

Development of a Scientific Methodological Approach to Expansion of Product Range for Treatment of Infected Wounds

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Abstract

Background: One of the most prominent problems of surgery and dermatology is the rational treatment of pyoinflammatory diseases of skin and post-operative pyogenic complications. **Objective:** The aim of the study was to develop a scientific methodological approach to expansion of product range for treatment of infected wounds. **Materials and Methods:** Development of methodology for unbiased assessment of prospects of development of novel drug products for the treatment of infected wounds was performed using information analysis methods. **Results:** A systemic analysis of active pharmaceutical ingredients used in drug products for wound treatment depending on the wound healing phase allowed to discover the most widely used drug products. A comparative assessment of dosage forms used in infected wounds treatment showed that local wound healing medications were represented primarily by gels or hydrophilic/hydrophobic ointments. **Conclusion:** Taking obtained results into account, it is shown that the novel drug product for the treatment of infected wounds should be represented by a hydrophilic multicomponent composition, which includes immobilized proteolytic enzymes and polysaccharide complex of chitosan and alkylamidopropyl dimethylbenzylammonium.

Key words: Active pharmaceutical ingredients, novel drug discovery, wound treatment

INTRODUCTION

The rational treatment of pyoinflammatory diseases of the skin and post-operative pyogenic complications is one of the most prominent problems of surgery and dermatology. The complexity of wound healing process is the critical problem for routine surgical practice.^[1,2] Moreover, this problem produces serious social and economic effects due to the wide distribution of wound pathology and its complications, difficulties of timely diagnostics, and treatment. Prolonged hospital care and outpatient rehabilitation lead to a serious increase in tangible costs adding to the value of the problem.^[2-4]

It is well recognized that wound healing process is divided into three consequent phases: Inflammatory phase which is characterized by presence of necrotic tissues, pus content in the wound proliferation phase characterized by clearance of the wound from pus and necrotic tissues and formation of new granulation tissue which gradually fills up wound cavity, and

maturation phase which occurs after the wound has closed. Wound healing process is cyclic by nature: Each phase can be considered as a preparatory for the next one.^[5,6] However, deviations from the abovementioned order of phases are possible due to the nature of the wound, surgical techniques, post-operative care, level of microbial contamination, and immune alterations.^[5,7]

Tissue regeneration is slowed down in case of chronic open wound; hence, it does not show signs of healing or show inadequate healing despite treatment and time. Complicated wound healing process is common in surgical practice; wound abscess is being the most common complication. Abscess development is the result of an infection which occurs in

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damaged tissues after injuries, in post-operative wounds (due to external and internal causes), and in wounds formed after incision and drainage of an abscess.^[8,9]

A prolonged negative impact results in chronic conditions: Diabetic foot, pressure ulcers, venous stasis ulcers, and ischemic ulcers. These pathological conditions are characterized by the presence of signs of all wound healing phases at the same time; therefore, treatment of chronic wounds is a very complicated clinical problem.^[10-12]

Wound treatment principles should take into account characteristics of biochemical processes which take place in the wound. To improve the results of pyogenic wounds, different local wound healing products^[5,7,10,13-15] can be used as an addition to the surgical treatment. These products are represented by hydrophilic and hydrophobic ointments, film dressings, foam dressings, gels, and traditional wound dressing materials based on cotton cellulose.^[16-19]

A number of recent publications suggest that current methods of pyogenic surgical infection treatment, particularly pyogenic wounds, are not suiting the needs of practical surgery.^[9,13,14,17,20] Therefore, development of novel drug products for the effective treatment of wounds is one of the important trends in pharmaceutical science.

The aim of this study was to develop a scientific methodological approach to expansion of product range for treatment of infected wounds.

MATERIALS AND METHODS

Development of an approach to the unbiased assessment of prospects of development of novel drug products for the treatment of infected wounds was performed using information analysis methods. It involved systemic analysis of active pharmaceutical ingredients (AFIs) used in drug products for wound treatment depending on the wound healing phase followed by comparative assessment of dosage forms used for the treatment of infected wounds.

RESULTS

Constant enhancement of wound treatment algorithm is the result of continuous scientific advances in wound therapy and dynamic development of novel surgical techniques and drug products.

Current methods of wound local treatment involve selection of drug products depending on the aim of the therapy and taking into account wound healing phase [Table 1].

Phase I of the wound healing process is characterized by the presence of necrotic tissues, pus, and infiltration of wound

margins. This is accompanied by high level of bacterial contamination. Changes in metabolic processes lead to an osmotic pressure increase in the tissues, microcirculation disturbance in the area of inflammation which results in secondary necrosis development. Thus, AFIs in the drug products used at Phase I of the wound healing process should have wide spectrum of antimicrobial activity, osmotic properties (to absorb wound exudates), provide penetration of the AFI into damaged tissues to build up therapeutic concentration with minimal absorption into the blood to minimize general toxic effects, and have anti-inflammatory and anesthetic effects. These AFIs can be represented by antibacterial substances, antibiotics, antiseptics, tissue regeneration stimulators, and enzymes.^[21,22]

One of the antibacterial substances is silver sulfadiazine which has a wide spectrum of antimicrobial activity and provides pressure injuries, wounds, trophic ulcers, and burns faster healing. Sulfanilamide is also used because of its activity against Gram-positive and Gram-negative cocci and faster wound healing when applied topically.

Wound surface faster clearance can be achieved using hydroxymethylquinoxalindioxyde - an antibacterial agent with a wide spectrum of activity. It also stimulates tissue regeneration and marginal re-epithelization and facilitates wound healing processes.

Mupirocin is not only active against Gram-positive aerobic microorganisms but also affects Gram-negative ones. Gentamicin is a bactericidal antibiotic with prolonged antibacterial action and wide spectrum of activity.

Erythromycin is a bacteriostatic antibacterial substance effective against several Gram-positive and Gram-negative bacteria and some other microorganisms.

Chloramphenicol is a substance with a broad spectrum of antibacterial action effectively fighting Gram-negative and Gram-positive microorganisms including causative agents of purulent infection. This substance also speeds up epithelization (regeneration of skin or cicatricial tissue formation) and aids clearance and healing of burn wounds and trophic ulcers.

Alkylamidopropyldimethylbenzylammonium possesses a broad range of antibacterial activity including hospital strains resistant against antibiotics. This substance shows pronounced bactericidal effects against Gram-positive and Gram-negative bacteria (both aerobic and anaerobic) in the form of a monoculture and microbial associations including polyresistant microbial strains. It is also used as an antifungal agent effective even against fungal flora resistant to chemotherapeutic substances and able to provide antiviral effects. Alkylamidopropyldimethylbenzylammonium prevents contamination of burns and wounds, activates regeneration processes, absorptive, and digestive functions of

Table 1: Local treatment of infected wounds

Wound healing process phase	Active pharmaceutical ingredient	Main pharmacological action
Phase I	Silver sulfadiazine	Antibacterial, wound healing
	Hydroxymethylquinoxalindioxyde	Antibacterial, reparative, wound surface clearance
	Mupirocin	Antibacterial
	Erythromycin	Antibacterial
	Chloramphenicol	Antibacterial, wound surface clearance, reparative
	Alkylamidopropylidimethylbenzylammonium	Antimicrobial, antifungal, reparative, dehydrative, osmotic
	Polyvinox	Reparative, wound surface clearance
	Dioxomethyltetrahydropyrimidine	Reparative, anti-inflammatory
	Chloramphenicol	Anti-inflammatory (dehydrative), antimicrobial, reparative
	Sulfadimethoxine	Antibacterial
	Trimecaine	Analgesic
	Biene	Biological cell membranes and tissues component
	Clostridiopeptidase	Proteolytic enzyme
	Phase II	Povidone-iodine
Diethylbenzimidazole triiodide		Reparative
Mother liquor of Pomorie Lake		Anti-inflammatory, antibacterial, wound healing, local anesthetic, phagocytosis and immune stimulator, reparative
Dimethyl sulfoxide		Local anesthetic, local anti-inflammatory, antimicrobial (antiseptic), fibrinolytic
Phase III	Dioxomethyltetrahydropyrimidine	Reparative, anti-inflammatory
	Deproteinized bovine serum derivate	Reparative, metabolic
	Dexpanthenol	Reparative

phagocytes, and potentiates mononuclear phagocyte system. Due to pronounce hyperosmolar activity, it neutralizes wound inflammation, absorbs purulent exudates, and assists in a formation of a dry crust.

Polyvinox aids wound clearance, tissue regeneration, and epithelization.

Dioxomethyltetrahydropyrimidine speeds up tissue regeneration, normalizes nuclein exchange, accelerates granulation, tissue growth, and epithelization, and stimulates leukopoiesis and erythropoiesis and humoral/cellular factors of innate immunity.

A dioxomethyltetrahydropyrimidine + chloramphenicol complex demonstrates anti-inflammatory (dehydrating) and antimicrobial effects against Gram-positive and Gram-negative microorganisms: *Staphylococcus*, *Pseudomonas aeruginosa*, and *Escherichia coli*. The complex does not affect biological membranes and can easily permeate into the depth of the tissues stimulating regenerative processes. It retains antibacterial activity in the presence of pus and necrotic debris.

Another effective wound healing product is represented by a complex comprising chloramphenicol + sulfadimethoxine (antibacterial agents), dioxomethyltetrahydropyrimidine (an anti-inflammatory agent; speeds up cell regeneration), and trimecaine (a non-toxic local analgesic, more potent than novocain, and has a longer duration of action not accompanied by irritation). The complex also contains polyethylene glycol which enhances antibacterial effect and prolongs the duration of action of AFI.

A hydroxymethylquinoxalindioxyde + biene complex is also characterized by a wide spectrum of bactericidal activity. Biene is an important component of biological cell membranes and tissues, whereas hydroxymethylquinoxalindioxyde is a potent antibacterial agent.

Proteolytic enzyme clostridiopeptidase aids wound clearance and granulation, prevents contamination and infection development, and aids regeneration.

Phase II of the wound healing process is characterized by the presence of serous exudates, edema, and infiltration. Usually, at this phase, purulonecrotic content should be cleared from

the wound. Granulation tissues are slowly filling the wound, so drug products used at this phase should protect them from mechanical damage and other negative factors, suppress microorganisms in the wound to prevent secondary infection, and stimulate reparative processes. These drug products should contain AFIs with antiseptic, anti-inflammatory, regenerative activity, and stimulate tissue repair.^[21,22]

Drug products used at this phase include, for example, povidone-iodine which interacts with microbial cell proteins yielding iodine-amines and causes cellular death. It has a broad spectrum of antimicrobial activity and is also active against fungi, viruses, and protozoa.

Diethylbenzimidazole triiodide has a direct regenerative action on damaged skin tissues, protects wound surface from infection, suppresses infection process, and aids wound healing.

Mother liquor of Pomorie Lake possesses anti-inflammatory and disinfective activity, suppresses pathogenic bacterial flora, stimulates immunobiological protective reactions - phagocytosis and antibody formation, and stimulates tissue regeneration and wound surface epithelization.

Dimethyl sulfoxide acts as a local anesthetic, local anti-inflammatory, antimicrobial, and fibrinolytic agent.

Dioxomethyltetrahydropyrimidine also can be used at this phase of wound healing process.

Phase III of the wound healing process is characterized by epithelization and hardening of cicatricial tissue. General requirements to the drug products used at this phase and similar to the products used at Phase II: Effective protection of granulation tissues, prevention of secondary infection, and stimulation of epithelization. Tissue reparation stimulators and metabolic AFIs are used at this phase.^[21,22]

Deproteinized bovine serum derivative activates metabolic processes in tissues, aids regeneration, and stimulates trophism.

Dexpanthenol stimulates skin regeneration.

Successful wound healing is achieved not only using drug products with specific AFIs but also by dosage forms.

DISCUSSION

It was found that drug products used in wound healing may contain one or several AFIs. All monoproducts possess only one single action (i.e., antimicrobial, anti-inflammatory, and dehydrative), and therefore, several products should be used to achieve necessary results. Combination of therapy products does not have such disadvantages as it affects different aspects of a wound healing process at once.

A systemic analysis of AFIs nomenclature shows that the number of antibacterial agents is quite high. One of the most promising substances used in wound treatment is alkylamidopropyltrimethylbenzylammonium - a substance with the broad spectrum of antimicrobial activity which also possesses regenerative activity is hyperosmolar; it does not damage granulation tissues and healthy skin cells, does not depress margin re-epithelization, and does not cause local irritation; and also it is non-allergic.

The results of the study show that the number of enzymes used in wound healing process is rather low. However, it is well recognized that the use of enzymes results in two-fold reduction of wound treatment time and improves pre-operative care results along with low numbers of post-operative pyogenic complications.^[3,8,9,13-15,23,24]

Immobilized proteolytic enzymes are of special interest since they lack disadvantages of native enzymes, which can be inactivated by inhibitors or autolyzed, are sensitive to pH changes, ionizing radiation, and can cause allergic reactions.^[8,25]

Immobilized enzyme products can be effectively used in wound healing process not only for clearance from detritus but also for preparation of the wound to secondary sutures, which results in a decreased duration of treatment and healing by first intention in 90% of the results.^[14,24,26]

A proteolytic enzyme trypsin can be used in novel drug products since it has pronounced anti-inflammatory and antiedemic properties; it is able to digest dead tissues, viscous secretion, and exudates. Moreover, it does not affect healthy tissues due to the presence of inhibitors against this enzyme.^[21,22]

Collagenase is also of particular interest because of its ability to lyse necrotic tissues which aid enzymatic wound clearance. This enzyme stimulates granulation processes (wound clearance from necrotic tissues, decrease in edema, and suppression of bacterial growth) and does not suppress epithelization; also, it does not cause proteolysis of non-damaged epithelium, granulation, fat, and muscular tissues.

Multienzyme complexes show a broad spectrum of therapeutic activity. Complexes' proteolytic activity may enhance wound surface clearance from necrotic tissues; elastolytic and collagenolytic activity optimizes regeneration processes and prevents scar tissue formation. An absorbent core absorbs wound secretions and indirectly lowers microbial contamination level.

Excess of free radicals is known as an oxidative stress and can be caused by various negative factors.^[17,27] Therefore, natural and synthetic antioxidants, used in wound coatings, prevent secondary necrosis, inhibit inflammation, and provide optimal conditions for the regeneration process.

Polyion polysaccharides, obtained from marine sources, (products of crab, shrimp, krill processing, and microbiological manufacturing wastes) are of particular interest due to their biodegradability, biocompatibility, and a wide spectrum of biological activity.^[28-35]

The use of chitin and chitosan in medicine is worth noticing. A unique complex of chitosan properties, its biocompatibility, biodegradability, and non-toxicity, along with high biological and sorption activity, makes this aminopolysaccharide one of the commercially available and ecologically safe polymers with high potential for use in medicine. Since chitosan quickly degrades by enzymes and does not form toxic substances, it becomes a good choice for the development of biodegradable protective material for treatment of burns and open wounds.^[36,37] It was shown that liquid drug products and ointments, containing chitosan, speed up wound epithelization and granulation processes and intensify wound clearance.^[38]

The results of the comparative study show that local wound healing products are represented primarily by gels and hydrophilic/hydrophobic ointments.

Hydrophobic ointments have some disadvantages. First of all, AFI release from ointment base is rather poor which results in low penetration of tissues. This type of ointments also blocks exudates flow and hermetizes wound. When treating gaping wounds, such products must be accompanied by systemic treatment.

A proper choice of a gel base for the drug products aimed at wound treatment is supported by the fact that the base can gently act on the wound, demonstrating anesthetic effects due to cooling, does not support microbial growth, and does not block tissue respiration.

CONCLUSION

A performed information analytic search allows us to conclude that the drug products for the treatment of complicated infected wounds should be represented by multicomponent compositions, which allows broader therapeutic action, and the base of such products should be hydrophilic for higher bioavailability.

Since it was shown that wound healing process is enzymatic in nature and wet environment is required for this process, the development of non-adhesive gel polymer coatings with immobilized proteolytic enzymes is of a special interest. Proteolytic enzymes are able to soften up and lyse necrotic tissues, they possess antimicrobial activity and provide cooling effect, have good modeling properties and does not traumatized the wound, and allow visual control of the wound condition. For example, the use of a natural mixture of proteolytic enzymes chymotrypsin and trypsin, which

enhance therapy effectiveness due to full and rapid hydrolysis of peptide bonds, is good candidates for the development of drug products for wound treatment. A polysaccharide complex of chitosan and alkylamidopropyl dimethylbenzylammonium will have prolonged antimicrobial and antifungal activity, enhancing functions of immune system cells during stimulation of local immunity.

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