

ΤΡΙΜΗΝΙΑΙΑ ΕΚΔΟΣΗ ΜΕ ΘΕΜΑΤΑ ΦΑΡΜΑΚΕΥΤΙΚΩΝ ΕΠΙΣΤΗΜΩΝ A QUARTERLY EDITION ON PHARMACEUTICAL SCIENCES' TOPICS



ΙΑΝΟΥΑΡΙΟΣ - ΜΑΡΤΙΟΣ JANUARY - MARCH 2020



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ΕΡΕΥΝΗΤΙΚΗ ΕΡΓΑΣΙΑ

RESEARCH ARTICLE

Choice of Mucosal Adhesive in the Composition of a New Dental gel

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KEYWORDS: Diseases of the periodontium and mucous membrane, dental gel, mucosal adhesives, OraRez[®] W-100L16

SUMMARY

One of the common disadvantages of dental dosage forms is the short-term therapeutic action due to the contact with saliva that dilutes medications, reducing the time of drug exposure on the mucous membranes. To overcome this point, the mucosal adhesives may be added in dental formulations. Therefore, the aim of this work was to study the effect of different adhesive polymers on properties of the dental gel prepared from Carbomer Polacril® 40P basis containing as APIs a combination of tincture «Phytodent», choline salicylate 80 % and lidocaine hydrochloride. The mucosal adhesives used in this study were polyvinylpyrrolidone PVP K90, hydroxypropyl methylcellulose HPMC 2208 90SH-100000 and OraRez®W-100L16. In order to choose a mucoadhesive polymer in dental gel formulation the microbiological, rheological, adhesion and osmotic characteristics have been investigated. Compared with the Carbomer Polacril[®] 40P gel the addition of mucosal adhesives has slightly improved the release of APIs from the gel base, however there are no statistically significant differences in the antimicrobial activity of the test samples. All the samples are non-Newtonian thixotropic systems and the gel with OraRez[®] W-100L16 has the closest rheological behavior to the reference drug - currently marketed dental gel. The rising of OraRez® W-100L16 concentration from 1.0 % to 1.5 % and 2.0 % leads to the increase of gel viscosity and improving the structural-mechanical properties of semisolid dosage form. Adhesion capacity is also improved by the addition of 1.5 % of mucoadhesive polymer, but further increase up to 2.0 % has no positive effect. The osmotic activity of dental gel samples is not observed to be affected by the change of OraRez® W-100L16 concentration.

Corresponding author Maslii Yuliia S. e-mail: julia.masliy@gmail.com Thus, the dental gel test samples show antimicrobial activity, thixotropic properties and non-Newtonian flow. The combination of Carbomer Polacril[®] 40P with OraRez[®] W-100L16 improve structural-mechanical and adhesive properties of the dental gel being developed. The optimal concentration of OraRez[®]W-100L16 is set to 1.5 %

1. Introduction

One of the common disadvantages of dental dosage forms is the short-term therapeutic action due to the contact with saliva that dilutes medications, reducing the time of drug exposure on the mucous membranes. A good distribution in the oral cavity tissues and the prolonged effect are characteristic of a dental gel, which is a modern dosage form for the treatment and prevention of inflammatory diseases of the periodontium and mucous membrane¹⁻⁵.

The dental gel, which is currently under development at the Department of Industrial Technology of Drugs of the National University of Pharmacy (Ukraine), contains a combination of active pharmaceutical ingredients (APIs), namely the tincture «Phytodent» (PJSC «CPP Chervona zirka», Ukraine), choline salicylate 80 % (Basf Pharma, Switzerland) and lidocaine hydrochloride (Societa Italiana Medicinali Scandicci, Italy), providing to the finished medicinal product anti-inflammatory, antimicrobial, reparative and analgesic properties. Based on previous studies, Carbomer Polacril® 40P at a concentration of 1.5% has been selected as a gel former, which, by neutralization with a solution of 10 % sodium hydroxide to the required pH (5.5-7.5), forms a transparent, homogeneous gel with satisfactory structural-mechanical properties¹.

In order to obtain the most suitable base for the dental gel the mucosal adhesives were decided to be added into it, that should contribute to increasing the gel retention time in the oral mucosa and, accordingly, improving its therapeutic efficacy⁶⁻⁹.

Thus, **the aim** of our study was to choose the type and concentration of mucosal adhesive in the formulation of the new dental gel.

2. Materials and Methods

2.1 Materials

The mucosal adhesives used in this study were polyvinylpyrrolidone PVP K90 (AppliGhem GmbH, Germany), hydroxypropyl methylcellulose HPMC 2208 90SH-100000 (Shin-Etsu, Japan) and OraRez[®] W-100L16 (BOAI, China)¹⁰⁻¹³. The dental gel samples were prepared using Carbomer Polacril[®] 40P (Amedeo Brasca & C. Srl, Italy) as a gel former. Model formulations of dental gel with different mucosal adhesives which were investigated are given in **Table 1**.

2.2 Methods

In order to choose a mucoadhesive polymer in dental gel formulation the microbiological, rheological, adhesion and osmotic characteristics have been investigated.

2.2.1 The antimicrobial activity determination

The antimicrobial activity of the test samples was studied in vitro by the method of diffusion into agar (the method of "wells")¹⁴, which is based on the ability of active substances to diffuse into agar medium, pre-inoculated with microorganism cultures. Antimicrobial activity was determined immediately after preparation of the samples. All studies were performed in aseptic conditions, using a laminar box (Biological Safety Cabinet AS2-4E1 "Esco", Indonesia). As test cultures the following pure cultures were used: gram-positive microorganisms Staphylococcus aureus ATCC 25293, spore culture of Bacillus subtilis ATCC 6633, gram-negative culture of Escherichia coli ATCC 25922, Proteus vulgaris ATCC 4636, Klebsiella pneumoniae ATCC 10031. Antifungal activity was evaluated with respect to the yeast-like fungus of the genus Candida - Candida albicans ATCC 885-653 [14]. One-day suspensions of bacterial microorganisms in physiological saline and a two-day culture of the yeast-like fungus were used in the experiments. The microbial load was 107 microbial cells in 1 ml of nutrient medium.

The diameter of the microbial growth inhibition zone characterized the antimicrobial activity of the experimental samples:

- absence of microbial growth inhibition zones around the well, as well as an inhibition zone with a diameter of up to 10 mm, was considered as insensitivity of microorganisms to the sample introduced into the well;

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Table 1. Formulation of model dental gel samples				
Formulation number	Mucosal adhesive(s)			
1	Carbomer Polacril® 40P 1.5%			
2	Carbomer Polacril® 40P 1.5% + PVP 1.0%			
3	Carbomer Polacril® 40P 1.5% + HPMC 1.0%			
4	Carbomer Polacril [®] 40P 1.5% + OraRez [®] W-100L16 1.0%			

- growth inhibition zones with a diameter of 11-15 mm indicated on a weak sensitivity of the culture to the concentration of the active antimicrobial substance being investigated;

- growth inhibition zones with a diameter of 16-25 mm evidenced on microorganism strain sensitivity to the sample;

- growth inhibition zones, whose diameter exceeded 25 mm, indicated a high sensitivity of the microorganisms to the test sample¹⁴.

2.2.2 Measurement of the rheological parameters

Measurement of the rheological parameters of the model samples was carried out on a rotary viscometer with coaxial cylinders "Rheolab QC" ("Anton Paar"). The studies were carried out at a temperature of $(25 \pm 0.1)^{\circ}$ C. Each experimental sample (about 20 g) was placed in a container in which the spindle was immersed. Viscometric measurements were recorded after achieving stable performance. The determination was carried out with increasing spindle speed and in the opposite direction¹⁵⁻²⁰. According to the results of the study, the rheograms showing dependence of the shear stress (τ r) on the velocity gradient (Dr) were plotted.

2.2.3 The adhesive ability determination

The adhesive ability of the gel samples was determined using the device depicted in **Fig. 1**. The device consisted of an electronic dynamometer (1) with a recording of a maximum value. A test sample, which mass was calculated based on the ratio of 0.25 g/cm²



Figure 1. Scheme of the device for adhesion determination: 1 - electronic dynamometer-strain gauge; 2 - rod for the transfer of the separation effort to the dynamometer; 3 - cover plate; 4 - the sample to be studied; 5 - petri dish; 6 - load

of the cover plate (3), was placed in a petri dish fixed on a horizontal surface (5), which provides an optimum thickness of the layer to measure the detachment effort from the contact surface of the sample and the plate. A test sample was pressed by a plate until its contact surface is completely wetted by a





Figure 2. Dialyzer scheme: 1 – dialysis chamber; 2 – internal cylinder; 3 – sample; 4 – semipermeable membrane; 5 – solution of artificial saliva

sample (4). The plate was equipped with a rod to transfer the detachment effort to the dynamometer (2). The contact surface of the plate was previously coated with a thin layer of paraffin. To provide a uniform effort, a load (6) weighing 1 kg was placed on the plate for 60 seconds, after which the load was removed. Then the dynamometer with the contact plate attached to it was lifted upright up to the detachment of the contact plate from the surface of the sample and recorded the necessary separation effort from the indications of the dynamometer (1).

The calculation of the adhesion was carried out according to the strength required for the separation of the two surfaces after the occurrence of adhesion. This force (Sm) is calculated as the ratio between the maximum detachment force (Fm) and the total area of the surface (Ao) involved in the adhesive interaction, using the formula: **Sm = Fm / Ao**]¹.

2.2.4 Osmotic activity determination

Osmotic activity of the gel was determined using di-

alysis through a semipermeable membrane method (cellophane film of the grade V-8079, GOST 7730-89) [4]. Scheme of the dialyser is presented in **Fig. 2**.

The test sample (3) (about 10.0 g) was applied uniformly to the surface of the semipermeable membrane (4), which area was about 2000 mm² while the cylinder diameter was 50 mm. The inner cylinder (2), together with the sample, was placed in the dialysis chamber (1), which was poured with a predetermined amount of artificial saliva solution (5). The internal cylinder previously wiped from its outside was weighed every 60 minutes till the constant weight was achieved. The analytical scales within the accuracy of 0.001 g were used for weightings. The experiments were conducted at a temperature of (37.0 ± 1.0) °C in the thermostat TS-80M-2. Periodically, the volume of the solution in the dialysis chamber was brought to the initial level. The amount of absorbed liquid was determined as the change in mass between two weightings.

2.3 Statistical analysis

Statistical analysis was carried out using Microsoft Excel 2010 software. All experimental determinations were done in triplicate and results are presented as mean value \pm confidence interval (CI). Significant levels were defined at p < 0.05.

3. Results and Discussion

The antimicrobial activity of the prototype samples was studied *in vitro* by the method of "wells", which allows characterizing both the antimicrobial activity of the drug and the release of antimicrobial substances from the base, since the microbial growth inhibition zones are formed due to the diffusion of these substances into the dense nutrient medium [1, 14]. "Metrogyl Denta[®]" gel (Unique Pharmaceutical Laboratories, India) was used as a reference drug. The results are shown in **Table 2**.

According to the results in **Table 2** the only sample which possesses the antimicrobial activity in relation to all cultures of bacteria and the fungus of the genus

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Table 2. Antimicrobial activity of dental gel formulations						
	Cultures of microorganisms					
Gel formulation	S. aureus ATCC 25293	B. subtilis ATCC 6633	E. coli ATCC 25922	Pr. vulgaris ATCC 4636	Kl. pneumoniae ATCC 10031	C. albicans ATCC 885- 653
Diameter of the microbial growth inhibition zone, mm						
1	21.2 ± 0.4	23.2 ± 0.4	28.4 ± 0.5	24.6 ± 0.5	24.4 ± 0.5	-
2	22.2 ± 0.4	25.6 ± 0.5	28.6 ± 0.5	25.2 ± 0.4	24.8 ± 0.4	-
3	22.4 ± 0.5	25.8 ± 0.4	28.8 ± 0.4	25.8 ± 0.4	24.4 ± 0.5	-
4	22.4 ± 0.5	25.6 ± 0.5	28.8 ± 0.8	26.2 ± 0.4	24.4 ± 0.5	-
Metrogyl Denta®	20.8 ± 0.4	23.6 ± 0.5	26.8 ± 0.4	23.2 ± 0.4	25.6 ± 0.5	18.6 ± 0.5

Note: "-" – microbial growth inhibition zone is absent; number of tests n = 3 for each formulation; values are mean \pm CI at p < 0.05

Candida was the reference drug. The test samples No. 1–4 possess a broad spectrum of antimicrobial action against bacterial strains but show no antifungal activity.

It should be noted that all test samples exhibit practically the same antimicrobial effect and the microorganisms used are sensitive (*S. aureus* ATCC 25293, *B. subtilis* ATCC 6633, *Pr. vulgaris* ATCC 4636, *Kl. pneumoniae* ATCC 10031) or highly sensitive (*E.* soli ATCC 25922) to the action of these samples. The antimicrobial activity of the samples No. 1–4 exceeds that one of the reference drug "Metrogyl Denta[®]", however the results obtained for test samples practically do not differ from each other, which does not allow concluding about a statistically significant advantage of any test sample.

Structural-mechanical characteristics significantly affect release and absorption of drug substances from semisolid dosage forms, as well as their consumer properties: spreadability, adhesion, and extrusion ability¹⁵⁻²⁰. Therefore, we have investigated the rheological performance of the above-mentioned gel samples compared to the "Dentinox-Gel N" ("Dentinox Gesellschaft für Pharmaceuticals, Praparate Lenk & Schuppan", Germany). In this case, the reference drug was chosen because of its similar composition – it contains a carbomer as a gel former and alcoholic herbal tincture and lidocaine hydrochloride as APIs.

Under the term spreadability it should be understood an attribute that characterize the texture during application of the dosage form as the ability to flow. To determine this attribute, measurements of the initial diameter of the test sample (weighing 1.0 g), which was placed between two glass plates, 10x10 cm in size, were carried out. Then a load of 100.0 g was placed from the top for 10 minutes, after that the sample spot diameter obtained in such a manner was measured. The results are presented in **Table 3**.

According to the results of the spreadability determination (**Table 3**), all the test samples had a large diameter of the spot after the load, which was ap-

Table 3. The spreadability of dental gel formulations							
	Gel formulation						
The measured value	1	2	3	4	Dentinox-Gel N		
The initial diameter of the spot (d ₁), mm	46.5 ± 1.0	41.3 ± 1.2	38.8 ± 0.9	45.2 ± 1.3	41.2 ± 0.3		
Spot diameter after the load (d_2) , mm	51.0 ± 1.1	50.2 ± 1.2	49.8 ± 0.9	50.0 ± 1.0	46.0 ± 1.0		
Coefficient (K = d_2/d_1)	1.10	1.22	1.28	1.11	1.12		

Note: number of tests n = 3 for each formulation; values are mean $\pm CI$ at p < 0.05



Figure 3. Rheograms of test gels compared with the drug "Dentinox-Gel N" (at 25 °C)

proximately of 50 mm for all of them. However, the spreadability coefficients of the samples No. 1 and No. 4 were closer to that of the reference drug "Dentinox-Gel N", indicating that they had the similar adhesion to the surface on which the drug was applied.

Samples No. 2 and No. 3 had a higher spreadability coefficient due to the difference between the initial diameter of the spot and the diameter after the load, which may indicate their unsatisfactory adhesion properties.

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Figure 4. Rheograms of gel with varying concentrations of OraRez[®] W-100L16 in comparison with "Dentinox-Gel N" (at 25 °C)



Figure 5. Adhesion of gel samples with different concentrations of OraRez W-100L16 (values are mean ± CI at p < 0.05)

In addition, we have plotted rheograms of gels based on Carbomer Polacril[®] 40P with different adhesive polymers. The results are shown in **Fig. 3**.

According to rheograms depicted in **Fig. 3**, all the test samples are non-Newtonian thixotropic systems with different hysteresis areas, which exceed the reference drug by the viscous characteristics^{21, 22}. A

similar rheological behaviour towards drug "Dentinox-Gel N" has gel sample No. 2 containing OraRez[®] W-100L16.

Thus, considering all of the above results, a combination of Carbomer Polacril[®] 40P with the addition of OraRez[®] W-100L16 was chosen as the optimal adhesive for the dental gel being developed.



Figure 6. Kinetics of artificial saliva solution absorption by gel samples with different amounts of $OraRez^{\otimes}$ W-100L16 (values are mean ± CI at p < 0.05)

The next stage of our work was to choose the concentration of mucosal adhesive in the dental gel through the study of structural-mechanical and adhesive characteristics^{7, 20}.

Rheological study of gel samples with varying concentrations of OraRez[®] W-100L16 and "Dentinox-Gel N" (**Fig. 4**) showed that the rising of OraRez[®] W-100L16 concentration leads to the increase of gel viscosity and improving the structural-mechanical properties of semisolid dosage form while the reference drug has a small area of hysteresis loop.

The analysis of adhesion capacity, which results are shown in **Fig. 5**, has proven that an increase in the concentration of polymer up to 1.5% significantly affects the adhesion ability of the gel (approximately in 1.2 times). However, further increase of OraRez[®] W-100L16 concentration up to 2.0 % does not improve adhesive properties.

It is known that the use of drugs with high osmot-

ic activity can lead to dehydration of the oral cavity tissues, which is manifested in the sense of dryness and, accordingly, increased sensitivity of the mucous membranes and discomfort. In addition, this is the basis for the development of other dental diseases⁴. Therefore, in order to finally choose the concentration of adhesive in the gel formulation, osmotic activity of the semisolid drug samples with different amounts of OraRez[®] W-100L16 has been investigated. The kinetics of artificial saliva solution absorption by gel samples with varying amounts of the adhesive is shown in **Fig. 6**.

According to the results (**Fig. 6**), the moderate osmotic activity of the dental gels has been determined – within 6 hours the amount of absorbed artificial saliva in samples did not exceed 70 %, there also was no observed increase in weight after 24 hours. At the same time, an increase in the concentration of OraRez[®] W-100L16 up to 2.0% practically did not affect this indicator. Therefore, based on rheology, adhesion capacity and osmotic activity studies the concentration of the mucosal adhesive OraRez[®] W-100L16 in dental gel formulation is set to 1.5%.

Nonetheless, some limitations of this study should be taken into account considering the results obtained herein. Thus, all experiments except osmotic activity study were performed at a room temperature (25 ± 0.1) oC, while the range for oral temperature is $33.2-38.2 \ ^{\circ}C^{23}$. However, because of comparative study design we believe that the above-mentioned limitations are not crucial and significantly do not affect the findings.

4. Conclusions

1. The addition of mucosal adhesives to the gel formulation slightly improve the antibacterial activity of dental gel samples, however there is no statistically significant difference in the type of mucoadhesive polymer. So, such a positive effect on antibacterial activity may be related to the improving of API release from gel base.

2. All dental gel test samples show thixotropic properties and non-Newtonian flow. The combination of Carbomer Polacril[®] 40P with OraRez[®] W-100L16 is the closest by the rheological behav-

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iour and spreadability and accordingly by consumer properties to the reference dental gel which is currently marketed.

3. The rising of OraRez[®] W-100L16 concentration from 1.0 to 1.5 % improve adhesive properties of the dental gel, but further increase up to 2.0 % has no positive effect. So, the optimal OraRez[®] W-100L16 concentration in the dental gel formulation is set to 1.5 %.

4. The dental gel formulation with 1.5 % OraRez[®] W-100L16 is characterized by moderate osmotic activity which will not lead to dehydration of the oral mucosa, but at the same time contribute to the decrease of periodontal inflammation. \Box

Conflict of Interest The authors declare that they have no conflict of interest.

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