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The use of alginate impression material for the controlled release of sodium fusidate

Zastosowanie alginatowej masy wyciskowej do kontrolowanego wydzielania fusydanu sodu

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Abstract

Introduction. Alginate impression material has the potential to act as a controlled release material, either for transmucosal drug delivery, or for use as a self-disinfecting impression material in clinical dentistry.

Aim of the study. To study whether sodium fusidate could be released from alginate impression material and, if so, to determine the release kinetics.

Material and methods. Sodium fusidate was incorporated into alginate impression material at the mixing stage (2% by mass). The mixed material was pressed into a sheet and, once cured, discs (6 mm diameter x 2 mm thick) were cut out, and stored in water, one disc in a 5 ml volume. Small samples (20 µl) were withdrawn at time intervals of 1, 2, 3, 4, 5, 24 h, 1, 2 and 3 weeks and analysed by HPLC.

Results. Sodium fusidate was released from the impression material in a process that was shown to be diffusion based for the first 5 hours or so. The diffusion coefficient was $2.25 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$, and the release corresponded to $36.0 \pm 1.0\%$ of the total loading. The system thus shows promise for clinical application.

Key words: alginate, impression material, sodium fusidate, controlled release.

Streszczenie

Wstęp. Alginatowe masy wyciskowe mogą być potencjalnie użyte jako materiały służące do kontrolowanego uwalniania, np. leków wchłanianych przez błonę śluzową czy środków dezynfekcyjnych, które umożliwiałyby autodezynfekcję wycisków w warunkach klinicznych.

Cel pracy. Ocena czy fusydan sodu może być wydzielany z alginatowych mas wyciskowych oraz ocena kinetyki wydzielania.

Materiał i metody. Fusydan sodu wprowadzono podczas mieszania do alginatowej masy wyciskowej w proporcji 2% masowych. Z zamieszanego materiału uformowano cienką warstwę, po związaniu wycięto próbki w kształcie krążka (6 mm średnicy x 2 mm grubości), każdą próbkę przechowywano oddzielnie w 5 ml wody. Po upływie kolejno 1, 2, 3, 4, 5, i 24 godzin a następnie 1, 2 i 3 tygodni pobierano niewielkie ilości roztworu, który poddawano analizie w HPLC.

Wyniki. Fusydan sodu w ciągu pierwszych 5 godzin był wydzielany z masy wyciskowej w procesie dyfuzji. Współczynnik dyfuzji wynosił $2.25 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$, wydzielona ilość odpowiadała $36.0 \pm 1.0\%$. W związku z tym ten system wydaje się być obiecujący w warunkach klinicznych.

Słowa kluczowe: alginate, masa wyciskowa, fusydan sodu, kontrolowane wydzielanie.

Introduction

Alginates are impression materials that have been used in a variety of forms for the controlled release of drugs [1]. This application is of growing importance in pharmacy because the classical approach of using tablets to deliver drugs may, in principle, lead to both unacceptably high dose of drug soon after administration and to poor targeting to the tissue of interest. These factors, in turn, may lead to possible unwanted side effects and also to low efficiency [2, 3].

Alginates have acceptable properties for this use [4]. Depending on factors such as crosslink density, molecular weight distribution and possible chemical modification, they can have good phy-

sical properties and be resistant to swelling and degradation within the body [1]. They are polysaccharides derived from brown seaweeds of the *Laminaria* genus [1]. The polysaccharide molecules, known as alginic acid, consist of linear block copolymers of -D-mannuronic acid and -L-guluronic acid. These molecules contain numerous pendant carboxylic acid groups that can be crosslinked by multivalent ions such as Ca^{2+} [5, 6]. As extracted, the polysaccharide molecules are typically neutralized with Na^+ ions, a state which renders them soluble in water [7]. Treatment with a calcium salt, such as CaSO_4 , leads to an ion-exchange reaction that yields a crosslinked polymer based on Ca^{2+}

crosslinks [8]. The crosslinked polymer is insoluble in water and also is elastomeric.

Release of drugs from alginate has been found typically to follow a diffusion mechanism. This means that it is a statistical process driven by a concentration gradient. Under these circumstances, the amount released varies with $(\text{time})^{1/2}$ [9]. Release from alginates can be complicated because the set alginate contains various ions, for example Na^+ and SO_4^{2-} and when the alginate is immersed in water or an aqueous solution, an osmotic potential is created that results in water being taken up [10]. Since this occurs in the opposite direction to the required flow of drug, release of the latter may be inhibited. However, as crosslinking develops fully, there is a decrease in osmotic potential which means that the driving force for water uptake is reduced, and may even be reversed, i.e. alginate starts to expel any water taken up earlier.

Drugs have been incorporated into alginates by modifying the chemistry of the alginate, for example, by grafting a series of covalent side chains to the polymer backbone and attaching the drug [1]. This was done with the drug duanomycin, an anti-neoplastic agent [11], where carboimide functional groups were used to secure the drug to the polymer. This structure is readily hydrolysed and, as hydrolysis occurs, so the drug is released. Drugs can also be incorporated without chemical modification, for example into the pores of an alginate structure, from which they can be released by simple diffusion. An example of this was the drug methotrexate, a folate antagonist useful in a wide range of oncological and non-oncological applications [13]. This was incorporated into an alginate carrier and found to be released at satisfactory levels over a prolonged period [14]. This approach – simple incorporation – appears to be the more commonly used method [1], and is the one we have used in the present study.

In our study, we have employed a dental impression material as our alginate delivery system. This follows from numerous recent studies of self-disinfecting impression materials in which an active molecule, such as chlorhexidine, has been added at the mixing stage [15]. The overall aim of such studies has been to address the concern that impression materials can contribute to the spread of infectious diseases through contamination by blood or saliva [15, 16, 17, 18]. This places various dental personnel (dentists, dental nurses, dental technicians) at risk, and this has led to the development of guidelines to limit cross-contamination arising from the use of dental impressions [19].

We have used the dental impression grade alginate in an experimental study of the release of sodium fusidate. This substance is a general purpose antibiotic that has a range of uses, and is becoming important against the increasingly prevalent methicillin-resistance *Staphylococcus au-*

reus, MRSA [20]. It is also of interest because of its anionic nature, since there is the possibility of it being trapped in the alginate by interaction with calcium ions. The nature and extent of its release is therefore of particular interest.

Material and Methods

Experiments were carried out using alginate impression material (ex Kent Dental, UK) which is supplied as a powder to which water is added in the ratio 1 g powder to 2 cm³ water. The active component, sodium fusidate (ex Sigma-Aldrich, Poole, UK) was incorporated during the mixing process at 2% by mass. Freshly mixed material was placed between glass microscope slides to give a thin sheet (2 mm depth), then cured at room temperature for 30 minutes. After this, small discs were stamped out using a standard hole puncher for paper, giving discs of diameter 6 mm. A total of five were prepared for the release experiment.

Specimens placed in individual 5 ml volumes of deionised water in plastic centrifuge tubes. The specimen tubes were stored at room temperature (20–22°C). For each specimen at appropriate time intervals (1, 2, 3, 4, 5, 24 h, 1, 2 and 3 weeks) a 20 µl aliquot was removed and analysed using HPLC, giving altogether 40 samples for analysis.

HPLC analysis was performed with an Agilent 1200 series high performance liquid chromatograph, fitted with a C18 column (Type C18–00F–3033–EO, 150 mm length x 4.6 mm internal diameter). Isocratic elution was employed using the mobile phase of water 20%: methanol 80% with a drop of 0.01 M aqueous ortho-phosphoric acid. All solvents were HPLC grade (ex Fisher, Loughborough, UK) and the blended mobile phase was degassed before use.

The LC detector was set at a wavelength of 235 nm and a flow rate of 2 cm³/min was used. The system was operated at room temperature and at approximately 100 bars of pressure.

Results

Sodium fusidate was found to be released from the discs of alginate impression material in increasing amounts with time over periods of up to 3 weeks. The conditions used in the HPLC led to elution of sodium fusidate at a mean retention time of 6.7 minutes (± 0.5 minutes). The release profile is shown in Table 1. These data were calculated as M_t/M_∞ , and plotted against square root of time (in seconds) as shown in the Figure 1. This enabled the diffusion coefficient to be determined by using the slope, s , and substituting into

$$D = s^2\pi l^2/4$$

where $2l$ is the thickness of the disc. In addition, the total release was determined. Both values are recorded in Table 2.

Table 1. Release profile of sodium fusidate from alginate impression material (estimated standard deviations in parentheses)

Tabela 1. Profil uwalniania fusydanu sodu z alginatowej masy wyciskowej (w nawiasach szacowane odchylenie standardowe)

Time/h	Amount released/ $\mu\text{g cm}^{-3}$
0.5	20.0 (2.4)
1.0	22.0 (2.6)
2.0	27.7 (3.1)
3.0	35.6 (4.3)
4.0	36.8 (5.8)
5.0	41.4 (6.5)
24	58.8 (6.8)
168	80.3 (9.2)
336	83.9 (9.7)
504	84.8 (9.8)

Table 2. Release data for sodium fusidate (2%) in alginate

Tabela 2. Uwalnianie fusydanu sodu (2%) w alginacie

Property	Value
Diffusion coefficient/ cm^2s^{-1}	2.25×10^{-5}
Total release/%	36.0 ± 1.0

Discussion

Our findings show that the alginate impression material is capable of releasing sodium fusidate in a controlled way at room temperature. Sampling was carried out using 20 μl volumes, with a total of ten being taken from a 5.0 cm^3 storage volume. This meant a total of 200 μl was removed over the time period of the experiment, which represents only 4% of the original volume of water. The volume can therefore be considered to be approximately constant, despite the sampling.

Release was shown to occur by a diffusion mechanism since the plot of M_t/M_∞ against square root of time was linear up to M_t/M_∞ of about 0.5, i.e. 5 hours. In the case of the 2% loading, equilibration was more or less complete at 2 weeks, and was definitely complete by 3 weeks. The value of release at this time period is taken to be M_∞ .

Data were examined using the so-called Stefan approximation, i.e.

$$M_t/M_\infty = 2\sqrt{(Dt/\pi l^2)}$$

This specifically neglects edge effects, and also any changes in dimension for the specimen, for example swelling caused by uptake of water. In both cases, these approximations seem acceptable, and the system obeys this mathematical form. Release can therefore confidently be classified as a diffusion process.

The ease of diffusion of sodium fusidate from the alginate suggests that there is little or no ion-exchange with the calcium sulphate to cause binding of the fusidate anion within the alginate. This result is similar to that obtained with glass-ionomer cements [21], where sodium fusidate was included, and found to be released at a satisfactory rate over a two week period. It is not clear why sodium fusidate is reluctant to undergo ion exchange within these materials to form the calcium salt, but this feature has now been confirmed for two very distinct systems.

The system based on alginate is of potential use in oral transmucosal drug delivery because alginate is biocompatible in contact with the oral tissues, as well as non-toxic and economical [22]. A number of other anionic polymer systems have been used in this way, such as cross-linked polyacrylic acid and

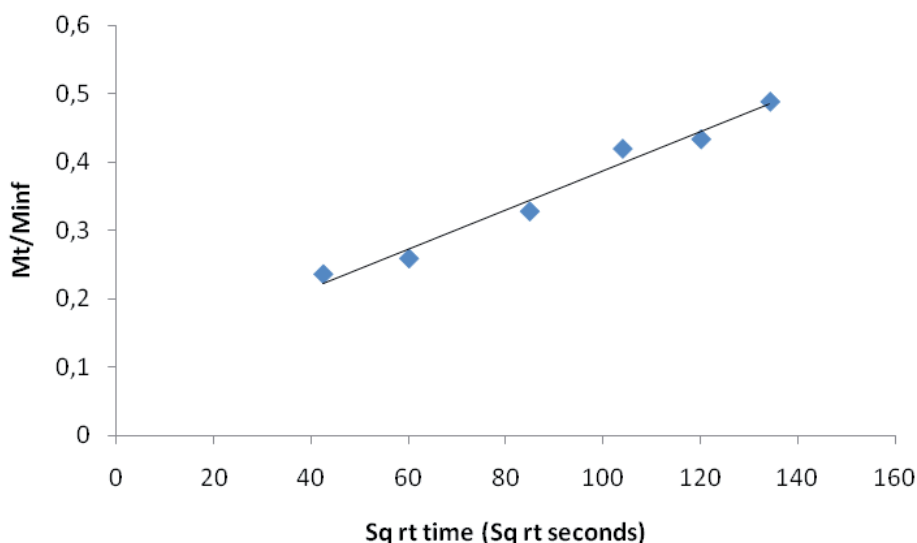


Figure 1. Plot of M_t/M_∞ against \sqrt{t} time for sodium alginate (2%) released from alginate impression material.

Rycina 1. Wykres M_t/M_∞ względem czasu \sqrt{t} dla alginianu sodu (2%) uwalnianego z alginatowej masy wyciskowej.

sodium carboxymethyl cellulose, and these prove to be adhesive to the mucosa. This so-called "bio-adhesive" character arises in part from the presence of the mucous coating on the tissue, and also from the ionic interactions of the functional polymer [23, 24]. The use of such systems for controlled drug delivery is a relatively new strategy, and is the subject of a considerable amount of current research [25]. One of the reasons for the interest is that drug delivery to the mucosa is more effective than to the skin, because absorption rates are four times those of the skin, due to the rich blood supply within the mucosa [26]. Alginates have the additional advantage that they are flexible, hence can be shaped to take up the contours of the mucosa. Thus, overall, the system we have studied is promising for use in this developing field of drug delivery.

Conclusions

It has been found that alginate impression material can be used to deliver the drug sodium alginate in a controlled manner. Release of sodium alginate following diffusion kinetics for the first five hours or so, and led to the release of $36.0 \pm 1.0\%$ of the overall loading. The measured diffusion coefficient was $2.25 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$.

The system, which is based on a widely used and inexpensive polymer system, shows promise for oral mucosal drug delivery. Release was efficient and the flexibility of the final product would allow it to take up the contours of the oral mucosa when used *in vivo*. There is also the possibility of employing sodium fusidate with alginate as a self-disinfecting impression material. This would offer protection from infection for dental personnel handling impressions, and could be advantageous given the effectiveness of sodium fusidate against MRSA.

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