

Evaluation of emulgel formulations contain diclofenac sodium via quality by design approach

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Received: 20 September 2021 / Revised: 15 February 2022 / Accepted: 15 February 2022

ABSTRACT: Emulgel is considered as emulsions, either oil-in-water or water-in-oil type, that is formed via blending with a gelling agent. Their common usage as pharmaceutical dosage form results from the broad utilization of emulsion systems, particularly for dermatological formulations. Quality by Design (QbD) is a scientific, holistic, risk-based, systematic, and proactive approach that starts with predefined objectives and assertiveness on product quality, procedure understanding, and process control. In this study, the QbD approach was implemented in the production of emulgel containing diclofenac sodium and the goal was to build quality into the product from the inception of formulation development. The hydrogel phase and oil phase of emulgel were prepared separately, then mixed. Emulgels were evaluated for their macroscopic, and microscopic examination, pH, electrical conductivity measurements, and viscosity. The optimum formulation was found by using the ANN Modelling program. According to macroscopic evaluation the optimum emulgel was an opaque white color, and homogeneous with no phase separation or grittiness. The viscosity of the optimum formula is 4600, pH value is 6.7, electrical conductivity is 120 μ S-1, and particle diameter was also 0,989 μ m. Results showed the optimized formula has the required properties. ANN modeling technique has been used to develop a pharmaceutical formulation via determining multivariate relations between independent parameters and quality properties affected by these parameters. Although artificial intelligence programs are not enough to build and develop formulations by itself, they play a significant role in formulation development.

KEYWORDS: Emulgel; quality by design; artificial neural network; diclofenac sodium; carbopol 940; optimization

1. INTRODUCTION

For a prolonged time, drug delivery through the skin has been a favorable concept due to the large space area and the easy absorbance by the skin, the large exposure to the lymphatic and circulatory networks, and the advantage of this route being non-invasive [1]. Creams, ointments, and gels are considered as semisolid dosage forms purposed for topical implementation. They are not only applied to the skin, but also can be placed on the superficies of the eye, or used vaginally, nasally, or rectally [2].

Emulgel have been gaining importance in pharmaceutical topical semisolid dosage forms since the middle of the 1980s. Their broad usage as pharmaceutical dosage form results from the broad utilize of emulsion systems, particularly for dermatological formula. Emulgels are considered as emulsions, either of the oil-in-water or water-in-oil type, that are gelled via blending with a gelling agent. Water-in-oil emulsions are utilized widely as an emollient action and for the treatment of dryish skin however oil-in-water emulsions are mostly beneficial in general cosmetic action as a water washable drug bases [3]. Despite the numerous advantages that gel has, the main restriction is in the delivery of hydrophobic drugs. Therefore, to pass this limitation emulgels are produced and applied in order to make some hydrophobic therapeutic moiety enjoy the unparalleled properties of gels [4].

Dr. Joseph M. Juran was the first who defined the quality by design. He accepted that almost all quality crises and problems stand out due to the insufficiency of importance assigned to it during product planning [5]. Pharmaceutical industries have been introduced to the Current Good Manufacturing Practices (cGMP) by Food and Drug Administration (FDA) in 2002 [6], and it started QbD and process analytical technology (PAT), and the goal was to build quality into the product from its inception [5]. QbD is a scientific, holistic,

Kalayi M, Yegen G, Üstündağ Okur N, Aksu B. Evaluation of emulgel formulations contain diclofenac sodium via quality by design approach. J Res Pharm. 2022; 26(3): 460-468.

risk-based, systematic, and proactive approach that starts with predefined objectives and assertiveness on the product, procedure understanding, and process control [7]. QbD identifies features that are important for quality from the patient's estimation and converts them into Critical Quality Attributes (CQAs) that the product should possess. In addition, it establishes the limits, the design space, for the Critical Process Parameters (CPPs) and Critical Material Attributes (CMAs) affecting the CQAs [6, 8]. For experimental design, to define the multivariate relations between CQAs and variables and also for optimization software like InForm ANN and GEP (Intellegency, UK), Minitab Statistical Software, MODDE (Umetrics, Sweden) which use mathematical modelling and statistical methods are commonly used in current studies [9, 10].

ANNs are computer programs outlined to show the connections between independent and dependent factors and are competent of demonstrating complex, non-linear connections straightforwardly from the crude data. Unlike classical statistical techniques, such as reaction surface strategy, ANNs do not require the prior assumption of the nature of the relationships between input and output parameters, nor do they require the crude information to be changed earlier to model generation. The basic reason of an ANN model is to predict, with satisfactory exactness, the output value(s) of input vector(s) lying inside the demonstrate space characterized by the training set. subsequently, the objective of ANN displaying is to limit the expectation blunders of records presented to the arrange after preparing has been completed [11].

Diclofenac Sodium is considered as the sodium salt form of diclofenac, it is a benzene acetic acid derivate, and it is a nonsteroidal anti-inflammatory drug (NSAID) it has antipyretic, analgesic, and anti-inflammatory activity. Diclofenac sodium is oftentimes applied for treating acute and chronic arthritic conditions. It is also prescribed for long-term treatment of osteoarthritis, ankylosing spondylitis, and rheumatoid arthritis. There is big attention to improve non-oral dosage forms of diclofenac sodium to reduce its gastric side effects and to supply comparatively harmonious drug levels at the implementation site for long periods. and one of these dosages is the topical delivery of diclofenac sodium [1].

In this study, the QbD approach was implemented in the production of emulgel containing diclofenac sodium and the goal was to build quality into the product from its inception. ANN modelling technique has been used to develop a pharmaceutical formulation via determining multivariate relations between independent parameters and quality properties affected by these parameters.

2. RESULTS and DISCUSSION

2.1. Macroscopic evaluation

The emulsions prepared as described in Section 4.2 are opaque white/cream in color; all except the F7 formulation are homogeneous as shown in Table 1. Reversible phase separation was observed in the F7 formulation.

Table 1. Macroscopic study data formulations F1-F12

Formulation code	Color	Phase separation	Grittiness	Homogeneity
F1	White	None	No	Homogenous
F2	Cream	None	No	Homogenous
F3	Cream	None	No	Homogenous
F4	White	None	No	Homogenous
F5	White	None	No	Homogenous
F6	White	None	No	Homogenous
F7	White	Yes	No	Heterogenous
F8	White	None	No	Homogenous
F9	Cream	None	No	Homogenous
F10	White	None	No	Homogenous
F11	White	None	No	Homogenous
F12	White	None	No	Homogenous

2.2. Globule size and its distribution in emulgel

According to microscopic measurements, the globule size, and the distribution of Emulgel formulations (F1-F12) are given in Table 2. The globule sizes of formulations ranged from 0.700 ± 0.05 to $2.085 \pm 0.05 \mu\text{m}$.

Table 2. Globule size and the distribution of Emulgel formulations F1-F12.

Formulation Code	Mean Diameter (μm)	SD
F1	1.014 $\pm$ 0.05	0.31
F2	2.085 $\pm$ 0.05	0.91
F3	1.050 $\pm$ 0.05	0.42
F4	0.760 $\pm$ 0.05	0.27
F5	0.94 $\pm$ 0.05	0.39
F6	1.062 $\pm$ 0.05	0.44
F7	1.137 $\pm$ 0.05	0.66
F8	0.815 $\pm$ 0.05	0.28
F9	1.017 $\pm$ 0.05	0.46
F10	1.640 $\pm$ 0.05	0.71
F11	0.700 $\pm$ 0.05	0.27
F12	0.709 $\pm$ 0.05	0.20

2.3. pH, electrical conductivity and viscosity measurements

The measured pH, electrical conductivity, and viscosity values of the prepared emulsion formulations are given in Table 3. The pH values of the formulations ranged from 5.9 to 7.1. The Electrical Conductivity values ranged from 20 to 210 $\mu\text{S-1}$. The viscosity ranged between 130 to 5250 Maps.

Table 3. pH, electrical conductivity, and viscosity values of the prepared emulsion formulations

Formulation code	pH value	Electrical Conductivity ($\mu\text{S-1}$)	Viscosity (Maps)
F1	6.3	20	5050
F2	6.6	110	655
F3	7.0	110	5250
F4	7.1	110	5010
F5	6.6	110	4800
F6	6.7	110	4375
F7	6.5	100	5250
F8	6.4	100	3270
F9	6.7	140	130
F10	5.9	150	160
F11	7.0	210	5000
F12	7.1	140	5220

2.4. Optimization studies

The optimum formulation given by the program is shown in Table 4. The optimized formula was prepared as described in Section 4.2 and tested in the laboratory. According to macroscopic evaluation, the optimum emulgel was an opaque white color, and homogeneous with no phase separation or grittiness. The viscosity of the optimum formula is 4600 pH value is 6.7, electrical conductivity is 120 $\mu\text{S-1}$, and particle diameter was also 0.989 μm (SD=0.2403) as shown in Figure 1.

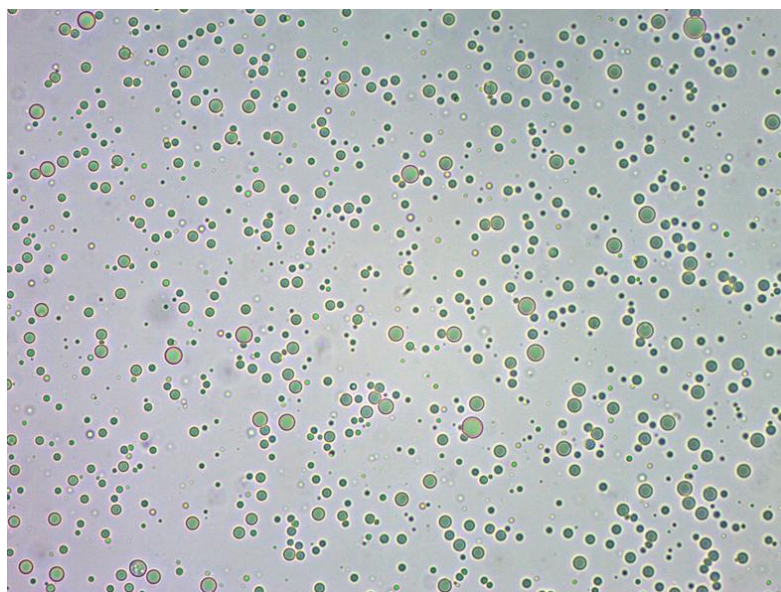


Figure 1. Microscopic display of optimized formulation

Table 4. Optimum formulation obtained from ANN model

Formulation	Content	Amount (g)
Hydrogel	Distilled water	16.05
	EDTA	0.025
	Carbopol940	0.22
	Triethanolamine	0.125
	Tween80	1.25
Oil phase	Span 20	0.25
	Ethanol	1.2
	Propylene Glycol	0.75
	Liquid Paraffin	1.33
	Oleic Acid	4.98
API	DS	1.25

3. DISCUSSION

3.1. Characterization of formulations

In this study the globule size of the formulations ranged from 0.700 ± 0.05 to 2.085 ± 0.05 μm . The globule size in the formulations that have oleic acid are less than the formulations that have liquid paraffin. The pH values of the formulations ranged from 5.9 to 7.1 which show that the pH value of formulations are between skin pH and neutral pH which is appropriate for topical application and acceptable for avoiding the risk of skin irritation. The electrical conductivity values ranged from 20 to 210 μS -1, according to this study the change in oleic acid and liquid paraffin cause change in electrical conductivity. For viscosity the increase in polymer concentration leads to increase in viscosity when it is added with liquid paraffin [12]. However, for oleic acid formulations, the viscosity somewhat did not change with increasing polymer concentration increase in pH of emulgel formulation also leads to increase in viscosity because the used gelling agent

(Carbopol 940) achieves maximum viscosity in neutralized pH level [13]. According to these measurements, polymer concentration and oil type are an important parameter and have a good impact on viscosity of formulations [14,15].

3.2. Optimization studies

Results showed the optimized formula has the required properties including pH level which is considered acceptable for avoiding the risk of skin irritation and convenience of viscosity which is contribute in ease of spreadability. [12,13]

4. CONCLUSION

As mentioned before, since 1980, emulgel has been gaining importance in pharmaceutical topical semisolid dosage forms. Their usage results from the broad utilize of emulsion systems, particularly for dermatological formulation. In this study, diclofenac sodium has been used as an active pharmaceutical ingredient. QbD approach was used in the production of emulgel and the goal was to build quality into the product from its inception. Diclofenac sodium was effectively combined with the jellified emulsion bases having a various gelling factor. ANN modelling technique has been used to develop a pharmaceutical formulation via determining multivariate relations between independent parameters and quality properties affected by these parameters. With the aid of artificial intelligence programs, an optimized emulgel formulation contains Diclofenac Sodium with the required properties was developed. With the help of the ANN program, a formulation has found different than 12 formulations. The formulation was tested and the ideal result were found. These kinds of programs are showing time and financial gains, especially for research and development (R&D) studies. Despite the beneficial role of artificial intelligence programs in formulation development, they are still not enough to build and develop formulations by itself.

5. MATERIALS AND METHODS

5.1. Materials

Diclofenac sodium was kindly donated from Santa Farma, Turkey. EDTA and Carbopol 940 were purchased from Doga Ilac, Turkey. Triethanolamine and Tween 80 were purchased from Merck, Germany. Span 20, Propylene glycol, Liquid Paraffin, ethanol, and Oleic Acid were purchased from Sigma, USA. The used solvents and chemicals were of analytical grade.

5.2. Preparation of emulgel formulations

Determination of emulgel formulation was done according to preformulation studies and formulation parameters considered to be effective and product quality was changed as in material and the using amount of the ingredients. Final formulations assigned to establish the experimental knowledge are given in Table 5. The hydrogel part (water phase) of emulsion gel was prepared by dispersing Carbopol 940 (Gelling agent) in purified water, and then EDTA, Triethanolamine, and Tween 80 were added to them, and in each formulation, the quantity of water and Carbopol 940 was changed. The oil phase was prepared by mixing span 20, Ethanol, Propylene Glycol, with Liquid Paraffin in some formulation and Oleic Acid in other, and the quantity of Liquid Paraffin and Oleic Acid was changed in each formulation. Diclofenac sodium was dissolved in the oil phase. Both oil phase and hydrogel were separately heated to 70 to 80 °C; then the oil phase was added to hydrogel with continuous stirring by using magnetic stirrer (MR Hei-Standard) until it cooled to room temperature (25 °C) [4, 15].

Table 5. Composition of emulgel formulations

Formulation	Content (g)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Hydrogel	Distilled water	16.15	13.65	16.15	13.65	16.15	13.65	16.15	13.65	16.15	13.65	16.15	13.65
	EDTA	0.025	0.025	0.025	0.025	0.025	0.025	0.025	0.025	0.025	0.025	0.025	0.025
	Carbopol940	0.125	0.125	0.125	0.125	0.25	0.25	0.25	0.25	0.0625	0.0625	0.0625	0.0625
	Triethanolamine	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125
	Tween80	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Oil phase	Span 20	0,25	0,25	0,25	0,25	0,25	0,25	0,25	0,25	0,25	0,25	0,25	0,25
	Ethanol	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
	Propylene Glycol	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
	Liquid Paraffin	5	7.5	-	-	5	7.5	-	-	5	7.5	-	-
API	Oleic Acid	-	-	5	7.5	-	-	5	7.5	-	-	5	7.5
	DS	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25

5.3. Physical and chemical tests applied to finished product

Emulgels were evaluated for their macroscopic examination, globule size, and its distribution in emulgel, pH, electrical conductivity measurements, and viscosity.

5.3.1. Macroscopic evaluations

The prepared formulations were examined visually for their homogeneity, color, grittiness, and phase separation [11].

5.3.2. Globule size and its distribution in emulgel

A 1g sample was agitated and dissolved in purified water to obtain a homogeneous dispersion. The dissolved sample was spotted under a binocular light microscope (Carl Zeiss Microscopy GmbH, Germany) with 40x magnification. By using ZEN 2.3 (blue edition) software distribution and mean globule diameter were acquired [16].

5.3.3. pH

The pH of the emulgel was determined by utilizing a digital pH meter (HI-9812-5 pH/EC/TDS/°C Portable Meter, Romania). 1g of the emulgel was dissolved in distilled water, and then the volume was made up to 100 ml (i.e. 1% of prepared emulgel formulations). And then pH examination was performed [15,17].

5.3.4. Electrical conductivity

The electrical conductivity of emulgel was determined by utilizing a digital electrical conductivity meter (HI-9812-5 pH/EC/TDS/°C Portable Meter, Romania). 1g of the emulgel was dissolved in distilled water, and the volume was made up to 100 ml (i.e. 1% of prepared emulgel formulations). And then the electrical conductivity examination was performed [13, 18].

5.3.5. Viscosity

Measurements of viscosity were done by Viscometer VR 3000 (Viscotech, Spain) by choosing the appropriate spindle number (L4) and rpm (100 rpm) at room temperature. An appropriate amount of each emulgel formulation was kept in a suitable beaker, and the spindle groove was dipped, and the rpm was set. Viscosity measurements were started, and the readings were measured after 1 minute, and the viscosity of each formulation was calculated [13, 19].

5.4. Evaluation of data with artificial intelligence programs

Artificial intelligence (AI) is considered as a computer science which is consecrated to developing software with the ability to produce intelligent and advanced calculations in a comparable technique to the regular activity of the human brain. INForm is considered as a neural network software package; besides

that, it also involves fuzzy logic, statistical techniques, genetic algorithms, and visualization capabilities. The software program contains ANOVA (variance analysis) statistics for the model's valuation. The train set r-squared and computed f-ratio studied. A higher train set r-squared value explains that more models have captured variation in the data; a value greater than 70 %, supported by an f-ratio higher than 4, is considered appropriate [20].

In this study, experimental data were evaluated via ANN Modelling. For data evaluation, the amount of distilled water, Carbopol940, Liquid Paraffin, Oleic Acid (the independent formulation parameters) were determined as inputs, and CQAs such as particle size, pH value, conductivity, and viscosity were used as outputs. And the training parameters are given in Table 6. Training results for each property shows convenience with the R-square value higher than 70 %. After the model training optimization process within the program was conducted according to parameters given in Table 7.

Table 6. ANN Model Training Parameters

ANN Model Training Parameters	
Network Model	Diameter- separately
Back Propagation Parameters	
Momentum	0.8
Learning Rate	0.7
Targets	
Target Epochs	1000
Target MS Error	0.0001
Random Speed	1000
ANN Model Training Parameters - Test Data	
Network Model	Diameter- separately
Screen Update Rate	5
Smart Stop	
Minimum Iteration	20
Test Error Weighting	0.1
Iteration Overshoot	200
ANN Model Training Parameters - Type	
Network Model	Diameter - separately
Back Propagation Type	RPROP
ANN Model Training Parameters - Network Structure	
Network Model	Diameter - separately
Number of Hidden Layers	1
Current Hidden Layers	1
1st Hidden Layer	
Number of Nodes	2
Transfer Function	Asymmetric Sigmoid
Output Transfer Function	Linear
* Parameters Apply to All models	

Table 7. Optimization Parameters

Optimization Parameters	
Number of Population	1
Number of Iteration	100
Population size	100
Replacement%	50
Mutation	0.1
Random Seed	1

Acknowledgements: -

Author contributions: Concept – M.K., G.Y., N.Ü.O., B.A.; Design – M.K., G.Y., N.Ü.O., B.A.; Supervision – G.Y., N.Ü.O., B.A.; Resources – M.K., G.Y., N.Ü.O., B.A.; Materials M.K., G.Y., N.Ü.O., B.A.; Data Collection and/or Processing – M.K., G.Y., N.Ü.O., B.A.; Analysis and/or Interpretation – M.K., G.Y., N.Ü.O., B.A.; Literature Search – M.K., G.Y., N.Ü.O., B.A.; Writing – M.K., G.Y., N.Ü.O., B.A.; Critical Reviews – M.K., G.Y., N.Ü.O., B.A.

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