THE DICLOFENAC SODIUM RELEASE KINETICS EXAMINATION FROM 3 % GEL "IN VITRO" EXPERIMENTS

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For the 3 % gel medicinal formulation of the diclofenac sodium by the single – factor analysis of the variance using with the repeated observations has been conducted the study on the scientific substantiation of the carrier – basis form. For the present purposes, the gels have already been developed at the 9 fundamentals, and, moreover, their qualitative characteristics have already been defined. According to the obtained final results, two formulations, due to the colloid and thermal stability absence, have already been excluded from the further special testing. The active substance release from the already developed gels has been defined by the equilibrium dialysis method by L. Kruvchinsky. The studies obtained results have been indicated, that the carrier – basis form has its significant influence upon the active ingredient release just from the already developed gels. Thus, the conducted analysis of the variance has been shown, that the diclofenac sodium optimum release has already been provided by the carrier on the basis of the carbomer 934P.

Keywords: diclofenac sodium, gel, carrier – basis, mathematical experiment planning, release

The non – steroidal anti – inflammatory drugs – is one of the most widely used groups of the medicinal preparations, which is included in itself the means of the quite different chemical structure, having united by the general pharmacodynamic properties and by the similar pharmacokinetic characteristics. The NSAID large "popularity" is explained by the fact that they are simultaneously possessed the anti – inflammatory, analgesic, and antipyretic effects, and they are brought the relief to the patients with the relative symptoms (e.g. the inflammation, pain, fever), which are celebrated in many diseases. Over the last 30 years (e.g. 360 months), the NSAID number has already been increased significantly, and today, the given group has the large number of the medicinal preparations and the drugs, having differed in their specific features, peculiarities, and application.

Thus, the given group is one of the most widely prescribed groups of the medicinal preparations and the drugs throughout the world. This is connected also with the fact, that many of them are practically included in the non – prescription lists, and, therefore, they are easily accessible especially for the population. At present, there is the NSAID large arsenal and the store of them (e.g. more, than 25 items), and in the practice of the medicine they are used to be treated more, than the 1,000 ones, having created on the basis of their medicinal preparations and the drugs [1, 2, 3, 4].

So, in the recent years, the tendency has been noted to be increased the NSAID range, in the form of the soft medicinal preparations. Thus, this fact is explained by the fact, that the external application method of the medicinal preparations with the method of the plastically viscoelastic dispersion medium (e.g. the gels, creams, ointments, liniments and etc.) are practically allowed to be provided the maximum concentration of the active substances directly to the lesion focus. For example, they are in the place of the skin integrity violation, the inflammations, the bedsores, the burns, the damaged mucous tunic, and etc. The transcutaneous and transdermal route of the medicinal substances and the drugs administration is practically considered the most secure one, since the large dose fraction is at the surface, and it can be easily changed and modified by the partial means removal [5, 6, 7].

So, according to the biopharmaceutical conception, the soft medicinal preparations and the drugs forms creation should be carried out, having taken into account the pharmaceutical factors, having affected the rate and the extent of the active substances release, i.e. the bioavailability. The scientifically – based approach to the selection of one of the major biopharmaceutical factors – in mind to be used the basics – is practically allowed greatly to be achieved the maximum pharmaco-therapeutic effect [8, 9, 10].

Thus, the biopharmaceutical substantiation of the gel composition of the diclofenac sodium medicinal form has been the main purpose of the present examinations.

Materials and methods of research

As the bases for the developing medicinal preparation form, – 3 % diclofenac sodium gel, – the carriers have been used, which are widely used in the soft medicinal preparations and the drugs forms manufacture, having listed in the specialized literature. For all this, the special attention has been paid to the basis selection of the allergenic and sensitizing properties absence. So, the already prepared gels composition of the diclofenac sodium has been given in the Table 1.

So, the main quality indicators have already been studied at all the received gel compositions, and, for all this, the special and particular attention has been paid to the characteristics, such as the colloidal stability during the centrifugation and the resistance to the temperature changes. As a result of the already conducted examinations and corresponding researches, the № 2 and № 9 compositions have not been past he special tests on the

above – mentioned indicators, the mass dilution, and the slight loss of the white precipitation have already been observed. Thus, all these compounds have already been excluded from the following examinations.

Table 1

The Composition of Gel Formulations with Diclofenac Sodium

Ingredients	Carrier – Basis								
	№ 1	№ 2	№ 3	№ 4	№ 5	№ 6	№ 7	№ 8	№ 9
Diclofenac sodium	3,0	3,0	3,0	3,0	3,0	3,0	3,0	3,0	3,0
Sodium CMC					2,0				
Glycerine	7,0	5,0		8,0	10,0	10,0		2,5	5,0
Methyl cellulose	5,0					7,5		5,0	
Propylene glycol	8,0		5,0	7,5		5,0	30,0	2,5	
Carbomer 934P		0,8		1,0			1,0		0,75
Polyethylene oxide 400			35,0					10,0	10,0
Sodium benzoate			2,5						
Disodium edentate							0,01		
Metiparaben					0,2				
Propylparaben							0,05		
Ethyl alcohol			25,0	8,0					
Menthol				0,5					
Neroli oil			0,5						
Sodium hydroxide solution 10%		0,5					0,15		0,5
Water purified to	100,0	100,0	100,0	100,0	100,0	100,0	100,0	100,0	100,0

The following and next stage of the examinations and researches on the scientific basis of the carrier – basis choice justification in the diclofenac sodium gel composition has been to be used the single – factor analysis of variance with the repeated observations [11]. So, the diclofenac sodium release has already been determined by the equilibrium dialysis method by L. Kruvchinsky [12]. So, the cellophane with the thickness of 50 mkm, as the semipermeable membrane, has been used by us. The dialysis medium has been served the purified water mixture, the carbon dioxide – free, and 0,1 M sodium dioxide solution. The examinations and investigations have been carried out under the thermostating conditions 37 ± 1 °C: the temperature, which is necessary for the occurrence of the medicinal substances and the drugs diffusion through the membrane. The diclofenac sodium concentration, having passed into the dialysis medium, has been adjusted spectrophotometrically at the wavelength of 276 nm.

Results of research and their discussion

The results of the release study and examination of the diclofenac sodium from the gels, as well as the planning matrix have been given in the Table 2. For all this, the carriers – bases numbers, having taken for the factor A, have been the adequate to the carriers – bases numbers, having listed in the Table 1.

Table 2

The Planning Matrix and Determination Results of Diclofenac Sodium Release (%) from the Gels

Number one after another	The carrier-basis type, according to the Table 1 (factor A)	Tests numbers			Total	Average
		I	II	III		
1	№ 1	46,44	47,29	46,15	139,88	46,63
2	№ 3	43,91	43,04	44,67	131,62	43,87
3	№ 4	57,28	56,31	57,11	170,70	56,9
4	№ 5	35,66	35,81	33,76	105,23	35,08
5	№ 6	42,70	40,85	39,18	122,73	40,91
6	№ 7	28,17	28,72	26,23	83,12	27,71
7	№ 8	37,70	35,60	37,75	111,05	37,02
Total					864,33	

So, it has been revealed, when estimating the model parameters that 3 effects (e.g. $\acute{a}_1 = 5{,}47$, $\acute{a}_3 = 2{,}71$, $\acute{a}_4 = 15{,}74$) have had the positive sign, and 4 effects (e.g. $\acute{a}_5 = -6{,}08$, $\acute{a}_6 = -0{,}25$, $\acute{a}_7 = -13{,}45$, $\acute{a}_8 = -4{,}14$) – the negative one. Since the response value (e.g. the diclofenac sodium release, in %) should be increased, it can be argued, that 3 types of carrier – bases № 1, № 3, № 4 have their efficient action.

The Cochran's test criteria has been used by us for the homogeneity of the variance to be checked. So, the Cochran's test criteria table value for $f_1 = 2$ b $f_2 = 7$ at the significance level $\alpha = 0{,}05$, has been made up 0,5612, which is significantly larger, than the experimental value. So, the given ratio has been confirmed by the equally accurate experiments.

The received results analysis of variance has been presented in the Table 3.

According to the data results received, $F_{exper} > F_{tabl}$, therefore, the Ho hypothesis is rejected, that, in its turn, it is suggested the fact, that the carrier – basis type has a direct impact upon the active substance release from the gels.

Table 3

The Experimental Data Variance Analysis,
to Be Determined the Diclofenac Sodium Release from the Gels

Source of invariability	Number of degrees of freedom	Sum of squares	Mean square	F_{exp}	F_{tab}
Carrier – basis type	6	1560,7	260,1	205,73	2,85
Errors	14	17,7	1,2643		
Total amount	20	1578,4			

The studies have been conducted on the examination the differences in the mean values of the data release of the diclofenac sodium from the gels with the multiple rank test Duncan [11] using. It, moreover, has been found, that by the influence of the gel carrier – basis to be completed the active ingredient release, they can be arranged in the following series: № 4 > № 1 (№ 3) > № 6 > № 8 (№ 5, № 7).

As a result of the conducted studies, the gel composition № 4, has been the most appropriate one, and it has been selected for the further studies.

Conclusions

As a result of the conducted studies with the method of the mathematical planning of the experiment using, it was found, that the type of the used carrier – basis had been made the significant influence upon the diclofenac sodium release from the gel.

Thus, the conducted variance analysis of the studies obtained results has been allowed to be determined, that the optimal release of the diclofenac sodium from the gel is practically provided to be supported on the basis of the Carbomer 934P.

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