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PRODUCTION OF SUSPENSIONS IN PHARMACY: CONTRADICTIONS AND INCONSISTENCIES IN THE REGULATORY FRAMEWORK

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The method of comparative analysis was used to study the regulatory documents governing the compounded production of suspensions in Russian pharmacies and pharmacies in the neighboring countries and far-abroad countries. The official formulas were considered, the production of which is difficult in accordance with the existing regulatory requirements. The need to improve the regulatory framework governing the production of suspensions in pharmacies is shown.

Keywords: suspensions, pharmaceutical preparation, regulatory documents

In modern conditions, the compounded production of dosage forms in pharmacy conditions continues to be in demand. Prescriptions for preparation of medicines are written by physicians of various specialties, including dermatologists. One of the most popular dosage forms in dermatological practice is suspensions [1].

In dermatocosmetological practice, suspensions are often called "magma" or liquid powders. Water suspensions have a cooling, superficial vasoconstricting and drying effect, as well as an anti-inflammatory effect. Water "magmas" are a convenient substitute for dusting powders, since after evaporation and drying of the aqueous dispersion medium, powdery substances settle on the skin as a uniform thin layer and remain on it for a longer time. Unlike dusting powders, "magmas" do not dry the skin so much and act longer, have a cooling, superficial vasoconstricting and drying effect and are used to treat superficial acute inflammatory processes without oozing lesion and excessive dryness of the skin. The quantitative ratio of the dispersed phase and the dispersion medium varies depending on the purpose for which this dosage form is used: if an anti – inflammatory effect is required, then the amount of the dispersion medium is increased – with a pronounced inflammatory reaction of the skin, more liquid is added (40–50%). To provide an antiseptic effect and accelerate drying, ethyl alcohol (10–15%) is added. If the mixture is required not to be dried for a long time after application to the skin, as well as to enhance the emollient action, glycerin (5–10%) shall be added. If it is necessary to provide a covering effect, take equal amounts of powdered substances and liquid [2]. Thus, varying the composition of the suspension allows dermatologists to choose the most optimal composition based on the individual problems of a particular patient, which in principle cannot be done for commercially available drugs.

Consider suspensions from the perspective of the pharmacologically active substances and excipients forming this dosage form and technologies in order to assess the availability of

the technology and the feasibility of this dosage form.

According to the State Pharmacopoeia of the XIV edition, "suspensions are a liquid dosage form that is a heterogeneous dispersed system containing one or more solid active ingredients distributed in a liquid dispersion medium. The size of solid particles in suspensions can vary widely – from 0.1 to 10 μm or more" [3]. Hydrophilic substances used in dermatocosmetological practice include zinc oxide, magnesium oxide, basic magnesium carbonate, basic bismuth nitrate, white clay, starch. As a dispersion medium, purified water or water and water-alcohol solutions of medicinal substances are used. Suspensions of hydrophilic substances are prepared by the dispersion method without the addition of a stabilizer. For preparation of suspensions of hydrophobic substances (sulfur, menthol, thymol, sulfonamide preparations, etc.), it is necessary to add a stabilizer, which is taken either an equal amount in the case of preparation of a suspension of substances with pronounced hydrophobic properties, or half the amount in the case of preparation of suspensions of substances with non-pronounced hydrophobic properties.

As features of the technology, the State Pharmacopoeia of the XIV edition establishes the possibility of preparation of suspension by dispersing a solid internal phase containing an insoluble, pre-crushed active ingredient (ingredients) with a liquid dispersion medium or by other methods. As excipients in suspensions, buffer solutions, stabilizers, correctives, preservatives, antioxidants, dyes and other substances approved for medical application can be used. The introduction of preservatives, antioxidants and dyes into the suspension is most relevant for mass-produced medicines, and their absence in compounded suspensions can be considered as a positive characteristic, since the suspension composition is not unnecessarily "become heavier" due to excipients, which independently can cause deterioration in a number of patients with dermatological problems [4].

The production of dosage forms in pharmacy conditions is regulated by the Order of the Ministry of Health of the Russian Federation No. 751n of 2015 "On Approval of the rules for preparation and dispensation of medicines for medical use by pharmacy organizations, individual entrepreneurs who have a license for pharmaceutical activities" [5]. In this order, the technology of suspensions is considered together with the technology of emulsions, and the order establishes that (quote) "Suspensions (and emulsions) are prepared in a mortar or using mixers of various designs. Suspensions (and emulsions), regardless of concentration, are prepared by weight. When making suspensions (and emulsions) in mixers, all the ingredients are placed into the apparatus and mixed until a homogeneous mixture is obtained. The mixing time is specified by the properties of the medicines and the design of the apparatus. Suspensions are not subject to filtration. Preparation of suspensions in a mortar by grinding the powdery insoluble medicines is provided according to the rules for the production of powders, followed by dispersion with an optimal amount of liquid (in the amount of 1/2 of the mass of the crushed medicine or the crushed medicine and stabilizer) and dilution with a dispersion medium. Preparation of a suspension of hydrophobic medicinal products is carried out using stabilizers of heterogeneous systems specified in the Appendix to these Rules, and taking into account the physico-chemical properties of medicinal products and stabilizers, as well as the method of application of the dosage form".

Taking into account all of the above, when considering the technology of real dosage forms prescribed by dermatologists, serious difficulties arise. The issues of calculations in the technology of suspensions were not thought out in previous regulatory documents, namely in orders No. 412 of 1972 [6], No. 435 of 1990 [7], No. 308 of 1997 [8],

it was often difficult to follow their requirements, at the present moment, according to order No. 751n of 2015, it is simply impossible to do this for a number of prescriptions of suspensions.

According to the previously existing regulatory documentation for preparation of liquid dosage forms in pharmacies – order No. 435 of 1990, and then order No. 308 of 1997, there was a differentiation: suspensions in the concentration of medicinal substances up to 3% were prepared in weight-volume concentration, suspensions in the concentration of medicinal substances of 3% and above were prepared by weight. The orders contained specific official formulas, on the example of which the preparation of suspensions was considered. For example, the following dosage form:

Take:

Zinc oxide	
Talcum powder	by 20.0
Glycerin	30.0
Purified water	100.0

Mix. Give. Specify "For external use"

In the order, the pharmaceutics was described as follows: In a mortar, zinc oxide is mixed with talc, dispersed with glycerin (the latter is pre-weighed into a bottle), 50 ml of water is added by parts while stirring. With the remaining water, the suspension is washed off into a bottle for dispensing. Since the concentration of the suspension is more than 3%, then, according to the previously valid regulatory document, the preparation was carried out by weight, which is 170 g, the pharmaceutics is adequate. However, in the following example, given in the same regulatory document, nothing was clear in terms of determining the total mass and calculations.

Take:

Precipitated sulphur	7.0
Salicylic acid	2.0
Streptocide	3.0
Camphora	3.5
Glycerin	3.0
Ethyl alcohol,	50 ml
Boric acid solution	3% 50 ml

The order provided the following recommendations for preparation. In a mortar, streptocide and sulfur are crushed with alcohol and glycerin. The contents of the mortar are washed off with a solution of boric acid in a bottle for dispensing, where an alcoholic solution of salicylic acid and camphor is added in the remaining amount of 90% ethyl alcohol.

Here, the suspension is formed by sulfur, streptocide and camphor, their total content is more than 3% – respectively, the preparation was carried out by weight. However, there was no information about the total mass. It is difficult to determine the total weight of the dosage form, if the composition includes an aqueous solution of boric acid and 90% ethyl alcohol. If alcohol can still be converted to mass, taking into account the density, the value of which can be taken from the alcoholometric table No. 1 of the SP, then the densities of boric acid solutions of various concentrations (in recipes there can be 0.5%, 1%, 2% solutions) are not listed in the Appendix to the Order (both old and current) (only the densities of boric acid solutions of 3% and 4% concentrations are given).

Thus, it is impossible to determine the total mass of the dosage form accurately. Accordingly, it will be difficult to analyze its quality. The current Order of the Ministry of Health of the Russian Federation No. 751n of 2015, which establishes the preparation of suspensions by weight, does not consider any examples illustrating the calculations and production of dosage forms, so the interpretation of this document in terms of the technology of real suspensions may be different. On January 1, 2021, the Order of the Ministry of Health of the Russian Federation No. 308 of 1997, which clarified some issues of suspension technology, became invalid. Since various

suspensions are also widely prescribed by dermatologists at the present time, it is absolutely impossible to adequately interpret the calculations for determining the total mass of the abovementioned dosage forms in accordance with the current regulatory document.

Consider the following example of another prescription:

Take:
Basic Bismuth Nitrate 6.0
Sodium hydrocarbonate 4.0
Purified water 200.0
Mix. Dispense. Specify "Lotion"

If we consider the preparation of this dosage form according to Order No. 751n of 2015, it should be prepared by weight, so the total weight will be 210 grams. The technology itself is not difficult. But if the same prescription is prescribed by a doctor in a different form, namely:

Take:
Basic Bismuth Nitrate 6.0
Sodium hydrocarbonate solution 2% 200.0
Mix. Dispense. Specify "Lotion",

then, it becomes completely incomprehensible the total weight of the dosage form and the calculations during its preparation. So, when determining the total weight, it would be necessary to take into account the density of the sodium bicarbonate solution, which is not possible for each of its concentrations, which may be in the official formula. If you make calculations for the preparation of a sodium bicarbonate solution in a weight concentration (that is, when determining the volume of water required for preparation, subtract the amount of sodium bicarbonate from the amount of water), this will contradict the legal framework, since in the preparation of aqueous solutions the weight-volume method of production of dosage forms is assumed. If you make calculations for the preparation of a sodium bicarbonate solution in a weight concentration (that is, when determining the volume of water required for preparation, subtract the amount of sodium bicarbonate from the amount of water), this will contradict the legal framework, since the weight-volume method of production of dosage forms is adopted for the preparation of aqueous solutions. If we prepare a solution of sodium bicarbonate, which is part of the suspension, in a weight-volume concentration, according to Order No. 751n of 2015, then this will again contradict the requirements of the Order on the mass method of preparation of the suspension, since we must take 4.0 grams of sodium bicarbonate and 200 ml of purified water for its preparation (the increase in the volume of the solution in this case is not taken into account, since it is in compliance with the standard permissible deviations of the total volume of the solution), while the total mass of such a solution will be 204 grams, respectively, the weight of the suspension itself will be 210 grams. This is not consistent with the recipe and the requirements of Order No. 751n of 2015. If the prescriptions are multi-component, then the problem is even more pronounced.

Let's consider how the issue of suspension technology is solved in the near abroad countries.

Suspensions are still an actual dosage form in pharmacies in Belarus, primarily for the treatment of dermatological diseases [9]. The preparation is regulated by the pharmacopoeial monograph "Suspensions" of the State Pharmacopoeia of the Republic of Belarus. The basic rules set out in this monograph are similar to the rules set out in the Order of the Ministry of Health of the Russian Federation No. 308 of 1997 (if the content of substances is up to 3%, the suspension is prepared by mass-volume method, if 3% or more, it is prepared by weight), but along with this there are significant differences. Firstly, the regulatory framework does not prohibit the use of concentrated solutions

of pharmaceutical substance, and secondly, the use of ready-made monopreparations instead of active pharmaceutical ingredients is allowed. But – just as in the Russian Order – there are no clear recommendations on how to make calculations if the content of pharmaceutical substances exceeds 3%, and the prescription contains a solution of a pharmaceutical substance [10].

In Ukraine, the production of medicines in pharmacies is regulated by the State Pharmacopoeia of Ukraine and the Orders of the Ministry of Health, which also do not have clear recommendations on how to act in the situation that we are considering [11]. Just as in Belarus, regulatory documents do not prohibit the use of concentrated solutions in the preparation of suspensions, and in the preparation of suspensions for oral and external use, the use of ready-made medicines is allowed, if this is specified by the physician in the inscription.

In accordance with the order of the Ministry of Health of the Republic of Kazakhstan No. 142 of 15.12.2004, suspensions with the content of insoluble solid pharmaceutical substances of 3% or more are prepared by weight, the concentrated solutions of water-soluble pharmaceutical substances are not used in the preparation of suspensions. This provision fully corresponds to the requirements of the Order of the Ministry of Health of the Russian Federation No. 308 of 1997. Both Orders contain almost identical examples. There are no differences in the approaches to the preparation of suspensions. But when analysing the following prescription:

Take:	
Precipitated sulphur	7.0
Salicylic acid	2.0
Glycerin	5.0
Streptocide	3.0
Camphora	3.5
Ethyl alcohol	50.0
Boric acid solution 3%	50 ml

the authors of the regulatory document rationally approached the determination of the total mass (weight) of the dosage form: the weight of the suspension is 112.41 g, since the weight of 50 ml of 90% alcohol is 41.46 g (density – 0.829 g/ml); the weight of 37.5 ml of a 4% solution of boric acid is 37.95 g (density – 1.010 g/ml) [12].

Suspensions of compounded preparation remain a popular dosage form in pharmacies of far-abroad countries [13]. In the educational literature of the United States and Great Britain, the issues of suspension technology are discussed in detail. The main difference in the approach to their production is that all suspensions are prepared by volume. After crushing and mixing, the active ingredients are dispersed in a mortar with a small volume of the liquid phase (water or solutions of water-soluble substances), diluted with the liquid phase, transferred to a measuring vessel and brought to the desired volume with water [14,15]. The production of suspensions by this method does not provide for the need to take into account the densities of incoming solutions of various pharmaceutical substances, thus, there is no need to perform calculations to determine the total weight of the dosage form.

CONCLUSIONS

In compounded production, suspensions remain an actual and popular dosage form. Analysis of the regulatory framework of the post-Soviet states shows that their Orders were based on the Orders of the Ministry of Health of the USSR and the Russian Federation. Common approaches to the preparation of suspensions have been preserved, but the regulatory framework requires careful consideration, specification and refinement in order to adequately interpret the technology of suspensions, depending on the method of prescribing the official formula.

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