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Film Forming, Antimicrobial and Growth Promoting Wound Healing Spray Formulation

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ABSTRACT

Background: Bacterial infections at wound site are one of the major causes for delayed healing. The aim of this study was to develop topical film forming spray having Combination of Simvastatin and Mupirocin which can avoid such infections and provide enhanced wound healing. **Methods:** Film forming spray formulation having Simvastatin and Mupirocin was formulated using Eudragit E100as film forming agent and Glycerol and Polyethylene glycol (PEG-400) as plasticizers. The effect of these excipients on the formulation was assessed by applying factorial design. Optimized formulation was evaluated for swelling index, spray angle, spray pattern, *in-vitro* drug release, evaporation time, average weight per dose, antimicrobial efficacy and *in-vivo* wound healing was assessed and compared with marketed formulation by excision wound healing model. **Results:** The optimized batch of topical film forming spray having combination of Simvastatin and Mupirocin was selected based on the results of swelling index and *in-vitro* drug release at respective drugs. Both the drugs gave more than 80% of drug release within 2 hrs and showed satisfactory physicochemical and mechanical properties along with potent antimicrobial efficacy against *S. aureus* and *E. coli*. Developed formulation showed comparative wound healing activity as that of marketed conventional formulation. **Conclusion:** Topical film forming spray was successfully developed using combination of Simvastatin and Mupirocin Calcium. Antimicrobial activity and results of animal studies indicated safety and efficacy of formulation.

Key words: Mupirocin, Simvastatin, Mupirocin, Eudragit E100, Wound healing, Factorial design

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INTRODUCTION

Whenever there is injury to skin resulting into wound, complications of risk of infection increases as protected layer get damaged. This can further lead to systemic infection increasing the level of complication.[1] To avoid or protect wound from infection it is advisable to use topical antimicrobial product. Some of the disease condition such as diabetes can create an additional challenge for wound healing.[2,3] Therefore, using growth promoting drug along with antimicrobial agent can enhance the wound healing process. Neomycin, bacitracin, silver sulphadiazine and mupirocin are some of the antibiotics used to prevent wound infection, but these are associated with some side effect such as allergies and hypersensitivity with repeated use.[4,5] Growth factors are generally used as growth promoting agent, but these have stability issues and are very costly to use for routine application.[6] If topical DDS is formulated with some antibacterial agent, then it can be a promising approach in preventing the wound infection as well as antibiotic resistance.[7] Simvastatin is reported to have growth promoting action by stimulating angiogenesis and it can be a drug of choice to be used along with antimicrobial agents.[8] Simvastatin is traditionally available as lipid lowering agent that exhibits its mechanism of action as a highly recommended as HMG-CoA inhibitor that was reductase the catalyses the conversion from HMG-CoA to mevalonate. But recently its wound healing activities have explored and it acts by improving vascular endothelial growth factor (VEGF) production and thus stimulating angiogenesis, reducing oxidative stress, improving micro vascular function and also enhancement of endothelial function, which ultimately improves the wound healing activity.[9,10]Mupirocin Calcium is known to be active against aerobic Gram-positive cocci such as *S. aureus, S. epidermidis* as well as some Gram-negative cocci including methicillin-resistant *S. aureus.*[11] It is available as 2% ointment as topical antimicrobial agent which can be used for wounds, burns as well as treatment of skin infection.[12] Topical formulation for wound application is available in the form cream, ointment, powder, solid film, spray, transdermal patch etc. Some of these formulations need use of preservatives and some causes stinging sensation after application. Spraying a medication on wound which can form a thin film can avoid some of these complications. Film formed on wound can provide physical protection and it is loaded with medication, it can provide favourable environment for wound healing.[13] Based on these reports, there is need to develop the topical wound management product which can be easily applied and will increase healing rate, avoid/cure infection and minimize antibiotic resistance.[14]

MATERIALS AND METHODS

Materials

Simvastatin and Mupirocin were received as gift samples from SAVA Healthcare Ltd. Eudragit E100 were received as gift sample from Evonik Degussa Pvt. Ltd. (Mumbai, Maharashtra, India).PEG-400 and Glycerol was purchased from the Loba Chemie Pvt. Ltd. (Mumbai, India). Sodium hydroxide and Potassium dihydrogen phosphate were obtained from Himedia chemical Laboratory (Mumbai, India). All solvents and chemicals used were of analytical grade.

Bacterial Strains

Bacterial strains of *Staphylococcus aureus (S. aureus)* and *Escherichia coli (E. coli)* were procured from Dr. D. Y. Patil Medical College, Hospital and Research Centre, Pimpri, Pune-411018.

Selection of Drug ratio

For formulation, ratio of Simvastatin and Mupirocin was selected based on its antimicrobial activity in the form of zone of inhibition against *S. aureus* and *E. coli*.

Simvastatin (1.0%): Mupirocin (1.0%) were mixed in different ratio (1:2, 1:1, 2:1) and mixture were checked for its antibacterial activity against *S. aureus* and *E. coli* by Zone of inhibition method. Ratio showing comparative zone with commercially available formulation (Tbact, gsk) was selected for further study.

Preparation and optimization of Film Forming Spray

Central Composite Design with 2 factors at 3 levels and 13 trial runs was used to determine the impact of film forming polymer (Eudragit E100), humectant and plasticizer; glycerol and PEG 400 on properties of spray formulation having combination of Simvastatin and Mupirocin using Design Expert software (Version 11). Spray was formulated with 1% w/v Simvastatin, 1% w/v Mupirocin having 20% w/v Eudragit E100. The concentration of plasticizer with respect to Eudragit E100 (P: E) were 0.5, 0.75 and 1 whereas PEG400: glycerol (PEG400: G) were in a ratio of 1:6, 1:1 and 6:1, respectively as shown in. All materials of formulation were dissolved in cosolvent mixture of absolute ethanol and acetone (4:1 v/v) under stirring. Final formulation was packed in spray container.

Physiochemical Properties

Spray formulations were evaluated for physicochemical properties and optimized formulas was evaluated for antimicrobial efficacy and *in-vivo* wound healing properties.

pH and viscosity

The pH of film forming spray formulation was measured using calibrated pH meter (EQUIP-TRONICS, EQ-614A). The viscosity of formulation at room temperature was measured using Brookfield digital CAP 2000+ Viscometer at 100 rpm.[15]

Spray pattern

Spray pattern was checked by spraying the formulation from final container on the white paper. Visualization of spray was facilitated by dissolving 1% Methyl red in final formulation. Formulation was sprayed on board at distance of 2.5-3.0 cm from the paper and the spots appeared were measured for its diameter after drying. Result was generated by taking average of three measurements.[16]

Spray Angle

Piece of white paper was clipped on board Methyl red was dissolved in the formulation to get 1 % solution and sprayed on paper keeping nozzle of spray 15 cm away from paper. Spray dots formed were measured for its radius from different angle and spray angle was calculated by following equation:

$$\text{Spray angle } (\theta) = \tan^{-1}[h/(r)] \quad (1)$$

Where h is the distance of paper from the nozzle and r is average radius of the circle. Experiment was performed in triplicate and average reading was taken as result.[17]

Leak Test

Ability of container to store the formulation and effectiveness of pump seal was evaluated by this test. The initial weight of the filled container was recorded and then placed in upright position at 30°C for three days. The containers were weighed after 3 days to check the leakage of the formulation from the container.[16]

Average weight per dose

The filled spray container was weighed and weight as initial weight (W1). Spray was delivered from bottle five times in succession and final weight (W2) was recorded. Average weight per dose was determined by following equation:[16]

$$\text{Average weight per dose} = (W1 - W2)/\text{No. of Deliveries} \quad (2)$$

Evaporation Time

Time required for the spray film to dry was calculated by spraying the formulation on white paper and estimating time required for drying the formed film. Average reading of three test was recorded as evaporation time.[17]

Film Thickness

The film formed after spraying was peeled off from Plastic sheet (PTFE) and film thickness was measured using micrometre at various places to determine uniformity of spraying of the film.[18]

Tensile Strength

Tensile strength of the film was evaluated using Brookfield Texture Analyser having cell load of 10 kg. Film strip having 2×4 cm dimension was held between two clamps at a rate of 1mm/s. The tensile strength was measured at the time of breaking of film. Tensile strength was computed using below equation.[19]

$$\text{Tensile strength} = \text{Force at break (kg)} / \text{Initial cross sectional area of the sample}(cm^2) \quad (3)$$

Swelling Index

The film was cut in 2cm ×2 cm and initial weight (Wi) was recorded. It was immersed in phosphate buffer (pH 7.4) at 37℃ and weight of swollen film (Ws) was recorded after every 1 hr. The swelling index of the film was calculated by equation below.[20]

$$\text{Swelling Index } (\%) = [Ws\text{-}Wi] / Wi \quad (4)$$

Folding Endurance

The folding endurance was determined by continuously folding the film at constant place up to the time it broke.[21]

Drug content

Appropriately 2 cm^2 area of film was cut and dissolved in methanol by sonication and filtered through Whatman filter paper. The appropriately diluted solution was analysed by HPLC. For HPLC analysis by validated analytical method using Kromasil C_{18} (250mm X 4.6mm, 5µm) Column and Acetonitrile: (30 Mm) Phosphate buffer pH 3.5 adjusted with orthophosphoric acid (70:30) mobile phase composition.[17]

In vitro Drug release

Approximately 2 cm^2 of film was placed in the modified paddle over disc dissolution vessel filled with 100 mL of phosphate buffer pH 7.4. The paddles attached to every vessel were positioned over the disc and maintained at 50 rpm and temperature of 37 ± 2°C. Samples were taken at regular intervals up to 6 hr. and were analyzed by HPLC to estimate the cumulative amount of drug released. Experiments were performed in triplicate and the mean percentage drug release was presented with standard deviation.[20]

Stability Study

Spray performance and physical stability of the optimized formulation was observed visually for color change and precipitation in the formulation of the stability sample stored at 40±2°C and 75%±5 % RH at periodic intervals of 3 months. The amount of drug Simvastatin and Mupirocin delivered from the spray canister per valve actuation was determined by actuating spray 10 times into a beaker of 30 ml ethanol and the % drug content for respective drug was estimated using HPLC.[22]

Antimicrobial Efficacy

Zone of inhibition method was employed for investigating antimicrobial efficacy of optimized formulation against *S. aureus* and *E. coli*. Test culture of 18 hr equivalent to 108CFU/ml was spread on agar surface. Wells of equal diameter were prepared into agar placebo and equal quantity of test solutions of optimized formulation and marketed formulation were poured into prepared wells. The agar plates were incubated at 37°C for 24 hr. and zone of inhibition was measured.[23]

In vivo wound healing

In-vivo wound healing study was performed by excision wound healing model on Wister rats after approval from institutional Animal ethical Committee (IAEC). Dr. D. Y. Patil Institution of Pharmaceutical Science and Research, Pimpri, Pune-411018(DYPIPSR/IAEC/18-19/P-09).

For 1 week before study, animals were acclimatized and body weight was recorded. Excision wound of uniform area (2 cm2) was prepared in all the animals. Six groups were made with 6 animals in each group. Group-I was treated as control (untreated) group. Group-II was treated with placebo formulation. Group III and IV were treated with 1% Simvastatin and 1% Mupirocin formulation, respectively. Group V was treated with combination formulation having 1% Simvastatin and 1% Mupirocin. Group VI was treated with commercially available 2% Mupirocin ointment for comparative purpose. With daily observation of animals wound area was measured as 1, 7, 14, 21 days of study period, Percent wound contraction was calculated to determine wound healing potential of applied formulation.[20]

Histopathological Study

Histopathology analysis was done to compare the tissue growth after wound healing in animals treated with different formulation. For histopathology animals were sacrificed to remove healed skin from all animals. Removed skin was fixed in neutral buffer formalin. Tissue processing was done by dehydrating it in ascending grades of alcohol, cleared in xylene and embedded in paraffin was to slice to thickness of 3 µm. Using rotatory microtome sliced tissues were stained with Haematoxylin and Eosin (H&E) stain and examined under a microscope to note histopathological lesions.[20]

RESULTS

Selection of Drug ratio

Mupirocin is conventionally used as topical antibacterial in concentration of 2% in the form of ointment and Simvastatin is reported to be effective as wound healing agent in concentration of 1%. To formulate combination topical formulation having these both drugs, concentration of drugs were selected by checking its antibacterial efficacy against commercially available formulation. Zone of inhibitions are shown in Figure 1.

Formulation of Film Forming Spray

Film forming spray formulation having combination of SIM and MUP was formulated using Eudragit E100 as film forming polymer. The formulations were analysed for its pH and viscosity. The composition which showed pH in the range of 6.5 to 7.5 which is non-irritant to human skin and viscosity suitable for spraying (20-27.5 CP) were selected for further optimization.[24]

Optimization of Film Forming Spray

Polynomial linear regression equations obtained after applying central composite design represents the relationship between the main factors viz. conc. of plasticizer (A) and ratio of PEG-400: Glycerol (B) for variable responses of swelling index, % drug release of simvastatin and % drug release of mupirocin.

Swelling Index: 31.01-3.41A + 2.86 B- 0.39 AB+2.03A2+ 5.35B2 (5)

% Drug release of Simvastatin: +92.22-1.85A-1.28B+1.92AB+1.79A2-0.072B2 (6)

% Drug release of Mupirocin: +92.70-0.76A-2.22B+1.26AB+ 1.15A2+ 0.35B2 (7)

Equations obtained and observation of Figure 2 indicated that both plasticizers used which are PEG400 and glycerol have different effect on properties of formulation.

Evaluation of physical stability, spray parameter and film properties

Evaluation of stability batches showed that all formulations were stable without any change in colour, precipitation or phase separation. The evaporation time of solution after spraying the formulation on skin was found less than 3 min.

Spray pattern, spray angle and leak test results of optimised formulation are shown in Figure 3.

Spray angle of formulation was also found to be 82.46° ± 0.39°. The thickness of the film formed after spraying was found to be within 12-18 mm with tensile strength of 0.67 ±0.12 N/mm^2. Folding endurance was found to be 290.6±4.0. The uniformity of drug content of the sprayed film of optimized formulation was found to be 96.95±1.68% and

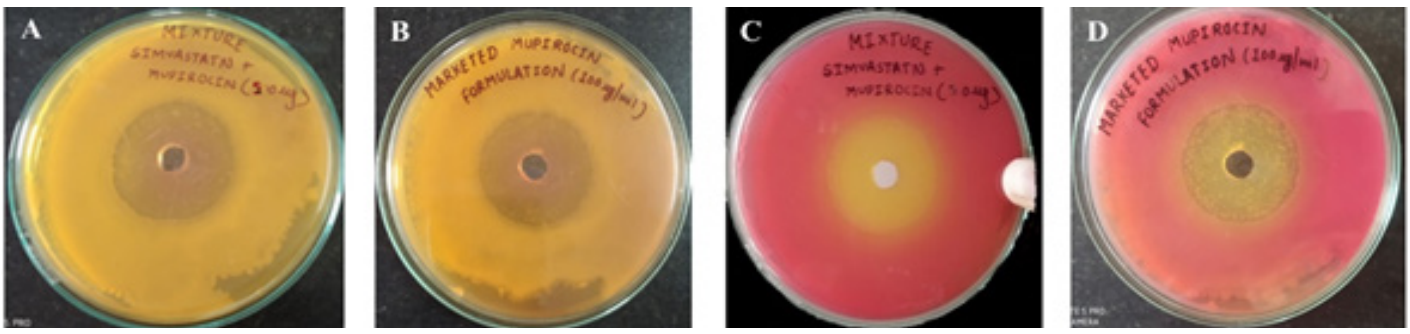

Figure 1: Zone of Inhibition for selection of drug ratio (A) Zone of Inhibition of Mixture in *S. aureus* (B) Zone of Inhibition of Marketed formulation in *S. aureus* (C) Zone of Inhibition of Mixture in *E. coli* (D) Zone of Inhibition of Marketed formulation in *E. coli.*

98.75±2.05% for Simvastatin and Mupirocin, respectively. The amount drug release per actuation was found to be in the range of 1.12 – 1.17 mg for both the drugs SIM and MUP even after storage. Final spray container shown in Figure 3 (C) did not show any leakage when placed in upright position at 30°C for 3 days

In vitro Drug release

SIM and MUP in optimized formulation both showed rapid burst release (90% for both drugs) within first two hours with no further release till next 24 hr whereas, Mupirocin ointment showed only 60% of drug release within first two hours.

Antimicrobial Efficacy

S. aureus and *E. coli* are commonly found organism which are responsible for causing infection.

Zone of inhibition produced by developed spray formulation at the concentration of 50 µg/ml at each drug and Marketed formulation at concentration of 100 µg/ml of MUP showed similar zones of 27.3 ± 0.2 mm and 27± 0.45 mm respectively against *S. aureus* whereas 38 ± 0.2 mm and 37 ± 0.12 mm respectively against *E. coli.*

In vivo wound healing and Histopathology

The wound healing observations throughout 21 days of treatment are shown in Figure 4 in the form of wound area. Percent wound contraction is also calculated to compare the wound healing in different treatment groups.

Results of histopathology study are shown in Figure 5 in the form of images.

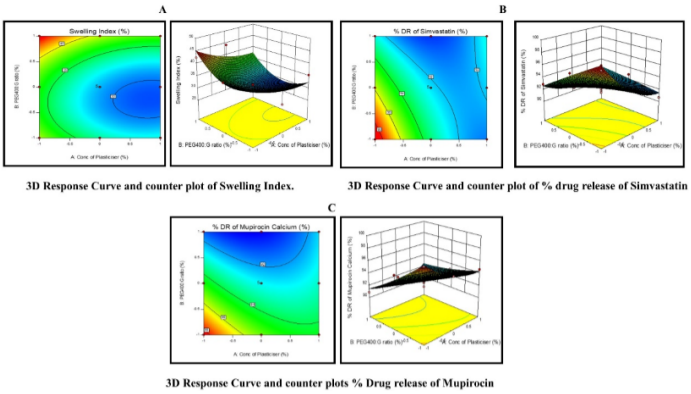

Figure 2: Optimized 3D response curve and contour plot.

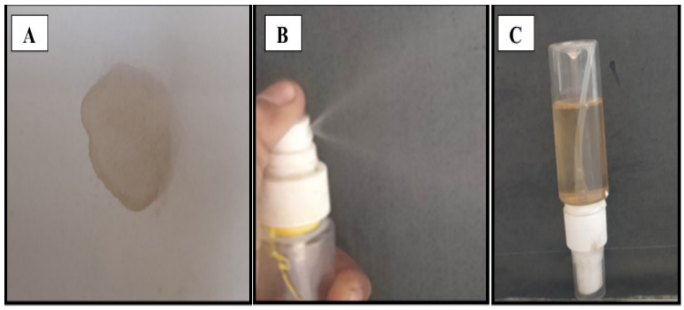

Figure 3: Physical properties of the Spray (A) Spray Pattern, (B) Spray Angle, (C) Leak Test.

DISCUSSION

Mupirocin is known antibacterial and Simvastatin is known to have growth promoting action. Antibacterial study indicated showed comparative antimicrobial efficacy in ratio of 1:1 for SIM: MUP against 2% of mupirocin ointment. SIM and MUP showed synergistic antimicrobial action in combination.

Eudragit E100 is commonly used as film forming agent for topical drug delivery system due to its non-irritant and non-toxic nature. It is considered as safe in human.[25] Since both, the drugs and polymer are hydrophobic in nature, ethanol was used along with acetone as co-solvent for the purpose of solubilisation as acetone has high

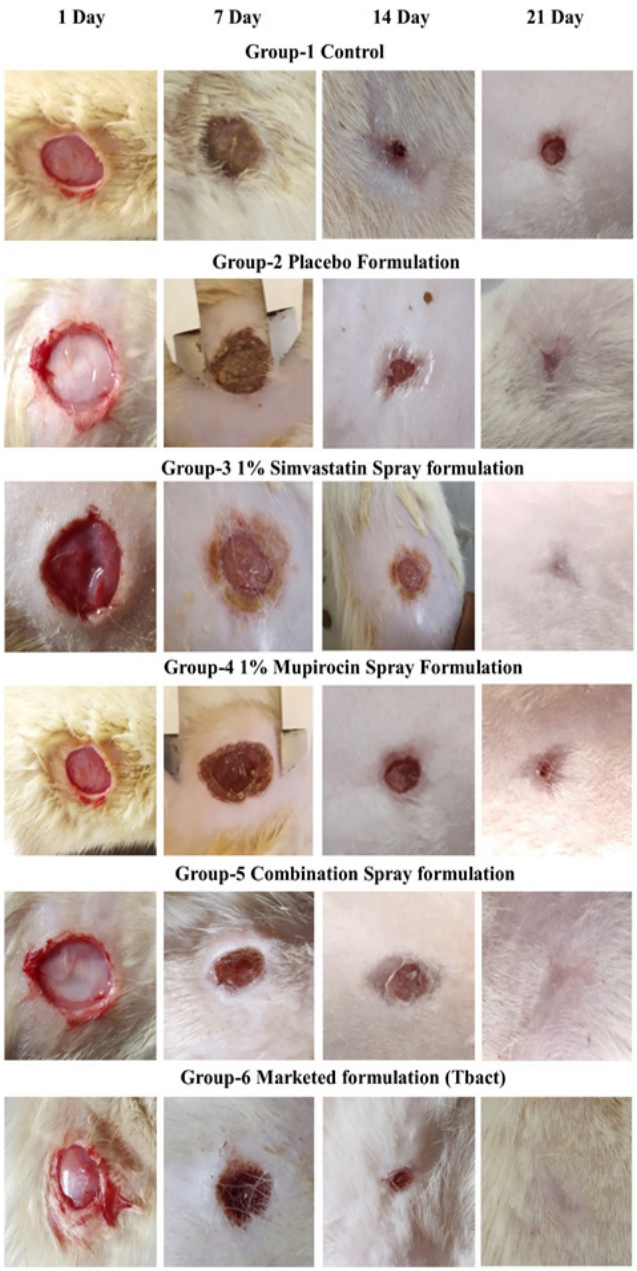

Figure 4: Progress of wound healing at different days of various groups.

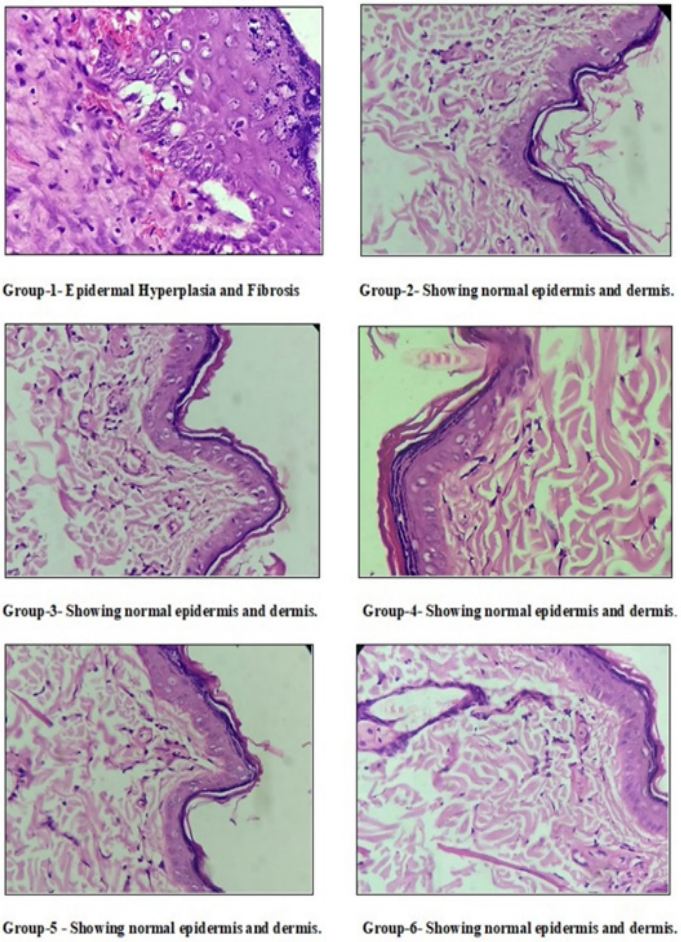

Figure 5: Observations of Histopathology study.

evaporation rate. Solvents gets immediately evaporated after spraying the formulation which minimises their contact time with area of application.[24] Polyethylene glycol which is non-irritant to skin was used as plasticizer and Glycerol acts both as humectant and plasticizer.[22] The formulations having pH in the range of 6.5 to 7.5 which is non-irritant to human skin and viscosity suitable for spraying (20-27.5 CP) were selected for further optimization.[20] Formulations optimization using central composite design indicated that the formulation loaded with the lower concentration of the PEG400: Glycerol ratio shows the better drug release as compared with other formulation. This may affect due to higher swelling of the formulation when these results are co-related with other results of the swelling index and thickness of film. Lower concentration of plasticizer shows better swelling and hence resulting into the better release. Hence, the properties of drug loaded film forming spray were dependent on both type and ratio of plasticizer.

Optimized formulation spray found to show good spray pattern with uniform and spherical spots as shown in Figure 3 (A) which is due to the flexible and cohesive film forming nature of the Eudragit E100.[25] Spray angle of formulation was also found to be good for easy activation of drug solution from the container and cover a maximum surface area within 5 min. Folding endurance and tensile strength results of the film indicated that film formed after spraying will be able to sustain body movements without any damage.

Optimized formulations were stable and final spray container found to be any leak-proof maintaining the effectiveness of the pump system in delivering reproducible amounts of the formulation per actuation and stability after storage. The thickness of the film formed after spraying is flexible enough to cover the wounds present in complicated sites such as joints.[22, 24] Folding endurance and tensile strength results of the film indicated that film formed after spraying will be able to sustain body movements without any damage with uniform drug content of Simvastatin and Mupirocin.

Drug release data indicated that wound infection can be efficiently controlled using topical spray formulation and wound healing agent will also be rapidly available to enhance wound healing process. These drug releases also can be controlled by application of thick coat of film to wound area, which can be selected based on wound conditions.

Zone of inhibitions observed after antimicrobial study indicated that Mupirocin and Simvastatin showed synergistic activity against micro-organism tested,[23] which justifies the reduction of Mupirocin dose from 2% to 1%.

Results on *in-vivo* wound healing indicated that spray formulation of Simvastatin and Mupirocin separately at concentration of 1% respectively did not show complete wound healing at the end of 21 days but was found to be better than placebo and control group. Whereas, developed spray formulation and commercially available ointment formulation showed complete wound healing at the end of 21 days. Histopathology study confirmed these results showing granulation tissue with epidermal hyperplasia and fibrosis control and normal epidermis and dermis in other groups.

Although animal studies showed preliminary positive results, study need to be conducted using a greater number of animals with proper statistical analysis. Since the developed formulation contains antimicrobial and wound healing enhancing drugs, these studies also need to be conducted using animal models where wound healing is delayed due to some disease conditions such as diabetes.

The research work in future may be extended to study pharmacokinetics parameters, *in-vitro-in-vivo* correlation as well as detailed investigation of role of individual drug in wound healing.

CONCLUSION

Topical film forming spray with combination of Simvastatin and Mupirocin was prepared using Eudragit E100, PEG-400 and Glycerol as film forming polymer, plasticizer and humectant-plasticizer, respectively. Formulation was optimized using Central composite design. Optimized formulation showed burst release of both the drugs within 2 hr. with desirable antimicrobial efficacy against *S. aureus* and *E. coli* in comparison with commercially available Mupirocin ointment. Formulation also showed comparative wound healing activity.

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CONFLICT OF INTEREST

The authors declare no Conflict of interest.

ABBREVIATIONS

SIM: Simvastatin; **MUP:** Mupirocin; **PEG:** Polyethylene Glycol.

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