

Preparation and *in vitro* characterization of etofenamate emulgels using quality by design

Gülşen YILMAZ¹ , Sakine TUNCAY TANRIVERDİ^{2*} , Buket AKSU³ , Gizem YEĞEN³ , Özgen ÖZER² 

¹ Turkish Medicines and Medical Devices Agency, Quality Department, Ankara, Turkey.

² Ege University, Faculty of Pharmacy, Department of Pharmaceutical Technology, İzmir, Turkey.

³ Altınbaş University, Faculty of Pharmacy, Department of Pharmaceutical Technology, İstanbul, Turkey.

* Corresponding author. E-mail: sakinetuncay@windowslive.com (S.T.T.); Tel: +90 232-311 39 81.

Received: 04 October 2018 / Revised: 22 July 2019 / Accepted: 01 August 2019

ABSTRACT: Quality by Design (QbD) emerged with quality guidelines issued by the International Council on Harmonization (ICH); is a concept that suggests the quality of product cannot be secured by the finish product tests; product quality should be ensured by starting from risk and scientific based work in process and product development through the whole product life cycle. Statistical studies, which are done by computer program, have important role in today's pharmaceutical area. ANN (Artificial Neural Network) and GEP (Gene Expression Programming) are modelling techniques can be used for analyzing big amount of data, in understanding the relations between dependent and independent variables affecting product quality and optimizing the formulation variables and process parameters to get the desired product quality continuously. In this study, different etofenamate emulgel formulations were prepared, the quality characteristics determined to be critical were evaluated separately with the ANN, and GEP modeling techniques for the optimization of the formulations examined. During the modeling, the input values were oil type, oil ratio and polymer ratio and the outputs were pH, conductivity, viscosity and flow properties of the emulgels. According to results of pre-formulation studies both of the programs suggested two optimized formulations. Depending on the further studies, the viscosity and rheological behavior showed that both formulations were could apply on skin.

KEYWORDS: Quality by design; etofenamate; artificial neural networks (ANNs); gene expression programming (GEP); emulgel.

1. INTRODUCTION

Quality by Design (QbD) is a concept that suggests the quality should not only be tested on the finish product; product quality should be ensured in formulation and process development stages, which are more robust and reliable when done by following QbD steps. While this concept established with quality guidelines of International Council on Harmonization (ICH) other approaches like risk assessment, mathematical modelling and optimization were recommended as helpful to determine critical attributes and parameters, also, create design space [1,2]. ANN (Artificial Neural Network) and GEP (Gene Expression Programming) are modelling techniques can be used for analyzing big amount of data, modelling the relations between dependent and independent variables affecting product quality and optimizing the formulation variables and process parameters to get the desired product quality continuously [3].

Etofenomate is a non-steroidal anti-inflammatory drug. Several preparations of etofenamate are available in the market as different topical preparations [4]. In spite of many advantages of gels used for topical delivery, a major limitation is in the delivery of hydrophobic drugs. Therefore, to overcome this limitation, emulgels are prepared and used for hydrophobic drugs [5, 6]. Emulgel formulations are using for topical delivery of both hydrophilic and hydrophobic drugs. They have many favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, long shelf life, biofriendly, transparent and pleasing appearance [7, 8]. In this study, QbD was used to optimize emulgel formulation of etofenamate for the first time. Different etofenamate emulgel formulations were prepared by using two types of oil with two ratios and different concentration of Carbopol® 940 [9]. The formulations were characterized via several parameters such as pH, conductivity, viscosity and flow properties [10].

How to cite this article: Yılmaz G, Tanriverdi Tuncay S, Aksu B, Yeğen G, Özer O. Preparation and *in vitro* characterization of etofenamate emulgels using quality by design. J Res Pharm. 2019; 23(6): 1033-1039.

2. RESULTS

2.1. Pre-formulation studies

The composition of emulgel formulation was given in Table 1. The hydrogel part of formulations was prepared with 0.125, 0.25 and 0.625% of polymer. The liquid paraffin or oleic acid was used for the part of oil phase of system. 12 emulgel formulations were prepared as shown in Table 2.

Table 1. The composition of emulgel formulations.

	Content	Amount (g)
Hydrogel	Distilled water	16.15/13.65
	EDTA	0.025
	Carbopol® 940	0.125/0.25/0.625
	Triethanolamine	0.125
	Tween 80	1.25
Oil Phase	Lipex Shea	0.125
	Phenoxyethanol capp.	0.125
	Transcutol® P	1.2
	Propylene glycol	0.75
	Liquid paraffin/Oleic Acid	5/7.5
Active Ingredient	Etofenamate	1.25

Table 2. The composition of emulgel formulations with different amount of oil and polymer amount.

Codes	Formulation Codes	Oil Type	Oil Ratio (%)	Polymer Ratio (%)
F1	F1-1	LP*	20	0.5
F2	F2-1	LP	20	1
F3	F3-1	LP	20	0.25
F4	F1-2	LP	30	0.5
F5	F2-2	LP	30	1
F6	F3-2	LP	30	0.25
F7	F1-3	OA*	20	0.5
F8	F2-3	OA	20	1
F9	F3-3	OA	20	0.25
F10	F1-4	OA	30	0.5
F11	F2-4	OA	30	1
F12	F3-4	OA	30	0.25

*LP is liquid paraffin; OA is oleic acid.

2.2. Characterization of formulations

The characterization studies of the formulations showed that the viscosity, pH and conductivity changed due to the composition. All formulations have non-newtonian behavior and pseudoplastic flow. The viscosity and rheological behavior showed that both formulations could be applied on skin. The pH of formulations was between 5.5 and 7.5 that are acceptable for topical application on skin. The viscosity, pH and electrical conductivity results of formulations were shown in Table 3 and Figure 1.

Table 3. The characterization results of formulations.

Codes	Macroscopic observation	Viscosity (Pas)	pH	Conductivity (μS/cm)
F1	White, homogeneous	10.55	7.41	430
F2	White	25.66	5.75	465
F3	White, homogeneous	4.30	7.41	205
F4	White, homogeneous	13.6	6.8	270
F5	White	29.8	5.3	280
F6	White, homogeneous	6.23	7.71	165
F7	White, homogeneous	8.91	5.75	520
F8	White	4.04	5.8	634
F9	White, homogeneous	5.61	6.45	444
F10	White, homogeneous	2.4	5.8	396
F11	White	6.60	5.5	460
F12	White, homogeneous	9.99	6.49	430

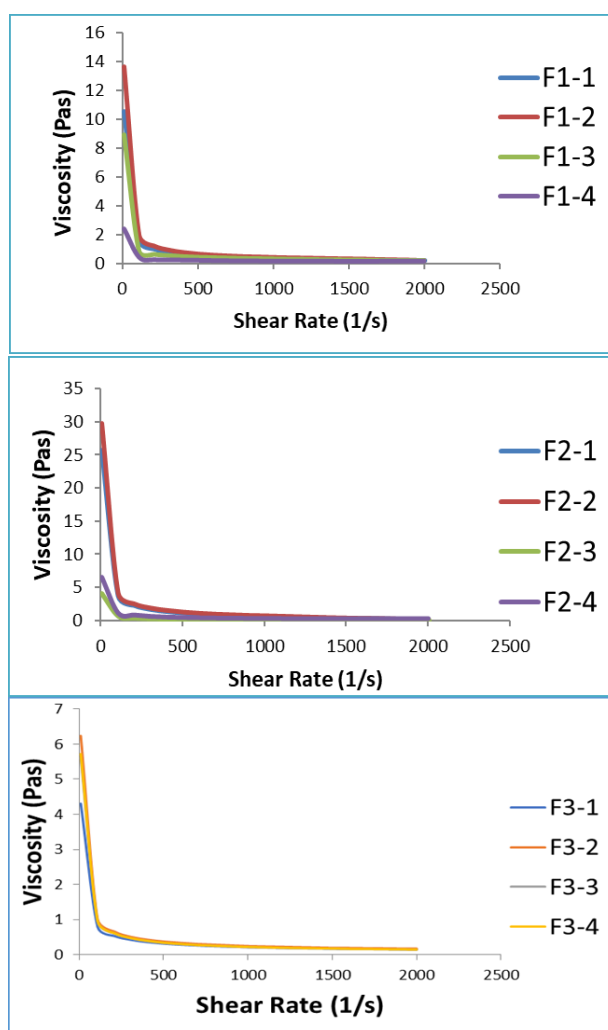


Figure 1. The graphs of viscosity versus shear rate.

3. DISCUSSION

3.1. Characterization of formulations

For the formulation prepared with liquid paraffin, viscosity increased with increasing polymer concentration as expected from pseudoplastic gels. However, for oleic acid formulations, the viscosity did not change with increasing polymer concentration. The result shows that oil type is an important parameter on viscosity of formulations. The pH of the formulations should be around skin pH (5.5) or neutral pH (7). The results show that the pH of formulations between skin pH and neutral pH which is appropriate for topical application of formulations. The results showed that pH is differed with the composition. The electrical conductivity is a parameter, which is tested during stability studies to show chemical stability. It was seen that conductivity was increased when polymer concentration was higher and the higher conductivity values were observed with the oleic acid formulations.

3.2. Optimization studies

Training result of the model is given at Table 4; and according to R^2 and f -ratio values, a robust model were obtained for all outputs. Both programs showed nearly same composition for the optimum formulation as shown in Table 5. The optimized formula given by ANN modelling (F1) was oil type 1 which is liquid paraffin, oil ratio 20.83%, polymer ratio 0.57; optimized formula given by GEP modelling (F2) was oil type 1 again, oil ratio 20%, and polymer ratio 0.71 (Table 6).

Table 4. Training results of specifications for each model.

Specifications	ANN		GEP	
	R^2 (%)	f -Ratio	R^2 (%)	f -Ratio
pH	97.52	- 17.03	90.69	- 6.75
Conductivity	97.84	- 19.37	95.57	-14.79
Viscosity	96.93	- 13.81	97.71	-30.39
Flow	97.95	- 8.71	98.56	- 50.51

Table 5. The composition of formulations that obtained by ANN and GEP.

Composition	ANN formulation	GEP formulation
Gel phase	Distilled water	64.2 g
	EDTA	0.1 g
	Carbopol® 940	0.57 g
	Triethanolamine	0.5 g
	Tween 80	5 g
Oil phase	Lipex Shea	0.5 g
	Phenoxyethanol caprylglycol	0.5 g
	Transcutol® P	4.8 g
	Propylene glycol	3 g
	Liquid Paraffin	20.83 g
Active ingredient	Etofenamate	5 g

Table 6. Oil type and polymer ratio of optimized formulations via ANN and GEP.

Composition	Optimum Formula by ANN	Optimum formula by GEP
Oil type	1	1
Oil ratio	20.83 mg	20 mg
Polymer ratio	0.57 mg	0.71 mg

3.3. Preparation of optimum formulations

The optimum formulations that specified by modelling programs were prepared and characterized by parameters as mentioned above. The pH of formulations were 5.76 (F1) and 5.94 (F2). Electrical conductivities were found 298 (F1) and 262 (F2) μ S-1. The viscosity and rheological behavior (Figure 2) showed that both formulations could be applied on skin.

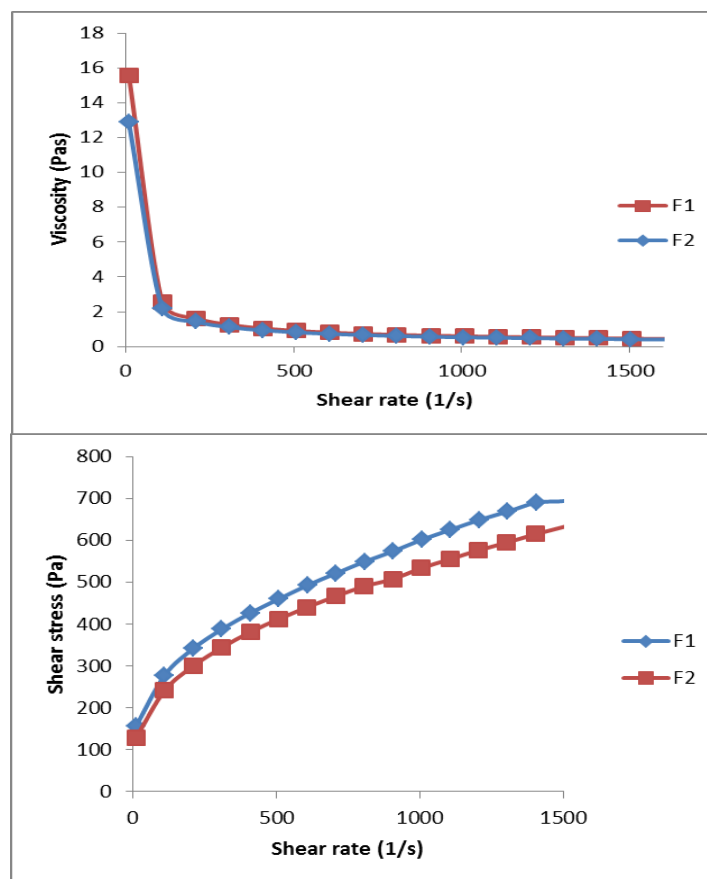


Figure 2. The viscosity and rheology graph of optimum formulations.

4. CONCLUSION

With this study, QbD approach and artificial intelligence modelling techniques were used to develop an etofenamate emulgel formulation for topical delivery, for the first time. Because of overall studies, an efficient formula, which can be applied topically, was obtained via mathematical modelling techniques. Even though there are few formulations appropriate for the topical delivery were obtained from the studies, the formulations show ideal rheological behavior and viscosity were formed by computer software. Especially, in the way input and output values modelling programs suggested different formulations, which were not evaluated in pre-formulation studies and the attributes of these formulations, were found proper. The results showed that both programs could be used to establish optimum formulation and these could be very helpful for research studies in universities and in industry as time and money savers.

5. MATERIALS AND METHODS

5.1. Materials

Etofenamate was a kindly gift from Union Quimico Farmaceutica, S.A.(Spain), Tween 80, triethanolamine, liquid paraffin and oleic acid was obtained from Merck KGaA (Germany). EDTA, Carbopol® 940 and lipex shea were purchased from Kale Kimya (Turkey), Corel Pharma Chem. (India) and AAK company (Sweedden), respectively. Phenoxyethanol capryl glycol, Transcutol® P and propylene glycol were provided from Verstatil PC (Germany), Gattefosse (France) and Sigma Aldrich (USA), respectively. De-ionized (DI) water was obtained from ultrapure water system (Model-Arium 611) of Sartorius AG (Germany).

5.2. Pre-formulation studies of emulgel formulations

Pre-formulation studies of etofenamate emulgels were performed to apply QbD and find optimum composition of etofenamate emulgel formulation. According to the compositions are given in Table 1 etofenamate emulgel formulations were prepared.

Firstly, EDTA was dissolved in distilled water and Carbopol® 940 was added to solution. Tween 80 as mixed with while the system was mixing under magnetic stirrer. Then, triethanolamine was added to obtain optimum pH for jellifying of polymer. Two types of oil (liquid paraffin and oleic acid) with two ratios were used for preparation of emulsion phase. The oil phase was composed of oil, shea butter, phenoxyethanol capryl glycol, Transcutol® P and propylene glycol. Then, etofenamate was added to oil mixture. As last step, oil phase was added to gel phase by drop by drop while the system is mixing under mechanic stirrer at 1000 rpm for 15 min.

5.3. Characterization of formulations

The formulations were characterized via macroscopic evaluation, pH, conductivity, viscosity and flow properties. The color, viscosity and phase separation of formulations were evaluated macroscopically. The pH values of the formulations were determined by using a pH meter (Jenway 3040 Ion Analyze, Staffordshire, UK) at 25±1°C. All experiments were replicated at least three times. Conductivity of formulations was measured by using a conductivity meter (Jenway, 4071, Staffordshire, UK) at 25±1°C.

The rheological analysis of the formulations was performed at 20±0.1°C using an AR 2000 controlled stress/controlled rate rheometer (Haake MARS, plate PP35 Ti, plate cover MPC35, Karlsruhe, Germany). The plate / plate system 60 mm diameter and 1 degrees angled with gap 0.3 mm was used. In continuous shear analysis, the upward and downward flow curves for each formulation were measured over shear rates ranging from 10 to 900 s⁻¹ [11, 12].

5.4. Optimization studies

ANN and GEP modelling systems were applied to experimental data to obtain a recommended optimized emulgel formulation and to enlighten the relationship between independent input variables and the CQAs. Oil type, oil ratio and polymer ratio were determined as inputs and pH, conductivity, viscosity, flow were determined as outputs. Liquid paraffin (oil type 1) and oleic acid (oil type 2) were used as oil phase in the range of 20% or 30%. The concentrations of polymer (Carbopol® 940) were changed as 0.25, 0.5 and 1%. Two different formulations obtained from ANN and GEP models with appropriate training results (ANOVA statistics). After models were created, two optimum formulations were recommended. Experimental studies further conducted on the optimized formulations [13, 14].

5.5. Preparation of optimum formulations

The optimum formulations were selected with ANN and GEP models. Two formulations were prepared as mentioned in Section 5.1. The formulations were characterized via parameters such as pH, electrical conductivity, macroscopic observation, viscosity and rheological analysis. Table 6 shows the oil phase and composition of optimum formulations selected by two models.

Acknowledgements: The authors would like to thank Ege University, Faculty of Pharmacy, Pharmaceutical Sciences Research Center (FABAL) for rheological analysis facilities.

Author contributions: Concept – G.Y, S.T.T., B.A., G.Y., Ö.Ö.; Design – G.Y, S.T.T., B.A., G.Y., Ö.Ö.; Supervision – G.Y, S.T.T., B.A., G.Y., Ö.Ö.; Resources – G.Y, S.T.T., B.A. Ö.Ö.; Materials – G.Y, S.T.T., B.A.; Data Collection and/or Processing – G.Y, S.T.T., B.A., G.Y., Ö.Ö.; Analysis and/or Interpretation – G.Y, S.T.T., B.A., G.Y., Ö.Ö.; Literature Search – G.Y, S.T.T., B.A.; Writing – G.Y, S.T.T., B.A., G.Y., Ö.Ö.; Critical Reviews – G.Y, S.T.T., B.A., G.Y., Ö.Ö.

Conflict of interest statement: The authors declared no conflict of interest.

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