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Quality Specification For Combined Action Suppositories With Benzetasone Content

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ABSTRACT
. Purpose is to conduct quality control and standardization methods of a combined action suppository containing benzketasone and papaya extract in accordance with modern requirements of good manufacturing practice.
Methods of natural and accelerated storage are used to study the factors affecting the stability of suppositories during storage (type of base used, temperature and storage time). It was revealed that under the conditions of a refrigerating chamber at a temperature of + 3-50 ° C, the studied suppositories practically did not change the quality indicators during 24 months of storage. The type of base slightly affected the change in the physicochemical parameters of the Benzpap and Benzpap 10 suppositories.

KEY WORDS: papaya, suppositories, drug forms, pharmacy

1. INTRODUCTION

In the Republic of Uzbekistan, special attention is paid to the development of the pharmaceutical industry and the provision of domestic products to the population. In this regard, the expansion of the range of antimicrobial and anti-inflammatory drugs, using domestic resources, is a priority in the development of science and technology in the direction of modernizing production and technology with the aim of introducing domestic development of medicines (drugs) and medical devices. Researchers of the Uzbek Scientific Research Chemical-Pharmaceutical Institute named after A. Sultanova carried out a number of works on the synthesis of new biologically active compounds based on aromatic α-keto acids and the study of their pharmacological activity (1,2). Biologically active compounds obtained on the basis of phenylglyoxylic acid have a wide spectrum of pharmacological activity, and in particular anti-inflammatory, without a number of side effects, which is why it becomes especially important to use them in domestic medicine as locally developed drugs. In its activity, benzketozone (47.7%) is superior to the well-known drugs: butadione (26.7%), voltaren (42.2%), while it has low toxicity (LD so 2394 mg / kg) (3).

Together with the Tashkent Pharmaceutical Institute, the development of anti-inflammatory drugs in the form of soft dosage forms (DF) of combined action is being carried out. A study on the creation of effective drugs with already known drugs, have proven themselves in the treatment of a particular disease, have been widely developed. And of certain interest in this direction are combined drugs, when they already have full characteristics of the dependence of the effects and a wide range of doses for each drug (4). The specific activity of suppositories is proved in comparison with single-component due to the potentiated action of the active substances, which allows to reduce the dosage and, accordingly, side effects of each of them. (5) The use of drugs of combined action is

increasingly used and the industrial production of a large number of those has been established, and they have a considerable percentage of the segment of registered drugs (6). Preparations containing antibacterial, steroidal and non-steroidal medicinal substances are among the appropriate combinations. (7,8,9)

Pharmacological interaction is due to the fact that one substance changes the pharmacokinetics or pharmacodynamics of another component of the mixture. The pharmacokinetic type of interaction may be associated with malabsorption, biotransformation, transport and excretion of one of the substances. The pharmacodynamic type of interaction is the result of direct or indirect interaction of substances at the level of receptors, cells, enzymes, organs or physiological systems. In modern medical practice, combined LFs are becoming increasingly important, for the treatment of complex pathologies associated with the process of enzyme deficiency, reduced body resistance and in drug mixtures, they most optimally show their pharmacological properties. (10) Modern medicine is increasingly using protein-based drugs as promising combination of drugs in one LF due to high activity and specificity (11). We conducted a content analysis using the pharmaceutical method by studying textual graphic information in quantitative indicators and its statistical processing. (12,13,14) Papaya (melon tree) is cultivated in Uzbekistan and has a proteolytic effect and is able to break down proteins into polypeptides and amino acids (15,16) .It is an indispensable tool for healing wounds, identified amino acids have anti-inflammatory and immunomodelling effects. the fact that NSAIDs with antibacterial agents and enzymes senergically enhances their positive effects. In order to obtain a targeted combination of drugs, we have developed suppositories containing benzetasone and papaya (extraserial parts) as active substances.

It is known that NSAIDs are long-term drugs and have undesirable side effects and adversely affect the gastrointestinal tract. For this purpose, it is rational to use rectal drugs. Purpose is to conduct quality control and standardization methods of a combined action suppository containing benzketasone and papaya extract in accordance with modern requirements of good manufacturing practice.

2. MATERIALS AND METHODS

For analysis, it should be noted that suppositories are prepared by the traditional method of pouring consisting of a suppository base and a drug. The substitution coefficient was calculated by a known method (I. Strakova). As a lubricant, a mixture of mild soap, glycerin and ethanol in a ratio of 1: 1: 5 was used. A weighted amount of pre-crushed drugs (the degree of grinding to the state “smallest” GF X.p.857) was added as a suspension to the molten base mixture and shaken until complete homogenization. Then the mold cells were filled to the edges with a mass of 2.6 g and placed in a refrigerator. By this method, we received several series of suppositories that were subjected to quality control.

Physico-chemical characteristics and indicators met the requirements of GF XI (issue 2). The average mass of suppositories is 2.6 (from 2.4 to 2.8). The melting temperature is not higher than 37 ° C, the time of complete deformation is not more than 15 minutes at a temperature (37 ± 1 ° C), and Kaminiski hardness. (17)

Investigation of the effect of the interaction of suppository bases (CO) with active substances (benzethasone and papaya) during storage. Considering that there is an interaction of CO with medicinal substances that are part of the suppositories, and CO can affect the properties of drugs, we determined the main parameters of the prepared suppositories: melting point, solidification temperature, acid number, viscosity and VPD. Placebo suppositories were used as control. The indicators were determined after the suppositories were melted and benzketasone and papaya were extracted by hot filtered. Before filtering, the

bases were cooled to solidification (on a CO filter), and the filtrate was used for further studies. The active substances at the time of preparation practically do not affect the main physicochemical and structural-mechanical parameters of the studied suppositories and vice versa.

Research during storage: for this, the prepared suppositories, after packaging in boxes, were divided into two series. One series was stored in the refrigerator at a temperature of 3-50C, the second - at room temperature 20 ± 20C. During storage (24 months), every 3 months, the following indicators were determined: melting point, acid number, iodine number and VPD. Table 1 shows the results of the definitions of the above indicators during storage.

From table 1 it can be seen that during the two-year storage of suppositories under various temperature conditions, the melting temperature of suppositories practically does not change. The iodine and acid numbers of suppositories at low storage temperatures remain virtually unchanged. A linear relationship is also observed between changes in the total deformation time (VPD) and the melting temperature. There is a slight increase in the VPD in all suppositories both at a temperature of 3-50C, and at 20 ± 20C. However, fluctuations in the values of all indicators do not go beyond permissible norms.

All indicators were determined in accordance with the requirements of the general article "Suppositories" GFXI.

Studies to determine the shelf life of the studied suppositories based on the method of "accelerated aging" at elevated temperatures were carried out in accordance with instruction I-42-2-82. The method of “accelerated aging” consists in keeping the test drug at temperatures above its melting point and allows you to establish the stability of the drug in rectal LF (RLF) for a relatively short period of time.

Table 1. Results of the study of the stability of the Benpap and Benzpap 10 suppositories during natural storage

Drug form	Indicator	Storage period in months					
		0	3	6	12	18	24
Suppositories Benzpap	Iodine number	70	65/65	64/65	68/66	67/66	66/65
	Acid number	0,25	0,26/0,25	0,27/0,25	0,28/0,26	0,29/0,26	0,31/0,29
	VPD, min	5’22’’	5’14”/5’12”	5’11”/5’16”	4’18”/4’26”	4’00”/4’39”	3’67”/4’43”
	Melting point, ^{0}C	37,0	37,0/37,0	36,8/37,0	36,5/36,8	36,0/36,5	34,0/35,0
Suppositories Benzpap 10	Iodine number	75	73/72	72/70	68/66	70/68	65/63

	Acid number	0,58	0,60 0,58	0,61 0,60	0,63 0,61	0,64 0,63	0,66 0,65
	VPD, min	5’15’’	5’04’’ 5’00’’	5’11’’ 5’16’’	4’18’’ 4’26’’	4’00’’ 4’39’’	3’67’’ 4’43’’
	Melting point, ^{0}C	36,8	36,8 36,8	36,6 37,2	36,5 36,5	36,0 36,0	33,0 35,0

Note: The upper digit indicates the value of indicators at storage temperature + 20 ± 20C.

The lower figure is at a temperature of + 3 + 50C. It is known that the quantitative content of active substances in the DF storage process is one of the main factors characterizing stability. To determine the quantitative content of active substances in the studied suppositories during storage, we used TLC and SF methods. In the process of “accelerated aging” research of samples of the studied suppositories stored at a temperature of 300C (the temperature recommended by I-42-2-82 for suppositories) for 3 months, we found insignificant losses of active substances in the suppositories, as well as traces of their decomposition products . In suppositories stored in the refrigerator, only small losses of substances were found. In this case, we also used the TLC method, which, in fact, is a semi-quantitative method and allows one to judge the content of substances in the test solution by the intensity of stain stains in comparison with CO. Therefore, it should be noted that to prolong or increase the stability of most suppositories, optimal storage conditions are storage at low temperatures. A significant influence on the stability of suppositories is exerted by the type of base and storage conditions (the presence of oxygen, storage temperature, illumination). As already noted, during storage of suppositories, active drugs can interact with CO, as a result of which the content decreases or the effectiveness of the drug decreases. As you know, when controlling the quality of the finished DF, the main requirement is a qualitative and quantitative determination of the active substances in the drug.

The quantitative content of the benzetasone acting in the developed suppositories was controlled according to the previously developed and validated SF method. (18) As shown by the results of table 1, in the conditions of the refrigerating chamber, the studied suppositories practically did not change the quality indicators during 24 months of storage. The separation of active substances from the formative components of RDF was carried out by extraction. When choosing an organic solvent, the solubility of the active substances was taken into account. The studied substances were extracted from 5 suppositories in 20-25 ml of purified water by heating in a water bath. The extract was filtered, the filtrate was divided into 5 parts and identification reactions were carried out. The methods of quality control and standardization developed using modern physicochemical methods were subject to certification, which in turn requires in order to confirm the suitability of this methodology for an objective assessment of the quantitative content of such as in a pharmaceutically active ingredient, and subsequently in various medicines obtained on their basis, as well as the justification of the parameters for the presentation of the validation of analytical methods, which is part of the registration application submitted to the EU, Japan, USA and others. (19,20) A further aim of the work is to assess the adequacy of the analytical method proposed

for quantitative determination of benzketozone in pharmaceutically active ingredient and from suppositories. The results of validation of the developed methods by parameters are presented below: specificity, linearity, correctness and repeatability.

The following instruments were used in the work: SF 2000 spectrophotometer, T-A-13 analytical balance. Solutions of standard samples (CO) of benzketozone (FS 42-0849-10) were prepared at a concentration of 0.05 mg / ml (for UV spectrophotometry) We used the benzketozone by UV spectrophotometry as previously developed [3]: about 0.1 g of the preparation (the so-called) dried to a constant weight of the benzketozone was transferred into a volumetric flask with a capacity of 200 ml, dissolved in 50 ml of purified water, heated in a water bath until complete dissolution, cooled, adjusted to the mark with the same solvent and stirred (solution A). 1 ml of solution A was transferred into a 100 ml volumetric flask, adjusted to the mark with the same solvent and stirred (solution B). The optical density of the obtained solution B was measured at 305 nm in a cuvette with a layer thickness of 10 mm. As a comparison solution used purified water.

In parallel, a solution of a working standard sample of benzketozone was prepared. For this, about 0.1 g of the preparation (the so-called) dried to a constant weight of benzketozone was transferred into a 200 ml volumetric flask, dissolved in 50 ml of purified water, heated in a water bath until completely dissolved, cooled, adjusted to the mark with the same solvent and stirred (solution A). 1 ml of solution A was transferred into a 100 ml volumetric flask, adjusted to the mark with the same solvent and stirred (solution B).

The quantitative content of benzketosone in% (X) was calculated by the formula:

where, Ah, Ast is the optical density of the analyzed solution and the CO solution of benzketozone, respectively;

ah, ast - sample of the analyzed solution and CO of benzketozone, respectively, g;

The content of benzketozone in the drug should be at least 97.5%.

3. RESULTS AND DISCUSSION

Before statistical data processing, a homogeneity of the samples was checked and it was found that all of them did not contain a gross error, because Q1 <Q (n = 5, P = 95%), i.e. Q1 <0.64. Validation of the developed methods was carried out in accordance with the draft OFS 42-0113-09 “Validation of analytical methods”.

The analytical region of the technique is within the linear dependence and amounts to 42–58 μg / ml of benzethozone and is described by the equation y = 128.7x-0.101 with a correlation coefficient r = 0.995, and the necessary condition for the linear dependence of 0.99 is also satisfied.

The correctness of the proposed methodology was determined on 6 samples of solutions of model mixtures of benzketozone (table. 2).

Table 2. Determining the correctness of the spectrophotometric method for determining benzketozone

Method	μ, г	x,%	R, %	Метрологические характеристики
UV spectrophotometry	0,1107	0,1098	99,57	$\bar{R}$=99,15
	0,1093	0,1021	96,56	s^2=4,91

	0,1098	0,1030	96,76	s=2,217
	0,1997	0,2040	102,15	$t_{выч}$ =0,93
	0,1985	0,2054	98,99	$t_{табл}$=2,57
	0,1992	0,2098	100,87	

In the methodology, the inequality t habit <ttable (P, f) is observed, therefore, the presented results are not burdened by a systematic error and are correct.

In order to verify the repeatability of the methods, a three-level experiment of 3 experiments at each level was carried out. The measurement range was selected based on the variation in the amount of benzketozone substance in the FAI (± 20%). Thus, the upper level corresponds to a sample of 0.18 g, the average - 0.20 g, the lower - 0.22 g.

In order to obtain the metrological characteristics of the methods, statistical processing of the results of the quantitative determination of benzketozone in the FAI and from suppositories by UV spectrophotometry was carried out (Table 3).

Table 3. The results of determining the repeatability (precision) of the method for determining the benzketosone metod UV spectrophotometry

Method	Level	Benzketozone,%		R, %	f	$\bar{x}$	s2	s	P	$\bar{\Delta x}$	ε	T	F (P, f1, f2)	F
		Taken	Found											
UV spectrophotometry	I	0,1810	0,1783	98,50	8	99,19	1,570	1,253	95%	0,915	0,92	1,93	3,44	8,77
		0,1807	0,1793	99,20										
		0,1824	0,1785	97,85										
	II	0,2107	0,2098	99,57										
		0,2080	0,2098	100,87										
		0,2075	0,2054	98,99										
	III	0,2215	0,2195	99,10										

		0,2188	0,2127	97,20										
		0,2210	0,2241	101,40										

According to the data in Table 3, t usual (1,2) <t table, which allows us to consider the results of the sample technique free from systematic error. Papaya (dry extract of the aerial part) was determined from the same filtrate and amino acid composition reactions were carried out for identification by TLC and paper chromatography.

TLC was also identified on alkaloids, flononoids and on ascorbic acid. The quantitative content on the MIKCROTECHNA-ANALIZER T-339 analyzer (Prague-Czechoslovakia), according to the order of the peaks, is therefore: aspartic acid, threonine, glutamic acid, glycine, alanine, valine, isoleucine, leucine, phenylalanine and lezins-serine, glycine, tyrosine, amino acids. The content of ascorbic acid was determined by TLC method: Silufol and Merck plates 200 x 150 ml., Witness solution 5% ascorbic acid, 80:20 system - ethyl acetate-glacial acetic acid.

Holding time 20 minutes. Drying: in air, the developer is 0.04% of 2,6-dichlorophenolindophenolate sodium solution (0.001 mol / l). Rf 0.42. The data corresponded to a previously developed technique (21). The proteolytic activity of the enzymes was also determined by the modified Anson method based on hydrolysis. The optical density was determined by the photoelectrocolorimetric method. A cuvette 10 mm thick., Wavelength 630-670 nm, optical density in the range of 0.2-0.60. Proteolytic activity was calculated according to the schedule of tyrosine equivalent (TE). 1 ml of standard solution corresponded to 1 μ tyrosine. (22)

4. CONCLUSION

1. Methods of natural and accelerated storage are used to study the factors affecting the stability of suppositories during storage (type of base used, temperature and storage time). It was revealed that under the conditions of a refrigerating chamber at a temperature of + 3-50 ° C, the studied suppositories practically did not change the quality indicators during 24 months of storage. The type of base slightly affected the change in the physicochemical parameters of the Benzpap and Benzpap 10 suppositories.
2. For the quality specification, the SF method was used; the absence of CO interaction with the active substances of the studied suppositories was proved.
3. Using a validation assessment, it was established that the developed end-to-end method for the quantitative determination of benzketasone suppositories using the spectrophotometric method is correct, precise, reproducible, and linear in the analytical field.
4. The developed methods are adapted as end-to-end for a qualitative assessment of the content of active substances in suppositories.

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