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RESEARCH ARTICLE

Development of Composition and Technology of suppositories based on substance from medicinal plant raw materials *Rosmarinus officinalis* L.

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ABSTRACT:
The therapeutic activity of suppositories is influenced by a large number of factors, for example, the solubility of the drug substance in the base, molecular size, ability to penetrate the membrane, particle size, interaction with the base and excipients, as well as surfactant concentration. These circumstances necessitate the search for optimal compositions and preparation methods in order to increase the effectiveness of the drugs. In order to develop optimal suppository technology, it was necessary to study the influence of a number of technological factors on the quality of the developed dosage form: temperature conditions at the stages of preparing the suppository mass and bottling it into blister packaging; speed and duration of homogenization of components, as well as experimentally determine consumption coefficients and carry out appropriate technological calculations. Based on this, we set the task of theoretically and experimentally substantiating the composition and developing the technology of suppositories using carbon dioxide extract isolated from the herb rosemary. The main technological parameters were theoretically and experimentally substantiated: temperature, stirrer speed, homogenization duration at the stages of preparation of the concentrate and suppository mass, cooling mode of molded suppositories. As a result of the research, a technology for the production of suppositories with CO_2 - rosemary extract and methods for quality control of the drug, included in the normative document, was developed. It was shown that the suppositories meet all the requirements of the State Pharmacopoeia of the Republic of Kazakhstan and remain stable over a 12-month observation period.

KEYWORDS: *Rosmarinusofficinalis*, Suppositories, Herbal raw materials, Medicinal plants, Pharmacological screening, Biological activity, Physical and chemical properties.

INTRODUCTION:
Currently, suppositories are becoming increasingly popular because... they provide the targeted action of the BAS complex, are not affected by digestive enzymes and do not have an irritating effect on the gastrointestinal tract. The bioavailability of most active ingredients in these dosage forms is significantly higher than that of oral ones, in some cases approaching injectable drugs[1-3]. As is known, the therapeutic activity of suppositories is influenced by a large number of factors, for example, the solubility of the drug substance in the base, molecular size, ability to penetrate the membrane, particle size, interaction with the base and excipients, as well as surfactant concentration.

These circumstances necessitate the search for optimal compositions and preparation methods in order to increase the effectiveness of the drugs[4-5].

In order to develop optimal suppository technology, it was necessary to study the influence of a number of technological factors on the quality of the developed dosage form: temperature conditions at the stages of preparing the suppository mass and bottling it into blister packaging; speed and duration of homogenization of components, as well as experimentally determine consumption coefficients and carry out appropriate technological calculations.

Based on this, we set the task of theoretically and experimentally substantiating the composition and developing the technology of suppositories using carbon dioxide extract isolated from the herb rosemary.

In recent years, in scientific and practical medicine and pharmacy there has been an increasing interest in lipophilic complexes of plant origin. This is explained by the fact that they contain polyunsaturated fatty acids, vitamins, phytosterols and a number of other chemical compounds specific to a particular type of plant material[6-9].

Due to the thermolability of these groups of biologically active substances, the most acceptable technology for their isolation from plant raw materials is extraction with liquefied gases, which allows the stage of solvent evaporation to be carried out under gentle temperature conditions[10-11]. As is known, the efficiency of the extraction process is in a complex and not always unambiguous dependence on a number of factors related to the technological properties of the raw material and hydrodynamic conditions in the solid-liquid system.

In order to develop optimal suppository technology, it was necessary to study the influence of a number of technological factors on the quality of the developed dosage form: temperature conditions at the stages of preparing the suppository mass and bottling it into blister packaging; speed and duration of homogenization of components, as well as experimentally determine consumption coefficients and carry out appropriate technological calculations.

MATERIALS AND METHODS:

Raw materials:

The object of the study is the above-ground parts of *Rosmarinus officinalis* L. collected on the territory of the Turkestan region of the Republic of Kazakhstan.

Study design:

The work was performed on the basis of the School of Pharmacy, the Department of Clinical Immunology, Allergology and Microbiology of the Non-Commercial Joint Stock Company "Medical University of Karaganda" (NCJSC MUK).

Pharmacological screening of suppositories with carbon dioxide extract from the herb rosemary:

The presence of drugs with anti-inflammatory activity in models of acute exudative inflammation induced by subplantar administration of a 1% carrageenan solution in outbred male rats weighing 180-220g.

The choice of this model is due to the fact that various mediators are involved in the development of the exudative stage: biogenic amines, the kinin system, prostaglandins, leukotrienes, etc. Thus, studying the effectiveness of drugs during the first 4 hours of the experiment allows us to determine the most optimal doses and calculate inflammatory processes for treatment reverse genesis.

All studied substances were administered rectally 30 minutes before the increase in carrageen.

The amount of edema in each case was determined by the difference in volume between the edematous and healthy paw. The anti-inflammatory activity of the drugs was assessed by the ability to reduce the development of edema in comparison with the control and expressed as a percentage A, %, indicating how much the test drug inhibits the development of edema in relation to the control, where the amount of edema was taken as 100%.

The activity of the studied samples and comparison drugs was calculated using the formula:

$$A,\% = 100 - \frac{(M_s - M_h)*100}{M_s^c - M_h^c}$$

Where M_s and M_h are the volumes of the swollen and healthy paws in the experiment, respectively;

M_s^c and M_h^c are the volumes of the edematous and healthy paw in the control, respectively.

Measurement of paw edema in rats was carried out after 1, 2, 3, 4 and 24 hours, taking into account the fact that 3 hours after the administration of carrageenan, maximum edema is observed, which then gradually decreases throughout the day.

As a comparison drug, diclofenac sodium suppositories were used, administered in a similar manner.

Theoretical and experimental justification of the composition suppositories with CO_2 extract of rosemary herb:

When developing drugs in the form of suppositories, one of the main tasks is to select a base that would promote maximum bioavailability of active substances and have the necessary technological and consumer properties[12].

The method of introducing drugs into the base also largely determines the therapeutic effectiveness of suppositories and the features of the technological process. The choice of the optimal method depends, first of all, on the solubility and polarity of medicinal substances, their ability to overcome the rectal barrier. For example, poorly soluble drugs quickly saturate the intrarectal secretion even at a low concentration, which prevents the further transfer of drug particles from the molten base. This in turn affects the viscosity of the molten suppository. On the other hand, highly lipophilic drug substances easily overcome the membrane barrier and penetrate into the plasma, maintaining a high diffusion rate and providing a resorptive effect[13].

Thus, the choice of base must be made for each drug substance individually. To prepare suppositories with carbon dioxide extract of the herb rosemary, lipophilic and hydrophilic bases were used.

In our studies, we used a lipophilic complex from the herb rosemary. The dosage of the drug ranged from 0.1 to 0.5g of CO_2 - extract of the herb rosemary per 1 suppository weighing 1.5g, which corresponded to 0.0006 and 0.003mg of the active ingredient chamazulene, respectively.

Study of the physicochemical properties of suppositories with CO_2 extract of the herb rosemary:
To select the optimal base, we studied the physicochemical properties of suppositories of the above compositions with and without the active ingredient (placebo).

Samples for research were obtained as follows. The components of the bases were fused in a heated reactor, stirring with a paddle stirrer at a rotation speed of 60 rpm (PE-0317, Russia). Then the calculated amount of CO_2 extract of the herb rosemary was added and mixing continued for 60 minutes. The homogeneity of the mass was controlled visually.

RESULTS AND DISCUSSION:

Pharmacological screening of suppositories with carbon dioxide extract from the herb rosemary:
As can be seen from the results obtained (Table 1), all studied dosages of the drug have anti-inflammatory activity[14-16]. Thus, suppositories with CO_2 extract of the herb rosemary in doses of 17.5–43mg/kg inhibit the initial phases of inflammation (1st and 2nd hours), where the leading role is played by histamine, serotonin and kinins.

Theoretical and experimental justification of the compositionsuppositories with CO_2 extract of rosemary herb:
When developing the optimal composition of suppositories, 9 compositions were studied (Table 2), composed by varying the following pharmaceutical factors: the nature and amount of the base, the uniformity of the suppository mass, the time of complete deformation, the melting temperature of the suppositories, the technological operations and equipment used in the manufacture of suppositories, and also taking them into account pharmaceutical availability *in vitro*. All of the above factors can significantly influence the processes of release of active substances from the suppository base, as well as the completeness and speed of their absorption.

To prepare suppositories, lipophilic bases were studied - presented in Table 2.

Table 1: Effect of preparations with CO_2 extract of the herb rosemary on the process of exudation during carrageenan inflammation in rats (n = 6)

Activeingredientsanddoses	Percentage of inhibition of edema A,% compared to control				
	Time after administration of carrageenan, h				
	1 hour	2 hours	3 hours	4 hours	24 hours
CO_2- rosemary herb extract 43 mg/kg (A)	36,4±1,7	37,7±2,0	38,0±2,1	36,4±2,4	95,0±1,4
CO_2- rosemary herb extract 35 mg/kg (B)	36,1±1,2	37,4±2,1	37,5±1,5	35,0±1,9	94,2±0,4
CO_2- rosemary herb extract 17,5 mg/kg (C)	36,0±1,0	24,4±1,2	24,1±0,6	21,9±1,4	66,0±1,7
CO_2- rosemary herb extract 8 mg/kg (D)	21,4±1,5	17,3±1,2	17,5±1,0	23,1±0,7	26,1±1,7
Diclofenac sodium 8 mg/kg (E)	30,2±1,2	32,4±1,1	43,5±1,5	47,2±1,1	62,0±1,7

Table 2: Options for suppository compositions

Ingredient	Composition options for 1 suppository, 1.5 g								
	1a	1b	1c	2a	2b	2c	3a	3b	3c
CO_2 extract of rosemary herb	0,1	0,3	0,5	0,3	0,3	0,5	0,1	0,3	0,5
Ethanol	Qu. satis	Qu.satis	Qu.satis	-	-	Qu.satis	-	Qu.satis	Qu.satis
Cacaobutter	1,0	0,8	0,6	-	-	-	-	-	-
Twin-80	0,05	0,05	0,05	-	-	-	-	-	-
Flaxoil	0,25	0,25	0,25	-	-	-	-	-	-
Supporin	-	-	-	1,2	-	-	-	-	-
Witepsol	-	-	-	-	1,2		-	-	-
Emulsifier T-2	-	-	-	-	-	0,2	-	-	-
Sunfloweroil						0,7		0,7	-
Paraffin	-	-	-	-	-	-		0,5	-
PEO -400 PEO - 500	-	-	-	-	-	-	1,4	-	1,0
Waxyellow	0,1	0,1	0,1	0,1	0,1	0,1	-	-	-

Table 3: Main indicators of suppositories with CO_2 - rosemary herb extract and placebo

Indicators Compositions	Appearance of the suppository	T_m, °C	Solidification temperature, °C	AN	PN	IN	Disintegration, min	Time of complete deformation, min
Suppositories - placebo								
1 c	Homogeneous, light brown, water washable	41,8 ±0,25	26,2 ±0,34	0,48 ±0,02	0,05 ±0,022	2,6 ±0,10	27,0 ±0,47	20,1 ±0,71
Suppositories with CO_2 extract of rosemary herb								
1 c	Homogeneous, dark blue with weak specificity smell	36,8 ±0,12	26,6 ±0,29	0,55 ±0,022	0,05 ±0,015	10,5 ±0,12	15,1 ±0,40	14,2 ±0,56

Study of the physicochemical properties of suppositories with CO_2 extract of the herb rosemary: The time of complete deformation of suppositories of CO_2 extract of the herb rosemary and placebo was determined according to the method of the State Pharmacopoeia of the Republic of Kazakhstan.

The melting and solidification temperatures of suppository bases and masses were determined in accordance with the State Pharmacopoeia of the Republic of Kazakhstan.

The disintegration of samples was studied using the method of the State Pharmacopoeia of the Republic of Kazakhstan.

Acid (AN), peroxide (PN) and iodine (IN) numbers were analyzed according to the method given in the State Pharmacopoeia of the Republic of Kazakhstan [10-11].

At the same time, the activity of the drug is slightly higher than that of diclofenac. The prostaglandin phase of inflammation is less affected by CO_2 rosemary herb extract, being inferior to the comparison drug.

Further study (Table 1) of the dynamics of inflammation showed that the herbal medicines reach their maximum activity after 24 hours, and the carbon dioxide extract of the herb rosemary in doses of 35 and 43 mg/kg exceeds diclofenac sodium by 1.4 times. This effect can be explained by a two-chamber pharmacokinetic model, according to which, 5 hours after administration, the drug is redistributed and accumulated in tissues, and its effect weakens. After 24 hours, due to release into the blood plasma, the effect appears again. The observed dynamics indicate the applicability of the carbon dioxide extract of the herb rosemary for the relief of both acute and chronic inflammation.

Reducing the dose of CO_2 extract of the herb rosemary by half (to 17.5 mg/kg) is accompanied by an average decrease in activity by 1.5 times, with the exception of the early phase of pathology. The dosage of the active ingredient 8 mg/kg in the drug is insufficient to treat inflammation. Increasing the dose to 43 mg/kg is not accompanied by an adequate increase in effect and is therefore inappropriate[17].

Thus, based on the results of screening pharmacological studies, the optimal dose of 43 mg/kg of the active substance - cineole - was established, which, according to the method, corresponds to a therapeutic dose for humans - 0.003 g in 1 unit of the drug (suppository).

Hydrophilic bases (mainly polyethylene oxide) have high osmotic activity (Table 2), which can slow down the release of certain substances [18-19]. This was also confirmed by our experimental studies.

The most optimal composition of suppositories was identified, consisting of a lipophilic base, namely suppositories with a dosage of CO_2 extract of rosemary herb 0.5 g, cocoa butter - 0.6 g, Tween-80 - 0.05 g, flax oil - 0.25 g and yellow wax - 0.1 g.

As can be seen from the data obtained (Table 3), the introduction of the active substance into the base has different effects on the physicochemical parameters of suppositories. Thus, the melting temperatures of compositions 1, 2, 4 and 5 are reduced by approximately 5°C, and the solidification temperatures by 3-4°C for compositions based on polyethylene oxide (PEO). Suppositories prepared with solid fat and with the addition of emulsifier No.1 do not change their temperature parameters.

Acid, peroxide, iodine numbers of bases comply with the requirements of the monograph of the State Pharmacopoeiaof the Republic of Kazakhstan. The introduction of CO2 extract of the herb rosemary has virtually no effect on the CN and IF, because the substance is also characterized by low values of these indicators. The iodine number in the drug samples increases compared to placebo, which is explained by the large amount of biologically active substances in the lipophilic complex.

The disintegration and time of complete deformation of composition 1c do not depend on the presence of carbon dioxide extract.

Acid, peroxide, iodine numbers of bases comply with the requirements of the monograph of the State Pharmacopoeia of the Republic of Kazakhstan. The

introduction of CO_2 extract of the herb rosemary has virtually no effect on the AN andPN, because the substance is also characterized by low values of these indicators. The iodine number in the drug samples increases compared to placebo, which is explained by the large amount of biologically active substances in the lipophilic complex.

The disintegration and time of complete deformation of composition 1c do not depend on the presence of carbon dioxide extract.

CONCLUSIONS:

Taking into account the peculiarities of the process of extraction of raw materials with liquefied gases, we studied only those indicators that have a decisive influence on the yield of the finished product.

Using a carbon dioxide extraction unit UE-1, a series of experiments was carried out to produce CO_2 extracts of the herb rosemary and an enriched fraction containing a maximum amount of 1.8-cineole, chamazulene and other components was obtained at an extraction mode at a temperature of 50º C and a pressure of 200 bar.

Based on physicochemical, biopharmaceutical and pharmacological studies, a composition was substantiated with a dosage of CO_2 extract of the herb rosemary 0.5 g, cocoa butter - 0.6 g, Tween-80 - 0.05 g, flax oil - 0.25 g and yellow wax – 0.1 g – to obtain a suppository weighing 1.5 g.

The main technological parameters were theoretically and experimentally substantiated: temperature, stirrer speed, homogenization duration at the stages of preparation of the concentrate and suppository mass, cooling mode of molded suppositories.

As a result of the research, a technology for the production of suppositories with CO_2 - rosemary extract and methods for quality control of the drug, included in the normative document, was developed. It was shown that the suppositories meet all the requirements of the State Pharmacopoeiaof the Republic of Kazakhstan and remain stable over a 12-month observation period.

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CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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