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Research on the Choice of an Emulsifier in the Development of the Composition of Tamsulosin Hydrochloride Suppositories.

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ABSTRACT

The article is devoted to the choice of the type and concentration of the emulsifier in the composition of Tamsulosin Hydrochloride suppositories on the basis of biopharmaceutical research. As a result of the experiment a complex emulsifier Lanette SX was chosen. The optimum surfactant concentration of 5 % provides the highest affinity of the active substance to the hydrophilic membrane of the rectum and contributes to the better release of Tamsulosin Hydrochloride suppositories. The increase of the concentration of emulsifier from 5% to 7% does not significantly affect the increase of Tamsulosin release and is therefore inappropriete. As a result of the studies it was found that the introduction of some emulsifier into the suppository basis reduces the surface tension of the former and contributes to the better release of the active substance.

Keywords: Tamsulosin hydrochloride, suppositories, biopharmacy.

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INTRODUCTION

Steady aging of the world population determines the relevance of the study of benign prostatic hyperplasia - one of the most common diseases among elderly men. Prostate adenoma is a benign tumor of paraurethral glands surrounding the urethra in its prostatic part.

There is an obvious dependence between the incidence of benign prostatic hyperplasia and the age of a patient. A detailed examination can detect symptoms in every fourth man at the age of 40-50 years [1].

Scientists believe that benign prostatic hyperplasia develops as a result of disturbances in male hormone profile at the occurrence of andropause. There are two groups of symptoms of benign prostatic hyperplasia: irritative and obstructive. The first group of symptoms includes an increased frequency of urination, persistent urge to urinate, urinary incontinence. The group of obstructive symptoms includes the difficulty in urinating, delay of the start and rise of urination time, feeling of incomplete emptying of the bladder, intermittent urination [3].

To reduce the severity of symptoms 5-alpha reductase inhibitors, herbal medicine are used [2]. Among a large number of drugs for the treatment of prostatic adenoma a prominent place is occupied by α- blockers - drugs of the first-line treatments that affect the α- receptors, reduce or completely eliminate the muscle tone of the prostatic urethra and bladder neck [6]. Tamsulosin hydrochloride - a selective and competitive blocker of postsynaptic α_{1A}-adrenergic receptors. The selectivity of Tamsulosin to α_{1A}-adrenergic receptors located in the bladder is 20 times greater than its ability to interact with α_{1B}-adrenoceptors that are located in the vascular smooth muscles, thus Tamsulosin has no effect on a patient's blood pressure [4,5].

Today one of the promising medicinal forms for the treatment of prostate hyperplasia is suppositories. Preparations in the form of suppositories have a greater bioavailability and their anatomic similarity to the target organ provides a therapeutic effect directly in the prostate. On the pharmaceutical market there are no medications with α-blockers in the form of suppositories, so the development of the composition and technology of such drugs is a rather important and promising area of the modern pharmaceutical science.

Making the effective pharmaceutical products requires not only use of active substances but also excipients with different properties. Surfactants make a large group of compounds whose molecules have lipophilic and hydrophilic groups and the ability to be adsorbed on the surface of phase distribution, which leads to a change in the molecular nature of the surface and reduce of the interphase surface energy. Surfactants alter the physicochemical properties of a disperse system, significantly affect the release of active ingredients and therapeutic efficacy of a preparation [8,9].

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The aim of our work was to select the type and concentration of an emulsifier in the composition of Tamsulosin hydrochloride suppositories based on biopharmaceutical research.

Objects and methods of research

The objects of study were samples of Tamsulosin hydrochloride suppositories weighing 1.6 grams made from solid fat by moulding, with the addition of different emulsifiers: Lanette SX, Cremophor RH- 40, Sympatens W/230. The criterion for the choice of an emulsifier became the results of the studies on the release of the active substance (the amount of Tamsulosin) from the suppositories.

The study of kinetics of the active ingredient release into the buffer solution with pH 7.3 (pH value corresponds to the acidity of the lower ampulla part of the rectum (by I.A. Churkin's classification) was performed by the dialysis method through a semipermeable membrane. Dialyzer is a device consisting of a dialysis chamber and an inner cylinder, the bottom of which is a semi-permeable membrane (cellophane of B- 8079 brand, thickness of the swollen film 45,0 ± 0,4 microns, the degree of porosity - 6.25 g/ml).

A suppository weighing 1.6 g was melted, then applied to the membrane surface in the area of 1808 mm^2 and placed into a dialysis chamber, into which the calculated amount of buffer solution (50 ml ± 0,5) was previously poured.

Samples were taken using a pipette at regular time intervals (1 h). The volume of each sample was 5 ml. After sampling the volume of the buffer solution in the chamber was brought to the base level. The selected samples were placed in a volumetric flask and the necessary dilutions were performed. The amount of the substance which passed to the solution was determined spectrophotometrically by the method of standard (SPhU 2.2.25) [7] using the SF-46 spectrophotometer. The determination of Tamsulosin was carried out at a wave length of 280 nm in a cuvette with a layer thickness of 1 cm; as a control solution a phosphate buffer solution with pH 7.3 was used.

The concentration of substances in the dialysates (g/ml) was calculated using the formula:

$$C = \frac{A \cdot C_{ст} \cdot b}{A_{ст}}, \text{ where}$$

A – optical densityof the test solution;
$\mathbf{A_{ст}}$ – optical densityof the standard solution;
$\mathbf{C_{ст}}$ – concentration of the standard solution;
b – dilution.

From the data obtained the total amount of the dissolved Tamsulosin was calculated, considering its amount in the samples selected before:

$$X_n = C_n \cdot V_p + \frac{X_{n-1}}{V_p} \cdot V_a,$$

where: X_n – total amount of active ingredient dissolved during n hours of the experiment;

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C_n – concentration of the active substance in the dialysate (g/ml) in n hours of the experiment;
V_p – total volume of the solution in a dialisys chamber (50 ml);
X_{n-1} – total amount of the active ingredient dissolved in n hours of the experiment;
V_a – an aliquot taken for the analysis (5 ml).

For each sample of suppositories at least 6 determinations were performed which then were subjected to statistical analysis.

RESULTS AND DISCUSSION

To increase bioavailability of the dosage form it seems possible to add some surfactants to its composition. In order to optimize the composition of the suppositories some emulsifiers in the amount of 3%, which have different chemical nature and the value of hydrophilic-lipophilic balance (HLB) were administered to the basis. The characteristics and properties of the emulsifiers are shown in Table 1.

Table 1: Characteristics and properties of emulsifiers

Emulsifier	HLB number	Consistency at 20^{0}C	Melting point, ^{0}C
Emulsifiers of the I kind oil/water			
Cremophor RH-40 (oxyethylated hydrogenated castor oil)	14-16	viscous mass	20-28
Lanette SX (alloy of fatty alcohols (C_{16}-C_{18}) and sulfoethers of fatty alcohols)	10,3	solid substance	50-60
Emulsifiers of the II kind water/oil			
Sympatens W/230	4,5	solid plastic mass	75-80

The dynamics of the release of Tamsulosin hydrochloride from the prototype suppositories, to which different emulsifiers were introduced is shown in Fig. 1.

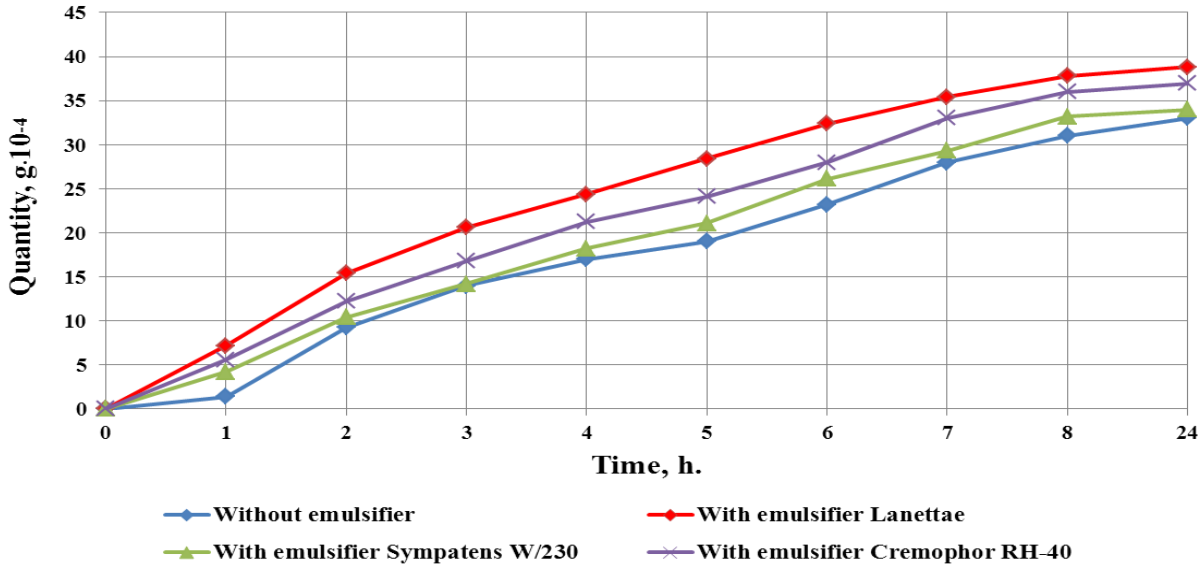

Figure 1: Dynamics of Tamsulosin hydrochloride release from suppositories, depending on the emulsifier nature

As one can see from the experiment data, the concentration of the active substance in the dialysate increases with time, but the release strongly depends on the emulsifier nature. The most complete release of Tamsulosin occurs from the suppositories sample containing emulsifier Lanette SX. In 8 hours of the experiment respectively $37{,}8 \cdot 10^{-4}$ g of Tamsulosin passed to the buffer solution, making 50.43 % of its total amount in the sample. The most dynamic release of substances is observed in the first 6 hours of the experiment, followed by a slowing of release directly up to 24 hours. The same dynamics is observed in the release of Tamsulosin from other suppositories samples, but with less intensity.

Analyzing the kinetics of release of Tamsulosin suppositories samples, which include Cremophor RH- 40 and Sympatens W/230 emulsifiers, the slow growth of concentration of the substance within 24 hours should be noted. The most satisfactory release indexes are observed from suppositories samples cotaining emulsifier Cremophor RH-40, - in 8 hours of the experiment the amount of Tamsulosin in the dialysate was $36 \cdot 10^{-4}$ r (48,03%). Within 24 hours of the experiment the concentration of Tamsulosin did not significantly change. In suppositories made of emulsifier Sympatens W/230 the similar dynamics of Tamsulosin release was observed, but the total amount of the substance that passed into the dialysate, was much smaller and made 33.2 · 10-4 g (44.29 %).

Analysis of the kinetics of release of the Tamsulosin suppositories made without addinion of any emulsifier indicated a significantly lower amount of the substance released - $31 \cdot 10^{-4}$ g (41.36 %). Considering the above studies, we selected emulsifier Lanette SX for our further studies,.

The next stage of our work was to choose the concentration of emulsifier Lanette SX. To do this, we made suppository samples with different concentration of this emulsifier: 3%, 5%, 7%, 10%. The dynamics of Tamsulosin hydrochloride release from the suppositories depending on the concentration of emulsifier Lanette SX is shown in Fig. 2.

As it can be seen from the figure, the lowest concentration of Tamsulosin hydrochloride in the dialysate is observed in the study of the suppository sample containing emulsifier Lanette SX 3%. In 8 hours of the experiment $41{,}7 \cdot 10^{-4}$ g (50.43 %) of the sample passed into the buffer solution. From the sample of the suppositories containing 5% of the emulsifier $41{,}7 \cdot 10^{-4}$ g released, making 55.63 % of its total amount in the sample. In the study of the samples, containing 7% and 10% of the emulsifier in 8 hours of the experiment $42{,}8 \cdot 10^{-4}$ g (57.10 %) and $43{,}2 \cdot 10^{-4}$ g (57, 63%) respectively of the active substance passed into the buffer solution. Based on the above information, we can see that the increase in the concentration of emulsifier Lanette SX from 5% to 7% did not significantly affect the increase of the release of Tamsulosin and is therefore inappropriate.

The studies have shown that the introduction of emulsifiers into the suppository base positively reflects on the increase of the interaction area of the drug substance with the target organ, reduces the surface tension of the suppository base, which leads to a greater absorption of the active substance. The absorption of the medicinal substance from the suppositories occurs through the mucosa of the rectum, the surface of which is covered with mucus, which has hydrophilic properties. Integrated emulsifier Lanette SX in this case provides the necessary polarity for the dispersed phase particles (Tamsulosin) in the

lipophilic medium. The optimum surfactant concentration of 5 % provides the highest affinity of the active ingredient to the hydrophilic membrane and contributes to the better release of Tamsulosin hydrochloride from suppositories.

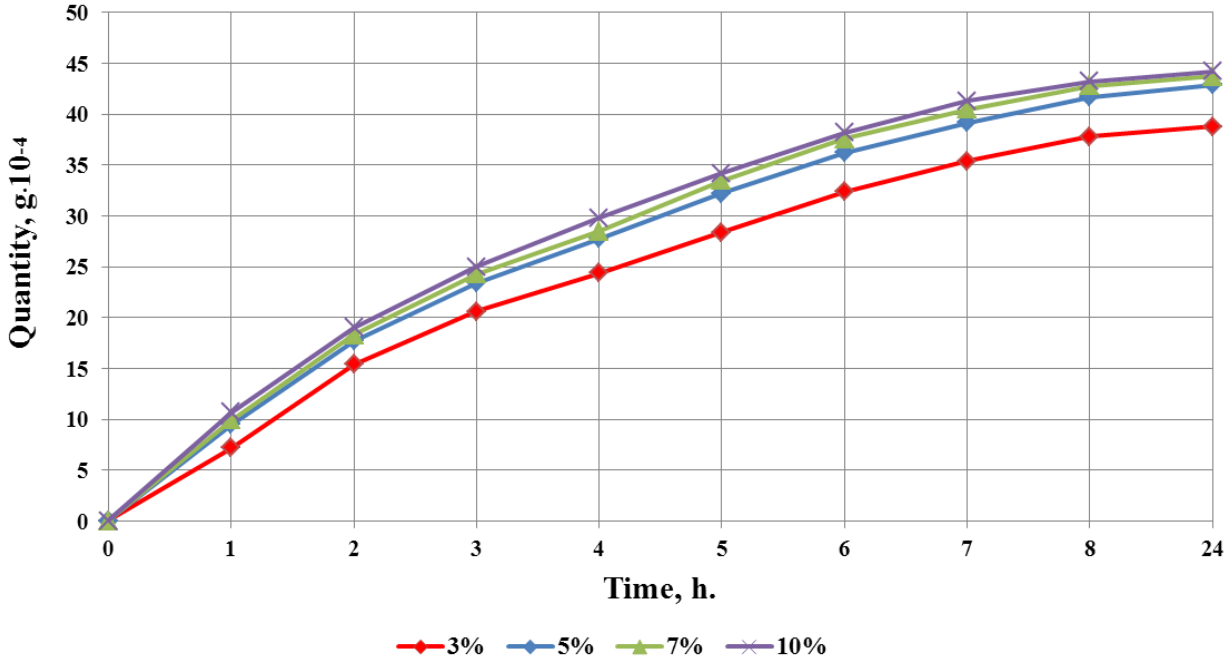

Figure 2: Dynamics of Tamsulosin hydrochloride release from the suppositories depending on the concentration of emulsifier Lanette SX

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