



## Formulation and Evaluation of Emulgel for Topical Drug Delivery

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### Abstract

Nowadays topical administration is the favored route for local or site targeted delivery of therapeutic agents due to its suitability and affordability. Conventional topical drug delivery systems suffer from various drawbacks such as poor retention and low bioavailability. So, to avoid these drawbacks emulgel is developed which can manipulate the skin barriers due to presence of soluble drug carrier. Emulgel is the combination of both gel and emulsion. Emulgel is the most effective delivery system for delivery of hydrophobic drugs. Emulgel, a colloidal system where the oil phase of the emulsion is dispersed in a gel medium. Delivery of hydrophobic drugs through the gel is due to the presence of oil globules in the emulsion which act as a carrier for drug molecules. Emulgel was prepared by adding gelling agent into the aqueous phase of emulsion and then oil droplets with drug into it was added dropwise. The emulgel was optimized using 33 (3 factors and 3 levels) Box-Behnken design. The independent variables that were taken into consideration were concentration of polymer, concentration of oil and concentration of surfactant. Whereas, dependent variables/ response variables were viscosity, spreadability and drug release. As the concentration of carbopol 940 increased, the value of spreadability decreases. It will also show that the drug release profile of the formulations will also be decreased.

**Keywords:** Dirac's elegant, Relativistic, Newtonian point

### Introduction

In the ever-evolving landscape of medical science and patient care, the development of efficient and effective drug delivery systems has garnered paramount significance (1). This study stands at the crossroads of innovation, aiming to bridge the gap between conventional topical applications and cutting-edge emulgel technology. Emulgels, a hybrid combination of emulsions and gels, present a versatile platform for delivering therapeutic agents through the skin (2,3). The intricacies of formulating such systems necessitate a profound understanding of both the physical and chemical aspects involved. This study embarks on a journey to not only formulate a stable and optimized emulgel but also meticulously evaluate its attributes and performance for topical drug delivery. In an era where localized treatments are gaining traction for their potential to enhance efficacy while minimizing systemic side effects, the significance of developing emulgel-based delivery systems cannot be overstated (4,5). This study aspires to contribute to the scientific discourse by unraveling the complexities and nuances of emulgel formulation, all while keeping the ultimate goal in mind: improving patient outcomes and quality of life through enhanced topical drug delivery (6,7). By amalgamating pharmaceutical expertise, rigorous experimentation, and analytical precision, this study endeavors to shed light on the promise of emulgel formulations as a vehicle for delivering therapeutic agents through the skin (8,9). As we embark on this intellectual expedition, let us delve into the formulation intricacies, evaluation methodologies, and potential

implications of this novel approach in the realm of topical drug delivery. Emulgel are the semi-solid preparations and the name indicates that it has characteristics of both emulsion and gel (10,11). An emulsion is the mixture of two immiscible liquids in which one liquid is dispersed into the other liquid with the help of emulsifying agent which increases the stability of the emulsion. The drug particles in the internal phase crosses the external phase to skin and slowly get absorbed through skin. Therefore, the emulsion releases the drug in a controlled manner (12). Problems related with emulsions are breaking, creaming, phase separation and flocculation during storage. A gel is the semi-solid preparations which consist of cross-linked networks where the drug particles are entrapped and drug is released in a controlled way. The bio adhesive property of the gel increases the contact period of drug over the skin (13). Because of the high-water content in the gel, it allows greater dissolution and easy migration of hydrophilic drugs but unable to deliver the hydrophobic drugs. The combination of emulsion and gel i.e; emulgel can be utilized to overcome these problems associated with individual dosage form. Emulgels are developed which offers longer residence time with controlled penetration through the skin (14). With emulgels even hydrophobic drugs can also incorporated for therapeutic delivery of topical agents. Emulsion in emulgels can either be oil/water or water/oil, based on purpose of application which can be easily obtained by the incorporation of gelling agent in the respective primary emulsions (15). Different types of emulsion are used for the different purposes i.e; water-in-oil emulsions are used to treat dried skin and for emollient applications, whereas oil/water is generally used as a water-washable base and for cosmetic reasons. Emulgels can be considered as a matrix of gel in which droplets are embedded preventing the emulsion from creaming and coalescence (16). Dermatological emulgels have several beneficial characteristics such as it exhibits non-newtonian shear thinning property i.e; thixotropic in nature, greaseless, easily spread and removed, emollient, non-staining, compatible with multiple excipients and greater shelf-life, and patient acceptability. The emulgel has dual controlled release system. The emulsified gel showed enhanced stability and better vehicle for poor water-soluble drugs. Therefore, emulgel can be a better alternative for topical delivery of hydrophobic drugs. Emulgels have now been used to treat multiple types of skin disorders including those infected by viruses, bacteria, and fungi e.g., eczema, herpes simplex, acne and provides relief from the pain.

### **Scope**

Development of novel formulations present unique challenges in selecting the optimum formulation type for a given active ingredient. The topical route has long been used for delivering drugs directly to the affected target site through the skin. Current approaches in design and optimization of topical formulations necessitate extensive decisions in choosing the right components for the formulation to achieve high safety, clinical efficacy, and patient compliance. The formulation and evaluation of emulgel containing etoricoxib as an active ingredient was carried out in order to develop a delivery system to treat the inflammation. Etoricoxib is a novel cyclo-oxygenase-2 inhibitor which is primarily treated for the diseases like osteoarthritis, rheumatoid arthritis, and acute gouty arthritis. The scope of developing emulgel is:

- Topical drug delivery
- Targeted drug delivery
- Better solubility and skin permeability for poorly water-soluble drugs.

- Better drug entrapment as compared to other vesicular systems like liposomes or niosomes.
- They are more stable as compared to vesicular carrier system

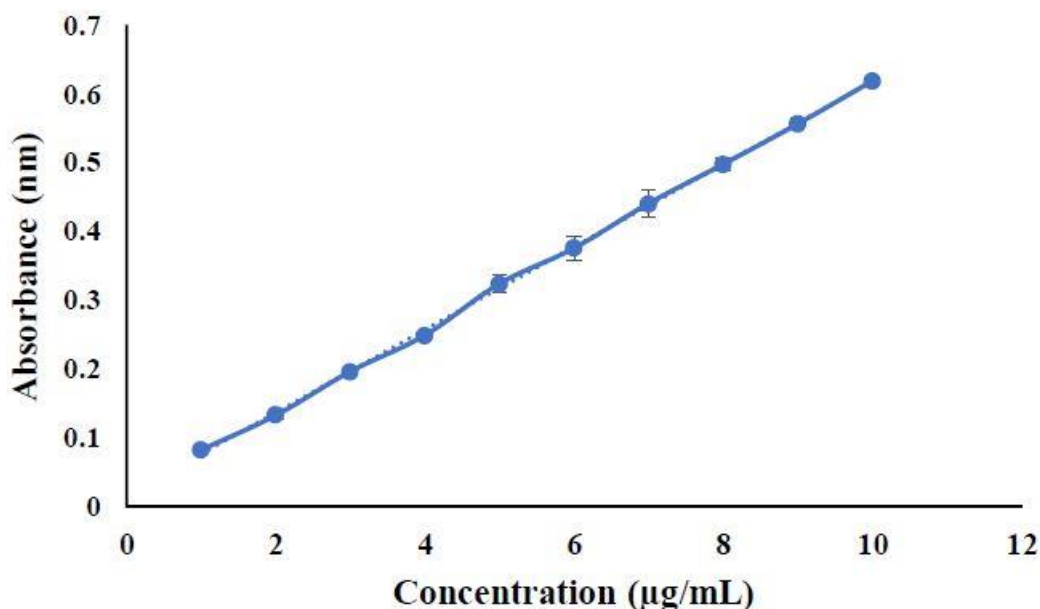
### Pre-Formulation Studies

The investigation begins by examining the organoleptic properties of Etoricoxib, encompassing its physical state, color, and odor. Subsequently, the study delves into a series of analyses aimed at assessing the compound's fundamental characteristics. The melting point (m.p) of Etoricoxib is determined as an indicator of its purity. This pivotal parameter provides insights into the potential presence of impurities, as shifts in melting point range can suggest the presence of contaminants. Solubility studies shed light on the compound's interactions with various solvents, oils, and surfactants, illuminating its solubility in oleic acid while remaining insoluble in water. Furthermore, the partition coefficient, a measure of a compound's preference for either oil or water, is calculated, providing insights into its potential distribution behavior. The study progresses to the development and validation of a UV-spectrophotometric method for quantifying Etoricoxib. The validation encompasses attributes such as linearity, accuracy, precision, and detection limits, adhering to stringent ICH guidelines. The methodology culminates in compatibility studies to assess the interaction of Etoricoxib with excipients, both physically and chemically. Visual observations and infrared spectroscopy are employed to discern any alterations in the compound or its mixtures. The results section highlights the findings of these analyses. Organoleptic properties confirm the compound's white color and lack of discernible odor. Melting point determination pinpoints its range between 134-140°C  $\pm$  0.5°C. Solubility studies reveal its compatibility with oleic acid while displaying insolubility in water. The pivotal development and validation of a UV-spectrophotometric method for quantification culminate in a calibration curve, showcasing the relationship between absorbance and concentration. Optical characteristics, regression analysis, and validation parameters further substantiate the reliability of this method.

**Table 1:** Data for the absorbance at various concentrations in phosphate buffer pH 6.8.

Concentration ( $\mu\text{g/mL}$ )	Absorbance (nm)
1	0.081 $\pm$ 0.000
2	0.132 $\pm$ 0.005
3	0.195 $\pm$ 0.001
4	0.248 $\pm$ 0.002
5	0.323 $\pm$ 0.011
6	0.375 $\pm$ 0.017
7	0.44 $\pm$ 0.019
8	0.497 $\pm$ 0.008
9	0.555 $\pm$ 0.008
10	0.618 $\pm$ 0.004

Data represented as mean $\pm$ SD (n = 3)



**Figure 1:** Calibration curve of drug in phosphate buffer pH 6.8

**Table 2:** Attributes determined for UV Spectrophotometric method in phosphate buffer pH 6.8

Category	Parameter	Results
Optical characteristics	$\lambda_{max}$	$234 \pm 0.5$ nm
Regression analysis	Slope	$0.0601 \pm 0.0002$
	Intercept	$0.0167 \pm 0.001$
	Correlation coefficient (R <sup>2</sup> )	$0.994 \pm 0.001$
	Regression equation	$0.0601x + 0.0167$
Validation	Concentration range	1-10 µg/ml

Data represented as mean $\pm$ SD (n = 3)

## Formulation, Development and Evaluation

### Preparation of Emulgel

Aqueous phase of the emulsion was prepared by dissolving tween 80 in distilled water along with the prepared mixture of propyl paraben and propylene glycol (propyl paraben in propylene glycol). Oil phase of the emulsion was formulated by solubilizing the drug in oleic acid along with definite quantity of span 80. At 70-80°C, both aqueous and oil phase was separately heated. Carbopol 940 (gelling agent) has been dispersed in distilled water with constant stirring and skin pH was maintained (6-6.5) using triethanolamine. To maintain the stability of the formulation, gel and aqueous phase was mixed and then oil phase was added dropwise with constant stirring. At last, it was kept aside for cooling at the

room temperature.

### Experimental Design using Box-Behnken model

The Box-Behnken design was particularly selected due to fewer runs when related to a central composite design based on similar variables. Box-Behnken design was used to create polynomial models for optimization purpose. In this design there are different set of points lying at midpoint of each edge and the replicated centre point of the multidimensional cube that are the region of interest. A 3-factor 3-level (33) Box-Behnken design allows the statistical optimization of independent variables i.e., polymer concentration, surfactant concentration and oil concentration to assess the main effects, interaction effects and quadratic effects of CMAs/CPPs on viscosity, spreadibility and drug release. The pre-optimization studies were carried out to determine the levels of the independent variables. Design-Expert® software (version 10.0, Stat-Ease, Minneapolis, USA) was used to carry out this study. This design consists of total 17 experiments with 5 centre points per block (in order to allow estimation of pure error) and the experiment run in random order. The relationship between the selected CMAs/CPPs and CQAs was delineated in this design space. The details of independent and dependent variables are given in table 6.1 and 6.2.

**Table 3:** Details of independent variables and their levels for emulgel

S.No.	Independent variables	Levels		
		Low (-1)	Medium (0)	High (+1)
1.	[F1] Concentration of polymer	0.5	1.0	1.5
2.	[F2] Concentration of surfactant	1	3.5	6
3.	[F3] Concentration of oil	7	8.5	10

**Table 4:** Details of dependent responses (CQAs) and goals to be achieved

S.No.	Responses	Goals
1.	[R1] Viscosity	Minimum
2.	[R2] Spreadibility	Maximum
3.	[R3] Drug release	Maximum

The experimental design matrix is presented in Table 6.3. Design-Expert software was used to evaluate the data acquired from the design. Numerical optimization was carried out for revealing the optimized formulation. The optimized formulation was prepared and evaluated. The prediction error was determined for the design from the data of dependent responses yielded from the experimental and predicted values.

**Table 5:** The Box-Behnken experimental design matrix for the optimization of emulgel

CODED VALUES				ACTUAL VALUES		
Run No.	Concentration of polymer	Concentration of surfactant	Concentration of oil	Concentration of polymer (%w/w)	Concentration of surfactant(%w/w)	Concentration of oil (%w/w)
1.	0	+1	-1	1.0	6.0	7.0
2.	+1	0	+1	1.5	3.5	10
3.	0	0	0	1.0	3.5	8.5
4.	0	0	0	1.0	3.5	8.5
5.	0	-1	+1	1.0	1.0	10
6.	-1	-1	0	0.5	1.0	8.5
7.	0	+1	+1	1.0	6.0	10
8.	0	0	0	1.0	3.5	8.5
9.	+1	0	-1	1.5	3.5	7.0
10.	-1	+1	0	0.5	6.0	8.5
11.	-1	0	+1	0.5	3.5	10
12.	0	0	0	1.0	3.5	8.5
13.	+1	-1	0	1.5	1.0	8.5
14.	0	0	0	1.0	3.5	8.5
15.	+1	+1	0	1.5	6.0	8.5
16.	-1	0	-1	0.5	3.5	7.0
17.	0	-1	-1	1.0	1.0	7.0

**Evaluation of emulgel**

Emulgel was evaluated and characterized for the following parameters:

**Physical appearance:**

Emulgel formulations were physically examined.

**pH measurement**

Digital pH meter was used to examine the pH values of different formulations.

**Viscosity**

Brookfield viscometer (spindle number 6) was used to determine the viscosity with rotation speed of 60 rpm.

### Spreadability

Two different sets of standard size glass slides have been taken. After that the emulgel was mounted over the ground slide that has been set. In addition, other slide was mounted on the top of the emulgel and 50g of weight was kept on the above slide for 5 minutes, so that the formulation was placed between the two slides and was pushed uniformly to shape thin film. The weight was withdrawn and the extra gel adhering to the slides was discarded. Then the two slides were set to stand without any of the minimal disruption but in such a way only the above slide could move freely by the force of 100g weight attached to it. The average time for the above slide to move a total distance of 7.0 cm apart from the bottom slide under the effect of weight was observed. The process was repeated thrice and the mean time was measured. Spreadability was measured using the following formula: [116]

$$S = M \times L / T \dots \dots \dots \text{Equation 6.1}$$

Where, S= Spreadability

M= Weight tied to upper slide (grams)

L= Length of the glass slide moved (centimeters)

T= Time taken (seconds)

### In-vitro drug release

Franz diffusion cell was used to determine the drug release. Gellified emulgel was evenly placed on the external surface of dialysis membrane which was clamped between the donor and receptor chamber of diffusion cell. The receptor chamber was filled with phosphate buffer pH 6.8 which was used as a dissolution medium. The samples were withdrawn at a suitable time interval and was analysed in UV spectrophotometer at  $\lambda$  max 234nm. An equal volume of fresh buffer was added after withdrawing each sample to maintain the volume. The absorbance was obtained using UV spectrophotometer and then converted to concentration by using the equation obtained from calibration curve.

In-vitro drug release kinetics

The release study was fitted to various release kinetic models i.e.

Zero order:

$$Q_1 = Q_0 + K_0 t \dots \dots \dots \text{Equation 6.2}$$

First order:

$$\log Q_t = \log Q_0 + K_1 t / 2.303 \dots \dots \dots \text{Equation 6.3}$$

### Stability studies

The motive behind the stability studies is to verify the quality of active pharmaceutical ingredients that differs with time under the influence of different environmental factors like temperature, humidity, and light. Optimized formulation was subjected to stability testing according to the International conference on harmonization (ICH) Q1C guidelines.

### Accelerated stability studies according to ICH guidelines

The formulation was preserved in the plastic bottle containers for 6 months and the percent drug remaining was calculated. The graph was plotted between % Drug remaining and time (months). Further the graph was extrapolated to calculate the shelf-life of the product.

### Accelerated stability testing by conventional method using Arrhenius Equation

The optimized formulation was subjected to accelerated stability conditions for 90 days. The graph was plotted between log % drug remaining and time (days). The K value at different storage conditions was calculated from the graph using the following equation

$$S=K/2.303.....\text{Equation 6.4}$$

Further the graph was plotted between the log k and 1/T (K) and k value at 25° C was calculated. Shelf-life of the optimized formulation was calculated using the given formula

$$\text{Shelf-life}=0.1052/k25^{\circ}\text{C}.....\text{Equation 6.5}$$

## Results and Discussion

### Nanoparticles Physical examination

Prepared formulations of emulgel were visually inspected and all formulations were white in color, no phase separation and was homogeneous and consistence in appearance.

### pH measurements

The pH of all the formulations were in the range of 6.5-6.8 which means that there will be no such irritation on the skin. Experimental design and statistical analysis.

According to Box-Behnken model all the 17 batches were prepared and evaluated for dependent responses i.e. viscosity, spreadibility and drug release. The results for different dependent responses with respect to the 17 experimental runs are represented in table 6.4.

**Table 5:** Experimental results for dependent responses for runs suggested by Box-Behnken model for the optimization of emulgel

- Independent variables
- Dependent variables



Run No.	Concentration of polymer (%w/w)	Concentration of surfactant (%w/w)	Concentration of oil (%w/w)	Viscosity (poise)	Spreadibility (g.cm/sec)	Drug release (%)
1.	1.0	6.0	7.0	15623 ± 1.5	21.48 ± 1.33	7.0
2.	1.5	3.5	10	21513 ± 2.5	10.44 ± 0.16	10
3.	1.0	3.5	8.5	14675 ± 3.2	24.79 ± 1.88	8.5
4.	1.0	3.5	8.5	14362 ± 2.0	24.71 ± 0.5	8.5
5.	1.0	1.0	10	14287 ± 1.1	29.97 ± 4.39	10
6.	0.5	1.0	8.5	11511 ± 1.5	36.23 ± 1.06	8.5
7.	1.0	6.0	10	16212 ± 2.5	30.46 ± 1.32	10
8.	1.0	3.5	8.5	14511 ± 0.5	24.71 ± 0.5	8.5
9.	1.5	3.5	7.0	23514 ± 2.0	8.50 ± 0.26	7.0
10.	0.5	6.0	8.5	12615 ± 0.5	42.89 ± 1.49	8.5
11.	0.5	3.5	10	11482 ± 1.1	38.13 ± 1.15	10
12.	1.0	3.5	8.5	14722 ± 2.3	26.23 ± 0.58	8.5
13.	1.5	1.0	8.5	22181 ± 1.1	7.16 ± 0.15	8.5
14.	1.0	3.5	8.5	14511 ± 0.5	26.23 ± 0.58	8.5
15.	1.5	6.0	8.5	20985 ± 0.5	5.6 ± 0.2	8.5
16.	0.5	3.5	7.0	11522 ± 1.1	51.27 ± 2.19	7.0
17.	1.0	1.0	7.0	15749 ± 1.0	35.0. ± 1.75	7.0

### Summary and Conclusion

The following thesis is divided into various sections i.e., Introduction, literature review, scope, objective and plan of work, drug and excipients profile, pre-formulation studies, formulation, and development. The summary of content includes individual section summarized as follows:

The introduction section focuses on the topical delivery of drug using emulgel as delivery system. Properties of drugs that are suitable in the formulation of emulgel are mentioned in the introduction part. It also emphasizes on the composition, preparation, applications. Marketed products, patents and in-vivo study was also described in brief.

The literature review section deals with the researches done previously on the formulation and development of emulgel. The literature review was very helpful in selection of drug and excipients for the formulation of emulgel.

The aim of the study was to formulate and evaluate the emulgel for topical drug delivery. The scope of the study was to deliver the hydrophobic drug directly to the affected site (site-targeted) through the gel using oil in the emulsion as the drug carrier. Emulgel confirms their advantages over the conventional delivery system with their ability to possess better spreadibility, adhesion, viscosity, extrusion, drug entrapment, and stability. To achieve the aim i.e., optimization, preparation and evaluation of emulgel, an effective plan of work is discussed.

The next chapter includes the detailed depiction of drug and excipient used in the study. Etoricoxib, carbopol 940, oleic acid, span 80 and tween 80 was used in the formulation process. All parameters those are important for the formulation and development of the emulgel were studied for the selection of suitable ingredients.

Different pre-formulation studies were carried out and their methods and results were discussed in this chapter. The different parameters are identification, spectroscopic analysis of drug. Organoleptic properties, solubility of drug in various solvents, melting point, partition coefficient. For the identification of drug concentration, calibration curve was drawn in phosphate buffer pH 6.8. The  $\lambda_{max}$  of etoricoxib was to be  $234 \text{ nm} \pm 0.5 \text{ nm}$ . The developed method was validated for the range of linearity, accuracy, precision, detection, and quantitation limits were assessed in phosphate buffer pH 6.8.

The emulgel was prepared by stirring the carbopol 940 in the aqueous phase of emulsion for 30 minutes. Then oil was added from the oil phase of emulsion drop by drop. The formulation was optimized by 33 Box-Behnken design. The independent variables were concentration of polymer, concentration of oil and concentration of surfactant. Dependent variables were spreadability, viscosity and drug release.

## Conclusion

After the literature survey and experimental study, it can be concluded that the emulgels appear better & effective drug delivery system as compared to other topical drug delivery system. The complete analysis of viscosity, spreadability and release properties will provide an insight into the potential usage of emulgel formulation as drug delivery system. In future Emulgel will provide a solution for topical delivery of hydrophobic drugs. Many of drugs that have utility in treatment of skin disorders are hydrophobic in nature. So, these drugs can be delivered through emulgel.

The spreadability results showed that increase in concentration of polymer, less will be the spreadability. Increase in viscosity can also hinder the release profiles. Therefore, the expected outcomes were to minimize the viscosity so that there should be a better spreadability and maximum drug release.

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