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Mucoadhesive Sustained Drug Delivery System Based on Cationic Polymer and Anionic Cyclodextrin/Triclosan Complex

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Abstract

In this study the interactions between a cationic polymer and an anionic cyclodextrin were investigated. The system has the potential for use in a sustained release dosage forms for use on mucous membranes. As mucous membranes are negatively charged the objective of this study was to investigate whether a drug delivery system based on a cationic polymer and an anionic cyclodextrin would be more mucoadhesive than a system containing a cationic polymer and a neutral cyclodextrin. For this purpose the cationic polymer hexadimethrine bromide (HDMBr) and anionic sulfobutylether β-cyclodextrin (SBEβCD) were utilized as well as the neutral hydroxypropyl β-cyclodextrin (HPβCD). Triclosan was used as a model drug. The drug delivery system was formulated as a solution or semi-solid and its adhesion to porcine buccal mucosa and cation exchange media was measured. In addition the release of triclosan from the system was quantified. No difference was observed between the two systems when they were applied to the mucosal surface. However, the formulations showed improved adhesion, compared to the neutral cyclodextrin/drug delivery system, when they could also reach the underlying surface of the excised tissue. The drug delivery system was much better retained on the cation exchange media than the uncharged system. Significant interactions were observed between the negatively charged cyclodextrin and the positively charged polymer. The results indicate that the interactions could be used to obtain a mucoadhesive sustained drug delivery system under certain circumstances. The positive charge of HDMBr did not have the expected effect on the buccal mucosa and it can be concluded that although a positive charge is likely to promote mucoadhesion, other attributes of polymers, such as molecular weight and viscosity, may have equally beneficial effect.

Introduction

Polymers are known to interact with cyclodextrins and drug/cyclodextrin complexes, either by interacting with the outer surface of the cyclodextrin molecules or by forming inclusion complexes [1]. Such interactions are usually governed by relatively weak forces such as van der Waals interactions and hydrogen bonding. Bioadhesive polymers are synthetic or natural polymers that can adhere to biological membranes [2]. These polymers are termed mucoadhesive polymers when they interact primarily with the mucus layer after application to a mucosal epithelium. [3, 4]. Many charged and neutral polymers have been classified as mucoadhesive polymers as they bind strongly to the mucus via non-covalent bonds. Mucoadhesive properties of polymers depend on their structure as well as the ionic strength and the pH of the surrounding aqueous medium [5]. Mucoadhesive polymers must be polar enough to be able to interact with the mucus and should be flexible enough so interpenetration of polymer and mucus can take place [6].

The mucus is a weak viscoelastic gel that adheres strongly to mucous membranes. It contains about 95% water and about 5% of structure forming components, mainly glycoproteins with negative charge. [5]. The glycoproteins are also known to interact with certain polymers in the aqueous phase and thus are likely to be participants of the mucoadhesion process [7].

In this study the interactions between a cationic polymer HDMBr and an anionic cyclodextrin, SBEβCD, were investigated, as well as the potential for such a system for mucoadhesive, sustained drug delivery. The uncharged HPβCD was used as a reference cyclodextrin and the very lipophilic, water insoluble antibacterial agent triclosan was used as a model drug.

Materials and methods

HPβCD (Encapsin HPB; Janssen, Belgium), SBEβCD (Captisol; Cydex, USA), HDMBr (Sigma-Aldrich, USA),

HPMC (Mecobenzon, Denmark) and triclosan (Ciba-Geigy, USA) are all commercially available.

The absorbance of SBEβCD /HDMBr solutions was measured in a UV meter at 600 nm. The concentration of HDMBr was kept constant at 0.5% (w/v) and the SBEβCD concentration varied from 0% to 5% (w/v).

Phase solubility studies were performed as previously described [8]. The solutions and semi-solids were prepared as follows. A concentrated stock solution of HDMBr and SBEβCD was dialyzed (SpectraPore® Cellulose Ether Dialysis membrane, MWCO 500) against deionized water for 48 hours before mixing with other ingredients. Appropriate amounts of HDMBr and either SBEβCD or HPβCD were weighed into a glass vial and dissolved in water. An excess amount of triclosan was added to the cyclodextrin solution, the vial sealed and heated in an autoclave (121 °C for 30 min). The solution were filtered (Schleicher & Schuell 0.45 μm nylon filters) after heating to remove undissolved triclosan.

Four different formulations were tested for triclosan release: semi solid formulations containing either 4.65% (w/v) SBEβCD or 4.65% (w/v) HPβCD, and 3% (w/v) HDMBr, 4% (w/v) hydroxypropyl metylcellulose 4000 (HPMC) and triclosan; and aqueous solutions which had identical compositions except HPMC was omitted. All four formulations were prepared from clear solutions saturated with triclosan. The viscosity was determined in a Brookfield DV-I+ digital viscometer.

The semi solids to be tested by the paddle method (5 ml) were applied onto Petri dishes (10.75 cm^2) and the dishes covered with a semi-permeable cellulose membrane (SpectraPore® Cellulose Ether Dialysis membrane, MWCO 12000–14000), which had been uniformly punched with a multipoint instrument. Then the Petri dishes were placed in a paddle apparatus (Prolabo Dissolutest 07 170.402) at 37 °C and 50 rpm. Samples were withdrawn and analyzed by HPLC [8].

Solutions to be tested on the cation-exchange media (SP Sepharose^{TM} Fast Flow, Pharmacia Biotech AB, Sweden) were applied to 1 ml columns containing 0.75 ml SP cation exchange media and 0.25 ml 1% (w/v) HPβCD solution (pH 5.20 $\pm$ 0.09). The columns were equilibrated for 15 min with a constant flow of 1% (w/v) HPβCD solution at a flow rate of 0.30 ml/min. 200 μl were then removed from the top and 200 μl of a solution, containing HDMBr and SBEβCD or HPβCD, saturated with triclosan, was loaded onto the column and the flow resumed. Samples were collected and measured by HPLC [8].

Two similar flow cell methods were designed to measure the attachment of the delivery system to porcine buccal mucosa (Figure 1). One consisted of donor chamber from Franz diffusion cell (22 mm diameter), a glass plate and a freshly collected porcine buccal mucosa located between them (Figure 1A). The other consisted of flat bottom glass vial (25 mm diameter) with a piece of buccal mucosa located at the bottom of the vial (Figure 1B). Both flow cells had a stopper wiht two small tubes for inlet and outlet. The solutions and semi solids (0.2 ml) to be tested were applied to the mucosal surface. In the "Franz" method the formulations came in contact only with the surface of the mucosa but in the "glass vial" method the preparations could also reach the bottom and side surfaces of the excised tissue. An aqueous mobile phase was pumped (Masterflexr L/S cartridge pump) at 0.20 ml/min over the mucosal surface. Samples of the outflow were collected and analyzed by HPLC [8].

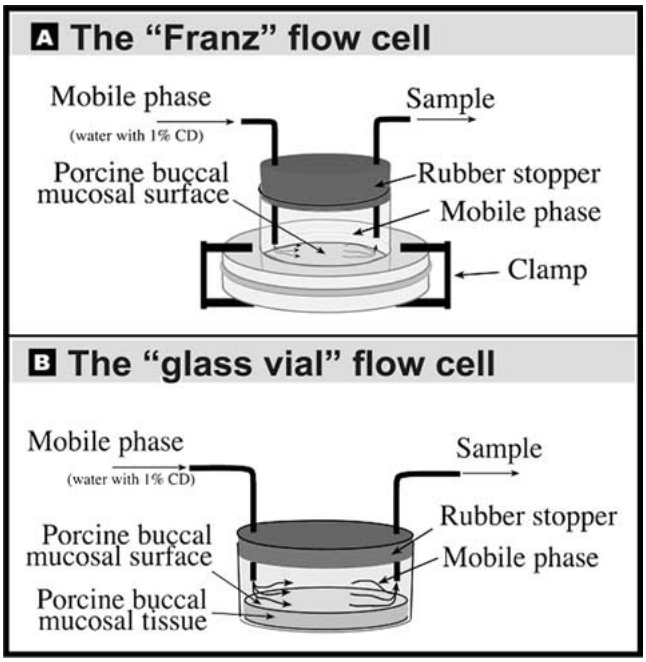

Figure 1. (A) The "Franz" flow cell consisting of a chamber from a Franz diffusion cell, a glass plate and a rubber stopper with two small tubes for inlet and outlet. The buccal mucosa is located between the chamber and the glass plate. (B) The "glass vial" flow cell consisting of a flat bottom glass vial and rubber stopper with two small tubes for inlet and outlet. The excised buccal mucosa is placed at the bottom of the vial.

Results and discussion

The SBEβCD/HDMBr solutions became cloudy when the ratio between the negative charges of SBEβCD and positive charges of HDMBr were approximately equal. When the SBEβCD concentration, and therefore negative charges, were increased further the solutions became transparent again. The absorption was measured and the results indicate the formation of an ion-pair between SBEβCD and HDMBr in solution.

The phase-solubility profiles of triclosan in aqueous HPβCD and SBEβCD solutions were linear with a slope of less than one indicating formation of a triclosan/cyclodextrin 1:1 complex. The solubility of triclosan in 6% (w/v) SBEβCD solution was 2.61 mg/ml without the presence of HDMBr, but 3.95 mg/ml when 3% (w/v) HDMBr was present. The values for 6% (w/v) HPβCD solution were 2.08 mg/ml and 2.12 mg, respectively. Thus, addition of HDMBr resulted in a significant enhancement of SBEβCD solubilization of triclosan, but did not have any effect in the case of HPβCD. The viscosity of the SBEβCD and HPβCD solutions was determined to be 1.1 and 1.9 mPa.s respectively.

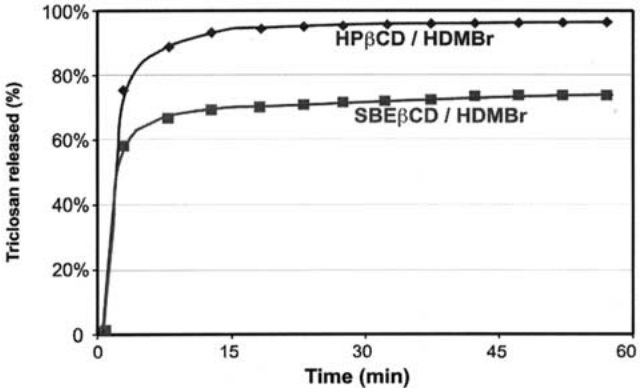

Figure 2. The cumulative release of triclosan from SP cation-exchange media (percent of loaded amount). Solutions containing 6.86% (w/v) HDMBr and 4.65% (w/v) HPβCD or SBEβCD, saturated with triclosan, 1 determination.

The viscosity profiles of the two semi-solids were identical and showed pseudoplastic character. The HPβCD formulations contained 1.2 mg triclosan per ml, but the SBEβCD formulations contained 1.4 mg triclosan per ml.

The release rate of triclosan from the semi solids determined by the paddle method was about twice as fast from the HPβCD semi solid than from the SBEβCD semi solid. Thus, the anionic triclosan/SBEβCD complex appears to be retained for a longer period of time in the cationic HDMBr/HPMC semi solid than the uncharged triclosan/HPβCD complex.

Triclosan was better retained on a cationic-exchange column when a triclosan/SBEβCD/HDMBr solution was applied to the column, compared to a triclosan/HPβCD/HDMBr solution (Figure 2). The triclosan amount retained could apparently be increased by increasing the HDMBr (excess of positive charge). The triclosan retained in the column was then slowly released.

Measurement of triclosan release from the solutions and semi-solids by the two different flow cell methods gave different results depending on which flow cell method was used, that is the “Franz” flow cell method or the “glass vial” flow cell method. When solutions and semi-solids were measured by the "glass vial" method, triclosan was better retained on the mucosa when the SBEβCD/HDMBr solution (or semi-solid) was applied to the mucosa than when the HPβCD/HDMBr solution (or semi-solid) was applied. Furthermore, based on the slopes of the release profiles from 150 to 360 min, the triclosan release rate from the mucosa was about three times larger for the HPβCD/HDMBr solution than for the SBEβCD/HDMBr solution (Figure 3).When semi-solids were measured by the “Franz” flow cell method, no difference in triclosan release between the SBEβCD/HDMBr and HPβCD/HDMBr was observed.

The difference between the two flow cell methods is that in the "franz" flow cell method, the sample solutions (or semi-solids) can only bind to the buccal mucosa surface but when the “glass vial” flow cell method is applied, the sample solution or (semi-solids) can bind to both the mucosa surface and the tissue at the side and bottom of the mucosal tissue. Thus, the "Franz" flow cell method is better suited

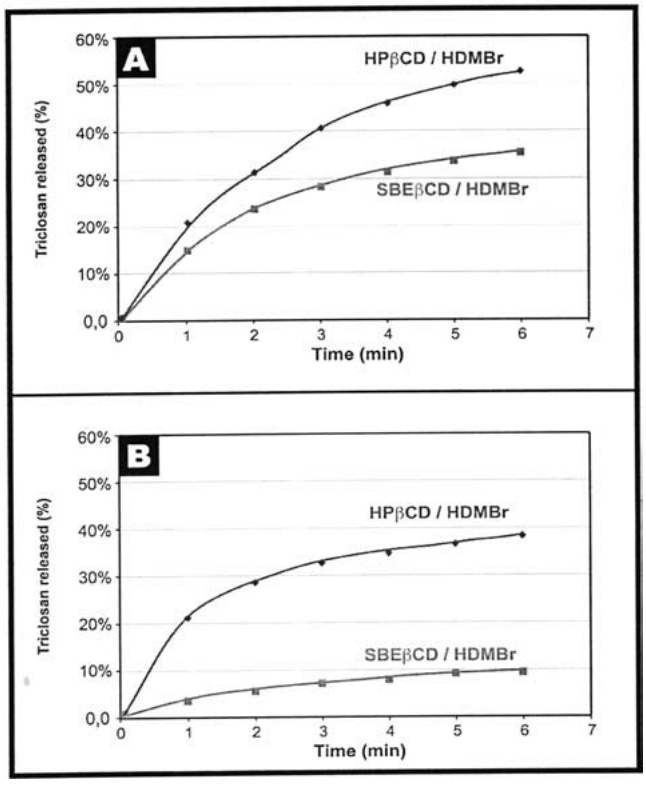

Figure 3. Triclosan release profiles from the A) semi solids and B) the solutions by the “glass vial” flow cell method. Solutions containing 3% (w/v) HDMBr and 4.65% (w/v) HPβCD or SBEβCD. The semi solids had identical composition except (w/v) 4% HPMC (4000) was added to the vehicle. 1 determination.

for measuring attachment of the delivery system to buccal mucosa and the “glass vial” flow cell method is better suited for measuring attachment of the delivery system to tissues.

Conclusion

The results show interaction between the anionic SBEβCD and the cationic HDMBr. The results indicates that these interactions can under certain conditions be used to obtain mucoadhesive sustained drug delivery system. Triclosan/SBEβCD/ HDMBr complex is better retained on a cation-exchange media than the triclosan/HPβCD/HDMBr complex. The positive charge of HDMBr did not have the expected effect on the buccal mucosa. It can be concluded that although a positve charge is likely to promote mucoadhesion, other attributes of polymers, such as molecular weight and viscosity, may have equally beneficial effects.

Acknowledgements

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References

1. T. Loftsson: *Die Pharmazie* **53**, 733 (1998).
2. N.A. Peppas and P.A. Buri: *J. Control. Release* **2**, 257 (1985).
3. H.E Juniger: *Pharm. Ind.* **53**, 1056 (1991).
4. F. Madsen , K. Eberth , and J.D. Smart: *J. Control. Release* **50**, 167 (1998).
5. S.A. Mortazavi, B.G. Carpenter, and J.D. Smart: *Int. J. Pharm.* **94**, 195 (1993).
6. H.E. Boddé, M.E. De Vries, and H.E. Junginger: *J. Control Rel.* **13**, 225 (1990).
7. R.G. Riley, J.D. Smart, J. Tsibouklis, P.W. Dettmar, F. Hampson, J.A. Davis, G.Kelly, and W.R. Wilber: *Int. J. Pharm.* **217**, 87 (2001).
8. T. Loftsson, N. Leeves, B. Bjornsdottir, L. Duffy, and M. Masson: *J. Pharm. Sci.* **88**, 1254 (1999).