

Validation of Soothing Compounding Mixture Technological Process Preparation

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Abstract: Validation of soothing compounding mixture technological process preparation in accordance with the requirements of the quality system organization was done. It is preparing serially in many pharmacies of Ukraine. Obtained results indicate conformity of the finished medicine quality with the regulatory framework requirements of Ukraine in regard to the content of all mixture components.

Keywords: Technological Process Validation, Compounding Preparation, Soothing Mixture

1. Introduction

There was decreasing of compounding preparations (CP) volume and number of compounding pharmacies until recent times in Ukraine. Large pharmacies which manufacturing a variety of dosage forms (DF) for stock and by individual prescriptions are appearing nowadays. Therefore, more often problem of approaches to their quality monitoring is discussing.

The harmonization of national legislation of Ukraine with international and European standards is observing now. Adaptation of legislation for ensuring medicines quality in accordance with the Guidelines adopted in the European Union [1] takes place as a part of this process. In particular, this applies to the State Pharmacopoeia of Ukraine (SPhU) and a range of quality Guidelines [1]. The Pharmacopoeial Centre of Ukraine was granted observer status in the European Directorate for the Quality of Medicines in 1998, which was changed on full membership in 2013. Articles of the SPhU completely had harmonized with the European Pharmacopoeia (EP), but also contain national parts that have advisory and informational purposes. In addition, SPhU contains articles that EP is not content.

It is also applying to the section "Medicinal products

prepared in pharmacies" [2] which was entered into the second edition of the SPhU. It contains six general articles which are regulating the quality of compounding non-sterile medicines, powders, ointments and suppositories. In accordance with the requirements of the SPhU article "Non-sterile compounding medicines" their production technology should ensure compliance with general articles about DF and existing regulations. Preparation of drugs for stock should be done by the previously developed technological instructions with indicating of necessary equipment, preparation standards, quality control methods, quantitative indicators with acceptable limits, labeling, conditions of storage and shelf life. In addition, a quality requirement to the CP common article «Medicines» of the SPhU contains [3]. It stated that during their preparation is necessary to conduct a risk assessment that would identify criticalness of various parameters impact on the medicines quality (e.g., the quality of active substances and excipients, preparation process mode, stability of medicine) and a negative impact on patients' health. This statement was introduced to the second edition of SPhU for the first time.

Attention to the CP quality also the adoption of Good Pharmacy Practice basic standards, developed by International Pharmaceutical Federation and World Health Organization emphasizes [4]. It claims the quality standards of

pharmacy services, identifying four main roles of the pharmacist. Those standards with national additions introduced and successfully operated in many countries around the world [5, 6]. Minimum national standards in accordance with which pharmacists could guarantee that the CP were made by the standards of raw materials quality, equipment and handling processes should be established on basis of its recommendations [7].

The SPbU requirements to the CP quality the Order № 812 of the Ministry of Health of Ukraine "On approval of manufacture (preparation) rules and quality control of medicines in pharmacies" from 17.10.2012 complements [8]. In accordance with its requirements the CP quality for series production ensured by technological instructions with detailed description of the production process (with specific materials and equipment). For the risks assessment of the CP preparation isn't enough to describe the process only. Conducting the validation process is necessary for assessment the impact of various factors that may affect the quality of the finished product. The results allow to document the possibility of preparation such compounding medicine which will meet all quality parameters, taking into account the technological scheme of its preparation and certain equipment that will be using for it.

The aim of the study was the validation of soothing compounding mixture preparation process for confirming offinished product quality correspondence to the regulatory framework of Ukraine legislation requirements. Soothing compounding mixture is commonly found in pharmacy practice and is preparing for stock by the following prescription in compounding pharmacies of Ukraine:

Composition:

Caffeine and sodium benzoate 12,0
Magnesium sulphate 24,0
Sodium bromide 90,0
Mint tincture 30 ml
Valerian tincture 300 ml
Water purified up to 6000 ml

2. Materials and Methods

Class A glassware and analytical balances AXIS BTU 2100 were used for the research. The equipment, which were used in the preparation of medicine were calibrated in due course and had a corresponding verification certificate.

Tests were carried out on three series of product prepared in compliance with all stages of the preparation process described in the technological instruction. After preparation of the total volume of pre-packing mixture we had taken 3 bottles with following composition:

Composition:

Caffeine and sodium benzoate 0,4
Magnesium sulphate 0,8
Sodium bromide 3,0
Mint tincture 1 ml
Valerian tincture 10 ml
Water purified up to 200 ml



Figure 1. Sample of the packaged and labeled mixture.

During the analysis, we evaluated the appearance of the product and components quantitative content in the final mixture.

Procedure of sodium bromide quantitative determination [9]. To 5 ml of the mixture were added 5-7 drops of potassium chromate solution and titrated with 0.1M silver nitrate solution until solution turned orange-yellow.

1 ml of 0.1 M silver nitrate is equivalent to 10.29 mg of NaBr.

Procedure of magnesium sulphate quantitative determination [10]. To 4 ml of the mixture was added 5 ml of ammonium chloride buffer solution pH=10.0 P and about 0.02 g of a mordant black 11 triturate R. The mixture was heated to about 40°C and titrated at same temperature with 0.01 M sodium edetate solution until colour changed from violet to blue.

1 ml of 0.01 M sodium edetate is equivalent to 2.465 mg of MgSO_4 .

Procedure of caffeine and sodium benzoate quantitative determination [11]. To 5 ml of the mixture was added 1 ml of 0.1 M hydrochloric acid solution and 10 ml of diethyl ether and shook for 1 minute. The ether layer was separated and filtered through a filter Tate containing 1 g anhydrous sodium sulphate. The aqueous phase was extracted twice with 5 ml of ether. The filter Tate was washed twice with 1 ml of ether and 2 ml of purified water R and 5 drops of phenolphthalein solution was added to the ether extract. The mixture was titrated with 0.01 M sodium hydroxide solution with shaking until a slightly pink colour of the aqueous layer appeared.

0.01 ml of 1 M sodium hydroxide is equivalent to 2.375 mg of caffeine sodium benzoate.

3. Results and Discussions

The process of mixture preparation consists of six stages: preparatory works, mixture preparation, medicine quality

control, pre-packing, packing and labeling. Operations that can directly affect on the finished mixture quality were marked out for the technological process validation (Tab. 1).

Table 1. Operations of technological process which can affect on the finished mixture quality.

Stages of technological process	The parameters that should be monitored during the validation
Stage 2. Mixture preparation.	<ul style="list-style-type: none"> measuring of purified water; weighting of caffeine sodium benzoate, sodium bromide and magnesium sulfate; measuring of Valerian and Mint tinctures; bringing of mixture to the common value with purified water; quality of component mixture.
Stage 3. Quality control of the mixture.	<ul style="list-style-type: none"> description; identification; qualitative determination.
Stage 4. Packing of mixture.	<ul style="list-style-type: none"> packing of the finished product.
Stage 5. Labeling.	<ul style="list-style-type: none"> correctness of label marking.

During of the mixture preparation on the measuring accuracy of its components among the above manufacturing operations affect measuring of water, weighing of ingredients, adding tinctures and medicine packaging in bottles for distribution. Therefore, for the validation process of mixture preparation took into account equipment error, which was used to carry out these operations. Uncertainty for each individual operation has been calculated (Tab. 2).

Table 2. Calculation of critical operations uncertainty of mixture preparation.

Critical operation	The equipment for measuring/weighting	Operation uncertainty, %	Criterion, %
Measuring of purified water (twice by 2000 ml)	graduated cylinder on 2000 ml class 2 performance 1 (limit of permissible absolute error ± 20 ml)	$\Delta_v = \sqrt{1.00^2 + 1.00^2} = 1.41$	
Weighting of caffeine sodium benzoate (12 g)	balance HB-20 (permissible error of maximum load ± 20 mg)	$0.02/12 \times 100 = 0.17$	± 8
Weighting of magnesium sulfate (24 g)	balance BP-4MCJSCNTMIP (permissible error at 1/10 of maximum load ± 60 mg)	$0.06/24 \times 100 = 0.25$	± 7
Weighting of sodium bromide (90 g)	balance BP-4M CJSC NTMIP (permissible error of maximum load ± 100 mg)	$0.1/90 \times 100 = 0.11$	± 4
Measuring of Valerian tincture (300 ml)	graduated cylinder on 500 ml class 2 performance 3, (limit of permissible absolute error ± 5.0 ml)	$5/330 \times 100 = 1.52$	
Measuring of Mint tinctures (30 ml)	bottle for the reagents of SIMAX company (mark of 6000 ml was calibrated with graduated cylinder on 2000 ml class 2 performance 1)	$20/6000 \times 100 = 0.33$	$\pm 1\%$
Mixing of all components, bring by purified water (to mark 6000 ml)	graduated cylinder on 250 ml class 2 performance 3 (limit of permissible absolute error ± 2.0 ml)	$2/200 \times 100 = 1.00$	$\pm 1\%$

The total calculation of mixture preparation process error includes all values had shown in the Tab. 2.

$$\Delta_{\text{mixture preparation}} = \sqrt{1.41^2 + 0.17^2 + 0.25^2 + 0.11^2 + 1.52^2 + 0.33^2 + 1.00^2} = 2.35\% \quad (1)$$

These theoretical calculations of medicine preparation critical operations deviation value do not exceed permissible limits. Obtained results are suggesting the possibility of the mixture preparation by using the listed equipment.

Quantification of sodium benzoate, caffeine, magnesium sulfate and sodium bromide for the determining of the finished medicine quality was conducted. Volumetric titration techniques were selected for analysis, as they are available for analysis in a pharmacy. Optimum volume of aliquots for

analysis of each component of the mixture was determined.

SPhU sets limits to the CP active ingredients quantitative content within $\pm 10\%$ regardless to the component dosage and the DF type. A more stringent are the Order № 812 requirements, with whom were the results compared.

Quantitation of sodium bromide was performed by the method of Moore argentometry [9]. The results suggest accordance of sodium bromide quantitative content to the acceptable standards (Tab. 3).

Table 3. The results of sodium bromide quantitative determination.

Measurement results					Acceptability criterion
	1	2	3	Mean/its deviation	
	June 2015				
Bottle 1	2,91 g	2,89 g	2,91 g	2,90 g/3,33%	
Bottle 2	2,91 g	2,89 g	2,89 g	2,90 g/3,33%	
Bottle 3	2,91 g	2,91 g	2,91 g	2,91 g/3,00%	
	July 2015				
Bottle 1	2,89 g	2,89 g	2,91 g	2,90 g/3,33%	$\pm 4\%$ (from 2,88 g to 3,12 g)

	Measurement results				Acceptability criterion
	1	2	3	Mean/its deviation	
Bottle 2	2,91 g	2,91 g	2,89 g	2,90 g/3,33%	2,91 g/3,00%
Bottle 3	2,89 g	2,91 g	2,91 g	2,90 g/3,33%	
October 2015					
Bottle 1	2,93 g	2,91 g	2,91 g	2,92 g/2,67%	
Bottle 2	2,91 g	2,93 g	2,91 g	2,92 g/2,67%	
Bottle 3	2,93 g	2,95 g	2,93 g	2,94 g/2,00%	
Mean of sodium bromide quantity of all series/its deviation					

Magnesium sulphate was determined by complexometric titration [10]. But for account of magnesium, which may be part of purified water a control experiment was carried out (Tab. 4).

Table 4. The results of magnesium sulphate quantitative determination.

	Measurement results				Acceptability criterion
	1	2	3	Mean/its deviation	
	June 2015				± 7% (from 0,744 gto 0,856 g)
Bottle 1	0,80 g	0,80 g	0,79 g	0,80 g/0%	
Bottle 2	0,79 g	0,79 g	0,79 g	0,79 g/1,25%	
Bottle 3	0,81 g	0,80 g	0,81 g	0,81 g/1,25%	
	July 2015				
Bottle 1	0,77 g	0,78 g	0,77 g	0,77 g/3,75%	
Bottle 2	0,78 g	0,78 g	0,79 g	0,78 g/2,50%	
Bottle 3	0,79 g	0,79 g	0,79 g	0,79 g/1,25%	
	October 2015				
Bottle 1	0,78 g	0,78 g	0,78 g	0,78 g/2,50%	
Bottle 2	0,78 g	0,78 g	0,78 g	0,78 g/2,50%	
Bottle 3	0,79 g	0,79 g	0,79 g	0,79 g/1,25%	
Mean of magnesium sulphate quantity of all series/its deviation					0,79 g/1,25%

Comparison of the results with the requirements is showing accordance of magnesium sulphate content to the regulatory framework requirements.

Caffeine and sodium benzoate determined by benzoic acid after reaction with hydrochloric acid in the presence of ether [9] (Tab. 5).

Table 5. The results of caffeine and sodium benzoate quantitative determination.

	Measurement results				Acceptability criterion
	1	2	3	Mean/its deviation	
	June 2015				
Bottle 1	0,43 g	0,42 g	0,43 g	0,43 g/6,67%	
Bottle 2	0,42 g	0,42 g	0,42 g	0,42 g/5,00%	
Bottle 3	0,42 g	0,43 g	0,43 g	0,43 g/6,67%	
	July 2015				
Bottle 1	0,42 g	0,41 g	0,41 g	0,41 g/2,50%	± 8% (from 0,368 g to 0,432 g)
Bottle 2	0,41 g	0,41 g	0,41 g	0,41 g/2,50%	
Bottle 3	0,41 g	0,41 g	0,41 g	0,41 g/2,50%	
	October 2015				
Bottle 1	0,41 g	0,40 r	0,41 g	0,41 g/2,50%	
Bottle 2	0,40 g	0,41 g	0,40 g	0,40 g/0%	
Bottle 3	0,40 g	0,40 g	0,40 g	0,40 g/0%	
Mean of caffeine and sodium benzoate quantity of all series/its deviation					0,41 g/2,50%

The caffeine and sodium benzoate content is also complying with the above norm.

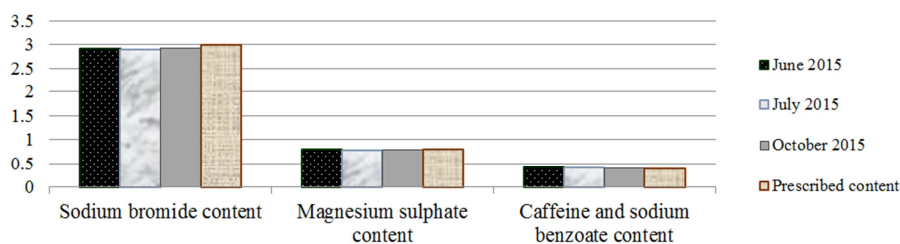


Figure 2. Mean of quantity each component of mixture.

4. Conclusions

- 1 The results of technological process validation of soothing mixture preparation confirm that the documented process for obtaining medicine allows to guarantee receiving a high quality finished product that meets the requirements of SPhU and the Order № 812 of the Ministry of Health of Ukraine.
- 2 The process of soothing mixture preparation is stable and reproducible, as indicated by the results of three different series of studies made at different times.

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