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Studies on dressings for mucosal oral cavity Part 6: Influence of a solvent and 1,2-propylene glycol on the pharmaceutic properties of dental xerogel dressings

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The usefulness of dental xerogel dressings for parodontosis treatment depends on their adhesiveness to gums, resistance to washing out with saliva, solubility in artificial gastric juice and the release speed of Kunitz protease inhibitor. The properties depend on: acetone to water ratio in a solvent used, Eudragit to methylcellulose ratio, type and contents of hydrophilising substance [1–4].

The purpose of this work was the examination of the dependencies between the above mentioned properties in the tested xerogel dressings and a diversified acetone to water ratio in the used solvent in the presence of 1,2-propylene glycol.

The adhesiveness of dressings for particular groups depends on the composition of a dressing and the acetone to water ratio in the solvent used in the technological process (Table). The lowest adhesiveness in particular groups is found in reference dressings containing no hydrophilising substance. The addition of 30% and 50% of 1,2-propylene glycol contributes to quadrupling the growth in adhesiveness regardless of the ratio of the used solvent.

The Table shows that the washing out rate in water depends on the quality and quantity composition. In all cases the addition of 1,2-propylene glycol shortens the washing out time in relation to reference dressings. At the same time dressings containing 50% of 1,2-propylene glycol show a longer wash out time than dressings with 30% contents of this hydrophiliser.

The composition of the dressings and the composition of the solvent do not have major influence on the wash out time in artificial gastric juice (*in vitro*), which amounts to 3–4 h.

It has been found out that the dressings are washed out *in vivo* within about 5 h. Only dressings in groups 2 and 3 containing 30% of 1,2-propylene glycol show a slightly shorter wash out time i.e. about 4.5 hours.

The release process of Kunitz prosthesis inhibitor is influenced by the percentage of 1,2-propylene glycol and the composition of the solvent. In groups 1 and 3 the longest release half-time was observed in the case of dressings containing no 1,2-propylene glycol. The increase in glycol percentage from 30% to 50% accelerates the release process.

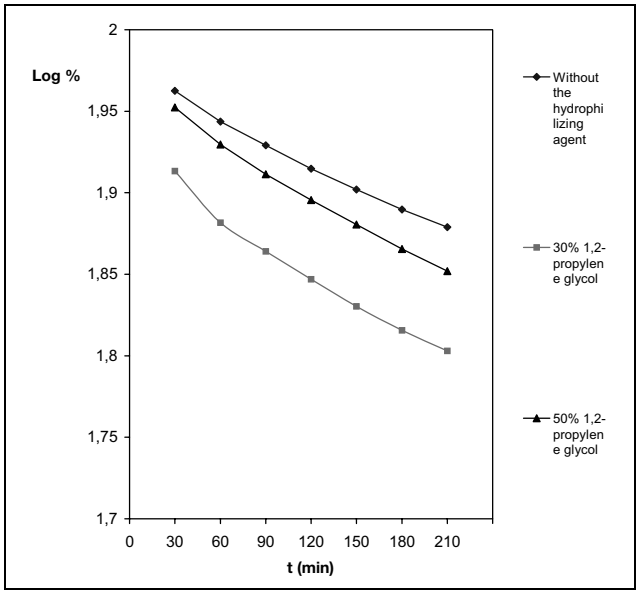

Fig.: Influence of 1,2-propylene glycol on availability of the Kunitz protease inhibitor (Fig. considers only aceton/water ratio 1 : 3)

From the results it may be concluded that xerogels applied between meals will not be damaged or displaced, while the shorter wash out time of dressings in artificial gastric juice ensures that in the case of swallowing a dressing will not be retained in stomach.

Dressings showing t 50% will release a significant part of the inhibitor within 6 h in the in-between meals periods. Those will most probably be used in clinical practice.

Experimental

1. Materials

Methylcellulose (Mc)(Loba Chemie Wien Fishamed Austria). Eudragit E 100 (E)(Rohn Pharma GmbH Darmstadt). 1,2-Propylene glycol, acetone, sodium chloride pro analysis (Polish Chemical Reagents Gliwice). White wax (Wytwórnia Pszczelarska Poznañ). Traskolan 5800 j.i.k./mg (Jelfa Jelenia Góra)

2. Apparatus

Apparatus for liberation of active substances from oinments, acc. to Olszewski and Kubis [1]. Apparatus for testing of adhesion of oinments, acc. to Műnzel. Spectrophotometr (Cecil Instruments Austria Chemist Handel).

Table: Influence of xerogel dressings composition on their pharmaceutical properties

Gel No	MC/E ratio	1,2-Propylene glycol (%)	Aceton/ water ratio	Adhesion (g)	Destruction rate (h)			$t_{50\%}$ [h]
					In vitro		in vivo	
					H_20	artif gastric		
1	1 : 1	0	1 : 2	172.5	8.5	4.0	5.0	11.1
1a	1 : 1	30	1 : 2	705.0	6.5	3.0	5.0	7.0
1b	1 : 1	50	1 : 2	767.5	8.0	3.2	5.0	8.2
2	1 : 1	0	1 : 2.5	192.5	6.8	4.7	5.0	10.0
2a	1 : 1	30	1 : 2.5	790.0	5.0	3.2	4.5	10.2
2b	1 : 1	50	1 : 2.5	795.0	6.5	3.2	5.0	11.1
3	1 : 1	0	1 : 3	215.0	8.0	4.3	5.0	11.4
3a	1 : 1	30	1 : 3	790.0	5.0	3.0	4.5	8.8
3b	1 : 1	50	1 : 3	862.5	6.0	3.3	5.0	9.4

3. Xerogel dressings preparation

The dressings [3] were prepared by dissolving Eudragit E and methylcellulose in a mixture of acetone and water with the addition of 1,2-propylene glycol. The obtained mixture was used to prepare xerogels by evaporating the solvent on a glass plate covered with white wax. The composition of the dressing is included in the chart.

4. Measurement of xerogel dressings adhesiveness

The adhesiveness was determined with Műnzel apparatus [3]. Xerogel dressings swelled in water were placed between the plates of the apparatus and the power necessary to separate them was measured in g.

5. Measurement of xerogel dressings wash out rate

5.1. In vitro wash out

The speed of dressings wash out in water and in artificial gastric juice was measured with a pharmacopeal apparatus for tests of therapeutic substances in pills [3].

5.2. In vivo wash out

Dressings were placed on gums after a meal and their performance was observed visually. The exact time of their wash out is difficult to determine thus the results may only be given approximately.

6. Measurement of Kunitz' protease inhibitor liberation rate

The measurements were carried out with the apparatus of Olszewski and Kubis [1], designed for measuring drug liberation rate from ointments. For 180 min, 2 ml portions of eluate were sampled in 30 min intervals. Amounts of inhibitor liberated were determined spectrophometrically by measurement of absorbance of particular eluates at 260 nm, with water as the reference.

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Activity of calvatic acid and its analogs against *Helicobacter pylori*

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Calvatic acid is an interesting antibiotic with a diazene N-oxide structure [1, 2]. Many of its derivatives display potent antibacterial, antifungal and antitumor properties [2–6]. In this communication we report the results of a study showing that calvatic acid and its analogues can display potent antimicrobial activity against *Helicobacter pylori*, the microorganism associated with a variety of gastric disorders and particularly with gastric ulcers [7]. *H. pylori* infections are usually treated using double or triple-therapy based on the combination of broad-spectrum antibiotics with inhibitors of acid secretion, such as H_2-antagonists or proton pump inhibitors. Several problems are associated with this complex therapy and great interest is devoted to novel agents suitable for a single-therapy treatment [8].

Calvatic acid and its analogues were evaluated for their antimicrobial activity against 19 clinical and NCTC 11637 *H. pylori* strains. Two of the used strains (NCTC 11637 and 102R) were metronidazole resistant. Metronidazole was taken as reference. The minimal inhibitory concentrations MIC_{50} and MIC_{90}, namely the minimal concentration able to inhibit 50% and 90% of the used strains respectively, were evaluated using the agar dilution method. The results are reported in the Table.

Calvatic acid (**1**) triggers potent inhibitory action against all strains tested, including the metronidazole resistant ones. The values of MIC_{50} and MIC_{90} are close and about 15 and 250 times, respectively, lower than those of their reference values. When the experiments were repeated in the presence of variable concentrations of cysteine, a strong decrease or disappearance of the activity was observed, depending on the amount of cysteine used. Such behaviour is in keeping with the known ability of **1** to react in physiological conditions with −SH groups [9, 10]. This reactivity, which was thought to be responsible for a number of biological properties of the antibiotic, could be also involved in its antimicrobial response. Action mechanism apart, the active form of calvatic acid, which is a rather strong acid with pKa = 3.2 [2], should be the ionised one. The small dimension and high polarity of this form should allow its permeation through the pores of the microorganisms membrane.

Shift of the −COOH group either to *m*- or to *o*-position reduces the activity, but the level of the antimicrobial action remains high, in particular in the *m*-analogue **2**. When other groups with different physicochemical properties are substituted for the −COOH in **1**, a modification of the anti *H. pylori* activity occurs. The most active compounds we found are the unsubstituted product **4** and the *m*-CH_3 derivative **9** which appear to be about 4 times more active than calvatic acid. The products are very active also against the two metronidazole resistant strains. A relevant decrease in the antimicrobial action occurs when the electron attracting substituents −CN and $-NO_2$. (**10**, **11**) are inserted in *p*-position.

Derivatives obtained by modification of −N(O)=NCN function are less active than calvatic acid. In fact when in