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Original article

DESIGN AND DEVELOPMENT OF NOVEL HERBAL SUPPOSITORY FORMULATION FOR PROSTATITIS TREATMENT

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Background. Prostatitis is a common inflammatory condition of the prostate gland, often treated with antibiotics and anti-inflammatory drugs, which may have limited efficacy and side effects. Herbal therapies offer a promising alternative due to their natural anti-inflammatory properties.
Objective. This study aims to design, develop, and evaluate physicochemical, biopharmaceutical and microbiological properties of novel herbal suppository formulations for the treatment of prostatitis, optimizing their biopharmaceutical profiles.
Methods. Excipients were selected to form suppositories with herbal ingredients known for their anti-inflammatory effects, specifically lovage, saw palmetto, and calendula CO_2 extracts. The formulations were assessed based on key quality parameters, including organoleptic characteristics, average mass, melting point, deformation time, disintegration time, microbiological purity, and pH, ensuring compliance with European Pharmacopoeia (*Ph. Eur.*) standards. Biopharmaceutical studies compared the release profiles of active compounds from different suppository bases.
Results. Suppositories based on Witepsol® H15 exhibited satisfactory organoleptic properties, appropriate melting points, and acceptable deformation and disintegration times. The pH levels were within the required range, and microbiological tests confirmed purity. Biopharmaceutical evaluations showed that Witepsol® H15 suppositories had the most appropriate release rates of active compounds compared to those made with other bases.
Conclusions. The novel herbal suppositories developed in this study show promise for managing prostatitis based on preliminary evaluations of their physicochemical, microbiological, and biopharmaceutical properties. Further clinical studies are required to confirm their efficacy and safety.

Keywords: prostatitis; herbal suppositories; Witepsol® H15; anti-inflammatory activity; therapeutic formulations.

Introduction

Prostatitis is a prevalent and often debilitating condition characterized by inflammation of the prostate gland [1]. It affects men of all ages but is particularly common in those aged 30–50 years [2]. Prostatitis manifests in various forms, including acute bacterial prostatitis, chronic bacterial prostatitis, chronic prostatitis/chronic pelvic pain syndrome, and asymptomatic inflammatory prostatitis [3, 4]. Symptoms range from urinary difficulties and pelvic pain to sexual dysfunction, significantly impacting the quality of life. Despite its prevalence, prostatitis remains a challenging condition to treat effectively, with current therapies often providing incomplete relief and being associated with undesirable side effects [5].

Traditional treatment methods for prostatitis include antibiotics, alpha-blockers, and anti-inflammatory agents [6, 7]. Antibiotics are typically prescribed for bacterial forms of prostatitis, though their effectiveness is often limited in chronic cases [3]. Alpha-blockers help relax muscle fibers in the prostate and bladder neck, easing urinary symptoms and can be prescribed in combination with antibiotics [8]. Non-steroidal anti-inflammatory drugs are used to manage pain and inflammation [9, 10]. However, these treatments frequently fall short in terms of efficacy, and long-term use can lead to adverse effects such as gastrointestinal issues, antibiotic resistance, and cardiovascular risks.

Given the limitations of conventional treatments, there has been a growing interest in alternative and complementary therapies, particularly those involving herbal ingredients. Herbal medicine offers a promising avenue due to its potential to provide symptomatic relief with fewer side effects. Several herbal ingredients, such as *Serenoa repens* (saw palmetto) [11–15] and *Calendula officinalis* (common marigold or calendula) [5, 16, 17] have demonstrated anti-inflammatory, analgesic, and antioxidative properties, making them suitable candidates for managing prostatitis. *Levisticum officinale* (lovage) showed promising results for treatment of

inflammatory diseases of the prostate, in particular prostatitis [18]. Lovage extracts demonstrated antibacterial, flushing, anti-inflammatory and spasmolytic action on the urinary bladder [19–22], therefore can also be included in a complex treatment of prostatitis.

The development of a new rectal suppository formulation incorporating these herbal ingredients is justified by the need to enhance therapeutic efficacy and improve patient convenience. Rectal suppositories offer several advantages over oral administration, including direct delivery to the prostate region, bypassing the gastrointestinal tract, and reducing systemic side effects. Additionally, this route of administration can enhance the bioavailability of active compounds, ensuring more effective relief from symptoms.

The importance of developing new formulations lies in addressing the unmet needs of prostatitis patients. Improved formulations can lead to better adherence to treatment, reduced incidence of side effects, and overall enhanced quality of life. By exploring novel delivery systems and integrating scientifically validated herbal ingredients, it is possible to create more effective and patient-friendly therapeutic options for prostatitis. The current study is a continuation of our previous work [23–25] aimed at improving methods of treatment and diagnosis of prostatitis.

This scientific article aims to discuss the rationale behind the selection of specific herbal ingredients for a rectal suppository, explore the benefits of this delivery method, and highlight the potential improvements in therapeutic outcomes and patient satisfaction.

Materials and Methods

Reagents and raw materials

Saw palmetto fruits CO_2 extract used for the novel herbal suppository formulation product development was purchased from EUROMED (Spain). Lovage roots CO_2 extract and Calendula flowers CO_2 extract used for the suppository formulation product development was purchased from FLAVEX Naturextrakte GmbH (Germany). Witepsol® H15 was purchased from IOI Oleo GmbH (Germany), and Suppocire AML from Gattefossé (France), Polyethylene glycol (PEG) 1000, and 6000 from Merk (USA), Polyethylene glycol 4000 (Pluracare® E 4000 Flakes) from BASF (Germany), cocoa butter from Cargill (Netherland). Potassium dihydrogen phosphate, sodium chloride, disodium hydrogen phosphate was acquired from Sigma-Aldrich (USA).

Preparations

Herbal suppository formulation product, 2 g rectal suppositories containing 150 mg of Saw palmetto fruits CO_2 extract, 50 mg of Lovage radix CO_2 extract and 50 mg of Common marigold flowers CO_2 extract were manufactured using standard processes of an active pharmaceutical ingredient (API) homogenization with different fatty and hydrophilic melted suppository bass, followed by suppository formation and packaging.

The selected fatty bases were cocoa butter (Formulation 1 (F1)), Suppocire AML (F2) and Witepsol H15 (F3). Hydrophilic bases composed of polyethylene glycol (PEG) 1000 (F4) and its mixtures such as PEG 1000/PEG 4000 (3:1) (F5), and PEG 1000/PEG 6000 (3:1) (F6) were prepared. All suppositories were kept in the refrigerator and were stored in a desiccator at room temperature for 24 h before use.

Methods of analysis

Visual characterization (appearance): Twenty suppositories from each batch were randomly selected, longitudinally cut and examined through naked eyes for the assessment of physical characters like absence of fissuring, pitting, fat blooming, exudation and migration of active ingredients.

Length and width: Twenty suppositories were selected randomly from each batch; their length and width were measured using vernier calipers.

Uniformity of mass of single-dose preparations (*Ph. Eur.*, 2.9.5) [26]*:* Twenty suppositories taken at random were weighed individually on electronic balance and average weight was calculated. Not more than 2 of the individual masses deviate from the average mass by more than the percentage deviation 5% and none deviates by more than twice that percentage (10%).

Hardness: A hardness test was performed for three suppositories using a tablet hardness tester YD-1 2–30 mm at 25 °C. The weight required to break the suppository was taken as a measure of its hardness.

Melting point: Macro melting range test was performed with the whole suppository. Suppository from each formulation was placed in a test tube with phosphate buffer pH 7.2 maintained at constant temperature 37 ± 0.5 °C. The time required by the whole suppository to melt or disperse in the media was noted.

Softening time determination of lipophilic suppositories (*Ph. Eur.*, 2.9.22): The test is intended to determine, under defined conditions, the time which elapses until a suppository maintained in water softens to the extent that it no longer offers resistance when a defined weight is applied. Apparatus type A designed and constructed by engineers on the biomedical engineering faculty of Igor Sikorsky Kyiv Polytechnic Institute was used for this measurement.

The test was achieved by the method described below. The glass tube containing 10 ml of water was placed in a water-bath and equilibrated at 36.5 ± 0.5 °C. This glass tube was fixed vertically and immersed to a depth of at least 7 cm below the surface but without touching the bottom of the water-bath. A suppository was introduced into the tube followed by the rod with the free gliding plastic covered into the glass tube until the metal needle touched the flat end of the suppository. The cover was put on the tube (beginning of time measurement). The time which elapses until the rod sinks down to the bottom of the glass tube was noted and the mark ring reaches the upper level of the plastic cover.

Disintegration test for solid rectal and vaginal dosage forms (*Ph. Eur.*, 2.9.2): The disintegration time of the suppositories was performed by using disintegration test apparatus ERWEKA ST 3. Phosphate buffer pH 7.2 maintained at 37 ± 0.5 °C was used for this testing. The test was performed using three suppositories, placed each one on the lower disc of a device. Disintegration was considered to be achieved when dissolution was complete, the components of the suppository or pessary had separated, no residue remained on the perforated disc. The time taken for the disintegration of entire suppository was recorded.

Assay: Product content was determined spectrophotometrically. One suppository in 200 ml of phosphate buffer pH 7.2 maintained at 37 ± 0.5 °C till it melted. 1 ml sample was withdrawn and diluted to 100 ml with phosphate buffer pH 7.2 and then lipophilic matters was extracted with hexane. The content of chlorophylls and carotenoids in hexane extracts was determined by using UV-Visible spectrophotometer by measuring absorbance of the diluted sample according the method of Lichtenthaler & Buschmann [27] using UV-Vis spectrophotometer Shimadzu-1280 (Japan). The absorbance of solutions was recorded at 450 nm for carotenoids, and 663 and 645 nm (chlorophylls *a* and *b*, respectively). The quantity of the active substance dissolved in a specified time was expressed as a percentage of the content stated on the label.

Study of the efficacy of antimicrobial preservation (*Ph. Eur.*, 5.1.3) and *Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use* (*Ph. Eur.*, 5.1.4). To prevent microbial contamination during storage, herbal suppository formulation product, in accordance with the requirements of *Ph. Eur.*, must have an effective preservative effect. Microbial purity of herbal suppository formulation product was provided by the preservative action of the active ingredients and appropriate production conditions.

To determine the effectiveness of the preservative action used the following test strains of microorganisms: *Staphylococcus aureus* (ATCC 6538); *Pseudomonas aeruginosa* (ATCC 9027); *Candida albicans* (ATCC 885/653); *Aspergillus brasiliensis* (ATCC 16404); *Escherichia coli* (ATCC 8739); *Salmonella enterica* subsp. (ATCC 14028).

The culture of microorganisms was cultured at 35 °C for 18–24 hours on nutrient medium No. 1. *C. albicans* – from 20 to 25 °C for 48 hours on medium No. 2 (*Ph. Eur.,* 2.6.13. Microbiological examination of non-sterile products: test for specified micro-organisms). Working suspensions of monocultures of test microorganisms in sterile 0.9% sodium chloride solution were prepared.

Samples of herbal suppositories were contaminated with a monoculture of one of the test microorganisms, providing a microbial load of 10^7 colony-forming units (CFU) per ml. To obtain a uniform distribution of microorganisms, the contaminated samples were thoroughly mixed. The samples were stored for 28 days at a temperature of from 20 to 25 °C, protecting from light.

Samples were taken from each test sample immediately after contamination and after 2, 7, 14 and 28 days and inoculated on an appropriate nutrient medium to determine the number of viable cells of microorganisms (bacteria and fungi).

The criterion for evaluating the effectiveness of the preservative action was to reduce the number of viable cells of microorganisms in the drug for a certain period of time after its contamination.

Dissolution test for lipophilic solid dosage forms (*Ph. Eur.*, 2.9.42): The study was carried out using a flow-through cell specifically intended for lipophilic solid dosage forms such as suppositories and soft capsules designed and created by engineers on the biomedical engineering faculty Igor Sikorsky Kyiv Polytechnic Institute. Dissolution medium was phosphate buffer, pH 7.2. Temperature of medium: 37 ± 0.5 °C. Carotenoids was extracted from disso-

lution media with hexane liquid-liquid extraction method. Collected samples at the outlet of the cell was filtered using an inert filter. The release rate of carotenoids was determined using UV-Vis spectrophotometer Shimadzu-1280 according validated in-house method. Absorbance of these solutions was recorded at 450 nm and the percentage content (mg%) of carotenoids, expressed as β-carotene, using the following expression was calculated:

$$X(\text{mg\%}) = (A \times b \times 2500)/(2773 \times \text{m}),$$

i.e., taking the specific absorbance of β-carotene to be 2773. A is absorbance of the test solution at 450 nm; b is average weight of suppositories, in grams, and m is weight of 1 suppository, in grams.

The quantity of the active substance dissolved in a specified time was expressed as a percentage of the content stated on the label.

Statistical methods. For each measurement, as well as their associated controls, the means and standard deviations of three replicates were determined. MS Excel (Microsoft, USA) and Statistica 9.0 (StatSoft Inc., USA) were used for quantitative statistics, and all data are represented as the mean ± standard deviation (SD). Student's t-test and ANOVA were used to analyze the differences between two or more groups, respectively, and $p < 0.05$ was considered to indicate a statistical difference.

Results

Pharmaceutical development for the herbal formulation, rectal suppositories, was carried out on the basis of own materials of search and experimental studies. The purpose of the development of this product was determined, which consisted in the selection of the optimal composition and technology, in the preservation of the pharmacotherapeutic properties of the product, followed by the formation of quality parameters and the production process. The correct selection of these parameters ensured the reproducibility of obtaining the herbal suppository formulation product, corresponding to all quality indicators in accordance with quality control methods, as well as the stability of the finished product in the form of rectal suppositories.

The development of the product was carried out using the raw materials of two manufacturers: EUROMED (Spain) and FLAVEX Naturextrakte GmbH (Germany).

At the previous stages of research [23, 24], we justified the design (qualitative and quantitative composition of active ingredients) of Saw palmetto fruits, Lovage radix and Common marigold (calendula) flowers CO_2 extracts.

Formulation design and optimization

Selection of excipients. The composition of the excipients was selected taking into account the compliance of the main indicators of the quality of suppositories (disintegration, dissolution, uniformity of dosage) and the possibility of using the technological equipment for the technological process of obtaining suppositories.

The excipients incorporated into the formulated product are selected based on stringent criteria to ensure compatibility, safety, and efficacy. These criteria include: non-Interaction with Active Substances, ensuring that the specific pharmacological activity of the APIs is not compromised. Excipients should not interact with each other, the materials of the primary packaging, or the technological equipment used in the manufacturing process. This prevents any adverse effects on the product's stability and efficacy. The selected excipients must be non-toxic, ensuring the overall safety of the product for human use. The physicochemical and technological characteristics of the excipients should be such that they provide the desired therapeutic effect with the minimal required quantity. Excipients must meet stringent chemical and microbiological purity standards. They should also comply with the specified physicochemical indicators outlined in the quality control methods for pharmaceutical formulations. Excipients must be stable under storage conditions, ensuring the product shelf life and efficacy over time.

The choice of a specific base depends on the physicochemical properties of the lipophilic CO_2 extracts, such as solubility, stability, and interaction with the base. Typically, hydrogenated vegetable oils and emulsifying bases are the best choices due to their high lipophilicity and stability. But to select an appropriate excipients solid fat, emulsifying bases and synthetic or semi-synthetic bases was studied. Hydrogenated vegetable oil such as cocoa butter, that has good lipophilic properties, high stability, and a melting point close to body temperature was chosen. As emulsifying bases Witepsol® and Suppocire®, hydrogenated glycerides with good lipophilic compatibility, was chosen.

Although more commonly used with hydrophilic substances, some PEGs can be compatible with lipophilic extracts, but this requires further investigation. Therefore, PEGs with high MW were also added to this study.

The effect of suppository bases on the release of the herbal extracts was studied using these suppository bases using the same production process (Table 1).

In pharmaceutical technology, tweed fat is used primarily as a carrier in rectal and vaginal drugs for local or systemic use. The choice of type and brand of base depends on many factors, the main of which are the physicochemical properties of the active substances, as well as the purpose and features of the use of drugs. Thus, bases with high melting point values are used for the manufacture of suppositories in countries with hot climates and for the introduction of fat-soluble substances that reduce the melting point of the base. Bases with low melting point values are used to incorporate insoluble active substances prescribed in large quantities. In this case, sedimentation is likely.

Bases with a low hydroxyl value are used for the manufacture of suppositories containing reactive active substances that can react with each other or with the base during the process and storage. Bases with a low value of the hydroxyl number, in contrast to others, are less malleable, and with rapid cooling can become excessively brittle. In addition to reactivity, the value of hydroxyl balance affects the hydrophilic properties of the system and, in turn, can change the rate of release of the active substance from the base and its adsorption in the body. The hydroxyl value also characterizes the resistance of the base to oxidation and, accordingly, to rancidity.

Particular attention must be given to three factors when preparing suppositories with cocoa butter base. Cocoa butter must not be heated above 35 °C because it is a polymorphic compound. Four major polymorphic forms (in order of increasing stability) are: γ (16–18 °C), α (21–24 °C), β1 (27–29 °C), β (34–35 °C) and β2 (36–37 °C). An overheat will convert this excipient to a metastable structure that melts in the 25 to 30 °C range. Thus, the finished suppositories would melt at room temperature and not be usable.

Compositions of PEG 1000:PEG 4000 (3:1) and PEG 1000:PEG 6000 (3:1) are also investigated to understand the influence of high MW PEG with melting range about 58°C and lower hydroxyl values (25–32 mg KOH/g for PEG 4000 and 15–22 mg KOH/g for PEG 6000).

Processing techniques for suppository preparation. The technology of herbal suppositories was selected taking into account local or systemic action, route of administration and physicochemical properties of API and excipients, their prescribed weight, method of preparation and the dispersed system to be formed.

The technology of suppositories was developed taking into account the physicochemical properties of active and auxiliary substances, their weight and existing technological equipment.

Molding (fusion) method was chosen as simple and fast process to obtain standardized suppositories. Molding involves first melting the suppository base, and then dispersing or dissolving the CO_2 extracts in the melted base. The mixture is removed from the heat and poured into a suppository mold. When the mixture has congealed, the suppositories are removed from the mold. The fusion method can be used with all types of suppositories.

As excipient available for this process different suppository bases are used. A suitable test was carried out to demonstrate the appropriate release of the active substances from suppositories intended for modified release or for prolonged local action.

Table 1: Overview of suppository bases and their impact on the release of herbal extracts using a standardized production process

Formulation	Excipient composition	Properties	Product form	Melting range (°C)	Hydroxyl value (mg KOH/g)
F1	Cocoa Butter	Hard fat	Pellets	31–35	1.72
F2	Suppocire® AML	Hard fat with additive (lecithin)	Pellets	34–38	<10
F3	Witepsol® H15	Hard fat	Pellets	33.5–35.5	5–15
F4	Polyethylene glycol 1000	Hydrophilic base	Waxy solid	33–40	107–118
F5	PEG 1000:PEG 4000 (3:1)	Hydrophilic base	Waxy solid	–	–
F6	PEG 1000:PEG 6000 (3:1)	Hydrophilic base	Waxy solid	–	–

Note. "–" – no available data.

Refined suppository technology consists of the following stages:

- production preparation: sanitary preparation, preparation for work, preparation of raw materials;
- production: weighing of raw materials;
- heating of active ingredients: extracts are heated up in the heating chamber at temperature (42.0 ± 2.0) °C to facilitate its mixing with suppository base. Control of critical step is temperature.
- preparation of suppository mass: melting of suppository base at temperatures (min 45.0, max 60.0) °C. In the course of the process, control of critical steps is temperature, uniformity of the melt (visually).
- introduction of active ingredients and mixing the two phases until homogeneous. Product temperature when the active substances are added should be (42.0 ± 2.0) °C. Homogenization is carried out under vacuum at (42.0 ± 2.0) °C and at least 40 min (max 90 min) at 600–1000 U/min in preparation vessel Glatt (Germany) or Unimix (India). The uniformity of homogenization is controlled visually (homogeneous yellow-green suspension, free of macroscopically visible particles);
- formation (production of suppositories). Filling processes passes in the FarmoRes machine (Italy). Product temperature of the finished suspension (filling temperature) and temperature of dosing pump should be (33.0 ± 2.0) °C. Mold time speed is 55–57 ms and temperature of the cooling unit per tunnel is (15.0 ± 2.0) °C. Sealing passes at (120.0 ± 2.0) °C.;
- packaging is provided in hard PVS film laminated with low-density PE (packaging of finished products, packaging in group packaging) with packaging machine Kartonetta (Germany). Cases containing each 10 suppositories are labelled with self-adhesive labels indicating batch number, code of drug product and shelf life and packed into carton boxes along with instruction; control of finished product, sampling, quarantine storage, permission for sale.

Almost all processes of suppository forming and filling passes in the FarmoRes machine.

As a result, herbal suppository formulation is solid, single-dose preparation. The shape, volume and consistency of suppositories are suitable for rectal administration. Herbal suppository formulation product contains three active substances dissolved in a suitable basis that melt at body temperature.

Physicochemical and microbiological characterization

As there are no special requirements for modified release or for prolonged local action. So, this test is excluded from the specification for the final product. The summary of the physicochemical characterization of the herbal suppository formulation is described in Table 2.

All suppositories exhibited acceptable weights, content uniformity, and disintegration time.

In the manufacture of suppositories containing dispersed active substances, measures are taken to ensure a suitable and controlled particle size. But supercritical extracts of raw material are lipophilic and mixed well with Witepsol® H15 and other fatty bases. Therefore, test for particle size is excluded from specification for final product.

Studies have shown that carotenoids have three absorption maxima by which they can be distinguished, but their determination by spectrophotometry is complicated by the fact that in the region 220–280 nm the spectrum of these substances coincides with the absorption maximum of tocopherols. Directly for carotenoids, the maximum absorption is observed at 425, 450 and 480 nm. Chlorophylls have absorption maxima at 663 and 645 nm (chlorophylls *a* and *b*, respectively). The absorbance values at 663 and 645 nm provided clear indicators of the release rates for chlorophylls *a* and *b*, respectively. Higher absorbance values corresponded to higher concentrations of the dissolved active substances, indicating more efficient release from the suppository base.

The content of chlorophylls *a* and *b* and the sum of carotenoids were calculated and release profiles was calculated.

The *in vitro* dissolution study of 12 individual suppositories of each formulation containing herbal extracts was conducted to evaluate the impact of different suppository bases on the release rate of carotenoids of calendula, proposed as characteristic marker for this assay. Using the *Ph. Eur.*, 2.9.42, dissolution test for lipophilic solid dosage forms, the study employed a flow-through cell specifically designed for such forms, as developed by the biomedical engineering faculty of Igor Sikorsky Kyiv Polytechnic Institute. This setup ensured that the dissolution conditions closely mimicked physiological environments, providing reliable and reproducible data. Phosphate buffer with a pH of 7.2 was chosen to simulate the neutral pH conditions typically found in the rectal environment. The medium

Table 2: Summary of physicochemical characterization of the herbal suppository formulation; Mean ± SD (%) ($p < 0.05$)

Physicochemical properties	F1	F2	F3	F4	F5	F6
Appearance	Yellow-green uniform color	Yellow-green uniform color	Yellow-green uniform color	Yellow uneven color, dark green inclusions	Yellow uneven color, dark green inclusions	Yellow uneven color, dark green inclusions
Shape	Torpedo	Torpedo	Torpedo	Torpedo	Torpedo	Torpedo
Fissuring	No	No	No	No	No	No
Length (cm)	3.00 ± 0.01	3.00 ± 0.01	3.0 ± 0.01	2.9 ± 0.04	3.00 ± 0.01	3.00 ± 0.01
Width (cm)	1.30 ± 0.05	1.30 ± 0.02	1.3 ± 0.01	1.3 ± 0.01	1.30 ± 0.03	1.30 ± 0.01
Weight variation (g)	2.01 ± 0.02	2.004 ± 0.57	1.998 ± 0.11	2.001 ± 0.14	1.978 ±0.59	2.054 ±1.22
Hardness (kg/cm^2)	3.641 ± 0.46	2.034 ± 0.12	2.311 ± 0.18	2.045 ± 0.17	3.283 ± 0.34	4.128 ± 0.10
Melting time at 37.5 °C (min)	3 ± 2.6	15 ± 0.4	32 ± 0.2	25 ± 1.6	27 ± 2.7	39 ± 3.3
Softening time at 36.5 °C (min)	6.5 ± 0.5	8 ± 1.7	6 ± 0.2	5 ± 0.01	10 ± 1.3	12 ± 0.9
Disintegration time (min)	5.5 ± 0.8	6 ± 1.3	15 ± 0.3	21 ± 0.01	26 ± 2.8	29 ± 3.7
Chlorophylls *a* content (% per suppository)	0.15 ± 0.45	0.19 ± 0.76	0.21 ± 1.12	0.10 ± 0.57	0.15 ± 1.13	0.12 ± 0.53
Chlorophylls *b* content (% per suppository)	0.08 ± 0.31	0.15 ± 0.91	0.13 ± 1.77	0.04 ± 1.89	0.06 ± 2.41	0.14 ± 0.74
Carotenoids content (% per suppository)	0.001 ± 1.22	0.001 ± 2.16	0.001 ± 2.54	0.001 ± 1.99	0.001 ± 2.44	0.001 ± 2.11

was maintained at 37 ± 0.5 °C, replicating the human body temperature to ensure physiological relevance.

Collected samples at the outlet of the cell were filtered using an inert filter to remove any undissolved particles or impurities, ensuring that only the dissolved active substances were measured. UV-Vis spectrophotometry method allowed for precise and accurate quantification of the active substances such as release rates of carotenoids (Fig. 1).

The results indicated that the choice of suppository base significantly influenced the dissolution rate of the active herbal extracts. Each base's physicochemical properties, such as hydrophilicity, melting point, and compatibility with the herbal extract, played a crucial role in modulating the release profile (Figs. 2–7 and Table 3).

The absorbance values at 450 ± 2 nm provided clear indicators of the release rates for carotenoids. Higher absorbance values corresponded to higher concentrations of the dissolved active substances, indicating more efficient release from the suppository base. The relative standard deviation of the mean value for each release time point was less than 20% at the first control point and no more than 10% from the second to the last control point. None of the trials fell within the data bias. However, for some sampling points, the relative standard deviation approached the critical value. Even with the same formulation, slight differences in the distribution of active ingredients and excipients can occur, leading to variations in release profiles. Also, small variations in sampling and analysis can lead to differences in the curves, especially if the process is not perfectly standardized. Samples were taken manually from the dissolution tanks, so this could lead to deviations in the measurements.

To determine the order of carotenoid release kinetics from suppositories, linear dependences were constructed for the zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Hickson-Crowell models. The model with the highest R^2 is considered the most appropriate for describing the kinetics of the release of carotenoids from this formulation of the suppository base.

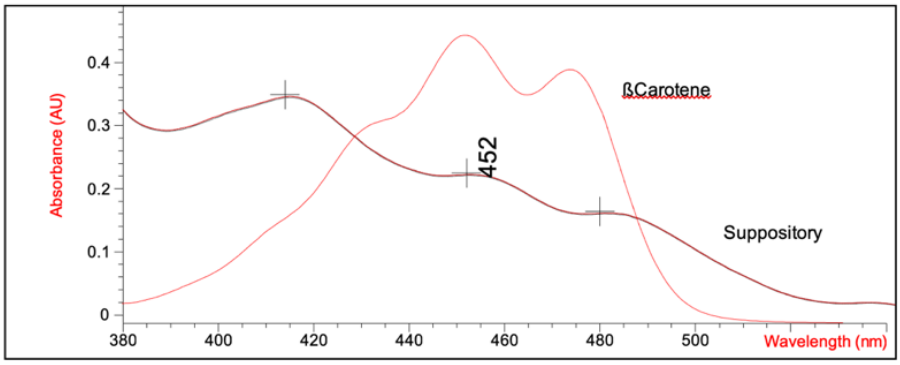

Figure 1: UV-Vis spectral characteristics of herbal suppository with Whitepsol® H15 as suppository base and β-carotene standard

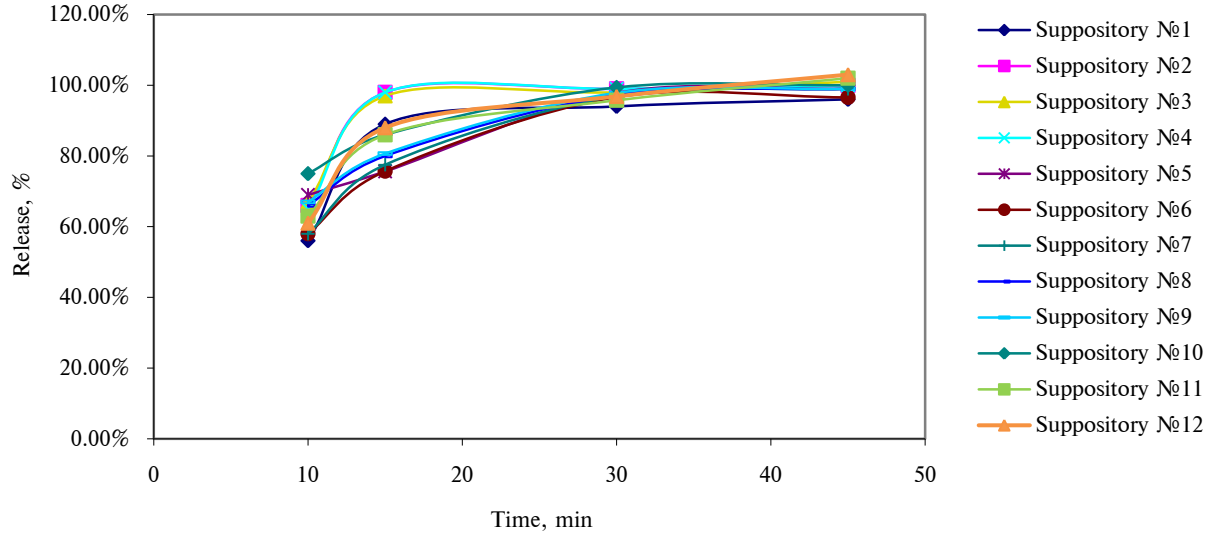

Figure 2: Dissolution profiles for herbal suppository formulation with cocoa butter (F1) as suppository base

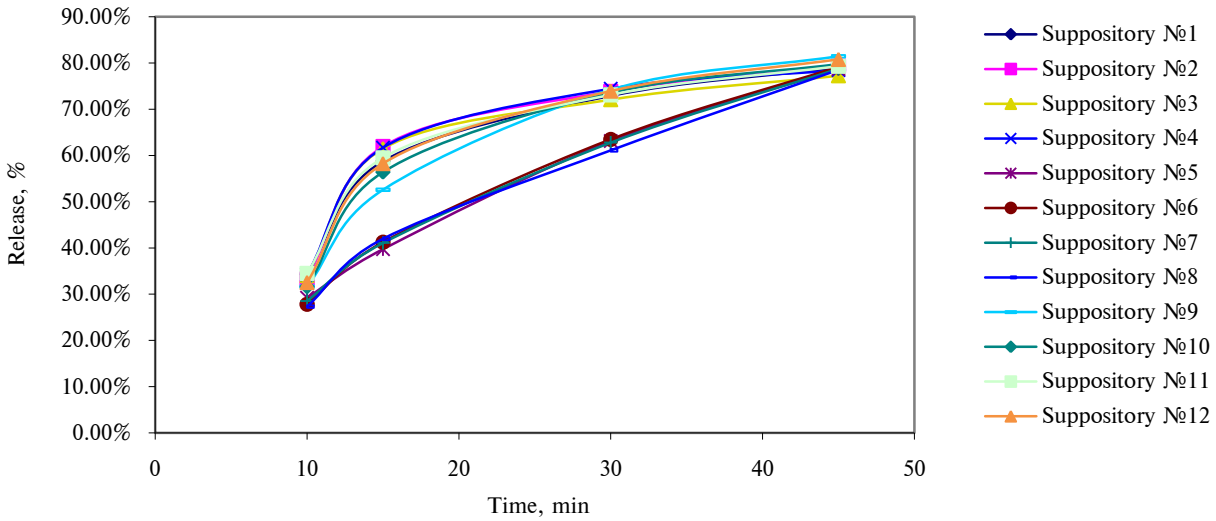

Figure 3: Dissolution profiles for herbal suppository formulation with Suppocire® AML (F2) as suppository base

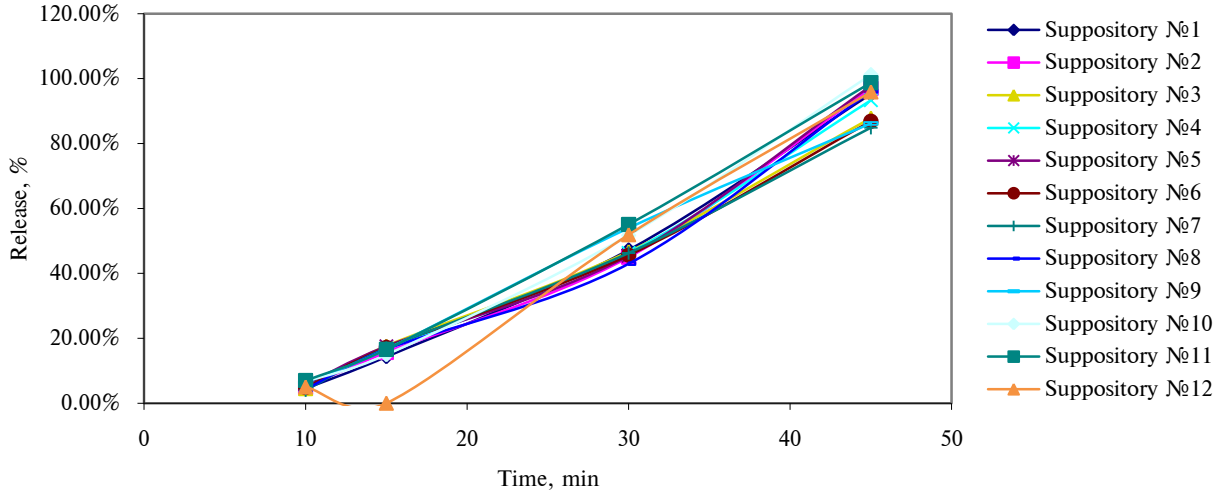

Figure 4: Dissolution profiles for herbal suppository formulation with Whitepsol® H15 (F3) as suppository base

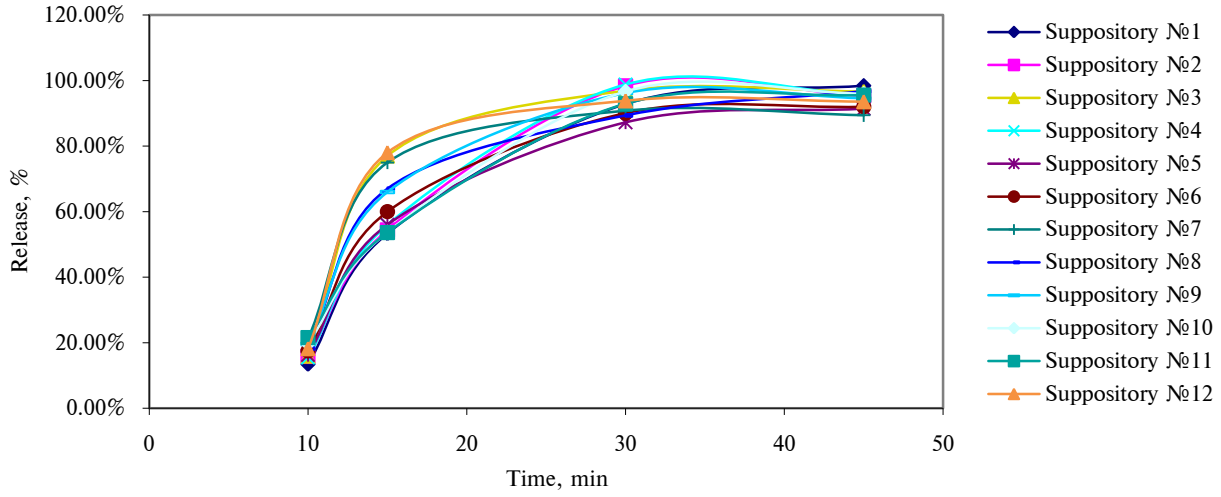

Figure 5: Dissolution profiles for herbal suppository formulation with polyethylene glycol 1000 (F4) as suppository base

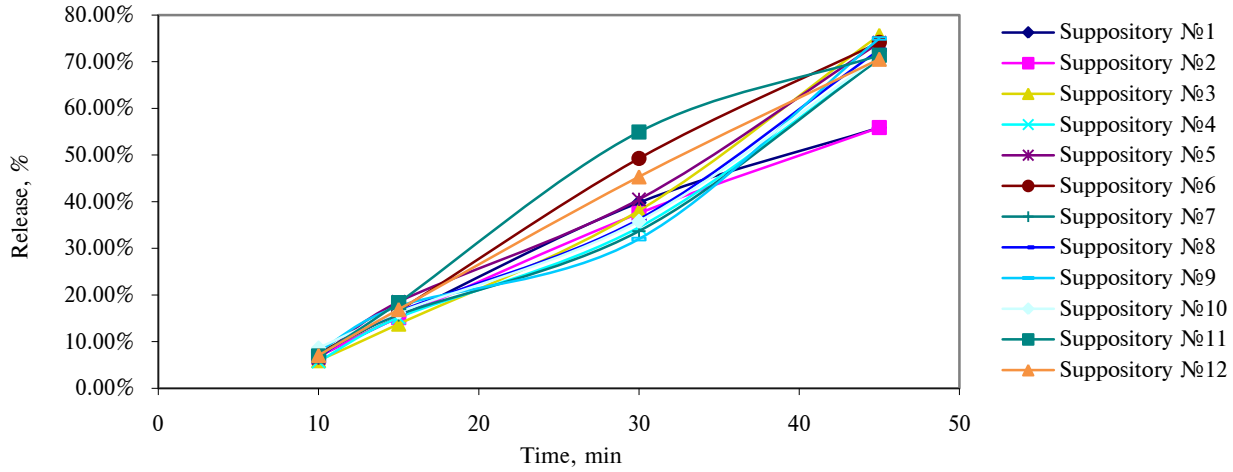

Figure 6: Dissolution profiles for herbal suppository formulation with PEG 1000:PEG 4000 (3:1) (F5) as suppository base

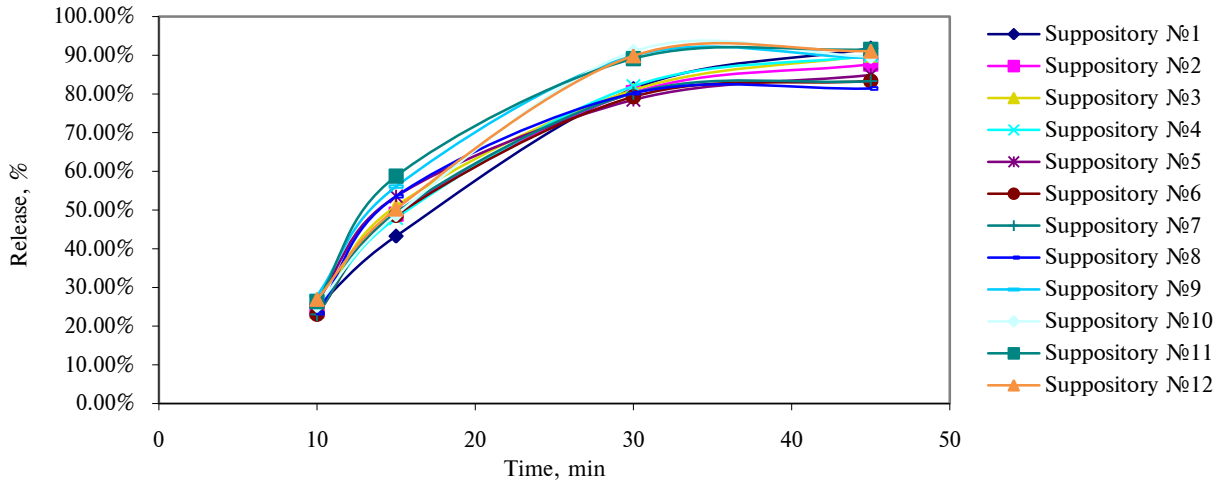

Figure 7: Dissolution profiles for herbal suppository formulation with PEG 1000:PEG 6000 (3:1) (F6) as suppository base

Table 3: Summary of results of studying the carotenoids release content from herbal suppository product with different suppository bases and release kinetic modeling

Release kinetic models	F1	F2	F3	F4	F5	F6
Carotenoids, % (average release percentage after 45 min experiment)*	99.95	79.22	93.42	94.62	69.77	87.85
Zero-order model kinetics R^2	0.6463	0.8716	**0.9549**	0.8407	**0.9799**	0.8955
First-order model kinetics R^2	**0.9862**	0.9726	0.8128	**0.9083**	0.9261	**0.9445**
Higuchi model kinetics R^2	0.8941	**0.9761**	0.7439	0.8708	0.8034	0.9314
Korsmeyer-Peppas model kinetics R^2	0.9661	0.9521	0.5832	0.8141	0.6521	0.8722
Hickson-Crowell model kinetics R^2	0.8962	0.9467	0.8705	0.8979	0.9485	0.9363

The study found that the release rates of carotenoids varied with different suppository bases, reflecting the bases' ability to interact with and release the herbal extracts into the dissolution medium.

As can be seen from Figs. 5–7, about 95% of lipophilic components passed from suppositories based on PEG 1000 (F4) in solution in 30 min, except for its combination with other PEGs of various scales (F5 and F6), which are solid substances and releases 40–50% of lipophilic components. A significant discrepancy in the results for the F4 composition is possible due to the poor miscibility of the lipophilic active substances and the hydrophilic base.

From suppositories based on Witepsol® H15 (F3) and Suppocire® AML (F2) – about 60% in 30 min, but the release is more linear and long-lasting.

Higuchi kinetics observed in suppositories based on Suppocire® AML describe the release of the active component from the matrix, where the process is controlled by diffusion. This means that the active component is distributed in the matrix and is released as the liquid (for example, rectal or vaginal fluids) penetrates into the suppository. Suppocire® AML can be a good choice for active ingredients that require controlled and slow release. This is especially important for drugs that have a long-lasting effect and must maintain a constant level of the active ingredient at the site of action or in the blood. However, suppositories based on Suppocire® AML also gave a significant error in the results (RSD 9.15% for values of 12 suppositories at the sampling point of 15 min), so this basis was rejected for further studies.

Witepsol-based suppositories are subject to zero-order kinetics. This may be due to the specificity of the release of the active component from the base of the suppository, which is released at a constant rate. The results of the experiment show that the selected amount of lipophilic extracts in the samples based on Witepsol® H15 ensures a complete and prolonged release of lipophilic components, which allows maintaining its effective concentration in the large intestine for a long time. In addition, it was for this formulation that the smallest deviations in values were observed (RSD 0.98–5.53%).

Suppositories based on cocoa butter (F1) melted too quickly and, accordingly, released lipophilic substances completely but at an undesirable rate. However, this basis is suitable for cases where the release of the drug must be fast and concentration-dependent. This can be useful when a rapid onset of action of the drug is required.

These findings underscore the importance of selecting an appropriate suppository base for optimizing the release of active herbal extracts. Formulators must consider the physicochemical interactions between the base and the extract to achieve the desired therapeutic effect. Bases that demonstrate controlled and higher release rates for the active substances could be more effective in delivering the herbal extracts *in vivo*.

According to the *Ph. Eur.*, 5.1.4. (Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use) the presence of certain micro-organisms in non-sterile preparations may have the potential to reduce or even inactivate the therapeutic activity of the product and has a potential to adversely affect the health of the patient. Microbial examination of non-sterile products such as herbal suppository formulation product under development is performed according to the methods given in general chapters 2.6.12 and 2.6.13. Acceptance criteria for non-sterile products based upon the total aerobic microbial count (TAMC) and the total combined yeasts/moulds count (TYMC) are given in Table 4.

Acceptance criteria are based on individual results or on the average of replicate counts when replicate counts are performed (e.g. direct plating methods).

The results of studying the effectiveness of antimicrobial preservative action of suppository product are presented in Table 4.

Based on the research, it is possible to conclude that the effectiveness of antimicrobial preservative action against bacteria and fungi of suppositories with lipophilic compounds meet the requirements of *Ph. Eur.* (criterion "A").

According to *Ph. Eur.* 11.0 rectal suppositories with herbal drugs and herbal drug preparations present in the dosage form are not subject to the provisions of Uniformity of dosage units (2.9.40).

According to *Ph. Eur.* 11.0 test for Uniformity of content of single-dose preparations (2.9.6) is not necessary as herbal suppository formulation product contains more than one active substance and the content of active substances is more than 2 mg and more than 2% of the total suppository mass.

Discussion

The development and evaluation of novel herbal suppository formulations for the treatment

Table 4: Summary of results of studying the effectiveness of antimicrobial preservative action of herbal suppository product with Witepsol® H15 as suppository base (CFU/g)

Types of microorganisms for antimicrobial testing	Microbial load	Acceptance criteria	Primary sowing Log	2 days	7 days	14 days	28 days
TAMC	10^6	10^3	–	–	–	8	25
TYMC	10^6	10^2	–	–	–	–	6
Staphylococcus aureus ATCC 6538	$5.5 \cdot 10^5$	Absence in 1 g	$5.0 \cdot 10^5$	$3.2 \cdot 10^4$	$1.1 \cdot 10^2$	–	–
Pseudomonas aeruginosa ATCC 9027	$5.5 \cdot 10^5$	Absence in 1 g	$5.0 \cdot 10^5$	$4.8 \cdot 10^4$	$2.3 \cdot 10^3$	$6.2 \cdot 10^2$	–
Candida albicans ATCC 885/653	$5.5 \cdot 10^5$	Absence in 1 g	$5.0 \cdot 10^5$	$4.6 \cdot 10^4$	$5.0 \cdot 10^3$	$2.0 \cdot 10^2$	–
Aspergillus brasiliensis ATCC 16404	$5.5 \cdot 10^5$	Absence in 1 g	$5.0 \cdot 10^5$	$7.5 \cdot 10^4$	$1.7 \cdot 10^2$	–	–
Salmonella enterica ATCC 14028	$5.5 \cdot 10^5$	Absence in 10 g	$5.0 \cdot 10^5$	$5.9 \cdot 10^3$	$1.1 \cdot 10^2$	–	–
Escherichia coli ATCC 8739	$5.5 \cdot 10^5$	Absence in 1 g	$5.0 \cdot 10^5$	$1.1 \cdot 10^3$	$0.5 \cdot 10^2$	–	–

Note. "–" – studies were not conducted.

of prostatitis present a promising alternative to traditional therapies, which often involve antibiotics and anti-inflammatory drugs with limited efficacy and undesirable side effects. This study focused on designing suppositories using herbal extracts known for their anti-inflammatory and therapeutic properties, aiming to optimize their formulation characteristics and therapeutic potential.

The idea of using plant components for rectal application in the inflammation diseases treatment is not new. Traditional medicine of Asia countries widely uses this approach [28–30].

The selection of herbal ingredients for herbal suppository formulation product is based on extensive documentation of their anti-inflammatory and therapeutic effects on prostatitis. Drug product contains three active ingredients – Saw palmetto fruits CO_2 extract, Lovage radix CO_2 extract and Common marigold (calendula) flowers CO_2 extract. The efficacy of these extracts is supported by both traditional use and contemporary scientific research, providing a robust justification for their inclusion in the formulation.

The active ingredients for herbal suppository formulation product are derived through supercritical fluid extraction using natural carbon dioxide (CO_2). This method ensures that the extracts are free from solvent residues, inorganic salts, heavy metals, and reproducible microorganisms. Supercritical CO_2 extraction is highly effective at selectively removing non-polar components with molecular weights less than 2,000 daltons. These components include aldehydes, terpene compounds, ketones, fat-soluble vitamins, esters, and alcohols, as well as high molecular weight saturated and unsaturated fatty acids. In contrast, proteins, starches, sugars, glycosides, mineral salts, and water are insoluble in liquid CO_2, ensuring their exclusion from the final extract. This purity and specificity of the extracts underpin the therapeutic potential of herbal suppositories, particularly in the treatment of prostatitis.

Saw palmetto CO_2 extract is rich in essential fatty acids (especially, oleic acid, lauric acid, and caprylic acid), sterols, and fatty alcohols [31], known for their anti-inflammatory and 5α-reductase enzyme inhibitory effects [32, 33] and is suitable for inclusion in a rectal suppository formulation for prostatitis treatment. The recommended dosage of 150 mg per suppository falls within the effective therapeutic range [34], providing sufficient bioavailability to reduce inflammation and promote urinary health. Lovage CO_2 extract's composition includes *cis*-ligustilide, phthalides, falcarinol, and phytosterols [35, 36] that ensures high anti-inflammatory, analgesic, antispasmodic, antioxidant, and diuretic properties, making it suitable for treating lower urinary tract conditions in 50 mg dosage [22].

Incorporating of 50 mg calendula CO_2 extract into suppository formulations for prostatitis treatment leverages its rich bioactive profile [37], including carotenoids, flavonoids, saponins, sterols, phenolic acids, and lipids [38–41]. Calendula's antimicrobial properties, as described in [17, 42], help manage infections that can worsen prostatitis, primarily due to its faradiol esters [43], while its antioxidants protect prostate tissue from oxidative damage.

According the requirements for suppositories and pessaries [44], to ensure their high efficiency and safety, it is necessary to theoretically and experimentally substantiate all pharmaceutical factors that affect the quality of the product: the nature of API, physical properties of active and excipients, quantity of suppository base (degree of dispersion, polymorphism, solubility, viscosity and other structural and mechanical characteristics), technological operations and equipment.

To allow for proper administration and drug delivery, suppositories require careful consideration of the following parameters: hardness, shape, drug solubilization, and melting range. Those parameters were achieved by usage of adequate excipients and preparation method.

The herbal suppositories were assessed for various quality parameters, including organoleptic characteristics (color, surface, odor, consistency), average mass, melting point, deformation time, disintegration time, and pH. The results indicated that the formulations with lipophilic bases exhibited satisfactory organoleptic characteristics, with consistent color, surface, odor, and consistency. The melting points were appropriate, ensuring that the suppositories would remain stable under normal storage conditions and melt at body temperature. Deformation and disintegration times were within acceptable limits, indicating that the suppositories would effectively release the active compounds upon administration. The pH levels were also within the required range, ensuring compatibility with the rectal environment and minimizing the risk of irritation.

Microbiological tests confirmed that the total aerobic microbial count (TAMC) and total yeast and mold count (TYMC) were within acceptable limits, ensuring the microbiological purity of the suppositories. This is crucial for patient safety, as it minimizes the risk of introducing pathogens into the body during treatment.

To achieve the desired therapeutic effect, it is important to take into account the pharmacokinetics of the active components. Active ingredients with different solubility and stability properties may be better released from certain bases. For example, chronic conditions may require a sustained release of the drug, making Witepsol® H15 a better choice. For acute conditions where a rapid onset of action is required, bases that provide first-order kinetics, such as cocoa butter or PEG 1000, may be preferable.

The addition of emulsifiers or stabilizers can improve the release properties of the active ingredient from the suppository base, as it was done by Melnyk *et al.* in [45] by addition of emulsion wax to cocoa butter for creation of vaginal suppositories with hyaluronic acid and CO_2 extracts of aloe, calendula and green tea. Biopharmaceutical studies revealed that herbal suppositories with only lipophilic CO_2 extracts formulated with Witepsol® H15 had the optimal release rates of active compounds compared to those made with other fatty and hydrophilic bases, it melts under acceptable temperature conditions, do not have polymorphic forms and mix well with active herbal ingredients. The latter statements are also substantiated by other researchers [46–48].

This finding underscores the importance of selecting an appropriate base to optimize the delivery of active herbal ingredients. The enhanced release profile observed with Witepsol® H15 suggests that it can improve the therapeutic outcomes of the suppositories by ensuring a more efficient delivery of the herbal extracts to the site of inflammation and could serve as a viable alternative to conventional treatments, offering patients a natural and efficacious option for managing prostatitis.

Further clinical studies are warranted to confirm these results and fully establish the therapeutic potential of these formulations. Clinical trials will help determine the efficacy and safety of the herbal suppositories in a larger patient population and under real-world conditions. Additionally, exploring the long-term stability of the formulations and their effects on various stages of prostatitis could provide deeper insights into their therapeutic benefits.

In conclusion, the study's findings highlight the potential of herbal suppositories formulated with Witepsol® H15 to offer a natural, effective, and safe treatment option for prostatitis. This approach not only leverages the therapeutic properties of herbal extracts but also addresses the limitations of conventional therapies, potentially improving the quality of life for patients suffering from this condition.

Conclusions

This study successfully designed, developed, and evaluated novel herbal suppository formulations for the treatment of prostatitis. By selecting lovage CO_2 extract, saw palmetto CO_2 extract, and calendula CO_2 extract for their potent anti-inflammatory and therapeutic properties, and utilizing Witepsol® H15 as the suppository base, we achieved formulations that met key quality parameters and demonstrated significant potential for therapeutic efficacy.

Witepsol® H15 was identified as the optimal base, providing favorable physicochemical properties and superior release rates for the active herbal ingredients compared to other tested bases.

The herbal suppositories exhibited satisfactory organoleptic characteristics, appropriate melting points, deformation and disintegration times, and pH levels within the required range, ensuring compliance with the standards of the European Pharmacopoeia.

The formulations maintained microbiological purity, with TAMC and TYMC within acceptable limits, ensuring suppositories' suitability for patient use.

Biopharmaceutical evaluations demonstrated that the suppositories formulated with Witepsol® H15 had the highest release rates of active compounds, indicating a more efficient delivery of herbal extracts.

These findings suggest that the developed herbal suppository formulations could serve as a viable alternative to conventional treatments for prostatitis, offering a natural and potentially effective therapeutic option.

Future clinical studies are recommended to further validate these results and establish the full therapeutic potential of these formulations in a clinical setting. Such studies will be critical in confirming the efficacy and safety of the herbal suppositories and their long-term benefits for patients with prostatitis.

In summary, the novel herbal suppository formulations developed in this study hold significant promise for advancing the treatment of prostatitis, providing a natural and efficacious alternative to conventional therapies, and potentially improving the quality of life for affected individuals.

Interests disclosure

Oleksandra Dmytrenko reports being employee of "UA "PRO-PHARMA" LLC; she does not declare any competing interests. Alexander Galkin is the Editor-in-Chief and Olena Golembiovska is the member of the editorial board of *Innovative Biosystems and Bioengineering*, they were not involved in the editorial evaluation and decision-making on the publication of the article.

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ДИЗАЙН ТА РОЗРОБКА НОВОЇ РЕЦЕПТУРИ РОСЛИННИХ СУПОЗИТОРІЇВ ДЛЯ ЛІКУВАННЯ ПРОСТАТИТУ

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Проблематика. Простатит – поширене запальне захворювання, що вражає передміхурову залозу і яке часто лікується антибіотиками та протизапальними препаратами, що можуть мати обмежену ефективність і побічні ефекти. Фітотерапія пропонує перспективну альтернативу завдяки своїм природним протизапальним властивостям.
Мета. Дослідження спрямоване на дизайн, розробку та оцінку фізико-хімічних, біофармацевтичних і мікробіологічних властивостей нових фітосупозиторіїв для лікування простатиту з фокусом на оптимізації їхніх біофармацевтичних профілів.
Методика реалізації. Для створення супозиторіїв були відібрані допоміжні речовини для комбінації їх із трав'яними інгредієнтами, відомими своїми протизапальними властивостями, зокрема CO_2-екстрактами любистку, карликової пальми та календули. Супозиторні композиції з різними основами оцінювали за ключовими якісними параметрами, такими як органолептичні характеристики, середня маса, точка плавлення, час деформації, час розпаду, мікробіологічна чистота та pH, що забезпечують відповідність стандартам Європейської фармакопеї. За допомогою біофармацевтичних досліджень порівнювали профілі вивільнення активних сполук із різних супозиторних основ.
Результати. Супозиторії на основі Witepsol® H15 продемонстрували задовільні органолептичні властивості, відповідні точки плавлення і прийнятні часи деформації та розпаду. Рівні pH відповідали вимогам, а мікробіологічні тести підтвердили чистоту. Біофармацевтичні оцінки показали, що супозиторії на основі Witepsol® H15 мали найкращі швидкості вивільнення активних сполук порівняно з іншими основами.
Висновки. Нові фітосупозиторії, розроблені в цьому дослідженні, на основі попередніх оцінок їхніх фізико-хімічних, мікробіологічних і біофармацевтичних властивостей демонструють значний потенціал для лікування простатиту. Проте потрібні додаткові клінічні дослідження для підтвердження їхньої ефективності та безпеки.

Ключові слова: простатит; рослинні супозиторії; Witepsol® H15; протизапальна активність; терапевтичні композиції.