UDC 615.014.22:615.454:661.719.2

Sv. N. Kovalenko

National University of Pharmacy, Kharkiv

DETERMINATION OF THE OPTIMAL PARAMETERS OF THE TECHNOLOGY FOR THE GEL WITH THIOCTIC ACID AND ALLANTOIN

Based on the experimental studies conducted the rational technology for a new combined drug in the form of gel for prevention and treatment of diabetic ulcers has been suggested.

In the article the technological parameters for preparing the gel with thioctic acid and allantoin for prevention and treatment of diabetic ulcers have been substantiated; they are the time and the speed of mixing.

Key words: allantoin, diabetic ulcers, gel, thioctic acid, the number of revolutions of the mixer, mixing time, diabetes mellitus

STATEMENT OF THE PROBLEM

As it is known, the skin of patients with diabetes mellitus (DM) has a number of features, it is sensitive, delicate, dry, thinning, etc. Because of neuropathy the perspiration and skin nutrition are inhibited. Taking into account the peculiarities of the skin of patients with diabetic foot syndrome (DFS) gels are the most promising medicinal form for local action [1– 3]. Gels exactly satisfy the requirements for external medicines for prevention and treatment of diabetic ulcers (DU): they are well-absorbed by the skin, soften and moisturize it, have a slight cooling effect, are readily applied on large affected areas, easily washed and leave no trace on the skin and clothes [4 –8].

Using a comprehensive research conducted the optimal composition and technology for a new drug – a gel with thioctic acid and allantoin for prevention and treatment of DU have been developed [9-14]. An important aspect of pharmaceutical development is providing drug stability during the period of storage, which largely depends on the rational technology and determination of the optimal parameters for obtaining a drug.

ANALYSIS OF RECENT RESEARCH AND PUBLICATIONS

One of the most important factors that affect the quality and stability of the gel, is the technology of the drug. The manufacturing process should consist of the rational, planned system of interrelated processes where each technological operation must be substantiated. To produce pilot batches of the gel for prevention and treatment of DU the introduction of ingredients was carried out in the sequence corresponding to the laboratory conditions proposed for the gel preparation [9]. When preparing the gel the standard equipment required in manufacture of soft dosage forms was used. Based on the technological studies conducted the flowchart and the process flowchart for the drug have been developed [9]. In accordance with the GMP requirements there are the following stages for obtaining the gel with thioctic acid and allantoin: obtaining a gel base, preparation of solutions of the active components and their introduction into the base, homogenization, filling the gel obtained in tubes, packing, labeling and transportation.

IDENTIFICATION OF ASPECTS OF THE PROBLEM UNSOLVED PREVIOUSLY

When developing the technology of the combined drug with thioctic acid and allantoin it was necessary to study the effect of the speed of mixing (rpm) and the mixing time in order to choose the rational technology of the gel. It has been noticed that the rotary speed of the mixer incorrectly selected can cause air bubbles, and it, in turn, will lead to difficulties when filling the finished gel. Taking

into account the multi-component composition and relatively high values of rheoparameters of the gel developed it is also necessary to select the optimal intervals of the mixing time to obtain a product with satisfactory consumer properties.

OBJECTIVE STATEMENT OF THE ARTICLE

The aim of our work is to determine the optimal parameters for conducting the technological process for obtaining the gel with thioctic acid and allantoin, namely the speed of mixing x1 and the mixing time x2.

PRESENTATION OF THE MAIN MATERIAL OF THE RESEARCH

The samples of the gel with thioctic acid and allantoin were chosen as objects of the study when developing the rational technology [11, 13].

To choose the optimal technological parameters a HS-30 D homogenizer of the Daihan, Scientific Co, Ltd Wide Stir company (Korea) was used.

To conduct the experiment a MM-1000 mechanical mixer of the BioSan company (Latvia) was used.

The pH value of the samples was determined by potentiometry (SPhU 1.2, 2.2.3 i) using a "pH Meter Metrohm 744" device (Germany) [14].

RESULTS AND DISCUSSION

It is known that the number of revolutions of the mixer (x1) and the mixing time (x2) have a significant impact on the quality of the gel in the process of its obtaining.

The temperature factor was kept at the constant level of 20 °C since according to previous experiments of derivatography [15] it was found that the limit of thermal stability of the gel was 29 °C.

Therefore, the process of obtaining a base for the gel should be carried out under normal conditions. To obtain the linear model of the dependence of the quality of the gel on the number of revolutions of the mixer and the mixing time in the first series of experiments the complete factorial experiment of type 2^2 was carried out [16] (Table 1).

Table 1

A NUMBER OF EXPERIMENTS FOR OBTAINING THE LINEAR MODEL OF THE DEPENDENCE OF THE QUALITY OF THE BASE ON THE NUMBER OF REVOLUTIONS X1 AND THE MIXING TIME X2

Variability interval and level of factors	x1	x2	y1	y2
Zero level, $x_i = 0$	40	6		
Variability interval δ_i	15	2		
Lower level, $x_i = -1$	25	4		
Upper level, $x_i = +1$	55	8		
Experiments				
1 and 5	-1	-1	8.6/8.8	1/1
2 and 6	+1	-1	8.2/8.5	1/1
3 and 7	-1	+1	8.0/7.8	0/0
4 and 8	+1	+1	7.5/7.6	1/0

The pH value – y1 was chosen as the main parameter of quality of the gel obtained, it should be within the range from 6.0 to 7.2. The gel begins to separate into layers at pH more than 6.0, and at pH more than 7.2 it densifies, i.e. gets unsatisfactory consumer properties.

The additional indicator is its appearance – y2 (the base should be uniform, the presence of air bubbles or undissolved particles of a structure-forming agent or stratification of the base is unacceptable). This indicator was assessed by score. When the base corresponds to this test, point "1" is assigned, and in case of nonconformity there are "0" points.

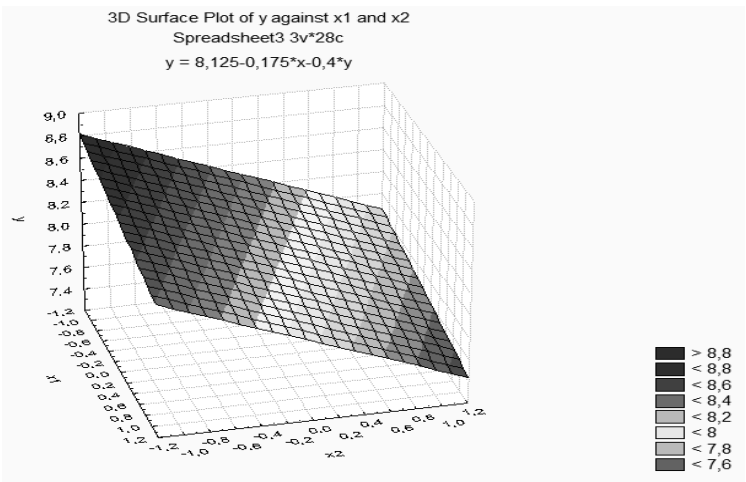

Fig. 1. *The linear model of the dependence of the pH value y1 on the number of revolutions (x1) and the mixing time (x2) in coded values*

The calculations were performed using such programmes as Statistica 8.0 and MS Excel 2013.

According to the results of the experiments (Table 1) the linear model (1) was obtained in coded values:

$$y1 = (8.13 \pm 0.15) - (0.18 \pm 0.15)x1 - (0.40 \pm 0.15)\,x2 \quad (1)$$

In addition, the coefficient of determination $R^2 = 0.9443$. This dependence is given below in Fig. 1.

The hypothesis about the adequacy of the regression equation was tested using Fisher test (F): if the Fisher experimental criterion (Fe) is less than the table one (Ft), the hypothesis of the adequacy of the model is considered to be correct.

According to the results of the data obtained (Tab. 2) the Fisher experimental criterion (Fe) equals 0.018, and the table value of Fisher test under these conditions equals 7.71, i.e. the condition $Fe > Ft$ is met conforming the adequacy of the model.

Using equation (1) the optimum value of the response can be determined by the method of motion with a gradient. All necessary calculations are summarized in Table 2.

Rows ***a***, ***b*** and ***c*** are filled with the data obtained in the experiments for linear approximation. In row ***d*** there is transfer to the natural scale of variability intervals.

Then the factor, for which the product $b_i \cdot \delta_i$ is the greatest by the absolute value, was chosen; the ratios for all factors were found $K_i = \frac{|bi \cdot \delta i|}{|bi \cdot \delta i|_{max}}$ and entered in row ***e*** of Table 2.

For the factor with the greatest product $|bi \cdot \delta i|_{max}$ the range of motion with a gradient was selected (step 10 was selected for factor x1).

The ranges of factors δ_i were obtained by multiplying the value of the range selected on the proportionality factor K_i (row ***f***).

Table 2

CALCULATIONS FOR THE METHOD OF MOTION WITH A GRADIENT

The row index	Variability interval and level of factors	x1	x2	y1	y2
a	Zero level	40	6		
b	Variability interval δ_i	15	2		
c	Regression coefficient b_i	0.18	0.40		
d	$b_i \cdot \delta_i$	2.7	0.8		
e	K_i	1.00	0.30		
f	δ'_i	10	3		
Experiments					
0		50	9	The experiment was not conducted	
9 and 13		60	12	7.0/6.9	1/1
10 and 14		70	15	6.8/6.9	1/1
11 and 15		80	18	6.7/6.8	0/0
12 and 16		90	21	6.8/6.9	0/0

As can be seen from the data of Table 2, Fig. 2, experiments 9, 10, 13, 14 give a stable pH value y1 that is close to neutral and equal 6.9 ± 0.1. However, experiments 11, 12, 15, 16 demonstrate that with the increase of the number of revolutions of the mixer x1 (more than 70 rpm) and the mixing time x2 (more than 15 min) such quality parameter for the base as appearance y2 becomes unsatisfactory. In the base obtained the air bubbles appear, which are difficult to remove.

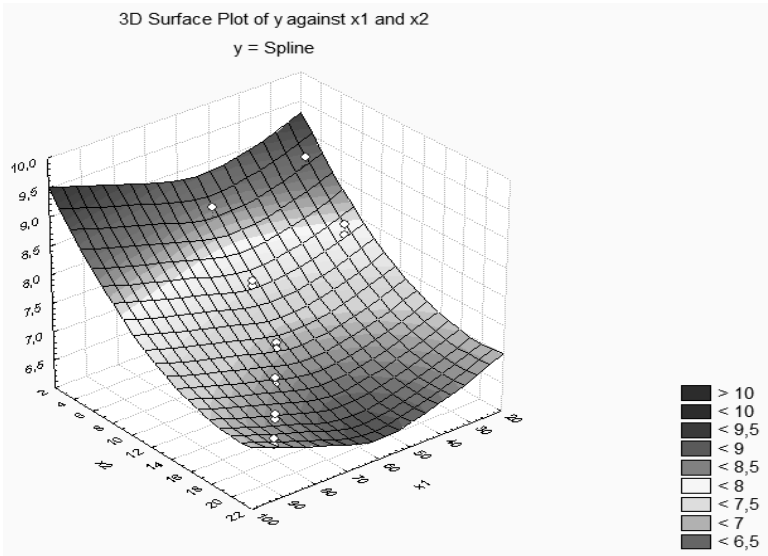

Fig. 2. *A graphic dependence of pH y1 on the number of revolutions of the mixer x1 and the mixing time x2 when moving with a gradient.*

Thus, the number of revolutions of the mixer – 60-70 rpm and the mixing time – (15 ± 2) min should be considered the optimal parameters for conducting the technological process of gel obtaining [273].

CONCLUSIONS AND PROSPECTS FOR FURTHER RESEARCH

1. Based on the studies conducted the rational technology of the gel with thioctic acid and allantoin for prevention and treatment of diabetic ulcers has been developed. It has been experimentally proven that the gel with allantoin and thioctic acid is a structured system with stable rheological indicators.

2. Using the experimental studies it has been found that the optimal technological parameters for obtaining the gel with thioctic acid and allantoin are the number of revolutions of the mixer 60-70 rpm) and the mixing time (15 ± 2) min.

REFERENCES

1. Huizinga M. // Clinical Diabetes. – 2007. — Vol. 25, № 4. — P. 135–140.
2. American Diabetes Association: Standards of medical care in diabetes 2008 //Diabetes Care.— 2008.— Vol. 31, Suppl. 1.— P. 12–54.
3. Грекова Н.М. Хирургия диабетической стопы /Н. М. Грекова, В .Н. Бордуновский. – М., 2009. – 188 с.
4. Основы фармацевтической разработки, стандартизации и технологии лекарственных препаратов в форме гелей на основе карбополов / Е.П. Безуглая, Н.В. Воловик, Н.А. Лянпунов [и др.] // Досягнення та перспективи розвитку фармацевтичної галузі України : матеріали VI Нац. з'їзду фармацевтів України. – Х., 2005. – С. 319 – 320.
5. Баранова І. І. Вивчення властивостей гелів з гідроколоїдами / І. І. Баранова, О. Г. Башура // Сучасні аспекти медицини і фармації – 2010 : тези доп. 70 ювілейної всеукр. наук.-практ. конф. молодих вчених та студ. з міжнар. участю, м. Запоріжжя, 13 – 14 трав. 2010 р. – Запоріжжя : ЗДМУ, 2010. – С. 85.
6. Баранова І. І. Розробка та вивчення властивостей комбінованих гелів / І. І. Баранова, О. Г. Башура // Фарм. часопис. – 2010. – № 1. – С. 35–37.
7. Penn L. E. Gel Dosage Form: Theory, Formulations and Processing / L. E. Penn. – New York : Marcel Dekker, 1990. – P. 338 – 381.
8. Fairclough J. P. A. Structure and rheology of aqueous gels / J. P. A. Fairclough // J. Norman Annu. Rep. Prog. Chem. – 2003. – Vol. 99, № 9. – P. 243 – 276.
9. Коваленко Св. М. Розробка технології гелю з тіоктовою кислотою та алантоїном для лікування діабетичних виразок / Св. М. Коваленко, І. І. Баранова // Актуальні питання фармацевтичної і медичної науки та практики. – 2011. – Вип. XXIV, № 3. – С. 32–35.
10. Коваленко Св. М. Реологічне вивчення комбінованого гелю з тіоктовою кислотою та алантоїном / Св. М. Коваленко, І. І. Баранова // Часопис. – 2012. – № 3. – С. 55–60.
11. Коваленко Св. М. Експериментальне дослідження з вибору гелеутворювача при розробці засобу для лікування діабетичних виразок / Св. М. Коваленко, І. І. Баранова // Актуальні питання фармацевтичної і медичної науки та практики. – 2012. – № 3 (10). – С. 80–82.
12. Коваленко Св. М. Термограіметричне дослідження нового лікарського засобу для лікування діабетичних виразок / Св. М. Коваленко // Український журнал клінічної та лабораторної медицини. – 2013. – Т. 8, № 2. – С. 59–62.
13. Коваленко Св. Н. Разработка состава геля с тиоктовой кислотой и аллантоином для лечения диабетических язв / Св. Н. Коваленко, И. И. Баранова // Хабаршысы «Весник». – 2014. – № 1. – С. 81–86.
14. Державна Фармакопея України / Держ. п-во «Науково-експертний фармакопейний центр». – 1-е вид., 2 доп. – Х. : РІРЕГ, 2008. – 620 с.
15. Коваленко Св. Н. Исследование структурно-механических свойств геля «Тиалан» при хранении / Св. Н. Коваленко, И. И. Баранова // Фармация Казахстана. – 2014. – № 2. – С. 53–56.
16. Математичне планування експерименту при проведенні наукових досліджень в фармації / Т. А. Грошовий, В. П. Марценюк, Л. І. Кучеренко та ін. – Тернопіль : ТДМУ, 2008. – 368 с.

УДК 615.014.22:615.454:661.719.2

Св. М. Коваленко

ВИЗНАЧЕННЯ ОПТИМАЛЬНИХ ПАРАМЕТРІВ ТЕХНОЛОГІЇ ОТРИМАННЯ ГЕЛЮ З ТІОКТОВОЮ КИСЛОТОЮ І АЛАНТОЇНОМ

На підставі проведених експериментальних досліджень було запропоновано раціональну технологію нового комбінованого лікарського засобу у формі гелю для профілактики та лікування діабетичних виразок.

В статті обгрунтовані технологічні параметри приготування гелю з тіоктовою кислотою та алантоїном для профілактики і лікування діабетичних виразок: час та швидкість перемішування.

Ключові слова: алантоїн, діабетичні виразки, гель, тіоктова кислота, частота обертів мішалки, час перемішування, цукровий діабет

УДК 615.014.22:615.454:661.719.2

Св. Н. Коваленко

ОПРЕДЕЛЕНИЕ ОПТИМАЛЬНЫХ ПАРАМЕТРОВ ТЕХНОЛОГИИ ПОЛУЧЕНИЯ ГЕЛЯ С ТИОКТОВОЙ КИСЛОТОЙ И АЛЛАНТОИНОМ

На основании проведенных экспериментальных исследований была предложена рациональная технология нового комбинированного лекарственного средства в форме геля для профилактики и лечения диабетических язв.

В статьи обоснованные технологические параметры приготовления геля с тиоктовой кислотой и аллантоином для профилактики и лечения диабетических язв: время и скорость перемешивания.

Ключевые слова: аллантоин, диабетические язвы, гель, тиоктовая кислота, частота оборотов мешалки, время перемешивания, сахарный диабет.

Адреса для листування:
61118, г. Харьков, ул. Блюхера, 4
Кафедра товароведения НФаУ
E-mail: aromafarm@mail.ru;
lana_koval@mail.ru

Надійшла до редакції:
15.05.2015 р.