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Original Article

Pharmacopaine aspects of extemporaneous technology of soft medicines and suppositories

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ABSTRACT

It is known that the preparation of extemporaneous medicines is strictly regulated by the provisions of Good Pharmacy Practice (GPP). Particular attention in the rules of GPP is given to ensuring the quality of dosage forms manufactured in pharmacies. In Ukraine, pharmacopoeial requirements for extemporaneous soft medicines and suppositories are set forth in the general pharmacopoeial articles of State Pharmacopoeia of Ukraine of the 2nd edition (volume 3). In this article, the authors present an analysis of the pharmacopoeia requirements for the indicated dosage forms, which showed that many pharmacopeias of developed countries have common pharmacopeia articles on soft medicines and suppositories. The requirements for these dosage forms are largely similar and do not have significant differences.

Keywords: Pharmacopoeia, technology, soft medicines, suppositories

Introduction

Despite the significant range of ready-made medicines, the preparation of extemporaneous medicines according to individual prescriptions does not lose its relevance today. Not all medicines can be obtained under industrial conditions; there are a considerable number of medicines that can only be prepared in a pharmacy. In addition, many patients need an individual approach to the choice of dose and composition of the medicine, taking into account their age, body weight, individual reactions, etc. [1, 2].

The preparation of medicines in a pharmacy is regulated by the provisions of Good Pharmacy Practice (c), the fundamental ideology of which is to provide patients with medicines, medical supplies, medical services, that is, to provide assistance to people and society as a whole with the greatest efficiency.

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To follow the GPP ideology means to carry out activities aimed at preventing the deterioration of the health of the population, achieving the maximum therapeutic benefit of medicines, minimizing their side effects, etc. But the main thing is the confirmation by the pharmaceutical industry of the share of responsibility for the result of treatment together with other health workers and patients.

The conditions for the implementation of GPP in different countries of the world have their own national characteristics. The fundamental role of this document is to initiate the establishment of standards in each country, taking into account national circumstances. Particular attention in the rules of GPP is given to ensuring the quality of dosage forms manufactured in pharmacies. Each country establishes a legal system to ensure compliance with good pharmacy practice [3].

The formation in Ukraine of a modern legislative framework for health care began in the 1990s when a number of laws were passed: "On Medicines", "On the Sanitary and Epidemiological Well-Being of the Population", "On Narcotic Drugs, Psychotropic Substances and Precursors". In recent years, a number of changes and additions have been made to existing laws in accordance with existing modern requirements.

In the early 2000s, a number of orders of the Ministry of Health of Ukraine were developed, which took into account the rich

experience of domestic pharmacy. The 1st (2001) and 2nd (2014) editions of State Pharmacopoeia of Ukraine, as well as additions to them, which are harmonized with European legislation, have been published. Today, work is actively continuing in the direction of improving the regulatory framework, including with regard to the pharmacy-based technology of medicines.

The objective of the work :

To study the pharmacopeia aspects of extemporaneous medicines technology by the example of soft medicines and suppositories.

Materials and Methods:

A comparative analysis of pharmacopeia requirements was carried out by the empirical method using information materials, in particular, pharmacopeia, literature data, and materials of our own research.

Results and Discussion:

The analysis of pharmacopeia requirements for extemporaneous soft dosage forms and suppositories was carried out using the corresponding general articles of State Pharmacopoeia of the Republic of Belarus (2009, 2013) and US Pharmacopoeia (2009, 2014), since these publications contain the most significant reference material for the indicated issue.

So, Volume III of State Pharmacopoeia of the Republic of Belarus "Quality Control of Pharmaceutical Substances" contains the section "Extemporaneous Medicines" (69 pages) [4].

This section includes information on the preparation of liquid, solid and soft dosage forms in pharmacies, as well as information on the express analysis of extemporaneous medicines and their quality assessment.

In paragraph 6.1.3 "Soft medicines" of State Pharmacopoeia of the Republic of Belarus (volume III), definitions of liniment and ointments, their classification and some prescription formulations are given. In addition, the rules for the introduction of active substances in the composition of ointments are indicated.

It is worth noting that this section also contains information on the preparation of eye ointments and ointments with antibiotics that are made under aseptic conditions. In a separate section of the preparation of sterile and aseptic medicines is not made.

Section 6.1.2 "Solid Medicines" provides brief information on the aspects of rectal suppository technology in pharmacies. The values of mass, the form of suppositories, a list of suppository bases and the rules for the introduction of active substances into them are presented. There is no information regarding the preparation of the pessaries.

"USP Pharmacist's Pharmacopoeia" contains the section "Information on the preparation of drugs in pharmacies". This section provides information on the preparation of ointments, pastes, creams, gels, suppositories and other extemporaneous dosage forms [5, 6].

The article "Bases of the preparation of ointments and pastes" contains information regarding their purpose and characteristics, aspects of technology, indicating the order of introduction of medicinal substances into ointment bases, and manual and mechanical methods for preparing ointments. Data on the stability, packaging and storage of these dosage forms are also provided.

In addition, the article presents the official prescriptions of some ointment bases (Table 1).

Table 1: Official prescriptions of ointment bases according to USP Pharmacist's Pharmacopoeia

The name of the ointment base	The composition of the ointment base	
White ointment, USP	White wax	50.0
	White petrolatum	950.0
Hydrophilic petrolatum, USP	Cholesterol	30.0
	Stearyl alcohol	30.0
	White wax	80.0
	White petrolatum	860.0
PEG base, NF	PEG 3350	400.0
	PEG 400	600.0

A separate subsection to the text of the article "Bases of the preparation of ointments and pastes" provides general requirements for their technological process. So, it is noted that when using powdered solid medicinal substances, it is necessary to grind them to the smallest particle size before being introduced into the ointment base, which is due to the possibility of improperly crushed particles to damage the skin and slow down the process of its regeneration. The list of auxiliary liquids with the help of which it is recommended to carry out the indicated technological operation is presented.

USP Pharmacist's Pharmacopoeia article, "Bases of Creams and Lotions", provides definitions for these dosage forms. Particular attention is paid to the definition and description of the emulsification process.

It provides information on the manual and mechanical method of preparing creams. The list of equipment is presented, which is represented by a mortar and pestle, an electric mixer, a manual homogenizer, etc. Information is also given on the introduction of medicinal substances into creams, depending on the type of emulsion system being created.

In addition, this article of the US Pharmacopoeia contains purely theoretical information on the theory of the formation of emulsions, the use of hydrophilic-lipophilic balance (HLB) values of emulsifiers. It should be noted that the text of the article provides information on the HLB of a sufficiently large number of emulsifiers (Table 2). Unfortunately, in the domestic literature information on this issue is not covered so widely, which significantly limits the possibility of using many emulsifiers in practical work.

Table 2: The value of HLB of emulsifiers by USP Pharmacist's Pharmacopoeia

Trade name	Chemical name	HLB value
1	2	3
Acacia	Acacia	12.0
Arlacel 83	Sorbitan sesquioleate	3.7
Bryj 30	Polyoxyethylene lauryl ether	9.7
Glyceryl monostearate	Polyoxyethylene lauryl ether	3.8
Methocel 15 cps	Methyl cellulose	10.5
Myrj 45	Polyoxyethylene monostearate	11.1
Myrj 49	Polyoxyethylene monostearate	15.0
Myrj 52	Polyoxyl 40 stearate	16.9
PEG 400 monooleate	Polyoxyethylene monooleate	11.4
PEG 400 monostearate	Polyoxyethylene monostearate	11.6
PEG 400 monolaurate	Polyoxyethylene monolaurate	13.1
Farmagel B	Gelatin	9.8
Potassium oleate	Potassium oleate	20.0
Sodium lauryl sulfate	Sodium lauryl sulfate	40.0
Sodium oleate	Sodium oleate	18.0
Spen 20	Sorbitan monolaurate	8.6
Spen 40	Sorbitan monopalmitate	6.7
Spen 60	Sorbitan monostearate	4.7
Spen 65	Sorbitan tristearate	2.1
1	2	3
Spen 80	Sorbitan monooleate	4.3
Spen 85	Sorbitan trioleate	13.2
Tragacanth	Tragacanth	13.2
Triethanolamine oleate	Triethanolamine oleate	12.0
Polysorbate 20	Polyoxyethylene sorbitan monolaurate	16.7
Polysorbate 21	Polyoxyethylene sorbitan monolaurate	13.3
Polysorbate 40	Polyoxyethylene sorbitan monopalmitate	15.6
Polysorbate 60	Polyoxyethylene sorbitan monostearate	14.9
Polysorbate 61	Polyoxyethylene sorbitan monostearate	9.6
Polysorbate 65	Polyoxyethylene sorbitan tristearate	10.5
Polysorbate 80	Polyoxyethylene sorbitan monooleate	15.0
Polysorbate 81	Polyoxyethylene sorbitan monooleate	10.0
Polysorbate 85	Polyoxyethylene sorbitan trioleate	11.0
-	Diethylene glycol monolaurate	6.1
-	Pluronic 68	17.0
-	Propylene glycol monostearate	3.4
-	Sucrose dioleate	7.1

In our opinion, the information on the HLB values of some excipients that can be used in the technology of pharmaceutical emulsions, creams, emulsion and combined ointments is also very interesting and necessary (Table 3).

Table 3: HLB values of some excipients by USP Pharmacist's Pharmacopoeia

Name of excipient	The value of HLB depending on the type of emulsion	
	w/o	o/w
1	2	3
Beeswax	4	9-12
Carbon tetrachloride	-	16
Carnauba wax	12	-
Castor oil	6	14
Cetyl alcohol	-	15
Cottonseed oil	5	6-10
Kerosene	-	14
Anhydrous lanolin	8	10-12
Lauryl acid	-	15-16
Lauryl alcohol	-	14
Methyl silicone	-	11
Mineral oil	5	11-12
1	2	3
Oleic acid	-	17
Olive oil	6	14
Paraffin	4	10-11
Petroleum	5	7-12
Stearic acid	6	15
Stearic alcohol	-	14

Special attention is paid to the prevention of microbial contamination of emulsion systems, their quality control and stability studies. The general requirements for creams are also presented: ensuring viscosity, observing the order of administration of medicinal substances, the correctness of the technological process, in particular mixing the components of the emulsion (emulsification).

The following article of USP Pharmacist's Pharmacopoeia devoted to the preparation of extemporaneous soft medicines, "Bases of the preparation of gels" contains the definition, characteristics of this dosage form, the classification of gels with their description and examples (Table 4).

Table 4: General classification and description of gels by USP Pharmacist's Pharmacopoeia

Class	Description	Examples
Inorganic gels	Usually biphasic systems	Aluminum hydroxide gel, bentonite
Organic gels	Usually monophasic systems	Carbopol, tragacanth
Hydrogels	Contain water	Bentonite, pectin, sodium alginate, methyl cellulose

Organogels	Hydrocarbon	Vaseline, mineral oil mixed with PEG
	Animal/vegetable fats, soaps	Cacao butter, aluminum stearate mixed with mineral oil PEG
	Hydrophilic organogels	

The text of the article provides very detailed modern information on gelling agents that can be used in the preparation of gels in pharmacies. Reference information on the values of viscosity and the scope of application of various grades of carbomer (carbopol) is very useful, which can greatly facilitate the choice for a practical worker (Table 5).

Table 5: Typical properties of some carbopol brands by USP Pharmacist's Pharmacopoeia

The product's name	Viscosity *	Properties and application
Carbopol 910, NF	3.000 – 7.000 centipoise	Used in low concentrations
Carbopol 934, NF Carbopol 934 P, NF Carbopol 974 P, NF	30.500 – 39.400 centipoise 29.400 – 39.400 centipoise 29.400 – 39.400 centipoise	Stable, high viscosity gelling agents that are used in the technology of high-viscosity gels, emulsions and suspensions for internal use, as well as in dermatology and dentistry
Carbopol 940, NF	40.000 – 60.000 centipoise	Gelling agent forming clear aqueous or alcohol gels for external use
Carbopol 941, NF Carbopol 981, NF	4.000 – 11.000 centipoise 4.000 – 11.000 centipoise	Forms low viscosity, clear gels; used as a stabilizer in suspension technology

Notes: * typical viscosity of 0.5 % solutions at pH = 7.5

In the section "Preparation/technology of gels" provides information on how to prepare gels in pharmacies. The information on the physical and chemical properties of excipients used in the technological process of producing gels is given. In addition, the text provides official formulations of gel bases with an indication of their technology.

As for the state pharmacopoeial requirements for soft dosage forms, it should be noted that until 2014 on the pages of State Pharmacopoeia of Ukraine (SPU) they were presented only for medicines manufactured under industrial conditions.

In 2014, the General Pharmacopoeia article "Soft medicines made in pharmacies" was included in the SPU of the 2nd edition (volume 3). This article is composed of the following sections: "General requirements", "Definition", "Preparation", "Packaging, labelling, quality control, storage". Features of the technology of extemporal ointments are set out in accordance with their dispersological classification. The proposed general requirements and methods for preparing these extemporaneous soft medicines correspond to existing regulatory documents approved by the Ministry of Health of Ukraine [7].

As for the general pharmacopeia article on rectal medicines, it is included in SPU and a number of foreign pharmacopeias. The International Pharmacopoeia (IntPh), Japanese (JPh), American (USP) and Pharmacopoeia of the Russian Federation (RPh) in the general pharmacopeia article entitled "Suppositories" consider both rectal and vaginal suppositories.

SPU, European Pharmacopoeia (EuPh), British Pharmacopoeia (BPh) and the Pharmacopoeia of the Republic of Belarus (BelPh) highlight the general pharmacopeia article "Medicines for rectal administration", which includes, in addition to suppositories, rectal capsules, solutions, emulsions and suspensions; powders and tablets for the preparation of rectal solutions and suspensions; soft dosage forms for rectal administration; rectal foams and tampons.

In addition, SPU 2nd edition (2014, volume 3) includes a general pharmacopeia article on the preparation of suppositories and pessaries in pharmacies.

All pharmacopeias define suppositories as solid dosage forms for administration into the rectal cavity, which melt or dissolve at body temperature. In SPU, EuPh, IntPh, BPh and BelPh definitions of other rectal dosage forms are also given.

Suppositories can be prepared on hydrophobic (cocoa butter, hard fat, hydrogenated fats), hydrophilic (macrogols, gelatin-glycerin gels) and other bases approved for use. In the section "Excipients" of SPU and a number of foreign pharmacopeias, the names of the groups of substances by their purpose (adsorbents, preservatives, dyes, solvents, etc.) that can be used in the preparation of suppositories are listed. At the same time, in the Russian Federation of the XI-th edition in a similar section, specific names of substances are given, which, in our opinion, may complicate the use of new ingredients (Table 6).

It is known that the convenience of using suppositories is to some extent provided by their shape. Specific suppository forms (conical, elongated, spindle-shaped) are indicated in IntPh, JPh, USP and RPh, while in SPU, EuPh, BPh and BelPh, only the correspondence of shape and size to rectal administration is discussed [4-10].

The mass of suppositories is regulated by BelPh, USP and RPh of the XI-th edition.

The main method of manufacturing suppositories is the pouring of the molten mass into an appropriate form with its subsequent cooling and solidification, as well as the pressing method. The pumping method is mentioned in USP, RPh and BelPh.

According to SPU, EuPh, IntPh, BPh and BelPh, when preparing suppositories containing dispersed particles of active substances, it is necessary to take measures to ensure a certain particle size and its control.

Since suppositories are a dosage form, they are required to determine the average weight. Tolerances of suppositories of average weight, according to SPU, EuPh, IntPh, RPh and BPh, are ± 5 %.

In this case, the mass of no more than two of the 20 samples taken for testing may differ by no more than ± 10 %, and in the RPh of the XI edition - not more than ± 7.5 %.

According to SPU, IntPh, EuPh, BPh, BelPh, JPh, tests are not carried out if the requirement for determining the uniformity of the content of active substances is advanced to suppositories.

Table 6: Requirements of pharmacopeias of different countries for rectal suppositories

Index	SPU	IntPh	RPh	EuPh, BPh, BelPh	USP	JPh
Suppository bases	solid fat, macrogols, cocoa butter, various gelling mixtures containing gelatin, water and glycerin	cocoa butter, hard fat, vegetable fats, macrogol	cocoa butter and its alloys, solid fat, PEO alloys, etc.	cocoa butter, hard fat, macrogol	cocoa butter, vegetable fats, esters of fatty acids and PEG, PEG mixtures	approved for use
Excipients	thinners, adsorbents, surfactants and lubricants, antimicrobial preservatives, preservatives	adsorbents, surfactants, preservatives, dyes, antioxidants, etc.	butyloxytoluene, butyloxyanisole, citric acid, emulsifiers No. 1, T-1, T-2, polysorbate-80, wool wax alcohols, aerosil, etc.	adsorbents, surfactants, preservatives, dyes, solvents, etc.	approved for use	
Form of suppositories	must comply with rectal administration	elongated	cone, cylinder, another shape with a diameter of 1.5 cm	must comply with rectal administration	cone	cone or spindle-shaped
Mass, g		not regulated	1.0-4.0; children's – 0.5-1.5		2.0	not regulated
Homogeneity	regulated		not regulated			
Melting temperature	given in separate articles	not regulated	≤ 37 °C	not regulated		
Time of deformation/dissolution, min		not regulated	15/60	given in separate articles	not regulated	
Disintegration, min.	30 - lipophilic, 60 - hydrophilic	not regulated				
Average weight, deviation in %	≤ ± 5				given in separate articles	≤ ± 15, not one – ± 25

The deviation in the content of active substances may be within ± 15 % of what is indicated on the package. According to SPU, IntPh, EuPh, BPh, BelPh, JPh, this test is carried out for suppositories with the content of active substances less than 2 mg, constituting less than 2 % of the total mass of the sample. 30 suppositories are selected for testing. If the deviation of the content of active substances in the first 10 samples is exceeded by more than ± 15 %, the following 20 samples are analyzed. The requirement is satisfied if the final value for 30 samples does not exceed ± 15 % and none of them differs by more than ± 15 %.

Pharmacopoeias, including SPU, classify rectal medicines of microbiological purity as Category III and have the same requirements for the total number of aerobic bacteria and yeast colonies in 1 g/ml of the dosage form. The absence of *E. coli* in 1 g/ml is not regulated only by JPh.

Unlike other pharmacopeias, except RPh, SPU contains a requirement for homogeneity in appearance, which is determined visually by the absence of inclusions on the longitudinal section of the candle; air rod or funnel-shaped recess is allowed. As defined in the IntPh, suppositories should be smooth, have a uniform mass and appearance.

For lipophilic suppositories, the melting temperature is regulated, which should not exceed 37 °C, and the deformation time is not more than 15 minutes. Hydrophilic suppositories should be dissolved in water within 1 hour. The deformation time and/or resistance of the suppositories to destruction is determined in SPU, EuPh, BPh and BelPh. The disintegration test of suppositories not intended for the modified release of substances allows one to determine whether the samples placed in a liquid medium disintegrate within a specified time of 30 or 60 minutes depending on the type of base.

By the release of substances, preliminary information on their bioavailability can be obtained. Evaluation of the release of active substances from suppositories by the "Dissolution" test is recommended to be carried out by SPU, EuPh, BPh and BelPh, as well as USP for suppositories with indomethacin. The tests are carried out on the devices "rotating basket", "paddle mixer", "flow cell" used for solid oral dosage forms. In the absence of instructions for 45 minutes, not less than 75 % and not more than 115 % of the active substance of the amount specified in the "Composition" section must pass into the dissolution medium.

The primary packaging for suppositories should be made from approved materials, thus protecting the preparations from environmental influences. According to IntPh, secondary packaging must be in accordance with Good Manufacturing Practices (GMP).

By BPh, contain the name and concentration of medicinal substances, information about the expiration date and storage conditions, as well as the name of the added preservatives. RPh of XI-th edition and SP regulate that the secondary packaging of suppositories made on the basis of PEO should indicate the need for their moistening before use in connection with the antiphysiological exosmosis of this base.

According to USP, suppositories based on cocoa butter should be stored at a temperature below 30 °C, on the basis of PEG - below 2 °C. According to SPU, suppositories are stored in a cool, dry place.

Thus, the analysis showed that many pharmacopeias of developed countries of the world have common pharmacopeia articles on soft medicines and suppositories. The requirements for these

dosage forms are largely similar and do not have significant differences.

Conclusions

Pharmacopoeia aspects of extemporal technology of soft medicines and suppositories were studied.
It is shown that many pharmacopoeias of developed countries have common pharmacopoeial articles on these dosage forms. The requirements for them are largely similar and do not have significant differences.

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