Whitehead et al., 1998). The sodium alginate solution contained either 0.35% ATH in solution or 1 and 2% ATH in suspension. Additionally, beads were prepared containing ATH and amylose at concentrations between 1 and 20% w/w.

2.3. Drug loading and encapsulation efficiency

Accurately weighed quantities of approx. 20mg beads were dissolved in 25ml Sorensen's phosphate buffer pH 7.4. The solutions were centrifuged using a Centuar model 2 centrifuge at 4200 rpm for 30 min, and assayed at 272 nm. The drug concentration in the sample was used to calculate the loading by dividing by the weight of beads initially dissolved. The encapsulation efficiency was calculated according to the following relationship

$$\text{Encapsulation efficiency} = \frac{\%\ \text{drug content} \times \text{amount (dried matrices produced)}}{\text{amount drug added} - \text{amount drug remaining in apparatus}}$$

2.4. Distribution of ATH within the beads

X-ray microanalysis was used to map the distribution of sulphur atoms and thus the ATH within the freeze dried beads. A linescan analysis was used to map for ATH across the complete cross-section of the bead. This was performed using the X-ray analysis unit of a Cambridge model S360 Scanning Electron Microscope. The beads were mounted on carbon DAG covered stubs and then carbon coated. An accelerating voltage of 20 keV was used, with a focus height of 25 mm, to image the beads. Measurements were made in duplicate.

2.5. Drug release

Dissolution studies were performed in triplicate using the USP XXII apparatus (Caleva Model 8ST) at 50 rpm. The media used was 900 ml deaerated 0.1 M HCl, pH 1.2, which was maintained at 37 ± 1°C. Approximately 0.6 g beads were used for each experiment. Samples were taken at appropriate time intervals and assayed spectrophotometrically at 272 nm. Fresh media was added to replace the sample taken.

2.6. Resultant weight

The resultant weights of the amoxycillin loaded beads were measured at known time intervals using the apparatus and method of Timmermans (1991). The media used was 0.1 M HCl containing 0.05% Tween 80.

3. Results and discussion

Fig. 1 shows scanning electron photomicrographs of beads prepared from ATH in solution or suspension. There is no evidence of precipitation or crystallisation of the drug in the beads prepared from the solution. In the beads prepared from the suspension, the crystals of ATH can be

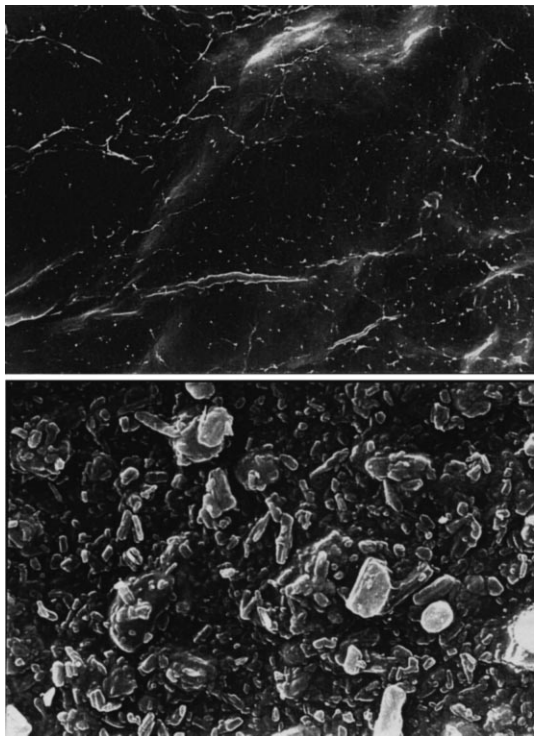

Fig. 1. Scanning electron photomicrographs of the surface of beads prepared from amoxycillin trihydate (ATH) solution (a) and suspension (b).

seen apparently covered with a layer of calcium alginate.

Fig. 2 shows the results from the linescan analysis for sulphur with the peak for the sulphur atoms present in the centre of the beads. This distribution of ATH within the beads was not

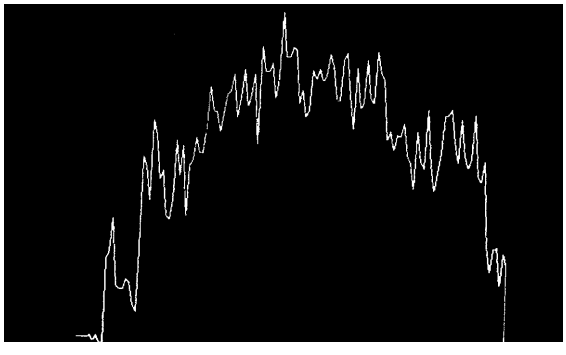

Fig. 2. Linescan analysis showing the distribution of sulphur atoms (present only in amoxycillin trihydate (ATH)) across the diameter of a bead.

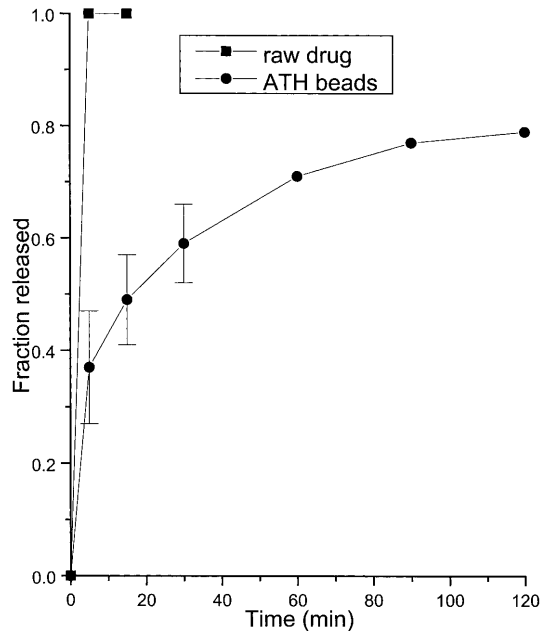

Fig. 3. Fraction of initial amoxycillin trihydate (ATH) load released with time ($n = 3 \pm$ S.D., drug in solution).

anticipated. In many drying processes, migration of drug to the peripheral layers of the solid as the solvent is removed, is a common phenomenon. The use of freeze drying should theoretically minimise this since water is removed by sublimation from the ice crystals and does not move as a liquid containing dissolved drug to the surface of the solid. The uneven drug distribution may have been due to leaching of the drug during the curing process. To test this possibility, the calcium chloride solutions were assayed for amoxycillin content both prior to and after bead curing. The results showed that the concentration did not change, suggesting that leaching did not occur. Migration of the drug must thus occur either during the gelation process or the freezing procedure prior to drying.

The fraction of the initial load of ATH released as a function of time from the beads is compared to that from the raw drug in Fig. 3. Although slower than that of the raw drug, incorporation into the beads did not result in sufficiently prolonged sustained release characteristics. Amylose was therefore incorporated into the beads to endeavour to retard the release rate further.

Table 1
Drug loading and encapsulation efficiencies for beads prepared with amoxycillin trihydate (ATH) and different concentrations of amylose

Initial amylose concentration	Drug in solution or suspension	Drug loading (%w/w)	Drug loading (mg ATH $\times 10^2$/bead)	Encapsulation efficiency (%)
0	Solution	17.8	9.1	92.1
1	Solution	12.1	9.5	87.1
2	Solution	9.8	10.0	88.1
0	Suspension	19.7	–	70.8
0	Suspension	34.8	–	71.7

The influence of amylose on drug loading and encapsulation efficiency is given in Table 1. The loading decreases as the amylose content increases, a reflection of the increasing amounts of insoluble amylose present in the beads reducing the capacity for the ATH. The encapsulation efficiencies are similar for each batch.

The fraction of ATH released from the beads containing different quantities of amylose are shown in Fig. 4. The release of ATH is moderately retarded by the incorporation of amylose. An initial 'burst effect' is seen, presumably due to rapid release from the surface. Treating the results in the manner of Higuchi (1963), relating the amount of drug released to the square root of time gave linear plots. This is consistent with the release of drug from a granular or porous matrix. It is proposed that the release of ATH in the current system is controlled by the diffusion of drug through water filled channels in the beads with the amylose acting as a filler material, reducing the volume fraction for diffusion and increasing the tortuosity.

The drug loading and encapsulation efficiencies for beads prepared from ATH suspensions are shown in Table 1. Higher loading was obtained than for dissolved drug, but the encapsulation efficiencies were lower. The latter is possibly due to leaching of dissolved drug, present as a saturated solution in the beads into the curing solution. Concentrations of drug, higher than that of the original curing solution, were found after curing indicating that leaching had occurred. Release of ATH from beads prepared from suspensions is shown in Fig. 5. Comparison of these results with those obtained from beads prepared from dissolved drug, (Fig. 3) shows that drug release is faster from beads prepared from a drug suspension. The purpose of using drug in suspension was to obtain higher drug loadings, which was achieved. Once the drug is dissolved from such a system however, the structure becomes more open allowing more rapid dissolution. The amount of ATH dissolved from the beads prepared from suspensions also showed a square root of time dependency, consistent with the work of Higuchi (1963).

The resultant weight values for the beads are shown in Fig. 6. Batches containing dispersed drug were less buoyant than those containing dissolved

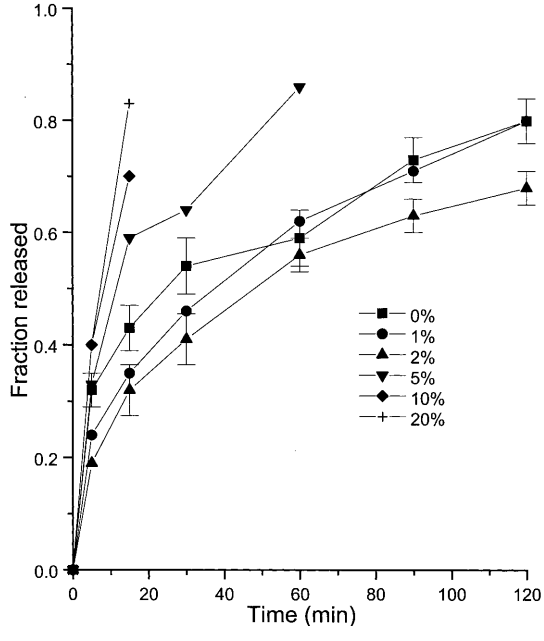

Fig. 4. Effect of amylose concentration on the fraction of amoxycillin trihydate (ATH) load released with time ($n = 3 \pm$ S.D., drug in solution).

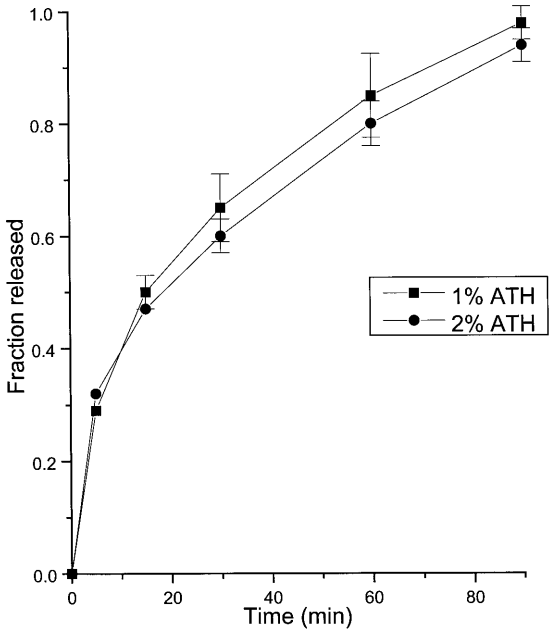

Fig. 5. Fraction of initial amoxycillin trihydate (ATH) load released with time from beads containing 2% amylose ($n = 3 \pm$ S.D., drug in suspension).

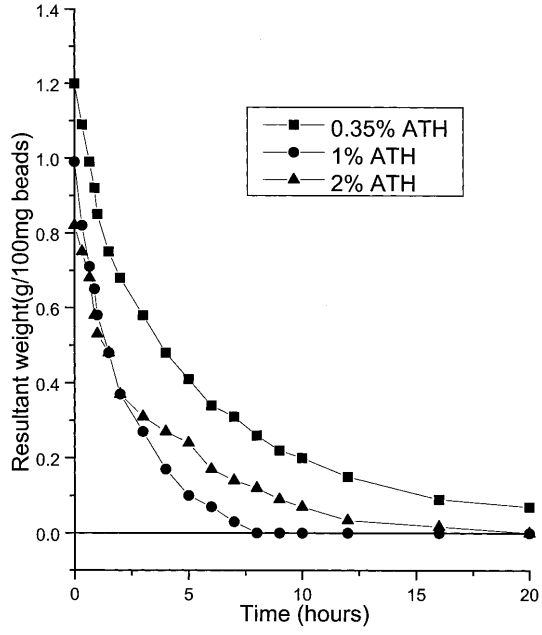

Fig. 6. Changes in the resultant weight of beads with time for beads containing 2% amylose.

drug and may not provide complete protection against early gastric emptying. The beads containing the dissolved drug remained buoyant for 20 h and would be acceptable.

4. Conclusion

The study has investigated the release of a soluble drug, ATH, from a gastric retentive system based on alginates. To provide an effective local action from a gastric retentive system, ideally it would be required to release drug rapidly in the initial stages to obtain the desired concentration, and then more slowly to replace drug lost, for example by gastric emptying. The incorporation of drug alone into the beads provides some delayed release which can be further enhanced by the addition of amylose. Incorporating the drug into the beads as a suspension achieves higher drug loadings but at the expense of a more rapid release and reduced buoyancy.

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