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THE OINTMENT CONTAINING $Ag@Fe_3O_4$ FOR REMOVAL AND TREATMENT OF SKIN NEOPLASMS

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Aim. *Priorities for improving the thermal conductivity values and the external controllability of the process of cryosurgical intervention have determined. The aim of this work is creation of soft dosage forms with a highly heat-conductive magnetic carrier of the multifunctional action for removal and treatment of skin neoplasms.*
Methods. *At the initial stage the required parameters and properties of the magnetic component introduced into the composition of magnetocontrollable ointments have been determined. The screening of the antimicrobial activity in terms of the impact of the composite on strains of microorganisms and fungi has been carried out. The magnetite ointments have been tested by the cryodestruction method of removal and treatment of skin neoplasms. For this purpose a special portable apparatus CRY-AC (Brymill) and a contact cryoprobe with nozzles are used.*
Results. *Based on the results of the research of the magnetic properties of the composite nanoparticles the sample has been selected, it has a high value of saturation specific magnetization σ=62.5 emu/g, the nanoparticle size (23 nm) has been determined. The presence of silver on the surface of magnetic nanoparticles makes a significant additional contribution to the thermal conductivity of the composite (the thermal conductivity coefficient of magnetite χ is ~5.3 W/(m×K), silver is 420 W/(m×K)), being one of the valuable properties for using it in cryosurgery.*
The composition of magnetocontrollable ointments I and II for cryodestruction and post-operative treatment of skin neoplasms has been developed and improved by the main magnetic indicators.
Conclusions. *To order to use ointments with a magnetic filler in cryosurgery the magnetic carrier of the "core-shell" type – $Ag@Fe_3O_4$ with the islet silver coating has been synthesized and tested.*
The advantages of the magnetite ointments with silver in cryointervention and postoperative treatment of skin neoplasms have been found. The use of ointment I has contributed to increase of the analgesic effect by 28 %, and decrease of the cryosurgery duration by 50 %. For the subsequent treatment and healing of wounds after surgical procedures ointment II is used, it improves the post-operative results on an average by 50 %
Key words: *nanoparticles, magnetocontrollable composite system, silver shell, magnetite ointment, cryoscopy*

Мета. *Вирішення першочергових завдань підвищення показників теплопровідності і зовнішньої керованості процесом кріохірургічного втручання визначило мету даної роботи - створення м'яких лікарських форм з високотеплопровідні магнітним носієм багатофункціональної дії для видалення і лікування новоутворень шкіри.*
Методи. *На початковому етапі встановили і визначили необхідні параметри і властивості магнітного компонента, введеного до складу магнітокерованих мазей. Проведено скринінг антимікробної активності за показниками впливу композиту на штами мікроорганізмів і грибів. Випробувано магнетитові мазі в кріодеструктівному методі видалення і лікування новоутворень шкіри, для цього використовували спеціальний портативний апарат CRY-AC, Brymill і контактний кріозонд з насадками.*
Результати. *За результатами досліджень магнітних властивостей наночастинок композитів обраний зразок, який має високий показник питомої намагніченості насичення σ=62,5 emu/g, встановлений розмір наночастинок – 23 нм. Присутність срібла на поверхні магнітних наночастинок вносить істотний додатковий внесок в теплопровідність композиту (коефіцієнт теплопровідності χ магнетиту ~5,3 Вт/(м×К), срібла ~420 Вт/(м×К)), що характеризує один з цінних властивостей для використання його в кріохірургії.*
За основними магнітними показниками розроблений і оптимізований склад магнітокерованих мазей I і II для кріодеструкції та післяопераційного лікування новоутворень шкіри.
Висновки. *Для використання в кріохірургії мазей з магнітним наповнювачем, синтезовані і апробована магнітний носій типу «ядро-оболонка» –$Ag@Fe_3O_4$ з срібним острівковим покриттям.*
Встановлено переваги магнетитових мазей з сріблом при кріовтручання і післяопераційному лікуванні новоутворень шкіри. Використання мазі I сприяло збільшенню анальгетичного ефекту на 20 %, глибини заморожування на 28 %, зменшення тривалості кріовпливу на 50 %. Для подальшого лікування і загоєння рани після хірургічних маніпуляцій була використана мазь II, яка покращила післяопераційні показники в середньому на 50 %
Ключові слова: *наночастинки, композитні магнітокеровані системи, срібна оболонка, магнетитові мазі, кріоскопія*

1. Introduction

In development of nanopharmacy the magneto-containing medicines take the first place [1]. To create external magnetic controlled drugs the studies are carried out in development of magnetic ointment compositions, pastes-concentrates, ointment bases and magnetic rectal suppositories [2, 3]. A modified magnetite is typically used as a magnetic filler of the ointment compositions [4]. Compatibility of nanoparticles of magnetite and traditional components of the ointment compositions in one dosage form has been proven by various studies [5].

At the intersection of many medical disciplines the current trend is to improve the use of new instrumental technological systems and devices that allow using the latest methods to diagnose and treat skin neoplasms in various pathological conditions. Typically, skin neoplasms have a papilloma-viral nature. One of the ways to optimize the existing methods for removal of benign neoplasms of the skin is the search for fundamentally new approaches that, in turn, will give an undeniable effect.

2. Formulation of the problem in a general way, the relevance of the theme and its connection with important scientific and practical issues

Low temperatures for destruction of various pathological tumors of the skin are widely used in medicine. Modern special cryogenic equipment allows affecting the pathological focus in the mode of spraying or contact method using a cryoadapter with a specially designed nozzle. Limiting abilities of the cryogenic method are due to thermophysical properties of tissues. It has been found that thermal conductivity and the cooling rate are the factors that determine the effect of cryodestruction. Thus, despite the advances and opportunities of the local low-temperature destruction the issue of intensification of the destructive action and increase of controllability of the cryological process itself remains open.

There are still many disadvantages in the existing approaches and methods of cryodestruction of skin neoplasms. Upon contact with a metal nozzle, which liquid nitrogen is supplied to, tissues are immediately cooled to very low temperatures. This leads to a simultaneous freezing of intercellular and intracellular water with formation of ice microcrystals and increased concentration of the cellular material to the toxic cell level. There is also a problem of the pathological focus freezing on a particular area and depth. Thus, direct cryodestruction of the surface in the damaged area does not always provide the ability to carry out the local freezing quickly and efficiently on the particular surface without damaging the healthy skin, and to the sufficient depth covering the entire affected thickness without leaving damaged tissues. Due to these disadvantages the harmful effect of freezing significantly increases.

3. Analysis of recent studies and publications in which a solution of the problem and which draws on the author

Analysis of the literature sources [6] shows that in practice such methods of treatment of the skin neoplasms as surgical (removal with a scalpel), cryotherapy (liquid nitrogen), electrocoagulation or diathermocoagulation (thermal effect on the tissue), chemical coagulation (the use of special chemical reagents causing the death of tissue), laser method (removal by the laser beam) are applied. Cryodestruction is the most common method due to the positive aesthetic effect, virtually painless manipulations, simplicity of the procedure, etc. [7]. This method is of the local action of low temperatures with a curative effect, in which the tissues to be removed are subjected to destruction by freezing with liquid nitrogen.

A review of the literature and results obtained in practice show that instrumental cryodestruction having the low rate of cooling of tissues does not guarantee the completeness and depth of cooling.

Tissue have rather low thermal conductivity (0.38 kcal×m/h/°C), and it is a natural limitation of the possibilities of the cryogenic method [8]. When measuring the temperature gradient in tissues by cryodestruction it has been found that the temperature is -160°C on the surface; and in about 7-8 min of the exposure only 0°C is recorded on the depth of 1.5–2.5 cm. It indicates the thermodynamic equilibrium and the growth termination in the freezing area.

Medical cryology has an experience of using ointments and creams [9]. But this treatment has some drawbacks, namely application of ointments and sprays on the affected area requires special requirements, damage of healthy tissues near the focus can cause complicated burns, they are not able to penetrate into the full thickness of lesions, and the relapse persists, the injury zone is not anesthetized causing discomfort, etc. That is why the use of soft magnetic dosage forms is rather promising in cryology. Their advantage is determined by the fact that using an external magnetic field they can penetrate to a sufficient depth and due to the high thermal conductivity facilitate freezing of the entire thickness of the affected tissues. Under the action of the external magnetic field the magnetic nanoparticles in the ointment are arranged in chains, remained on the surface by "one drop" and due to heterogeneity of the surface deeply immersed into the base of the focus of inflammation, thereby evenly settling in the affected area and around it [10].

Creation of externally controllable ointments (a filler – magnetite nanoparticles with the islet silver coating – $Ag@Fe_3O_4$) with a high thermal conductivity (the thermal conductivity coefficient χ of magnetite is ~5.3 W/(m×K), silver is ~ 420 W/(m×K)) and the use of an external magnetic field for penetration of the ointment to the entire depth of the affected focus due to the uneven surface of the tumor (penetration of nanoparticles of this size is impossible in healthy undamaged tissues) provide the increase of cryoeffect almost by 50 %.

It is known that skin neoplasms can be burnt by “lapis” (silver nitrate). It has necrotizing and antiseptic properties, but its efficiency is very low since it remains only on the surface. Creation of an ointment containing magnetite modified with silver provides the appearance of bactericidal, bacteriostatic and wound-healing properties of such a system since silver ions help to restore the skin damaged tissues, destroy old and cancer cells, normalize the state in inflammatory processes, etc. [11].

4. Allocation of unsolved parts of the general problem, which is dedicated to the article

To improve the efficiency of the cryodestruction process and the external controllability of cryosurgical intervention it is necessary to solve several problems: development of a magnetocontrollable component with a high thermal conductivity; its introduction in a soft dosage form, which, in turn, will provide penetration of the substance to the entire depth of the affected focus under the action of the external magnetic field, in addition to the analgesic effect of deep freeze, as well as reduce the time for surgery and healing; simplification of the operation due to the properties of the ointment components and their easy availability.

5. Formulation of goals (tasks) of Article

The aim of this work is to introduce the magnetite ointment consisting of a magnetic carrier with the islet silver coating of the "core-shell" type – $Ag@Fe_3O_4$ [12, 13] in the known method of cryodestruction of skin neoplasms. The ointment proposed contains ingredients that reveal the anti-bacterial, analgesic, anti-inflammatory and wound-healing properties.

6. Statement of the basic material of the study (methods and objects) with the justification of the results

The object of research is the nanocomposite, which is part of the ointment intended for cryotherapy on skin neoplasms. Ointments I and II were developed with the participation of professor D.I. Dmytryevsky. Optimization of the magnetite ointment composition included the stage of substantiation of the required properties of $Ag@Fe_3O_4$ magnetocontrollable nanocomposite by microbiological indicators – the impact of the composite on such strains of microorganisms as S. aureus ATCC 25923, Str. pneumoniae ATCC 49619, B. subtilis ATCC 6633, P. aeruginosa ATCC 27853, C. albicans ATCC 885-653. These studies were conducted at the Mechnikov Institute of Microbiology and Immunology. The magnetic properties of the composite were studied on a VMP 3000 vibrating magnetometer at the Department of General Physics of the V. N. Karazin Kharkiv National University; and medical and biological properties – at the Department of Dermatology, Venereology and Medical Cosmetology of the Kharkiv National Medical University. The experiment was performed in liquid nitrogen using a special portable apparatus for cryosurgery CRY-AC (Brymill) and a contact cryoprobe with nozzles that were used depending on the shape and location of skin lesions.

6. 1. Preparation of ointments

Ointment I consists of Ag@Fe3O4 magnetic substance with the islet silver coating of the "core-shell" type (19 %), the rest is the base of PEO-400 and PEO-1500 (8:2).

The composition of ointment II (%) is:
Magnetic carrier with a silver coating – 19.0
Levomycetin – 1.0
Ciprofloxacin – 1.0
Methyluracil – 4.0
Trimecaine – 3.0
DMSO – 10.0
PEO - 400 – 55.8
PEO - 1500 – 6.2
100.0

6. 2. Conducting the experiment

In the selected area ointment I is applied, and on the opposite side a magnet, which allows the ointment to penetrate in the possible depth, is placed. After complete penetration of the ointment the cryosurgery of the tissue in liquid nitrogen is carried out (on the average from 30 to 120 s) and covered the surface with a sterile cloth for 25–30 s. The external magnetic field is imposed on the surface of the cloth. This results in the complete removal of the necrotized fragment and exudate. On the cleaned surface ointment II is applied, covered with a sterile cloth and kept for 24 h. After that the remains of the ointment, as well as dead and non-viable tissues are removed by magnet.

Example 1. The patient is 54 years old. *The anamnesis of the disease*: in patient's words, about a year ago she saw the appearance of body-pink neoplasms in the area of the wrist of the right hand. When the skin was pressed, a discoidal induration of 6–7 mm clearly appeared, and the nodule itself sank down. At the moment of examination the neoplasm was of a brown color, there was a slight hyperkeratosis and scarring in its center. When using a dermatoscope there was the symptom of "white flies" on the top of the nodule.

The clinical diagnosis: dermatofibroma (benign fibrous histiocytoma) with the size of 2–3 mm on the surface, and the depth of about 5 mm.

Dermatofibroma was removed with liquid nitrogen (cryosurgery) by the irrigation/spray method (the freezing temperature on the surface was – 180 °C, and reached – 25 °C at a sufficient depth). Before the beginning of freezing ointment I with the thickness of 1–2 mm was applied on the affected area of the skin, leaving 1 mm beyond the area specified for manipulations. By using an external magnet from the opposite side of the neoplasm ointment I was kept for 30–120 s for penetration to the depth of 5 mm. Duration of the cryodestruction procedure was 63 s. The procedure was carried out using a one-time touch applicator for freezing since the ointment prevented freezing of the applicator needle to the surface of the affected area. After manipulation the removal space was covered with a sterile cloth, to its surface the magnet was applied from the outside and kept for 23–25 s. The frozen tissue fragment was removed together with a cloth under the action of the external magnet due to the magnetic properties of the ointment. After that the magnetite ointment II was applied to the area for 24 h healing. The magnet was applied again from the opposite side for 30–120 s for the ointment penetration to the bottom of the wound. After the final removal of the ointment from the surface a significant acceleration of the tissue regeneration was found (healing accelerated by 20 % compared to cryodestruction conducted without the magnetite ointment). The affected area had a pink color indicating the absence of the secondary infection and termination of inflammation. Allergic reactions were absent. Com-

plete healing with the disappearance of the scar was within 2 weeks.

Example 2. The patient is 60 years old.

The anamnesis of the disease: in patient's words about 6 months ago he noticed the appearance of a neoplasm in the chest on his right. The neoplasm was the pedunculated base. At the top of papilloma hyperkeratosis with the size of 2–3 mm on the surface, and the depth of about 2 mm was observed. *The clinical diagnosis*: acanthoma verrucosum.

The acanthoma verrucosum was removed with liquid nitrogen (cryosurgery) similar to Example 1. After the treatment process a significant acceleration of the tissue regeneration was found on the exposed area (healing accelerated by 30 % compared to magnetite cryodestruction conducted without ointments). Complete healing with disappearance of the scar was within 1 week.

6.3. Results and Discussion

Creation of magnetocontrollable ointments with the multifunctional action provides determination of the required parameters and properties of the magnetic component of ointments – $Ag@Fe_3O_4$ at the initial stage.

According to the studies of magnetic properties of the composite nanoparticles, such as $Ag@Fe_3O_4$, the sample with the high values of saturation specific magnetization σ=62.5 emu/g (the reference sample Fe_3O_4 with σ=67.5 emu/g), and the coercive force HC ~ <15 Oe was selected.

Magnetic hysteresis loops in magnetization and demagnetization were virtually identical, it indicated the superparamagnetic condition of nanoparticles of $Ag@Fe_3O_4$ composite, while the values of the residual magnetization and HC were zero.

Using scanning electron microscopy it was determined that the size of magnetite nanoparticles with the islet silver coating was 23 nm, the specific surface area of the composite was 145 m^2/g, the thermal conductivity coefficient of magnetite χ was ~5.3 W/(m×K), silver was ~ 420 W/(m × K) [14]. The presence of silver on the surface of magnetic nanoparticles made a significant additional contribution to the thermal conductivity of the composite [15], being one of the valuable properties for using it in cryosurgery. By all indices studied the sample corresponded to the mole ratio of Ag/Fe_3O_4 of 1:0.5.

The screening of the antimicrobial activity in terms of the impact of the composite on strains of microorganisms and fungi was carried out. The sample was selected; its inhibition zone against such microorganisms as gram-positive S. aureus was 12.0 mm, B. subtilis – 15.0 mm, Str. pneumoniae – 15.0 mm, gram-negative P. aeruginosa – 0 mm, fungi of C. albicans genus – 15.0 mm; it satisfied the conditions of the antibacterial activity of substances for creating medicines.

The biomedical aspect of the research was based on improving the method of cryotherapy on pathological neoplasms of the skin due to the use of magnetocontrollable ointments with $Ag@Fe_3O_4$ to increase cryotherapy. For this purpose magnetocontrollable ointments were used: I (applied before performing the removal manipulation) and II (applied to improve and promote healing without complications and relapses). The biological effect of the magnetic field and its ability to potentiate the effect of drugs allows creating magnetic dosage forms, which along with magnetocontrollability should have a high pharmacological activity and biocompatibility of the components [16].

The results of the pharmacological action were assessed by the dynamics of the main clinical symptoms observed in patients before and after treatment (Table 1).

Table 1

Dynamics of the basic clinical symptoms

The effects of cryosurgery	Methods of cryodestruction	
	without the magnetite ointment	using the magnetite ointments I and II
Time of cryoscopy	1–2 min	30–60 s
Depth of freezing	65–70 %	95–98 %
Sensitivity during the operation (freezing)	30 %	10 %
Postoperative infiltration	10–20%	3–5 %
Postoperative wound suppuration	45–55 %	absent
Secondary infection	30 %	absent
Termination of inflammation (period)	7 weeks	48–72 hours
Regeneration of the tissue in the affected area in 24 hours	5 %	accelerated by20–30 %
Allergic reactions	5 %	absent
Complete healing with formation/disappearance of the scar	4–5 weeks, scarring	2 weeks, the scar is not formed

The results obtained show that the use of the improved method can significantly improve the results of cryosurgical intervention by:

– creating a close thermal contact of the tool with the entire surface of the affected area due to ointment I and the ability to penetrate to a certain depth of the disease outbreak;

– decreasing the time of freezing by 50 %, and increasing the depth of penetration and the devastating effect of cold, reducing the operation time to 30–60 s;

– providing the complete removal of the destruction tissue with exudate by the external magnet action;

– preventing infection and inflammation of the operated area due to the analgesic, anti-inflammatory and regenerative effects of ointment II applied after cryointervention;

– reducing the post-operative recovery by 55 %.

7. Conclusions

The result of the research is creation of magneto-controllable ointments for cryodestruction of skin neoplasms:

1. The sample of $Ag@Fe_3O_4$ magnetocontrollable composite has been selected by the physical-chemical and microbiological properties for the subsequent creation of magnetite ointments.

2. The magnetic characteristics of the nanocomposite studied provide the sufficient control of thermal conductivity and the antibacterial activity of ointments due to the islet silver coating.

3. Application of ointments based on $Ag@Fe_3O_4$ nanoparticles for microsurgical interventions has the following advantages: ointment I provides a deep and complete freezing of the tissues without damaging the healthy skin; ointment II has the bactericidal, anti-inflammatory and wound-healing ability, and its use significantly reduces the time of cryodestruction and the subsequent rehabilitation.

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РОЗРОБКА МЕТОДИКИ КІЛЬКІСНОГО ВИЗНАЧЕННЯ ФЕНОЛЬНИХ СПОЛУК У ПИЖМА КВІТКАХ

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Великий асортимент сировини дикорослих лікарських рослин використовують для лікування та виготовлення препаратів на їх основі, однією із таких є пижмо звичайне. Обмежена кількість лікарських препаратів пижма на вітчизняному ринку та відсутність сучасних національних вимог до якості цього виду сировини, вказує на актуальність досліджень по розробці методів контролю якості як самої сировини пижмо, так і препаратів на її основі.

***Мета**. Розробка методики кількісного визначення суми флавоноїдів у квітках пижма звичайного методом спектрофотометрії, гармонізованої з вимогами ЄФ.*

***Методи.** Для досягнення поставленої мети використовували уніфіковану спектрофотометричну методику, яка описана в монографіях Державної фармакопеї України (ДФУ) для кількісного визначення суми флавоноїдів в різних видах ЛРС. Для досліджуваного виду сировини проводили визначення валідаційних характеристик.*

***Результати.** Розроблено методику кількісного визначення суми флавоноїдів у перерахунку на лютеолін методом спектрофотометрії у сировині пижма квітки з урахуванням сучасних підходів та вимог до стандартизації ЛРС ДФУ. Розроблена методика є уніфікованою, що є однією із вимог для методик кількісного визначення біологічно активних речовин в ЛРС, які передбачаються для включення в монографії ДФУ.*

***Висновки.** Вперше розроблено методику кількісного визначення суми флавоноїдів у перерахунку на лютеолін у пижма звичайного квітках методом спектрофотометрії, гармонізовану з ЄФ. Методику запропоновано для включення у проект монографії «Пижмо звичайного квітки» у розділ кількісне визначення*

***Ключові слова:** лікарська рослинна сировина, стандартизація, пижма квітки, флавоноїди, метод спектрофотометрії*

Large assortment of wild herbs is being used for treatment and manufacturing of herbal remedies, and common tansy is among them. Limited number of remedies containing tansy flowers in the domestic market, as well as the absence of modern national requirements regulating quality of this product, points to the relevance of research devoted to development of the quality control methods of both tansy herbal material, and remedies on its basis.