JUSTIFICATION OF SURFACE-ACTIVE SUBSTANCES CHOICE IN COMPOSITION OF SUPPOSITORIES FOR TREATMENT OF PROSTATE GLAND BENIGN DISEASES

V. S. Zaychenko, O. A. Ruban, Ju. S. Masliy, N. A. Gerbina
National University of Pharmacy

Introduction. Prevention and treatment of benign prostatic diseases remain one of the pressing problems of modern medicine. Rectal suppositories are one of the main dosage forms used in urological practice. In order to provide the necessary organoleptic, physico-chemical, technological and osmotic properties, into their composition surfactants are introduced.

The aim of this work was to select the optimal surfactant and to substantiate its concentration in the suppositories with indole-3-carbinol and meloxicam.

Materials and methods. As the research objects have been selected: the carrier – PEO-base, emulsifiers – Montanox 80, Lanette SX, Cremophor RH-40, Myverol 18-04K NF, soy lecithin. The investigation of organoleptic (appearance, absence of inclusions and stratifications, homogeneity at the cut), physico-chemical (pH, time of decomposition), technological (resistance to destruction) and osmotic (dialysis through a semipermeable membrane) properties of the suppositories by the methods of SPU has been performed.

Results and discussion. Model specimens of suppositories with Montanox 80, Lanette SX and soy lecithin comply with the requirements of the SPU for all quality indices. In order to reduce the osmotic activity of the developed suppositories, the addition of Montanox 80 emulsifier in the amount of 3% was found to be most appropriate, which would not result in dehydration and overdrying of the rectum mucosa.

Conclusions. Experimental researches have established that the optimal surfactant in the composition of the suppositories with indole-3-carbinol and meloxicam, which provides the necessary qualitative characteristics and reduces the hyperosmotic properties of the polyethylene oxide base, is Montanox 80 in the amount of 3%.

Key words: benign diseases of prostate gland; rectal suppositories; PEO-base; surface-active substances; organoleptic; physico-chemical and technological properties; osmotic activity.
INTRODUCTION

The growth of benign prostatic diseases among men over 30 years is a serious problem, the solution of which depends on the availability and implementation of modern medical products in the medical practice [1-3]. It is known that the result of treatment depends not only on the correctly chosen medicinal product, but also on the way of its administration. Many clinicians prefer rectal administration, noting its positive aspects such as: increasing the speed of absorption and local effect of drugs on inflammation, prolonged therapeutic effect, reduced levels of side effects, the possibility of combination of several drugs, etc. [4-6]. In this regard, the aim of our research was to develop the composition and technology of rectal suppositories containing as API’s indole-3-carbinol and meloxicam [7].

The main step in creating a new dosage form is the choice of pharmaceutical factors, since by their regulation it is possible to change the pharmacokinetic parameters, biological availability and pharmacological effect [8].

As is known, the properties of drugs in the form of suppositories are most affected by the presence in their composition of surface-active substances (surfactants). According to literature, they can exacerbate, diminish or stabilise hyperosmotic properties of suppositories. Therefore, the following indices were assessed: organoleptic properties of suppositories; physical and chemical (pH, time of decomposition) and technological (resistance to destruction) properties of suppositories was carried out by dialysis through a semipermeable membrane with subsequent determination of the mass of the sample at regular intervals of time for 7 hours [13-14].

RESULTS AND DISCUSSION

In order to select the optimal emulsifier, suppositories were made on a polyethylene oxide basis, which was selected on the basis of previous pharmacological studies, with the addition of various surfactants: Montanox 80 (polysorbate-80), Lanette SX (emulsifier No. 1), Cremophor RH-40 (PEG-40 hydrogenated castor oil), Myverol 18-04 K NF (distilled monoglycerides) and soy lecithin [5].

Suppositories were prepared by pouring. Subsequently, the following indices were assessed: organoleptic (appearance, absence of inclusions and stratifications, homogeneity at the cut), physical and chemical (pH, time of decomposition) and technological (resistance to destruction). The study of model samples of suppositories was carried out in accordance with the SPU according to standard methods [12].

The study of surfactants influence on the osmotic properties of suppositories was carried out by dialysis through a semipermeable membrane with subsequent determination of the mass of the sample at regular intervals of time for 7 hours [13-14].

MATERIALS AND METHODS

The following objects were selected for research: the suppository base – an alloy of polyethylene oxides with a molecular weight of 400 and 1500; surfactants – Montanox 80 (Seppic, USA), Lanette SX (Basf, Germany), Cremophor RH-40 (Basf Personal Care and Nutrition GmbH, Germany), Myverol 18-04 K NF (Kerry Group, Malaysia) and soy lecithin (Kanav Aronomy, India).

Suppositories that contained Cremophor emulsifier RH-40 also did not meet the requirements in appearance and time of disintegration. Thus, for further research, model suppository samples with Montanox 80, Lanette SX and soy lecithin have been chosen.

An important specific indicator that characterizes certain properties of drugs in the form of suppositories for
the treatment of benign prostatic diseases is their osmotic activity. It should be noted that the value of this indicator depends mainly on the type of suppository base and, if necessary, can be corrected by the addition of a surfactant [13].

It is known that one of the disadvantages of the polyethylene oxide base is its high osmotic activity, which can lead to dehydration of cells at contact of the base with the affected inflammatory sites [14-15]. The hydrophilic part of a surfactant is capable of forming hydrogen bonds to the active centers of polyethylene oxide, and with its long lipophilic “tail” shield a part of its hydroxyl groups, thereby blocking access of water molecules to them. This is what causes the decrease of the PEO-base osmotic activity.

Therefore, the next step in our work was the final selection of surfactant and determination of its amount in order to reduce the hyperosmotic properties of the suppository base.

When choosing a surfactant, samples of suppositories without and with the addition of such emulsifiers as Montanox 80, Lanette SX and soy lecithin at a concentration of 3% were studied.

The study of osmotic activity was carried out by dialysis through a semipermeable membrane with the following determination of the weight of the sample at equal intervals of time for 7 hours. The research results are shown in Fig. 1.

The conducted studies have shown (Fig. 1) that the smallest osmotic activity has a sample with Montanox 80 –

---

**Table**

| Name of surfactant | Appearance                                                                 | Quality indices                          |
|--------------------|---------------------------------------------------------------------------|-----------------------------------------|
|                    |                                                                           | Average weight, g | pH of aqueous solution | Time of disintegration, min | Resistance to destruction, kg |
| Montanox 80        | Suppositories of torpedo shape, homogeneous, light yellow, with a weak specific odor. No inclusions are observed on the cut | $2.95 \pm 0.03$ | $6.58 \pm 0.04$ | $43 \pm 3$ | $3.0 \pm 0.1$ |
| Lanette SX         | Suppositories of torpedo shape, homogeneous, light yellow, with a weak specific odor. No inclusions are observed on the cut | $2.96 \pm 0.03$ | $6.55 \pm 0.05$ | $45 \pm 2.5$ | $3.2 \pm 0.1$ |
| Cremophor RH-40    | Suppositories of torpedo shape, light yellow, with a weak specific odor. On the cut inclusions are observed | $2.99 \pm 0.04$ | $6.74 \pm 0.04$ | $62 \pm 3$ | $3.5 \pm 0.1$ |
| Myverol 18-04K NF  | Suppositories of torpedo shape, light yellow, without a specific odor. Heterogeneous | $3.05 \pm 0.03$ | $7.08 \pm 0.06$ | $52 \pm 3$ | $3.1 \pm 0.1$ |
| Soy lecithin       | Suppositories of torpedo shape, homogeneous glossy, light yellow, with a weak specific odor. There are no inclusions on the cut | $3.06 \pm 0.04$ | $6.25 \pm 0.05$ | $44 \pm 3$ | $3.05 \pm 0.1$ |

Note. $n = 5; P = 95\%$.
The amount of absorbed fluid was 215 % for 7 hours of research. The amount of absorbed liquid in samples with other surfactants (Lanette SX, soy lecithin) and without emulsifiers was within the range of 225-285 %.

Thus, on the basis of the conducted studies it can be concluded that to reduce the hyperosmotic properties of the polyethylene oxide base, it is most appropriate to add emulsifier Montanox 80.

The next step in our research was to find the optimal concentration of Montanox 80 needed to reduce the osmotic activity of suppositories. To do this, samples were prepared with the addition of 1, 3, 5 and 7 % Montanox 80 to the PEO-base. The results are presented in Fig. 2.

The results of the study have shown (Fig. 2) that the addition of Montanox 80 at a concentration of 1 % did not significantly reduce the osmotic activity – the total amount of absorbed water for 7 hours of the experiment was 195 %. Adding Montanox 80 at concentrations of 3 % and 5 % provided absorption of water at almost the same level – 215 % and 230 % respectively. Addition of Montanox 80 at a concentration of 7 % proved to be inappropriate as it resulted in loss of mechanical stability of suppositories.

CONCLUSIONS
1. The analysis of scientific literature has established the importance of developing a domestic medicinal product in the form of rectal suppositories for the treatment of benign prostatic diseases.
2. It has been established that one of the most important issues in the creation of suppositories on the PEO-base is the choice of emulsifiers in their composition, as which Montanox 80, Lanette SX, Cremophor RH-40, Myverol 18-04K NF and soy lecithin have been used.
3. The influence of surface-active substances on the organoleptic, physical-chemical, technological and osmotic properties of model samples of suppositories has been studied.
4. Based on the data obtained, as a surfactant Montanox 80 was chosen in a concentration of 3 %, which allowed obtaining the most aggregately stable systems and provided the necessary osmotic activity for the suppositories being developed.

Conflict of Interests: authors have no conflict of interests to declare.

REFERENCES
1. Болезни предстательной железы / ред. Ю. Г. Аляев. – М. : ГЭОТАР-Медиа, 2009. – 240 с.
2. Haverkamp, J. Prostate inflammation and its potential impact on prostate cancer : a current review / J. Haverkamp, B. Charbonneau, T. L. Ratliff // J. Cell. Biochem. – 2008. – Vol. 103, Issue 5. – P. 1344–1353. doi: 10.1002/jcb.21536
3. Филиппович, В. А. Доброкачественная гиперплазия предстательной железы : современный подход к медикаментозной терапии / В. А. Филиппович // Журн. Гродненского гос. мед. университета. – 2008. – № 1. – С. 93–101.
4. Проблемы создания и стандартизации суппозиториев на современном этапе / Т. А. Панкурушен, Л. Н. Брофеева, Т. В. Орлова и др. // Курский научно-практический вестник «Человек и его здоровье». – 2016. – № 2. – С. 108–112.
1. Aliyev, Yu. G. (2009). Bolezn EI predstavnEl Ehelezey, 240.
2. Haverkamp, J., Charbonneau, B., Ratliff, T. L. (2008). Prostate inflammation and its potential impact on prostate cancer: A current review. Journal of Cellular Biochemistry, 103 (5), 1344–1353. doi:10.1002/jcb.21536
3. Filippovich, V. A. (2009). Zhirnial Grodzenskogo gosudarstvennogo meditsinskogo universitetas, 1, 93–101.
4. Pankrushina, T. A., Erskov, L. N., Orlova, T. V., Kurlina, O. O., Chekmareva, M. S. (2016). Karazi naukho–practichekii vestnik "Cholevek i ego zdorove", 2, 108–112.
5. Dziuba, A. S., Trofimova, E. O. (2014). Farmatciia, 3, 27–30.
6. Orlova, T. V. (2014). Vestnik Voronezhskogo gosudarstvennogo universiteta. Seria : Khimiia. Biologiia. Farmatciia, 1, 126–133.
7. Zaichenko, V. S., Ruban, O. A., Madil, Ju. S., Gerbina, N. A. (2017). Journal of Pharmaceutical Ingredients Administration at the Development of Suppositories for the Treatment of Benign Prostate Gland Diseases. Asian Journal of Pharmacology, 11 (2), 129–134.
8. Bykovskiy, S. N. et al. (2015). Farmatsevticheskaya razrabotka. Moscow: Perou, 472.
9. Abramovich, R. A., Vorobev, A. A., Elagina, I. A., Sinitsyna, N. I. (2012). Nauchnye vedomosti Belgorodskogo gosudarstvennogo universiteta. Seria: Farmaciia, 10, 27–30.
10. Zorro, M. Dal, Franceschinis, E., Punchina, A., Realdon, N. (2012). Effect of the surfactant on the availability of piroxicam as a poorly hydrosoluble drug from suppositories. Pharmazie, 1, 37–45.
11. Orlova, T. V., Pankrushina, T. A. (2013). Vopomogatelnye vezhchestva v tehnologii suppositoriyi i naukho–metodicheskie podkhody k dush yishlyu, 160.
12. Gerdes, A. (2012). Derzhavna Farmakopeia Ukrainy : v 3 t. / Derzhavno priberezenne gosudarstvenno gosudarstvennogo medicinskih institutia, 3, 101–104.
13. Tootou, E. New hydrophilic vehicles enabling rectal and vaginal absorption / E. Tootou, M. Dombrv, A. Ezz / Drug Delivery. – 2005. – Vol. 1. – P. 399–407.
14. Dzuban, A. S., Trofimova, E. O. (2014). Farmatciia, 3, 27–30.
15. Orlova, T. V. (2014). Vestnik Voronezhskogo gosudarstvennogo universiteta. Seria : Khimiia. Biologiia. Farmatciia, 1, 37–45.
16. Abramovich, R. A., Vorobev, A. A., Elagina, I. A., Sinitsyna, N. I. (2012). Nauchnye vedomosti Belgorodskogo gosudarstvennogo universiteta. Seria: Farmaciia, 10, 27–30.
17. Zaitchenko, O. A., Ruban, Ju. S., Maslii, N. A. Gerbina / Asian J. of Pharmac. – 2017. – Vol. 11, Issue 2. – P. 129–134.
18. Farmatsevticheskaya razrabotka : konceptsiia i prakticheskie rekomendatsii. Nauchno–prakticheskoe rukovodstvo dlia farmatsevtov. – Moscow, 2015. – 472 s.
19. Romanina, D. M., Gladyshev, V. V., Lisianskaia, A. P., Chekmareva, M. S. (2016). Aktualni pytannia farmatsevtychnoi i medychnoi nauky ta praktiky, 3 (22), 23–27.
20. Orlova, T. V., Pankrushina, T. A. (2014). Farmatciia, 1, 34–38.

**REFERENCES**

**Information about authors:**
Zaychenko V., graduate student department of Industrial Technology of Drugs, national university of pharmacy.
E-mail: schweeps15975@gmail.com. ORCID – http://orcid.org/0000-0002-3801-9853
Ruban O., Doctor of Pharmaceutical Sciences, professor, Head of the department of Industrial Technology of Drugs, national university of pharmacy.
E-mail: ruban_elen@ukr.net. ORCID – http://orcid.org/0000-0002-2456-8210
Masliy J., Candidate of Pharmaceutical Sciences, associate professor, Head of the department of Industrial Technology of Drugs, national university of pharmacy.
E-mail: julia.masliy@gmail.com. ORCID – http://orcid.org/0000-0002-8968-0262
Gerbina N., Candidate of Pharmaceutical Sciences, assistant, Head of the department of Industrial Technology of Drugs, national university of pharmacy.
E-mail: n.a.gerbina@gmail.com. ORCID – http://orcid.org/0000-0001-9826-7552

**Відомості про авторів:**
Зайченко В. С., аспірант кафедри заводської технології ліків, Національний фармацевтичний університет.
E-mail: schweeps15975@gmail.com. ORCID – http://orcid.org/0000-0002-3801-9853
Рубан О. А., д-р фарм. наук, професор, завідувач кафедри заводської технології ліків, Національний фармацевтичний університет.
E-mail: ruban_elen@ukr.net. ORCID – http://orcid.org/0000-0002-2456-8210
Маслій Ю. С., канд. фарм. наук, асистент кафедри заводської технології ліків, Національний фармацевтичний університет.
E-mail: julia.masliy@gmail.com. ORCID – http://orcid.org/0000-0002-8968-0262

**Сведения об авторах:**
Зайченко В. С., аспірант кафедри заводської технології ліків, Національний фармацевтичний університет.
E-mail: schweeps15975@gmail.com. ORCID – http://orcid.org/0000-0002-3801-9853
Рубан Е. А., д-р фарм. наук, професор, завідувач кафедри заводської технології ліків, Національний фармацевтичний університет.
E-mail: ruban_elen@ukr.net. ORCID – http://orcid.org/0000-0002-2456-8210
Маслій Ю. С., канд. фарм. наук, доцент кафедри заводської технології ліків, Національний фармацевтичний університет.
E-mail: julia.masliy@gmail.com. ORCID – http://orcid.org/0000-0001-9826-7552

Рекомендована д. фарм. н., професором Е. В. Гладуходом Надійшла до редакції 24.10.2017 р.