Original Article

Formulation and Evaluation of Antibacterial Topical Gel of Doxycycline Hyclate, Neem Oil and Tea Tree Oil

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ABSTRACT

Purpose: To formulate novel topical antibacterial gel containing Doxycycline Hyclate, Tea tree oil and Neem oil to evaluate their antibacterial activity. **Methods:** Formulation excipients were selected using Drug-excipients compatibility study. Prepared gel was subjected to various evaluation parameters like pH, viscosity, spreadability, homogeneity, drug content uniformity, *in-vitro* drug diffusion and antibacterial activity. **Results:** Prepared topical gel of doxycycline Hyclate was shown pH range 5.3 ± 0.010 to 6.7 ± 0.015, viscosity range 386 ± 28.70 to 680 ± 50.40 cp, spreadability range 18.14 ± 0.98 to 28.13 ± 2.18 g.cm/s and homogeneous. Prepared gel was shown uniformity in drug content which ranges from 94.41 ± 0.61 to 97.44 ± 0.69%, zone of inhibition ranges 13.66 ± 1.69 to 32.00 ± 1.63 mm for *Staphylococcus aureus*, 04.00 ± 1.63 to 12.33 ± 0.94 mm for *Pseudomonas aeruginosa* and 11.66 ± 0.94 to 33.33 ± 1.24 mm for *Propionibacterium acne*. Prepared gel formulations were shown the negligible amount of drug diffusion, not more than 3.22 ± 0.04% was shown the non-fickian type of diffusion through the egg membrane. **Conclusion:** Formulation F8 was shown better antibacterial activity as compared to its other formulations. As the concentration of neem oil and tea tree oil was increased from 0.5 to 3% and 0.5 to 2% respectively in the gel, antibacterial activity was synergistically improved against *Staphylococcus aureous, Pseudomonas aeruginosa* and *Propionibacterium acne*. The prepared gel formulation was found useful for topical application due to its negligible diffusion, good spreadability, neutral pH, low viscosity and no irritation on human skin.

Key words: Doxycycline Hyclate, Neem oil, Tea tree oil, Drug diffusion study, Antibacterial activity.

INTRODUCTION

Acne, folliculitis and cellulitis are very painful conditions require topical treatment. The given topical gel formulation of Doxycycline Hyclate is used to treat acne, folliculitis and cellulitis types of skin infections. More than 90% of the world population is affected by acne. Hence, Doxycycline Hyclate and other related antibiotic are used in the treatment of Acne, Folliculitis, Cellulitis, urinary tract infection and other bacterial infection. In a market, the oral antibacterial drugs are available but the disadvantages of the oral formulation of drugs are more as compare to the topical formulation. Oral administration of Doxycycline Hyclate produces a side effect like abdominal pain, mouth ulcer, difficult and painful urination, GI irritation and other side effect are produced.[1,2]

Doxycycline Hyclate and Doxycycline monohydrate are 2 different salts of Doxycycline belong to a tetracycline antibiotic class. Doxycycline Hyclate is reversibly bound to the 30S ribosomal subunits and prevent the formulation of peptide chain of amino acid to inhibit protein synthesis.[3]

Tea Tree oil is used as an active ingredient in many types of bacterial infections.[4] Tea tree oil possesses antibacterial, anti-inflammatory, antiviral and antifungal properties. It has a minimum content of terpinene-4-ol

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and a maximum content of 1, 8-cineole. Terpinen-4-ol is a major component which exhibits strong antimicrobial and anti-inflammatory properties. Terpinen-4-ol is a potent agent against methicilin-resistant *Staphylococcus aureus* (MRSA) inhibits the growth of bacteria.[5]

Neem is belonging to family Meliaceae. It can be used in the treatment through the inhibition of bacterial growth, enhancement of antioxidant activity and modulation of the genetic pathway. Because of its powerful antiseptic and antifungal properties, Neem oil may rid the skin of bacteria and certain fungal infection, including Candida Albicans, while reducing redness and inflammation. It may help to prevent and relieve a bacterial or fungal infection on the skin or scalp.[6]

Hence, to overcome the above problems novel topical gel formulation of Doxycycline Hyclate was prepared. The proposed topical antibacterial gel can avoid drawbacks of drug administration by the oral route.

MATERIALS AND METHODS

Materials

Doxycycline Hyclate was obtained from Ajanta pharma, Aurangabad, India. HydroxypropylMethylcellulose (HPMC K-100 M) was obtained from Vishal Chemicals, Carbopol 934P was obtained from Vishal Chemicals, Glycerin was obtained from Pallav Chemicals, Sodium hydroxide was obtained from Pallav Chemicals, Propyl paraben was obtained from Pallav Chemicals, Neem oil was obtained from Omkarayurved and Tea tree oil was obtained from Organix Mantra, Australia.

Methods

Preparation of Gel formulation

Different gel formulations were formulated by a cold mechanical method as per the composition is given in Table 1. The 0.1 g of Doxycycline Hyclate active drug was dissolved in 15 ml of glycerin with the aid of mild heat (solution A). Weighed quantity of HPMC K100M and Carbopol 934P were dispersed in 75 ml of distilled water with constant stirring by using magnetic stirrer so that there was no lump in the dispersion and propylparaben was added in it (solution B). Solution A was added into the solution B and mixed thoroughly with constant stirring and homogeneous dispersion was obtained. Dropwise 10 % sodium hydroxide solution was added in it up to gel get formed. Finally, the required quantity of Neem Oil and Tea Tree Oil was added at room temperature and formulation were evaluated.[7-9]

Drug-excipients compatibility study

FTIR studies were carried for the Doxycycline Hyclate and gel formulation containing HPMC K100M, Carbopol 934P, Propyl paraben, Glycerin, Neem oil and Tea tree oil using FTIR spectrophotometer (Agilent technology), over the wavenumber range 4000-400 cm^{-1}. Drug- excipients compatibility was interpreted.[10]

pH

1 % aq. a solution of gel formulation was prepared and stored for 2 h and pH was determined using a digital pH meter. The pH of each gel formulation was done in the triplicate, average value and ± standard deviation was calculated.[11,12]

Viscosity

Brookfield digital viscometer was used to measure the viscosity of developed gel formulations. The spindle no. 6 was dipped in gel sample rotated at 10 rpm and 20 ± 1°C temperature for 15 min. The reading in triplicate was noted. Viscosity in centipoise (cp) was measured.[13]

Rheological study

Shear stress (rpm) was applied to the gel preparation and viscosity in centipoise was determined. Spindle no 6 was rotated at 5, 10, 20, 30, 50, 60, 100 rpm for 15 min.[14]

Spreadability

Method 1: Parallel plate method.

Determined the spreadability by using 'Wooden block' and 'Glass' slide apparatus. By this parallel plate method, two glass slides were used for determined spreadability. Fixed one slide on this wooden block (i.e. ground slide) and place 1.0 g of gel sample on the ground slide. The applied 1.0 g gel sample was then sandwiched between these two slides. Place 1.0 kg wt. on the top glass slide for 5.0 min to expel the air bubbles and provided a uniformed film of sample gel and scraped off the excess of gel from edges. The top glass slide was then subjected to pull with the help of string attached to a top glass slide by using 20 g weight and cover a distance of 7.5 centimeters be noted. Calculate the spreadability by using the following equation. Measured the spreadability of each gel formulations was done in the triplicate and the average value was calculated.[15,16]

$$\text{Spreadability} = \frac{\text{Wt. tide to upper slide sample was then sa}}{\text{Time is taken to separate both slides}}$$

Method 2: Arvouet-Grand Method

Spreadability of gels was determined by pressing 1 g of a sample between two 20 X 20 cm horizontal plates, the upper of which weighed 125 g. The spread diameter was measured after 1 min. Under this experimental condition, semistiff gel should show spreadability diameter

$\phi \leq 50$ mm and semifluid gel should show spreadability diameter $\phi > 50$ mm but < 70 mm. Measured the spreadability of formulations was done in the triplicate and the average value was calculated.[17]

Homogeneity

All developed gel formulations were allowed to set in a suitable container and tested for homogeneity by visual inspection and gel appearance was reported.[18,19]

Drug content

100.0 mg of gel sample was dissolved in 100.0 ml Phosphate buffer pH 5.5 and shaken the gel solution for two hrs on a mechanical shaker to dissolve drug completely. Then the given solution of prepared gel formulation was filtered and determined drug content by spectrophotometrically at 271 nm using a blank solution (phosphate buffer pH 5.5). Drug content of formulations was measured in the triplicate and average value ± standard deviation was calculated.[20]

Determination of antibacterial activity

i) Preparation of inoculums

Fresh bacterial culture of *Staphylococcus aureous, Pseudomonas aeruginosa* and *propionibacterium acne* was suspended in sterile water for 24 hr to obtain uniform suspension of a micro-organism.[21]

ii) Preparation of Nutrient Agar Media

Beef extract 3.0 g, Peptone 5.0 g, Agar 15.0 g were accurately weighed and transferred into a conical flask. Then add required quantity of distilled water and stirred the mixture of nutrient agar media for 2 min at the boiling condition. Then sterilized in an autoclave at 121°C for 15 min.[22]

iii) Determination of the zone of inhibition

Agar well diffusion method was used for the determination of the antibacterial activity of all gel formulations. In this method, transferred the 15-20 ml of a previously liquefied medium into sterile test tubes and cool all test tubes to 42°C-45°C temperature. One loopful of the culture was transferred in each agar medium containing test tube and mix. Then all inoculated liquid agar medium was poured into a separate sterile petri plate and allowed to solidify the agar medium. After solidification of the medium, the required quantity of gel formulation was applied into the cavities of the agar plate and agar plate was incubated at 37°C ± 1°C for 24 hrs.[23]

In-vitro Drug Diffusion Study

In-vitro Drug Diffusion study of all gel formulations was determined by using Franz-diffusion cell. The egg membrane was used in drug diffusion study and mounted in between the receptor and donor compartment of the Franz-diffusion cell. The receptor compartment contained 10.0 ml of phosphate buffer pH 5.5 and maintained the temperature at 37 ± 1°C. The assembly was fixed on a magnetic stirrer. 0.1 g quantity of gel sample was placed over the egg membrane and solution of phosphate buffer pH 5.5 in the receptor compartment was stirred constantly using magnetic bead at 50.0 rpm. Then withdrawn the 1.0 ml of sample at 1, 2, 3, 4, 5 and 6 h and diluted with 10.0 ml of blank solution and analyzed the withdrawn sample by spectrophotometer at 271 nm. Diffusion study of formulations was measured in the triplicate and average value ± standard deviation was calculated.[24]

RESULTS AND DISCUSSION

Topical gel preparation of Doxycycline Hyclate, neem oil and tea tree oil was developed using HPMC K-100 M and Carbopol 934P as a gelling agent. Propyl paraben was used as a preservative; Glycerin was used as humectant and emollient. 10 % of sodium hydroxide was used to produce viscosity of the gel. Doxycycline Hyclate was used as antibacterial agent at 0.1 % level in all formulations. Neem oil was used as a natural antibacterial agent at 05 to 2.0 % level and Tea tree oil was used as a natural antibacterial and antifungal agent at 0.5 to 3.0 % level to produce more effective topical antibacterial gel formulation.

FTIR spectrum of Doxycycline Hyclate and its gel formulation F8 was obtained shown in Figure 1. Doxycycline Hyclate was shown frequency at 3352.30 cm^{-1} due to O-H stretching, 2885.21 cm^{-1} due to N-H stretching, 2970.57 cm^{-1} due to C-H stretching, 1665.59 cm^{-1} due to C=O stretching, 1595.43 cm^{-1} due to aromatic N-H bending and 1078.35 cm^{-1} due to C-N stretching which are match with its gel formulation at 3294.53 cm^{-1} due to O-H stretching, 2996.98 cm^{-1} due to N-H stretching, 2889.37 cm^{-1} due to C-H stretching, 1694.04 cm^{-1} due to C=O stretching, 1602.23 cm^{-1} due to aromatic N-H bending and 1153.84 cm^{-1} due to C-N stretching, Drug excipients were found compatible.

After performing FTIR of the Doxycycline Hyclate and gel formulation. It was found that the peaks obtained in the formulation were in between the range of main principle peaks and were found to be very near to previously performed FTIR of Doxycylinehyclate. No major deviation in peaks was obtained in FTIR spectra, hence this indicates that drug was compatible with other ingredients.

Results of pH, viscosity, spreadability and homogeneity are shown in Table 2. The pH values lie in the normal

Table 1: Formulation development of Doxycycline Hyclate topical gel.

Sr. no.	Ingredients (Quantity in gram)	Formulations							
		F1	F2	F3	F4	F5	F6	F7	F8
1	Doxycycline Hyclate	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
2	HPMC K100M	0.3	0.5	0.5	0.7	0.7	0.7	0.7	0.7
3	Carbopol-934P	0.2	0.3	0.5	0.5	0.5	0.5	0.5	0.5
4	Propyl paraben	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
5	Glycerin %	15	15	15	15	15	15	15	15
6	Neem Oil %	0.5	1.0	1.0	0.5	1.0	1.5	1.5	2.0
7	Tea Tree Oil %	0.5	0.5	1.0	0.5	0.5	1.0	2.0	3.0
8	10 % NaOH	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
9	Distilled Water upto	100	100	100	100	100	100	100	100

Table 2: Evaluation of topical gel for pH, Viscosity, Spreadability and Homogeneity.

Batch no.	pH	Viscosity (cp)	Spreadability		Homogeneity
			Method I (g.cm/s)	Method II (mm)	
F1	6.71±0.015	402±32.65	28.13±2.18	40±1.63	Homogenous
F2	6.44±0.011	386±28.70	24.32±1.93	42±2.16	Homogenous
F3	6.02±0.020	480±41.43	21.14±2.32	38±0.81	Homogenous
F4	5.36±0.015	603±29.43	18.81±0.93	30±1.41	Homogenous
F5	5.41±0.005	646±40.20	18.26±0.98	25±1.63	Homogenous
F6	5.47±0.015	621±35.59	18.14±0.98	26±1.64	Homogenous
F7	5.33±0.010	680±50.40	16.81±0.35	23±1.63	Homogenous
F8	5.59±0.011	587±45.46	18.62±1.05	33±9.81	Homogenous

Table 3: Evaluation of topical gel for Drug content and antibacterial activity.

Formulation	Drug content (%)	Zone of inhibition (mm)		
		Staphylococcus aureous	*Pseudomonas aeruginosa*	*Propionibacterium acne*
F1	95.20 ± 0.32	14.00±0.81	04.33±1.24	12.00±2.44
F2	94.82 ± 1.06	17.00±1.63	05.66±0.94	16.66±0.94
F3	95.11 ± 0.92	21.33±1.24	07.00±0.81	21.66±1.69
F4	95.62 ± 0.91	13.66±1.69	04.00±1.63	11.66±0.94
F5	94.41 ± 0.61	16.00±1.63	06.33±1.24	14.00±1.41
F6	96.10 ± 0.69	25.66±1.66	08.00±1.41	24.66±1.66
F7	97.44 ± 0.69	30.00±0.81	11.66±1.66	31.00±1.63
F8	96.52 ± 0.77	32.00±1.63	12.33±0.94	33.33±1.24

pH range which is compatible with a normal pH range of skin. The pH values of all formulated gel formulations range from 5.33 to 6.71 which lies in the normal pH range. Result of viscosity measurement shown in Table 2 indicates that prepared gel was low viscosity gels which can satisfy ease of application of delivery on skin. The viscosity of topical gel was adjusted by the addition of a small quantity of 10% sodium hydroxide. It was also observed that as the concentration of the gelling agent was increased, the viscosity of gel formulation was also increased. The viscosity of gel was controlled at 587 ± 45.46 to 603 ± 29.43 Cp for formulations F4 to F8 which contain 0.7 % HPMC K 100 M and Carbopol 934P were shown solution form and were not formed a gel-like consistency.

Rheological studies were performed on the prepared gel. Viscosity in centipoise was determined against applied stress (rpm) and depicted in Figure 2. It was observed that all prepared gel preparations were shown a decrease in viscosity with an increase in stress. This type of rheo-

Table 4: *In-vitro* Drug diffusion kinetic kinetics study constants.

Formulation Code	Zero-order		First Order		Higuchi Plot		Korsmeyers Peppas		
Code	R^2	K_0	R^2	K_1	R^2	K_h	R^2	K_p	n
F1	0.9086	0.260	0.8903	0.0014	0.8596	0.884	0.8848	0.372	0.6984
F2	0.9883	0.368	0.9525	0.0021	0.8393	0.765	0.8154	0.411	0.7148
F3	0.9962	0.327	0.9623	0.0018	0.9786	1.154	0.9734	0.473	0.8106
F4	0.9808	0.366	0.9317	0.0016	0.9437	1.264	0.7245	0.367	0.7654
F5	0.9839	0.328	0.9383	0.0019	0.9889	1.186	0.9862	0.431	0.6030
F6	0.8996	0.361	0.9325	0.0016	0.8322	1.196	0.8424	0.573	0.7342
F7	0.9020	0.229	0.9310	0.0012	0.9771	1.319	0.9771	0.866	0.6482
F8	0.9604	0.179	0.9381	0.0010	0.9104	0.611	0.8953	0.377	0.7032

logical behavior is useful for better spreading and use of application of gel formulation on the skin. **Method 1:** Parallel plate method and **Method 2:** Arvouet-Grand-method was used for spreadability determination. In the method I, spreadability ranges from 16.81 ± 0.35 to 28.13 ± 2.18 g.cm/s while in method II, spreadability ranges from 23 ± 1.63 to 42 ± 2.16 mm diameter. Method II indicated that prepared gels were semi stiff gels. All developed topical gels formulations showed good homogeneity with an absence of lumps.

Drug content

Percentage of drug content was measured for all topical gel formulations shown in Table 3. The results revealed that the drug content was almost uniform in all the topical gels with low standard deviation values. We can preclude that uniform drug loading of Doxycycline Hyclate was found in a gel formulation.

The antibacterial activity of the given formulations is shown in Table 3. The zone of inhibition of all formulations is different because of the change in the concentration of Tea tree oil and Neem oil. Increasing the concentration of oil showed a greater zone of inhibition to treat bacterial infection. i.e. F7 and F8 showed the greater the zone of inhibition than other formulations. It was observed that prepared gel formulations were more effective against *Propionibacterium acne* and *Staphylococcus aureous*. It was also observed that the addition of Neem oil and Tea tree oil in Doxycycline Hyclate gel was shown the synergistic effect to treat skin infections.

Drug diffusion study

Drug diffusion study was performed to determine drug diffusion across the egg membrane. It was observed that a very small quantity of drug diffused 2.8 ± 0.1 to 0.87 ± 0.02 % across the egg membrane. The results of diffusion indicated that less diffusion of the drug is not beneficial for systemic delivery of the drug. Prepared gel formulations were useful for topical treatment of acne, folliculitis and cellulitis.

Drug diffusion study was performed on prepared gel formulations. Drug diffusion kinetics results are shown in Table 4. The prepared gel formulation was exhibited zero-order drug diffusion as R^2 value were close to 0.99. Formulations were exhibited non-ficking type diffusion as n value of Korsmeyers Peppas model was greater than 0.45.

CONCLUSION

The antibacterial topical gel of Doxycycline Hyclate, tea tree oil and neem oil formulation F8 showed better antibacterial activity as compared to its other formulations. As the concentration of neem oil and tea tree oil was increased from 0.5 to 3% and 0.5 to 2% respectively in antibacterial gel, antibacterial activity was synergistically improved against *Staphylococcus aureous, Pseudomonas aeruginosa* and *Propionibacterium acne*. The prepared gel formulation was found useful for topical application due to its negligible diffusion, good spreadability, neutral pH and low viscosity

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

g: Gram; **%:** Percentage; **cm:** Centimeters; **min:** minutes; **rpm:** Rotation per minute; **%CDR:** Percentage Cumulative Drug Release; **Conc:** Concentration; **°C:** Degree Celsius; **g.cm/s:** Gram centimeter per second;

ml/min: Milliliter per minute; **ppm:** Parts per million; **cps:** Centipoise.

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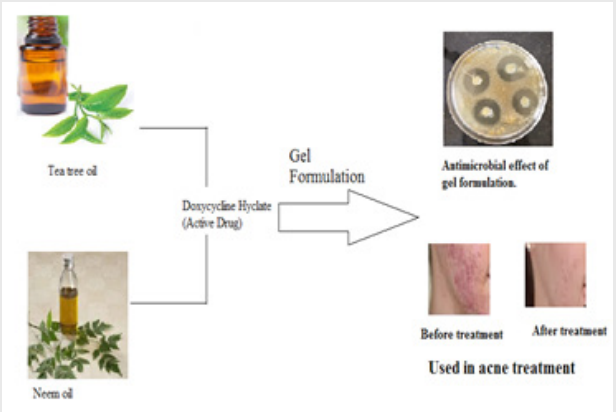
PICTORIAL ABSTRACT



SUMMARY

The antibacterial topical gel of Doxycycline Hyclate, tea tree oil and neem oil showed better anti-bacterial activity as compared to its other formulations. As the concentration of neem oil and tea tree oil was increased in antibacterial gel formulation, antibacterial activity was synergistically improved against *Staphylococcus aureous, Pseudomonas aeruginosa* and *propionibacterium acne* bacterial infection. The prepared gel formulation was found useful for topical application due to its negligible diffusion, good spreadability, neutral pH and low viscosity.

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