ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Biopharmaceutical and Physicochemical Study of Substance and Suppositories with Tamsulosin Hydrochloride

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ABSTRACT

The advisability to use tamsulozin hydrochloride to treat for prostate hyperplasia is presented in the article. For the purpose to choose the rational composition and technology to produce suppositories it has been determined the form and size of tamsulozin hydrochloride particles and also defined fraction composition of the powder by means of microscopy method. Biopharmaceutical researches of tamsulozin hydrochloride release out of the suppositories were made on the basis of firm fat by means of dialysis through semipenetrate membrane depending on working substance fraction composition.

Keywords: tamsulosin hydrochloride, suppositories, physicochemical properties, biopharmacy.

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ISSN: 0975-8585

INTRODUCTION

Recently in Ukraine prostate diseases have taken one of the leading places among male urological pathologies. Benign prostatic enlargement (adenoma or hyperplasia) is one of the most common ones [1].

Causes of hyperplasia have not been reliably established so far, however, it has been proved that the poor state of androgen production in men is an integral condition for the emergence and development of benign prostatic hyperplasia.

Prostatic hyperplasia leads to a sharp deterioration in the quality of life, constant discomfort, disorder of urinary excretion, urinary retention, and kidney failure [2].

For a long time the only way of treatment was operative. The development of the global pharmaceutical market enables us to reconsider the treatment of prostate diseases towards the conservative therapy.

Among a large number of drugs for the treatment of prostate diseases a prominent place is occupied by alpha-adrenoblockers, which are drugs of the first-line treatment that affect the α-receptors, reduce or completely eliminate the muscle tone of the prostatic urethra and bladder neck [3].

There are several groups of α-blockers used for the treatment of prostatic hyperplasia: nonselective (Phenoxybenzamine), selective α_1-blockers (Prazosin, Indoramin, Terazosin, Doxazosin, Alfuzosin), superselective $\alpha_{1A/D}$-adrenoblockers (Tamsulosin).

Tamsulosin hydrochloride is a selective and competitive blocker of postsynaptic α_{1A}-adrenergic receptors, which are found in smooth muscle of the prostate, bladder neck and prostatic urethra. At present the existence of three types of α_1-adrenergic receptors - A, B and D has been confirmed, and in the prostate gland the receptors of subtype A account for 70% of the total amount. The selectivity of Tamsulosin to α_{1A}-adrenergic receptors, which are 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 [4].

One of the systemic hemodynamic effects of α_1-blockers drug group is lowering of the blood pressure. The mechanism of the side effects development is caused by the blockage of alpha-1A and alpha-1B receptors located in blood vessels, which promotes blood deposition in veins and reduces blood pressure. The side effects are more characteristic of non-selective and selective α-blockers.

Due to the high selectivity Tamsulosin has no effect on the patients' blood pressure. Tamsulosin bioavailability is about 100%. Typically, the therapeutic effect of Tamsulosin is observed in 2 weeks after the beginning of treatment. High pharmacological selectivity of Tamsulosin determines its clinical safety [5].

One of the urgent tasks of the modern pharmaceutical science is to create new high-performance drugs in dosage forms that provide optimal therapeutic effect with minimal adverse complications.

Today one of the promising medicinal forms for the treatment of prostate diseases is suppositories. The advantages of this dosage form are: high rate of absorption of active pharmaceutical ingredients, entering of drugs directly into the systemic blood flow, lowering the allergic drug action, reduction of the side effects, simplicity of use, ability to eliminate some unpleasant organoleptic properties of substances. 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 their development is a rather important and promising area of the modern pharmaceutical science.

The aim of our work was the investigation of the physicochemical and technological characteristics of Tamsulosin hydrochloride substance and the determination of their impact on the full release of the active substance from the suppositories.

Objects and methods of research

The objects of research were Tamsulosin hydrochloride powder and samples of suppositories containing this substance on a solid fat base. The suppositories of 1.6 g weight were produced by moulding.

The microscopic research was performed considering the existing methods for the determination of powder dispersion. In accordance with the accepted classification all the methods can be divided into the following groups:

- Mechanical separation of particles which includes sieve and filtration analyses;
- Sediment analysis, which includes fractional sedimentation, elutriation, sediment accumulation and the selection of weighted samples;
- Dynamic methods based on the separation of particles in the flow in vertical tanks and centrifugal devices;
- Individual study of particles, including microscopic and ultramicroscopic analyses;
- Determination of specific surface, which includes the adsorption method as well as the rate of solution one and so on.

The most common methods of express analysis of the powders disperse content in the range of measured sizes > 0.5 micron are sieve and microscopic.

Each of these methods has its advantages and disadvantages, which makes their equal application in practice. Unfortunately, the sieve analysis does not give the sufficiently reliable data on the size of powder particles due to agglomeration inevitable when dispersed dry. Microscopic analysis allows us to determine more accurate parameters of a fine-dispersed powder [6].

Microscopic analysis was carried out using a laboratory microscope «Konus-Akademy» with the eyepiece camera ScopeTek DCM510. To visualize the obtained images the software ScopePhoto ™ was used, which allowed measurements of linear sizes in real time and on a static image.

Particle sizes were measured observing individual fields of view which were selected in the studied powder sample by moving it to a value greater than the rectangle diagonal or circle diameter, which limits the field of view. The area in which the measurements were carried out and the number of particles equals the sum of their areas when observing the individual fields of view. The determination of particles in individual fields of view is done using the obtained images by measuring the maximum chord in horizontal or vertical directions [7].

A particle is considered belonging to the observed field, if it is on one of the limit halves. For example, if working with a rectangle, the particles that are inside it, on the left vertical and top horizontal sides, at the intersection of the sides and at another end of one of them are taken into consideration. Particles that are on the other sides and corners are not considered.

The solubility was determined by the method of the State Pharmacopoeia of Ukraine at the temperature of 25^0C [8].

The release of the active ingredient from the samples was determined by the degree of its diffusion in the phosphate buffer solution with pH 7.3 through a semi-permeable membrane (thickness of the swollen film 45,0 ± 0,4 microns, the degree of porosity – 6.25 g/ml). To do this, a dialysis unit with two working chambers was used. To the lower opening of an inner cylinder of the dialysis chamber a semi-permeable membrane was tightly attached. The testing sample in the molten state (1.6 g) was applied uniformly to the membrane surface whose area with a 50 mm in diameter is 1963 mm^2. The inner cylinder with the testing sample was placed in a dialysis chamber, which contained 50 ± 0,5 ml of purified water.

The dialysate samples of 10 ml volume were collected with the help of a pipette at regular intervals (1 h), adding the same volume of the buffer solution into the chamber. The concentration of Tamsulosin hydrochloride in the dialysate samples was determined spectrophotometrically at a wavelength (280 ± 2) nm on a spectrophotometer SF-46 using the calibration graph method. During the experiment, the samples were kept in a thermostat TS-80-M-2 at the temperature 38±1 ^{o}C, that models the temperature of the human body. The duration of the research was 6 hours [9].

RESULTS AND DISCUSSION

In the development of a pharmaceutical preparation active ingredients should have predictable physicochemical properties such as solubility, particle size, stability and wettability [10,11].

ISSN: 0975-8585

The research of Tamsulosin hydrochloride powder solubility showed that the powder is practically insoluble in most common solvents used in the creation of medicinal formulations in the form of suppositories: in the melt of solid fat, polyethylene oxide - 1500, corn oil, and purified water. Rise of the solvent temperature of the solvent did not improve the solubility. The biggest cosine of the wetting angle was using solid fat (Table 1).

Table 1: Cosine of Tamsulosin wetting angle

Solvent	Cos of the wetting angle
The melt of solid fat	0,92
Polyethylene oxide - 1500	0,86
Corn oil	0,56
Purified water	0,24

Therefore, the next stage of our work was to determine the way of administration of the active substance into the solid fat.

The appropriate biopharmaceutical properties of the studied suppositories in case of their unsatisfactory solubility can be provided by defining the required particle size of the active substance. To determine the fractional composition of Tamsulosin hydrochloride the microscopy analysis was used.

The results of the microscopic studies showed that the substance of Tamsulosin hydrochloride has a polydisperse composition (Fig 1).

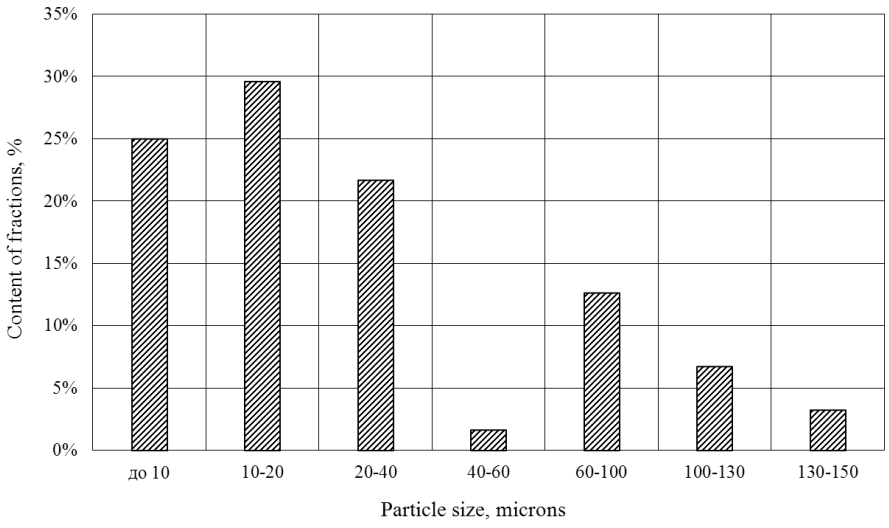

Fig. 1. Fractional composition of Tamsulosin hydrochloride

As it can be seen from the Figure, the particle size ranges from 10 to 150 microns, which allows to add it to fine-dispersed ones [SPhU 02.09.12]. The major fraction consists of particles up to 40 microns – 78%.

According to the microscopy analysis Tamsulosin hydrochloride powder can undergo aglomeration under mechanical and electrostatic forces, which might have an adverse effect on the dosage uniformity and sedimentation degree.

ISSN: 0975-8585

The image analysis at a magnification of 100 (Fig. 2) suggests that the particles relate to the monoclinic crystal system, have a rectangular shape with a smooth surface, and the form factor approaches one.

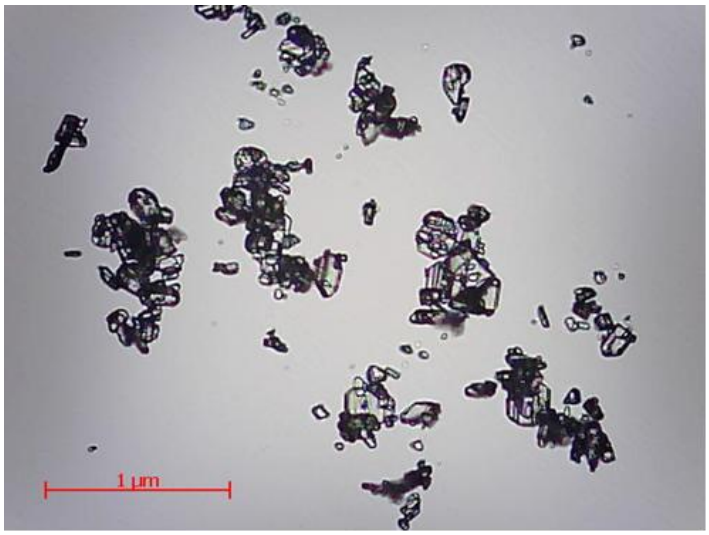

Fig. 2. Particles of Tamsulosin hydrochloride

The research done allowed to forecast a satisfactory distribution of the powder in the solid fat, taken into account its good wettability. To study the degree of release of the drug active ingredient from the suppositories sample two fractions were chosen: up to 40 microns (sample number 1) and from 40 to 150 microns (sample number 2). The kinetics of Tamsulosin hydrochloride release from the testing samples is shown in Fig. 3.

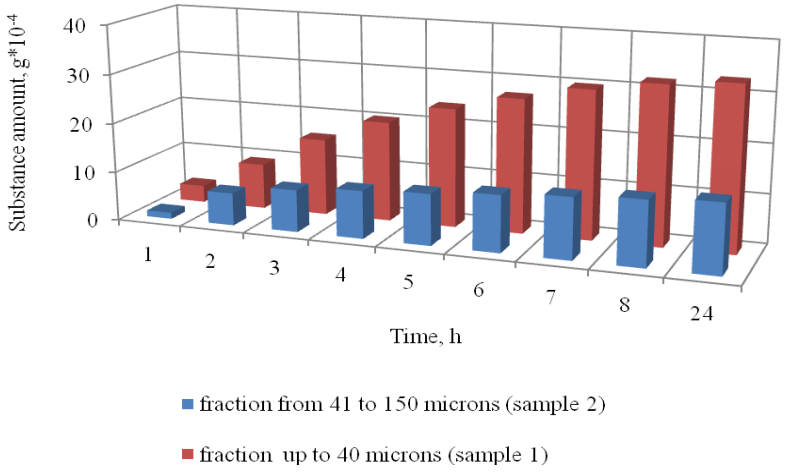

Figure. 3. Kinetics of Tamsulosin hydrochloride release depending on the fractional composition of the substance.

According to the data of the experiment, the concentration of active substance in the dialysate increases with time and strongly depends on the fractional composition of the active substance.

The most complete release of Tamsulosin occurs from a sample of suppositories containing particles up to 40 microns (sample number 1). After 8 hours of the experiment $33{,}101 \cdot 10^{-4}$ g of Tamsulosin respectively passed into the buffer solution. The most dynamic release of the active ingredient is observed during the first 6 hours of the experiment, followed by a gradual deceleration.

Analysis of the kinetics of Tamsulosin release from the suppositories with fractional composition from 40 to 150 microns (sample number 2), shows significantly lower rates of the substance which came into the solution. Similarly to sample number 1, the largest concentration of Tamsulosin in the dialysate is observed at the eighth hour of the experiment and is $13{,}212 \cdot 10^{-4}$ g. The obtained research results allows to assume that low values of the release from the suppositories samples with the fraction of particles over 40 microns are connected with some rheological processes occurring at the substance-solid fat interface, which depends on filling the microdefects of the powder surface, so that there is no limit strengthening and uniform wetting of the substance. The fractional composition of Tamsulosin hydrochloride powder has been determined using the microscopic method. It was found that the bulk of the substance is made with particles up to 40 microns, which is 78% of the total mass. The form and size of Tamsulosin hydrochloride particles were studied. According to the microscopy studies it was revealed that the particles relate to a monoclinic crystal system, have a rectangular shape with a smooth surface, and the form factor approaches one.

A biopharmaceutical research of Tamsulosin hydrochloride release from the suppositories made from a solid fat base was done by dialysis through a semi-permeable membrane, depending on the fractional composition of the active substance. During the experiment it was proved that Tamsulosin with particle size up to 40 microns has significantly higher rates of release from suppositories compared with the fraction from 40 to 150 microns.

The obtained results will be considered in the development of technology for suppositories with Tamsulosin for the treatment of prostatic hyperplasia.

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