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DEVELOPMENT OF TECHNOLOGY AND RESEARCH OF GEL WITH PENTOXIFYLLINE

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Abstract: The development of gel that meets modern requirements for the effectiveness and safety of a medicinal product the treatment of cardiovascular disease is a serious scientific study related to the selection of active and auxiliary substances, providing the necessary biopharmaceutical and rheological properties of the gel composition, standardizing the quality of the dosage form.

Key words: pentoxifylline, gel, dispersion analysis, gel bases, method of equilibrium dialysis.

Pentoxifylline (oxpentifylline) is an orally active haemorheological agent for the treatment of peripheral vascular disease, cerebrovascular disease and a number of other conditions involving a defective regional microcirculation. Pentoxifylline acts primarily by increasing red blood cell deformability, by reducing blood viscosity and by decreasing the potential for platelet aggregation and thrombus formation [1].

Pentoxifylline is a xanthine derivative with vasodilatory activity, which improves the microcirculation by increasing of erythrocyte flexibility and reducing blood viscosity and decreases the ability for platelet adhesion and aggregation and thrombus formation [2].

Dosage form in the form of a deserves special attention due to the provision of various substances for the manifestation of high therapeutic activity and prolonged action.

For pentoxifylline is known injectable form (vazitren, latren), used for the treatment of acute and chronic forms of heart failure, cerebral ischemia and other diseases. However, the widespread use of this effective drug is constrained by its lack of stability and inconvenience of administration.

We set ourselves the goal of developing alternative to the injectable drug «Latren» dosage forms with pentoxifylline. This paper presents the results of the selection of excipients for endonasal gel and the study of their effect on the release and local irritant and allergenic effects of pentoxifylline.

Hydrophilic and hydrophilic-lipophilic bases, which are widely used in the production of this dosage form, have been studied as carriers for pentoxifylline gel. They provide comfort and ease of application and do not cause allergic and sensitizing manifestations. Given the feasibility of a high degree of dispersion of drugs in gels for application to the skin and mucous and physicochemical properties of pentoxifylline, the latter was introduced into all bases after pre-dissolution in polyethylene oxide 400, glycerol, propylene glycol or mixtures there of (1:1:1).

Pentoxifylline is soluble in water drug (~77 mg/mL) [3], which is readily absorbed in the gastro-intestinal tract. The choice of composite gel compounds with pentoxifylline, taking into account the biopharmaceutical release rate was carried out according to the scheme of the Latin square 4x4. As solvents for pentoxifylline (factor A) was used: a_1 - polyethylene oxide 400 (PEO 400), a_2 - glycerin, a_3 - propylene glycol (PG), a_4 - mixture PEO 400, glycerin, PG (1:1:1). Type of base (factor B): $в_1$ - lanolin 20.0, vaseline 80.0; $в_2$ - aerosil 7.5, glycerin 92.5; $в_3$ - PEO 4000 30.0, PEO 400 70.0; $в_4$ - wax 20.0, vegetable oil 80.0. Surface active substances (SAS) (factor C): c_1 - twin 80; c_2 - pentol; c_3 - monodistilled glycerides (MDG); c_4 - emulsifier 1.

Apart from the properties of the matrix, the rate of release also depend on the properties of the active substance (e.g. the particle size distribution of the drug particles is a critical parameter determining the rate of release of hydrogel matrix formulations). Therefore, in a validated technology regime, changing the manufacturer of the substance is always risky. At the same time, changes in the

market and the drive of generic manufacturers to lower the cost of manufactured medicines require the inclusion of active substances from new manufacturers. It is not uncommon when, although the substance meets the specification, the release of the drug of the respective dosage form has been changed. Resolving the problem through substantial changes in composition is undesirable from a regulatory point of view, and any changes in the appearance of the drug are met with suspicion by the patient. It is preferable, where possible, to regulate the release rate by minimal changes in the technology [4].

The influence of these factors on individual indicators of gel quality - resistance to delamination during centrifugation and release of substances from the dosage form was studied.

Gels with 1% pentoxifylline content were prepared according to recipes (table.1) by fusion on a water heater (50-60°C) basics and SAS (1 % of the total mass). To the solidified alloy was added a solution of pentoxifylline and the mixture was stirred in a chamber PT-2 (300 rev/min) for a minute. After a day, and then after 7 days, visually determined the absence of stratification of the systems and subjected them to centrifugation for 10 min at 5000 rpm. It turned out that under these conditions, none of the 48 prepared gel systems did not delaminate. The release of pentoxifylline from gels was studied by equilibrium dialysis at temperature 32 ± 0,5C in water through cellophane with a total area of 9.8 cm^2 (brand C-100), used in the device «artificial kidney» (technical conditions 6-517- 18-71).

The selection of samples for analysis was performed after 30 min from the beginning of dialysis. Quantitative content of the substance in dialysate samples was determined by photocolorimetric method in cuvettes with a layer thickness of 2 cm at a wavelength of 750 ± 5 Nm, the comparison solutions were dialysates from placebo gel samples. The results of the definitions are given in table.1.

Table 1

The plan of the experiment on the choice of gel composition and the results of determinations of the release of pentoxifylline

Factor A	Factor B				Amount for A
	B_1	B_2	B_3	B_4	
a_1	2.84 c_1 2.76 2.98 8.58	9.60 c_2 8.60 9.47 27.67	16.22 c_3 16.27 16.27 48.76	1.16 c_4 1.24 1.16 3.56	88.57
a_2	2.84 c_2 2.89 3.11 8.84	24.89 c_1 24.89 24.89 74.67	6.18 c_4 6.22 6.31 18.71	4.67 c_3 4.13 4.31 13.11	115.33
a_3	0.98 c_3 0.98 0.98 2.94	6.18 c_4 6.0 6.0 18.18	14.58 c_1 14.67 14.58 43.83	2.80 c_2 2.98 4.44 10.22	75.17
a_4	1.11 0.98 1.07 3.16	1.38 c_3 1.33 1.33 4.04	7.16 c_2 7.16 7.11 21.43	3.78 c_1 2.89 2.98 9.65	38.28
Amount B_1	23.52	124.56	132.3	36.54	
Amount $C_к$	$c_1 = 111.08$	$c_2 = 89.25$	$c_3 = 47.76$	$c_4 = 69.26$	$y = 317.35$

Analysis of variance of experimental data (table 2) showed that the release of pentoxifylline from resistant to stratification gel systems has a significant impact (at 95% confidence level) all the studied factors. For all significant factors, the difference between the mean values of the results was tested using the Duncan rank test (at $p = 0.05$).

It is established that according to the influence on the release of pentoxifylline levels of significant factors can be placed in the following series: for factor A - $a_2 > a_1 > a_3 > a_4$, for the factor B - $в_2 > в_3 > в_4 > в_1$, for the factor C - $c_1 > c_2 > c_4 > c_3$.

Table 2

Analysis of variance of the results of the study of the release of pentoxifylline from different gel compositions (dialysis interval - 30 min)

Dispersion source	The sum of squares	The number of degrees of freedom	Middle square	$F_{experiment}$ p = 0,05	$F_{table.}$ p = 0,05
(A)	256.99	3	85.67	920.11	2.90
(B)	1120.72	3	373.58	4012.59	2.90
(C)	183.72	3	61.23	657.77	2.90
Residue interaction	456.62	6	76.11	817.42	2.38
Error inside cells	2.99	31	0.09		
Total amount	2020.11	48			

Based on the obtained data for the following biopharmaceutical studies, the formulation of gels with the composition of components that provide the best release of pentoxifylline, in particular:

– recipe 6: 10% solution of pentoxifylline in glycerol 10.0, tween 80 0.5, aerosil 7.5, glycerin 82.0;

– recipe 3: 10% solution of pentoxifylline in PEO 400 10.0, pentol 0.5, PEO 4000 30.0, PEO 400 59.5;

– recipe 11: 10% solution of pentoxifylline in PG 10.0, twin 80 0.5, PEO 4000 30.0, PEO 400 5.5.

To prepare samples of gels under the same conditions according to the above regulations, the dynamics of pentoxifylline release was established by the method of equilibrium dialysis. The results of the determinations (average of five) are presented in Fig. 1.

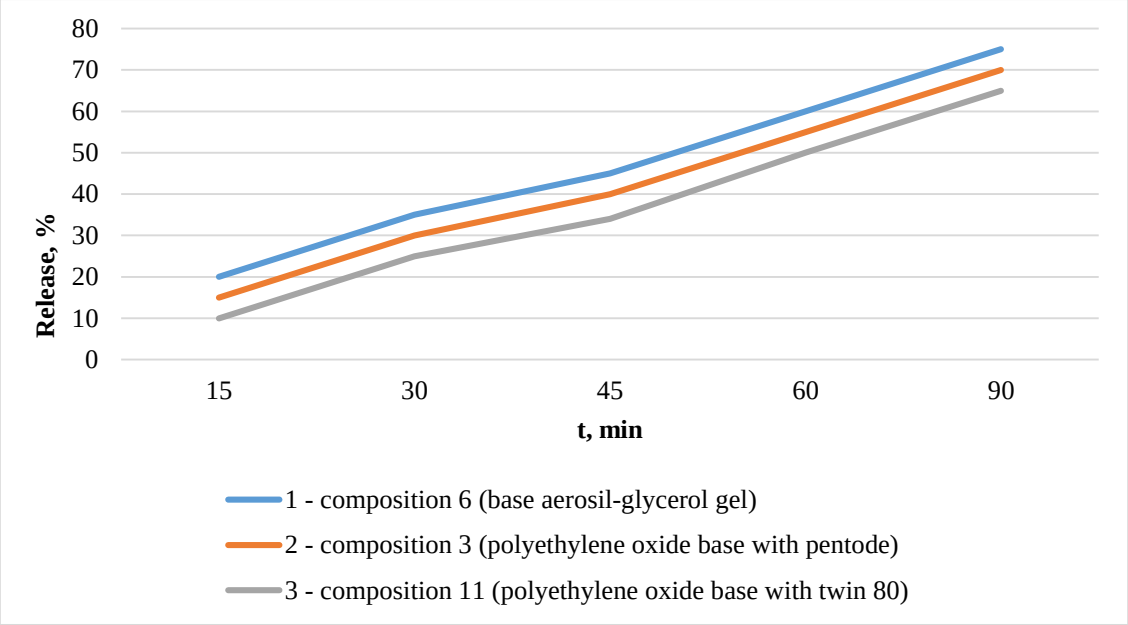

Fig. 1. Dynamics of pentoxifylline release from gel compositions through cellophane membrane

As can be seen from the above data, the highest level of pentoxifylline release through the semipermeable membrane is provided by the gel composition according to recipe 6. Thus, after 60 min 58% of the included dose is released from the system, while for gels 3 and 11 these values are 44 and 32% .

Release rate constants and periods of pentoxifylline release from selected compositions 6, 3 and 11 are respectively 0.00954 min^{-1} and 72.64 min, 0.00327 min^{-1} and 211.93 min, 0.00208 min^{-1} and 333.17 min. Taking into account the obtained results, as well as the technological availability of excipients, for the following studies, a glycerin-aerosil-based gel with the addition of tween 80 was selected.

The study of the local irritant effect of 1% pentoxifylline gel was performed on guinea pigs weighing 250 - 300 g. To detect the irritating effect of this gel on the skin of the lateral surface of the torso of the experimental animals, the hair was cut and 0.5 g of gel was rubbed into this area daily for two weeks. Control groups were given the same amount of placebo base. This experiment also stated the absence of an irritant effect for the test gel.

To study the allergenic effect on the day after the 14^{th} application, the same guinea pigs continued to apply the drug for two weeks on the opposite side of the body, but in one metamer. There were no signs of irritation on both areas of the skin,

there was a uniform growth of hair. Histological examination of the skin of the animals, conducted after the study, showed that the structure of the skin of experimental and control animals did not differ.

Conclusions

1. The choice of composite compounds of the gel with pentoxifylline, taking into account the biopharmaceutical release rate according to the scheme of the Latin square 4x4.

2. Selected formulation of 1% gel with pentoxifylline on aerosil-glycerol basis with the addition of tween 80. The gel of this composition provides a uniform, prolonged release of the substance through the cellophane membrane into physiological solution.

3. It was found that pentoxifylline in the form of a gel does not cause local irritation and allergies in experiments on guinea pigs.

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