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European Journal of Pharmaceutics and Biopharmaceutics 57 (2004) 295–298
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Feasibility of a bioadhesive drug delivery system targeted to oesophageal tissue

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Received 4 June 2003; accepted in revised form 7 October 2003

Abstract

This contribution examines the feasibility of utilising an oesophageal-adhesive alginate layer to support model drug particles. Such a bioadhesive system offers the prospect of local drug delivery to the oesophagus, which in turn has applications in the treatment of conditions including gastro-oesophageal reflux disease and oesophageal cancer. Surface-modified (amine, carboxylate and sulfate) as well as neutral fluorescent beads were investigated as model drug particles. A fluorescence assay technique was utilised to quantify the extent and duration of adhesion of a fixed dose of these particles to excised porcine oesophageal tissue. Retention of the particles was investigated both from aqueous systems and within an adhesive alginate solution. After 30 min significantly higher adhesion of neutral beads was recorded from the alginate solution as compared to the aqueous suspension ($n = 6$, $P < 0.05$). The beads that possessed a negative charge showed significantly greater retention within the alginate carrier ($n = 6$, $P < 0.05$). However, the amine-modified beads showed retention profiles that were similar both within the alginate carrier and within the aqueous suspension ($n = 6$, $P > 0.05$).

Keywords: Bioadhesion; Model drug particle; Oesophagus; Alginate; Drug delivery

1. Introduction

Bioadhesive drug delivery systems have previously been targeted to many gastro-intestinal sites as a means of prolonging local residence times and thus increasing the oral bioavailability of a drug. Many studies have been performed investigating the bioadhesive potential of the oral cavity, buccal pocket, gastric region and small intestine (for a review, see Ref. [1]). In comparison, few studies have been undertaken that investigate the oesophagus as a potential site of bioadhesion. Advantages of targeting the oesophagus as a means of drug retention include treatment of localised conditions, an alternative potential mucosal platform for orally delivered controlled release formulations as well as avoidance of first pass metabolism.

Reflux of gastric acid and pepsin into the lower oesophagus results in symptoms such as heartburn as well as tissue injury that may lead to erosive oesophagitis and stricture formation. A protective layer resident on oesophageal tissue would limit the contact between refluxed gastric contents and the oesophageal epithelial layer, thus reducing these effects. Alginate is particularly suited to such a role, due to its current use in anti-reflux therapy. Particles suspended within such a layer could be used to treat local ailments of the oesophagus. Alternatively acid or pepsin neutralising particles may be suspended within such a layer to provide a secondary defence to the refluxed material.

Initial studies that investigated adhesion within the oesophagus focussed on tablets or capsules lodging within the oesophageal cavity where they caused local irritation [2]. However, more recent studies have examined the local delivery of topical anticancer agents to sites within the oesophagus [3]. In another study, it was noted that oesophageal retention of sucralfate in a gel suspension was far greater than retention from an aqueous suspension [4]. It has also been suggested that sucralfate in a gel form exhibits rheological synergy in combination with mucin aiding the retention of such a formulation [5]. These data

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doi:10.1016/j.ejpb.2003.10.007

suggest that a gel or viscous liquid formulation provides greater retention of particulate material to oesophageal tissue. Using a novel in vitro method it has been shown that the solutions of sodium alginate adhere to oesophageal tissue for time periods of up to 30 min [6]. Incorporation of drug particles into this adherent layer offers a potential retentive formulation appropriate for oesophageal drug delivery.

2. Materials and methods

2.1. Materials

Sodium alginate of medium viscosity, a 2% w/v solution had a viscosity of 0.51 Pa s at 25 °C with a shear rate of 10 s^{-1}, was kindly donated by FMC Biopolymer, Norway. Porcine oesophageal tissue was obtained from freshly slaughtered animals sacrificed at a local abattoir. The outer muscles layers were removed exposing the inner epithelial tube. These inner tissue sections were flash frozen and stored at −70 °C until required; this method of preparation has been shown to retain the histological integrity of the tissue [7]. The tissue was allowed to thaw overnight in a refrigerator then equilibrate to room temperature prior to use.

Polysciences (UK) supplied neutral fluorescent bends of diameter 0.05, 0.5 and 2.0 μm. Their excitation and absorption maximum were determined to be 458 and 540 nm, respectively. Amine-, carboxylate- and sulfate-modified beads of 2.0 μm diameter were supplied by Sigma (UK). The excitation and absorption maxima for these yellow–green beads were 490 and 515 nm, respectively.

2.2. Methods

2.2.1. Preparation of the suspensions

All the fluorescent beads were obtained as aqueous suspensions. To 100 ml deionised water, 0.2 ml of the bead suspension was added. This suspension was stirred thoroughly to ensure homogenous distribution of the beads. A calibration curve was performed from this suspension to correlate bead concentration with fluorescence obtained using a fluorescence spectrometer (Perkin Elmer PE-LS-5 Luminescence Spectrometer with a xenon power supply). Sodium alginate 2% w/v solutions were prepared by addition of the appropriate quantity of alginate powder to a volume of the bead suspension. Calibration curves were prepared from the alginate-bead suspensions to ensure that the alginate component did not affect the fluorescence produced by the beads.

The surface potential of the beads in both the aqueous and the alginate media was determined using a Brookhaven ZetaPlus zeta potential analyser.

2.2.2. In vitro retention testing procedure

The retention apparatus used in this study was an adaptation of the falling film method [8,9]. Batchelor et al. described the methodology and parameters in further detail [2]. The basis of the technique lies in the application of a fluorescently labelled dose of the test formulation to porcine oesophageal tissue, followed by fluorimetric analysis of the eluted material, allowing determination of the percentage of the original dose washed from the tissue surface at given time points. Such data allows a retention profile of the dose to be visualised. In this study, fluorescent beads were used as model drug particles. The fluorescent nature of these beads ensured that no additional labelling techniques were required in the fluorimetric assay.

3. Results

3.1. Measurement of the particulate surface potential

The surface potential of the suspended charged beads was measured in both aqueous and alginate environments. Table 1 shows how the surface charges altered for the beads within the media examined.

3.2. The effect of bead size on retention

One millilitre doses of aqueous suspensions of the three different-sized neutral beads were dispensed onto the tissue surface. At 3 min, 13.7 (±2.5), 10.5 (±3.0) and 11.2 (±2.4)% of the original doses were retained for the 0.05, 0.5 and 2.0 μm beads, respectively. At 6 min, the entire dose had been collected from the tissue surface. This result suggests very poor retention of the beads in an aqueous suspension.

A comparative study was performed using suspensions of the beads within 2% w/v alginate suspensions. Their retention profiles were compared at 3, 15 and 30 min and ANOVA analysis confirmed that, at each time point investigated, no significant differences were observed in the retention of the beads according to their size ($P > 0.05$, $n = 6$). In each case the retention at 3 min was significantly higher than at 15 and 30 min ($P < 0.05$). No significant

Table 1
Comparison of the surface charge of the modified beads within aqueous and alginate suspensions

	Surface charge measured in: ($n = 10 \pm$ SE)	
	Aqueous suspension (mV)	Alginate suspension (mV)
Amine-modified beads	+14.99 ± 1.62	−6.53 ± 0.50
Carboxylate-modified beads	−35.59 ± 0.87	−43.00 ± 0.80
Sulfate-modified beads	−37.48 ± 1.74	−45.33 ± 1.32

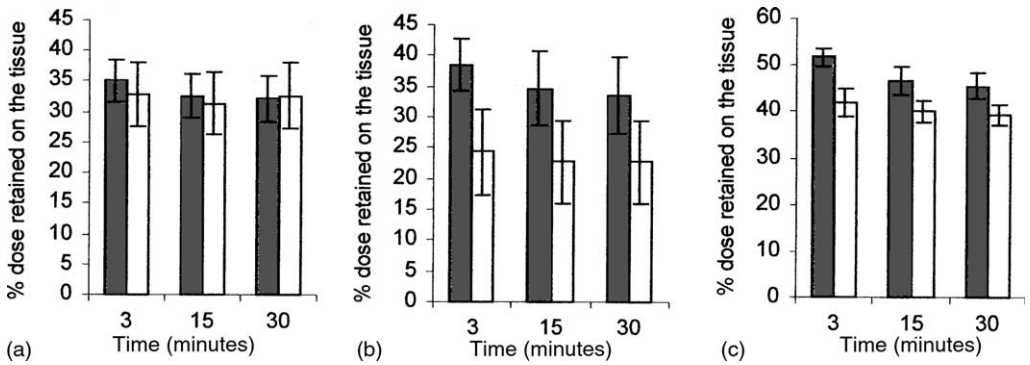

Fig. 1. Retention data for surface-modified beads suspended within both 2% w/v alginate (grey bars) and aqueous (white) solutions: (a) amine beads; (b) carboxylate beads; and (c) sulfate beads.

differences were observed between the retention at 15 and 30 min. These results suggest that an adhesive alginate layer is able to support neutral beads of diameter 0.05–2 μm for up to 30 min.

3.3. Retention of surface-modified beads

One millilitre doses of both aqueous and alginate suspensions and of the 2.0 μm diameter-modified beads were applied to the tissue surface. The retention profiles at 3, 15 and 30 min were compared in Fig. 1.

Fig. 1 shows that, at the time points investigated, the retention of both sulfate- and carboxylate-modified beads was significantly enhanced in the presence of alginate at 3 min. Although at 15 and 30 min the retention of both these negatively charged beads was greater in the alginate suspension, only the sulfate-modified beads showed a significant effect ($P < 0.05$). The positively charged amine beads showed statistically similar retention profiles at all time points in both carriers investigated ($P > 0.05$), indicating that the presence of the viscous alginate carrier did not enhance the retention of these particles.

4. Discussion

Solutions of sodium alginate have an overall negative charge due to the ionisation of the carboxylic acid groups. Mucus that covers most internal membranes is also an anionic entity with an overall negative charge. Positively charged entities are expected to interact with this surface mucus leading to adherence; this was observed with the amine particles even when there were suspended within the alginate solution. Although the zeta potential of the particles was masked; they were still able to directly interact with the oesophageal surface. Solutions of sodium alginate adhere to the oesophageal mucosal surface through a variety of mechanisms, including the formation of an electrical double layer. This overall adhesion aids in the retention of negatively charged particles, demonstrated using sulfate and carboxylate particles. The retention of sulfate-modified particles was noted to be greater than that of carboxylate particles; this may be due to the divalent nature of these ions although further work is required to prove this.

5. Conclusion

Previous work has shown that alginate solutions may adhere to oesophageal tissue for periods of up to 30 min [6]. This study has shown that such an adhesive layer is capable of supporting both neutral and model drug particles with a negative surface charge at a greater level than an aqueous solution.

Acknowledgements

The authors would like to thank both the BBSRC and Reckitt Benckiser Healthcare Ltd for funding the research highlighted in this paper.

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