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OPTIMIZATION AND DEVELOPMENT OF TOPICAL METAL ION - CONTAINING ANTIBACTERIAL CREAM AND GELS

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Keywords:

Zinc Sulfate, Copper Sulfate, Antibacterial, Metal-Ions, Antimicrobial drug resistance, Cream, Gel

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ABSTRACT: Normally and often skin infections present therapeutic challenges to practitioners and researchers due to the growing concern regarding multi-drug resistant bacterial, Viral, and Fungi Strains. The Antibacterial properties of zinc sulphate and copper sulfate are well known and have been investigated for many previous years. However, the synergistic effect between both metal ions as antibacterial ingredients has not been evaluated in topical formulations like gels and creams. The aim of the present study to formulate cream and gels containing zinc and copper individually or in combination and evaluate the *in-vitro* antibacterial activity of these metal ion in the formulation. Zinc sulfate and copper sulfate had a strong synergistic antibacterial activity in cream and gels. By evaluating the various parameters such as pH, Spreadability, viscosity, and antibacterial properties it is confirm that the metal gel and cream enhance the antibacterial activity. This study evaluated and confirmed the synergistic *in-vitro* antibacterial effect of copper sulfate and zinc sulfate in cream and gels.

INTRODUCTION: The many established antibacterial medicines are already in the market. The need for new antibacterial technologies has grown dramatically as a result of growing worries about viral, bacterial, and fungal strains that are multidrug-resistant [1-4]. As a result, in the field of antimicrobial radiation therapy, focus has been placed on secure, novel, and/or alternative antibacterial materials. A type of irritating contact dermatitis is a nappy rash. It is one of the dermatological problems that babies who use diapers are most likely to have [5] and is thought to affect 7–35% of infants around the ages of nine months and twelve months [6, 56].

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The growth of bacteria like Candida and Streptococcus is favored by a variety of factors, including skin moisture, friction, skin irritants, and pH change [7, 57]. *Candida albicans* have been demonstrated to be resistant to the antibacterial effects of zinc and copper ions [8]. *Herpes labialis*, often known as cold sores, is a common viral illness of the lips that is usually brought onby type 1 of the virus known as herpes simplex virus (HSV) [9, 58]. Studies have demonstrated that HSV is inactivated by zinc and copper salts both in vivo as well as *in-vitro* [10–13].

Cold sores can be treated with zinc sulphate thanks to its antibacterial properties [14]. Its therapeutic activity was discovered to have as its molecular mechanism the severe deactivation of free virus in epidermal tissues, as well as blisters [15, 16]. This condition has been successfully treated with zinc and copper sulphates, respectively [17, 18]. In recent years, several metal ions, including copper [19] silver

[20] copper [21] iron [22] mg [23] and silicon [24] have been investigated as possible antibacterial agents. The ability of copper to inhibit microbial growth is widely documented. It has long been employed as a fungicide, germicide, and algaecide [25-27].

Recent articles have proposed several copper's antimicrobial mechanisms, such as reactive hydroxyl radical generation that compromises cell credibility, copper's binding to protein molecules, denaturing of DNA, deactivation of enzymes, and blockage of functional groups in proteins due to the displacement of vital ions [28–30]. Additionally, it was discovered that *Hypericum perforatum* and topically administered copper sulphate were effective *in-vivo* in the management of herpes lesions of the skin [13, 59].

Antimicrobial Drug Resistance (AMR): Due to its rising prevalence and the elevated mortality risk associated with persons infected with micro-organisms resistant to antimicrobials, antimicrobial drug resistance (AMR) is one of the biggest public health issues of the modern era [31-35].

Metal-based Antibacterial Compounds: Metal ions have been employed for antibacterial reasons frequently in the past. Salvarsan, containing substance that was discovered at the start of the 20th century, was the first successful therapy for syphilis, a condition caused by bacteria brought on by *Treponema pallidum* subtype pallidum. The clinical usage of metal-based antibacterial agents, however, has decreased since the development of penicillin and the subsequent antibiotics [36-40].

Investigation into the application of metal-based medicines as antibacterial medications has reappeared as a result of an increase in AMR and the challenges in developing antibiotics having novel modes of action.

Metals can be combined to an antibiotic, combined to a biomolecule, or employed independently of an antibiotic to achieve antibacterial effects. Complexing an element with a biological molecule facilitates access of the metal into a specific location of the cell, where it can exert its antibacterial properties because biomolecules are substances that are frequently absorbed into a bacterial cell [41, 60].

Copper: Copper has a long history of use as an antibiotic. Herodotus mentioned the Persian monarchs' use of copper to transport water to preserve it fresh, especially during times of war when clean water from earth's resources was in short supply.

In 980 C.E., Avicenna wrote about the application of copper filings as a blood-purifying remedy for arrhythmias and foul breath. There are numerous uses for copper nowadays which take advantage of its antibacterial qualities. It serves as an antibacterial agent in skincare and is used in fabrics and sprays to stop sweat-related smells. Another important ingredient in burn injury treatments is copper [42, 61, 62].

Copper and zinc sulphates have both been studied for their potential antibacterial properties for a long time. However, topical preparations have not been tested to determine the synergistic action of these pair of metals as antibacterial components.

The current study's objectives were to create topically applied lotions and gels containing zinc sulphate, copper sulphate, or a mixture of these metal salts, and to assess the formulations' *in-vitro* antibacterial effectiveness against *E. coli* and *Staphylococcus aureus* [42-54].

Tetracycline: Chlortetracycline, a type of antibiotic derived from the bacteria *Streptomyces aureofaciens*, is converted semi-synthetically into an antibiotic such as a broad-spectrum naphthalene antimicrobial. Tetracycline inhibits protein production in bacteria by attaching to the 30S ribosome subunit and interfering with aminoacyl-tRNA's ability to bind to the mRNA- ribosome combination.

MATERIAL AND METHODS:

Materials: Tetracycline, Xanthan gum, Carrageenan, Guar gum, Deionized water, Zinc sulfate, Copper sulfate, Paraben, Lecithin, HPMC, Poloxamer, NaOH, HCl, Methanol, Ethanol, Triethanol amine, Propanol.

Methods:

Formulation Development:

TABLE 1: INGREDIENTS OF FORMULATIONS OF CREAM ALONG WITH THEIR AMOUNT (%)

Ingredient	F1	F2	F3	F4	F5
Drug	0	3	0	3	3
Copper sulfate	0	0	3	0	3
Zinc sulfate	3	0	3	3	3
Sweet almond oil	0	6	1	0	5
Coconut oil	6	0	5	4	0
PEG-8 Bee wax	4	6	7	6	5
Span 80	1	2	5	1	3
Tween 60	5	2	4	5	4
Xanthan gum	0.5	0.25	0.25	0.25	0.25
Carrageenan	0.36	0.36	0.36	0.36	0.36
Glycerine	5	5	5	5	5
Citric acid	1	1	1	1	1
Stearic acid	5	3	5	4	3
DW	q.s.	q.s.	q.s.	q.s.	q.s.
BHT	0.06	0.06	0.06	0.06	0.06

Formulation of the Topical Cream: The waxes will be melted at 75°C and the components uniformly combined to prepare the oil phase. The water-soluble components will be dissolved in deionized water to create the aqueous phase. The water phase will be heated to a temperature between 75 and 80 °C until all ingredients have dissolved. Once both the oil and water stages are at the same climate, the aqueous phase is introduced gradually while being agitated moderately until the temperature falls to 40 °C. To create a semisolid cream foundation, the emulsion will be chilled to room temperature. Using an overhead stirrer, add the evaporated copper and zinc sulphate to the cream base after dissolving them in warm water that has been deionized.

TABLE 2: INGREDIENTS OF FORMULATION OF GEL ALONG WITH THEIR AMOUNT (%)

Ingredient	F6	F7	F8	F9	F10
Drug	0	3	0	3	3
Copper sulfate	0	0	3	0	3
Zinc sulfate	3	0	3	3	3
Poloxamer 407	0	0	34	26	24
Xanthan gum	0	1	0	0	2
Guar gum	1	0	0	0	2
Lecithin	0	10	8	0	10
IPM	0	10	8	0	10
Carbomer 940	0	0	3	1	0
Carrageenan	0	0	1	0	1
TEA	1.35	1.01	0	0	0
HPMC	q.s.	q.s.	q.s.	q.s.	q.s.
Stearic acid	5	3	5	4	3
DW	q.s.	q.s.	q.s.	q.s.	q.s.
BHT	0.06	0.06	0.06	0.06	0.06

Formulation of the Topical Gels: The powder polymers for carrageenan, the use of xanthan and guar gum should be dissolved in 75°C warm deionized water for 15 minutes while being stirred. The mixture will be taken off the hot plate once all of the polymers have been dissolved. With vigorous stirring, the necessary concentration of zinc and copper sulphates will break down in the transparent gel. After cooling the mixture to room temperature, paraben concentration will be used to protect it. The material will be dissolved in 75°C warm ionized water while being stirred incompositions where HPMC will serve as the thickening component. The resultant solution will be kept overnight at room temperature to create a transparent gel. Following full dissolution, the copper sulphate crystals and subsequently zinc sulphate crystals will be agitated vigorously into the gel. The final phase of the formulation will involve the addition of a preservative. The oil phase will be made by combining lecithin & isopropyl myristate in a ratio of 1:1after poloxamer has been dispersed in cold water and chilled at 4°C for a night. The mixture will be stored at room

temperature overnight for the complete dissolution of lecithin. The water phase will then be given a direct addition of the active substances. Using the vortex mixer, the gel will be made by combining 1 part of the oil phase with 4parts of the aqueous phase (poloxamer gel).

Direct dispersion of Kollidon 90F, FlexiThix, and Carbomer 940 will take place in deionizedwater while being vigorously agitated at room temperature. The gel's active components will be evenly distributed throughout. Triethanolamine will be utilized to neutralize the pH to 6-6.5 in order to help carbohydrates 940 gel.

Evaluation:

Physical Evaluation of the Topical formulation:

Organoleptic Characteristics: Physical appearance, color, texture, separation of phases, and homogeneity will all be examined on blank formulations that have drug-loaded formulations using visual inspection.

The consistency and texture of the prepared cream and gels can be evaluated by pressing a tiny amount of each between the index and thumb fingers. The uniformity and smoothness of the formulas was assessed using the cohesiveness of the formulas and the presence of coarse particles. Immediate skin sensation will also be assessed, including rigidity, greasiness, and grittiness.

Spreadability: To test the spread ability of the formulations, the distributing breadth of 1 g of material acrosstwo horizontally glass plates (10 cm 20 cm) will be determined after one minute. To the top of the plate was placed a normal weight of 25 g.

pH Values: Deionized water (25ml) will be used to dissolve 1gm of each formulation. A pH meter was used to determine the pH. Three copies of each measurement will be made. Prior to each usage, the pH meter will be calibrated using standard buffer solutions (pH 4, 7 and 10).

Viscosity: The viscosity of the various topical preparations will be assessed using a Brookfield DV-I viscometer and a concentric cylinder spindle. The experiments will take place at 21 °C. Every measurement was made in triple and the spindle will be revolved at speeds of 0, 0.5, 1, 2, 2.5, 4, 5, 10, 20, 50, and 100 rpm.

Antibacterial Activity Studies:

Preparation of Culture: The MH broth medium in 10 ml was sterilized. Both *S. aureus* and *E. coli* bacterial cultures were injected into medium. 48 hours of incubation at 37 °C.

Agar well Diffusion Method: MH agar media was produced in 20 ml per petri plate after Autoclave for 15 minutes at 121 °C and 15 pressure. Laminar air flow was used to pour the media into the plates. The media was given time to solidify. After solidifying using a sterile cork borer, holes were created and a 50 µm culture solution was distributed. holes were filled with 50 microliters worth of sample. All the petri plates were incubated at 37°C for 48 hr., and Zone of inhibition (ZOI) were calculated.

Stability Study: Using the agar well diffusion assay previously described, all chosen drug-loaded compositions will be evaluated against *E. coli* for 12 weeks (measurements will be taken on day 1, week 3, week 6, week 9, and week 12). The antibacterial activity of the formulations will be tested on samples stored at room temperature (25°C) and in a refrigerator (4°C), as well as on samples packaged in glass vs plastic containers. The aforementioned approaches will measure the pH levels, colour, physical properties, and texture as well as the antibacterial activity over the course of the 12 weeks.

RESULTS & DISCUSSIONS:

Formulation of Topical Cream and Gels: F5 was chosen as the ultimate formulation out of the five creams that were created, while F8 and F10 were chosen as the best compositions for additional testing out of the five gels that were created in this study.

Physical Evaluation of Topical Cream and Gels

Organoleptic Characteristics: Table 3 shows the topical preparations' organoleptic characteristics, such as their physical appearance, colour, texture, separate phases, uniformity and initial skin sensation. All of the formulations were blue because of copper sulphate, findings indicated that the cream as well as both jellies had a velvety feel and an aesthetically pleasing aspect; they were all homogeneous and exhibited no symptoms of phase separation.

TABLE 3: ORGANOLEPTIC PROPERTIES STUDIES OF FORMULATIONS

Sample	Appearance	Colour	Homogeneity	Phases	Skin test
F1	Opaque	Bluish	Homogenous mix.	No phase separation	Non greasy & Moisturizing
F8	Translucent	Bluish	Homogenous mix.	No phase separation	Refresh, cool and greasiness
F10	Transparent	Bluish	Homogenous mix.	No phase separation	Coat after dry, non-greasy

Spreadability: The capacity of a cream or gel to spread evenly on the skin, or the spreadability of semisolid products, is crucial to the delivery of an average amount of a medicated composition to the skin therefore the effectiveness of a topical therapy.

TABLE 4: SPREADABILITY STUDIES OF CONTROL CREAM AND GEL WITH FORMULATIONS

Sample	Spreading diameter after 1 min (mm)
Commercial cream	16
F5	18
Campho - Phenique gel	15
F8	18.5
F10	22

The numbers describe how easily the formulations spread over the application surface when a tiny amount of shear is applied. The findings showed that the spreadability of our cream as well as gels was comparable to that of the commercial goods utilized in the study as comparators.

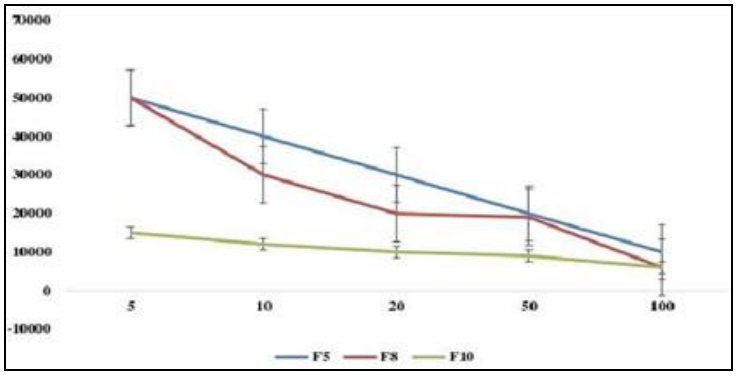
pH Values: Table 5 show the pH readings for the drug-free and drug-loaded creams and gels. When the active compounds were introduced to the bases, the formulations' pH dropped.

The usual pH range for skin is 4 to 6. The pH of the gels was close to the usual pH of the skin, whereas the pH of the cream was more alkaline compared to the pH of the skin. Over the course of 12 weeks, there was little change in the formulation's pH levels.

TABLE 5: STUDY OF PH OF FORMULATIONS UPTO 12 WEEKS

Sample	pH		
	Blank Formulation	Formulation at 1st day	Formulation at 12th week
F5	3.1	2.5	2.8
F8	6.1	4.8	4.85
F10	6.6	4.5	4.53

Viscosity Measurement: The graph below displays the values of viscosity for the drug-loaded creams and gels. All of the products displayed expected pseudoplastic behaviour. While F10 had a lower beginning viscosity, F5 and F8 exhibited similar viscosity curves.



GRAPH 1: GRAPHICAL PRESENTATION OF VISCOSITY MEASUREMENT

Antibacterial Activity:

TABLE 5: ANTIBACTERIAL STUDY OF THE FORMULATIONS

Sample	Zone of Inhibition (mm)	
	E. coli	*S. aureus*
F5	12	13
F8	13.3	14.2
F10	15.9	16.2
Control	10.9	11.5

TABLE 6: ANTIBACTERIAL STUDY OF THE FORMULATIONS AT DIFFERENT CONCENTRATIONS

Conc.	Zone of Inhibition (mm)					
	F5		F8		F10	
	E. coli	*S. aureus*	*E. coli*	*S. aureus*	*E. coli*	*S. aureus*
Blank	0	0	0	0	0	0
Control	13.5	14.3	13.5	14.3	13.5	14.3
0.5%	10.5	11.6	12.2	12.8	14.5	14.2
0.1%	15.6	14.39	16.59	16.32	18.52	18.97
0.2%	20.4	19.78	20.58	21.3	25.1	24.5

Stability Study: For 12 weeks under all storage circumstances, all formulations kept their blue hue and saturation. By the conclusion of the period of storage, all formulations had the same exterior appearance, Uniformity and texture. In any of the containers or temperatures, none of the formulations exhibited any physical or chemical instability. All compositions' antibacterial properties persisted for a twelve-week period in both receptacles and at all temperature.

CONCLUSION: In this investigation, several creams and gels with copper and zinc sulfates antimicrobial agents were created. Numerous creams and gels' quality, look, and stability were impacted by the extremely reactive metal ions during the formulation process. Based on their physical characteristics, in vitro antibacterial properties, and product stability, a cream and three gels were determined to be the best options for our needs. These were chosen for further research. The integrity, pH levels, texture, look, and antibacterial capacity of these chosen goods have been preserved for 12 weeks, despite the fact that only a tiny portion of the manufactured items were judged to be ideal.

This study's key finding is that creams and gels containing copper sulphate and zinc sulphate have synergistic antibacterial activity. For both active compounds, the lowest concentration that worked *in-vitro* was discovered to be 3%. The antibacterial efficacy of the compositions versus other germs could be confirmed in an appropriately designed and carried out in vitro follow-up study, and a more accurate comparison between our medicines and commercial medications for diverse skin disorders could be established.

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CONFLICTS OF INTEREST: Nil

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