30 ml Et_2O und schüttelt die vereinigten Et_2O-Extrakte mit je 20 ml H_2O, ges. $NaHCO_3$-Lsg. und H_2O aus. Nach dem Trocknen über Na_2SO_4 wird eingeengt und i. Vak. der Kugelrohrdestillation unterworfen. Ausbeute: 87%, $Sdp._{0,15}$: 74 °C.
^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) = 0,90 (d, J = 6,6 Hz, 6 H); 1,80 (m_c, 1 H); 2,05 (d, J = 7,1 Hz, $-CH_3$); 2,47 (d, J = 7,2 Hz, $-CH_2-$); 5,23 (q, J = 6,9 Hz, −CHBr); 7,05 u. 7,37 (4 H_{ar}).
$C_{12}H_{17}Br$ (241,2)

2. N-Ethoxycarbonyl-1-(4′-isobutylphenyl)-1-nitramino-ethan (**2**)

Man löst 2,0 g (0,015 mol) N-Nitrourethan in 25 ml trockenem CH_2Cl_2 und tropft unter Feuchtigkeitsausschluss und Rühren sowie unter Kühlen im Eisbad 1,7 g (0,017 mol) frisch dest. Et_3N hinzu, wobei die Temp. 25 °C nicht überschreiten soll. Nach langsamer Zugabe von 5,8 g (0,024 mol) **1** erhitzt man 8 h lang zum Rückfluss, rührt nach dem Erkalten 3 h lang bei Raumtemp. und filtriert $Et_3N \times HBr$ ab. Nach dreimal. Waschen der CH_2Cl_2-Phase mit je 20 ml H_2O wird über Na_2SO_4 getrocknet, eingeengt und durch SC an Kieselgel 60 F_{254} Merck gereinigt. Ausbeute: 57%.
^{1}H-NMR ($CDCl_3$, 200 MHz): δ (ppm) = 0,88 (d, J = 6,6 Hz, 6 H); 1,23 (t, J = 7,1 Hz, $-CH_2-CH_3$); 1,80 (d, J = 7,1 Hz, $-CH-CH_3$); 1,85 (m_c, 1 H); 2,45 (d, J = 7,2 Hz, $-CH_2-$); 4,26 (m, $-O-CH_2-$); 5,86 (q, J = 7,1 Hz, $-CH-CH_3$); 7,13 u. 7,23 (4 H_{ar}).
$C_{15}H_{22}N_2O_4$ (294,4)

3. 1-(4′-Isobutylphenyl)-1-nitramino-ethan (**3**)

2,1 g (7 mmol) **2** werden in 25 ml trock. CH_2Cl_2 gelöst, auf −5 °C abgekühlt und so lange mit trockenem NH_3 begast, bis die Temperatur nicht mehr ansteigt. Das Ammoniumsalz wird abfiltriert, mit Et_2O gewaschen, über $CaCl_2$ getrocknet, in 10 ml H_2O gelöst und unter Eiskühlung mit 2 M HCl angesäuert. Man extrahiert dreimal mit je 20 ml Et_2O, trocknet über $CaCl_2$ und engt ein. Ausbeute: 87%, Schmp. 56 °C (EtOH/H_2O).
^{1}H-NMR ($CDCl_3$, 200 MHz): δ (ppm) = 0,91 (d, J = 6,6 Hz, 6 H); 1,55 (d, J = 7,1 Hz, $-CH_3$); 1,86 (m_c, 1 H); 2,48 (d, J = 7,2 Hz, $-CH_2-$); 5,15 (q, J = 7,1 Hz, $-CH-CH_3$); 7,15 u. 7,23 (4 H_{ar}); ^{13}C-NMR ($CDCl_3$, 50,3 MHz): δ (ppm) = 19,74 (CH_3); 22,35 (2 × CH_3); 30,15 ($-CH-CH_2-$); 45,05 ($-CH_2-Ar$); 56,28 ($-CH-NNO_2$); 126,07 (C3, C5); 129,71 (C2, C6); 136,62 (C4); 142,08 (C1); MS: m/z (%) = 222 (7, M^+), 175 (100), 160 (36), 146 (5), 132 (84), 118 (59), 105 (24), 91 (46), 77 (13), 65 (14), 57 (25).
$C_{12}H_{18}N_2O_2$ (222,3)

Danksagung: Die Autoren danken Prof. Dr. G. Dannhardt, Mainz, für die in seiner Gruppe erarbeiteten Messergebnisse.

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Eingegangen am 9. April 2001
Angenommen am 20. Mai 2001

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Sustained drug delivery system based on a cationic polymer and an anionic drug/cyclodextrin complex

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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 (e.g. polyrotaxanes) [1, 2]. Such interactions are usually governed by relatively weak forces such as van der Waals interactions and hydrogen bonding. The purpose of the present study was to investigate ionic interactions between a cationic polymer, i.e. hexadimethrine bromide (HDMBr), and an anionic cyclodextrin, i.e. sulfobutylether β-cyclodextrin (SBEβCD), and the potential of such system for sustained drug delivery. The very lipophilic, water-insoluble antibacterial agent triclosan was used as a model drug and the uncharged 2-hydroxypropyl-β-cyclodextrin (HPβCD) was used as a reference.
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 [3]. The solubility of triclosan in 6% (w/v) SBEβCD solution was 2.61 mg/ml when no HDMBr was present in the solution 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/ml, 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.
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 methylcellulose 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 of the SBEβCD and HPβCD solutions was determined to be 1.1 and 1.9 mPas, respectively. The viscosity profiles of the two semi solid formulations were identical and both 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 formulations was determined by either a paddle method (semi solids) or by a flow cell method (solutions). The release rate of triclosan from the semi solids was about twice as fast from the HPβCD semi solid than from the SBEβCD semi solid (Fig. 1A). 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 release from the solutions could not be determined by the paddle method. Thus, a flow cell method was designed which measured the attachment of the delivery system to porcine buccal mucosa (Fig. 2). A small amount of the solution was applied to the mucosa and the release of triclosan from the mucosal surface determined. Fig. 1B shows that triclosan was better retained on the mucosa (i.e. much smaller initial triclosan burst was observed) when the SBEβCD/HDMBr solution was applied

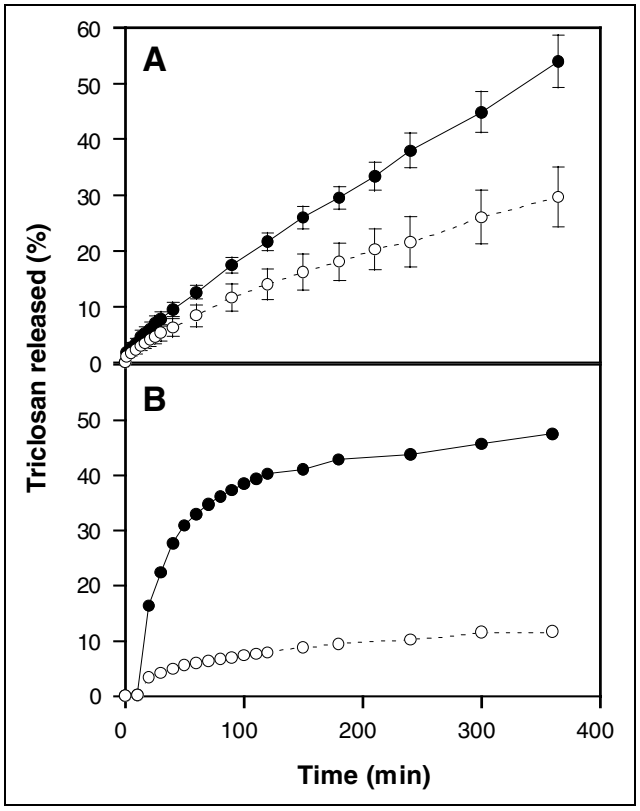

Fig. 1: Triclosan release profiles from the semi solids by the paddle method (A, n = 4, ± stanard error of the mean) and from the solutions by the flow cell method (B, n = 2)
Triclosan/HPβCD/HDMBr system (●)
Triclosan/SBEβCD/HDMBr system (○)

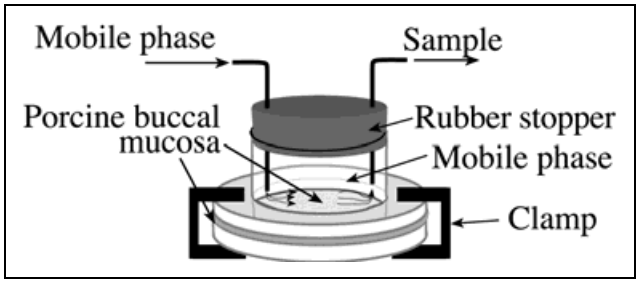

Fig. 2: The flow cell setup

to the mucosa than when the HPβCD/HDMBr solution was applied. Furthermore, based on the slopes of the release profiles from 150 to 360 min (Fig. 1B) the triclosan release rate from the mucosa was about three times larger for the HPβCD/HDMBr solution than for the SBEβCD/HDMBr solution.

In conclusion, the results show that ionic interactions between the anionic SBEβCD and the cationic HDMBr can be applied to obtain sustained drug delivery.

Experimental

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.

Phase-solubility studies were performed as previously described [3]. 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 h before mixing with other ingredients. Appropriate amounts of HDMBr and either SBEβCD or HPβCD were weighted 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 solutions were filtered (Schleicher & Schuell 0.45 μm nylon filters) after heating to remove undissolved triclosan. An appropriate amount of HPMC was added to a portion of each solution, with stirring to form semi solids. 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 discs (10.75 cm^2) and the discs covered with a semi-permeable cellulose membrane (SpectraPore® Cellulose Ether Dialysis Membrane, MWCO 12–14,000), which had been uniformly punched with a multipoint instrument. Then the petri discs were placed in a paddle apparatus (Prolabo Dissolutest 07 170.402) at 37 °C and 50 rpm. Samples were withdrawn and analyzed by HPLC [3].

The flow cell consisted of a glass plate, donor chamber from a Franz diffusion cell (25 mm diameter) and a stopper with two small tubes for outlet and inlet (Fig. 2). Freshly collected porcine buccal mucosa was placed between the glass plate and the donor chamber. The bottom of the flow cell was fully covered by the mucosa. The sample (0.2 ml) was distributed evenly on the surface of the mucosa and a mobile phase (aqueous 1% (w/v) HPβCD solution) pumped (Masterflex® L/S cartridge pump) at 0.20 ml/min over the mucosal surface. Samples of the outflow were collected and analyzed by HPLC.

Acknowledgement: Porcine buccal mucosa was kindly donated by Grísabær slaughterhouse.

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Received May 15, 2001
Accepted May 30, 2001

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