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STUDY THE ANTIMICROBIAL ACTIVITY OF TOPICAL GEL FORMULATION OF "ERYTHROMYCIN AND DEXAMETHASONE" IN VITRO & IN VIVO

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Abstract

The present study focused on antimicrobial activity of a combined topical veterinary medicinal formulation of erythromycin ethyl succinate with dexamethasone for treatment skin infections, otitis, ocular infections and infectious wounds. In vitro, gel formula result showed good antibacterial activity with high stability after storage at (30-40) °C for 6 months. In vivo, formulated gel has shown a significant effectiveness promoting faster wound healing in lab animals (albino mice) and that result combined with histopathological view. Gel formula acts as a scaffold biomaterial for wound closure besides, antibacterial effective role that represent a promising strategy to increase the effective of erythromycin as topical delivery drug. The present study suggests that erythromycin gel is stable, safe, provides remarkable antibacterial susceptibility, reduces pain and wound recovery**.**

Keywords: *Antimicrobial activity, Erythromycin, Dexamethasone, Gel formula.*

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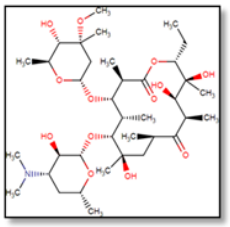
Introduction

Skin infections in pets are considered one of the most dangerous types of infections because they are multiple and branched. Some are caused by bacteria and other types are caused by fungi or parasites, which may lead to death of animals if not treated (1, 2). Most infections are caused by Staphylococcus or Streptococcus, where the skin pus caused by Streptococcus is spread over large areas of skin, sores and abscesses on the dog's skin while infections caused by Staphylococcus are localized mainly in ulcers and accompanied by itching and local pain in area of infection (3, 4, 5). Staphylococcus is causes pyoderma in small animals such as dogs and cats due to it colonizes the skin and mucous membranes (6). *S.aureus and E. coli* are considered the most important causes of mastitis which is the most common skin disease in dairy cows (7). Staphylococcus is a common type of bacteria often found on the skin or in the nose and sometimes can get inside the body through a wound or injury because of blood poisoning called an 'invasive' infection. Some species of staph infection can be resistant to common antibiotics and the symptoms of staph infections will depend on the type of infection that sometimes causes serious infections like septicaemia (blood poisoning) , pneumonia, redness, swelling of the infected area, pain or hot and Sores are often filled with pus (5, 6, 7).



Erythromycin (EM); one of the antibiotics belonging to macrolide family, produced by Saccharopolyspora erythraea strain and it is chemical composition is C37H67NO13 with a wide antibacterial range topically considered as the best antibiotic for the treatment of skin bacterial infection (8, 9). Due to its hydrophobicity, erythromycin has low water solubility, poor stomach pH stability, an unpleasant taste, a decreased oral bioavailability of 35%, and a lesser half-life (1-1.5 h). For that reason restrict its oral administration and emphasize the requirement for topical formulations (8, 10).

Topical drug administration still faces challenges with drug delivery, it is difficult to control the drug's penetration through the skin, even though it may be beneficial for treating skin conditions because it reduces systemic adverse effects and increases patient compliance (10). This antibiotic has an antibacterial action spectrum resembling to or slightly larger than penicillin working by breaks the membrane of the bacterial cell, binds reversibly to the ribosome (50s), and inhibiting the production of new proteins (11, 12). Additionally, EM is given to newborns in order to avoid eye infections (13). It also has an effective effect on gram- positive and negative bacteria, Haemophilus, Moraxella and chlamydia (11). Erythromycin has a fast role in treating Skin infections by *Staphylococcus* and its superior to penicillin due to increase Penicillin- resistant to *S.aurous* Infections (12). This antibiotic is used externally to treat various skin infections like erythema, infectious lesions in soft tissues and skin including wounds, burns, ulcers and bacterial infectious around the eyes and eyelids (14, 15). Eye injuries especially, conjunctivitis is among the most common injuries in veterinary clinical cases which cause great harm to pets, with infection rate 5.3% (7, 8).

Dexamethasone is a broad-spectrum synthetic corticosteroid and one of the glucocorticoid steroids that resembles natural cortisone, which is secreted from the body. It prevents the secretion of substances responsible for the occurrence of inflammation and tissue damage (16). Dexamethasone reduces inflammation by inhibiting the movement of polymorphonuclear leukocytes, which reduces the body's immune response. Also inhibits the action of prostaglandins and cytokines, reduces the permeability of capillaries, increases the concentration of vitamin A and increases the synthesis of Surfactant. Dexamethasone acts to improve blood circulation, increase blood flow to the affected area, reduce pain, and treating eye infections, hypersensitivity to some medications. In addition, treating many autoimmune diseases including; rheumatoid arthritis, ulcerative colitis and Stevens- Johnson syndrome (17, 15). Ant-inflammatory drug has antagonist interactions which rising with minimum inhibitory concentrations (MICs) and increased biofilm formation particularly corticosteroids like dexamethasone (18). NSAIDs and corticosteroids are the two categories of anti-inflammatory medications. Since these medications are designed to treat infections by lowering inflammation, discomfort, and fever, they are frequently used in conjunction with antibiotics to treat infections (18, 19). Corticosteroid medications, such as dexamethasone and betamethasone, are synthetic analogs of glucocorticoids with anti-inflammatory and immunosuppressive properties, and their actions are dependent on blocking receptors as well as genomic and nongenomic mechanisms (19). Bacteria can develop antibiotic resistance via biofilm development, acquisition of resistance genes, and chromosomal changes (17, 20). In addition to antibiotic resistance, biofilm development in bacteria is a key defensive strategy against the host immune system, resulting in recurring infections and increased bacterial pathogenicity (20, 21). Furthermore, a robust association has been shown between the emergence of bacterial biofilm and the progression of urinary tract infections, atherosclerosis, and infective endocarditis (19).

The aim of this study is to prepare gel formulation for treatment of various bacterial infections which present clinically effect small animal especially because skin infection with severe pain, the formulation consists of erythromycin (2.5%) w/v, a broad- spectrum antibiotic linked synergistically with dexamethasone (0.5%) w/v from hydrocortisone group as topical gel.

Materials and Method

Preparation of topical Gel Formulation

Current gel formula was prepared as following (22):

1. Erythromycin (2.5gm), Dexamethasone (0.5gm), Propylene glycol (10 ml), Glycerin (10ml), NF Polymer (20gm), Distilled water (100ml).
2. All material was dissolved in 1 ml of 70% ethyl alcohol.
3. Propylene glycol and glycerin were added to glass beaker and placed on a hot plate with a magnetic stirrer with stirring for 10- 20 minutes with 20 C°.
4. The mixture from point (2) gradually was added to the mixture from point (3) with continuing stirring for an hour until a homogeneous transparent liquid was obtained.
5. NF Polymer was dissolved in distilled water and continued mixing with a blender until a smooth gel with uniform particles is obtained.
6. The mixture obtained from point (5) was added to the mixture from point (4) with mixing for 20 minutes until a dusty gel without lumps was obtained, finally gel formula was packaged in plastic cups.
7. Formula samples were examined by *S.aureus* and different bacterial in Zoonosis Diseases Research Unit/ College of Veterinary Medicine/ University of Baghdad.
8. The stability of gel formula after storage in temperature (30-35) to (40-45) °C for 6 months was studied.
9. Formula samples were evaluated healing effect on lab animals.

Antibacterial analyses by agar diffusion method

Gram positive and gram negative bacteria like (*E. coli, Pseudomonas aeruginosa, E. coli O157:H7, Salmonella typhimurium, Listeria monocytogenes, Proteus Sp., Klebsiella Sp.*) were used to test the gel formulation's antibacterial efficacy. The gel formula's antibacterial efficacy was assessed using the agar well diffusion method. A 0.5 µl bacterial culture was spread out on a plate and holes measuring 6 mm were inserted to the well. Plates were subsequently incubated for 24 hours at 37 °C, and the zone of inhibition around each well was measured to assess the antibacterial activity (23).

Evaluation of gel formula for wound healing in vivo

Ten albino mice (weighted 25–30 g) were used in the investigation. The mice were housed at AL-Razi animal house care, and the results were confirmed by histopathological examination of the skin of mice treated daily with the formula for 15 days. The lab animals were divided into two groups; each group consisted of 5 animals, as follows:

- Group A: Excision wounded mice without treatment.
- Group B: Excision wounded mice treated with gel erythromycin formulation

Histopathological examination

After the end of the experiment and complete healing a biopsy is taken from the skin of the treated area and histological sections send to Laboratory Center / Medicine City Hospital in order to identify the histopathological changes that occurred in the treated group compared to the untreated group.

Results

In table (1): show the antibacterial activity of erythromycin formulation at room temperature for 6 month against *S.aureus* according to the standard limitation value (90-110).

Table (1): antibacterial activity of gel formula (%) compared to erythromycin standard material with

Limitation value (90- 110%) for 6 month in (Room Temperature)

Substance	Evaluation time	antibacterial activity
Erythromycin gel formula	Zero time	97.1
	After 6 month	97.5

In table (2) analyzed the biological effectiveness of gel formula after stored at temperature between (30-35) To (40-45)°C for 6 month was (97.4-97.1) and (97.2-95.4) respectively.

Table (2): Stability study of gel formula after storage at temperature (30-35) °C to (40-45)°C for 6 months

Substance	Evaluation time	antibacterial activity after storage (30-35) C^0	antibacterial activity after storage (40-45) C^0
Erythromycin gel formula	After month	97.4	97.2
	After 6 months	97.1	95.4

The result of formulation prepared after the initial examination (zero time) showed a good result (97%) Table (1) compared to standard material which ranged (90-110) %. The current study proved that the stability of the preparation formula was biologically stable. As the inhibitory activity of the formulation was stable at room temperature using S. aureus within permissible limits. The stability of formulation was studied after storage in ovens at

temperature and humidity for 6 months Table (2). The test results after storing were (97-95) % at 30 C.

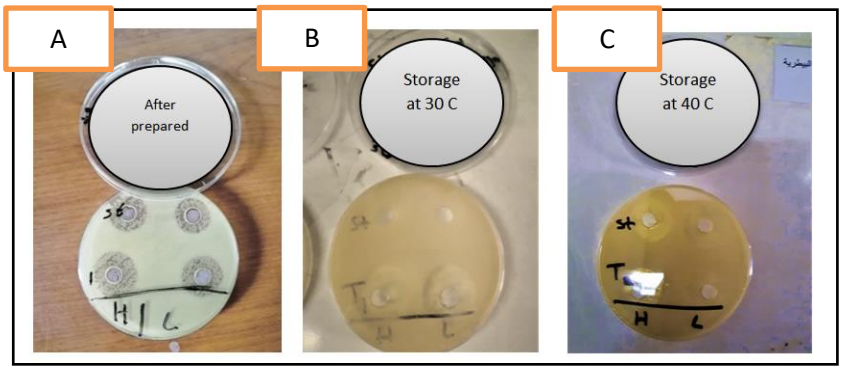


Figure (1): Biological activity of erythromycin & dexamethasone gel formula (T) compared to erythromycin standard (St) against *S.aureus* in room temperature (A), after storage at (30) (B), storage at (40) (C) °C.

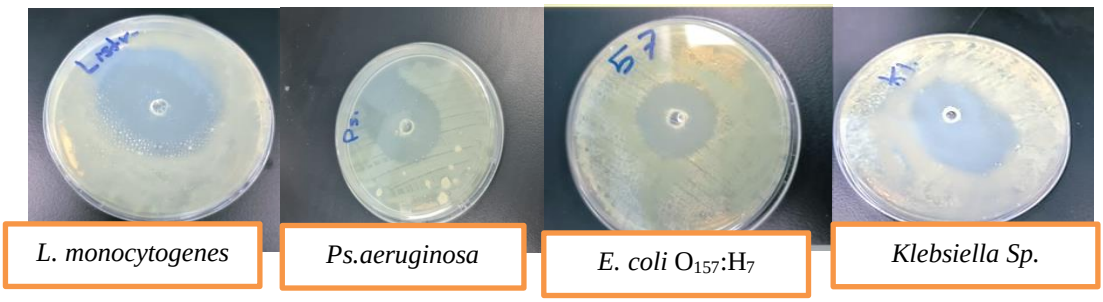


Figure (2): Biological activity of gel formula using different gram positive and negative bacteria.

In table (3): show the antibacterial effect of gel formula against different type of bacteria like *(E. coli, P. aeruginosa, E. coli O157:H7, Listeria monocytogenes, Proteus Sp., Klebsiella Sp.).*

Table (3): Zone of inhibition of different pathogenic bacteria using well diffusion method

Isolated bacteria	**Zone of inhibition (m.m)**
E. coli	28
Pseudomonas aeruginosa	20
***E. coli* O_{157}:H_7**	22
Salmonella typhimurium	20
Listeria monocytogenes	25
Proteus Sp.	19
Klebsiella Sp.	24

In figure (3), Gel formulation used to treat skin wound of albino mice which showed highly effectiveness of the treatment and speeding up healing without any side effects after 15 days of treatment in group B compared to Group A (control),

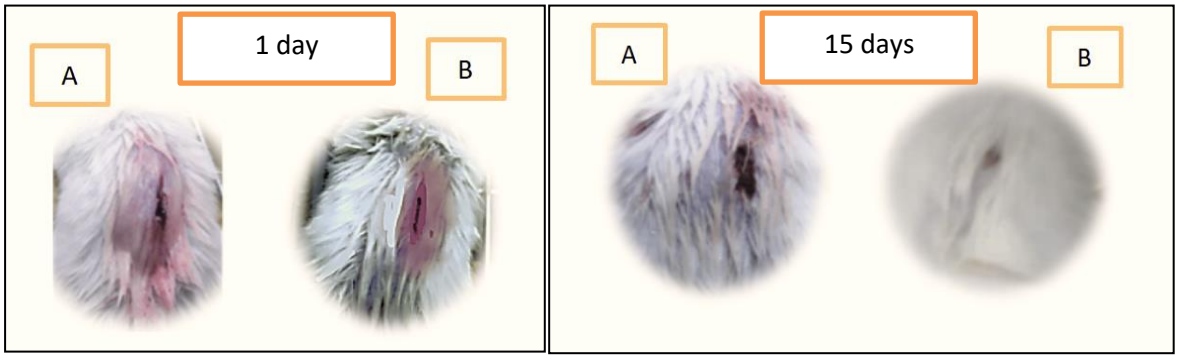


Figure (3): The healing effect of erythromycin gel formula compared to control group from 1 day to 15 days of treatments. A) Control group B) Gel treated group.

The result confirmed histopathologically in skin section stained with H&E of treated group of mice after 15 days examined microscopically with (100×). In control skin section (untreated) show uncompleted healing of epithelial layer and inflammatory cells were present (A) while in (B) Wound section showed complete healing and well developed and arranged of new epithelium layer and compact collagen tissue (Figure 4).

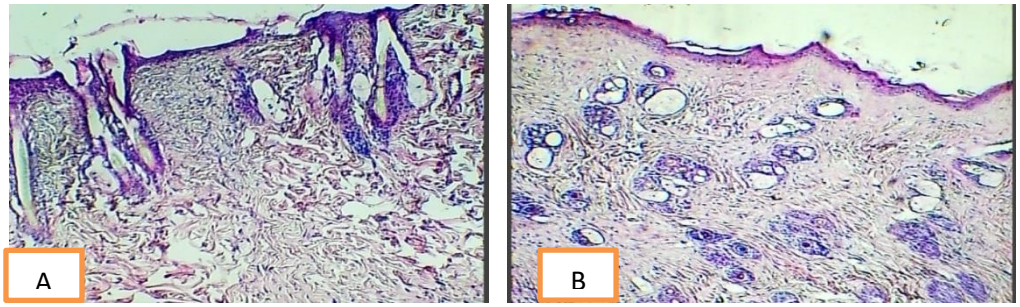


Figure (4): Histopathological section of gel erythromycin showed complete healing of skin injury in treated groups after 15 days of treatment (B) compared to control group (A).

Discussion

The results revealed a good stability of the gel formula and the temperature of long storage for 6 months which had a slight effect on components and the highly biological action may be due to the synergistic relationship between its active ingredients (24). In addition, the presence of Propylene glycol in gel formula may be maintain the moisture of the formula, prevent drying and resist storage conditions of heat and humidity (25). In pharmaceutical formulations, Propylene glycol is a solvent or stimulant that can enhance penetration into skin tissue mainly in topical formulas also acting to regulate the permeability of impermeable compounds through the spread of the substance on the surface of the skin and speed up its absorption, as well as, act to distribute homogeneously in the different layers of the skin

(dermis and epidermis) lead to higher and faster medical effects. (26). Gel formula showed antibacterial activity against different bacteria one of them *Ps. aeruginosa* which is widely spread in local infections of the skin, these bacteria have a high ability to resist antibiotics and thus treatment failure (27, 28). Gel formulation has potent inhibitory effectiveness against gram- positive and gram- negative bacteria with highly treatment may be due to the suitable concentration of the antibiotic linked with additives to the formula, the therapeutic drug of the gel has the ability to reduce the increasing bacterial resistance to antibiotics beside reduces the risks of secondary bacterial infections that affect the skin (29, 30, 31). In figure (3), Gel formulation examined on ulcerated skin wound of mice which showed recovery of ulcer skin in group B compared to Group A (control). Beside highly effectiveness of the treatment and speeding up healing without any side effects and these findings are consisting with histological sections of skin of mice after 10 days of treatment were appear real tissue changes during treatment periods (Figure 4). In this study we explore the ability of prepared gel formulations of "erythromycin and dexamethasone " on healing wound through promoting generation of epithelial cells beside vascular improvement supply lead to regulate and accelerate the proliferation phase of wound healing. In other way; these processes may induced the antibiotics to reduce the biological effect and remodeling through increasing granulomatous tissue formation and repair the destruction or damage in tissue increase collagen fiber deposition (31). Corticosteroids act to reduce the inflammations and improve the body's immune response (32, 33). Moreover, adding an antibiotic that has been synergistically action-linked with Dexamethasone results in a reduction of inflammations locally, an increase in the inhibitory action of bacteria and an increase in the speed of recovery on the other hand (34, 35). Finally; the results improve the effectiveness of the gel preparation of Erythromycin and Dexamethasone in treating different bacterial infection, and accelerate of wound healing.

Conclusion

According to the previous result the gel formulation shows highly antibacterial effect against different gram-positive and negative bacteria. The current study proved that gel formula of erythromycin and dexamethasone has good value of stability after storage at different temperature (30-40)°C for 6 months within permissible limits. In other way; gel formula show speed healing effect in experimental skin injury in lab animal.

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