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Research Article

The Utilization Of The Strategy Of Mathematical Planning Of The Experiment In The Selection Of Auxiliary Substances For A Gel Based On Dry Extract "Fitoinflam"

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ABSTRACT
For a deductively grounded approach to the choice of excipients within the advancement of gel innovation based on dry extract "Fitoinflam" the strategy of numerical arranging of the try was utilized. The ponder of scholarly sources appeared that the completeness of the discharge of naturally dynamic substances from gel compositions, in most cases, is affected by such assistant substances as a gelling specialist and a plasticizer. For the investigation, 8 shapers and 3 moisturizing operators were chosen. The comes about of thinks about carried out by the strategy of two-way investigation of change 8x3 with repeated observations appeared that the foremost total discharge of tannins and the entirety of flavonoids was watched when utilizing sodium carmelose as a gelling operator, and propylene glycol or glycerin as a moisturizing operator.

Keywords: Mathematical planning of the experiment, gel, dry extract, gelling agents, plasticizers, release of biologically active substances, tannins, flavonoids.

INTRODUCTION

Nowadays, inflammatory diseases of the oral cavity are one of the most common pathologies in dental practice. According to the World Health Organization, these diseases, depending on the severity, occur in 45% of cases, and at the age of 35 to 44, this indicator is 69-98% worldwide [1,2].

We analyzed the pharmaceutical market of the Republic of Uzbekistan for 2015-2018. Based on the State Register there were registered medicines and medical devices. The results of the analysis indicate the insufficient production of medicines for use in dental practice by domestic enterprises. The share of drugs for this purpose in the total volume of registered drugs is no more than 0.2%. Registered drugs are presented only in 3 dosage forms: gels, solutions and sprays. In more than 2/3 of the registered drugs, the active principle is represented by substances synthesized by chemical means, while herbal preparations, despite their widespread use in traditional medicine, are in the minority.

According to the analysis of the scientific literature helped to determine the medicinal plants that are most often and effectively used in the treatment of inflammatory diseases of the oral cavity, as well as those growing mainly in the territory of the Republic of Uzbekistan: they turned out to be oak bark (Corticis Quercus), chamomile flowers (Flores Chamomillae) and a series of grass (Herba Bidentis). Further pharmacological screening revealed the ratio of medicinal plants exhibiting the maximum anti-inflammatory effect.

Within the basis of the selected composition, a complex extract was obtained: its anti-inflammatory and wound-healing activity, as well as harmlessness, was scientifically proven.

The following stage of the investigation was the selection of the composition and development of the gel technology for use in dental practice. As you know, when selecting the composition of a gel dosage form, a whole complex of excipients is used that play the role of gelling agents (form-forming substances), stabilizers, plasticizers, prolongers, substances that improve the solubility and bioavailability of substances, preservatives, pH regulators, odor flavors, etc. Each of the above constituent parts of the gel plays an important role in the release of active substances

from the dosage form, and, consequently, in the manifestation of pharmacotherapeutic efficacy. Scientifically based selection of excipients is a necessary and voluminous task that requires a detailed approach, which in recent decades has been solved by applying the method of mathematical experiment planning. The use of these methods can significantly reduce the volume of research, which, accordingly, entails saving time and financial costs [3-6].

Examination of modern scientific literature has appeared that nowadays, within the improvement of the innovation of measurement shapes, strategies of one, two and multivariate (Latin, grecolatin cubes, hypercubes and parallelepipeds) examination of variance are broadly utilized. The foremost promising are multifactorial methods, in which the impact of a few variables on the subjective and quantitative markers of the measurement frame is considered [7-9].

Taking into account the above, the purpose of these studies was the selection of excipients using the method of mathematical experimental planning for the development of dental gel technology.

MATERIALS AND METHODS

Dry extract "Phytoinflam" is a nebulous hygroscopic brown powder with a greenish tint, with a particular odor and impossible to miss zesty taste. For all quality markers, such as appearance (GPA.1.4.1.0021.15), realness, misfortune in mass on drying (GPA.1.2.1.0010.15, strategy I), overwhelming metals (OFS.1.2.2.2.0012.15, strategy 1) and microbiological immaculateness (OFS.1.2.4.0002.15) meets the necessities of GP XIII [10].

In terms of biologically active substances, tannins were studied in terms of tannin and flavonoids in terms of rutin. The following content rate has been established: the sum of tannins in terms of tannin is not less than 14%, the content of the sum of flavonoids in the dry extract in terms of rutin is not less than 2.5%.

According to the analysis of literature sources, it was decided to study the effect of the used gelling agents and plasticizers on the release of active substances from the gel dosage form. For this, the method was chosentwo-way analysis of variance with repeated observations [7]. The studies studied the effect of the type of gelling agent and its concentration (factor A), as well as the type of plasticizer (factor B) on the release of tannins and flavonoids in in vitro experiments. Factors and their levels are shown in Table 1.

Table 1:Factors and their levels used in the experiment

Factor and its levels	Excipient name	Normative document
Gelling agents		
a_1	aerosil 5%	British Ph. 2016, Ph Eur monograph 0434, 2013
a_2	aerosil 7%	British Ph. 2016, Ph Eur monograph 0434, 2013
a_3	carbomer 1%	British Ph. 2016, Ph Eur monograph 1299, 2013
a_4	carbomer 1.5%	British Ph. 2016, Ph Eur monograph 1299, 2013
a_5	carmellose sodium 3.5%	British Ph. 2016, Ph Eur monograph 0472, 2013
a_6	carmellose sodium 4%	British Ph. 2016, Ph Eur monograph 0472, 2013
a_7	polyethylene glycol 1.5%	British Ph. 2016, Ph Eur monograph 1444, 2013
a_8	polyethylene glycol 2%	British Ph. 2016, Ph Eur monograph 1444, 2013
Plasticizers		
b_1	sorbitol solution	British Ph. 2016, Ph Eur monograph 0437, 2013
b_2	propylene glycol	British Ph. 2016, Ph Eur monograph 0430, 2013
b_3	Glycerol	British Ph. 2016, Ph Eur monograph 0496, 2013

Biopharmaceutical studies in vitro experiments were carried out by the method of equilibrium dialysis according to L. Kruvchinsky [11].

Experimental conditions:

- semi-permeable membrane - cellophane with a thickness of 50 microns, brand MC AT-100;
- dialysis medium - selected based on the quantitative determination method;
- temperature – 37 ^{0}C ± 1 ^{0}C;
- The amount of released biologically active substances was determined by the following methods:

- tannins, in terms of tannin - by titration;
- flavonoids, in terms of rutin - spectrophotometrically.

RESULTS AND DISCUSSION.

The plans of the 8x3 experiment and the results of the study of gels for the release of biologically active substances over a time period of 3 hours are shown in Table 2.

Based on the data in Table 2, the evaluation of the results obtained when studying the release of tannins from gels made it possible to reveal that for factor A, six effects were positive (a_3 = 6.93, a_4 = 7.46, a_5 = 7.04, a_6 = 5.62, a_7 = 2.50, a_8 = 0.10), the other two effects were negative (a_1 = -13.76; a_2 = -15.90). For factor B, two effects were positive (b_1 = 0.04, b_3 = 0.38), and one effect was negative (b_2 = -0.43). The response (% of released tannins) must be increased. Thus, the use of carbomer at a concentration of 1% and 1.5% (a_3 and a_4), carmelose at a concentration of 3.5% and 4% (a_5 and a_6), as well as polyethylene glycol at a concentration of 1.5% and 2 % (a_7 and a_8) increases the release of tannins from gels. The use of a solution of sorbitol and glycerin (b_1 and b_3) as a plasticizer also increases the percentage release of this group of biologically active substances. When considering the effects of interactions, positive results are given by a_1b_2, a_1b_3, a_2b_3, a_3b_1, a_4b_1, a_4b_2, a_5b_3, a_6b_3, a_7b_1, a_7b_2, a_8b_1. Interaction effects indicate the complex influence of factors. For example, the a_7 level has a positive effect on average. However, its effect depends on the combination with other levels: in combination with b_1 and b_2, it increases the percentage of dissolution and, accordingly, the release of tannins. The a_7 level has a positive effect on average. But, its effect depends on the combination with other levels: in combination with b_1 and b_2, it increases the% of dissolution and, accordingly, the release of tannins. The a_7 level has a positive effect on average. However, its effect depends on the combination with other levels: in combination with b_1 and b_2, it increases the percentage of dissolution and, accordingly, the release of tannins.

Carrying out similar calculations in the study of the release of the sum of flavonoids, in terms of rutin, revealed that for factor A (a type of gelling agent), three effects were positive (a_3= 1.69, a_5 = 15.76, a_6 = 11.46), the rest five - had a negative sign (a_1 = -5.71; a_2 = -6.55, a_4= -1.74; a_7 = -5.64, a_8 = -9.28). For factor B (type of plasticizer), two effects had a positive sign (b_2 = b_3 = 0.48), and one effect was negative (b_1 = -0.97). As in the case of tannins, the % of the released amount of flavonoids must be increased. Therefore, the use of carbomer at a concentration of 1% (a3) and carmelose at a concentration of 3.5% and 4% (a5 and a6) as a gelling agent increases the release of flavonoids from gels. The use of a solution of sorbitol and glycerin (b1 and b3) as a plasticizer also increases the magnitude of the response.

The homogeneity of dispersions was checked using the Cochran test. The table value of the Cochran criterion for f_1 = 2 and f_2 = 24 at a significance level of α = 0.05 was 0.2354 for both tannins and the sum of flavonoids. This value is significantly higher than the experimental value (yexp for tannins is 0.1213, and for the sum of flavonoids - 0.1689). This ratio confirms the uniformity of the experiments.

The analysis of variance of the results obtained is presented in Table 3.

Table 2:The planning matrix and the results of determining the concentration (%) of the released tannins from gels in a two-factor plan 8x3 with three repeated experiments

Tannins, in terms of tannin				
FACTOR A	FACTOR B			Sums by factor A levels
	b_1	b_2	b_3	
a_1	54.86	58.37	60.18	505.98
	52,60	56.11	54.82	
	57.09	55.64	56.31	
	164.55	170.12	171.31	
a_2	52.39	53.54	57.30	486.72
	54.28	51.46	55.91	

	51.34	54.80	55.70	
	158.01	159.80	168.91	
a_3	78.26	74.63	75.83	692.23
	76.30	77.08	76.27	
	79.46	77.49	76.91	
	234.02	229.20	229.01	
a_4	79.22	77.38	74.64	696.96
	77.60	77.60	76.58	
	78.34	79.41	76.19	
	235.16	234.39	227.41	
a_5	75.03	76.22	81.01	693.14
	77.12	73.49	79.18	
	74.31	74.09	82.69	
	226.46	223.80	242.88	
a_6	74.26	75.83	78.15	680.43
	76.11	72.60	76.26	
	72.38	73.44	81.40	
	222.75	221.87	235.81	
a_7	72.38	72.60	71.84	652.35
	75.42	74.59	69.08	
	73.16	74.17	69.11	
	220.96	221.36	210.03	
a_8	74.54	71.12	66.18	630.76
	70.68	68.37	68.73	
	73.45	69.29	68.40	
	218.67	208.78	203.31	
Sums by factor B levels	1680.58	1669.32	1688.67	5038.57

Flavonoids, calculated as rutin				
FACTOR A	FACTOR B			Sums by factor A levels
	b_1	b_2	b_3	
a_1	69.38	67.60	65.73	603.36
	72.19	66.91	63.68	
	70.40	64.26	63.21	
	211.97	198.77	192.62	
a_2	68.67	64.60	62.31	595.74
	69.49	65.02	64.84	
	69.08	65.87	65.86	
	207.24	195.49	193.01	
a_3	73.62	74.08	77.46	669.95
	69.06	75.01	76.16	
	72.43	74.83	77.30	
	215.11	223.92	230.92	
a_4	69.22	71.56	74.18	639.09
	67.00	70.38	72.81	
	67.28	72.04	74.62	
	203.50	213.98	221.61	
a_5	84.06	89.37	92.24	796.58
	83.49	90.92	92.90	
	83.10	89.43	91.07	
	250.65	269.72	276.21	
a_6	79.43	84.64	86.40	757.87
	79.29	83.92	88.61	

	82.30	84.09	89.19	
	241.02	252.65	264.20	
a_7	68.17	68.39	66.15	603.95
	67.34	68.72	64.37	
	67.07	70.24	63.50	
	202.58	207.35	194.02	
a_8	62.32	66.48	61.83	571.21
	64.27	64.66	62.11	
	64.03	64.49	61.02	
	190.62	195.63	184.96	
Sums by factor B levels	1722.69	1757.51	1757.55	5237.75

Table 3:**Analysis of variance of experimental data for determining the release of biologically active substances from gels**

Sources of dispersion	Number of degrees of freedom	Sum of squares	Middle squares	Fexp	Ftabl
Tannins					
FACTOR A	7	5699.56	814.22	309.72	2.21
Factor B	2	7.87	3.93	1.50	3.19
AB interaction	14	220.90	15.78	6.00	1.90
Mistake	48	126.19	2.63		
total amount	71	6054.52			
Flavonoid amount					
FACTOR A	7	5212.05	744.58	539.36	2.21
Factor B	2	33.72	16.86	12.21	3.19
AB interaction	14	423.57	30.25	21.92	1.90
Mistake	48	66.26	1.38		
total amount	71	5735.60			

There was shown that the completeness of the extraction of tannins directly depended on the type of gelling agent (F_{exp}> F_{tabl} (309.72> 2.21)), while the type of plasticizer was statistically insignificant (1.50 <3.19), the interaction between factors A and B present (6.00> 1.90). At the same time, for the completeness of the extraction of the total of flavonoids, the choice of both a gelling agent (539.36> 2.21) and a plasticizer (12.21> 3.19), as well as the interaction between these two factors (21.92> 1 , 90).

There given the usage of Duncan's multiple rank test [7], studies were conducted to study the difference in the mean values of the release data of two groups of biologically active substances from gel compositions. It was found that according to the effect of gelling agents on the completeness of the release of tannins, they can be arranged in the following row: a_5 (a_4, a_3, a_6)> a_8 (a_7)> a_1 (a_2), and for the sum of flavonoids, this series can be represented as a_5> a_6> a_3> a_4> a_7 (a_1, a_2)> a_8. From the above, it follows that for gels based on the dry extract "Phytoinflam" the most promising gelling agent is sodium carmelose: the response when using this excipient in both cases was maximum. The least satisfactory in this aspect were polyethylene glycol and aerosil in the given concentrations.

The analyses of the effect of plasticizers (solution of sorbitol, propylene glycol and glycerin) on the response showed that the effect of all three auxiliary substances used did not differ significantly. However, when evaluating the effects of interaction between levels, it was shown that carmelose sodium gave positive results when combined with propylene glycol and glycerin. In addition, already when choosing one of these moisturizing agents, one can rely on its availability and economy.

CONCLUSIONS

In this way, as a result of the studies carried out using the method of mathematical planning of the experiment, it was found that the type of gelling agent has a significant effect on the release of tannins and the amount of flavonoids from the studied gel compositions. At the same

time, the selection of a plasticizer can be approached from the point of view of its effective combination with a gelling agent, as well as availability.

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