УДК 615.454:014.22:242:281.9
DOI: 10.15587/2519-4852.2019.189949

RESEARCH ON THE DEVELOPMENT OF DENTAL GEL TECHNOLOGY WITH METRONIDAZOLE BENZOATE AND HYALURONIC ACID

D. Orlenko, V. Yakovenko, L. Vyshnevska

Мета. *Розробка технології стоматологічного гелю комбінованого складу, встановлення оптимальних технологічних параметрів щодо уведення діючих та допоміжних речовин.*
Методи. *Для виготовлених експериментальних зразків гелю визначали однорідність за методикою ДФУ 1.1, с. 511. Розмір часток суспензії вивчали з використанням мікроскопу XY-B2TLED при поляризованому світлі, згідно ДФУ 2.9.37. Кількісне визначення метронідазолу бензоату та супровідних домішок А, В, С, мірамістину, натрію гіалуронату проводили методом рідинної хроматографії , згідно ДФУ п. 2.2.29, п. 2.2.46.*
Результати. *За результатами хімічних та мікроскопічних досліджень оптимальним способом уведення метронідазолу бензоату в гелеву основу є метод суспензії. Для забезпечення найкращого розподілення метронідазолу бензоату використовували мікронізовану субстанцію та визначили технологічні параметри попередньої гомогенізації метронідазолу бензоату у пропіленгліколі при температурі 20–25 °С. Мікрофотографії досліджуваних зразків гелю показали, що гомогенізація метронідазолу бензоату з пропіленгліколем зі швидкістю від 3000 до 4000 об/хв забезпечує отримання однорідного напівпрозорого гелю білого кольору. Дослідження хімічної стабільності та реологічних показників отриманого гелю, як на момент виготовлення так і про подальшому зберіганні, довели що обрані способи розчинення та технологічні параметри дозволяють отримати стабільний гель без продуктів деградації діючих речовин.*
Висновки. *Обґрунтовано оптимальний спосіб уведення в гелеву основу комбінації діючих речовин: метронідазолу бензоату, мірамістину, натрію гіалуронату. Розроблена раціональна технологія виробництва комбінованого стоматологічного гелю. Визначені критичні стадії та параметри технологічного процесу, встановлені критерії їх прийнятності*
Ключові слова: *технологія, розчинність, суспензія, гомогенізація, гель, стоматологія*

1. Introduction

Inflammation and pain are associated with many diseases of the periodontal and oral mucous membranes (periodontitis, gingivitis, stomatitis, red plaque, multiform exudative erythema, herpes, etc.) develop with any traumatic effect on the mucous membrane [1]. Various antibacterial agents in the form of solutions, such as 2–5 % solution of hydrogen peroxide, 0.2–0.06 % solution of chlorhexidine, etc. are still widely used to influence the nonspecific inflammation cell. Solutions and liquids are also often used to accelerate the regeneration and epithelialization of erosive ulcers in the oral mucosa. This includes in particular applications such as sea buckthorn oil, rose hips, oil solutions of vitamins A and E, carotolin. Longer and deeper the oral mucosa affected by soft dosage forms on lipophilic or hydrophilic bases [2, 3].

The special properties of gels (the combination of solids and liquids, hydrophilicity) make them a new generation of dentistry. They can be kept on the surface of the mucous membrane for a long time, providing its treatment with a medicinal substance [4, 5].

With the regard to the clinical aspects of the use of dental gels, their first and most famous group is represented by antimicrobial and anti-inflammatory drugs, the standard of which is the use of metronidazole. Gel form allows you to apply and keep the drug on the gums, in the gums or pockets, that is, on a specific area where it realizes its antibacterial, anti-inflammatory effect, contributes to the termination of bleeding gums. A clear tendency of modern dental practice is the use of metronidazole in combination with other drugs - antiseptic, anti-inflammatory, reparative action [6, 7].

Our dental gel, in addition to metronidazole benzoate, includes miramistin and sodium hyaluronate. The creation of combination drugs is appropriate from the pharmacotherapeutic point of view and compliance of the patient. At the same time, the combination of several active pharmaceutical ingredients should be studied for compatibility of the ingredients, stability, influence of external factors in the process of production and storage.

The aim of our study is to develop the technology of dental gel with combined composition, the establishment of optimal technological parameters for the introduction of active and auxiliary substances.

2. Planning (methodology) of research

According to State Pharmacopoeia of Ukraine (SPhU), gels are soft topical medicines that are single, double or multiphase dispersed systems with a liquid dispersed medium, whose rheological properties are due to the presence of a gel in relatively small concentrations [8]. The hydrophilic nature of the gels implies the water solubility of the active substances. For poorly soluble substances can be used non-aqueous hydrophilic solvents, which are well mixed with gels of carbomers. Gels can also be heterodispersed systems and contain a solid or liquid dispersed phase.

Among the three active pharmaceutical ingredients (APIs) that make up the gel, only metronidazole benzoate dissolves poorly in water, which requires the selection of another solvent. The increase of the solubili-

ty of metronidazole can be done in different ways: the formation of clathrate complexes with cyclodextrins, the addition of water-soluble vitamins (niacinamide, pyridoxine), and the formation of chemically modified forms of metronidazole [9]. Finding the best way to introduce metronidazole benzoate into the gel base, taking into account the physicochemical properties of the active and auxiliary substances, general requirements for the dosage form was the task of our research. As the efficiency criteria, we choose the homogeneity of the gel and its physico-chemical stability. The result of the research is the development of technological process for the production of combined dental gel and its reproducibility in industrial production.

3. Materials and methods

The subjects of study were metronidazole benzoate [10], solution and suspension of metronidazole benzoate in propylene glycol, model gel samples with metronidazole benzoate, miramistin [10] and sodium hyaluronate [10].

In the manufacture of gels we used following excipients: Carbopol® Ultrez 10 [11], sodium hydroxide, propylene glycol, disodium edetate, purified water, saccharin sodium, purified water [8].

The determination of the uniformity of the gel samples prepared by the above technology was performed according to the method of SPhU 1.1, section 511.

The particle size of the samples was studied using a XY-B2TLED microscope under polarized light according to SPhU 2.9.37.

About 10 mg of the gel sample was placed on a glass slide and covered with a glass cover, the sample distributed to form a thin uniform layer. The samples were examined at magnification using a 40 x 0.65 lens under a microscope under polarized light.

The quantitative determination of metronidazole benzoate, miramistin, hyaluronate sodium and the accompanying impurities A, B, C was performed by liquid chromatography according to SPhU section 2.2.29, section 2.2.46. The structural viscosity η (MPa * s) was determined by the method of SPhU 2.0, vol. 1, section 2.2.8, on Agilent 1200 LC chromatograph with diode-matrix detector.

4. Results of the research

From a biopharmaceutical point of view, the most optimal is the presence of an API in the finished dosage form in solution form. In this regard, we have studied the solubility of metronidazole benzoate, sodium salt of hyaluronic acid and miramistin in water and hydrophilic non-aqueous solvents [12].

Based on the obtained results, propylene glycol is the most preferred hydrophilic non-aqueous solvent for dissolving metronidazole benzoate. The complete dissolution of the therapeutic dose of metronidazole benzoate contained in the gel occurs at a temperature of 80±5 °C at a concentration of propylene glycol 50 mg / g. The sodium salt of hyaluronic acid and miramistin are well soluble in purified water.

A laboratory sample of the gel was analysed, in which metronidazole benzoate was obtained as a solution in propylene glycol at 80±5 °C. The results of the analysis shown in Table 1.

The obtained results (Table 1) indicated that metronidazole benzoate is unstable in gel when it previously dissolved in propylene glycol at a temperature of 80±5 °C. Heating leads to an increase of impurities in the quantitative content, the maximum content of which is set by the regulatory documentation for API. In addition, the resulting gel is opaque, has a white colour, that is, with the introduction of a solution of metronidazole benzoate in the gel base and further cooling the active substance is crystallized.

As an alternative technology, we investigated the possibility of introducing metronidazole benzoate into the gel in the form of fine powder by type of suspension. The results of the studies are shown in Table 2.

Table 1

The results of the analysis of the gel after introduction of metronidazole benzoate in the form of a solution

No.	Indicator	Requirements	Analysis result
1	Description	Homogeneous transparent or translucent gel	Translucent homogeneous gel of white colour
2	Quantitative content: – metronidazole benzoate	 15.2–16.8 mg/g	 13.52 mg/g
3	Related impurities: – impurity B – impurity A – impurity C – not identified impurities	 Not more 1.0 % Not more 1.0 % Not more 0.5 % Not more 0.2 %	 0.31 % **1.43 %** 0.1 % not found

Table 2

The results of the analysis of the gel after introduction of metronidazole benzoate in suspension

No.	Indicator	Requirements	Analysis result
1	Description	Homogeneous transparent or translucent gel	Translucent homogeneous gel of white colour
2	Quantitative content: – metronidazole benzoate	 15.2–16.8 mg/g	 16.12 mg/g
3	Related impurities: – impurity B – impurity A – impurity C – not identified impurities	 Not more 1.0 % Not more 1.0 % Not more 0.5 % Not more 0.2 %	 <0.05 % 0.06 % <0.05 % <0.05 %

The results of the analysis of the gel are given in Tab. 2 showed that the introduction of metronidazole benzoate in suspension provides its chemical stability in the composition of the gel.

We also conducted a comparative study to determine the size and distribution of metronidazole benzoate crystals in gel samples using two of the following technologies.

The particle size of the test samples was studied using a XY-B2TLED microscope under polarized light according to SPhU 2.9.37.

Micrographs of the gel samples are shown in Fig. 1, 2.

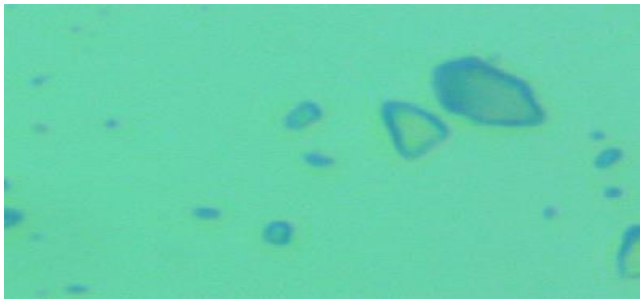


Fig. 1. Micrographs of metronidazole gel benzoate, which is introduced as a solution

As can be seen from Fig. 1, 2, regardless of the method of introduction of metronidazole benzoate into the gel base, its particles are evenly distributed in the mass of the gel, and their size is almost indistinguishable.

Thus, guided by the results of chemical and microscopic studies, the optimal method of introducing metronidazole benzoate into the gel base is the suspension method.

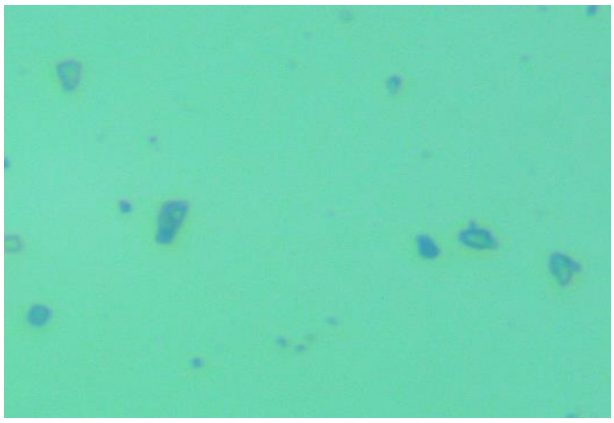


Fig. 2. Micrographs of metronidazole benzoate gel, which is introduced as a suspension

To ensure the best distribution of metronidazole benzoate, we used a micronized substance and determined the technological parameters for the preliminary homogenization of metronidazole benzoate in propylene glycol at a temperature of 20–25 °C. For the preparation of the suspension we used a reactor homogenizer with a turbo stirrer of a rotary type.

Several experimental gel samples were developed according to different technological homogenization parameters, shown in Table 3.

Table 3

Variations of technological parameters at gel homogenization

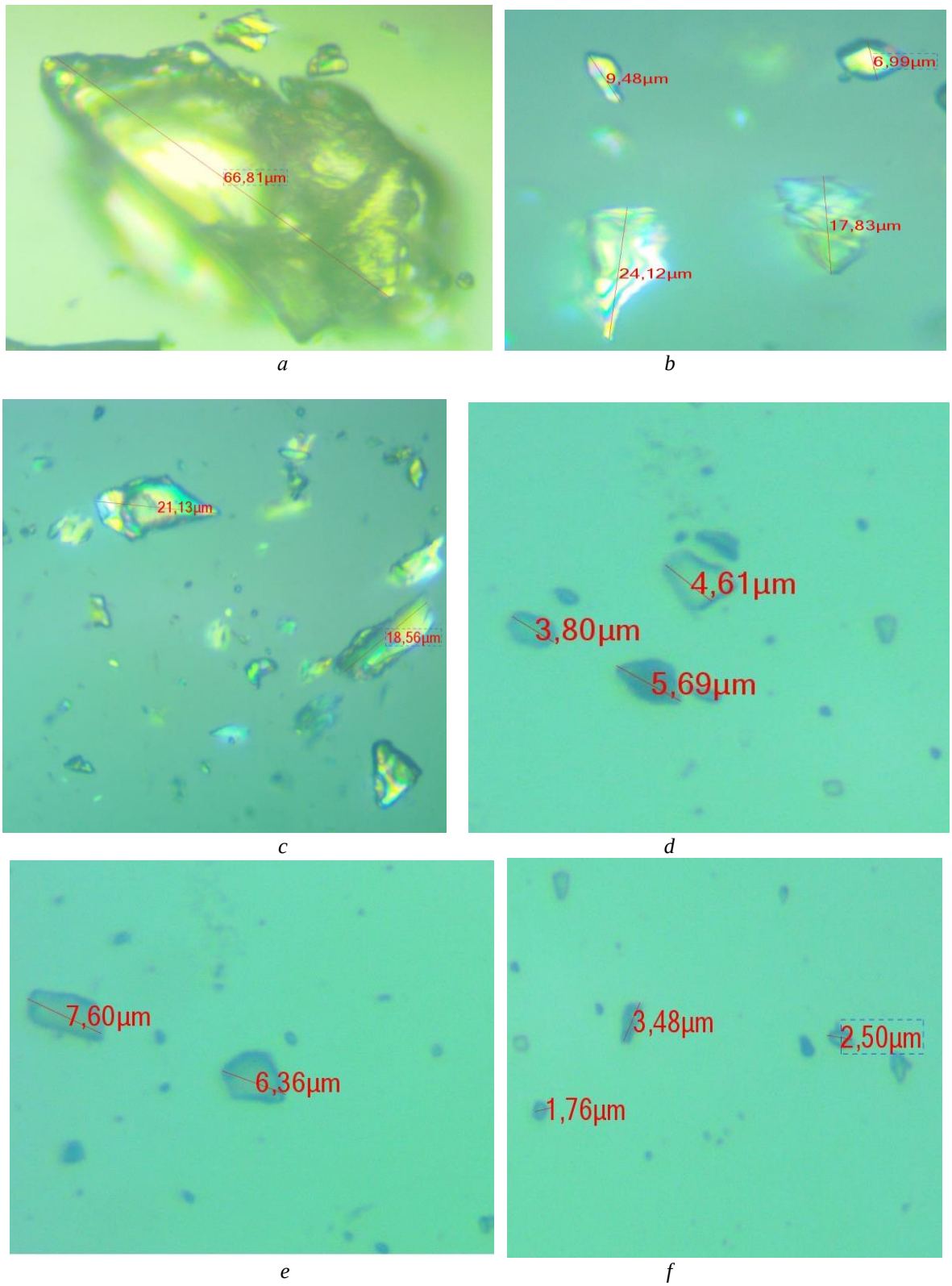
Sample No.	Homogenization rate, rpm	Duration of homogenization, min	Conclusion
1	1000	10	The resulting gel is not homogeneous, there are particles of large size
2	1500		
3	2000		
4	3000	10	The resulting gel is homogeneous, there are no visible particles
5	3500		
6	4000		

These samples were examined under a XY-B2TLED microscope under polarized light according to SPhU 2.9.37. Microphotographs of the gel samples are shown in Fig. 3.

As can be seen from Fig. 3, even the smallest homogenization rates provide a dispersion of the suspension that meets the requirements of SPhU, i.e. the particle size does not exceed 90 microns. Increasing the speed to 3000 rpm, the sizes of the largest particles of metronidazole benzoate do not exceed 10 μm, which can be seen in the drawings of gel samples No. 4–6. Homogenization of metronidazole benzoate with propylene glycol at a speed of 3000 to 4000 rpm for 10 min provides a homogeneous translucent white gel.

During the pharmaceutical development of the gel, the necessity of introducing into the gel composition a stabilizer – disodium edetate and taste corrector - saccharin was established. The total composition of the excipients and their amounts are shown in Table 4.

According to the results in Tab. 4, all excipients are well soluble in water. To prepare the gel base, it is necessary to disperse the carbopol in purified water, and then neutralize it with an alkaline agent (sodium hydroxide solution).



a *b*

c *d*

e *f*

Fig. 3 Micrographs of gel samples obtained from different homogenization parameters:
a – sample 1; *b*– sample 2; *c*– sample 3; *d*– sample 4; *e*– sample 5; *f*– sample 6;

In the development of the gel technology we studied the method of obtaining a gel base, which was neutralized with a multicomponent solution, namely an aqueous solution of disodium edetate, sodium saccharine and sodium hydroxide. AFIs were introduced into the base of the gel, taking into account their solubility. Studies of chemical stability and rheological parameters of the obtained gel, both at the time of manufacture and subsequent storage have shown that the selected methods of dissolution and technological parameters allow obtaining a stable gel without degradation products of active substances.

According to the results of the research, the technology of combined dental gel for the treatment of infectious-inflammatory diseases of the oral cavity was developed. The technological scheme of gel production is shown in Fig. 4.

Table 4

Excipients in dental gel composition

The name of the excipient	Amount, mg/g	The functional significance
Propylene glycol	50.00	co-solvent
Carbomer	11.00	gel-forming agent
Sodium hydroxide	3.20	neutralizer, pH regulator
Saccharin sodium	1.00	taste corrector
Disodium edetate	0.50	stabilizer
Purified water	up to 1.00 g	solvent

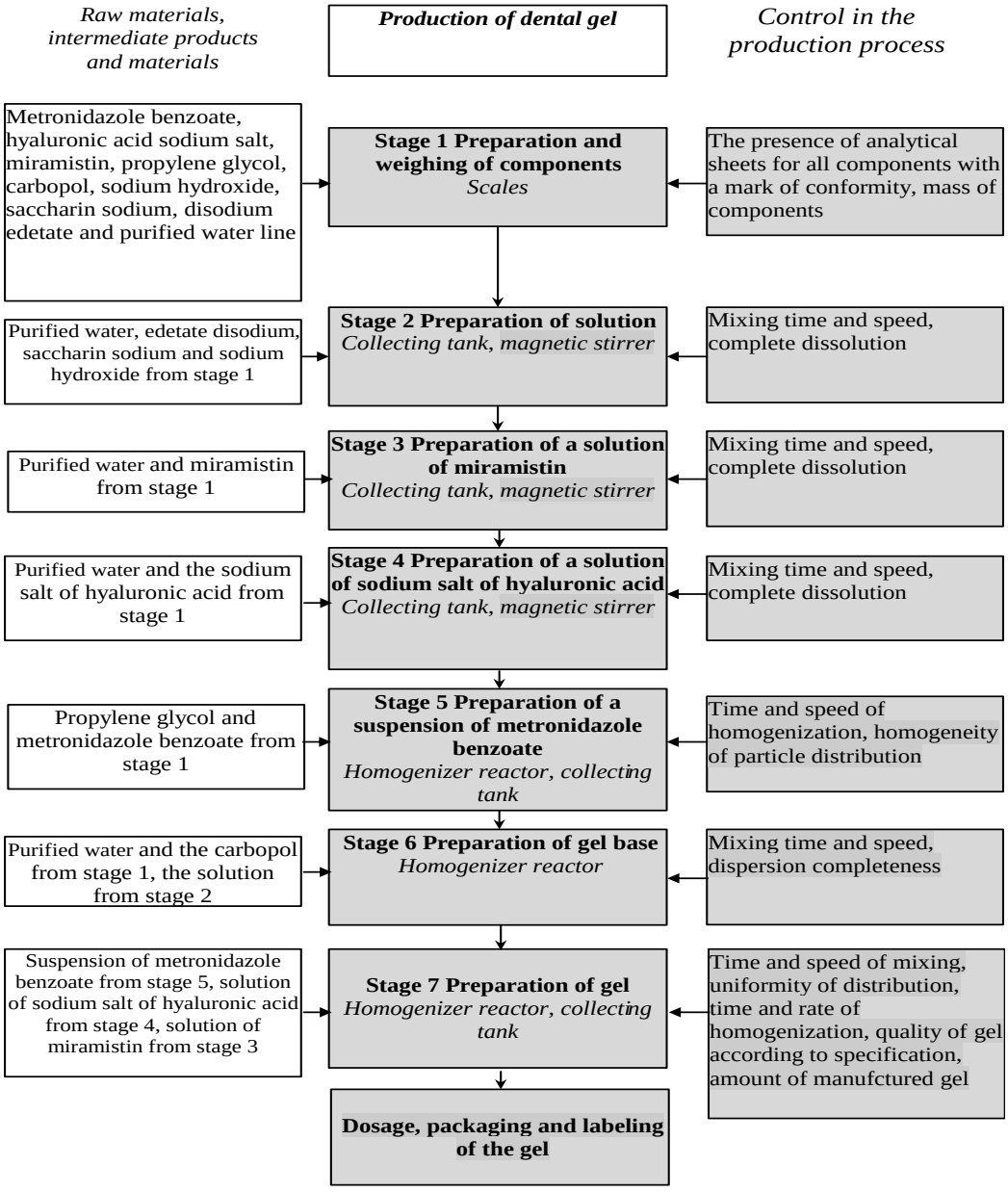


Fig. 4. Technological diagram of the production of dental gel

5. Discussion of the results

The physical properties of the drug, the nature and quantity of the excipients, the dosage form and the process are interrelated pharmaceutical factors that significantly affect the therapeutic efficacy of the medicinal product. The dispersion of the drug particles is not only of technological importance, but also of the speed and completeness of the absorption of the drug in any method of its administration significantly depends on the particle size [13, 14].

The results of studies have shown that the effect of temperature on dissolution of the active substance can be critical and lead to chemical degradation. The introduction of a suspension of metronidazole benzoate in the gel base provides a uniform distribution of the active substance, the particle size of the dispersed phase does not exceed 90 microns. Opting for the suspension route of administration of metronidazole involves the homogenization of the suspension. The technological

stages have certain parameters and regimes that are justified and determined in the development of the medicinal product and should be adhered to in the manufacturing process. Homogenization of the suspension at a speed of 3000 rpm ensures maximum dispersion of the solid phase. Based on the results of our research, we have developed a technology for the production of combined dental gel, which includes 9 stages. Critical operations (weighting of raw materials, component heating, component dissolution, homogenization) and critical parameters (quantity of raw material, temperature of heating, completeness of dissolution, speed of rotation of stirrers, homogenization rate, homogeneity of the finished gel) were determined.

Study limitations. Soft dosage forms containing the active substance in the form of a suspension are usually investigated by in vitro methods for the effect of particle size on the release of the active substance. The obtained homogenized suspension and gel contained extremely small particles of metronidazole benzoate, the size of which is 7–8 microns, which allowed us to believe that this factor will not have a critical effect on the process of release of active substances from the base and does not need further study.

The prospects for further research. The result of the work was the substantiation of rational technology of combined gel, the critical parameters of its production were determined. The next stage is the scaling and transfer of technology, the validation of the process in an industrial environment, the analysis and assessment of risks to the quality of the new drug.

6. Conclusions

The rational way of introduction into the gel basis of a combination of active substances: metronidazole benzoate, myramistin, sodium hyaluronate is substantiated. The need for homogenization of the suspension of metronidazole benzoate in propylene glycol before its introduction into the gel base was proved. It was found that homogenization at a speed of 3000 rpm for 10 min provides micronized dispersed phase.

The rational technology of production of the combined dental gel is developed. Critical stages and parameters of technological process are defined, criteria of their acceptability are established.

Conflict of interests

Authors declare no conflict of interests

References

1. Alimskii, A. V., Dmitrieva, L. A., Maksimovskii, Iu. M. et. al.; Dmitrieva L. A., Maksimovskii Iu. M. (Red.) (2009). Terapevticheskaia stomatologiia. Moscow: GEOTAR-Media, 908.

2. Mazur, I. P., Peredrii, V. A., Dulko, S. V. (2010). Farmakolohichni zasoby dlia mistsevoho likuvannia tkanyn parodontu. Sovremennaia stomatolohyia, 5, 47–52.

3. Sreenivasan, P. K., Gaffar, A. (2007). Antibacterials as anti-inflammatory agents: Dual action agents for oral health. Antonie van Leeuwenhoek, 93 (3), 227–239. doi: http://doi.org/10.1007/s10482-007-9197-8

4. Pattanshetti, J. I., Tiwari, I., Singh, G., Tazyeen, F., Parihar, A. S., Khare, N. (2016). Local drug delivery modalities in treatment of periodontitis: a review. Journal of International Oral Health, 8 (2), 296–301.

5. Ofner, C. M., Klech-Gelotte, C. M.; Swarbrick, J., Boylan, J. C. (Eds.) (2002). Gels and jellies. Encyclopedia of Pharmaceutical Tehnology. Vol. 2. New York; Basel: Marsel Dekker, 1327–1344.

6. Shafiei, F., Memarpour, M. (2012). Antibacterial activity in adhesive dentistry: a literature review. General dentistry, 60 (6), e346–356.

7. Vynohradova, O. M. (2013). Vykorystannia suchasnykh antymikrobnykh i protyzapalnykh preparativ mistsevoi dii v likuvanni zapalnykh zakhvoriuvan parodontu. Zdobutky klinichnoi i eksperymentalnoi medytsyny, 2, 47–49.

8. Derzhavna farmakopeia Ukrainy. Vol. 2 (2014). Kharkiv: Derzh. p-vo «Naukovo-ekspertnyi farmakopeinyi tsentr yakosti likarskykh zasobiv», 724.

9. Ialkaev, A. G., Kataev, V. A., Kildiiarov, F. Kh. (2014). Lekarstvennye formy metronidazola s modificiruemym vysvobozhdeniem. Medicinskii vestnik Bashkortostana, 9 (6), 112–115.

10. European Pharmacopoeia. EDQM (2016). Strasbourg: Council of Europe, 4016.

11. Carbopol® Ultrez 10 Polymer, Technical Data Sheet (TDS-225) (2002). Lubrizol: Cleveland.

12. Doslidzhennia z vyboru dopomizhnykh rechovyn u skladi kombinovanoho stomatolohichnoho heliu (2018). Suchasni dosiahnennia farmatsevtychnoi tekhnolohii i biotekhnolohii, 5, 272–275.

13. Setkina, S. B., Khishova, O. M. (2014). Biofarmacevticheskie aspekty tekhnologii lekarstvennykh sredstv i puti modifikacii biodostupnosti. Vestnik VGMU, 4, 162–172.

14. Rowe, R. C., Sheskey, P. J., Cook, W. G., Fenton, M. E. (Eds). (2012). Handbook of Pharmaceutical Excipients. London: Pharmaceutical Press, 1064.

Received date 20.11.2019
Accepted date 10.12.2019
Published date 30.12.2019

Dmytro Orlenko, Postgraduate Student, Department of Industrial Pharmacy and Economics, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002, E-mail: dmitryorlenko@gmail.com

Volodymyr Yakovenko, Doctor of Pharmaceutical Sciences, Professor, Department of Industrial Pharmacy and Economics, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002
E-mail: v.iakovenko@gmail.com

LiliiaVyshnevska, Doctor of Pharmaceutical Sciences, Professor, Department of Pharmacy Technology of Medicines, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002
E-mail: liliiavyshnevska@gmail.com