CONTROLLED RELEASE OF DRUGS FROM CD POLYMERS SUBSTITUTED WITH IONIC GROUPS

FENYVESI, É.[1], UJHÁZY, A.[1], SZEJTLI, J.[1], PÜTTER, S.[2], GAN, T. G.[2]
[1]*Cyclolab R&D Lab., Ltd., H-1525 Budapest P.O. Box 435, Hungary*
[2]*Medice Chem.-pharm. Fabrik, Pütter GmBH, D-58638 Iserlohn P.O. Box 2063, Germany*

ABSTRACT

Various disinfecting drugs (ethacridine lactate, methylene blue, gentian violet, brilliant green, fuchsin acid, cetylpyridinium chloride) were incorporated into CD bead polymers substituted with carboxymethyl groups and a retarded release rate was measured. These polymers were successfully used as sustained release wound powders as well as in chewing gum formulations.

1. INTRODUCTION

The insoluble cyclodextrin polymers (CDP) usually prepared in the form of tiny beads are special sorbents for binding certain components from aqueous solutions. Beside the physical adsorption on the surface and inside the pores of the gel structure inclusion complex formation in the cyclodextrin cavities also takes place. When ionic groups are linked covalently in the polymer the interactions between the matrix and the substance are supplemented with salt formation. Cationic polymers are the suitable sorbents for anionic substances, like ethacridine lactate (EAL), brilliant green, methylene blue, fuchsin acid, cetylpyridinium chloride (CPC), etc. The effect of carboxymethylation of the polymer on the release rate of these drugs has been studied.
Controlled release wound powder and chewing gum formulations have been developed applying drug/carboxymethyl cyclodextrin polymer (CMCDP) complexes [1, 2].

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2. EXPERIMENTAL

2.1. Materials

βCD polymer prepared by crosslinking with epichlorohydrin, ethyleneglycol bis(epoxypropyl) ether mixed crosslinking agent in the presence of polyvinyl alcohol (swelling: 5 mL/g, CD content 55 %) was used.
EAL and CPC (Fluka) as well as the other dyes (Reanal) were of analytical grade.

2.2. Methods

Carboxymethylation of the polymer
The polymer was swollen in a chloroacetic acid solution. Concentrated NaOH solution was added and the suspension was stirred gently or shaken in a shaking machine at room temp. for 24 h. After that it was filtered, neutralized, dehydrated and dried. The COOH-content was measured by titration.
Preparation of polymer complexes
The polymer was swollen in the aqueous ethanolic (50 v/v %) solution containing the proper amount of the active ingredient, then shaken for 2 h and dried.
Measurement of the dissolution rate:
The sample of the polymer complex (0.2 g) was stirred in 20 mL phosphate buffer solution at 37 °C and aliquots of the supernatant were measured spectrophotometrically.
Multilayer model-wound experiments
For modeling a wet wound 4 sheets of 4x4 cm filter paper were put on each other and wetted with 1.5 mL of 0.05 M pH=7.0 phosphate buffer and 50 mg dry EAL/CDP complex beads were spread on the top sheet. After a given time the beads were removed and the EAL diffunded into the filter paper layers was washed out with 4x20 mL 50 % (v/v) aqueous ethanol by stirring at room temp. for 1 h. The dissolved EAL was measured spectrophotometrically after filtration.
Preparation and investigation of chewing gums
The chewing gums of the following composition were prepared by warming the gum base to about 70 °C in a kneader, adding glycerol, sorbitol solution and the active ingredient either in itself or complexed with CDP. The composition was kneaded after each addition until homogeneous mass was achieved.

300 g base
20 g glycerol
230 g 70 % sorbitol solution
ad.450 g sorbitol powder
+ 5 g CPC with or without CDP

The formulations were subjected to test panel studies with multiple panelists. The CPC released during mastication was measured by assaying the gum bolus after chewing it for an appropriate time (5 and 30 min).

Assay of the gums

A 3 g piece of chewing gum is weighed into a round flask. 20 mL chloroform, 10 mL 0.004 M sodium lauryl sulfate, 5 mL 2 N sulfuric acid solution and 35 mL distilled water were added and boiled for 20 min at 60 °C under reflux. The emulsion is cooled, 1 mL butter yellow indicator solution is added and titrated with 0.004 M CPC solution till orange color.

3. RESULTS AND DISCUSSION

The dissolution rate of the cationic disinfectant, EAL decreased by using carboxymethyl polymer supports. The higher the carboxymethyl content of the polymer the lower is the rate of dissolution of the drug (Fig. 1). On the basis of these results the release of EAL can be controlled by introducing the proper amount of COOH groups. The EAL/CMCDP polymer complex is suitable to develop a controlled release wound powder formulation [1].

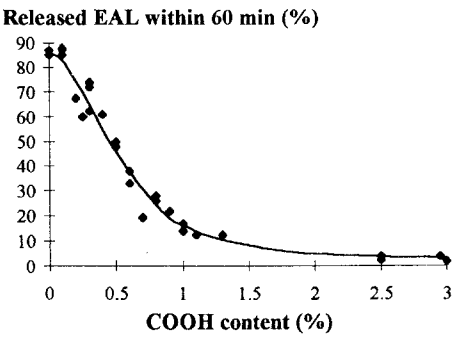

Fig. 1 Release of Ethacridine Lactate from carboxymethyl cyclodextrin polymers as a function of the COOH content of the polymer

Three formulations with identical (2%) EAL content were selected for clinical trial as wound powder for the healing of ulcus cruris and other oozing wounds. The results of the dissolution rate measurement are not characteristic because of the high excess of dissolution medium. The wound powder acts in the low volume of the wound exudate. The release rate of the drug in the multilayer model-wound experiment can be seen in Fig. 2.

The salt formation with the carboxymethyl polymer resulted in decreased release rate in case of some other disinfectants, such as cetylpyridinium chloride, acridine derivatives, methylene blue, triphenyl methane dyes, too (Table I).

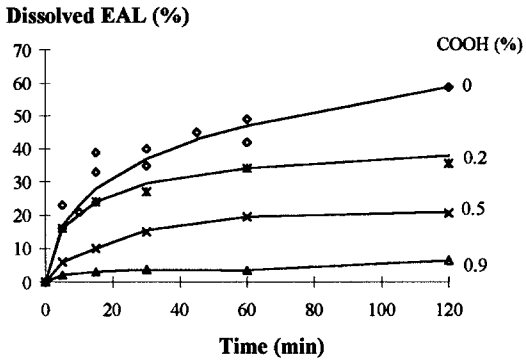

Fig. 2 Dissolution of Ethacridine lactate from CDP-25 in the multilayer model-wound experiment

Table I Effect of carboxymethylation on the drug release from cyclodextrin polymer

disinfectant	carboxymethyl group content of the polymer (mmole/g)	molar ratio of drug/CD	dissolved drug into water in 60 min (%)
CPC	0	1:1	45
	1.0	1:1	23
EAL	0	0.4:1	86
	0.2	0.4:1	60
methylene blue	0	0.1:1	34
	0.6	0.1:1	9.2
brilliant green	0	0.1:1	23
	0.2	0.1:1	1.7
fuchsin acid	0	0.1:1	17
	0.2	0.1:1	1.2

Cetylpyridinium chloride (CPC) was used as model drug, a possible candidate for the development of a chewing gum formulation against sore throat and mouth infections.
Using CPC/CDP or CPC/CMA (carboxymethyl amylose of about the same COOH content: 2 %) complex a higher percentage of CPC is released from the gum but only in the first 5 min. Thus, no retardation effect was observed. This means that neither the complex formation nor the salt formation alone can retard the drug release from the gum. The formulation with CPC/CMCDP, which combines the salt and complex formation has more favorable properties: both the release rate and the amount of unused drug is lower

than in case of the other formulations (Fig. 3). The carboxymethyl cyclodextrin polymer has a significant retardation effect.

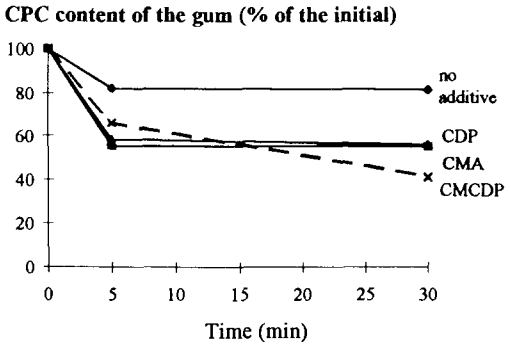

Fig. 3 Release of CPC from chewing gums during mastication

4. CONCLUSIONS

Carboxymethyl polymers are good sorbents for cationic drugs. The release rate of the drug can be controlled by the degree of the carboxymethylation.
By combining the effect of cationic disintegrants with the effect of the swelling carboxymethyl polymers controlled release wound powders have been developed for the treatment of infected wounds, ulcus cruris, traumatic injuries and burns.
The disinfectant/carboxymethyl polymer combination can be successfully used to obtain sustained release chewing gum formulations against sore throat and mucosal infections.

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