https://doi.org/10.33472/AFJBS.6.6.2024.5784-5798

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Application of Central Composite Design in Optimization of Topical Gel from Solid Dispersion of Clarithromycin to Enhance its Solubility

Pooja N. Jadhav[1]*, Amir A. Shaikh[2], Rahul S. Buchade[3]

[1]Research scholar, Department of Pharmaceutics, SCES's Indira College of Pharmacy, Pune, 411033, Maharashtra, India.
[2]Associate Professor, Department of Pharmaceutics, SCES's Indira College of Pharmacy, Pune, 411033, Maharashtra, India.
[3]Associate Professor, Department of Pharmaceutical Chemistry, SCES's Indira College of Pharmacy, Pune, 411033, Maharashtra, India.

*Corresponding Author: Pooja N. Jadhav
Research Scholar, Department of Pharmaceutics, SCES's Indira College of Pharmacy, Pune, 411033, Maharashtra, India.
Email Address:pnj1990@rediffmail.com

Article Info

Volume 6, Issue 6, June 2024

Received: 23 April 2024

Accepted: 26 May 2024

Published: 19 June 2024

doi: 10.33472/AFJBS.6.1.2024.5784-5798

ABSTRACT:

Although not life-threatening, acne can negatively affect the body and mind. Topical therapy of antibiotics agents are one of the important treatment for acne. Clarithromycin is a class II macrolide antibiotic. It is used in the treatment of severe acne and also in the treatment of soft tissue and skin diseases. With aim to enhance the solubility of Clarithromycin by preparing their solid dispersion using kneading and spray drying methods we prepared the solid dispersion of drug and polymer. Formulation F7 showed % CDR 90.80±2.67% at 60 min which is much higher than the % CDR of pure drug i.e. 25.66±0.77 at 60 min, therefore, it can be concluded that aqueous solubility of clarithromycin can be increased by complexing the drug with HP-β-CD and PVP K-30. The optimized solid dispersion powder (F7) was used to prepare the topical gel of clarithromycin. The optimized formulation G6 showed 82.99±2.70 % CDR at 720 min which is much higher than the % CDR of the pure drug. The significant antimicrobial activity of optimized Clarithriomycin gel formulation (G6) was found compared with marketed Clarithromycin gel formulation. The optimized formulation can be considered as promising and suitable for the topical application of clarithromycin into the skin for effective control of acne.

KEYWORDS: Topical gel, Clarithromycin, Solid dispersion, BCS Class II drugs.

INTRODUCTION

Acne Vulgaris is a common skin condition that is more common in young people. Although acne is not serious, it can cause serious health problems. [1] Acne is typically brought about by increment in androgens level like testosterone mostly during puberty in both males and females. [2] Acne reduces after some time and will, in general, vanish over the age. [3] Over the past 25 years, various topical and systemic therapies have been developed for the treatment of acne vulgaris. Oral antibiotics are particularly indicated for anti-inflammatory acne. [4] Tetracycline and derivatives remain the first choice. Macrolides, co-trimoxazole, and trimethoprim are different options for acne. [5]

Solid dispersions constitute a favorable approach for enhancing the oral bioavailability of poorly water-soluble drugs. Although the term “solid dispersion” remains somewhat ambiguously defined, the aim when preparing it is to disperse a hydrophobic drug homogenously within an inert carrier matrix. In recent technologies, the development of combinatorial chemistry and high-throughput screening (HTS) can effectively discover new drugs with better pharmaceutical activity. However, 35-40% of these new drug discoveries are due to poor water quality. In the Biopharmaceutical Classification System (BCS), drugs with high systemic absorption and low water content are classified as class II drugs. Therefore, solid dispersion technologies are mainly for improving the oral absorption and bioavailability of BCS Class II drugs. [6]

Clarithromycin is a macrolide antibiotic which is practically insoluble in water. Hence, there is need to increase the solubility of Clarithromycin. [7] The efflux of drugs commonly used in dermal delivery systems into the skin depends on the physicochemical properties of the drug, such as molecular weight, tame coefficient, and solubility, and the vehicle in which the drug is dissolved or suspended. Absorption of topical or transdermal water-based compounds has repeatedly demonstrated good dermal absorption of insoluble drugs. [6]
In a water-based environment, cyclodextrins render lipophilic drug molecules insoluble in solid drug form and deliver them to the skin surface in a larger volume, resulting in increased absorption from the skin and therefore easier distribution of the drug over the skin. [8] To address all these issues we aimed for formulation and evaluation of Clarithromycin topical gel by enhancing the solubility of Clarithromycin by preparing their solid dispersion using kneading and spray drying methods.

MATERIAL AND METHODS

Formulation design

Table 1: Design suggested by Central composite design for Solid dispersion method:

Mixture no.	Drug (mg)	PVP K30 (mg)	HP-β-CD (mg)
F1	250	125	250
F2	250	50	300
F3	250	125	250
F4	250	125	250
F5	250	231.066	250
F6	250	200	200
F7	250	125	250
F8	250	125	179.289
F9	250	125	320.711
F10	250	200	300
F11	250	18.934	250
F12	250	125	250
F13	250	50	200

After the literature survey, upper and lower limits of PVP K30 and Hydroxy Propyl-β-Cyclodextrin which are independent (input) variables were found to be in a ratio 2:1:2. These are fed to the Design-Expert software. Design-Expert software then gave 13 runs which were used for the formulation of mixtures. Mixtures were prepared by the Kneading and Spray drying method using the above formula mentioned in table 1.

a) Kneading method

HP-β-CD and PVP K30 were added to the mixture and a small amount of 50% v/v ethanol was added with stirring to stabilize. The drug was then slowly added to the mixture and the extract was maintained at 25°C for 1 hour. It was filtered and passed through a #100 sieve and stored in a desiccator over calcium chloride. [9]

b) Spray drying method

The actual weight of CLT was dissolved in ethanol. The required amount of PVP K30 and HP-β -CD was dissolved in pure water. The solution was remixed with continuous stirring and spray dried (Labultima LU-222). The drying conditions were as follows: inlet temperature 120°C; discharge temperature 70°C; candidates 80%; nutritional dose 3 mg/ml. [9]

Evaluation of solid dispersion formulation

1. Characterization of powder

For Characterization of powder Angle of repose, Bulk density, Tap density, Car's Index and Hausner's Ratio were calculated. [10, 11]

2. Saturation Solubility Study

A saturation solubility study was carried out to determine the increase in the solubility of the pure drugs compared with the solid dispersion methods. [12]

3. In-vitro Drug release study:

Drug release studies were performed using USP dispersion equipment (type II). Dispersion powder equivalent to 250 mg Clarithromycin & Drug tablets was added to a vial containing 900 ml dispersion, kept at 37 ± 0.5°C and stirred 50 rpm. Concentration and solid dispersion of clarithromycin were both determined at 210 nm. [9]

4. FTIR Spectroscopy

IR spectroscopy of the optimized formulation was performed using an FT-IR spectrophotometer (Jasco FT/IR-4200). The image was scanned with a diameter of 4000 to 400 cm-1 at a resolution of 4 cm-1.

5. Powder X-Ray Diffraction Study of optimized formulation (PXRD)

X-ray diffraction of the optimized formulation was monitored using an X-ray diffractometer (Bruker D8 Advance) using Ni-filtered Cuk(a) radiation, 35 kV voltage, 30 mA electric current, and 0.2 In receiver section. . Samples were analyzed over 50–500 2θ.

6. DSC Study of optimized formulation

Thermodynamic studies were performed on a TA spectrometer from SII Nanotechnology (METTLER DSC). An aluminum foil pan was used as a reference. DSC measurements were performed using a sealed aluminum pan from 25 to 350°C at a heating rate of 10°C/min. Sample size was kept at approximately 5 mg for each measurement. During analysis, sample cells were flushed with nitrogen gas. [9]

6. Particle size analysis:

Dimensional analysis was performed using a Malvern Zetasizer ZS90 (Malvern Instruments, Worcestershire, UK) with a laser diffraction beam length of 2.40 mm, a 300 mm RF lens, and a reflectance of 14.4%. The mean diameter of the formula was recorded.

Formulation design & Formulation of gel

Table 2: Design suggested by Central composite design for preparation of topical gel:

Mixture no.	**Optimized Drug mg**	**Carbopol 934 %**	**HPMC K4M %**
G1	125	2.5	2
G2	125	0.37868	2
G3	125	2.5	2
G4	125	2.5	2
G5	125	2.5	0.58578
G6	125	2.5	2
G7	125	1	1
G8	125	4.62132	2
G9	125	2.5	3.41421
G10	125	4	3
G11	125	1	3
G12	125	4	1
G13	125	2.5	2

Various gels formulation was prepared using carbopol-934 and HPMC K4M as gelling agents (Table 2). The required amount of gel formation was measured and dispersed in a small amount

of deionized water to form dispersion. Clarithromycin solid dispersion was dissolved in a suitable solvent and added to the above solution. With continued extraction, other products (methylparaben and propylparaben) are also added. The pH of the gels is adjusted to the pH of the skin using tea.The final weight of the gel was adjusted to 100 grams with distilled water. (Table 3). [13]

Table 3: Formulation table of Topical gel

Sr. No.	Ingredients	Quantity (mg)
1	Dispersed drug mixture	125
2	Hydroxypropyl methyl cellulose (HPMC K4M)	2
3	Carbopol 934	2.5
4	Methyl paraben	0.2
5	Propyl paraben	0.1
6	Triethanolamine	Q.S
7	Water	Q.S

Evaluation of prepared topical gel

Formulated gel is evaluated for Homogeneity, Determination of pH, Viscosity, Spreadability and drug content. [14-16]

In-vitro release study

Franz cells were used in the experiment. A gel prepared with clarithromycin (500 mg) was applied evenly to the cell surface. The cells bind between the donor and recipient cell receptors. The receptor chamber was filled with fresh PBS solution (pH 5.5) to dissolve the drug. The receiving chamber was mixed with a magnetic stirrer at 50 rpm; the temperature was maintained at 37 ± 0.5 °C. Samples (5.0 ml aliquots) were collectedtimes. Samples were analyzed for drug content after transformation using UV-visible spectrophotometry. Adjustments were made to obtain total clarithromycin intake at each time point. [17]

In-vitro antimicrobial activity study

In vitro antimicrobial activity was evaluated using the Agar Well Diffusion technique. Sterile agar was inoculated with bacterial culture (S. aureus) for 48 hours at 37°C. Antimicrobial activity was tested against S. aureus, a representative species of Gram-positive organisms. The well was opened using a sterile drill and gel was placed. The plates were then incubated overnight (24 hours) at 37°C. AntiMicrobial activity was determined by measuring the diameter of the recorded inhibition zone. [18, 19]

RESULT AND DISCUSSION

Evaluation and characterization of solid dispersion formulations

a) Characterization of solid dispersion powder:

All parameter found to be with in the normal range.

b) Saturation solubility study

The solubility data showed a significant increase in the observed results when the amount of PVP K30 & HP-β-CD increased. This may be due to the absorption effect of PVP K30 and the complex formation of Clarithromycin and HP-β-CD.

c) *In-vitro* dissolution study:

Response 1: % cumulative drug release

Kneading method

From Fig.1 the formulation F7 shows better cumulative drug release than other formulation which is 70.74±2.12% at 60 min.; because it contains the maximum amount of both polymers i.e. β-Cyclodextrin and PVP K30. From the above observation and graphs, it is seen that the concentration of polymer increases, solubility and rate of dissolution increase.

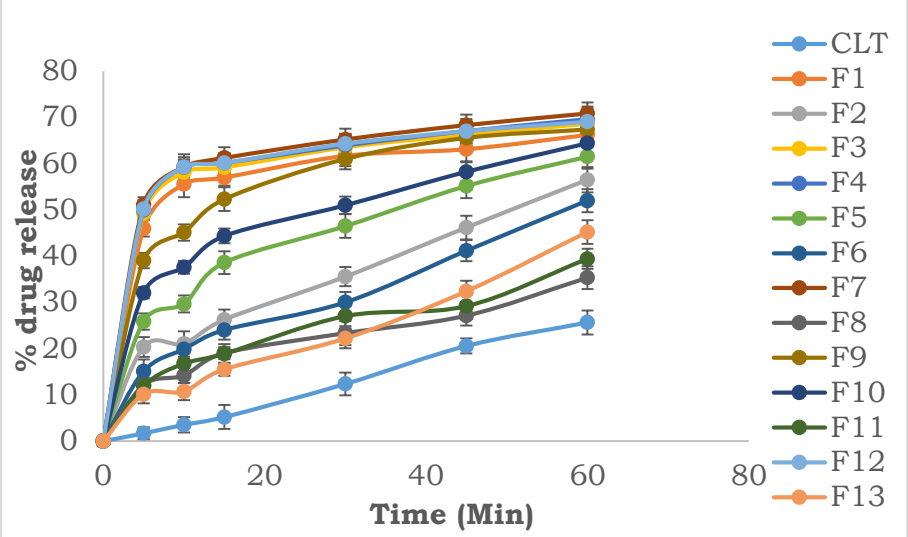

Fig.1: % Cumulative Drug release by Kneading method

Spray drying method

From Fig.2 the formulation F7 shows better cumulative drug release than other formulation which is 90.80±2.67% at 60 min.; because it contains the maximum amount of both polymers i.e. HP-β-CD & PVP K30. It is clear from observation and graphs, it is seen that the concentration of polymer increases, solubility, and rate of dissolution increase.

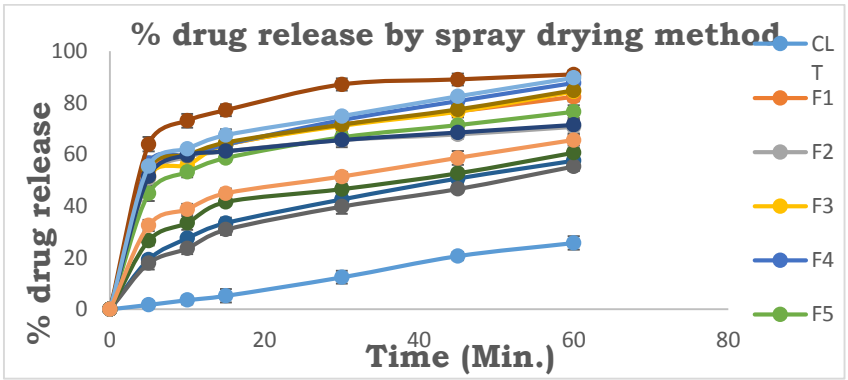

Fig.2: Graph No.8: % Cumulative Drug release by Spray drying method

Response 2: % dissolution efficiency

I) Kneading method

DE enables the summation of the large dissolution data into a single figure. The DE values were calculated using PCP disso V3 software. The formulation F7 showed better dissolution efficiency than other formulations which is 61.56±2.19%; because it contains the maximum amount of both the polymers i.e. HP-β-CD & PVP K30. It is clear from observation & graph it is seen that the concentration of the polymers increased, solubility and rate of dissolution increased. HP-β-CD helps to solubilize the drug in aqueous medium and PVP K30 was responsible for the increased rate of dissolution of the drug.

II) Spray drying method

The formulation F7 showed better dissolution efficiency than other formulations which is 79.68±2.45%; because it contains the maximum amount of both the polymers i.e. HP-β-CD & PVP K30. The concentration of the polymers increased, solubility and rate of dissolution increased. HP-β-CD helps to solubilize the drug in aqueous medium and PVP K30 was responsible for increased the dissolution rate of the drug.

Response 3: Mean dissolution time

I) Kneading Method

From Fig.3 the formulation F7 showed better mean dissolution time than other formulations which is 7.31±0.35 min; because it contains the desired amount of both the polymers i.e. HP-β-CD & PVP K30. It is clear from observation and graph it is seen that the concentration of the polymers increased, solubility and rate of dissolution increased. HP-β-CD helped to solubilize the drug in aqueous medium and PVP K30 was responsible for increasing the dissolution rate of the drug. Hence it shows that minimum time required to dissolve the maximum amount of drug.

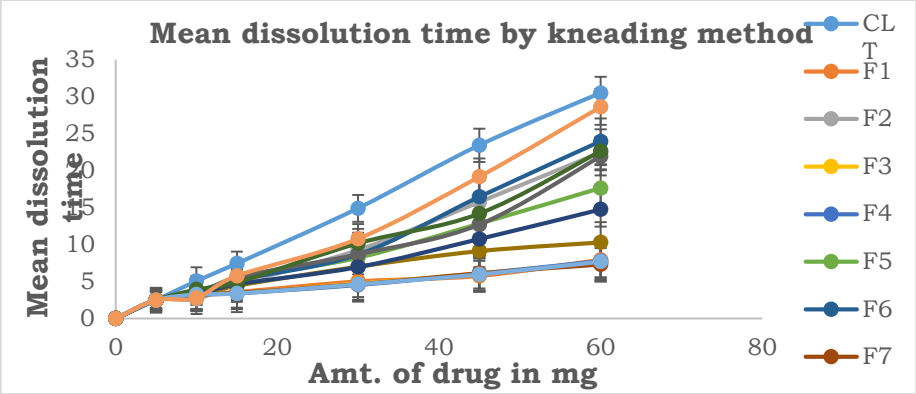

Fig.3: Mean dissolution time by kneading method

II) Spray drying Method

From Fig.4 the formulation F7 showed better mean dissolution time than other formulations which is 7.65±0.41 min; because it contains the desired amount of both the polymers i.e. HP-β-CD & PVP K30. It is clear from the above observation and graph it is seen that the concentration of the polymers increased, solubility and rate of dissolution increased. HP-β-CD helped to solubilize the drug in aqueous medium and PVP K30 was responsible for the increasing rate of dissolution of the drug. Hence it shows that minimum time required to dissolve the maximum amount of drug.

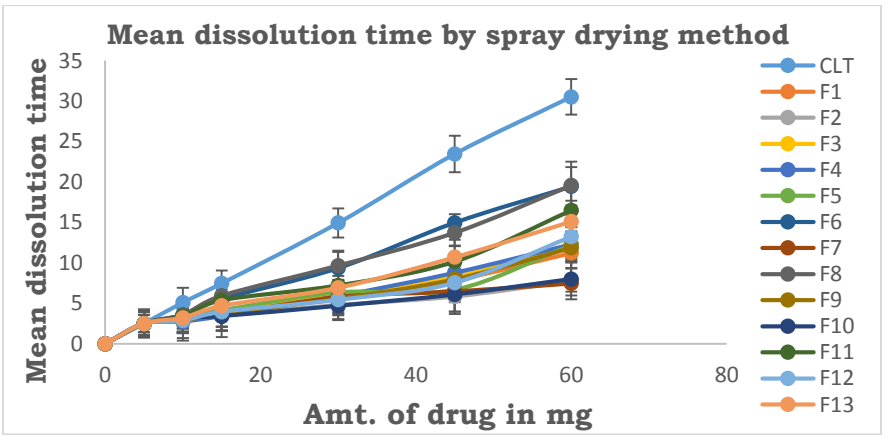

Fig.4: Mean dissolution time by spray drying method

FTIR spectra of dispersed drug

The Spectrum Exhibit hydroxyl group at 3420 cm-1 and vibration bands of C=O and C-O group at 1455 cm-1 and 1373 cm-1 respectively. The absence or absence of peaks in the drug and mixture confirmed that there was no chemical interaction between the drug and the polymers. (Fig 5).

XRD Spectra of optimized dispersed drug

XRD technique was used to define the nature of drugs in the microparticles. The X-ray powder diffraction patterns of Clarithromycin with polymers are shown in Fig 5. The optimized solid dispersion showed a lower intensity clarithromycin peak than the optimized solid dispersion; this indicates loss of crystallinity. The difference between the number and shape of diffractograms confirmed complex formulation.

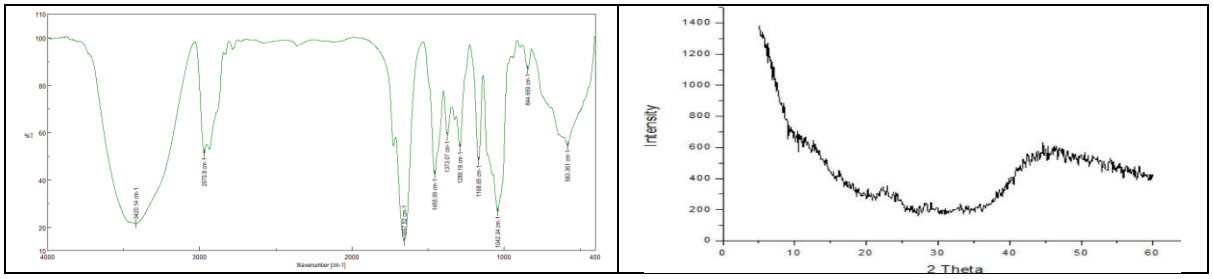

Fig.5: FTIR Spectra and XRD Spectra of Optimized dispersed drug

DSC Spectra of optimized dispersed drug

DSC of the CLT-PVP-HPBCD sample did not show any melting peak (224.59°C). This indicates that the drug is trapped in the cavity of the HPBCD, where it complexes and turns into amorphous substances. (Fig 6).

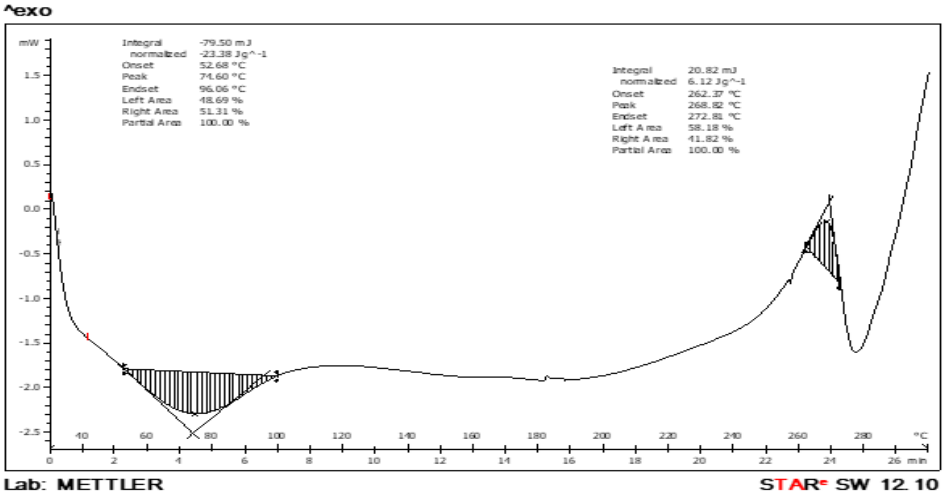

Fig.6: DSC Spectra of optimized dispersed drug

Particle size analysis:

Analysis of particle size was best performed in the ternary system (CLT: PVP K30: HP-β-CD). The size of the selected particle was found to be 312 nm. Analysis of responses for optimized method solid dispersion by ANOVA and Response surface methodology (RSM)

A) Kneading method

Response 1: % Drug release

A model F value of 17.49 indicates that the model is significant. There is only a 0.08% chance of such an F value occurring due to noise. "Probability > F" values are below 0. 0500 shows useful example words. In this case, A, B are model words. Values greater than 0.1000 indicate that the model expression is not significant. From Fig 7 it can be observed that as the concentration of HPB and PVP K30 increases % DR increases.

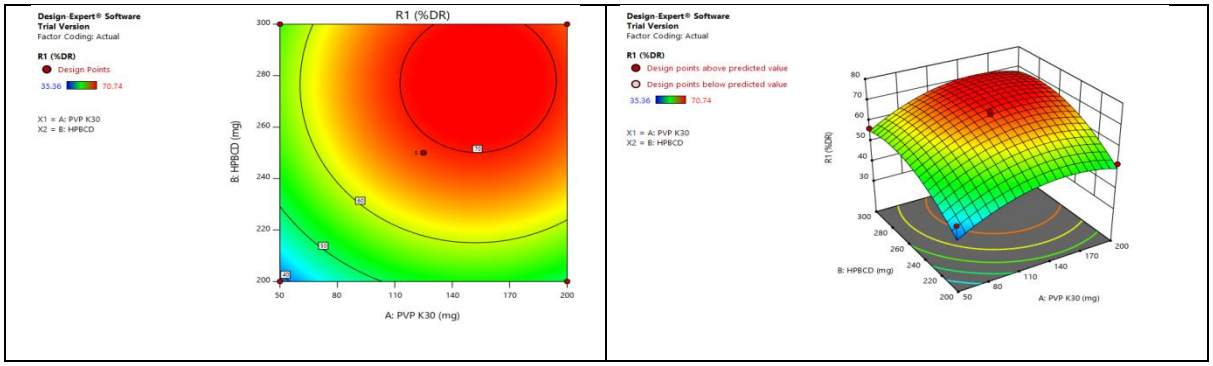

Fig.7: Effect of HPB and PVP K30 by kneading method on drug release (Contour graph and 3D graph)

Response 2: Dissolution efficiency

A model F value of 61.30 indicates that the model is significant. There is only a 0.01% chance of such an F value occurring due to noise. "Probability > F" values are below 0. 0500 indicates useful example words. In this case, A, B are model words. Values greater than 0.1000 indicate that the model expression is not meaningful. From Fig 8, it can be observed that as the concentration of HPB and PVP K30 increases % DE also increases. HPB has a greater effect on DE as compared to PVP K30.

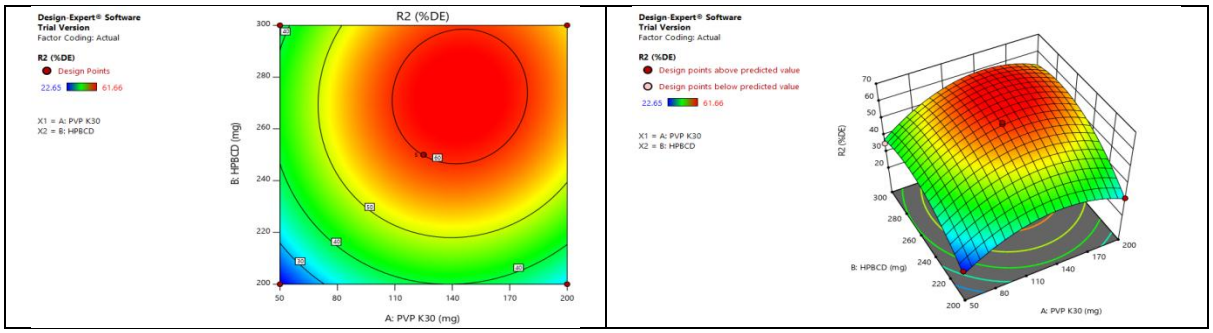

Fig.8: Effect of HPB and PVP K30 by kneading method on dissolution efficiency (Contour graph and 3D graph)

Response 3: Mean dissolution time

A model F value of 23.47 indicates that the model is significant. There is only a 0.03% chance of such an F value occurring due to noise. "Probability > F" values are below 0. 0500 shows useful example words. In this case, A, B are model words. Values greater than 0.1000 indicate that the model expression is not significant. From Fig 9, it can be observed that as the concentration of HPB and PVP K30 increases MDT decreases.

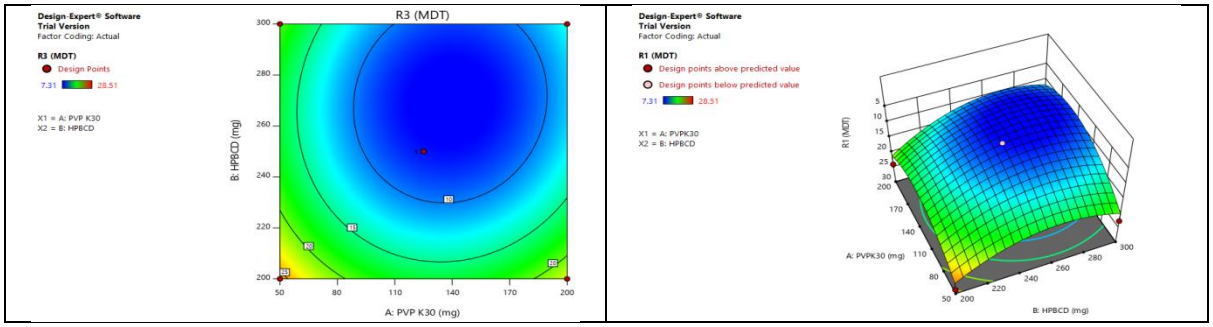

Fig.9: Effect of HPB and PVP K30 by kneading method on mean dissolution time (Contour graph and 3D graph)

B) Spray drying method

Response 1: % Drug release

A model F value of 11.95 indicates that the model is significant. There is only a 0.25% chance of such an F value occurring due to noise. "Probability > F" values are below 0. 0500 shows useful example words. In this case B is an example word. Values greater than 0.1000 indicate that the model expression is not significant. From Fig 10, it can be observed that as the concentration of HPB and PVP K30 increases % DR increases.

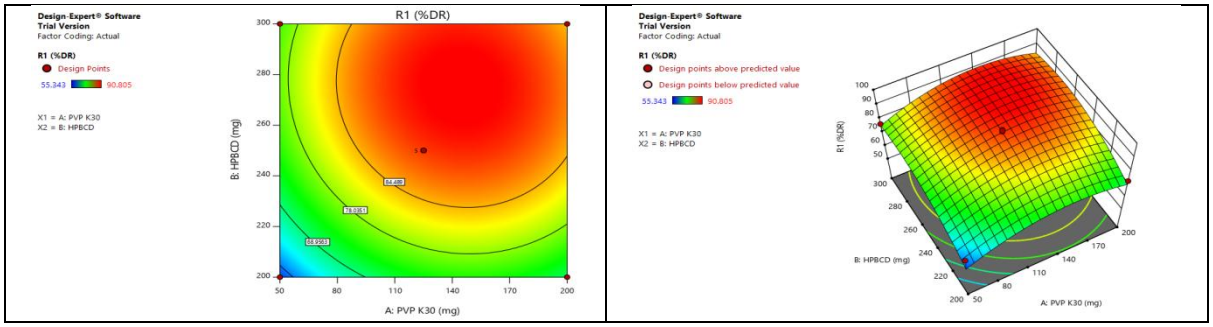

Fig.10: Effect of HPB and PVP K30 by spray drying on drug release (Contour graph and 3D graph)

Response 2: Dissolution efficiency

A model F value of 13.55 indicates that the model is significant. The probability of such an F value occurring due to noise is only 0.17%. "Probability > F" values are below 0. 0500 shows useful example words. In this case, B, A^2, B^2 are model terms. Values greater than 0.1000 indicate that the model expression is not significant. From Fig 11, it can be observed that as the concentration of HPB and PVP K30 increases % DE also increases. HPB has a greater effect on DE as compared to PVP K30.

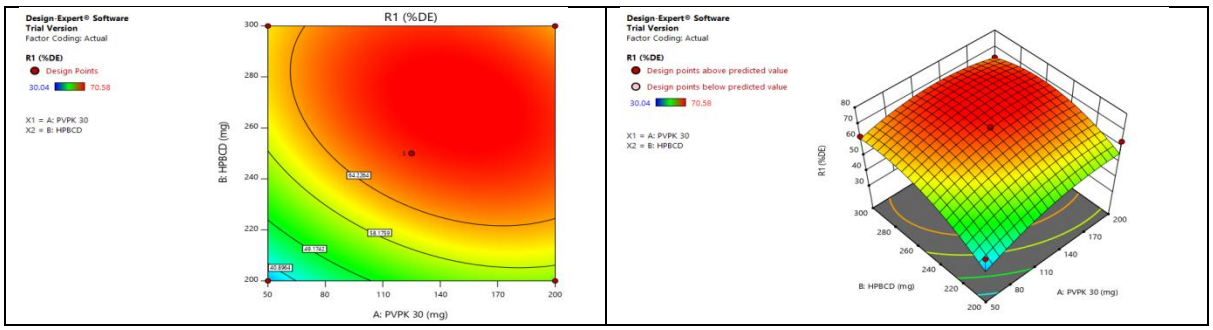

Fig.11: Effect of HPB and PVP K30 by spray drying on dissolution efficiency (Contour graph and 3D graph)

Response 3: Mean dissolution time

A model F value of 8.94 indicates that the model is significant. There is only a 0.60% chance of such an F value occurring due to noise. "Probability > F" values are below 0. 0500 shows useful example words. In this case B is an example word. Values greater than 0.1000 indicate that the model expression is not significant. From Fig 12, it can be observed that as the concentration of HPB and PVP K30 increases MDT decreases.

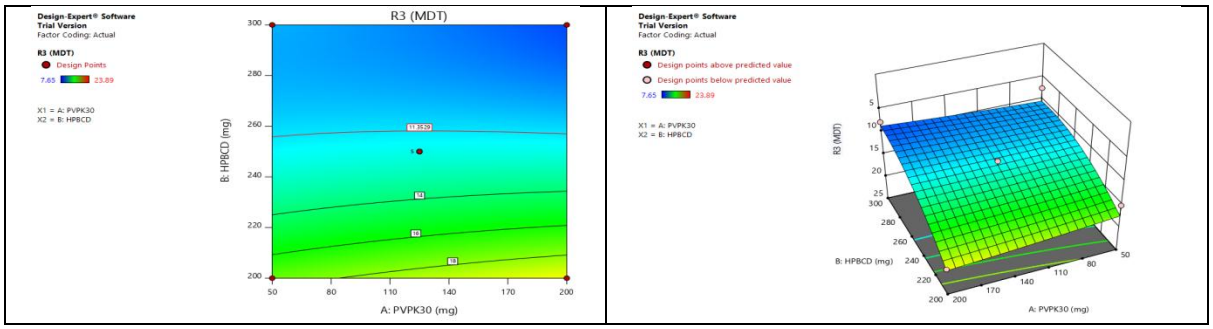

Fig.12: Effect of HPB and PVP K30 by spray drying on mean dissolution time (Contour graph and 3D graph)

Evaluation of topical gel formulation:

a) Homogeneity

After formulating topical gel firstly it was evaluated for its physical appearance. The topical gel was transparent white gel formulation having a pleasant appearance to touch. It does show phase separation. All developed gel forms showed good uniformity and lack of agglomeration.

b) Determination of pH

The pH values of all developed gel formulation were found in the range of 5.45-6.35 it is considered acceptable to avoid the risk of skin irritation.

c) Determination of Viscosity

Viscosity is an important physical property of the gel and affects the rate of drug release. The Viscosity of the gel was determined with a Brookfield viscometer and was found to be between 1885 ± 2.36 and 6109 ± 1.33. The viscosity increased as the polymer became more concentrated in the gel.

d) Determination of Spreadability

Spreadability is very important because it indicates the behavior of the gel coming out of the tube. Gel spreadability was found to range from 2.0 ± 0.05 to 4.5 ± 0. 50 gr. cm/second. The distribution of the data shows that the dispersion of the gel core decreases with the increase of the concentration of gelling agent.

e) Determination of Drug content:

After preparing several Clarithromycin gels, the drug content of the gel was measured with a UV spectrophotometer at λmax 210 nm in phosphoric acid at pH 5.5. The rate of the drug was found to be between 89.02±1.22 and 95.93 ± 3.51%.

f) In-vitro drug permeation study:

Table 4 and 5 reflect the results of In-vitro drug permeation study.

Table 4: In-vitro drug permeation study of Clarithromycin Gel Formulations (G1-G6)

Time (min)	**G1**	**G2**	**G3**	**G4**	**G5**	**G6**
30	12.49±0.31	8.82±0.20	13.32±0.38	14.27±0.42	5.85±0.12	**15.39±0.50**

60	16.52±0.60	12.37±0.29	16.05±0.55	17.00±0.67	8.46±0.16	**20.49±0.80**
120	25.30±0.87	18.07±0.72	20.32±0.78	21.15±0.82	12.85±0.34	**27.46±0.95**
180	32.18±1.07	24.83±0.84	26.13±0.88	27.20±0.90	17.35±0.65	**33.89±1.10**
240	39.88±1.22	29.57±0.98	31.35±1.01	32.06±1.04	22.88±0.84	**41.45±1.29**
300	45.81±1.40	34.67±1.14	37.51±1.18	38.11±1.20	28.15±0.96	**47.62±1.45**
360	52.93±1.51	40.95±1.23	43.09±1.33	44.98±1.36	31.94±1.08	**54.78±1.60**
420	60.64±1.76	49.25±1.49	53.64±1.55	53.64±1.55	34.67±1.12	**62.67±1.80**
480	65.73±1.89	57.43±1.60	62.65±1.81	63.13±1.84	36.92±1.16	**68.56±1.96**
540	70.24±2.06	65.12±0.87	70.71±2.09	71.07±2.14	38.22±1.21	**74.49±2.20**
600	74.21±2.18	67.89±1.94	75.34±2.27	76.17±2.33	39.05±1.20	**78.67±2.45**
660	76.41±2.30	69.53±2.01	78.90±2.50	79.73±2.58	40.12±1.27	**81.45±2.62**
720	77.18±2.38	70.15±2.03	80.56±2.54	81.27±2.60	41.66±1.30	**82.99±2.70**

(Mean ± SD) n=3

Table 5: In-vitro drug permeation study of Clarithromycin Gel Formulations (G7-G13)

Time (min)	**G7**	**G8**	**G9**	**G10**	**G11**	**G12**	**G13**
30	10.66±0.25	5.73±0.10	9.83±0.21	8.58±0.17	12.85±0.32	4.90±0.06	14.34±0.44
60	16.24±0.57	8.70±0.18	12.43±0.31	11.43±0.28	15.46±0.51	6.56±0.09	18.49±0.75
120	24.30±0.82	13.80±0.34	18.07±0.70	17.59±0.68	19.61±0.75	9.41±0.19	23.47±0.80
180	31.18±0.99	18.90±0.77	25.89±0.89	24.71±0.81	25.66±0.85	12.73±0.32	29.16±0.95
240	38.88±1.25	23.64±0.82	32.03±1.04	30.28±0.97	30.53±0.98	17.12±0.66	36.82±1.13
300	44.81±1.34	29.92±0.97	38.41±1.24	35.85±1.15	36.92±1.18	22.22±0.80	42.63±1.30
360	51.93±1.48	34.67±1.12	43.34±1.35	41.07±1.26	42.14±1.29	26.72±0.88	49.08±1.48
420	59.64±1.74	38.58±1.25	50.22±1.52	44.75±1.34	51.93±1.51	29.81±0.87	56.46±1.58
480	64.73±1.89	40.36±1.27	55.78±1.60	46.89±1.42	60.58±1.64	32.30±1.88	64.02±1.65
540	69.24±1.99	41.31±01.30	59.78±1.62	49.73±1.49	68.77±1.97	33.48±1.08	71.49±2.16
600	72.68±2.19	43.68±1.36	62.67±1.80	51.39±0.47	73.63±2.17	34.55±1.11	75.76±2.30
660	74.89±2.23	45.10±1.71	64.56±1.68	52.57±1.50	76.71±1.32	35.02±1.14	79.32±2.55
720	75.69±2.29	45.81±1.47	65.97±1.90	53.28±1.53	78.61±2.44	35.73±1.15	82.23±2.68

(Mean ± SD) n=3

Characterization of topical gel formulation:

A model F value of 18.92 indicates that the model is significant. There is only a 0.06% chance of such an F value occurring due to noise. "Probability > F" values are below 0. 0500 shows useful example words. In this case, A, B are model words. Values greater than 0.1000 indicate that the model expression is not significant. Figure 13 shows that as the concentration of Carbopol 934 increases, drug release decreases, and as HPMC increases, drug release increases.

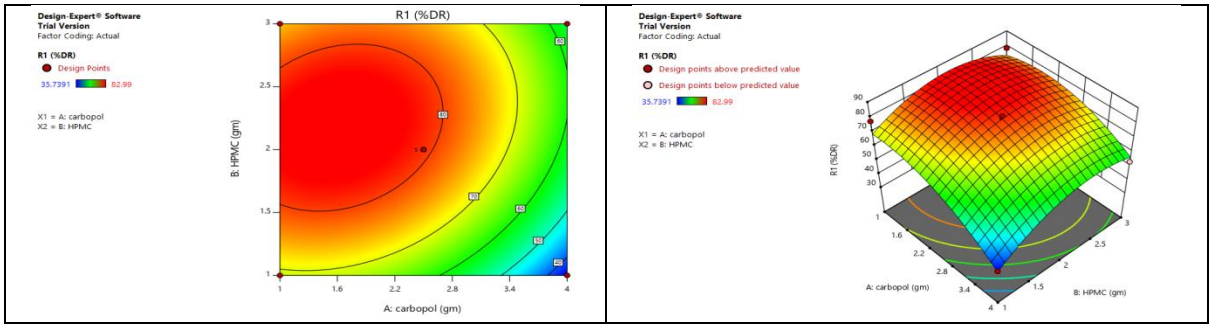

Fig.13: Effect of Carbopol 934 and HPMC on drug permeation (Contour graph and 3D graph)

Response 2: Viscosity

A model F value of 33.92 indicates that the model is significant. There is only a 0.01% chance of such an F value occurring due to noise. "Probability > F" values are below 0. 0500 shows useful example words. In this case, A is the model word. Values greater than 0.1000 indicate that the model expression is not significant. It can be seen from Figure 14 that as the density of Carbopol 934 increases, the Viscosity increases, and as HPMC increases, the Viscosity of decreases.

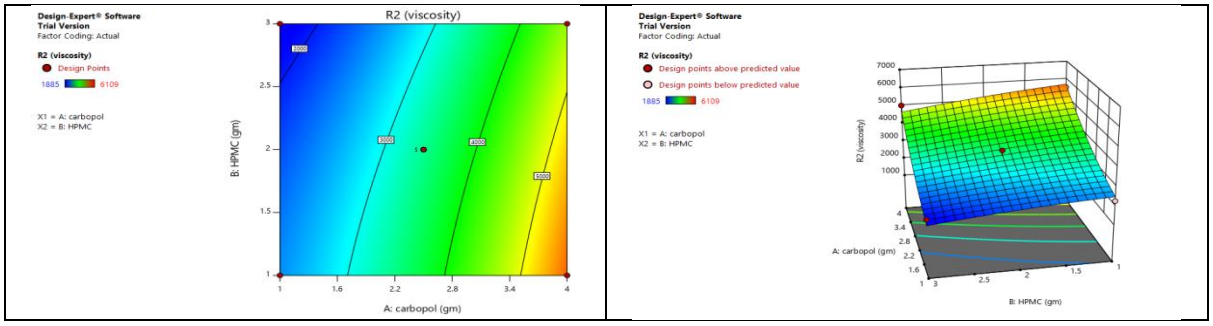

Fig.14: Effect of Carbopol 934 and HPMC on Viscosity (Contour graph and 3D graph)

g) *In-vitro* antimicrobial activity study

The *in vitro* antimicrobial studies revealed that the optimized formulation of G6 was fast released as compared to the marketed drug. The Inhibition zone for Optimized formulation was found to be 2.7 ± 0.15 cm. The drug from solid dispersion was released at a fast rate so that more inhibition activities has been observed as compared to that of the marketed drug 2.1 ± 0.090 cm (Fig 15).

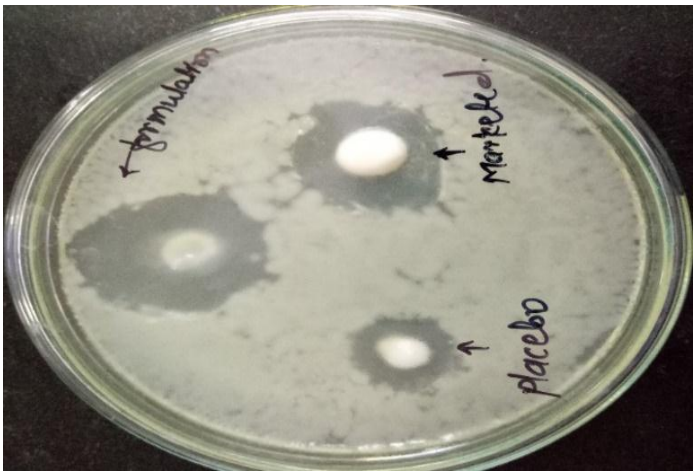

Fig No.15: In-vitro antimicrobial activity Optimized formulation and Marketed Gel

CONCLUSION

In the present study, the solid dispersions of Clarithromycin with different proportions of HP-β-CD & PVP K-30 were formulated using the Kneading & Spray drying method to Increase the speed of dissolution and dissolution of water and has been proven to be powerful. dispersions directed to enhanced the dissolution rate compared to pure clarithromycin drug. The optimized solid dispersion powder (F7) was used to prepare the topical gel of clarithromycin. The formulation contains Carbopol 934 and HPMC K4M as gelling agents and triethanolamine as pH adjuster. The optimized formulation G6 showed 82.99±2.70 % CDR at 720 min which is much higher than the % CDR of the pure drug.

The antimicrobial activity of optimized Clarithriomycin gel formulation (G6) was compared with marketed Clarithromycin gel formulation. The highest activity was found in the optimized formulation which is 2.7±0.15 cm and ZOI of marketed Clarithromycin gel was found to be 2.1±0.090 cm which is less than optimized gel (G6) formulation.

ACKNOWLEDGEMENTS

Authors acknowledge the help and support provided by our principal Dr. Anagha Joshi and management of SCES's Indira College of Pharmacy.

REFERENCES

Lever L, Marks R. Current views on the etiology, pathogenesis, and treatment of acne vulgaris. Drugs. 1990; 39(5):681-692. DOI: 10.2165/00003495-199039050-00005

James WD. Acne, New Engl J Med. 2005; 352(14): 1463-72. DOI: 10.1056/NEJMcp033487

Rathi SK. Acne vulgaris treatment: the current scenario. Indian J Dermatol. 2011; 56(1): 7-13. DOI: 10.4103/0019-5154.77543

Tan AU, Schlosser BJ, Paller AS. A review of diagnosis and treatment of acne in adult female patients. Int J Womens Dermatol. 2018; 4(2):56-71.DOI: 10.1016/j.ijwd.2017.10.006

Mernadier J, Alirezai M. Systemic antibiotics for acne. Dermatology 1998;196(1):135-9. DOI: 10.1159/000017847

Patil RM, Maniyar AH, Kale MT, Akarte AP, Baviskar DT. Solid dispersion: strategy to enhance solubility. *Int. J. Pharm. Sci*. Rev. Res. 2011; 8(2): 66-73.

Esfandi EH, Ramezani V, Vatanara A, Abdolhossein RN, Seyyed PHM. Clarithromycin Dissolution Enhancement by Preparation of Aqueous Nanosuspensions Using Sonoprecipitation Technique. Iran J Pharm Res. 2014; 13(3): 809-818. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4177641/

Chandrashekar NS, Shobha Rani RH. Physicochemical and Pharmacokinetic Parameters in Drug Selection and Loading for Transdermal Drug Delivery. Ind J Pharm Sci. 2008; 70(1): 94-96. DOI: 10.4103/0250-474X.40340

Hiremath SN, Raghavendra RK, Sunil F, Danki LS, Rampure MV, Swamy PV, Bhosale UV. Dissolution enhancement of gliclazide by preparation of inclusion complexes with ß-cyclodextrin. Asian J Pharm. 2008; 73-76.DOI:10.22377/AJP.V2I1.335

Abolfazl A, Hajar J. Formulation, Characterization and Physicochemical Evaluation of Ranitidine Effervescent Tablets. Advanced Pharmaceutical Bulletin 2013; 3(2): 315-322. DOI: 10.5681/apb.2013.051

Vanarase AU, Osorio JG, Muzzio FJ. Effects of powder flow properties and shear environment on the performance of mixing of pharmaceutical powders. Powder technology. 2013; 246: 63-72. https://doi.org/10.1016/j.powtec.2013.05.002

Kamble KK, Mahadik KR. Solubility enhancement of Olmesartan Medoximil by spray drying technique. Der Pharmacia Sinica. 2014; 5(3):18-27.

Verma A, Singh S, Rupinder K, Ajay K, Jain UK. Formulation, Optimization and Evaluation of Clobetasol Propionate Gel. Int J Pharm Pharm Sci. 2013; 5(4): 666-674.

Kaur LP, Garg R, Gupta GD. Development and evaluation of topical gel of Minoxidil from different polymer bases in Application of Alopecia. Int J Pharm Pharm Sci. 2010; 2(3):43-47.

Gupta V. Dwivedi A, Trivedi N, Jain NK, Garud N, Jain DK. Formulation and evaluation of naproxen gel containing Tulsi oil as penetration enhancer. Int J Pharm Clin Res. 2009; 1(3): 153-155. http://impactfactor.org/PDF/IJPCR/1/IJPCR,Vol1,Issue3,Article15.pdf

Tous SS, Sayed AME, Abd EM, Youssef EMK, Agban MN, Boushra MF. Formulation and clinical evaluation of some new nalidixic acid topical formulations. J Drug Del Sci Tech. 2014; 24 (5): 507-513. DOI https://doi.org/10.1016/S1773-2247(14)50096-2

Swetha H, Sellappan V, Raju PN, Reddy GN. Formulation and evaluation of Clarithromycin Topical Gel. Int J Drug Dev Res. 2013; 5 (4): 194-202. https://www.ijddr.in/drug-development/formulation-and-evaluation-of-clarithromycin-topical-gel.pdf

Bhinge SD, Bhutkar MA, Randive DS, Wadkar GH, Todkar SS, Kakade PM. Formulation development and evaluation of antimicrobial polyherbal gel. Ann Pharm Fr. 2017;75: 349-358. DOI: 10.1016/j.pharma.2017.04.006

Joshi B, Singh G, Rana AC, Saini S. Development and Characterization of Clarithromycin Emulgel for topical delivery. Int J Drug Dev Res. 2012; 4 (3): 310-323. https://www.ijddr.in/drug-development/development-and-characterization-of-clarithromycin-emulgel-fortopical-delivery.pdf