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Design, Development and In-Vitro Evaluation of Clarithromycin Loaded Anti Acne Gel

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ABSTRACT

In the present study, several concentrations of polymers (singly or in combination) including hydroxy propyl cellulose, Xanthan Gum, HPMC K4M, and carbopol were used to produce topical gel formulations of clarithromycin. The colour, pH, homogeneity, spread-ability, drug content, viscosity, and invitro drug release of 15 formulations were all evaluated. Using a Franz diffusion cell for dialysis, drug release studies were conducted. A 15-day stability study on a formulation with favorable release properties was also investigated. In terms of medication release and physical features, formulation F11 performed well. When evaluated under accelerated storage settings after 15 days, there was no discernible medication loss.

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INTRODUCTION

1.1 Pharmaceutical Gels

Gel is derived from the word “Gelatin” and means of gel is “frozen” or “congeal”. Both gel and jelly word derived from the Latin gelu means “frost”**[1].** According to USP definition “gel is defined as the semi-solid system containing either large organic or small inorganic molecules which are interpenetrated by the liquid phase”. Generally, gel system is made up of the two phases i.e., single phase system &two-phase system. Water and hydrophobic solution are most common in the pharmaceutical gel in which 99% by weight liquid. Polymer gel is the irreversible in nature due to their cross- link covalent bonded and concentration of gelling agent is less than10% (0.5-2.0%)**[2, 3].**Pharmaceutical gels have many properties such as solid like consistency, sterile, safe, and inert and not react with other formulations. Thermal changes, flocculation and chemical reaction are method of preparation of the pharmaceutical gels **[4].**

1.1.1 Advantage of pharmaceutical gels [5]

- It is a non-greasy and control release formulation.
- It should be easy to formulate.
- Gels have biodegradable, biocompatible and good adherence properties.
- Gels have higher retention time as compare to the topical dosage form.
- They have no toxic, washable, and tolerability properties.

1.1.2 Characteristics of pharmaceutical gels [6]

- **Swelling-** Gels can swell kept in contact with the liquid media then increase in volume. It means that the solvent makes a whole in the gel matrix i.e., gel-gel interaction is replaced by the gel- solvent interactions.

- **Ageing-** Colloidal system generally shows the slow speed spontaneous aggregation that is referred to as the ageing process.

- **Structure-** The rigidity of gel comes about from a network formed by the gellingagents. Particle size and type of the forces are depending on the structure of the network of the gel.

- **Syneresis-** Several gels often spontaneous contraction upon standing and interstitial liquid is collected at the surface of the gel that is known as the Syneresis process. It inversely

proportional to the concentration and Syneresis indicated that the original gels are thermodynamically unstable.

- **Rheology-** Solution of gelling agent show the Viscosity reduction and shearing rate rise are characteristics of non-Newtonian behaviour.

Acne vulgaris, a chronic autoimmune illness of the sebaceous glands, is a prevalent dermatitis ailment that affects people all over the world **[7].**There are various types of acne e.g., Acne vulgaris, Acne rosacea, Acne cosmatica, Acne fulminans and Acne mechanical and its sign and symptoms are erythema, desquamation burning, itching, dyschromia and pain etc.**[8].**Some factors are responsible for the formation of acne such as Genetic (People have XYY karyotype), Diet (high glycemic load, insulin resistance, occlusion cosmetic, and age of puberty etc.). **[9].** Epidemiology involves 650 million people are affected from the acne in which 95% boys and 85% girls are affected from this disease. 50% peoples suffer acne in adulthood stage. In 2010 report estimated that the acne influences the 9.4% of the populations. Acne is most common in face, chest, back and neck **[10, 11].**

1.1.3 Acne Vulgaris disease has four main classes [12]

1. Sebaceous hyperplasia and hypermenorrhea.
2. Hyper-keratinization and consequent keratinocytes accession.
3. Colonization of Propionibacterium acne and respective staphylococcus album.
4. Inflammation and immune responses.

1.1.4 Clinical classifications of the Acne Vulgaris [13]

Non-Inflammatory

Injury type: Black heads

Type of acne: Comandancia

Degree- 1st

Gravity- Mild

Inflammatory

Injury type: Pimple, pustule, nodule, cyst, scars.

Type of acne: Nodular, pustular, and popular

Degree: 1st, 3rd, 4th or, 5th or fulminant.

Gravity: Moderate, moderate to severe, severe, serious.

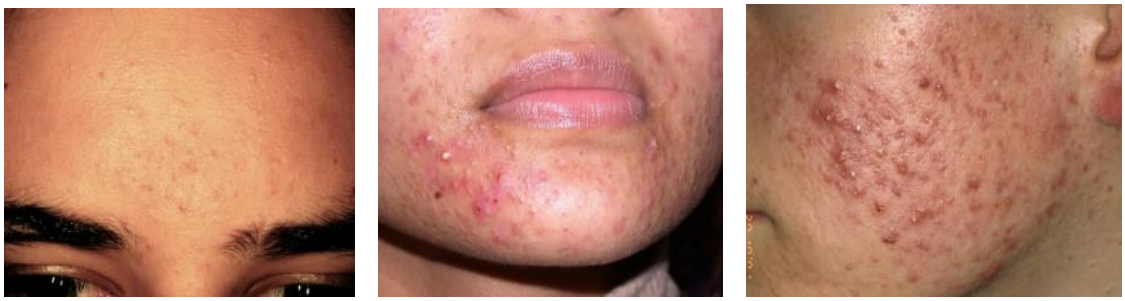

Figure No. 1: Various types of acne (from left to right mild acne, moderate acne, severe acne)

1.2 Clarithromycin

Clarithromycin is a novel Macrolide antibiotic with broad spectrum of activity and have highly effective against the staphylococcus aureus, haemophilus influenza, chlamydia trachomaitis, E. coli, proteus and klebsiella. It is widely utilized to treat RTI, tissue infection, skin related disorder, Lyme disease and helicobacter pylori infections. Clarithromycin is better tolerable, less frequently and good absorbed than erythromycin **[14].** It is acid stable and better absorbed than erythromycin. Clarithromycin has poor bioavailability (50%) in the presence of cytochrome P450 (CYP3A) **[15].** According to the U.S.Pat.No.4331803 Clarithromycin is the derivative of the erythromycin **[16].** Topical formulations of Clarithromycin were challenges due to its instability properties in the liquid media **[17].** It brings into play antibacterial activity by binding to the 50S ribosome subunit. Clarithromycin has many advantages such as increase oral bioavailability (52-50%), increase plasma concentration (maximum range from 1.01- 1.52mg/L) and longer elimination life time (3.3-4.9%) **[18].** Clarithromycin has pH based on solubility and lower solubility in liquid media. Limited absorption based on the biopharmaceutics classification system class 2. **[19].**

2. MATERIALS AND METHOD

2.1 Materials

Clarithromycin was received as a free gift sample from Valence Pharma Pvt. Ltd., HPMCK4M, Xanthan gum was procured from Colorcon, Carbopol 934 was purchased from Corel pharma chem. and all other ingredients used was of analytical grade.

2.2 Methods

2.2.1 Identification of drug (Clarithromycin)

Identification by UV absorption spectrum

Prepare 2mg/ml solution of drug (clarithromycin) in various solvent like ethanol and methanol then draw the spectra by UV Spectrophotometer and matched all the spectra and maximum wavelength (λ_{max}) with the standard value.

2.2.2 Preparation of Gel Formulations

Composition of clarithromycin topical gel formulae are depicted in following Table 1. The gels formulation was prepared by using either or combination of gelling polymers: HPMC, Carbopol, HPC, Xantham gum. In case of formulation not containing Carbopol, gelling polymers was dispersed in a suitable amount of water with the constant stirring by using the magnetic stirrer. Clarithromycin was completely dissolved in ethanol and propylene glycol and added to the dispersion. Preservative as methyl paraben were added with constant stirring. The whole mixture was stirred with spatula until homogenous clarithromycin gel was formed. The make ready clarithromycin gel were filled in lacquered aluminum collapsible tube and stored in cool and dark places. In case of formulations containing Carbopol and other gelling polymer, gelling polymer was first hydrated in water as in above procedure, and subsequently Carbopol was added under vortex stirring on a magnetic stirrer. 2-3 drops of triethanolamine were added to neutralize the Carbopol and cause the gel formation.

Table No. 1 Composition (% w/w) of various formulations of Clarithromycin Gel

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Clarithromycin	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
HPC	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0
Xantham gum	0	0	1	2	0	0	0	0	0	0	0	0	0	0	0
HPMCK4M	0	0	0	0	1	2	0	0	0.5	1.0	1.5	2.0	0.5	0.5	0.5
Carbopol 934	0	0	0	0	0	0	1	2	0.5	0.5	0.5	0.5	1.0	1.5	2.0
Triethanolamine	-	-	-	-	-	-	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Methyl paraben	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Propylene glycol	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Ethanol	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Water (q.s.)	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100

2.3 EVALUATIONS OF PREPARED CLARITHROMYCIN GEL [20, 21, 22]

2.3.1 pH Measurement

The pH measurement of each gelwas estimated by the digital pH meter, which was calibrated before various uses with standard buffer solution at pH 4 and 7. 1gm of prepared gel was dissolved in 100ml of distilled water and kept for 2hr. The estimation of pH of various formulations is done in triplicate and calculated the average value.

2.3.2 Viscosity Measurement

Viscosity of prepared gel was measured by Brookfield viscometer type viscometer using spindle 2 at 3rpm. The torque value was between (20-80%).

2.3.3 Spreadibility

Spreadibility of prepared gel was determined by glass slides apparatus. 1gm of prepared gel was put on a glass plate (10 cm X 20 cm), over which another similar glass plate was placed and 25 g weight was placed on the upper glass plate for 1minute, spreading diameter was calculated. Procedure was repeated three times and average value was calculated.

2.3.4 Appearance and Homogeneity

Various prepared gels were estimated by the visual examination after the gels have set in containers. They are estimated for their appearance and presence of any aggregates.

2.3.5 Extrudability

The prepared gel is filled in collapsible tube and tubes were crimped. Force required to extrude the gel out from tube was evaluated subjectively on the scale 1. Easy Force, 2. Moderate Force, 3. High Force.

2.3.6 Grittiness study

All the various prepared gels are estimated by the microscopically for the appearance of any particles matter.

2.3.7 Drug Content Study

1 gram of prepared gels was dissolved in 100ml of PBS pH 5.5 solutions and filter it. Then filtrate is studies undergoing spectrophotometer analysis for clarithromycin 209nm and

absorption were calculated. Drug content study is finalized by the regression linear analysis of calibration curve.

2.3.8 In vitro diffusion study

Franz diffusion cell are used for the in vitro diffusion study, in which 0.5 gm of gel sample was spread out on the cellophane membrane positioned between the donor and receptor chamber was filled with Phosphate buffer saline at pH 5.5 and stirred with magnetic stirrer at 37 ± 0.5 ºC. The sample (1 ml) was drawing out at various time intervals and put back with the same value of phosphate buffer saline. Sample was examined by the spectrophotometric at 209 nm.

2.3.9 Stability study

Samples of selected formulation were stored at ambient temperature; refrigerator and thermostability chamber at 40 ± 2°C and 75 ± 5 %RH for 15 days. Samples were withdrawn at day 7 and day 15. Samples were examined for drug content and visual appearance.

3. RESULT AND DISCUSSION

3.1 Identification of drug (clarithromycin)

Identification by UV absorption spectrum

The λ max observed with the solvent system such as ethanol at 209 nm. These are matched with the standard value.

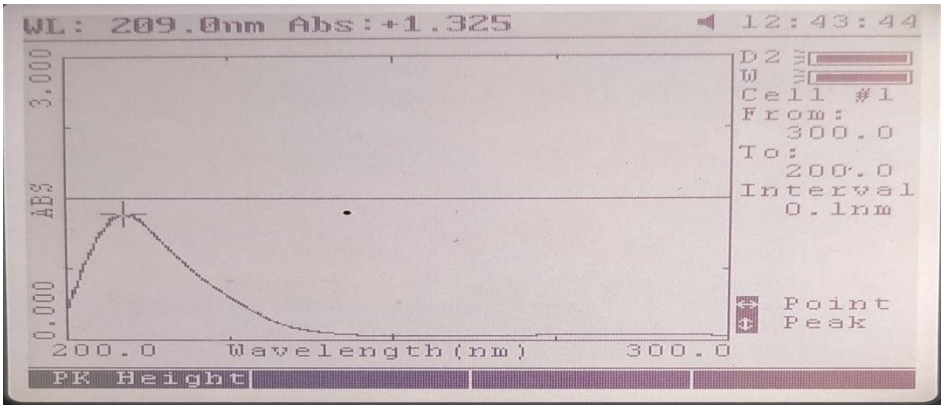

Figure No. 2: λ_{max} curve of clarithromycin in ethanol solvent

3.2 Standard calibration curve of clarithromycin in ethanol

Peak area of calibration sample of various concentrations is shown in Table 6. And calibration curve plot in Figure 11.

3.3 Linearity: Value of correlation coefficient (R) was 0.994. This indication linear relationship between peak area and concentration.

Table No. 2: Absorbance and concentration of calibration sample

1.	10	0.055
S. No.	**Concentration (µg/ml)**	**Absorbance**
2.	20	0.098
3.	30	0.142
4.	40	0.179
5.	50	0.199
6.	60	0.239
7.	70	0.272
8.	80	0.296

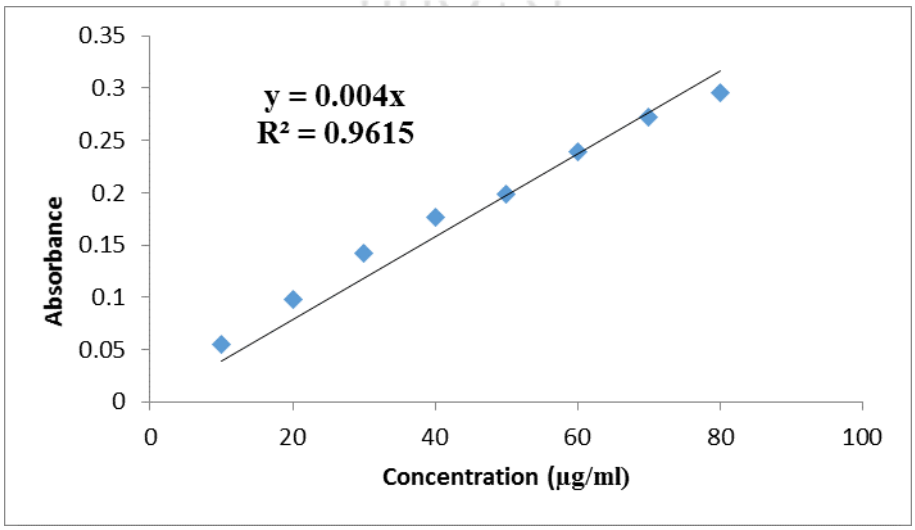

Figure No. 3: Standard calibration curve of clarithromycin

3.4 Evaluations of prepared clarithromycin gel [23, 24, 25]

Various gel formulations of clarithromycin were prepared as shown in Table 7. Initially formulations containing single polymers were prepared using hydroxy propyl cellulose or Xanthum gum or HPMCK4M or Carbopol (F1 to F8). However, single polymer formulations

had one or other problem like thin gel formation or difficulty in spreading or lack of visual transparency. Based on this preliminary investigation, gels containing Carbopol and HPMCK4M (F9 to F15) were formulated and taken up for further studies. The result of various evaluation parameters like physical appearance, phase separation, homogeneity, spread-ability, extrudability, grittiness, pH value, viscosity is given in Table 3 & 4**.** All of these formulations were good in terms of above parameters.

Table No. 3: Values of various evaluation parameters of formulated gels from F1-F8

Formulation	Physical Appearance	PS	HOM	Spreadibility	Extrude	Grittiness	pH	Viscosity (cps)	% Drug Content
F1	Transparent	No	+	2.9 ± 0.03	Easy	No	6.61	5698	96.00
F2	Transparent	No	+	3.4 ± 0.01	Easy	No	6.65	5700	99.82
F3	Transparent	No	+++	4.4 ± 0.05	Easy	No	7.12	5090	99.90
F4	Transparent	No	+++	4.5 ± 0.01	Easy	No	6.92	5703	98.91
F5	White Transparent	No	++	3.8 ± 0.07	Easy	No	7.46	6500	98.99
F6	White Transparent	No	++	3.6 ± 0.06	Easy	No	7.62	7023	97.87
F7	White Transparent	No	+	4.2 ± 0.02	Easy	No	6.96	8862	96.98
F8	White Transparent	No	+	4.1 ± 0.02	Easy	No	6.97	8862	96.98
F9	Transparent	No	+	2.8 ± 0.03	Easy	No	6.62	5698	96.00
F10	Transparent	No	+	3.5 ± 0.01	Easy	No	6.68	5700	99.82
F11	Transparent	No	+++	4.5 ± 0.05	Easy	No	7.01	5090	99.90
F12	Transparent	No	+++	4.6 ± 0.01	Easy	No	6.98	5703	98.91
F13	White Transparent	No	++	3.7 ± 0.07	Easy	No	7.45	6500	98.99
F14	White Transparent	No	++	3.5 ± 0.06	Easy	No	7.61	7023	97.87
F15	White Transparent	No	+	4.1 ± 0.02	Easy	No	6.98	8862	96.98

Table No. 4: Values of various evaluation parameters of formulated gels from F9-F15

Formulation	Physical Appearance	PS	HOM	Spreadibility	Extrude	Grittiness	pH	Viscosity (cps)	% Drug Content
F9	Transparent	No	+	2.8 ± 0.03	Easy	No	6.62	5698	96.00
F10	Transparent	No	+	3.5 ± 0.01	Easy	No	6.68	5700	99.82
F11	Transparent	No	+++	4.5 ± 0.05	Easy	No	7.01	5090	99.90
F12	Transparent	No	+++	4.6 ± 0.01	Easy	No	6.98	5703	98.91
F13	White Transparent	No	++	3.7 ± 0.07	Easy	No	7.45	6500	98.99
F14	White Transparent	No	++	3.5 ± 0.06	Easy	No	7.61	7023	97.87
F15	White Transparent	No	+	4.1 ± 0.02	Easy	No	6.98	8862	96.98

PS-Phase Separation; HOM-Homogeneity; Extrude-Extrudability

Excellent +++, Good ++, Satisfactory +

3.5 *In-vitro* drug release study

The in vitro release study profile of clarithromycin topical gel formulations for 4 hours is shown in Table 8 and Figure 12. It was estimated that the release of clarithromycin drug from different formulations can be ranked in the following descending order such as F11 > F12 ~F10~F15~F9~F14 >F13.These results indicate that the F11 is releases drug effectively up to 4hr.

Table No. 5: Percentage drug release data for various gel formulations from F1 – F8 for 4 hours.

Time (Min)	F1	F2	F3	F4	F5	F6	F7	F8
15	4.315	3.945	2.931	1.383	3.334	2.356	5.357	4.352
30	6.546	5.545	4.524	3.542	5.356	5.654	7.542	7.541
45	9.542	7.325	7.245	5.245	7.345	8.654	10.652	12.652
60	12.231	10.352	9.652	6.965	11.564	10.365	16.257	19.257
90	14.264	16.654	14.365	10.756	14.025	17.657	21.035	28.035
120	21.962	28.32	26.356	18.356	25.321	21.302	33.357	37.357
180	52.361	49.672	46.396	37.254	45.367	43.278	42.025	44.025
240	61.335	62.357	64.251	59.032	57.096	68.324	58.248	56.248

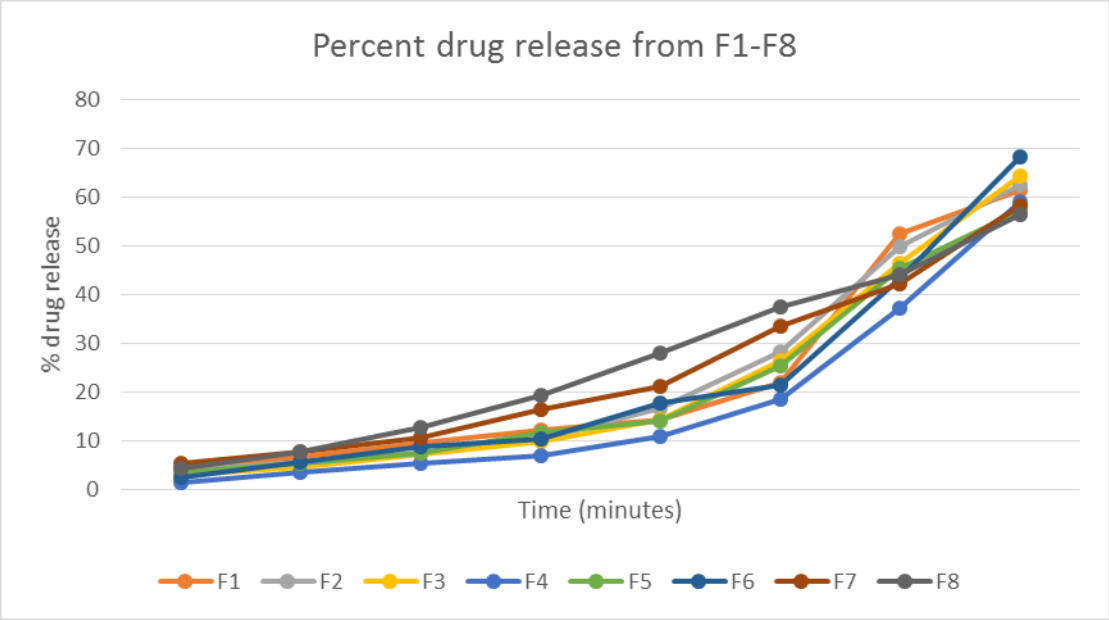

Figure No. 4: Drug release profile of various gel formulations from F1-F8 for 4 hours

Table No. 6 Percentage drug release data for various gel formulations from F9 – F15 for 4 hours.

Time(Min)	F9	F10	F11	F12	F13	F14	F15
15	3.908	2.944	3.939	0.386	0.332	2.359	0.354
30	5.547	3.545	6.524	2.540	0.356	2.654	3.542
45	7.542	4.325	8.245	3.245	2.345	3.654	4.652
60	9.234	6.352	10.652	4.965	3.564	4.365	6.257
90	12.967	13.654	15.365	9.756	15.025	10.657	12.035
120	19.965	25.32	28.356	16.356	26.321	18.302	17.357
180	48.367	45.672	68.396	35.254	48.367	38.278	39.025
240	59.335	60.957	**83.251**	65.032	54.096	58.324	60.248

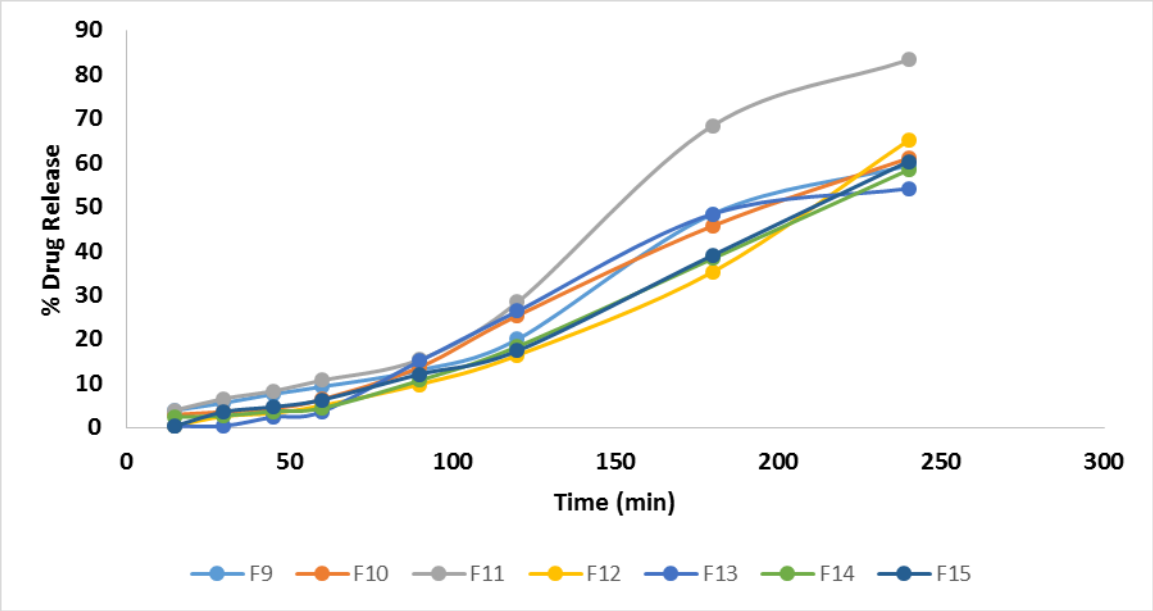

Figure No. 5: Drug release profile of various gel formulations from F9-F15 for 4 hours

3.6 Stability study

Based on the drug release profile of F11 formulation, same was taken up stability studies for 15 days. There was no visual change and drug content change in formulation on day 7 and 15. Percentage drug content of at various storage conditions after 7 and 15 days is shown in Figure 13.This indicate that formulation F11 was stable.

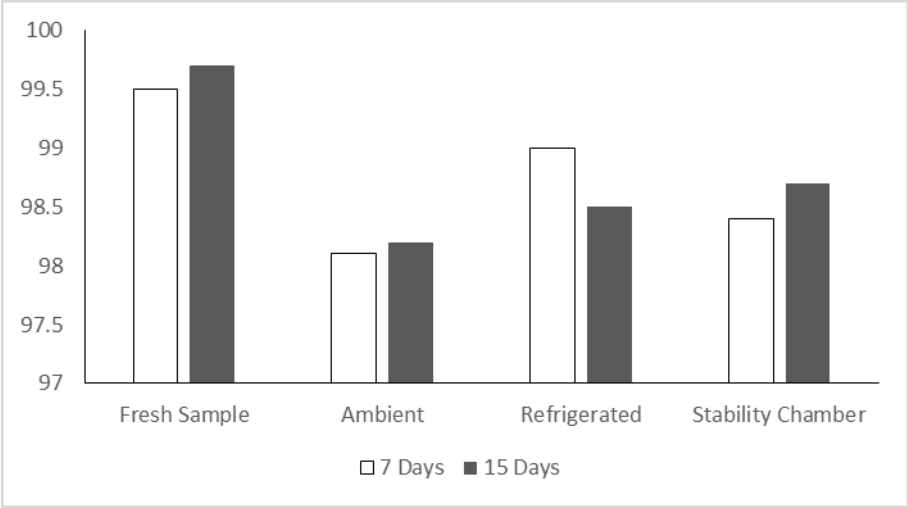

Figure No. 6: Percentage of drug gel formulation at various storage condition at 7 and 15 days.

4. CONCLUSION

Clarithromycin gel formulations prepared with different concentration of HPC, Xantham gum, Carbopol, HPMC and in combination of HPMC and Carbopol. Combination of HPMC and Carbopol showed the accepted physical properties concerning color, spreadibility, homogeneity, extrudability pH, drug content, stability, compatibility and in vitro drug release study. Formulation F11 had good drug release in comparison to other formulations when tested in Franz diffusion cell. The Formulation was stable when tested for stability for 15 days at accelerated stability conditions of 40 °C, 75 % RH.

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