SHORT COMMUNICATIONS

Study of local anaesthetics – Part 196*
Formulation of the local anaesthetic heptacaine into hydrogel on the basis of chitosan

Štúdium lokálnych anestetík – časť 196*
Formulácia lokálneho anestetika heptakaín do hydrogélov na báze chitosanu

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Summary

The study aimed to formulate the local anaesthetic heptacaine into hydrogels on the basis of chitosan. The gel-creating compounds used included natural polymers – three different types of chitosan, namely those of a medium molecular weight, from the shells of shrimp, and from the bumblebees species *Bombus terrestris*. The prepared hydrogels were evaluated on the basis of their rheological properties and drug liberation. From the point of drug liberation and flow properties, the optimal gel composition was as follows: 0.1% heptacaine + 2% chitosan (medium molecular weight) + 0.2% carbaethopendecinium bromide.
Keywords: hydrogel • heptacaine • chitosan • drug liberation

Súhrn

Cieľom práce bola formulácia lokálneho anestetika heptakaín do hydrogélov na báze chitosanu. Ako gélotvorné látky boli použité prírodné polyméry – tri rôzne typy chitosanu- o strednej molekulovej hmotnosti; zo schránok kreviet a z čmeliakov rodu Bombus terrestris. Pripravené hydrogély sa hodnotili na základe reologických vlastností a liberácie liečiva. Z hľadiska liberácie liečiva a tokových vlastností bol vyhodnotený gél optimálneho zloženia: 0,1% heptakaín + 2% chitosan (stredná molekulová hmotnosť) + 0,2% bromid karbaethopendecínia.
Kľúčové slová: hydrogél • heptakaín • chitosan • liberácia liečiva

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Introduction

The study is focused on heptacaine, a local anaesthetic of the carbamate type, chemically *N*-[2-(2-heptyloxyphenylcarbamoyloxy)-ethyl]-piperidinium chloride[1, 2].

The release of drugs from semisolid dosage forms, to which also hydrogels belong, is controlled by the modification of their viscosity. With increasing hydrogel viscosity the drug release as well as its absorption is slower and the action is prolonged.

The paper focuses on the formulation of the local anaesthetic heptacaine into hydrogels on the basis of chitosan. The preparations were 2% hydrogels on the basis of three different types of chitosan with a content of 0.1% of the anaesthetic and 0.2% of the antiseptic agent carbaethopendecinium bromide. The liberation of the local anaesthetic from hydrogels and their flow properties were evaluated. The study was motivated by the requests of dermatologists.

Experimental part

Material

Heptacaine chloride (HEP) – N-[2-(2-heptyloxyphenylcarbamoyloxy)-ethyl]-piperidinium chloride was prepared at the Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Comenius University, Bratislava, Slovakia. Three types of chitosan CHIT were used: that of the medium molecular weight (190 000–310 000 Da), chitosan from shrimp shells (molecular weight 190 000–375 000 Da) – practical grade, and chitosan from *Bombus terrestris*. Other materials were lactic acid, carbaethopendecinium bromide, and cellophane.

Instruments

Spectrophotometer – Philips Pyll Unicam Ltd., Cambridge (United Kingdom); Permeation apparatus – R&D laboratory of the Department of Galenic Pharmacy, Faculty of Pharmacy, Comenius University in Bratislava; Viscotester VT 500 – Haake Mess-Technic GmbH (Germany).

Preparation of hydrogels

The 2% chitosan hydrogels containing a lactic acid solution were prepared without and with 0.1% heptacaine chloride. By way of the antiseptic ingredient, 0.2% carbaethopendecinium bromide was added. The mixture was homogenised and left to stand for 48 h.

Evaluation of HEP release

A series of six permeation chambers was used. An amount of 3.0 g of the studied hydrogel was placed in the donor chamber and 20 ml of isotonic NaCl solution was placed into each acceptor part. The acceptor phase was mixed with a magnetic stirrer. HEP was left to permeate at 37 °C through a hydrophilic membrane into the isotonic NaCl solution. The amounts of the released drug were determined by spectrophotometry at λ = 233 nm after 15, 30, 45, 60, 90, 120 and 180 min. The results were evaluated from released cumulative amounts of the drug and represent the averages of 6 measurements.

Determination of rheological properties

Rheological properties were measured by a Viscotester VT 500 at 20°C (three parallel measurements) 48 h after hydrogel preparation.

Results

It was found that the highest percentage of HEP was released from the gel on the basis of CHIT – medium molecular weight, namely 0.81%. In the case of hydrogels on the basis of CHIT from shrimp shells (0.76%) and from *Bombus terrestris* (0.77%), almost the same amount of HEP was released (see Fig. 1); no statistical significant differences were observed.

Based on the rheological evaluation of prepared hydrogels the highest value of structural viscosity was found for CHIT hydrogels from shrimp shells (13 390 Pa.s), lower viscosity was achieved by CHIT – medium molecular weight (7570 Pa.s), and the lowest value was achieved in the case of CHIT gel from *Bombus terrestris* (5240 Pa.s). Based on the flow curves of the hydrogels prepared from three types of chitosan, it was found that all are non-Newtonian systems with a time independent flow of a pseudoplastic character (Fig. 2).

In comparison with the previous study[3], where the liberation of heptacaine from the gels based on cellulose derivates was evaluated, it was found that the drug release was slower from chitosan hydrogels. After 3 hours, less than a half was released in comparison with celullose derivates. On the other hand, it has been demonstrated that after 15 min a double amount of the drug was released from chitosan hydrogels than from the

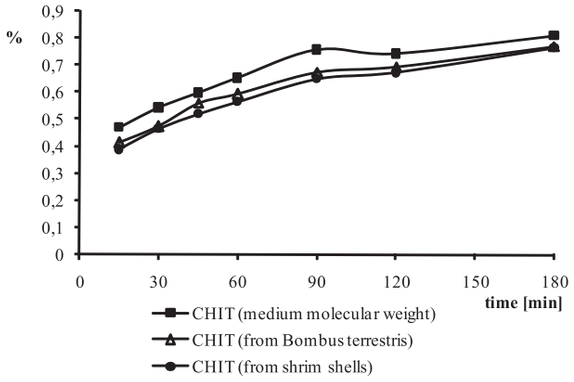

Fig. 1. Release of HEP from CHIT gels after 15, 30, 45, 60, 90, 120 and 180 min

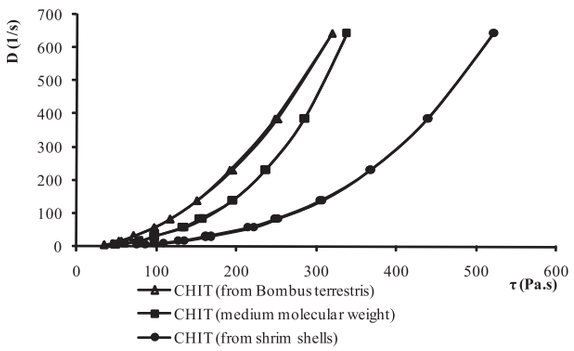

Fig. 2. Rheogram of 2% CHIT hydrogels containing 0.2% carbaethopendecinium bromide and 0.1% HEP

gels on the basis of cellulose derivates. Finally, one can say that the polymer itself influences heptacaine liberation. At the beginning of the liberation from chitosan gels, the percentage of the drug liberated was higher, which means a faster onset of heptacaine effect as well as its longer local anaesthetic activity. From the aspect of the local anaesthetic effect, the chitosan hydrogels with heptacaine may be characterised very positively.

Conflicts of interest: none.

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