2. Preparation of the gels

The composition of NM gel formulations (F1–11) and the control (FC) is given in Table 1. Carbopol® 934 was dispersed in distilled water and left overnight, and then, triethanolamine was added to provide gelation. NM was separately incorporated with penetration enhancer(s) mentioned in Table 1. Subsequently, the latter was added to carbomer dispersion. The control formulation (FC) omitting enhancer was also prepared using the same process. Final pH of all the formulations was adjusted to 6.0 ± 0.1.

3. Solubility studies

The solubility of NM in each vehicle used for formulations was determined by suspending an excess amount of drug in 15 ml of aqueous solution of penetration enhancer(s). These mixtures were shaken continuously in a water-bath (25 ± 0.5 °C) for 24 h. Samples were filtered through a membrane filter and assayed spectrophotometrically at 393 nm for NM content.

4. Viscosity determinations

Viscosity measurements (Brookfield DV-II model viscometer) were performed for each gel formulation using a RV-7 spindle rotated at 100 rpm (25 ± 1.0 °C).

5. In vitro release studies

Cellophane membrane was presoaked in distilled water for 24 h (1 g) spread over cellophane membrane was mounted on Franz-type diffusion cells with a receptor compartment volume of 33.2 ml and an effective diffusion area of 3.14 cm^2. The receptor fluid was selected as phosphate buffer (pH 7.4) containing 25% (v/v) ethanol to maintain sink conditions. During the experiments, the receptor phase was kept at 37 ± 0.5 °C and continuously stirred at 600 rpm. At certain time intervals, 1 ml samples were withdrawn from the receiver compartment and replaced with an equal volume of fresh receptor fluid. The amount of the NM released through the cellophane membrane was analyzed spectrophotometrically at 393 nm. The results were the mean of five experiments. The release rate of NM from formulations was calculated from the slope of the curve where drug released per unit area was plotted versus time. The effectiveness of penetration enhancers (enhancement factor) was determined as the ratio of drug release rate to that of control (FC).

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Study of local anaesthetics, part 161: Influence of additives upon the release of a potential drug of a group of esters of phenylcarbamic acids from a hydroxyethyl cellulose hydrogel

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The paper is concerned with the influence of additives on the release of a derivative of phenylcarbamic acid from a hydrogel. The substance XIX Z [1], a potential local anaesthetic agent which is 129 times more efficient than the standard cocaine used in surface anaesthesia and 66 times more efficient than procaine used in infiltration anaesthesia has been studied.

The influence of the ointment base on the release of XIX Z was studied in a previous work [2], whereby hydroxyethyl cellulose (HEC) hydrogel was selected as the most suitable base. Since hydrogels inevitably contain humectants, emollients and preservatives, we studied the effects of these additives on the release of XIX Z with the objective to select such optimum composition that would ensure the fastest release of the substance.

The influence of humectants (propylene glycol (PG), glycerol (GL), sorbitol (SO)) on the release is shown in Table 1. The release is influenced by the type of humectant and its concentration. From the viewpoint of humectant effects highest rates of release of XIX Z were observed in the presence of sorbitol > glycerol > propylene glycol.

Since largest amounts of XIX Z were released in the presence of 5% SO > 15% GL = 5% PG, these concentra-

Table 1: Influence of the humectants on the release of XIX Z from hydrogels

Humectant	Liberated amount (%) after		k_H (h^{-1})	i_k	η_Q (Pa · s) (D = 220.5 s^{-1})
	0.25 h	3 h			
	17.94	71.09	0.419	0.994	1.230
PG 5%	17.66	72.43	0.414	0.991	1.264
10%	12.80	62.55	0.346	0.980	1.310
15%	12.32	66.77	0.362	0.975	1.369
20%	9.27	57.32	0.301	0.964	1.460
GL 5%	15.32	68.09	0.393	0.990	1.274
10%	13.91	69.15	0.389	0.986	1.320
15%	16.82	72.43	0.416	0.991	1.416
20%	14.24	67.70	0.376	0.985	1.463
SO 5%	21.48	76.56	0.460	0.995	1.110
10%	20.52	73.48	0.439	0.996	1.192
15%	18.37	68.71	0.404	0.996	1.241
20%	17.85	69.34	0.405	0.997	1.358

k_H: liberation rate constant
i_k: correlation index
η_Q: structural viscosity
PG: propylene glycol, GL: glycerol, SO: sorbitol

Table 2: Influence of additives on the release of XIX Z from hydrogels

Additive	Liberated amount (%) after		k_H (h^{-1})	i_k	η_Q (Pa · s) ($\dot{D} = 220.5\ s^{-1}$)
	0.25 h	3 h			
5% SO + PAB	21.79	79.25	0.471	0.996	1.107
15% GL + PAB	14.70	70.30	0.398	0.990	1.288
15% PG + PAB	14.66	64.95	0.359	0.985	1.339
5% SO + AJA	19.64	69.93	0.417	0.995	1.218
15% GL + AJA	16.62	71.20	0.416	0.993	1.334
5% PG + AJA	21.57	79.82	0.473	0.996	1.192
5% SO + ISO	20.08	71.81	0.418	0.996	1.246
15% GL + ISO	17.19	67.66	0.384	0.993	1.399
5% PG + ISO	14.48	66.54	0.381	0.993	1.250

PAB: methyl- and propyl-4-hydroxybenzoate
AJA: Ajatin
ISO: Isopropanol

tions were applied in the following experiments with preservatives. As an exception due to interactions, a sample with 15% PG and methyl and propyl-4-hydroxybenzoate (PAB) was used in the experiments.

In combinations of humectants with PAB (Table 2), the highest release of XIX Z was observed with 5% SO whereas 15% GL and 15% PG reduced the release with respect to the hydrogel without additives. Release from samples containing humectants and Ajatin® (AJA) decreased in the order: 5% PG > 5% SO ≥ 15% GL. Release from samples containing humectants and isopropanol (ISO) decreased in the order: 5% SO > 15% GL ≥ 5% PG.

The amount of XIX Z released from the hydrogel without additives increased in the presence of 5% PG + AJA and 5% SO + PAB. Since turbidity appeared in the sample containing PAB, the gel composition with PG and AJA is considered more suitable.

The remaining combinations of humectants and preservatives were unsuitable, as they slowed the release. In addition, samples containing PAB were cloudy probably as a result of interactions.

Using the Higuchi constants (Table 2) the following final liberation rate series was established: [PG + AJA] > [SO + PAB] > [SO + ISO] ≥ [SO + AJA] ≥ [GL + AJA] > [GL + PAB] > [GL + ISO] > [PG + ISO] > [PG + PAB]

In addition, the influence of structural viscosity upon the release was followed. The hydrogels are non-Newtonian thixotropic systems. Structural viscosity increased with increasing humectant concentrations. However, the influence of combinations of humectant with preservative could not be generalized. Influence of structural viscosity upon the release was not confirmed.

From aspects of liberation parameters the most suitable combination of additives was: 5% propylene glycol and 0.01% benzododecinium bromid.

Experimental

1. Materials

XIX Z, chemically *N*-[2-(2-heptyloxyphenylcarbamoyloxy)-ethyl]-pyrrolidinium chloride [1] was prepared at the Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Comenius University, Bratislava, Slovakia. 2-Propanol, Donau Chemistry, Austria. Hydroxyethyl cellulose (Natrosol), sorbitol and benzododecinium bromid (Ajatin® roztok), Slovakofarma a.s., Slovakia. Propyl-4-hydroxybenzoate, methyl-4-hydroxybenzoate and propylene glycol, Lachema a.s., Czech Republic. Glycerol 85%, Medika, Slovakia.

2. Composition of hydrogel bases

As gelling agent hydroxyethyl cellulose was used (2%). Hydrogel samples contained the following humectants: propylene glycol, glycerol, sorbitol (5%, 10%, 15% and 20%) and the following preservatives: propyl-4-hydroxybenzoate (0.025%), methyl-4-hydroxybenzoate (0.01%), benzododecinium bromid (0.01%) and 2-propanol (5.0%). XIX Z was applied in 0.1% concentration. Blank samples were prepared similarly.

3. Determination of release

Potential drug was left to permeate at 37 °C through a hydrophilic membrane (19.6 cm^2) (Nephrophan, Filmfabrik Wolfen, Germany) into isotonic NaCl solution. Released drug amounts were determined by spectrophotometry (Philips Pye UV VIS, Unicam Ltd., UK) at 233 nm in the respective intervals. The results of release experiments were evaluated from the following aspects: 1. Liberated cumulative amount (%) in 0.25 h and 3.0 h, 2. Liberation constant by Higuchi function [3–5].

4. Determination of rheological properties

Rheological properties were determined at 20 °C in a rotating viscometer (Rotovisko RV, Gebrüder Haake, Germany) after 48 h.

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