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The study of biopharmaceutical and adhesive characteristics of a dental gel

Significant prevalence of dental pathologies among different age groups of the population of Ukraine dictates the need to find new effective medicines used in the treatment of oral cavity diseases. The choice of a dosage form and the optimal composition of the active pharmaceutical ingredients introduced in it to provide the necessary therapeutic effect is of importance in the treatment of periodontal diseases. For local treatment in dentistry gels are widely used; due to formation of aqueous internal structures they can include various chemotherapeutic substances in their composition, which makes it possible to obtain a dosage form with the multi-profile action. Considering the above, the research on developing the composition and technology of the dental gel with "Phytodent" tincture (PJSC "CPP Red Star", Ukraine), choline salicylate 80 % (Basf Pharma, Switzerland) and lidocaine hydrochloride (Societa Italiana Medicinali Scandicci, Italy) has been conducted.

Aim. To select the optimal gel base from the solutions of polymers of the semi-synthetic and synthetic origin tested in different concentrations by studying the biopharmaceutical and adhesion characteristics of six samples of gels.

Materials and methods. The biopharmaceutical studies were performed by the method of direct diffusion in 2 % agar gel containing iron (III) chloride solution as an indicator. The degree of bioavailability of the amount of active substances from gels was determined by the diameter of the colored zone. The adhesive ability was studied using an electronic dynamometer.

Results and discussion. It has been found that addition of mucosal adhesives to a gel-former provides the prolonged action to gels and increases their adhesion ability.

Conclusions. The results of the biopharmaceutical studies have not been allowed determining the statistically reliable advantage of any of the gel samples. Based on the results of their adhesion ability the gel compositions with the best adhesion characteristics have been found; they can be recommended for further screening studies on creation of a new dental gel.

Key words: periodontal diseases; dental gels; polymer gel base; mucosal adhesives; bioavailability; adhesion ability

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Вивчення біофармацевтичних і адгезійних характеристик стоматологічного гелю

Значна поширеність стоматологічних патологій серед різних вікових груп населення України диктує необхідність пошуку нових ефективних лікарських засобів, що застосовуються в терапії захворювань ротової порожнини. Важливе значення в терапії захворювань пародонту має вибір лікарської форми і оптимального складу активних фармацевтичних інгредієнтів, введених у неї з метою забезпечення необхідного терапевтичного ефекту. Для місцевого лікування в стоматології широко використовують гелі, які завдяки утворенню водних внутрішніх структур дозволяють включати до свого складу різні хіміотерапевтичні речовини, що обумовлює можливість отримання однієї лікарської форми багатопрофільної дії. Враховуючи вищесказане, нами були проведені дослідження з розробки складу та технології стоматологічного гелю з настойкою «Фітодент» (ПАТ «ХФЗ «Червона зірка»», Україна), холіну саліцилатом 80 % (Basf Pharma, Швейцарія) і лідокаїну гідрохлоридом (Societa Italiana Medicinali Scandicci, Італія).

Мета роботи – вибір оптимальної гелевої основи, в якості якої були досліджені розчини полімерів напівсинтетичного і синтетичного походження в різних концентраціях, шляхом вивчення біофармацевтичних і адгезійних характеристик 6-ти зразків гелів.

Матеріали та методи. Біофармацевтичні дослідження проводили методом прямої дифузії в 2 % агаровий гель, що містить розчин заліза (III) хлориду в якості індикатора. Ступінь біодоступності суми діючих речовин з гелів визначали за діаметром забарвленої зони. Адгезійна здатність була досліджена за допомогою електронного динамометра.

Результати та їх обговорення. Доведено, що додавання до гелеутворювача мукозальних адгезивів забезпечує гелям пролонговану дію та підвищує їх адгезійну здатність.

Висновки. Результати біофармацевтичних досліджень не дозволили статистично достовірно встановити перевагу одного із зразків гелів. На підставі отриманих результатів їх адгезійної здатності виявлені гелеві композиції з найкращими адгезійними характеристиками, які можуть бути рекомендовані для проведення подальших скринінгових досліджень зі створення нового стоматологічного гелю.

Ключові слова: захворювання пародонту; стоматологічні гелі; полімерна гелева основа; мукозальні адгезиви; біодоступність; адгезійна здатність

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Изучение биофармацевтических и адгезионных характеристик стоматологического геля

Значительная распространенность стоматологических патологий среди различных возрастных групп населения Украины диктует необходимость поиска новых эффективных лекарственных средств, применяемых в терапии заболеваний полости рта. Важное значение в терапии заболеваний пародонта имеет выбор лекарственной формы и оптимального состава активных фармацевтических ингредиентов, введенных в нее с целью обеспечения необходимого терапевтического эффекта. Для местного лечения в стоматологии широко используют гели, которые благодаря образованию водных внутренних структур позволяют включать в свой состав различные химиотерапевтические вещества, что обусловливает возможность получения одной лекарственной формы многопрофильного действия. Учитывая вышесказанное, нами были проведены исследования по разработке состава и технологии стоматологического геля с настойкой «Фитодент» (ПАО «ХФЗ «Красная звезда»», Украина), холина салицилатом 80 % (Basf Pharma, Швейцария) и лидокаина гидрохлоридом (Societa Italiana Medicinali Scandicci, Италия).

Цель работы – выбор оптимальной гелевой основы, в качестве которой были исследованы растворы полимеров полусинтетического и синтетического происхождения в различных концентрациях, путем изучения биофармацевтических и адгезионных характеристик 6-ти образцов гелей.

Материалы и методы. Биофармацевтические исследования проводили методом прямой диффузии в 2 % агаровый гель, содержащий раствор железа (III) хлорида в качестве индикатора. Степень биодоступности суммы действующих веществ из гелей определяли по диаметру окрашенной зоны. Адгезионная способность была исследована при помощи электронного динамометра.

Результаты и их обсуждение. Доказано, что добавление к гелеобразователю мукозальных адгезивов обеспечивает гелям пролонгированное действие и повышает их адгезионную способность.

Выводы. Результаты биофармацевтических исследований не позволили статистически достоверно установить преимущество одного из образцов гелей. На основании полученных результатов их адгезионной способности выявлены гелевые композиции с наилучшими адгезионными характеристиками, которые могут быть рекомендованы для проведения дальнейших скрининговых исследований по созданию нового стоматологического геля.

Ключевые слова: заболевания пародонта; стоматологические гели; полимерная гелевая основа; мукозальные адгезивы; биодоступность; адгезионная способность

The oral cavity diseases no matter what caused them (trauma, infection, allergen, heredity) greatly complicate everyday life being a stressful factor for most people. In recent decades, there has been a tendency of constant increase of various pathologies of the parodentium and the mucous membrane of the oral cavity throughout the world, leading to various complications not only of the local, but also of the general nature [1-3].

As is known, the choice of dosage form is important to provide the effectiveness of pharmacotherapy for various diseases. In particular, a significant progress in the treatment of many dental pathologies has been achieved due to the use of dosage forms of the prolonged application action in the form of gels. Compared with other dosage forms gels have a number of advantages: they are easily applied to the surface of the mucous membrane of the oral cavity, are well kept on it and provide prolonged contact with the treated surface, substantially prolonging the action of the drug. The form of the gel allows including chemically incompatible substances in its composition since the high viscosity of the dispersion medium prevents the interaction between them. Gels have good thixotropic properties, and it determines their optimal spreadability, good extrusion from the tube, and efficiency of production [4-6].

In case of periodontal disease, the mucous membrane of the oral cavity is inflamed and is sensitive to coarse food and medicines; therefore, the use of a semi-solid dosage form is the best option for the treatment of these pathologies.

The development of a dental gel is a serious scientific research that involves solving a range of issues related to selection of active substances and excipients, as well as providing the necessary biopharmaceutical and rheological properties of the gel composition.

The treatment and prevention of periodontal diseases usually involve an integrated approach that combines the use of medicines with the antimicrobial, immunomodulatory, anti-inflammatory, local anesthetic, reparative and other actions [1-5]. The development of a dental gel designed for the treatment and prevention of inflammatory diseases of the parodentium and oral mucosa, adaptation to removable prostheses and expansion of the range due to the combination of "Phytodent" tincture, choline salicylate and lidocaine hydrochloride in the composition of the gel was, in our opinion, of the unquestionable theoretical and practical interest. Their concentrations were determined taking into account the data of scientific literature and the microbiological studies of the dental gel samples developed [4].

One of the disadvantages of a dental gel is its low adhesion on the surface of the mucus; it is associated with the constant formation of saliva (0.5-2 L/day) and the mobility of the oral cavity tissues. Therefore, this dosage form should possess a good adhesion, which leads to an increase in the concentration of drugs in the

application site and allows decreasing the dose of active pharmaceutical ingredients (APIs) introduced both systemically and locally [7, 8].

When adding mucoadhesive polymers to the gel compositions the effectiveness of their application increases due to an increase in the retention time on the mucous membranes, therefore providing the prolonged action. These substances include anionic polyelectrolytes, for example, derivatives of cellulose and acrylates characterized with a strong mucoadhesion with the minimal toxic effects [6-9].

Therefore, **the aim** of the work was to select the optimal gel base from the solutions of polymers of the semi-synthetic and synthetic origin tested in different concentrations by studying the biopharmaceutical and adhesion characteristics of six samples of gels.

Materials and methods

As the APIs in the dental gel "Phytodent" tincture (PJSC "CPP Red star", Ukraine), 80 % choline salicylate (Basf Pharma, Switzerland) and lidocaine hydrochloride (Societa Italiana Medicinali Scandicci, Italy) were used.

As mucosal adhesives permitted for use in oral products carbopol of Polacril 40P brand (Amedeo Brasca & C. Srl, Italy); polyvinylpyrrolidone PVP K90 (AppliGhem GmbH, Germany); hydroxypropyl methylcellulose HPMC 2208 90SH-100000 (Shin-Etsu, Japan); OraRez® W (BOAI, China) in liquid (OraRez® W-100L16) and powder (OraRez® W-100P) form; hydroxyethyl cellulose (HEC) Tylose® H 100000 YP2 (SE Tylose GmbH & Co.KG, Germany) were used. To achieve the required pH (5.5-7.5) triethanolamine was used as a neutralizer.

The APIs release degree was assessed using the method of agar diffusion [10]. For this purpose, 100 ml of 2 % agar solution was prepared in a standard solvent using 3 % iron chloride (III) as an indicator in the amount of 3 %. In Petri dishes a hot solution of agar was placed and cooled. In the agar gel the wells were formed using a hollow metal cylinder with the diameter of 8 mm, then 0.3 g of test samples of gels were placed in them. Petri dishes were kept in a thermostat for 24 hours at 37 °C. The degree of the APIs release from gels was estimated by the diameter of the color zone formed around the well.

The adhesion ability of the gel samples was determined under the supervision of prof. M. O. Lyapunov at the premises of the Laboratory of Drug Technology and Analysis of the State Scientific Institution "Institute for Single Crystals" of the National Academy of Sciences of Ukraine, Kharkiv. The adhesion was determined using the device (Fig. 1) consisting of the electronic dynamometer (1) with the maximum reading fixation. In a Petri dish fixed on the horizontal surface (5) the test sample was placed, which mass was calculated based on the ratio of 0.25 g/cm^2 of the area of the cover plate (3) providing the optimal thickness of the layer to measure the separation effort from the contact surface of the sample and the plate. The sample taken was pressed by a plate equipped with a rod to transfer the separation effort to the dynamometer (2) until its contact surface was completely wetted with the sample (4). The contact surface of the plate was previously covered with a thin layer of paraffin. To provide a uniform effort the load (6) weighing 1 kg was placed on the plate for 60 sec, then the load was removed. Then the dynamometer with the contact plate attached to it was lifted upright to the detachment of the contact plate from the surface of the sample, and the applied separation effort was recorded by the dynamometer readings (1).

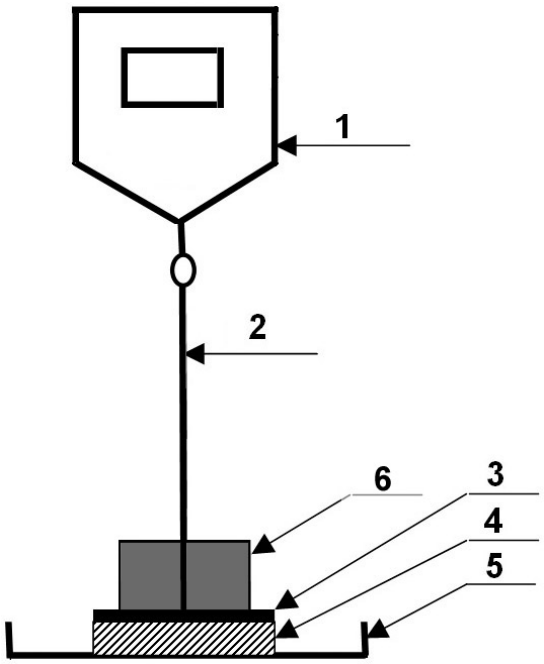

Fig. 1. The scheme of the device for adhesion determination: 1 – an electronic dynamometer-tensometer; 2 – the rod for the separation effort transfer to the dynamometer; 3 – a cover plate; 4 – the test sample; 5 – Petri dish; 6 – the load

The adhesion was calculated using the force required for separating two surfaces after the adhesion appeared. This force (S_m) was determined as the ratio between the maximum breaking force (F_m) and the total area of the surface (A_o) involved in the adhesive interaction by the formula: $S_m = F_m / A_o$.

Results and discussion

In order to study the biopharmaceutical and adhesion characteristics, as well as to select the gel base six model samples of gels with adhesives given in Tab. 1 were prepared.

Table 1

The compositions of the dental gel model samples

Sample, No.	Mucosal adhesives used
1	1.5 % carbopol of Polacril 40P brand
2	1.5 % carbopol of Polacril 40P brand + 1.0 % PVP
3	1.5 % carbopol of Polacril 40P brand + 1.0 % HPMC
4	1.5 % carbopol of Polacril 40P brand + 1.0 % OraRez ® W-100L16
5	1.5 % carbopol of Polacril 40P brand + 1.0 % OraRez ® W-100P
6	3.0 % HEC

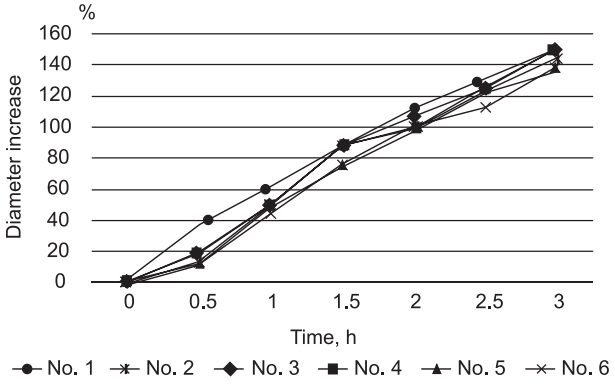

Fig. 2. The dynamics of APIs release from gels

In order to study the bioavailability of the gel samples developed on the basis of various mucoadhesive polymers 3 % iron (III) chloride solution was used as an indicator. "Phytodent" tincture contains phenolic compounds, which under the interaction with the indicator form a dark brown color with a green tint, and in contact with choline salicylate there is an intense dark-violet coloration.

The dynamics of APIs release from various gel samples into agar with an indicator is shown in Fig. 2.

According to the data presented in Fig. 2, in general, the positive dynamics of API release from all gel samples can be noted. At the same time, changes in the degree of release are insignificant. Within the first hour the maximum release was observed in gel sample 1 on the basis of carbopol of Polacril 40P brand without addition of adhesives, while the minimal release was in samples 5-6 based on carbopol of Polacril 40P brand with addition of OraRez® W-100P adhesive and based on HEC. Samples 2-4 within the first hour had the same results – 20 mm. This confirms the fact that addition of mucosal adhesives to the gel-former provides the prolonged action of gels. For 3 hours of their testing all samples had almost identical values of this indicator.

In order to select a rational gel base the adhesion characteristics of the gels developed were also studied. The adhesion of six samples was compared with dental drug "Metrogyl Denta®" in the gel form ("Unique Pharmaceutical Laboratories", India). The indicators of the electronic dynamometer (n = 3) obtained are shown in Tab. 2.

The adhesion characteristics of the samples are given in Tab. 3.

It is known that in pharmacy polymers with mucoadhesion to the mucous membrane in the range of 2000-9000 Pa are used [7]. According to the results obtained samples 1-4 have the best adhesion. In addition, sample 1 based on carbopol of Polacril 40P brand, sample 3 on carbopol of Polacril 40P brand with 1.0 % HPMC and sample 4 – carbopol of Polacril 40P brand P with 1.0 % OraRez® W-100L16 by the adhesion strength exceed the reference drug by 5.0 %, 43.8 % and 3.8 %, respectively. The samples of the gel based on carbopol of Polacril 40P brand with addition of 1.0 % OraRez® W-100P (sample 5) and based on HEC (sample 6) have the worst adhesive properties leading to rapid leaching of the gel from the surface of the mucous membranes of the oral cavity and reducing its pharmacological action.

Table 2

The electronic dynamometer readings, g

Sample No.	Experiment 1	Experiment 2	Experiment 3	Average value, g
1	660	670	690	673.3
2	395	415	440	416.7
3	1125	1135	1150	1136.7
4	660	660	670	663.3
5	300	315	320	311.7
6	215	245	245	235.0
Metrogyl Denta	625	640	650	638.3

Table 3

The adhesion of the gel samples

Sample No.	The dynamometer reading,			Adhesion,	
	g	kg	N	kgf/cm^2	N/m^2 (Pa)
1	673.3	0.6733	6.605	0.08374	8215.17
2	416.7	0.4167	4.088	0.05183	5084.58
3	1136.7	1.1367	11.151	0.14138	13869.40
4	663.3	0.6633	6.507	0.08250	8093.28
5	311.7	0.3117	3.058	0.03877	3803.48
6	235.0	0.2350	2.305	0.02923	2866.92
Metrogyl Denta	638.3	0.6383	6.262	0.07939	7788.56

Note: the area of the plate used is 8.04 cm^2 or 0.000804 m^2.

CONCLUSIONS

1. In order to increase the retention time of the dental gel on the mucous membranes and, therefore, to provide it with the prolonged action various mucoadhesive polymers were introduced into the drug being developed.

2. The results of the biopharmaceutical studies using the method of agar diffusion have not shown a clear dependence of the degree of release from the type of a mucoadhesive polymer. The diameter of the painted zones of all samples for 3 hours of the study was within the range of 27.5 ± 0.5 mm, which did not allow concluding about the statistically significant advantage of one of the samples.

3. Using an electronic dynamometer the adhesion ability of 6 gel samples has been studied when adding mucosal adhesives allowed for oral use in various concentrations.

4. It has been determined that introduction of mucoadhesive polymers to the composition of the dental gel increases its adhesion characteristics, which, therefore, increases the time of its contact with the surface of the mucous membrane and bioavailability of the drug.

5. Based on the results of the adhesion study the gel compositions with the best adhesion characteristics, namely samples 1-4, have been identified; they can be recommended for further screening studies on creation of a new dental gel.

Conflict of Interests: authors have no conflict of interests to declare.

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