

## Formulation and evaluation of Clarithromycin Topical Gel

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### Abstract:

The present study was designed to formulate and evaluate different formulae of topical gel containing Clarithromycin for treatment of skin infections. The gel was formulated by using different polymers with different concentrations of HPMC K4M, carbopol 934 and sodium alginate. Twelve different formulae were prepared and characterized physically in terms of color, pH, homogeneity, spreadability, drug content, viscosity and invitro drug release. Clarithromycin -excipients compatibility studies were confirmed by carrying out FTIR studies. In-vitro drug release study through dialysis membrane using a modified Franz diffusion cell was performed. The results of in-vitro release studies showed that the highest values was from F9 (90.6% of drug released after 12hrs). Also F9 formulation revealed that the viscosity was very less compared to other formulations and it was concluded that sodium alginate gel (F9) containing Clarithromycin showed good consistency, spreadability and homogeneity. Moreover, the stability study results of F9 formulation revealed no significant difference between before and after storage for selected formula.

**Keywords:** Clarithromycin, FTIR studies, In vitro release, HPMC K4M, carbopol 934, sodium alginate, topical gel.

### INTRODUCTION

Topical dosage forms are formulae which are applied directly to an external body surface by spreading, spraying or instillation, rubbing. The topical route of drug administration has been exploited either to produce local effect or to produce systemic effects [1]. Topical delivery of drugs provides an attractive alternative to the oral route of drug administration, because it overcoming drawbacks associated with the oral mode of dosing such as first pass effects, gastrointestinal irritation and metabolic degradation[2]. Topical preparations circumvent GI irritation, prevent the metabolism of drug in the liver and increase the bioavailability of the drugs and provide its action directly at the site of action[3]. Gel base formulations for dermatological use have several favorable properties such as greaseless, easily spreadable,

easily removable, thixotropic, water soluble or miscible, non- staining and emollient[4,5].

Clarithromycin is a novel macrolide antibiotic with broad spectrum of activity. It is better absorbed than erythromycin, is well tolerated and is to be administered less frequently. It is the most effective macrolide against *haemophilus influenza*, *staphylococcus aureus*, *Chlamydia trachomaitis*, *klebsiella*, *E.coli*, *proteus*[6]. Clarithromycin is used to treat respiratory tract infections, skin and soft tissue infections; it is also used to treat *helicobacter pylori* infections and Lyme disease [7]. Clarithromycin is acid stable and is well absorbed from GIT irrespective of presence of food. It has poor bioavailability (50%) in the presence of intestinal metabolic enzymes like cytochrome P450 (CYP3A), resulting in numerous drug interactions [8]. Acne vulgaris is a chronic inflammatory disorder of the sebaceous glands

and most common disorder treated by dermatologists [9].

The main objective of the present work was to develop topical gels of Clarithromycin using three types of gelling agents: HPMC K4M, carbopol 934, sodium alginate and study the formulation variables affecting the release of drug.

## MATERIAL AND METHODS

### MATERIALS

Clarithromycin was a gift sample from Aurobindo Pharma Ltd, Hyderabad. Carbopol 934, HPMCK4M and sodium alginate procured from S.D. fine chemicals Pvt. Ltd. All other chemicals were used of analytical grade and without any chemical modification.

### METHODS

#### Preparation of Clarithromycin topical gel

The composition of Clarithromycin topical gel formulae are shown in table 1. Clarithromycin gel formulations were prepared using hydroxypropylmethyl cellulose (HPMC K4 M), carbopol 934 and sodium alginate as gelling

agents. Gelling agent (1%, 2%, 3% and 4%) was dispersed in a calculated amount of water with constant stirring using magnetic stirrer at a moderate speed overnight to ensure complete hydration. Clarithromycin was dissolved in methanol or ethanol and added to the dispersion. Methyl paraben (0.2%) and Propyl paraben (0.1%) as preservatives were added slowly with continuous stirring. In carbopol gels adjust the pH of the gel compatible with the normal pH of the skin by using TEA (triethanolamine) until the desired pH value was approximately reached (6 - 7). During pH adjustment, the mixture was stirred gently with spatula until homogenous Clarithromycin gel was formed. The final weight of the gel was adjusted to 100 gm with distilled water. Entrapped air bubbles were removed by keeping the gels in vacuum desiccators. The prepared Clarithromycin gels were filled in lacquered aluminium collapsible tubes and stored in dark and cool place.

**Table 1:** Formulation of Clarithromycin gels using different gelling agents

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Clarithromycin	1	1	1	1	1	1	1	1	1	1	1	1
HPMC K4M	1	2	3	4	-	-	-	-	-	-	-	-
Carbopol 934	-	-	-	-	1	2	3	4	-	-	-	-
Sodium alginate	-	-	-	-	-	-	-	-	1	2	3	4
Propylene glycol	10	10	10	10	10	10	10	10	10	10	10	10
Methyl paraben	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Propyl paraben	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

\*All ingredients in gram

### Physicochemical Evaluation of Prepared Clarithromycin Gel

#### Measurement of pH

The pH of various Clarithromycin gel formulations was determined by using digital pH meter, which

was calibrated before each use with standard buffer solutions. 1g of Clarithromycin gel was dissolved in 100 mL freshly prepared distilled water and stored for two hours. The electrode was inserted in to the sample solution 10 min priors

to taking the reading at room temperature.

Each measurement was carried out in triplicate and the average pH was calculated [10].

### Homogeneity

All developed Clarithromycin gels were tested for homogeneity by visual inspection after the gels have been set in the container. They were tested for their color, appearance and presence of any aggregates or lumps [11].

### Viscosity

The viscosity of the different Clarithromycin gel formula was determined at 25°C using Brookfield digital viscometer. The gels were rotated at 20 and 30 rpm with spindle no. 64. At each speed, the corresponding dial reading was noted. Evaluation was conducted in triplicate [12].

### Spreadability test

A sample of 0.5 g of each developed Clarithromycin gels formula was pressed between two slides (divided into squares of 5 mm sides) and left for about 5 minutes where no more spreading of gel was expected. Diameters of spreaded circles were measured in centimeter and were taken as relative values for spreadability. Evaluation was conducted in triplicate and the average spreadability values were calculated [13].

### Drug content

100mg of gel from each formulation were weighed and it was dissolved in 100ml of phosphate buffer of pH 5.5. The conical flask containing gel was shaken for 2hrs on mechanical shaker in order to get complete solubility of Clarithromycin. The resulting solution is filtered through Whatman filter paper, the Clarithromycin content was analyzed spectrophotometrically at 205nm using an UV spectrophotometer (Elico, India). Each measurement was carried out in triplicate and the

average Clarithromycin content in the topical gel was calculated [14].

### In-vitro release study

Franz diffusion cell (with effective diffusion area 3.14 cm<sup>2</sup> and 24.5 ml cell volume) was used for the studies. Prepared Clarithromycin gel (500 mg) was applied uniformly on the surface of dialysis membrane (Himedia). The membrane was clamped between the donor and the receptor compartment of diffusion cell. The receptor chamber was filled with freshly prepared PBS (pH 5.5) solution to solubilize the Clarithromycin. The receptor chamber was stirred by magnetic stirrer at 50 RPM; the temperature was maintained at 37 ± 0.50 °C. The samples (5.0 ml aliquots) were collected at suitable time interval. Samples were analyzed for Clarithromycin content by UV visible spectrophotometer after appropriate dilutions. Cumulative corrections were made to obtain the total amount of Clarithromycin permeation at each time interval [15, 16].

### Release kinetic studies

To find out the mechanism of drug release from Clarithromycin topical gel, the *in vitro* release data was treated with different kinetic models, namely zero order, first order, Higuchi, Hixson Crowell and Korsmeyer-Peppas. A criterion for selecting the most appropriate model was based on goodness of fit, high regression coefficient value [17, 18]

### FTIR Spectra

Drug-excipients compatibility studies were carried out using FT-IR infrared spectrum of pure drug Clarithromycin was taken in between 400 to 4000 cm<sup>-1</sup> using KBr pellet method. The study was carried out on individual pure drug Clarithromycin, polymer and optimized formulation F9.

### Stability studies

The stability study was carried out for the most satisfactory Clarithromycin formulation F9. The most satisfactory F9 formulations were packed in lacquered aluminium collapsible tubes (5g) and stored at 40°C/75 % RH for 3 months. At the end of each month the Clarithromycin gel samples were analyzed for their physical appearance, pH and the drug content by procedure stated earlier. All the test results were found to be in limits. Hence the formulations were stable under stated storage condition [19, 20].

## RESULTS AND DISCUSSION

### Characterization of formulations

**Table 2:** Shows the characterization results of Clarithromycin topical gel

Formulation code	Color	Phase Separation	Homogeneity	Spreadability	pH	Viscosity	Drug content
F1	White	No	+++	4.4±0.05	6.68±0.01	3124.33±2.51	97.78±0.55
F2	White	No	+	3.6±0.05	7.09±0.02	3653.67±1.23	97.04±0.18
F3	White	No	+	2.7±0.06	6.97±0.02	4169.25±2.55	97.49±0.41
F4	White	No	+	2.1±0.10	7.06±0.01	5328.11±2.49	97.18±0.25
F5	Transparent	No	+++	4.5±0.15	7.16±0.015	3245.31±1.47	96.03±0.20
F6	Transparent	No	+++	4.0±0.10	6.77±0.01	4208.35±0.85	96.05±0.11
F7	Transparent	No	++	2.8±0.05	6.21±0.03	5319.42±1.72	95.22±0.67
F8	Transparent	No	++	2.5±0.50	6.81±0.02	6108.33±0.95	95.32±0.57
F9	Brownish	No	+++	4.8±0.10	6.59±0.005	2809.42±0.33	98.79±0.21
F10	Brownish	No	+++	4.5±0.11	6.81±0.032	3217.43±0.53	98.32±0.20
F11	Brownish	No	+++	3.7±0.10	6.54±0.015	3687.33±0.40	97.77±0.13
F12	Brownish	No	+++	3.5±0.05	6.85±0.03	4165.41±0.36	97.3±0.57

Excellent +++, Good ++, Satisfactory +

### Homogeneity

The prepared Clarithromycin gel formulae were inspected visually for their color and syneresis. All developed gel formulae showed good homogeneity with absence of lumps and syneresis.

### Viscosity

Viscosity is an important physical property of Clarithromycin topical gel formulations, which affects the rate of drug release. In general, an increase of the viscosity vehicles would cause

Topical drug delivery systems offer several advantages over oral drug delivery systems. However it has been found so many side-effects were proved by the oral delivery system of Clarithromycin and here to over the side-effects of oral dosage form. The oral dosage form has been changed by formulation and evaluation of Clarithromycin topical gel.

### pH Determination

The pH values of all developed Clarithromycin formulae was in range 6-7 which is considered acceptable to avoid the risk of irritation upon application to the skin. There was no significant change in pH values as a function of time for all Clarithromycin topical gel formulations.

high degree of cross linking with a consequent decrease of the rate of Clarithromycin release.

Viscosity increased (from 2809.42±0.33 to 6108.33±0.95cPs,) as polymer concentration increased in all gel formulations. Viscosity of gel formulation with carbopol 934 was high as compared to that of HPMC k4 and sodium alginate.

### Drug content

After various formulation of Clarithromycin gel the drug content of the formulated gel was

estimated by Elico spectrophotometer at  $\lambda_{\text{max}}$  205 nm in phosphate buffer of pH 5.5. The results were in the official limits as shown in Table 2.

### Spreadability

The spreadability is very much important as it shows the behavior of Clarithromycin gel comes out from the tube. The spreadability indicates that the Clarithromycin topical gel is easily spreadable by small amount of shear. The diameters of the spreaded circles ranged from 3-4 cm seen with the sodium alginate gel and 2-4 cm seen with carbopol and HPMC gel. Spreadability Data revealed that Spreadability of the Clarithromycin topical gel decreases with the increase in the concentration of the gelling agents as expressed by the lower diameter of the spreaded circle.

### In-vitro release studies

The in-vitro release profile of Clarithromycin topical gel formulae was represented in Fig 1.1-1.3. it was observed that the release of the Clarithromycin drug from its different formulae can be ranked in the following descending order  $F9 > F5 > F1 > F10 > F2 > F11 > F12 > F6 > F3 > F4 > F7 > F8$  where the amounts of the drug released after 12hrs were 90.6%, 88.8%, 84.6%, 72.2%, 69.2%, 65.5%, 59.5%, 51.8%, 50.8%, 48.7%, 48.1% and 40.9% respectively. These results suggested that F9 is effective for topical application as highest percentage of drug released after 12hrs (90.6%). It was observed that the most influenced factor in the Clarithromycin release is polymer type followed by the concentration of the polymer.

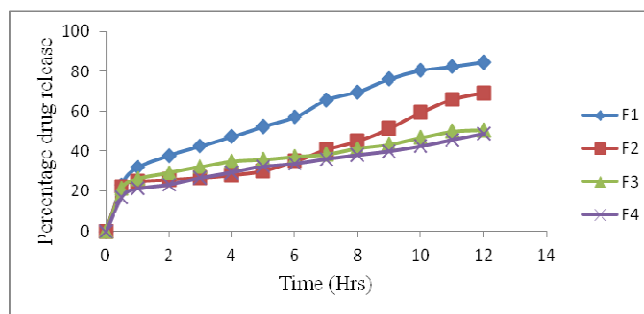


Fig 1.1: Comparative release profile of formulation F1 to F4

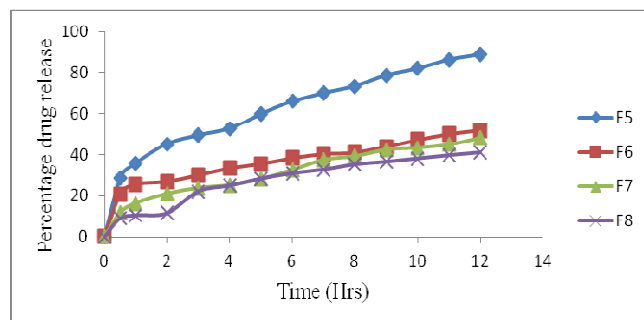


Fig 1.2: Comparative release profile of formulation F5 to F8

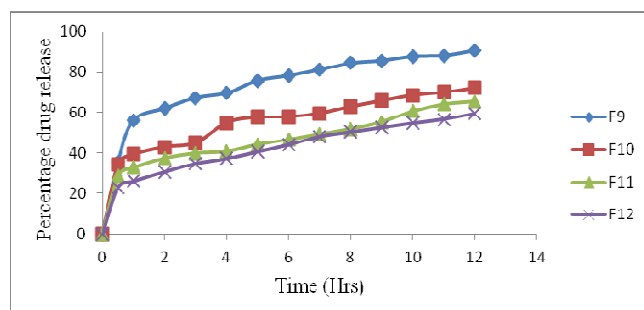


Fig 1.3: Comparative release profile of formulation F9 to F12

### Drug Release Kinetic Study

The release data analysis was carried out using the different kinetic models. The Regression coefficient ( $R^2$ ) values of different kinetic models are tabulated in table 3. This indicated that the release data of best formulation (F9) showed best fitting to Higuchi model kinetics. The mechanism of drug release is determined by Korsmeyer Peppas where 'n' is the release exponent hence the mechanism of Clarithromycin release is fickian diffusion for F9 formulations given in table 3.

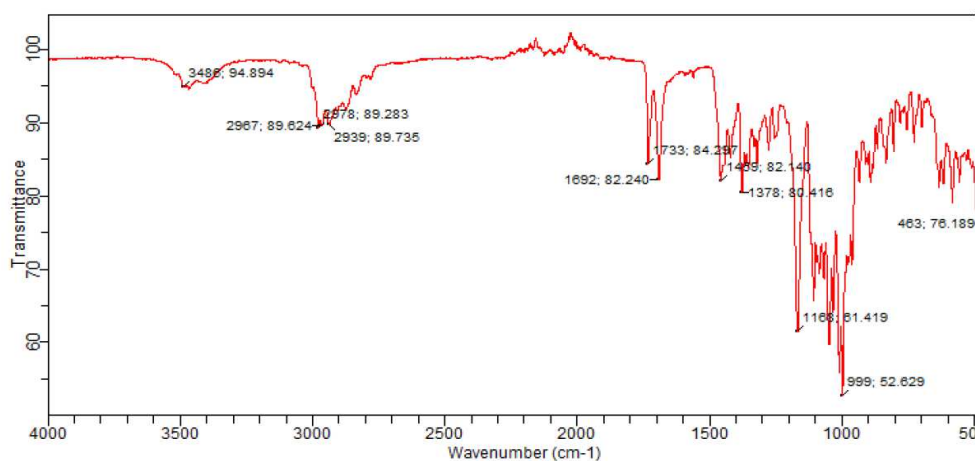
**Table 3:** Kinetic parameters of Clarithromycin topical gel

Formulation Code	Zero order	First order	Higuchi	korsmeyer peppas	Hixons	n value
F1	0.9848	0.9798	0.9828	0.9756	0.9702	0.4085
F2	0.9356	0.8846	0.8297	0.7615	0.874	0.3534
F3	0.9723	0.9775	0.9736	0.9644	0.9773	0.2568
F4	0.9006	0.9894	0.9941	0.9824	0.9906	0.2998
F5	0.9782	0.9813	0.9945	0.9875	0.9656	0.3588
F6	0.9863	0.9902	0.9806	0.9592	0.9898	0.2819
F7	0.9788	0.9889	0.9842	0.982	0.9896	0.44
F8	0.9291	0.9577	0.9703	0.944	0.9604	0.5479
F9	0.8372	0.9761	0.9319	0.9425	0.9856	0.2565
F10	0.9525	0.9819	0.9835	0.966	0.9842	0.2384
F11	0.9861	0.973	0.9591	0.9332	0.9685	0.2543
F12	0.9836	0.9968	0.9929	0.9741	0.9974	0.299

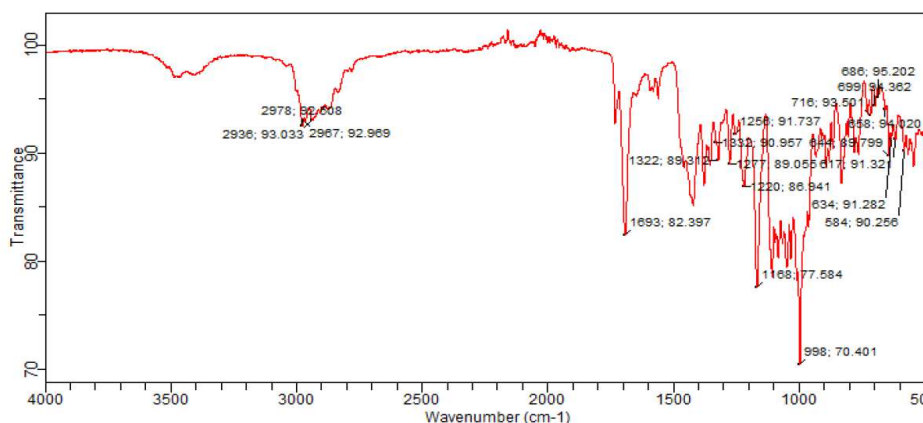
### Drug-Excipients Compatibility Studies

Drug-excipients compatibility determined by FT-IR analysis. FT-IR study revealed that there was no major change in the position of peak obtained in the Clarithromycin alone and in formulation of

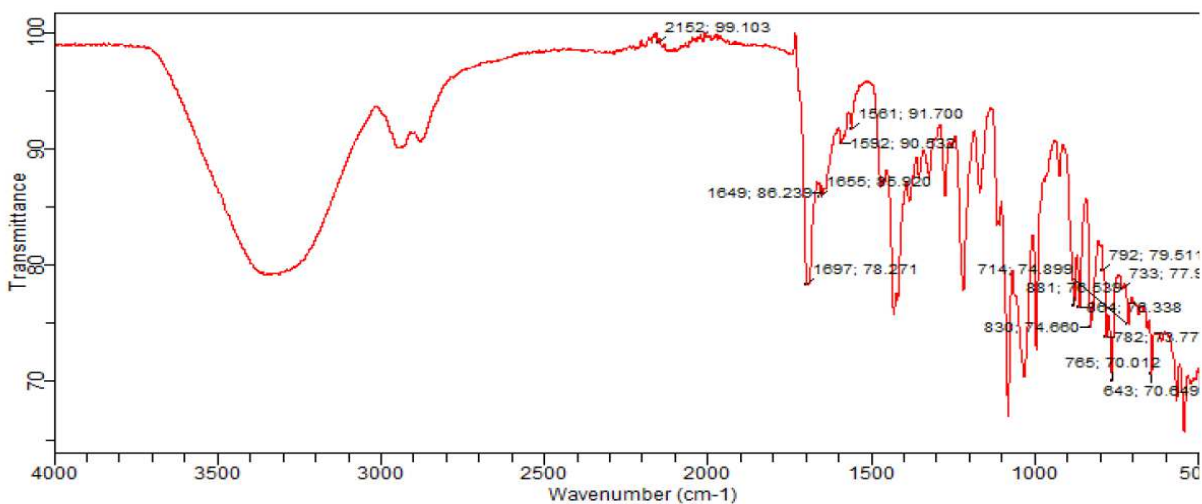
Clarithromycin topical gel with excipients, which shows that there was no interaction between Clarithromycin and excipients. Results are shown in figures (2.1-2.3).



**Fig. 2.1:** FTIR spectra of formulation pure drug Clarithromycin



**Fig. 2.2:** FTIR spectra of pure sodium alginate polymer



**Fig. 2.3:** FTIR spectra of Clarithromycin topical gel formulation F9

### Stability study

The selected formulations F9 were subjected to the accelerated stability at  $40 \pm 2^\circ\text{C}$  /  $75 \pm 5\%$  RH for 3 month and evaluated for their physical appearance, drug content and pH. There were

no significant variations in the physical appearance, drug content and pH (table 4). So, the formulated transdermal gel of Clarithromycin is stable at  $40 \pm 2^\circ\text{C}$  /  $75 \pm 5\%$  RH.

**Table 4:** Stability data of F9 Clarithromycin gel formulations

Formulation code	Months	Color	Homogeneity	pH	Drug content
F9	0	Brownish	+++	$6.59 \pm 0.01$	$98.89 \pm 0.55$
	1	Brownish	+++	$6.51 \pm 0.06$	$98.82 \pm 0.64$
	2	Brownish	+++	$6.49 \pm 0.13$	$98.73 \pm 0.72$
	3	Brownish	+++	$6.47 \pm 0.52$	$98.65 \pm 0.23$

### CONCLUSION

From above results, we can conclude that Clarithromycin gel formulations prepared with different gelling agents HPMCK4M, carbopol 934 and sodium alginate showed acceptable physical properties concerning color, pH, homogeneity, spreadability, drug content, consistency and drug release study. Among all Clarithromycin gel formulations F9 proved to be the formula of choice, since sodium alginate gels shows superior drug release after that carbopol 934 and HPMCK4M shows decreasing order of Clarithromycin release. In sodium alginate gel

formulations the Clarithromycin release was decrease with increase in sodium alginate concentration because polymer concentration increases, viscosity increases. Stability studies of F9 Clarithromycin gel formulations showed that, the physical appearance, drug content and pH remain unchanged upon storage for three months. Therefore, it was concluded that Clarithromycin gel formulation F9 containing sodium alginate could be very promising topical alternative for the treatment of skin infections. However, further preclinical and clinical studies are recommended to support its efficacy claims in humans.

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