World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 6.129

STUDYING OF THE INTERACTION OF SUPPOSITORY BASES WITH MEDICINAL SUBSTANCES OF COMBINED ACTION IN SUPPOSITORIES.

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Article Received on 10/03/2020 **Article Revised on 30/03/2020** **Article Accepted on 21/04/2020**

ABSTRACT

Of the currently existing dosage forms (DF) in medical practice, rectal DF are of significant interest, among which the most common suppositories.[1] The creation of suppositories of combined action is an urgent problem of the pharmaceutical industry of the Republic.

KEYWORDS:

Currently, of the existing dosage forms (DF) in medical practice, rectal dosage forms (RDF) are of considerable interest, among which the most common suppositories.[1] The creation of suppositories of combined action is an urgent problem of the pharmaceutical industry of the Republic.

From the point of view of modern pharmaceutical science, there can be no universal basis for all medicinal substances (MS). And in each case, in the manufacture of suppositories, a specific basis should be used, which should ensure stability, high therapeutic activity of MS in rectal dosage form (RDF).

Therefore, the search for more accessible and indifferent suppository bases (SB) that meet the modern requirements of pharmaceutical technology currently has not lost its relevance.

Lipophilic SBs are widely used in medical practice. The characteristics and technology of the bases for suppositories obtained on their basis are described in detail in the works.[2-3]

Analysis of a priori data showed that lipophilic and hydrophilic bases, as well as mixtures thereof, are widely used to obtain suppositories. Among them, cocoa butter occupies a leading position. But after prioritization, such as profitability and the use of local raw materials, we used JODS and JODS PM-10 as the basis for obtaining suppositories containing fensulcal.[4]

Suppository compositions according to physico-chemical and structural-mechanical indicators must meet the requirements of fatty SBs.

Taking into account the pronounced anti-inflammatory, antimicrobial effect and wound healing effect of fensulcal, as well as the recommendations of pharmacologists on its use in gynecological practice, we conducted studies to standardize vaginal suppositories of combined action.

Fensulkal is a bisulfite derivative of phenylglyoxylic acid and has an anti-inflammatory effect of a non-steroidal series.[5]

The purpose of this work is to conduct research on factors affecting stability for the standardization of combined-action vaginal suppositories.

MATERIALS AND RESEARCH METHODS

To obtain the suppository of the combined action of fensulcal,[6-8] from the studied compositions, we used the two above most optimal compositions for suppositories (hereinafter JODS and JODS - PM-10) and Vitebsol (currently used in the production of domestic pharmaceutical practice).

The main method of obtaining suppositories in industrial production is pouring into molds.

To obtain fensulcal suppositories, combined action (cetirizine, sea buckthorn oil) on the selected SB, the method of pouring into the forms was used stepwise: preparing the base, introducing the drug into the base, forming and packing the suppositories.

Preparation of suppositories

Suppositories were made by pouring suppository mass, consisting of a base and a MS. A mixture of mild soap,

glycerin and ethanol in a ratio of 1: 1: 5 used as a lubricant. A weighed amount of the base was placed in a conical flask with a capacity of 100 ml and kept in a boiling water bath at a temperature of 80-85^{0}C until 2/3 of the part was dissolved; the residue was melted by shaking. A weighted amount of pre-shredded drug (the degree of shredding to the state "to the smallest" SPh X, p.857) was added as a suspension into the molten base. The mixture was shaken until complete homogenization. The resulting mixture was filled into the cell molds to the edges, weighing 2.6 g and placed in the refrigerator for 20-30 minutes.

The replacement coefficient was taken into account by calculation by a known method, of I. N. Starkova.

The resulting suppositories are conditionally called "phenobzin", and "phenobzin 10", respectively.

By the above method, several series of vaginal suppositories were obtained, which were subjected to quality control. A quantitative analysis of the active substances in suppositories was determined according to previously developed methods,[9,10,11] and their physicochemical parameters according to the general article of the SPh XI (issue 2). When controlling the quality of drugs in suppositories, the most important place is the separation of active substances from formative ones.

The fensulcal suppositories obtained in this way with a combined action of 0.1 g, weighing 2.6 g, have a cylindrical shape, from light cream to cream color, with a specific smell. A homogeneous mass, without crystals, is noted in the longitudinal section. In the slice, the presence of an air and porous rod and a funnel-forming recess is allowed. The average weight of suppositories is 2.6 g (2.4 to 2.8). The melting temperature is not higher than 37^0 C, the time of complete deformation is not more than 15 minutes at a temperature (37 ± 1^{0}C) according to hardness according Kaminsky.[12] Physical and chemical characteristics of suppositories are given in table 1.

Investigation of the effect of the interaction of suppository bases with fensulcal and cetirizine during storage on the shelf life of the studied suppositories.

The study of factors affecting the stability of suppositories in the production and storage process helps to determine their effectiveness and the content of active substances quantitatively changed to acceptable limits. The determining factor here is the temperature and storage time, which has a significant impact on the quality indicators of suppositories.

Given that there is an interaction of SB with medicinal substances (MS) that are part of the suppositories, and SB can affect the properties of MS, we determined the main parameters of the prepared suppositories: melting point, solidification temperature, acid number, viscosity and total deformation time. Placebo suppositories were used as controls.

The indicators were determined after the suppositories were melted and fensulcal and cetirizine were extracted by hot filtration. Before filtering, the bases were cooled to solidification (SB and sea-buckthorn oil on the filter), and the filtrate containing fensulcal and cetirizine was used for further studies.

The active substances - conditionally named fensulcal and cetirizine at the time of preparation of suppositories, practically do not affect the main physicochemical and structural-mechanical parameters of the studied SB and vice versa.

The determination of the above structural, mechanical, and physicochemical parameters of suppositories is not enough to judge the interaction of SB with MS. The next stage of our research was the study of suppositories during storage.

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 3-5^{0}C, the second at room temperature 20 ± 2^{0}C. During storage (24 months), every 3 months, the following indicators were determined: melting point, acid number, iodine number and total deformation time. 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 a low storage temperature remain practically unchanged. A linear relationship is also observed between changes in the total deformation time (TDT) and the melting temperature. There is a slight increase in the total deformation time in all suppositories both at a temperature of 3-5^{0}C, and at 20 ± 2^{0}C. 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" SPhXI.

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 exceeding its melting temperature and allows us to establish the stability of the MS in the RDF for a relatively short period of time.

Table 1: The results of the study of the stability of the suppositories "Phenobzin" and "Phenobzin 10" during natural storage.

Dosage form	Indicators	Shelf life in months					
		0	3	6	12	18	24
Suppositories "Phenobzin"	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
	Total deformation time, min	5’22’’					
	Melting temperature, ^{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 "Phenobzin 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
	Total deformation time, min	5’15’’					
	Melting temperature, ^{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 figure indicates the value of indicators at storage temperature + 20 ± 2^{0}C. The lower figure is at a temperature of + 3 + 5^{0}C.

It is known that the quantitative content of active substances in the DF during storage process is one of the main factors characterizing stability.

To determine the quantitative content of fensulcal and cetirizine in the suppositories under study during storage, we used TLC and HPLC methods.

In the process of “accelerated aging” research of samples of the studied suppositories stored at a temperature of 30^{0}C (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 coloring in comparison with SB.

Therefore, it should be noted that to prolong or increase the stability of most suppositories, optimal storage conditions are storage at low temperatures.

The type of base and storage conditions (the presence of oxygen, storage temperature, illumination) has a significant impact on the stability of suppositories.[8]

As already noted, during storage of suppositories, active drugs can interact with SB, as a result of which decreases the content of the MS or the effectiveness of the MS.
We also carried out a series of experiments to study the interaction of the studied SB - JODS and JODS PM-10 with the active substances of the suppositories “Phenobzin and Phenobzin 10”, stored in a refrigerator, using the HPLC method.[11]

As you know, when controlling the quality of the finished dosage form, the main requirement is a qualitative and quantitative determination of the active substances in the drug.

Control of the quantitative content of active substances in the developed suppositories of fensulkal was performed using a previously developed and validated HPLC technique.

The research results are presented in table 2.
As the results of tables 1 and 2 show, in the conditions of the refrigerating chamber, the studied suppositories practically did not change the quality indicators during 24 months of storage. The studied parameters differ slightly in the case of using both JODS and JODS PM-10.

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.

Of the previously developed methods, the optimal conditions for the identification and quantification of active substances are:

- Analytical column with size 150 x 3.0 mm, filled with Zonbax Eclipse XDB sorbent with 18 s. particles of 3.5 microns;
- Temperature of column - room;
- Detection - 254 nm;
- Mobile phase - degassed and profile a mixture of methanol and water in a ratio (25:75);
- The volume of the injector loop is 20 µl;
- Flow rate - 0.6 ml / min.

The developed and used technique was validated where the accuracy expresses the degree of dispersion of the results for a series of measurements determined by two parameters: convergence and reproducibility.

Table 2: The quantitative content of fensulcal and cetirizine in suppositories by HPLC stored in a refrigerator.

Dosage form	Medicinal substance	Amount of MS content, %					
		0	3	6	12	18	24
Suppositories "Phenobzin"	fensulcal	98,86	98,38	98,16	98,10	97,34	97,17
	cetirizine	98,69	98,60	98,12	98,02	97,14	97,04
Suppositories "Phenobzin 10"	fensulcal	98,95	98,80	98,45	98,00	97,48	97,29
	cetirizine	98,81	98,68	98,30	97,87	97,39	97,00

The data obtained confirm the advisability of storing suppositories at low temperatures.

CONCLUSIONS

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 + 3-5 ° 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 suppositories “Phenobzin” and “Phenobzin 10”.
2. The method of HPLC proved the absence of interaction of SB with the active substances of the studied suppositories.

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