INFLUENCE OF SOLID PARTICLE AND SOYBEAN OIL OF PICKERING EMULSION DICLOFENAC DIETHYLAMINE USING TAGUCHI METHOD

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Abstract

Emulsions stabilized by solid particles are called Pickering emulsions, using diclofenac diethylamine for topical use. In this study, screening for the effect of the type of solid particles (bentonite 3%; Avicel RC-591 2.5%; and kaolin 15%) and soybean oil concentration (10%; 20%, and 30%) using the Taguchi orthogonal array method, with independent variables (type of solid particles and concentration of soybean oil, dependent variables (viscosity, pH, %EE, creaming index, globule size, and % cumulative penetration). The Pickering emulsion with Avicel RC-591 for solid particles produced a stable emulsion during 21 days of storage. Using the Taguchi orthogonal array method, the best formula based on the dependent variable is Formula 4 with physical test results at viscosity 566 cp, pH value 8.18, adsorption efficiency 55.70%, creaming index 100%, globule size 57.1 µm, cell diffusion Franz test at 120 minutes resulted in a cumulative penetration of 69.829%. The penetration power of Formula 4 is better than the emulsion with tween and span emulsifiers, which has a cumulative amount at 120 minutes of 12.609%. Therefore, Avicel RC-591 2.5% solid particles with 10% soybean oil concentration resulted in a stable Pickering emulsion and better penetration than emulsions with tween and span emulsifiers.

***Keywords**: Avicel RC-59, bentonite, diclofenac diethylamine, kaolin, Pickering emulsion, soybean oil*

Introduction

In recent years, Pickering emulsions in topical formulations have garnered significant interest in both academic and industrial fields, particularly in cosmetics and pharmaceuticals. An emulsion is an unstable system because it consists of two or more immiscible liquids with a dispersed phase (Zhang *et al.*, 2022). Therefore, the development of solid-stabilized emulsions, known as Pickering emulsions, has been a notable advancement. These were first discovered by Ramsden (Ramsden, 1904) and Pickering (Pickering, 1907). Pickering emulsions are stabilized by solid particles that adsorb at the interface of the two phases, acting as emulsifiers without the need for amphiphilic surfactants, thereby avoiding the use of potentially toxic surfactants (Wu *et al.*, 2020; Kpogbemabou *et al.*, 2014).

Several studies have shown that effective Pickering emulsifiers include both inorganic and organic particles. These can be combined with different types of oils, such as oleic acid, coconut oil, and sesame oil, as the oil phase. The use of bentonite particles in Pickering emulsions is advantageous due to their very small colloidal particle size and high ion surface capacity, making them excellent adsorbents (Atikah, 2017; Lestari *et al.*, 2022). Kaolin particles exhibit strong dipole interactions, with the siloxane surface being hydrophobic and

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negatively charged and the aluminol surface being hydrophilic and positively charged, resulting in stable oleum in water Pickering emulsions (Kpogbemabou *et al.*, 2014; Kargar *et al.*, 2012). Meanwhile, microcrystalline cellulose (MCC) particles can prevent pickering emulsion instability due to their ability to form interfacial layers around oil droplets (Nurhadi *et al.*, 2022; Kargar *et al.*, 2012).

Topical pain relief formulations often use diclofenac diethylamine in gel or emulgel forms, typically at a concentration of 1%. Diclofenac diethylamine is slightly soluble in water, with a partition coefficient (log P) of 0.853, ionization percentage of approximately ±0.2%, and molecular weight of 369.29 g/mol (Windhu Wardhana *et al.*, 2014; Williams, 2003). It has a bioavailability of 40-60% and a half-life of 2-3 hours (Panchaxari *et al.*, 2013). To increase the penetration and stability of diclofenac diethylamine Pickering emulsions, a combination of solid particles (bentonite, Avicel RC-591, and kaolin) and varying concentrations of soybean oil as the oil phase was used. Soybean oil is chosen due to its long-chain fatty acids and lecithin content, which can lower the surface tension of the emulsion system (Rizqiyah and Estiasih, 2016; Fitriani *et al.*, 2016). The longer the hydrocarbon chain in fatty acids, the greater the lipophilicity (Daniel, 2016). Moreover, soybean oil has been utilized in various drug delivery systems such as dry emulsions, self-emulsifying systems, microemulsions, nanoemulsions, and many emulsions (Rowe *et al.*, 2009).

In this study, screening was conducted using the Taguchi Orthogonal Array method to identify the best formula from the combination of solid particles and soybean oil for each response. Various types of solid particles (bentonite, Avicel RC-591, and kaolin) and oil phases (soybean oil at 10-30% concentration) were used to increase the stability of the emulsion and the penetration of diclofenac diethylamine. Therefore, a study was investigated the effect of soybean oil concentration and solid particles in diclofenac diethylamine Pickering emulsions. This aims to determine the impact of each solid particle on soybean oil compared to conventional emulsions to words of physical stability and penetration efficiency of the formulations.

Research Methods

Materials

Diclofenac diethylamine (Aarti Drugs, India), bentonite (cosmetic grade), Avicel RC-591 (FMC International, Ireland), kaolin (Aeon Procare, India), soybean oil (cosmetic grade), Natrosol 250HX (Zhejiang, China), and distilled water (PT Zenith Pharmaceutical, Indonesia).

Instrumentation

Droplet size analyzer (Malvern, U.S.A), Franz diffusion cell (Iwaki), analytical balance (Ohaus), magnetic stirrer, hotplate stirrer (Thermo Scientific, China), pH meter (Eutech Instrument), viscometer (Rion VT-04F), HPLC (Waters), UV-Vis spectrophotometer (Hitachi), glassware (Pyrex, Japan), and other non-glassware equipment available in the laboratory.

Procedure

Experimental design

Experimental design using the Taguchi orthogonal array method L9 (3^2) with two factors and three levels was conducted using Minitab® software version 18. The solid particle factor consisted of three levels: 3% bentonite, 2.5% Avicel RC-591, and 15% kaolin. The soybean oil factor had three levels: concentrations of 10%, 20%, and 30%. Table 1 presents the formulation of ingredients in the Pickering emulsion.

Table 1. Experimental design Taguchi L9 (3^2) orthogonal array

Factor	Level		
	1	2	3
Solid particles	Bentonite (3%)	Avicel RC-591 (2.5%)	Kaolin (15%)
Concentration of soybean oil (%)	10	20	30

Response: Entrapment efficiency and penetration cumulative

Table 2. Experimental design formula Taguchi orthogonal array method L9

Formulation code	Independent variables		Dependent variables	
	A	B (%)	X1 (%)	X2 (%)
Formula 1	1	1	44.58	67.645±0.049
Formula 2	1	2	59.54	45.426±0.018
Formula 3	1	3	57.10	41.806±0
Formula 4	2	1	55.70	69.829±0.259
Formula 5	2	2	58.78	85.060±0.056
Formula 6	2	3	66.95	67.825±0.008
Formula 7	3	1	56.03	67.486±0.088
Formula 8	3	2	47.30	68.110±0.005
Formula 9	3	3	48.08	65.901±0.138

A: Solid particle; B: Concentration of soybean oil (%); X: Entrapment efficiency (%); X2: penetration cumulative (%)

Preparation of Pickering emulsion and diethylamine diclofenac emulsion

In the emulsion preparation, modifications were made based on the research conducted by Prasanthi et al., (2020). Natrosol was dissolved in distilled water, and then solid particles (3% bentonite, 2.5% Avicel RC-591, and 15% kaolin) as shown in Table 2 were added and dispersed in distilled water for 10 minutes with a homogenizer at 1500 rpm. Diethylamine diclofenac was dispersed into the oil phase for 5 minutes at speeds of 700 - 1000 rpm. Then, the water phase was added to the oil phase and mixed at 2500 rpm for 10 minutes. The nine formulations were prepared in Taguchi orthogonal array, and then compared with a surfactant-based emulsion.

The surfactant-based emulsion consists of 1.5 g of soybean oil as the oil phase, and the surfactants (0.19 g Tween 20 and 0.8 g Span 60). Span 60 for oil phase and tween 20 for water phase. Diethylamine diclofenac active ingredient was added to the oil phase and stirred until homogeneous. Then, added the oil phase to the water phase and stirred until homogeneous.

Stability testing and physical test of Pickering emulsions and diclofenac diethylamine emulsions.

1) Type of Emulsion
   The staining method was performed according to the procedure outlined by (Kemenkes, 1995).
2) pH test
   The pH was conducted accordance to the procedure outlined by the Ministry of Health (Kemenkes, 2020).
3) Viscosity test.
   This test is conducted using a viscometer apparatus, mounted on its clamp horizontally or perpendicular to the clamp direction. The rotor is attached to the viscometer by locking it in the opposite direction to the clockwise direction. The bowl is filled with the emulsion sample to be tested, then the rotor is positioned precisely in the middle of the bowl containing the emulsion, and the apparatus is turned on. The rotor begins to rotate, and the

viscosity indicator needle automatically moves to the right. Once stabilized, the viscosity is read on the scale corresponding to the rotor used. After the viscosity measurement is complete, the viscometer is turned off. Testing is conducted one day after the Pickering emulsion formulation is prepared and again on the 21st day after the emulsion is made.

4) Entrapment efficiency
   The entrapment efficiency is obtained by calculating the amount of drug absorbed in the oil phase, evaluated by centrifuging 1 ml of the formula at a speed of 5000 rpm for 30 minutes. Then, the supernatant (unabsorbed drug) is determined using a UV-VIS spectrophotometer. The percentage of drug entrapment was calculated as $(C_t - C_f)/C_t$, where C_t is the total (entrapped and unentrapped) concentration of diclofenac diethylamine and C_f is the concentration of unentrapped diclofenac diethylamine (Prasanthi *et al.*, 2020).
5) Creaming index.
   In the reaction tube, measure the initial height (H_0) of 20 ml of the Pickering emulsion formula containing diclofenac diethylamine. Then stored at room temperature for 21 days, and the final height (H_1) of the emulsion is measured. The %CI value can be calculated as H_1/H_0 (Alcântara *et al.*, 2019).
6) Characteristics of diclofenac diethylamine Pickering Emulsion.
   The sample is diluted with purified water at a ratio of 10 times its volume, and then measured three times. The globule size is indicated by the D(4,3), and the globule size distribution is assessed based on the span value.
7) Freeze and thaw.
   The physical stability of the diclofenac diethylamine Pickering emulsion can be evaluated using the accelerated freeze & thaw method for 3 cycles. In one cycle, the emulsion is subjected to temperatures of 4–8 °C for 48 hours followed by temperatures of 40–48 °C for another 48 hours, after which phase separation is observed (Falahi *et al.*, 2022).
8) Penetration test.
   In vitro, penetration testing is conducted using a Franz diffusion cell apparatus. The penetration test for the Pickering emulsion and diclofenac diethylamine emulsion is performed using a membrane that mimics the skin, such as a cellophane membrane. The membrane is placed between the donor and receptor compartments, with the stratum corneum facing upwards. Each Pickering emulsion sample, weighing 0.15 g, is then applied to the surface of the membrane in the donor compartment. During the Franz diffusion cell process, the temperature is constant at 37±0.5°C using a water jacket, and stirring is conducted at 600 rpm with a magnetic stirrer to maintain fluid homogeneity. Samples of 3 mL are collected from the receptor compartment solution at 30, 60, 90, and 120 minutes. The sampled solution is immediately replaced with fresh phosphate buffer pH 7.4 to maintain a constant fluid volume. The samples are measured using a UV-Vis spectrophotometer at their respective maximum wavelengths. Subsequently, the flux and cumulative amount of diclofenac diethylamine penetrated per unit area is calculated from the regression equation obtained from the standard curve to determine the concentration of diclofenac diethylamine.

Results and Discussion

Stability test and physical test of Pickering emulsions and diclofenac diethylamine emulsions.

1) Type of emulsion
   The type emulsion of conventional emulsion and Pickering emulsion

diclofenac diethylamine emulsion (Table 3) on day 1 and day 21 using the dilution method and staining method with methylene blue show that all emulsion formulations and Pickering emulsions have an oil-in-water emulsion type without undergoing any changes during storage.

2) pH measurement.
pH measurement of the emulsion aims to determine the acidity and alkalinity level of the formulation to avoid skin irritation. Meanwhile, the diclofenac diethylamine emulsion and Pickering emulsion have a basic pH value or higher than the pH value of normal skin, which ranges from 4.5 to 6.5 (Da Costa *et al.*, 2014).
3) Viscosity measurement.
The viscosity test results of Pickering emulsions vary due to the influence of solid particles used as emulsifiers and variations in the oil phase used. Based on the tests, the oil phase concentration is directly proportional to the viscosity results. The higher of viscosity obtained, the higher concentration of soybean oil used. The highest viscosity of the Pickering emulsion is achieved using Avicel RC-591 with 30% soybean oil because of the mechanism of Pickering emulsion using microcrystalline cellulose (MCC) absorbed onto the surface of virgin coconut oil droplets, thereby covering the droplet surface and forming a thick layer that acts as a barrier to prevent flocculation between virgin coconut oil droplets (Xu *et al.*, 2016). Additionally, increasing the concentration of MCC can increase viscosity to create a continuous phase resembling a gel (Wei *et al.*, 2019). Avicel RC-591 has high viscosity because it contains a sodium carboxymethyl cellulose (sodium CMC). Pickering emulsion formulations with kaolin solid particles have low viscosity due to controlled by the rheological behavior of suspensions with low exponent values and low yield stress (Kpogbemabou *et al.*, 2014). The yield stress value is determined from stable conditions with strain examination over time. The higher the yield stress, the lower the likelihood of particle interaction (Paineau *et al.*, 2011). This decrease in viscosity occurs with all types of solid particles in Pickering emulsions.
4) Entrapment efficiency
Based on the test results (Table 3), the highest absorption efficiency percentage is obtained in formula 6. Meanwhile, Pickering emulsion using 3% bentonite solid particles shows absorption efficiencies ranging from 44.58% to 57.10% when using soybean oil as the oil phase. In a study by Prasanthi et al. (2020), bentonite with a concentration of 4% using oleic acid achieved an absorption efficiency of 91.2%. Using bentonite solid particles combined with different types of oil significantly affects the percentage of absorption efficiency. This is because soybean oil contains long-chain fatty acids and lecithin, which can reduce surface tension in the emulsion system (Rizqiyah and Estiasih, 2016; Fitriani *et al.*, 2016).
5) Indeks creaming
The instability of emulsions can occur during long-term storage. Creaming is the separation of an emulsion into two layers due to gravity. Pickering emulsions require a large amount of energy to release the solid particles from the emulsion system to become more stable (Ahsan *et al.*, 2020). In general, emulsion stability by solid particles involves the accumulation of particles on the oil-water interface in the form of a solid layer with the entire aggregate structure held together by attractive inter-particle forces (Dickinson, 2010). Based on the creaming index test results (Table 3), Formulas 7 to 9 show sedimentation and creaming after 21 days of storage.

This is consistent with the research conducted by Silva et al., (2018), where sedimentation occurred after 24 hours of storage with a concentration of 1.15% kaolin and Brazil nut oil. This is because hydrophobic kaolin particles are adsorbed onto the previously formed O/W emulsion, thus the Pickering emulsion can be influenced by the type of oil phase used. Pickering emulsion using Avicel RC-591 with various concentrations of soybean oil did not experience flocculation or coalescence because Avicel RC-591 is an MCC with a mixture of sodium CMC. Sodium CMC can prevent flocculation because it is absorbed onto the surface of soybean oil droplets forming a thick layer. (Xu *et al.*, 2016). The presence of sodium CMC forms a three-dimensional network between MCC and water, tightly binding soybean oil droplets to prevent phase separation. According to Stokes' law, emulsion stability is directly proportional to viscosity, so this mechanism is consistent because increasing emulsion stability will increase emulsion viscosity (Nurhadi *et al.*, 2022).

6) Characteristics of diclofenac diethylamine Pickering emulsion
   Particle aggregation at the interface prevents droplet shrinkage, flocculation, and coalescence through steric mechanisms, and the stability strength depends on how easily particles can be removed from the interface (Dickinson, 2010). Based on the globule size testing of Pickering emulsion observed from the D(4,3), the smallest size is obtained in Formula 9. However, the globule size of diclofenac diethylamine emulsion using Tween and Span surfactants has a smaller globule size of 0.885 µm. This is because high surfactant content can reduce the size of emulsions or emulsion droplets (Guillot *et al.*, 2009). The globule size of Pickering emulsion is larger than surfactant emulsion because Pickering emulsion is stabilized by particles through particle aggregation at the interface, preventing droplet shrinkage.
7) Freeze and thaw
   The stability test results indicate that after conducting 3 cycles of testing, formulas 3 to 6, which are Pickering emulsions using solid particles of Avicel RC-591 as the emulsifying agent, did not show phase separation.

Table 3. The results of stability testing and physical property examination of Pickering emulsion and diclofenac diethylamine emulsion.

Formula	pH		Viscosity ± SD (Cp)		%EE	%CI	Span	D(4,3)
	Day-1	Day-21	Day-1	Day-21	(%)	(%)		(µm)
Formula 1	9.22±0.03	7.72±0.38	1148±7.6	955±11.8	44.58	100	2.479	112
Formula 2	9.24±0.05	7.81±0.01	1476±25	358±4.2	59.54	100	2.919	106
Formula 3	9.18±0.02	8.01±0.03	3051±2.5	704±2.5	57.10	100	2.77	116
Formula 4	8.18±0.01	7.92±0.02	566±1.7	364±5.5	55.70	100	2.167	57.1
Formula 5	8.36±0.02	7.91±0.04	1652±2.5	355±2.8	58.78	100	2.395	50.7
Formula 6	8.61±0.06	8.26±0.03	3931±60.5	1330±7.0	66.95	100	3.137	42.8
Formula 7	8.48±0.12	7.39±0.06	82±2.5	63±2.5	56.03	75	2.863	19.9
Formula 8	8.22±0.02	7.54±0.01	165±2.5	97±1.3	47.30	81.82	1.887	14.5
Formula 9	8.28±0.04	7.53±0.11	469±2.5	177±1.3	48.08	87.88	1.683	13.3
Diclofenac Diethylamine emulsion	7.26±0.01	7.25±0.01	4525±5.5	4524±4.9	-	100	1.453	0.885

Penetration test

The penetration test is an in vitro examination using the Franz diffusion cell method with cellulose membrane. The penetration test is conducted to determine the comparison of the amount of diclofenac diethylamine penetrated from Pickering emulsion and conventional diclofenac diethylamine emulsion through the skin over a certain time interval. In this study, the penetration test of Pickering emulsion and conventional diclofenac diethylamine emulsion is performed using Franz diffusion cells and magnetic stirring inserted into the diffusion cell apparatus containing phosphate buffer with a volume of 20 ml at a temperature of 37±2 °C. Phosphate buffer pH 7.4 is used because it represents physiological body fluid. The temperature used aims to create conditions similar to human body temperature, and in this case, a thermostat is used to maintain the fluid temperature within the diffusion cell. Meanwhile, the magnetic stirrer functions to homogenize Pickering emulsion and conventional diclofenac diethylamine emulsion penetrating the receiving fluid. The membrane used in this study is a cellulose membrane resembling the human membrane with a surface area of 0.94985 cm^2.

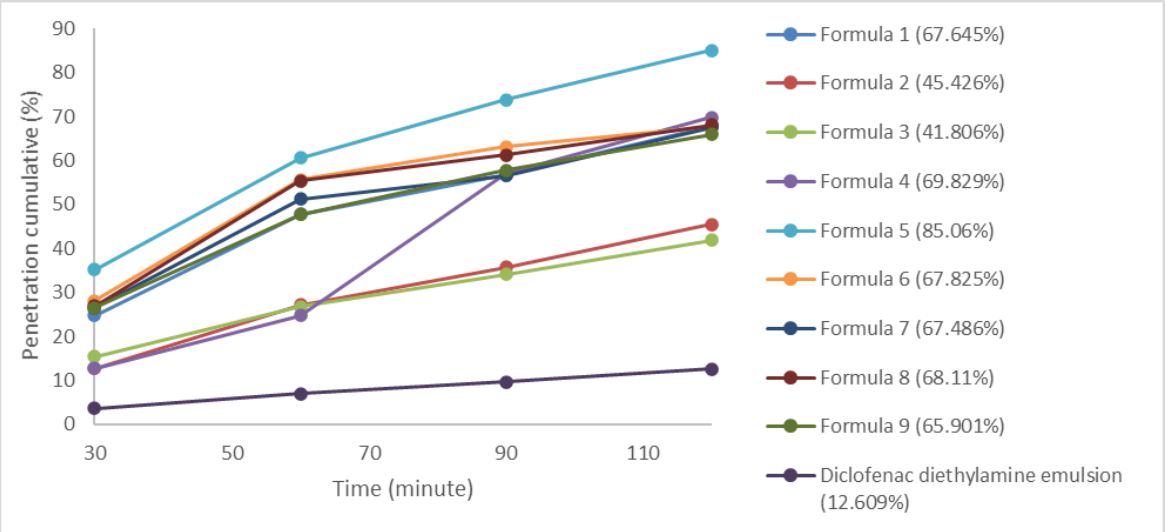

Figure 1. Penetration cumulative percentage

The cumulative penetration percentage graph in Figure 1 shows an increasing curve with time. This indicates that as time increases, the penetration of diclofenac diethylamine into the skin also increases. The initial minute penetration in Formula 5 is higher than that of the other formulas, up to minute 120. With the use of soybean oil, the cumulative penetration percentage of Pickering emulsion with solid bentonite particles is higher.

Based on previous research, the combination of solid particles with oleic acid or sesame oil has a lower penetration percentage compared to using soybean oil, with oleic acid being 17.0% and sesame oil being 32% (Patricia Wahyu Haumahu1, 2011). This can happen because soybean oil contains long-chain fatty acids and lecithin, which can enhance its lipophilic properties (Daniel, 2016). Diclofenac diethylamine Pickering emulsion has higher penetration than diclofenac diethylamine emulsion using Tween and Span as emulsifying agents. The increased absorption of diclofenac diethylamine into the skin, especially in Pickering emulsion formulations, can be attributed to specific interactions of the formula with the skin structure. The adhesion energy of Pickering emulsion water droplets is higher than emulsions stabilized by classic surfactants. Better

adhesion to the skin structure allows for faster drug release into the stratum corneum (Silva *et al.*, 2018). Pickering emulsion provides better penetration than Tween and Span emulsion because the penetrated drug increases with increasing concentrations of soybean oil. Soybean oil contains long-chain fatty acids and lecithin, which can reduce surface tension in the emulsion system (Fitriani *et al.*, 2016; Rizqiyah and Estiasih, 2016). The longer the hydrocarbon chain in fatty acids, the higher their lipophilicity, leading to increased penetration.

Screening of the best formula

To determine the best formula from the changes in product parameter design, the Signal to Noise Ratio (SNR) model is used. The SN Ratio values are obtained from the transformation of several data iterations, representing the quality of variation (Aprilyanti and Suryani, 2020). In this experiment, the parameters measured are the entrapment efficiency and penetration cumulative of solid particles with various concentrations of soybean oil. The criterion in this experiment is "Larger the better," meaning the higher the entrapment efficiency and penetration cumulative values, the better the results.

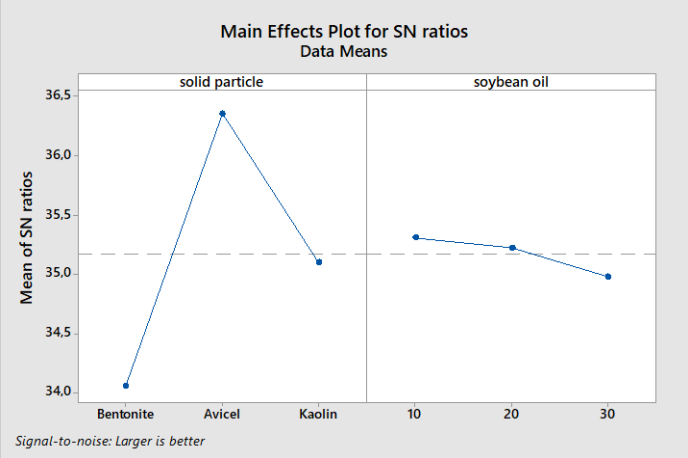

Figure 2. The influence of levels and factors on the signal to noise ratio for Larger is better

From Figure 2, as concluded in Table 4, the factor with the greatest influence on the entrapment efficiency and cumulative penetration of diclofenac diethylamine Pickering emulsions is the solid particles. As determined by selecting the highest SNR values at the most significant factor levels, the best formulation is solid particles Avicel RC-591 combined with 10% soybean oil. Formula 4 has a higher cumulative penetration percentage compared to the diclofenac diethylamine emulsion formula using Tween and Span as emulsifying agents. Therefore, it can be concluded that formula 4 produces a diclofenac diethylamine Pickering emulsion that meets the characteristics and has the best stability.

Table 4. SNR for Larger is better

Factor	Level			Rank
	1	2	3	
Solid Particle	34.05	36.35	35.10	1
Soybean Oil	35.31	35.22	34.98	2

Table 5 indicates that solid particles have a higher contribution compared to soybean oil. Based on the P-value of the solid particle factor is less than 0.05, it is concluded that the solid particles have a significant effect on the entrapment efficiency and penetration cumulative of the diclofenac diethylamine Pickering emulsions. Then, the F-table (0.05, 2, 6) 5.14 is less than the F-value of 10.13, indicating that solid particles significantly affect the entrapment efficiency and penetration cumulative of diclofenac diethylamine Pickering emulsions. The P-value of soybean oil is greater than 0.05; we conclude that soybean oil does not have a significant effect on the entrapment efficiency and penetration cumulative of the diclofenac diethylamine Pickering emulsions. F-value for soybean oil with F-table (0.05, 2, 6) 5.14 is greater than F-Value of 0.40, shows that soybean oil does not significantly affect the entrapment efficiency and penetration cumulative of diclofenac diethylamine Pickering emulsions.

Table 5. Analysis of Variance (ANOVA) test

Source	DF	Seq SS	Contribution	Adj SS	F-Value	P-Value
Solid Particle	2	352.94	80.82%	325.94	10.13	0.027
Soybean oil	2	12.99	3.22%	12.99	0.40	0.692
Error	4	64.38	15.96%	64.38		
Total	8	403.31	100.00%			

Based on the ANOVA results, it can be concluded that solid particles are the most influential factor in determining the entrapment efficiency and penetration cumulative of diclofenac diethylamine Pickering emulsions, while soybean oil does not significantly affect these parameters. The significant effect of solid particles underscores their crucial role in stabilizing the emulsion and enhancing the penetration efficiency.

Conclusions

The formula of Pickering emulsion using 3% bentonite, 2.5% Avicel RC-591, and 15% kaolin solid particles with a combination of soybean oil ranging from 10% to 30% resulted in a stable Pickering emulsion. Based on the Taguchi orthogonal array method, Formula 4 is the best in terms of percent entrapment efficiency and cumulative percent penetration. Furthermore, compared to the diclofenac diethylamine emulsion formulation using Tween and Span as emulsifiers, Formula 4 exhibits higher penetration.

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Conflict of Interest

All authors declare no conflicts of interest and concur with the manuscript's contents.

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