

Justification for the Composition and Method of Active Pharmaceutical Ingredients Administration at the Development of Suppositories for the Treatment of Benign Prostate Gland Diseases

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Abstract

Introduction: Diseases of the prostate gland occupy one of the main places in the structure of urological diseases and acquire ever increasing social significance. They are the most common diseases associated with aging in men. In conservative treatment of patients with diseases of the prostate gland, considering pathogenetic mechanisms, medicines of different directionalities are used, eliminating infectious agents, correcting the immune status, contributing to the regression of the inflammatory process and restoring the functional activity of the prostate. **Materials and Methods:** Indole-3-carbinol (Sigma-Aldrich Co., USA) and meloxicam (Boehringer Ingelheim GmbH, Germany) were chosen as the study objects. Studies of the active pharmaceutical ingredients (APIs) solubility were made, their crystallographic and thermogravimetric analyses. **Results and Discussion:** In the work, it has been substantiated the composition of rectal suppositories for the treatment of benign prostatic diseases using a combination of indole-3-carbinol and meloxicam, which possess anti-inflammatory, analgesic, and antibacterial properties and also contribute to the restoration of the hormonal background of men with age-related changes and activation of regeneration processes of the injured organ. A microscopic and thermogravimetric analysis of selected APIs was carried out, and their solubility in aqueous and non-aqueous solvents was investigated. **Conclusions:** Based on research results, the optimal auxiliary substances were selected for rational introduction of substances into the suppository base – polyethylene oxide-400, Tween-80. The results of thermogravimetric analysis have proven the thermostability of the investigated APIs in the temperature range the suppository bases melting.

Key words: Diseases of the prostate gland, indole-3-carbinol, meloxicam, suppositories, technology

INTRODUCTION

Nowadays, diseases of the prostate gland remain very common, difficult to treat and violating patients quality of life.^[1,2] Hence, obvious is not only medical but also social significance of the problem of treatment of these pathologies.

Prostate diseases are considered in three directions – inflammatory diseases (prostatitis), prostatic disease associated with age-related changes in the body of men (prostate adenoma), and malignant tumors (prostate cancer).^[1,3]

Prostatitis, symptoms of which are more common in men of reproductive age (20-40 years), on

average, is diagnosed in 35% of the population. The main symptom of this disease is a violation of urination. In addition to severe pain, reduced sexual desire and potency in most cases, there is oppression of the prostate gland function and violation of its trophism. Quite often, prostatitis occurs in combination with diseases such as vesiculitis or urethritis, in the elderly patients – in conjunction with benign prostatic hyperplasia (BPH).^[4]

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BPH or prostate adenoma is the most common urological disease in older men. BPH occurs more often after 45 years. Thus, at the age of 50 years, around 25 % of men have symptoms of prostatic hyperplasia and aged 65 – already 50%. Overtime, the disease occurs in 85% of men. Causes of BPH vary, but the most important is the age-induced hormonal change. With age, male testosterone levels drop, and the level of estrogens increases, which can also be a trigger of prostate growth mechanism. In this disease of the prostate gland, tissue grows and increases in volume. As with prostatitis, at prostate adenoma appears urination and sexual sphere disorders. Worsening of symptoms is often associated with such provoking factors as cooling, alcohol intake, stress, and aggravation of chronic prostatitis.^[5,6]

Drug treatment of benign diseases of the prostate is carried out according to their causes and symptoms. Since the cause of prostatitis is basically an infection, patients are prescribed antibiotics, anti-inflammatories, immunomodulating therapy, and physical therapy.^[7]

The treatment of prostate adenoma is the elimination of symptoms and prevention of tumor growth. Treatment includes application of various groups of pharmaceuticals: antibiotics; anti-inflammatory medicines; alpha-blockers; antispasmodics; drugs intended to improve circulation and others. An important role in the complex treatment and prevention of this disease play herbal products (sabal palm fruit extract, pumpkin seeds, aspen bark, nettle, and many others). It is known that herbal raw materials inhibit the growth of the prostate gland and relieve inflammation and swelling.^[8]

Preparations for the treatment of the above diseases are represented in various dosage forms, however the optimal are suppositories: Rectal route of administration allows maximum influence on the diseased prostate; active substances enter into the systemic circulation, bypassing the liver, which ensures rapid therapeutic effect, excludes body intoxication and accumulation of the drug in the liver and digestive tract.^[9]

The aim of our work is justification for the choice of active pharmaceutical ingredients (APIs), study of their properties and determining the mode of administration in the composition of rectal suppositories for the treatment of benign prostate diseases.

MATERIALS AND METHODS

The objects of our study were chosen indole-3-carbinol (Sigma-Aldrich Co., USA) and meloxicam (Boehringer Ingelheim GmbH, Germany). Solvents were used as follows: Purified water, peach oil, propylene glycol (PG), polyethylene oxide-400, Tween-80, 96% ethyl alcohol. Investigations of the solubility of APIs, their crystallographic, and thermal

gravimetric analysis have been performed.

Crystallographic properties of powders (SPhU, 2nd ed., Vol. 1., 2.9.37, and p. 481-483) and their solubility (SPhU, 2nd ed., Vol. 1., 1.4, p. 33) were studied using a laboratory microscope “Konus Academy” at the eyepiece magnification of 40-60 times equipped with a camera ScopeTek. Images processing was carried out in the program Scope Photo (version 3.0.12.498).^[10]

Thermogravimetric analysis was performed according to SPhU, 2nd ed., Vol. 1, 2.2.34, and p. 101-3^[10] in derivatograph Q-1500-D of system “F. Paulic, G. Paulic, L. Epdey” of Hungarian Company “MOM” with platinum-platinum-rhodium thermocouple, which allows to measure the temperature (T), the change in weight (TG), the rate of weight change (DTG), and change of thermal effects (DTA) of the test sample versus time. Studies carried out in the temperature range from 22°C to 500°C in air when heated samples in ceramic crucibles. Thermograms were recorded in the following mode: API weight was 100 mg and temperature rise rate was 2.5°C/min. The standard served calcined alumina.

RESULTS AND DISCUSSION

According to the literature, at regular use in food of cruciferous, namely broccoli, reduces the risk of cancer of small intestine and colon, mammal glands diseases in women and prostate in men.^[11,12] The uniqueness of action of this kind of vegetables is explained by the presence of natural indole compounds, the most active of which is indole-3-carbinol, belonging to the class of glucosinolates. This unique component of vegetable origin possesses an antiproliferative effect on hormone-sensitive tissues, exhibits antitumor effect, and regulates estrogen background. One of the main and most powerful properties of indole-3-carbinol is the ability to inhibit the activity of androgen and estrogen receptors, which plays an important role in the pathogenesis of BPH. It induces apoptosis of tumor cells, is a natural antioxidant, and has a positive effect on the body's rejuvenation processes. Indole-3-carbinol has antibacterial action, which is confirmed by clinical trials. It also enhances and supports the activity of the natural systems of the body in chronic inflammatory processes, eliminating toxic breakdown products.^[13] Indole-3-carbinol is found in many dietary supplements manufactured in the form of capsules, for example, “Indole-M” (Ukraine), “NOW Foods, indole-3-carbinol” (USA), “Nature's Sunshine, indole-3-carbinol” (USA), “ExPress Essentials” (USA), “Indinol,” “Indinol Forto,” “Indole Forte,” “Stella,” “Estrovel” (Russia), and others. Considering its properties, indole-3-carbinol was proposed by us as an API in the composition of the developed formulation.

Natural origin substances effectively act both at individual application and in combination with other drugs.

Inflammation and severe pain accompanying the course of benign prostate diseases are the leading pathogenetic links of many urological diseases, so the search for highly effective drugs that suppress inflammation, pain, and have minimal side effects for the treatment of these pathologies remains today an urgent task. As is known, a similar effect has non-steroidal anti-inflammatory drugs (NSAIDs) which include meloxicam – selective cyclooxygenase-2 inhibitor having antipyretic, analgesic, and anti-inflammatory effects. In diseases of the prostate, meloxicam provides an analgesic effect by blocking the synthesis of prostaglandins, improves microcirculation in blood vessels, and reduces inflammation, which eases the condition of patients with acute and chronic forms.^[14,15] Today in the pharmaceutical market of Ukraine, meloxicam is presented in a variety of dosage forms: Injectable solution, tablets, suspension, gel, and suppositories and is indicated for the therapy of osteoarthritis, rheumatoid arthritis, and other degenerative–dystrophic diseases of the musculoskeletal system. For the treatment of prostatitis, only one drug with this NSAID in the form of suppositories is known – “Movalis[®]” (Boehringer Ingelheim, Germany).^[16] In addition, it should be noted that most of the meloxicam drugs presented are monopreparations of foreign production.

The study of physicochemical and technological properties of substances is crucial in the process of highly effective drugs creation and has a direct impact on the technological process parameters.^[17,18]

Therefore, the first step of our work was to study the crystallographic characteristics of indole-3-carbinol and meloxicam, the results of which are shown in Figure 1.

The results obtained indicate [Figure 1a] that the particles of indole-3-carbinol are transparent plates with smooth surface and rough edges. Solid particles tend to agglomerate forming layers of broken particles. The size of solid particles and their fragments ranges from 0.5 to 2 μm . Form factor – 0.6. Meloxicam [Figure 1b] is a powder with oval particles of size 0.01–0.02 μm . The particles tend to form conglomerates up to 0.4 μm of indefinite shape. In the total, mass dominates fraction of particles with a linear dimension of 0.2 μm and shape factor – 0.7.

As it is known, an important step in the development of a medicament in the form of suppositories is selecting the mode of API administration to the base,^[19] so we investigated the solubility of indole-3-carbinol and meloxicam in the different solvents (1:1): Purified water, peach oil, PG, polyethylene oxide-400 (PEO-400), Tween-80, and ethyl alcohol 96 %.

Figure 2 shows the results of microscopic analysis of indole-3-carbinol solubility in various solvents.

Results of the study [Figure 2] have shown that indole-3-carbinol is insoluble in water and peach oil. In the field of view, redistribution or change in particle size in the volume of solvents is not observed. Adding PG and ethanol helps to

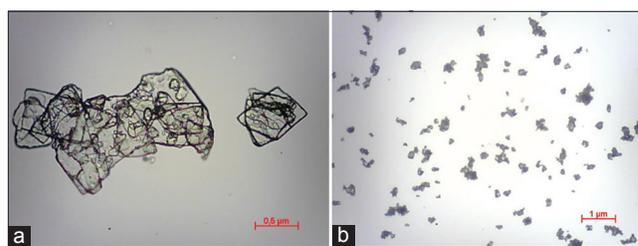


Figure 1: Microscopic analysis of the substances powders: (a) Indole-3-carbinol, (b) meloxicam

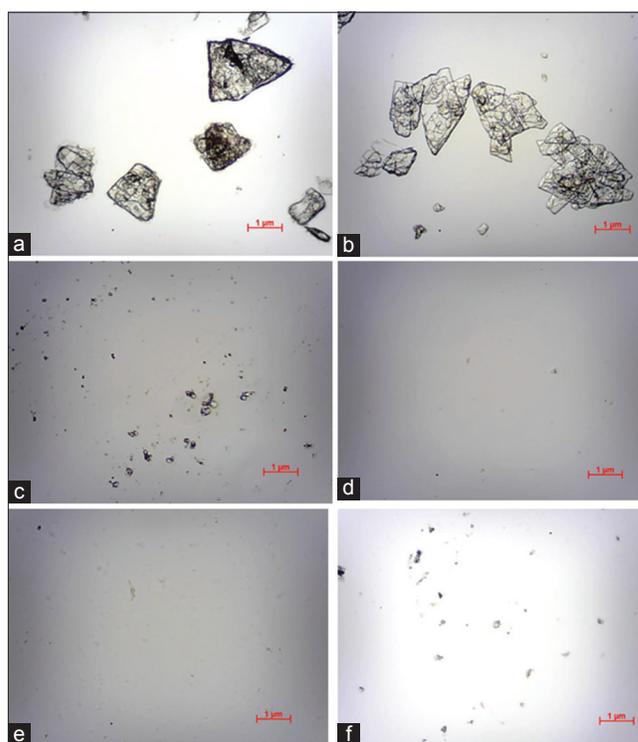


Figure 2: Solubility of indole-3-carbinol in various solvents: (a) purified water; (b) peach oil; (c) propylene glycol; (d) polyethylene oxide-400; (e) Tween-80; (f) ethyl alcohol 96%

reduce the linear dimensions of indole particles to 0.1 μm . Dissolution occurs across all the surface of the substance. In PEO-400 and Tween-80, the substance readily undergoes the action of a solvent; in the field of view is traced quick change of linear sizes of the powder particles. After 10 min, there are individual particles up to 0.01 μm observed.

Results of meloxicam solubility study by microscopic method are shown in Figure 3.

The results obtained [Figure 3] indicate that the substance does not dissolve completely in all solvents examined. Meloxicam solubility decreases in the row – PEO-400 > Tween-80 > Ethyl alcohol > PG > water > oil. Addition of water and oil does not contribute to change in linear dimensions of particles, although in contact with oil agglomeration of the powder particles is reduced. The sample with ethanol, in the field of view, is observed particles of size 0.01–0.2 μm , with a uniform distribution over the entire volume and the change

in appearance due to wetting. Samples with Tween-80 and PEO-400 are observed a decrease in meloxicam particle size to 0.01-0.05 μm .

Thus, according to the results obtained, rational solvents for the investigated APIs are PEO-400 and Tween-80.

It is known that with decreasing particle size increases the dissolution rate of the active substance, which usually leads to increase in the rate and extent of its absorption.^[20,21] From a biopharmaceutical point of view, optimal is administering the active ingredient to the dosage form in the most dispersed state. This connection has been studied behavior of meloxicam at its grinding in the given solvents and mixtures thereof in a ratio of 1:1. Photomicrography results are shown in Figure 4.

Results of the studies [Figure 4] have shown that at meloxicam grinding in the medium of PEO-400 occurs sufficiently good dissolution of its particles – isolated transparent particles with size of 0.1 μm are observed. After grinding of meloxicam in Tween-80 a uniform distribution of particles throughout the volume of solvent is observed without decreasing linear particle size. Grinding in a mixture of PEO-400 and Tween-80 reduces the particle size and leads to its uniform distribution. The field of view is observed single particles with size of 0.01 μm .

Thus, as a result of the research, it was found that indole-3-carbinol is rational to administer as a solution and meloxicam as a suspension in PEO-400. In preparing the concentrate, it is efficient to add Tween-80 to increase the wettability, and consequently, reduces the linear dimensions in the composition of the suspension.

To determine the optimal technology of manufacturing the drug, we have studied the decomposition temperature of the APIs included in the composition of suppositories. These data allow determining the temperature modes of suppositories preparation and administration of active substances in the base without the risk of substances' structure decomposition and their pharmacological effect changes. The study was conducted using thermogravimetric analysis.^[22,23] Derivatograms of indole-3-carbinol and meloxicam substances are shown in Figure 5.

As seen from the results [Figure 5], at a temperature of 95°C, there is melting of indole-3-carbinol without loss in weight. In the temperature range 110-233°C, the loss in mass was 11.5% of the sample, with the maximum rate of decomposition at 152°C that is most probably followed by boiling. At calcination of the substance up to 500°C, decomposition occurs in two stages – at temperatures of about 343°C and about 365°C; above 365°C, there is combustion process.

In the study of meloxicam, it was found that the substance is stable up to 257°C, and no weight loss occurs. This temperature is observed the process of substance melting and the maximum rate of decomposition is at 260°C. At a

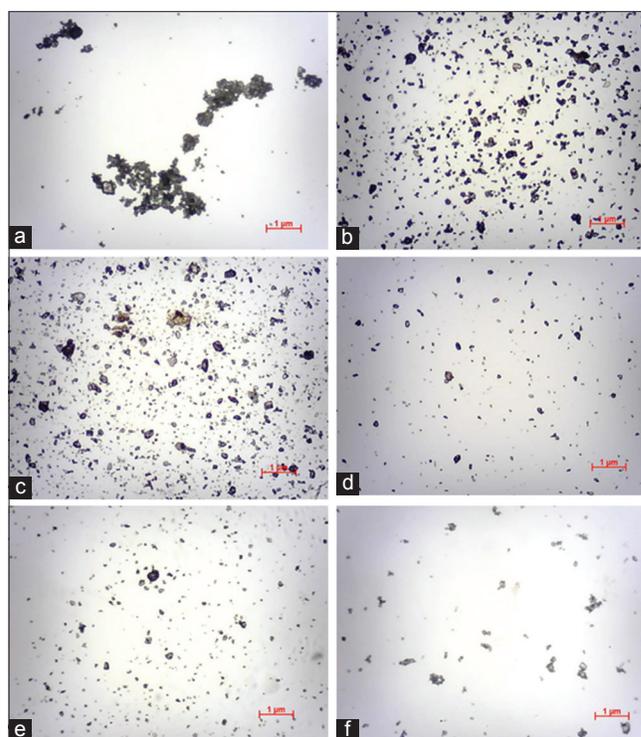


Figure 3: Solubility of meloxicam in various solvents: (a) purified water; (b) peach oil; (c) propylene glycol; (d) polyethylene oxide-400; (e) Tween-80; (f) ethyl alcohol 96%

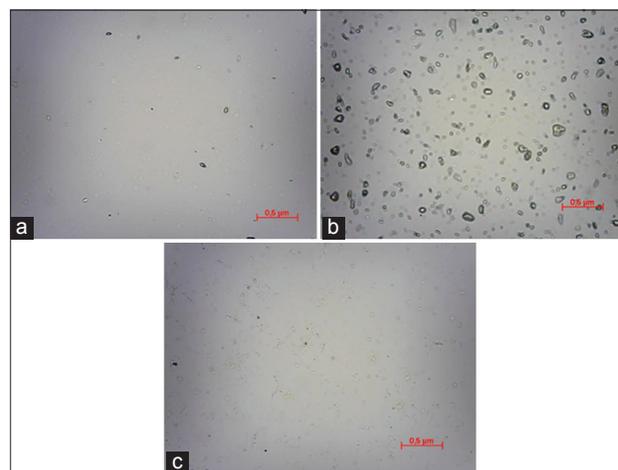


Figure 4: Photomicrography of meloxicam in the medium: (a) Polyethylene oxide-400; (b) Tween-80; (c) the mixture of PEO-400 and Tween-80

temperature of 278°C, the combustion process is observed and in the range 315-393°C – boiling. To 315°C, loss in weight was 57% and at the temperature increases to 460°C – 72% and mass isolation process suspends.

The conducted studies of the thermal behavior of the APIs allow concluding that the thermal conversion of indol-3-carbinol substance starts at 95°C and meloxicam – at 257°C. This demonstrates the thermal stability of these substances at administration to suppository bases.

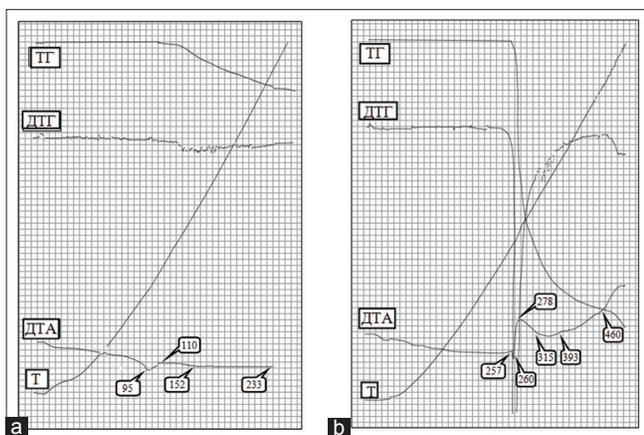


Figure 5: Derivatograms of substances: (a) Indole-3-carbinol; (b) meloxicam

CONCLUSIONS

1. The choice of APIs in the composition of rectal suppositories for treatment of benign prostate disease has been justified. Due to combination of these APIs, the developed drug will have anti-inflammatory, analgesic, and antibacterial properties and also will help to restore hormonal status of men at age-related changes and activation of regeneration processes of the damaged organ.
2. A microscopic analysis of the substances has been performed, which has confirmed the polydispersity of the mixture and the need for grinding when administered in suppository base.
3. Solubility of indole-3-carbinol and meloxicam in various solvents has been studied, which allowed determining a rational method of APIs administration. It was found that with PEO-400, indole-3-carbinol is efficient to administer as a solution and meloxicam as a suspension. It is also recommended for the concentrate preparation to add emulsifier Tween-80, which improves wettability and uniformity of the particles distribution in the suppository mass.
4. Thermogravimetric analysis has shown the thermal stability of the studied APIs in the temperature range of suppository bases melting.

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