

Formulation Development and Evaluation of Topical Nanoemulgel of Crisaborole

Yogesh B. Mahajan¹, Bhavika Sanjay Mahajan², Sheetal gondkar³, Rushikesh Bachhav⁴

^{1,3}Department of Pharmaceutics, R.G. Sapkal College of Pharmacy, Anjaneri, Nashik – 422213

²Department of Pharmaceutics Divine college of pharmacy Satana, Nashik-423301

⁴Department of Pharmacology, R.G. Sapkal College of Pharmacy, Anjaneri, Nashik – 422213

Abstract—Topical Nanoemulgel usage has expanded in recent years because to the preparation's better patient acceptance due to its non-greasy, convenient Spread ability, easy administration, and good therapeutic and safety profile. Nanoemulgel has a strong potential of being the primary topical delivery route for lipophilic medications in the future, despite several challenges. Amongst all the formulations, Nanoemulsion loaded emulgel prepared with the tween 80, Oleic acid was found to be better with the drug diffusion. Zeta potential of optimized formulation (Nanoemulsion) -28.32 mV which indicates the thermodynamic instability of the dispersion. The percentage of drug content was found to be in 77-96% hence, uniformity of content was maintained. When the improved formulation was compared to the marketed formulation for in-vitro drug release, it was discovered that the optimized batch (F1) had regulated release in 24 hours. In addition, the formulation was launched in 12 hours. The formulation followed the Higuchi Kinetic model of drug release. Accelerated stability study showed no significant change in the formulation upto 3 months. Finally, it can be summarized and concluded that the Nanoemulsion loaded emulgel of Crisaborole can be one of the promising tools in controlling the drug release via. Percutaneous mechanism for effective and longer treatment required for fungal infections with increased stability.

Index Terms—Crisaborole, Topical Emulgel, Atopic Dermatitis, Psoriasis, Nanoemulsion.

I. INTRODUCTION

Numerous illnesses and conditions have been developed for topical application. Since topical administration dramatically minimizes oral side effects while enhancing patient compliance, it may be helpful for the treatment of musculoskeletal and skin

problems. [1] A non-steroidal topical drug called crisaborole is used to treat mild to moderate atopic dermatitis. [34]

Thus, the goal of the current study was to create Crisaborole (2% w/w) in the form of an emulgel that contained the drug's nanoemulsion.

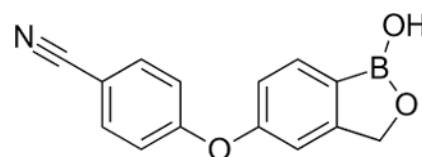


Figure 1: Structure of Crisaborole

Crisaborole is a brand-new oxaborole that the FDA authorized for use as Eucrisa on December 14, 2016, to treat mild to moderate atopic dermatitis. In patients 2 years of age and older, this non-steroidal medication effectively lessens the severity of the condition, lowers the risk of infection, and lessens the signs and symptoms. It has an excellent safety profile, lowers localized skin inflammation, and stops the condition from becoming worse. Its structure includes a boron atom, which makes it easier to penetrate the skin and attach to the phosphodiesterase 4 enzyme's bimetal core. It is now being developed as a topical psoriasis therapy. [34]

II. MATERIALS AND METHODOLOGY

Materials

Crisaborole was purchased Yarrow Chem Products, Oleic acid (Research -lab Fine Chem Industry, Mumbai), Transcutol HP and Tween 80 also from Research -lab Fine Chem Industry. Carbopol 934 was from Molychem, Mumbai. All other reagents used were of analytical grade. Methodology

High pressure homogenization methods are used for the formulation of nanoemulgel. There are three steps involved in the formulation of nanoemulgel which are given follows.

1. Preparation of Nanoemulsion
2. Preparation of hydrogel and
3. Finally, nanoemulgel will be produced by the incorporation of Nanoemulsion into gel with continuous stirring.

3² Full Factorial Design

A 3-factor, 3-level Box-Behnken statistical design

which requires 17 experimental runs was used to optimize the Nanoemulsion formulation. The observed ranges of responses i.e., Y1, Y2, and Y3 for all experimental runs were found as 34.64 ± 0.21 - 88.16 ± 0.36 nm, 0.210 ± 0.002 - 0.382 ± 0.004 and (-15.15 ± 0.34) - (-28.54 ± 0.44) mV respectively. All the responses observed for 17 prepared formulations were simultaneously fitted to first order, second order and quadratic models and it was observed that the best-fitted model was quadratic for response Y1, Y2, and Y3.

Table 1: Composition of Nanoemulsion formulation

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ingredients	%								
Crisaborole (w/w)	10	10	10	10	10	10	10	10	10
Oleic acid (v/v)	6	6	6	9	9	9	12	12	12
Tween 80 (v/v)	22.5	28.5	33.75	22.5	28.5	33.75	22.50	28.5	33.75
Transcutol HP (v/v)	7.5	9.5	11.25	7.5	9.5	11.25	7.5	9.5	11.25
Methyl Paraben (w/w)	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Propyl Paraben (w/w)	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
BHT	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Water Q.S (v/v)	100	100	100	100	100	100	100	100	100

III. METHOD OF PREPARATION FOR NANOEMULSION

Preparation of aqueous phase 'A': A precisely weighed amount of Transcutol HP was added to distilled water. (800c).

Preparation of Oil phase 'B': A weighed amount of Oleic acid and tween 80 were mixed together in a heated condition, then a weighed amount of Crisaborole was added, followed by the addition of methyl paraben, propyl paraben, and BHT.

Incorporation of solution 'A' in dispersion 'B': Both the phases were mixed properly with the help of High-pressure Homogenizer maintaining the respective rpm.

Preparation of gel

Table 2: Composition of gel

Sr. No.	Ingredients (% w/w)	Quantity
1	Carbopol 934	1%
2	Triethanolamine	0.1%
3	Water (q.s.)	100

The weighed quantity of carbopol 934 was mixed in distilled water (400c) further addition of triethanolamine to maintain the desired pH range of

the solution. The uniformity in the stirring was maintained and then the gel was kept in the refrigerator for 24 hrs.

Preparation of Emulgel: Further incorporation of 20 % nanoemulsion was incorporated to obtain 100 % (w/w) emulgel which contains 2% of drug.

Filling to container: The formulation was transferred into previously cleaned and dry containers.

IV. EVALUATION OF NANOEMULSION

Scanning Electron Microscopy

Scanning electron microscopy (SEM) may be used to analyze the morphology of a nanoemulsion. A three-dimensional picture of the particle is produced using SEM. The samples are inspected at various magnifications and an appropriate accelerating voltage, typically 20 kV. [4]

Particle Size Analysis

Developed Nanoemulsion's hydrodynamic particle size has to be examined. In most cases, the dynamic light scattering method for measuring particles and further particle size distribution is utilized with nanoemulsions. [4]

Zeta potential measurements

Zetasizer hsa 3000 (Malvern Instrument Ltd., UK) was used to calculate the zeta potential for nanoemulsion. Results were obtained after samples were put in transparent disposable zeta cells. Before each experiment, cuvettes were cleaned with methanol and rinsed with the sample to be analyzed before adding the fresh sample. [5]

V. EVALUATION OF NANOEMULGEL

Physical Appearance

Visual examination of the produced nanoemulgel formulations was done to check for color, homogeneity, consistency, and pH. [4]

Determination of pH

With the use of a digital pH meter, the formulation's pH was determined. The pH meter electrode was cleaned with distilled water before being put into the mixture to test the pH. [6, 7]

Measurement of viscosity

A Brookfield Viscometer (RVDV-I Prime, Brookfield Engineering Laboratories, USA) with spindle 63 was used to determine the viscosity of the prepared batches. The viscosity-to-be-determined formulation was added to the beaker and left to settle for 30 minutes at the assay temperature ($25 \pm 1^\circ\text{C}$) before testing. [6, 7]

Drug content study

A drug content analysis was carried out to assess the amount of drug contained in a certain quantity of the formulation. 1 g of the formulation was placed in a 10 ml volumetric flask.

Methanol was added to it, and it was shaken thoroughly to make up the volume. The Volumetric flask was maintained for 2 hours and well mixed in a shaker. The solution was passed through filter paper and filtered the mixer before measuring absorbance at 324 nm with a spectrophotometer. [6, 7, 9]

In-vitro Drug release study

Emulgel in-vitro drug release investigations were conducted on Diffusion cells employing egg membrane. This was gently clamped to one end of the dialysis cell's hollow glass tube. On the surface of the egg membrane dialysis membrane, 1gm of emulgel was placed. The receptor chamber was filled with

freshly produced PBS solution (pH 7.4). The total amount of gel used to solubilize the medication in the tube. The magnetic stirrer was used to agitate the receptor chamber. After proper dilutions, samples (1ml aliquots) were collected and tested for drug content using a UV visible spectrophotometer at 324 nm. [6, 7, 10]

Release kinetics of selected formulation

The cumulative release data were fitted to models representing Zero order (cumulative% drug release v/s. time), First order (log cumulative% drug retained v/s. time), and Higuchi model (cumulative% drug retained v/s. square root of time) to investigate the drug release kinetics and mechanism. [6, 7]

Accelerated stability studies of Emulgel [3, 5]:

Guidelines govern the conduct of stability studies. For three months, the organized emulgels were filled in aluminum collapsible tubes (5 g) and subjected to strength leans at 5°C , $25^\circ\text{C}/60\% \text{ RH}$, $30^\circ\text{C}/65\% \text{ RH}$, and $40^\circ\text{C}/75\% \text{ RH}$ and $60 \pm 2^\circ$. Tests were drawn back at 15-day intervals and inspected for physical appearance, pH, rheological characteristics, and medicinal content. [11,12]

VI. RESULT AND DISCUSSION

Determination of (λ_{max}) of Crisaborole in Methanol:

The UV spectrum of Crisaborole solution ($10\mu\text{g/ml}$) scanned between 400-200 nm using UV spectrophotometer exhibited wavelength of absorbance maxima at 324 nm.

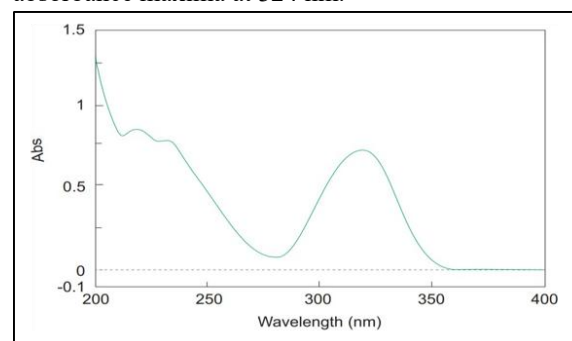


Figure 2: Ultraviolet Spectra of Crisaborole in Methanol

Calibration of Crisaborole in Methanol

Crisaborole calibration curve was produced in methanol because Crisaborole is soluble in methanol. The drug solution in methanol was highly transparent

and easily analyzed using a UV-visible spectrophotometer. The calibration curve was determined to be linear in the concentration range of 2-10 µg/ml, as shown in the table below. [14]

Table 3: Calibration Curve of Crisaborole in Methanol

Sr. No.	Conc.(ppm)	Absorbance
1	2	0.2451
2	4	0.4515
3	6	0.6331
4	8	0.8146
5	10	0.9947

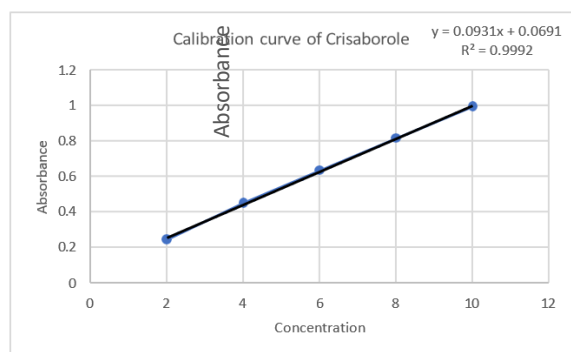


Figure 3: Calibration curve of Crisaborole in Methanol

Solubility study of drug in different oils:

Table 4: Solubility of Crisaborole in different oils:

Sr. No.	Oils	Solubility
1	Castor oil	11.65
2	Oleic acid	25.36
3	Almond oil	19.36
4	Liquid paraffin	9.87
5	Isopropyl myristate	24.46

Solubility determination of Crisaborole in surfactants and co-surfactant

Table 5: Solubility of Crisaborole in different surfactants and cosurfactant

Sr. No.	Excipients	Solubility (mg/ml)
1	Tween 20	10.85
2	Span 20	12.63
3	Tween 80	36.40
4	Transcutol HP	32.36
5	Propylene glycol	24.10

Fourier Transform Infrared Spectroscopy
The FTIR spectrum of Crisaborole has been shown in

below figure. The major peaks observed, and corresponding functional groups are given in below Table. The spectrum shows characteristic peaks for Crisaborole. [16,18]

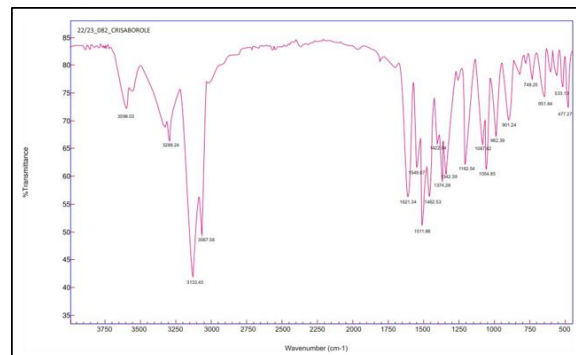


Figure 4: Representative IR spectrum of Crisaborole

The absorption bands shown by Crisaborole are characteristics of the groups present in its molecular structure. The presence of absorption bands corresponding to the functional groups present in the structure of Crisaborole confirms the identification and purity of the Crisaborole sample used in the study. [19,20]

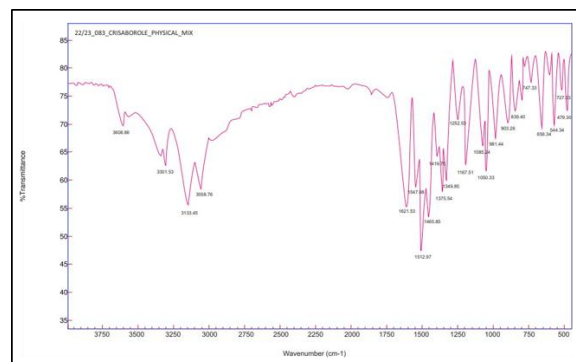


Figure 5: FTIR of Physical mixture

Table 6: Interpretation of FTIR Spectrum of physical mixture

Functional Group	Peaks Pure Drug	Physical Mixture
O-H Stretch	Yes	Yes
C-H Stretch	Yes	Yes
C=N	Yes	Yes
C=C	Yes	Yes

Optimization of Nanoemulsion formulation using response surface methodology

Table 7: Box-Behnken experimental designs using factors and obtained responses.

Sr. No.	Independent variable			Dependent variable		
	Oil (%) X1	Smix (%) X2	Water (%) X3	Particle size Y1 (nm)	PDI Y2	Zeta potential Y3 (mV)
1	6	45	45	52.64	0.361	-15.19
2	9	45	50	54.52	0.316	-21.56
3	9	37	45	35.26	0.293	-25.14
4	9	30	55	85.65	0.256	-21.02
5	8	37	55	36.54	0.316	-20.48
6	6	37	45	35.50	0.315	-19.10
7	6	30	55	50.23	0.220	-28.54
8	9	45	45	55.16	0.254	-26.49
9	9	30	50	84.64	0.310	-21.54
10	6	37	55	88.16	0.382	-20.48
11	12	37	50	34.64	0.216	-26.15
12	9	37	45	36.46	0.264	-19.01
13	9	37	55	36.46	0.349	-20.87
14	12	45	50	38.10	0.261	-19.14
15	12	30	55	60.15	0.210	-17.46
16	9	37	55	84.64	0.301	-16.41
17	12	37	45	46.12	0.264	-15.15

Contour plots and response surface analysis to optimize Nanoemulsion on the basis of particle size, PDI and zeta potential. [25,27]

The contour plots and response surface were analysed as shown in Figures.

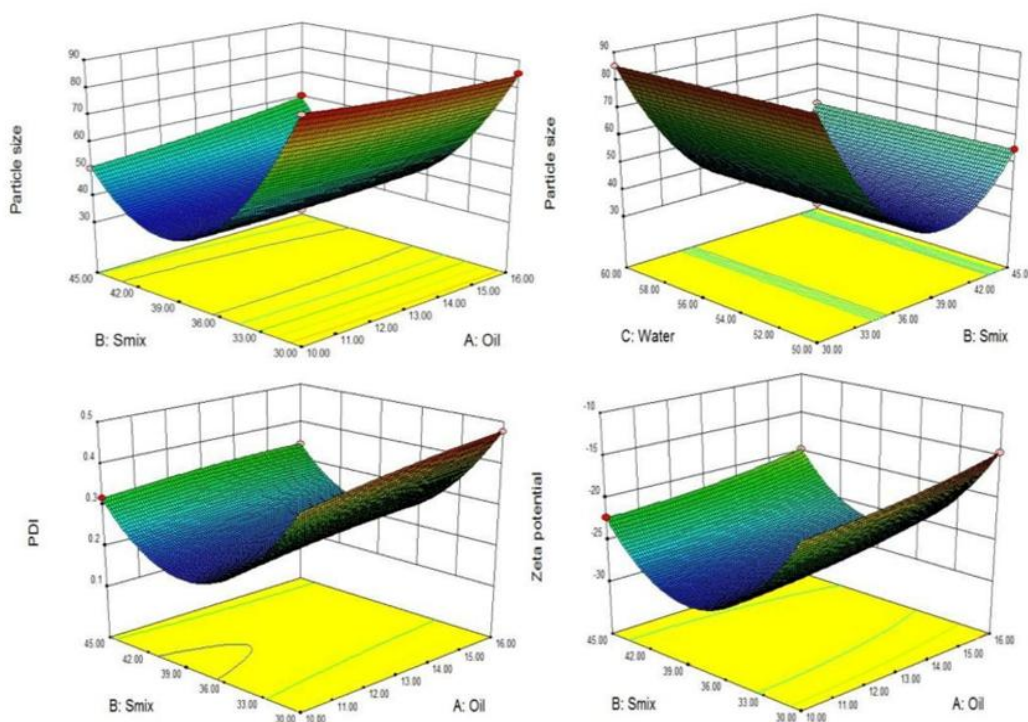


Figure 6: Response surface plots (3D) showing the effect of the amounts of oil, Smix (Tween 80 and Transcutol HP 3:1) and water on particle size, PDI and zeta potential of nanoemulsion.

VII. EVALUATION OF NANOEMULSION

Scanning Electron Microscopy

Figure 7 depicts scanning electron microscopy of a

nanoemulsion. The form of the Nanoemulsion was spherical, and its size was in the micrometer range. Furthermore, the micrograph exhibited some nanoemulsion agglomeration, which might be related

to the evaporation of water contained in the formulation during sample preparation prior to SEM examination. The particle size of the optimized batch's nanoemulsion was determined to be 50 nm. It is observed that when the concentration of Oleic acid increases with the speed of the homogenizer, the particle size decreases. [28-30]

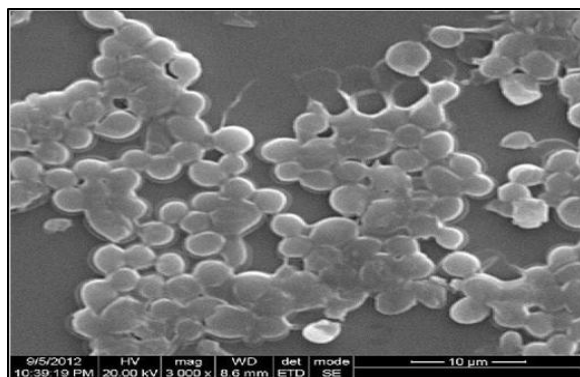


Figure 7: Scanning Electron Microscopy

Particle size and polydispersity index

The particle size of the optimized batch's nanoemulsion was determined to be 100 nm. It is observed that when the concentration of Oleic acid increases with the speed of the homogenizer, the particle size decreases.

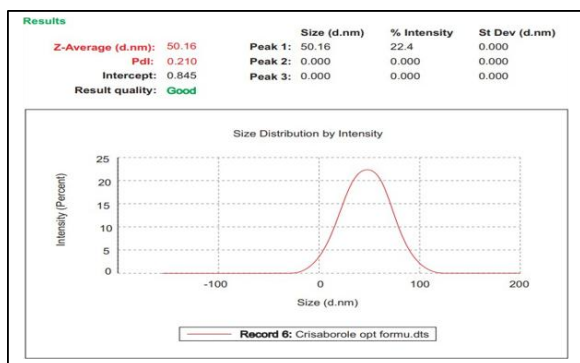


Figure 8: Particle Size of Optimized Formulation

Zeta Potential

According to the ICH recommendations for stability tests of different pharmaceutical formulations, zeta potential indicates the stability of the (colloidal dispersion) nanoemulsion under stress testing conditions. The zeta potential is altered by particle size; the lowest particle size in nano size, i.e., 100, exhibits -32 mV. The zeta potential implies thermodynamic instability of the dispersion.

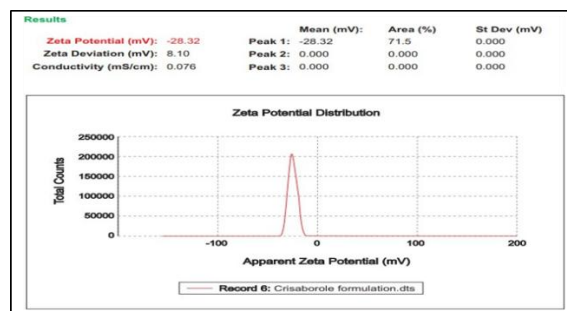


Figure 9: Zeta Potential of Optimized formulation

VIII. EVALUATION OF NANOEMULGEL

- **Physical Appearance:** The emulgel formulation's physical characteristics were determined to be transparent, homogenous, and consistent. [18]
- **pH:** pH of various emulgel is shown in the following table 28 which was found to be in range of 5.05 to 5.98 pH values indicate the suitability of emulgel for topical application, so as to minimize discomfort or irritation due to acidic pH and microbial growth due to basic pH.
- **Viscosity:** The viscosity values of formulations are shown in the Table 09.
- **Spreadability:** Spreadability and emulgel viscosity exhibit an inverse connection. The spreadability of Formulation F1 is 14.32 gm.cm/sec, which is the formulation's ideal viscosity. Spreadability is shown in Table 10.
- **Drug Content:** Table No. 11 displays the formulation's medication composition. All produced emulgel formulations were found to have a medication content that ranged from 77 to 96%.
- **In-vitro drug release:** The in-vitro release of Crisaborole from its various emulgel formula are represented in Table 12.

Table 8: pH values of formulation

Sr. No.	Formulation code	Observed pH ($\pm$ SD)
1	F1	5.34 $\pm$ 0.014
2	F2	5.45 $\pm$ 0.065
3	F3	5.05 $\pm$ 0.025
4	F4	5.98 $\pm$ 0.002
5	F5	5.61 $\pm$ 0.019
6	F6	5.24 $\pm$ 0.046
7	F7	5.16 $\pm$ 0.096
8	F8	5.63 $\pm$ 0.079
9	F9	5.12 $\pm$ 0.024

Table 9: Viscosity of formulations

Rpm	Viscosity (cP) at Room Temperature								
	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
10	15423	13542	14875	14012	13644	14023	13658	14088	12606
20	14326	12364	14023	13645	12045	13245	12398	13556	12266
30	13264	12645	13645	12597	11620	12924	12065	12646	11306
40	12984	11648	12025	12056	10925	12364	11564	11329	9463
50	12645	10640	10460	12002	10564	11066	10325	12064	8931

Table 10: Spreadability values of formulation

Sr. No.	Formulation code	Spreadability (g.cm/sec) $\pm$ S.D.
1	F1	14.32 $\pm$ 0.036
2	F2	11.64 $\pm$ 0.054
3	F3	13.04 $\pm$ 0.013
4	F4	11.65 $\pm$ 0.062
5	F5	12.45 $\pm$ 0.003
6	F6	13.85 $\pm$ 0.041
7	F7	16.85 $\pm$ 0.062
8	F8	17.02 $\pm$ 0.046
9	F9	18.64 $\pm$ 0.063

Table 11: Drug content of formulation

Sr. No.	Formulation code	Drug content (%) $\pm$ SD
1	F1	96.02 $\pm$ 0.61
2	F2	92.31 $\pm$ 0.14
3	F3	93.85 $\pm$ 0.63
4	F4	89.65 $\pm$ 0.03
5	F5	85.12 $\pm$ 0.95
6	F6	87.01 $\pm$ 0.10
7	F7	79.86 $\pm$ 1.55
8	F8	77.43 $\pm$ 0.03
9	F9	77.63 $\pm$ 0.25

Table 12: Cumulative amount of Crisaborole diffused (%) from all the emulgel formulations through egg membrane using Modified Franz diffusion cell

Time hrs.	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	9.81	8.23	7.15	6.78	5.15	8.54	7.02	6.85	8.47
2	18.45	14.65	12.64	12.15	9.54	10.84	9.65	8.64	10.28
3	23.14	25.35	23.54	26.15	22.15	20.49	16.42	15.48	21.48
4	35.64	32.65	31.02	33.54	28.64	26.14	29.41	21.16	28.74
5	42.31	41.64	44.64	45.1	43.15	40.74	36.87	32.78	32.59
6	52.14	48.64	45.64	49.45	52.64	51.04	48.79	45.65	40.81
7	58.01	56.94	55.98	51.52	53.41	54.98	52.41	50.98	48.85
8	69.15	63.85	61.02	64.15	65.85	63.1	61.07	59.84	57.89
12	79.64	73.15	70.54	74.48	72.41	70.48	69.46	66.14	63.41
16	86.14	80.65	82.45	80.31	78.54	75.14	75.82	71.48	69.01
24	95.31	91.45	93.15	89.15	84.18	86.98	79.15	76.87	77.10

Drug release Kinetics: The drug release was studied in this work to determine the kinetics of the drug release mechanism. Figures 10 and 11 demonstrate the results for zero order model kinetics and Higuchi model kinetics, respectively. [31]

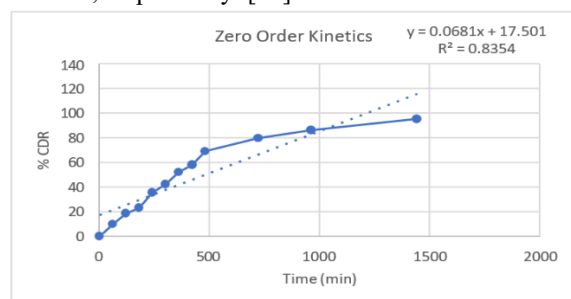


Figure 10: Model graph for comparative evaluation of Zero order Kinetics

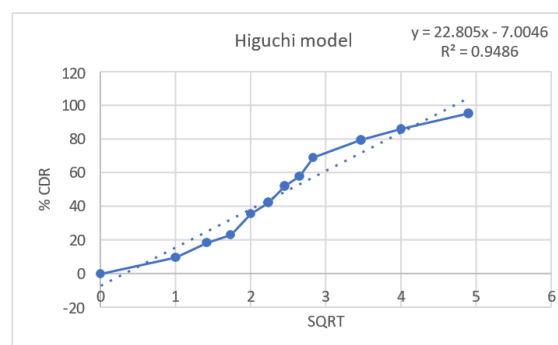


Figure 11: Model graph for comparative evaluation of Higuchi Kinetics

Stability study: The improved formulation was tested after accelerated storage and at room temperature. Stability experiments revealed that the formulation

was stable at accelerated temperatures ($400\text{C}\pm 20\text{C}$, $75\% \text{RH} \pm 5\% \text{RH}$). At room temperature, the stability of the optimized batch F1 was investigated. [19]

Table 13: Stability Study data for F1 formulation at Accelerated condition ($400\text{C}\pm 20\text{C}$, $75\% \text{RH}\pm 5\% \text{RH}$)

Sr. No.	Observations		Before Stability Testing	During study 3rd month
1	Clarity		Translucent	Translucent
2	pH		5.34 ± 0.014	5.32 ± 0.056
3	% Drug content		96.02	95.12
4	Viscosity	10	15423	15132
		20	14326	14886
		30	13264	13426
		40	12984	13021
		50	12645	12463

VIII. CONCLUSION

Before formulating this formulations Preformulation testing were performed for drug characterization and to analyse its purity and compatibility. Organoleptic properties, melting point, solubility testing, UV spectroscopy studies and FTIR were performed for the Crisaborole and the drug sample procured were found to be and compatible with the excipients used in formulation.

The drug loaded Nanoemulsion's were evaluated for Particle size, Poly-dispersibility index, Zeta potential and scanning electron microscopy analysis. Drug loaded emulgel were evaluated for physical appearance, pH, viscosity, spreadability, drug content, in vitro drug release study (diffusion study), antibacterial activity and Accelerated stability studies. After accelerated storage and room temperature, the improved formulation was assessed. Stability tests revealed that the formulation was stable at accelerated temperatures ($400\text{C}\pm 20\text{C}$, $75\% \text{RH} \pm 5\% \text{RH}$). At room temperature, the stability of Optimized batch F1 was studied.

REFERENCES

- [1] Pavia, D. L., G. M. Lampman, and G. S. Kriz. *Introduction to Spectroscopy: A Guide for Students of Organic Chemistry*. 4th ed. Cengage Learning Pvt. Ltd., 2007, pp. 13–27.
- [2] Patel, C. J., S. Tyagi, A. K. Gupta, P. Sharma, P. M. Prajapati, and M. B. Potdar. "Emulgel: A Combination of Emulsion and Gel." *Journal of Drug Discovery and Therapeutics*, vol. 1, no. 6, 2013, pp. 72–76.
- [3] Subramanian, S. *Biostatistics*. 1st ed. Career Publications, 2005, pp. 145–159.
- [4] Shaikh, Y. I., A. R. Paradkar, and M. G. Dhayugade. *Introduction to Biostatistics and Computer Science*. 11th ed. Nirali Prakashan, 2009, pp. 7.1–7.10.
- [5] Aiswarya, G., K. Hussan Reza, and R. Kumaravelrajan. "Development, Evaluation, and Optimization of Flurbiprofen Nanoemulsions Gel Using Quality by Design Concept." *Asian Journal of Pharmaceutics*, 2015, p. 37.
- [6] Verma, S., A. K. Singh, and A. Mukharjee. "Formulation and Evaluation of Ketoconazole Nanoemulgel." *World Journal of Pharmacy and Pharmaceutical Sciences*, vol. 5, no. 2, 2016, pp. 899–911.
- [7] Jaiswal, M., R. Dudhe, and P. K. Sharma. "Nanoemulsion: Advanced Mode of Drug Delivery System." Springer, 2015, vol. 5, pp. 123–127.
- [8] Chavda, V. P., and D. Shah. "A Review on Novel Emulsification Technique: A Nanoemulsion Research and Reviews." *Journal of Pharmacology and Toxicology Studies*, vol. 5, no. 1, 2007, pp. 31–32.
- [9] Dhas, A., G. Deshmukh, and V. Andhale. "Review on Nanoemulsion: A Novel Drug Delivery System." *European Journal of Biomedical and Pharmaceutical Sciences*, vol. 3, no. 4, 2016, p. 160.
- [10] Vijaya, R., S. S. Kumar, and S. K. Kannan. "Preparation and In Vitro Evaluation of Miconazole Nitrate Nanoemulsion Using Tween 20 as Surfactant for Effective Topical/Transdermal Delivery." *Journal of Chemical and Pharmaceutical Sciences*, vol. 8, no. 1, 2015, pp. 92–93.
- [11] Aarora, R., G. Aggarwal, S. L. Harikumar, and K. Kaur. "Nanoemulsion Based Hydrogel for Enhanced Transdermal Delivery of Ketoprofen." *Advances in Pharmaceutics*, p. 3.
- [12] Shahavi, M. H., M. Hosseini, and M. Jahanshani. "Evaluation of Critical Parameters for Preparation of Stable Clove

- Oil Nanoemulsion.” *Arabian Journal of Chemistry*, vol. 8, 2015, pp. 1878–1882.
- [13] Kute, S. B., and R. B. Saudagar. “Emulsified Gel: A Novel Approach for Delivery of Hydrophobic Drugs—An Overview.” *Journal of Advanced Pharmacy Education and Research*, vol. 3, no. 4, 2013, pp. 368–376.
- [14] Bolton, S., and C. Charles. *Pharmaceutical Statistics: Practical and Clinical Applications*. 4th ed. Marcel Dekker Inc., 2005, pp. 265–281.
- [15] Banker, G. J., and C. T. Rhodes. *Modern Pharmaceutics*. Marcel Dekker Inc., New York, 2008, pp. 265–266, 121–611.
- [16] International Conference on Harmonisation Steering Committee. *ICH Harmonized Tripartite Guideline: Stability Testing of New Drug Substances and Products, ICH Q1A (R2)*. February 6, 2003.
- [17] Patel, M. R., M. H. Patel, and R. B. Patel. “Preparation and In Vitro/Ex Vivo Evaluation of Nanoemulsion for Transnasal Delivery of Paliperidone.” Springer, 2016, vol. 6, p. 1098.
- [18] Jivani, M. N., C. P. Patel, and B. G. Prajapati. “Nanoemulgel: Innovative Approach for Topical Gel-Based Formulation.” *Research and Review on Healthcare, Open Access Journal*, vol. 1, no. 2, 2018, p. 05.
- [19] Bhattacharya, S., and B. G. Prajapati. “Formulation and Optimization of Celecoxib Nanoemulgel.” *Asian Journal of Pharmaceutical and Clinical Research*, vol. 10, no. 8, 2017, pp. 353–365.
- [20] Alam, S., S. Ali, N. Alam, I. Alam, and T. Anwer. “Design and Characterization of Nanostructure Topical Gel of Betamethasone Dipropionate for Psoriasis.” *Journal of Applied Pharmaceutical Science*, vol. 2, no. 10, 2012, p. 150.
- [21] Nawaz, A., S. U. Jan, N. R. Khan, A. Hussain, and J. M. Khan. “Formulation and In Vitro Evaluation of Clotrimazole Gel Containing Oleic Acid and Tween 80 as Penetration Enhancer for Topical Application.” *Pakistan Journal of Pharmaceutical Sciences*, vol. 26, no. 3, 2013, pp. 617–622.
- [22] Lachman, L., H. A. Lieberman, and J. L. Kanig. *Theory and Practice of Industrial Pharmacy*. 3rd ed. Varghese Publishing House, Mumbai, 1991, pp. 502–508.
- [23] Raju, K., and G. Sneha. “Formulation and Evaluation of Ornidazole Topical Emulgel.” *World Journal of Pharmacy and Pharmaceutical Sciences*, vol. 8, no. 7, pp. 1179–1197.
- [24] Pavani, et al. “Design, Formulation and In Vitro Evaluation of Microsponges Based Gel for Topical Delivery of Ketoconazole.” *International Journal of Pharmaceutical Sciences and Research*, vol. 8, no. 10, 2017, pp. 4222–4229.
- [25] Karade, Preeti G., and Rohit R. Shah. “Formulation and Evaluation of Celecoxib Gel.” *Journal of Drug Delivery and Therapeutics*, vol. 2, no. 3, 2012, pp. 132–135.
- [26] Verma, Swati. “Formulation and Evaluation of Ketoconazole Nanoemulgel.” *World Journal of Pharmacy and Pharmaceutical Sciences*, vol. 5, no. 2, 2016, pp. 899–911.
- [27] Modi, Jignesh. “Nanoemulsion-Based Gel Formulation of Aceclofenac for Topical Delivery.” *International Journal of Pharmacy and Pharmaceutical Science Research*, vol. 1, no. 1, 2011, pp. 6–12.
- [28] Syamala, Urmilasri. “Development & Optimization of Allyl Amine Antifungal Nanoemulgel Using 2³ Factorial Design: For the Treatment of Tinea Pedis.” *European Scientific Journal*, December 2013, Special Edition, vol. 4.
- [29] Bhattacharya, Sankha. “Formulation and Optimisation of Celecoxib Nanoemulgel.” *Asian Journal of Pharmaceutical and Clinical Research*, vol. 10, no. 8, 2017, pp. 353–365.
- [30] Harshan, Hiba. “Emulgel: An Advance Technique for Penetration of Hydrophobic Drugs.” *World Journal of Pharmacy and Pharmaceutical Sciences*, vol. 5, no. 3, pp. 343–358.
- [31] Rathod, Hemendrasinh J., and Dhruvi P. Mehta. “A Review on Pharmaceutical Gel.” *International Journal of Pharmaceutical Sciences*, vol. 1, no. 1, 2015, pp. 33–47.

- [32] Verma, Ashni. "Topical Gels as Drug Delivery Systems: A Review." *International Journal of Pharmaceutical Sciences Review and Research*, vol. 23, no. 2, 2013, pp. 374–382.
- [33] Sharma, Nitin. "Nanoemulsion: A New Concept of Delivery System." *Chronicles of Young Scientists*, vol. 1, no. 2, 2010, pp. 2–6.