THE ASPECTS OF DEVELOPMENT AND STANDARDIZATION OF CHILDREN'S SUPPOSITORIES WITH EXTRACT OF LICORICE ROOT

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Abstract: The aim of this work was the development of technology of rectal suppositories of immunomodulatory action for children and their standardization.

To obtain suppositories, a licorice root extract, chamomile and tea tree essential oils were used. Given that the introduction of ingredients in a dissolved form is preferable, we studied the possibility of using emulsion suppository bases. To evaluate the compositions, the homogeneity and colloidal stability of the suppositories obtained were studied. Estimation of homogeneity, melting temperature, decay time, average mass was carried out according to the State Pharmacopoeia. To confirm the authenticity of the active ingredients, a chromatography method was used. The quantitative determination of glycyrrhizin acid was carried out by spectrophotometric method.

Suppositories were prepared by the pouring method. The licorice root extract was added to the suppository when dissolved in the hydrophilic phase of the base. Essential oils of chamomile and tea tree were introduced when a solid fat of type A dissolved in a melt, at a temperature of (42.0±2.0) °C. Optimum indices for the criteria of "homogeneity" and "colloidal stability" were noted for the samples of the composition: purified water, polysorbate-80, lecithin, solid fat type A. To prove the authenticity of the licorice root extract in suppositories, the chloroform-methanol-water system was optimal (26:14:3). Identification of essential oils on a gas chromatograph showed that on the chromatogram the peaks and retention times of the solution under study coincide with the peaks and retention times of the reference solutions. The conducted studies of quantitative determination of glycyrrhizin acid have shown that its content in one suppository is not less than 0.035 g in terms of glycyram.

Keywords: development, technology, standardization, children's suppositories, extract of licorice root, chamomile essential oil, tea tree essential oil.

1. Introduction

One of the most serious problems in pediatric practice today is the problem of frequent diseases in children. At the majority of children of early age, various diseases are diagnosed periodically, in the development and progress of which the state of the body's immune system is crucial. In a certain part of children, immunocompromised diseases take a protracted character and are accompanied often by the development of complications and constant relapses.

This category of children's population deserves special attention, since frequent relapses of diseases can cause a weakening of the basic compensatory-adaptive mechanisms, lead to significant violations of the functional state of the organism, in particular, respiratory, gastrointestinal, autonomic nervous system, to reduce immunorefection of the organism in general and early development of chronic pathologies [1].

Currently, a large number of drugs are widely used in the therapy of often-ill children, including salicylates and antibiotics of various groups that have a pronounced immunosuppressive effect, which aggravates the observed immunodeficiency in these children. Among drugs that reduce the terms of recovery of children and prevent the development of severe complications, it is necessary, first, to identify a group of immunomodulators. Oral and parenteral dosage forms mainly represent the existing assortment of this group of drugs on the pharmaceutical market [2].

However, in some cases, oral administration of drugs is not possible due to a number of side effects from the gastrointestinal tract, the pathology of the esophagus and stomach, and the low compliance of children. The use of injectable dosage forms, in turn, is associated with the painful introduction, the need to attract medical personnel, which also significantly limits the possibility of their use in pediatric practice.

In connection with the above factors, there is a need to develop immunomodulators in other dosage forms. In this regard, it is very interesting to develop rectal suppositories, the advantage of which is the intake of the substance directly into the large circulation, the absence of taste and odor problems, and the ease of use.

In connection with this, the aim of this work was the development of technology of rectal suppositories of immunomodulatory action for children and their standardization.

2. Material and methods

To obtain suppositories, a licorice root extract, chamomile and tea tree essential oils were used. The concentration of active substances was determined based on the study of the antiviral and antimicrobial activity of the drug samples [3].

Given that the introduction of active ingredients in a dissolved form is preferable, we have studied the possibility of using emulsion suppository bases consisting of a lipophilic, hydrophilic phase and an emulsifier. As a lipophilic component of the emulsion, we studied the possibility of using solid fat type A and a mixture of cocoa butter with bee wax, as a hydrophilic component – purified water, propylene glycol, glycerin, and as an emulsifier – surfactants of different nature: polysorbate-80, lecithin, emulsifier No. 1, lanolin, cetostearyl alcohol [4].

To evaluate the emulsion compositions, the homogeneity and colloidal stability of the suppositories obtained were studied. Estimation of homogeneity, melting temperature and decay time, as well as determination of the average mass was carried out according to the requirements of the State Pharmacopoeia [5, 6].

To confirm the authenticity of the active ingredients, a chromatography method was used in a thin layer of the sorbent. When choosing the optimal system, various solvents were used. The main active compounds of the licorice root extract in UV-light were shown. Glycyrrhizin acid was detected by violet fluorescence, and licurazide was detected as a yellow spot. Chamomile and tea tree essential oils were identified by gas chromatography in accordance with the State Pharmacopoeia technique [7].

The quantitative determination of glycyrrhizin acid was carried out by spectrophotometric method; glycyram was used as a standard. The determination procedure was as follows: 1 suppository is placed in a 250 mL flask; 20 mL of 96 % alcohol was added and vigorously stirred for 20 minutes. The resulting solution was filtered through a "blue tape" filter, previously rinsed with 96 % ethanol, into a 150 mL flask. After that,

20 mL of 96 % ethanol three times were added to the flask, shaken for 15 minutes and filtered into the same flask. The precipitate from the filter was transferred quantitatively to a 150 mL flask, 25 mL of a 3 % acetone solution of nitric acid were added, and the mixture was stirred for 10 minutes.

The resulting solution was filtered through a "blue tape" filter; the flask was washed with 10 mL of a 3 % acetone solution of a nitric acid, filtering through the same filter (solution A). Solution A was added dropwise with ammonia, a solution concentrated to pH from 8.3 to 8.8, according to the universal indicator (solution with precipitate of ammonium salt of glycyrrhizin acid).

The salt solution was transferred to a glass filter No. 4; the liquid was aspirated with a vacuum unit. The filter cake was washed with 10 mL of acetone in two steps. The precipitate was transferred quantitatively by means of water to a 10 mL volumetric flask; the volume of the solution was adjusted to the mark with water and mixed (solution B). The optical density of test solution B was measured on a spectrophotometer at a wavelength of (258±2) nm, in a cuvette with a layer thickness of 10 mm, water was used as the reference solution.

In parallel, the optical density of solution B (glycyram) was measured under the same conditions. The content of glycyrrhizin acid (X) in one suppository, in grams, was calculated by the formula:

$$X = \frac{A_0 \times 10}{1\ \text{sup} \times 135.4},$$

where A_0 is the optical density of the test solution; 135.4 is the specific absorption index of glycyram at a wavelength of 258 nm.

The content of glycyrrhizin acid in one suppository should not be less than 0.035 g in terms of glycyram.

3. Results

Suppositories were prepared taking into account the physical and chemical properties of the main components and auxiliary substances by the pouring method. The licorice root extract was added to the suppository when dissolved in the hydrophilic phase of the suppository base (purified water). Essential oils of chamomile and tea tree were introduced into the composition of suppositories when a solid fat of type A dissolved in a melt, at a temperature of (42.0±2.0) °C (lipophilic phase of the emulsion system) [8, 9].

We investigated compositions with various polar phases and emulsifiers. In the case of the formation of stable emulsions, their appearance and uniformity were evaluated. When assessing the quality of samples of suppositories based on cocoa butter with bee wax, after preparation they were heterogeneous, in the longitudinal section there were inclusions and other manifestations of instability of the system.

Optimum indices for the criteria of "homogeneity" and "colloidal stability" were noted for the samples of the following composition: purified water, polysorbate-80, lecithin, solid fat type A. The resulting suppositories had the correct shape of the torpedo with a smooth brown surface. There were no inclusions on the longitudinal section; in some cases, there was an air rod [10].

The results of the study of the average mass of the developed suppositories, the melting point and the decay time are shown in **Table 1**.

The data of Table 1 indicate that prepared suppositories for all quality indicators meet the requirements of State Pharmacopoeia for this dosage form.

Table 1

Some quality indicators of children's suppositories with licorice root extract

Indicator name	Requirements of draft quality control methods	Analysis results
Average weight, g	1.09–1.20	1.15
Melting point, °C	36.0±1.0	36.0
Decay time, min.	not more than 30 min.	12

To prove the authenticity of the licorice root extract in suppositories, the chloroform-methanol-water system is an optimal solution (26:14:3). It was found that the main active compounds of the licorice root extract had R_f values for glycyrrhizinic acid of about 0.3; for licurazide – about 0.5.

Identification of essential oils of chamomile and tea tree on a gas chromatograph with an automatic injector and flame ionization detector in the conditions chosen by us showed that on the chromatogram the peaks and retention times of the solution under study coincide with the peaks and retention times of the reference solutions [11].

The conducted studies of quantitative determination of glycyrrhizin acid have shown that its content in one suppository is not less than 0.035 g in terms of glycyram. Metrological characteristics of the method are presented in **Table 2**.

Table 2

Metrological characteristics of quantitative determination of glycyrrhizin acid in one suppository in terms of glycyram

X	X_{mid}	f	t (P, f)	X, %	ΔX
0.0410 0.0430 0.0441 0.0420 0.0450 0.0420	0.0428	5	$2.17 \cdot 10^{-6}$	2.57	3.60

4. Discussion

Summarizing the obtained results of studies, it can be concluded that a rational technology of combined children's suppositories based on natural plant raw materials and methods for qualitative and quantitative determination of active ingredients in the drug have been developed. Suppositories obtained with the developed technology, according to organoleptic, physical, chemical and technological indicators meet the requirements of State Pharmacopoeia.

Well-known scientists [12, 13] have studied main active ingredient of the designed drug, licorice root extract, for many years. Based on licorice root extract in Ukraine, syrup for the treatment of diseases of the respiratory tract was registered.

Composition of designed suppositories based on licorice root extract is new, previously not described in the literature. Conducted research of rectal suppositories with the composition given above is original for such combination of active substances.

Since the medicine is new and is in the process of development, other scientists can use the obtained results for further researches. They can be used to develop rational technology and methods for quality control of suppositories when they are manufactured both under pharmaceutical and industrial conditions.

References

1. Romantsov, M. G., Ershov, F. I., Kovalenko, A. L. (2010). Protivovirusnyie preparatyi dlya lecheniya ORVI i grippa u detey (klinicheskiy obzor) [Antiviral drugs for treatment of acute respiratory viral infections and influenza in children (clinical review)]. Fundamentalnyie issledovaniya [Basic research], 9, 76–87.
2. Yarnykh, T. H., Melnyk, H. M., Rukhmakova, O. A. (2013). Analiz farmrynku protyvirusnykh dytiachykh preparative [An analysis of the pharmaceutical market of antiviral children's products]. Proceedings from Functional foods – dietary supplements – as an effective means of diverse prevention of diseases. Kharkiv: ESEN, 283–284.
3. Yarnykh, T. H., Melnyk, H. M. (2013). Rozrobka skladu dytiachykh supozytoriiv na osnovi pryrodnoi roslynnoi syrovyny [Development of children's suppositories based on natural raw materials]. Farmatsevtychnyi chasopys [Pharmaceutical magazine], 1 (25), 98–101.
4. Yarnyih, T. G., Tolochko, E. V., Chushenko, V. N. (2010). Izuchenie assortimenta suppozitornyih osnov (obzor) [The study of the assortment of suppository bases (review)]. Himiko-farmatsevticheskiy zhurnal [Chemical-Pharmaceutical Journal], 44 (10), 21–26.
5. Tykhonov, O. I., Yarnykh, T. H. (Eds.) (2015). Vymohy do vyhotovlennia nesterylnykh likarskykh zasobiv v umovakh aptek [Requirements for the manufacture of non-sterile medicines in pharmacies]. Kyiv: Ministerstvo okhorony zdorovia Ukrainy.
6. Derzhavna farmakopeia Ukrainy [State Pharmacopoeia of Ukraine] (2001). Derzhavne pidpryiemstvo «Naukovo-ekspertnyi farmakopeinyi tsentr». Kharkiv: RIREH, 531.
7. Georgievskiy, V. P. (Ed.) (2011). Analiticheskaya himiya v sozdanii, standartizatsii i kontrole kachestva lekarstvennyih sredstv [Analytical chemistry in the creation, standardization and quality control of medicines]. Kharkiv: NMT, 1440.
8. Yarnyih, T. G., Melnik, G. N., Ruhmakova, O. A. (2013). Izuchenie vliyaniya temperaturyi na nekotoryie tehnologicheskie parametryi detskih suppozitoriev [The study of the effect of temperature on certain technological parameters of children's suppositories]. Retsept [Recipe], 3 (89), 93–97.
9. Yarnykh, T. H., Melnyk, H. M. (2012). Rozrobka tekhnolohii kombinovanykh supozytoriiv dlia vykorystannia u pediatrii [Development of technology of combined suppositories for use in pediatrics]. Visnyk farmatsii [Pharmacy Review], 4 (72), 12–14.
10. Yarnykh, T. H., Melnyk, H. M., Rukhmakova, O. A., Chushenko, V. M. (2013). Vyznachennia pokaznykiv yakosti ta vyvchennia stabilnosti rektalnykh supozytoriiv z ekstraktom solodkovoho korenia dlia ditei [Determination of quality indices and study of the stability of rectal suppositories with licorice extract for children]. Liky Ukrainy Plius [Medicines of Ukraine Plus], 2 (15), 16–18.
11. Yarnykh, T. H., Melnyk, H. M., Rukhmakova, O. A., Chushenko, V. M. (2013). Rozrobka metodyk identyfikatsii diiuchykh rechovyn u dytiachykh supozytoriiakh na osnovi pryrodnykh spoluk [Development of methods for the identification of active substances in children's suppositories on the basis of natural compounds]. Farmakom [Farmakom], 3, 44–48.
12. Amosov, A. S., Litvinenko, V. I. (2004). Solodka: tehnologiya preparatov (kratkiy obzor) [Licorice: technology of medicines (short review)]. Farmakom [Farmakom], 1, 53–61.
13. Egorov, M. V., Kurkin, V. A., Zapesochnaya, G. G. (2005). Validatsiya metodik kachestvennogo analiza syirya i preparatov solodki [Validation of methods for the qualitative analysis of raw materials and licorice medicines]. Farmatsiya [Pharmacy], 1, 9–12.