Journal of Advanced Zoology
ISSN: 0253-7214
Volume 45 Issue 01 Year 2024 Page 658:675

Effect Of Surfactant Chain Length Difference In Mixed Surfactant Systems On Self Emulsification Of Poorly Soluble Drug

Shailendra Chouhan[1*,2], **L. S. Chauhan**[1], **Hemant Khambete**[2]

[1*]*Department of Pharmaceutical Sciences, Mohanlal Sukhadia University, Udaipur, Rajasthan, India*
[2]*Faculty of Pharmacy, Medi-Caps University, Indore, Madhya Pradesh, India*

***Corresponding Author:** Shailendra Chouhan*
E-mail: shailendra.chouhan26@gmail.com, Orcid ID: 0000-0002-0121-3329

Article History

Received:
Revised:
Accepted:

Abstract:

In the present investigation the effect of chain length difference (Δn) of different surfactant mixtures was evaluated on self emulsifying capability of self emulsifying drug delivery system of aceclofenac. Three surfactants of Tween series namely Tween 20, Tween 40 and Tween 80 were used for the study. The lipid carrier used was almond oil. Surfactant mixtures were prepared by combining Tween 20 and Tween 80 (Δn=6), Tween 20 and Tween 40 (Δn=4), Tween 40 and Tween 80 (Δn=2) in definite proportion. Pseudoternary diagram study was carried out to determine the surfactant mixture which provides the largest microemulsifying region. The pseudoternary diagram study revealed that the microemulsifying region increases as the difference in chain length increases. So, Tween 80 and Tween 20 were selected for formulation development, the proportion of which is further optimized by simplex lattice design. The formulations were prepared and subjected to different evaluation parameters. The optimized formulation has a particle size of 68.95 nm and zeta potential of -15.3 mV.

Keywords: Self emulsifying drug delivery system, microemulsion, globule size, zeta potential, tyndall effect, simplex lattice design

1. Introduction

Self emulsifying drug delivery systems (SEDDS) are one of the most promising drug delivery system to overcome poor solubility of drugs. These are mixtures of a lipid carrier, surfactants and co-surfactants which spontaneously emulsify on dilution. Self emulsifying drug delivery systems can improve permeability and help to overcome gastro-intestinal instability[1]. Self emulsifying drug delivery system improves drug bioavailability by enhanced gut absorption owing to surfactant action[2]. SEDDS spontaneously disperse in micro-droplets on aqueous dilution which facilitates their lymphatic transport and prevent first pass metabolism[3].
Surfactants are amphiphilic molecules with both polar and non-polar character. Thus surfactants are desired excipients for a number of pharmaceutical preparations owing to their amphiphilic properties[4].Above critical micelle concentration surfactants form a hydrophobic core surrounded by hydrophilic surface in a polar solvent. Poorly soluble drug gets entrapped in the hydrophobic core and gets solubilized[5]. Surfactant when combined together forms mixed surfactant systems which remains an area of research amongst various

researchers[6]. The structural parameters of surfactants, specially the chain length of surfactants has most prominent effect on globule size, permeability, entrapment efficiency and stability of lipid vesicles[7]. Thus behavior of surfactants in mixed miceller systems remains a field of study[8].
Tweens are the most commonly employed nonionic food-grade surfactants. Tweens surfactants differ only in alkyl chain length which makes them ideal for study of chain length effect on emulsification dynamics of self emulsifying drug delivery system[9]. Also it has been found earlier by some workers that mixed surfactant systems have good emulsifying ability as compared to single surfactant[10].
Chai JL et al. studied the solubilization parameters of Tween containing microemulsions and found that the solubilization was highest with Tween 60 followed by Tween 80 and Tween 20[11].
Maulvi FA studied the effect of chain length of sodium caprylate, Tween 20 and Tween 80 as well as effect of molecular weight of block copolymers on cyclosporine microemulsion which was loaded on hydrogel contact lenses[12].
Earlier a different study was carried out in which effect of chain length of Tween surfactants was assessed on self emulsifying ability of poorly soluble drug aceclofenac in which it has been found that as the chain length increases the self emulsifying ability of Tween surfactant increases when a common co-surfactant PEG-400 was used but in this study difference in chain length of Tween surfactants was determined on emulsification ability of self emulsifying system of aceclofenac[13].
Self emulsifying drug delivery system can be employed for BCS Class II and BCS Class IV drugs to enhance their bioavailability due to poor solubility. The excipients used in formulating self emulsifying drug delivery system plays a crucial role in improving absorption and hence bioavailability of poorly soluble drugs[14]. Aceclofenac is one of the BCS Class II drug. Aceclofenac is a non steroidal anti-inflammatory drug which is widely used in treatment of acute and chronic pain associated with various maladies with minimum risk of adverse effect[15]. So aceclofenac is an ideal candidate to study the effect of surfactant mixtures on self emulsifying drug delivery systems.
The aim of present investigation is to study the effect of difference in chain length of Tween surfactants on self emulsifying drug delivery system of aceclofenac.

2. Materials and methods

2.1 Materials

Tween 20, Tween 40 were purchased from Loba Chemie; Tween 80 was purchased from S. D. Fine-Chem Limited. Almond oil was purchased from Dabur India Limited. The model drug aceclofenac was gifted from Wilcure Remedies Pvt. Limited, Indore.
Distilled water was used for construction of pseudoternary phase diagrams and dilutions. All other reagents and chemicals used were of analytical grade.

2.2 Methods

2.2.1 Selection of oil, surfactant and co-surfactant

The selection of oil, surfactant and co-surfactant was based on capacity of oil to solubilize the drug aceclofenac. Additionally, the surfactants and co-surfactants were examined for their capacity to solubilize the selected oil. Aceclofenac in excess amount was added to vials containing test vehicles. The vials were subjected to continuous shaking up to 24 hours. After 24 hours the equilibrated samples were subjected to centrifugation at 5000 rpm for 10-15 minutes to remove the precipitate. The supernatant liquid obtained after centrifugation was filtered using 0.45 µm filter. The dilution of supernatant liquid was done with methanol. The solubility of aceclofenac was determined by the aid of UV-Visible spectrophotometer (UV1800, Shimadzu Corporation, Japan) at λmax of 275 nm[16][17]. All the samples were analyzed in triplicate.

2.2.2 Pseudoternary phase diagram study

The pseudoternary phase diagrams were constructed using almond oil, Smix 1 (Tween 80 and Tween 20), Smix 2 (Tween 40 and Tween 20), Smix 3 (Tween 80 and Tween 40) and water. The compositions of Smix 1, Smix 2 and Smix 3 is shown in Table 1. The phase diagrams were pseudoternary when mixture of two surfactants were used. Oil and Smix were combined in different weight/weight ratios: 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1. This combination of oil and Smix was prepared for all the three Smix. The different combinations of oil and Smix were prepared with the aid of magnetic stirrer with slight heating. The mixtures were then transferred to beaker and water was added in 5% w/w increments till the final mixture contain 95% w/w of water. The addition of water was done along with continuous stirring at 37ºC by the aid of magnetic

stirrer. A visual examination has been done for transparent to translucent mixtures to identify the microemulsifying region. The experiment has been performed thrice and good correlation between all the sets of experiment has been observed[18][19].

Table 1: Different ratios of surfactants used

S. No.	Smix	Surfactant 1	Surfactant 2	Difference in chain length of two surfactants (Δn)	Ratio of Surfactant: Surfactant (Smix)
1.	1	Tween 20	Tween 80	6	1:1
2.	2	Tween 20	Tween 40	4	1:1
3.	3	Tween 40	Tween 80	2	1:1

2.2.3 Simplex lattice experimental design

One of the standard mixture design that is widely used for formulation and optimization is simplex lattice design. In the present study simplex lattice design was used to optimize the formulation components for emulsification time, percentage transmission and drug release in 15 minutes. Seven runs were performed and the design points were represented on an equilateral triangle. The obtained data was fitted to most suitable model. Mathematical equations were generated which defines the relationship of one or combination of components on selected parameters[20][21]. The procedure for determination of emulsification time, percentage transmission and drug release are described under characterization section.

2.2.4 Preparation of self emulsifying drug delivery system of aceclofenac

Oil, surfactant and co-surfactant in a proportion pre-determined by pseudoternary diagram study and simplex lattice experimental design were used for formulation development. The selected ratios of surfactant and co-surfactant were taken and moderately stirred using magnetic stirrer with hotplate. To the prepared mixtures 100 mg of drug was added with continuous stirring on magnetic stirrer till a homogeneous mixture is formed. Finally, the oil is added with slight heating at 40ºC to form an isotropic preconcentrate. The proportion of each component was adjusted in such a way to give a final batch weight of 10 g. Different batches were prepared and subjected to evaluation after being equilibrated for 24 hours[22][23]. The self emulsifying drug delivery systems of aceclofenac were prepared using the excipient proportions as shown in Table 2.

Table 2: Composition of SEDDS formulations of aceclofenac

Formulation code	Drug (mg)	Almond oil proportion	Tween 80 proportion	Tween 20 proportion
F1	100	0.50	0.30	0.20
F2	100	0.30	0.40	0.30
F3	100	0.40	0.30	0.30
F4	100	0.20	0.40	0.40
F5	100	0.40	0.40	0.20
F6	100	0.30	0.30	0.40
F7	100	0.30	0.50	0.20

2.2.5 Characterization of self emulsifying drug delivery system of aceclofenac

2.2.5.1 Emulsification time

1 g of the self emulsifying preconcentrate was taken and filled into a hard gelatin capsule. The capsule is placed in 250 mL of 0.1N HCl, at 50 rpm at 37 ±0.5°C and dispersed using paddle type dissolution apparatus (EDT-406Lx, Electrolab India Private Limited, India) at 50 rpm. The samples are withdrawn at 5 minutes intervals and inspected visually for self-emulsification. The time taken for formation of spontaneous dispersion is noted[24].

2.2.5.2 Percentage transmission

In 100 mL of distilled water 0.1 mL of the self emulsifying preconcentrate was added and stirred at 50 rpm at 37 ±0.5°C for 5 minutes. For each dilution percentage transmission was measured using UV-Visible spectrophotometer (UV1800, Shimadzu Corporation, Japan) at 650 nm. All samples were analyzed in triplicate[25].

2.2.5.3 pH

The pH of all the formulations was determined by using digital pH meter (HI-98107, PHeP®, Hanna, USA). The readings were taken in triplicate and the mean was calculated[26].

Globule size, polydispersity index and zeta potential analysis

A dispersion of self emulsifying preconcentrate was prepared by adding 100 mL of distilled water to 0.1 mL of self emulsifying preconcentrate. The mean globule size. polydispersity index and zeta potential was determined using Malvern Zetasizer (Malvern, Nano Series ZS90, Malvern Instruments Limited, UK) at 25°C. All the measurements were done in triplicate[27].

2.2.5.4 Rheology

The viscosity of prepared self emulsifying pre-concentrate was determined by the aid of Brookfield viscometer DV-II+ (Brookfield Engineering Laboratories, Inc., USA) using spindle SC4-34LV. The assemble was attached to circulating water bath the temperature of which is maintained at 25° ± 0.5°C. All the measurements were done in triplicate[28].

2.2.5.5 Refractive index

The Abbe's refractometer was used to determine the refractive index of the prepared self emulsifying drug delivery system of aceclofenac at 25° ± 1°C. Distilled water was used for calibration of refractometer. All readings were taken in triplicate[29][30].

2.2.5.6 Tyndall effect

1 ml of optimized self emulsifying pre-concentrate, F16 was diluted up to 100 ml with distilled water. A laser beam is passed from the dilution and is visually examined for scattering of light[28][31].

2.2.5.7 Drug content

5 ml of the prepared formulations were dissolved separately in 25 ml of ethanol in a 100 ml volumetric flask and volume was made up t0 100 ml by methanol. The mixture is shaken well for 15-20 minutes and kept for 24 hours. The solution was filtered through 0.45 µm filter paper. The filtrate was assayed spectrophotometrically at 275 nm using UV-Visible spectrophotometer[32][33].

2.2.5.8 In vitro dissolution study

In vitro dissolution study of aceclofenac self emulsifying system at three different pH by using dissolution media as 0.1 M hydrochloric acid pH 1.5, acetate buffer pH 4.5 and phosphate buffer pH 6.8 was performed by the aid of USP II dissolution apparatus (EDT-406Lx, Electrolab India Private Limited, India) at 37 ± 0.5°C. 1 mL of the self-emulsifying preconcentrate was taken in 900 mL of dissolution media rotated at 100 rpm for 240 minutes. 5 mL aliquots were withdrawn at 5, 15, 30, 45, 60, 90, 120, and 240 minutes. The samples were then filtered using 0.45 µm filter. To maintain the sink condition immediate replacement with the equivalent volume of fresh dissolution medium equivalent was done after withdrawal. Samples were analyzed using UV-Visible spectrophotometer at 275 nm and percent dissolution efficiency at 5, 15, 30, 45, 60, 90, 120, 180 and 240 minutes was calculated[34][35].

2.2.5.9 Statistical analysis

One way ANOVA was used to determine significance of obtained data. Throughout the study p-values < 0.05 were considered significant throughout the study. All the measurements were done in triplicate in whole study. The data was analysed using Excel software (Excel 365, Microsoft, USA)[36][37].

3. Results and discussion

3.1 Selection of oil, surfactant and co-surfactant

The selected oil and surfactants are almond oil, Tween 20, Tween 40 and Tween 80. The solubility of aceclofenac in almond oil, Tween 20, Tween 40 and Tween 80 is shown in Table 3.

TABLE 3: Solubility of drug in different vehicles

S. No.	Name of Excipient	Solubility (mean ± SD, n = 3) (mg/mL)
1.	Almond oil	58.89 ± 1.2
2.	Tween 20	142.24 ± 3.1
3.	Tween 40	150.31 ± 3.2
2.	Tween 80	62.42 ± 2.3

3.2 Pseudoternary phase diagram study

The phase diagrams were constructed using almond oil; Tween 20, Tween 40 and Tween 80 combined in 1:1 ratio as shown in Table 1 and water. The pseudoternary phase diagrams are shown in Figure 1, Figure 2 and Figure 3. As it is evident from the pseudoternary diagram study that the largest self emulsifying region is observed when combination of Tween 20: Tween 80 was used as Smix i.e. when the value of difference in chain length is 6 (Δn = 6). When the combination Tween 20: Tween 40 was used as Smix i.e when the value of difference in chain length is 4 (Δn = 4) the self emulsifying region obtained is comparatively less than when Δn = 6, but slightly more than when the combination Tween 40: Tween 80 is used as Smix i.e when difference in chain length is 2 (Δn = 2).

So it is clearly observed that larger self emulsifying region is observed when difference in chain length is more and follows the order Δn = 2 <Δn = 4 <Δn = 6. The reason which can be attributed to this observation is that there is possibility that when two surfactants chain have larger difference in chain length, the smaller chain surfactant can get accommodated easily between the larger chain surfactants and provides better shielding to the hydrophobic core. As the difference in chain length decreases the compact packing of two different chain decreases and the shielding of hydrophobic core decreases which in turn is evident by the smaller self emulsifying region observed[6][38].

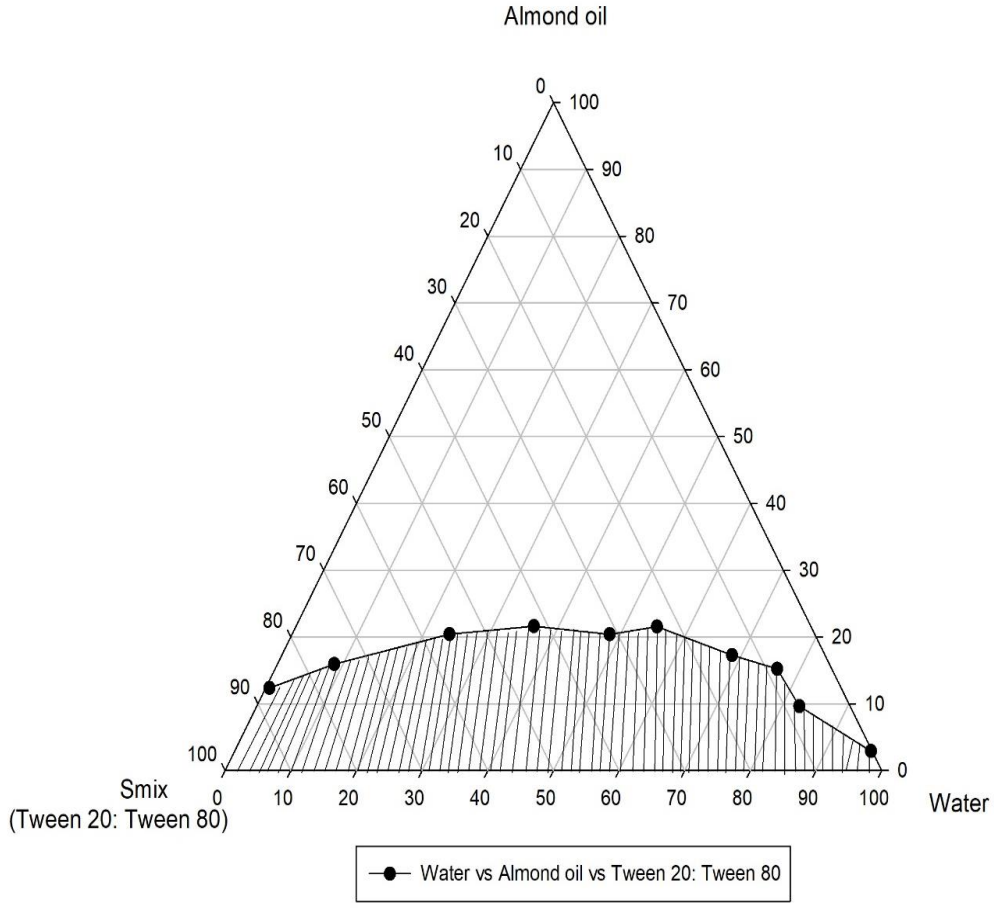

Figure 1: Pseudoternary phase diagram of almond oil, Smix (Tween 20: Tween 80 in 1:1 ratio) and water containing system(the shaded region represents the microemulsifying region)

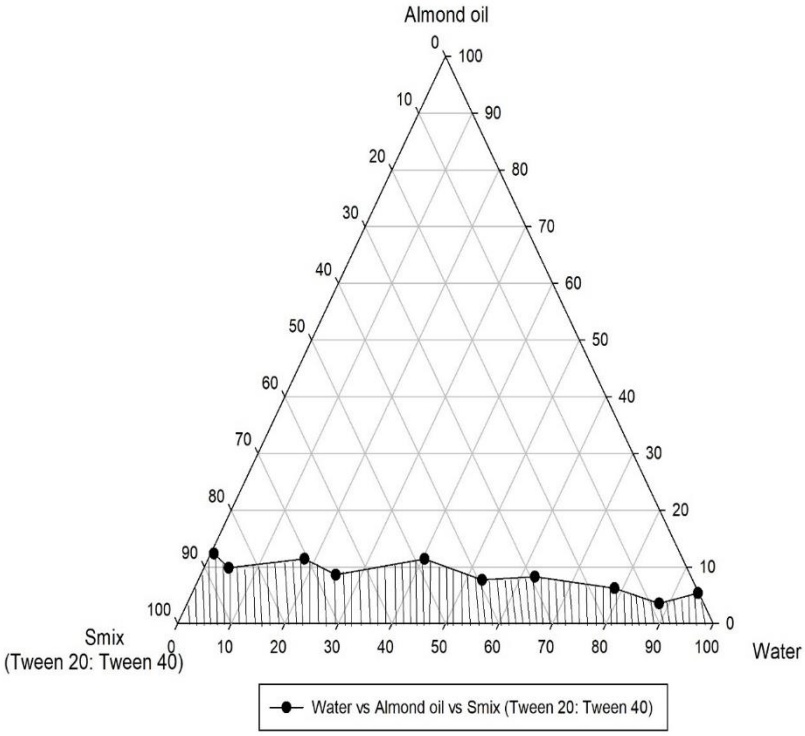

Figure 2: Pseudoternary phase diagram of almond oil, Smix (Tween 20: Tween 40 in 1:1 ratio) and water containing system(the shaded region represents the microemulsifying region)

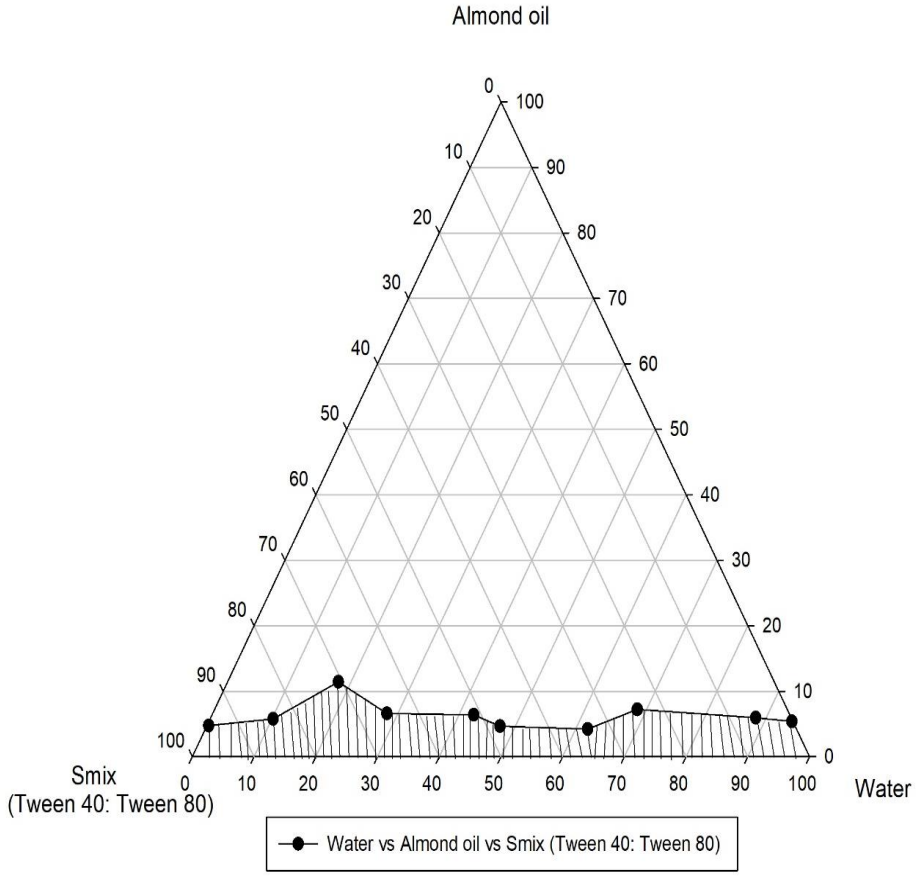

Figure 3: Pseudoternary phase diagram of almond oil, Smix (Tween 40: Tween 80 in 1:1 ratio) and water containing system (the shaded region represents the microemulsifying region)

3.3 Simplex lattice experimental design

3.3.1 Emulsification time

The emulsification time for prepared batches is shown in Table 4. The data is analyzed by regression for mixtures at 95% confidence interval. ANOVA was applied to establish correlation between emulsification time and excipients concentration. Emulsification time depends on relative proportions of almond oil, Tween 80 and Tween 20. The mixture contour plot and mixture surface plot for emulsification time is presented in Figure 4 (A and B). It is evident from mixture contour plot and mixture surface plot that as the proportion of Tween 80 and Tween 20 increases the emulsification time decreases; with increase in proportion of oil it increases. The model fit summary is presented in Table 5, which indicates good fit with R square value of 86.23% and adjusted R square value of 79.34%. ANOVA indicates good correlation between excipients concentration and emulsification time (p value < 0.05). Multiple regression analysis is used to generate equation 1, the high coefficient of oil (62.48) indicates that increase in concentration of oil will lead to increase in emulsification time, negative coefficient of Tween 80 (-17.52) indicates that increase in concentration of Tween 80 leads to decrease in emulsification time, low coefficient of Tween 20 (24.48) indicates that concentration of Tween 20 has comparatively little effect on emulsification time.

YET= 62.48A – 17.52B + 24.48C + 194AB + 344AC - 406BC…… (1)

In above equation A, B, C are almond oil, Tween 80 and Tween 20 respectively. The terms AB, AC and BC shows interaction between main effects A, B and C.

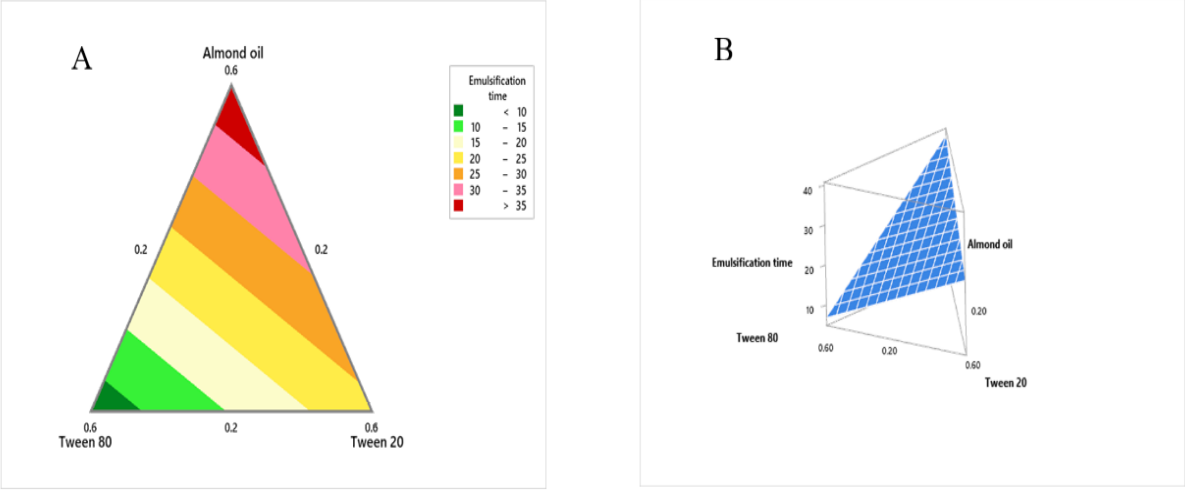

FIGURE 4: A: Mixture contour plot of emulsification time, B: Mixture surface plot of emulsification time

3.3.2 Percentage transmission

The percentage transmission for prepared batches is shown in Table 4. The data is analysed by regression for mixtures at 95% confidence interval. ANOVA was applied to establish correlation between percentage transmission and excipients concentration.

Percentage transmission depends on relative proportions of almond oil, Tween 80 and Tween 20. The mixture contour plot and mixture surface plot for percentage transmission is presented in Figure 5. It is evident from mixture contour plot and mixture surface plot that as the proportion of Tween 80 and Tween 20 increases the percentage transmission increases. The model fit summary is presented in Table 5, which indicates good fit with R square value of 77.86% and adjusted R square value of 66.80%. ANOVA indicates good correlation between excipients concentration and emulsification time (p value < 0.05). Multiple regression analysis is used to generate equation 2, the high coefficient of Tween 80 (106.24) and Tween 20 (89.15) indicates that increase in concentration of Tween 80 and Tween 20 will lead to increase in percentage transmission, relatively low coefficient of almond oil (81.67) indicates that concentration of almond oil has comparatively low effect on percentage transmission.

YPT= 81.67A + 106.24B + 89.15C - 115AB + 11AC + 95BC…… (2)

In above equation A, B, C are almond oil, Tween 80 and Tween 20 respectively. The terms AB, AC and BC shows interaction between main effects A, B and C.

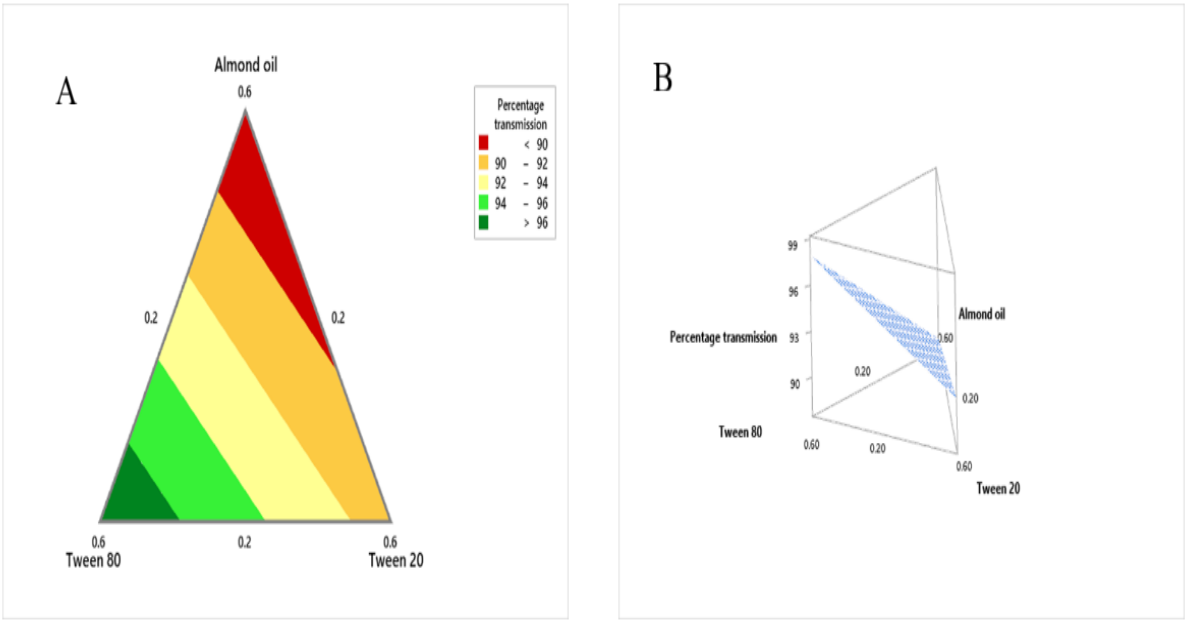

FIGURE 5: A: Mixture contour plot of percentage transmission, B: Mixture surface plot of percentage transmission

3.3.3 Drug release in 15 minutes

The drug release in 15 minutes for prepared batches is shown in Table 8. The data is analysed by regression for mixtures at 95% confidence interval. ANOVA was applied to establish correlation between drug release in 15 minutes and excipients concentration.

Drug release depends on relative proportions of almond oil, Tween 80 and Tween 20. The mixture contour plot and mixture surface plot for drug release is presented in Figure 6. It is evident from mixture contour plot and mixture surface plot that as the proportion of Tween 80 and Tween 20 increases the drug release increases; with increase in proportion of oil it decreases. The model fit summary is presented in Table 9, which indicates good fit with R square value of 85.38% and adjusted R square value of 78.06%. ANOVA indicates good correlation between excipients concentration and emulsification time (p value < 0.05). Multiple regression analysis is used to generate equation 6, the high coefficient of Tween 80 (64.52) and Tween 20 (47.70) indicates that increase in concentration of Tween 80 and Tween 20 will lead to increase in drug release.

$$YDR = 8.74A + 64.52B + 47.70C - 128AB - 246AC + 167BC \quad \ldots\ldots\ldots\ldots (3)$$

In above equation A, B, C are almond oil, Tween 80 and Tween 20 respectively. The terms AB, AC and BC shows interaction between main effects A, B and C.

An overlay contour plot of emulsification time, percentage transmission and drug release in 15 minutes is shown in Figure 7. The overlay plot is plotted by the overlapping of contour plots of emulsification time, percentage transmission and drug release in 15 minutes. The white region in the figure below indicates the feasible region for emulsification time within upper and lower limits of 50 seconds and 1 second respectively, for percentage transmission for upper and lower limits of 100% and 90% respectively, drug release in 15 minutes for upper and lower limits of 50% and 25% respectively.

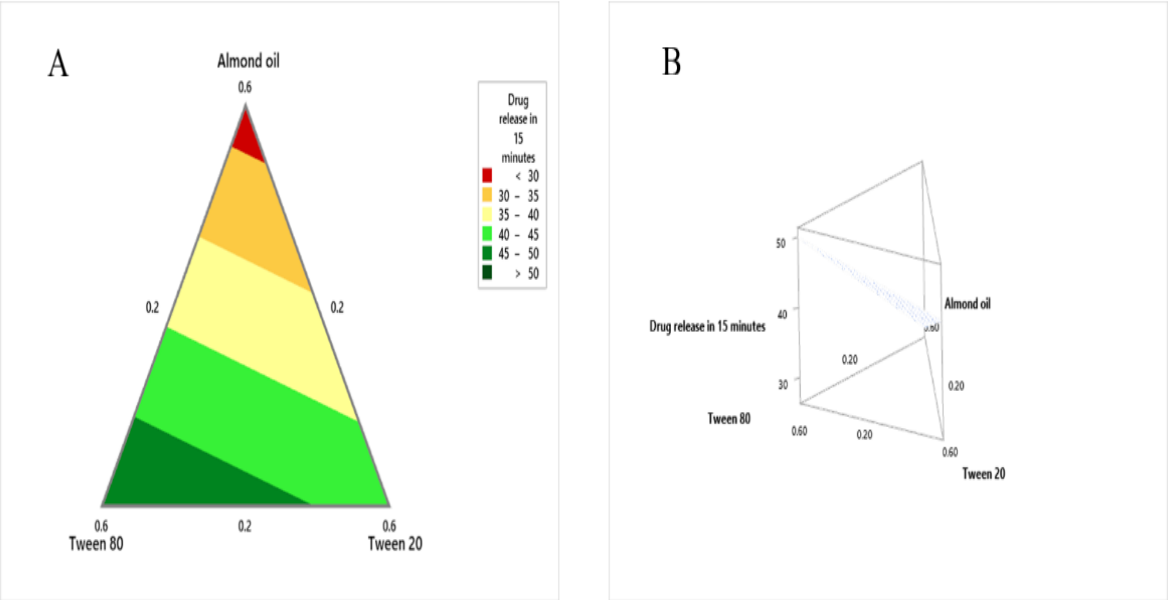

FIGURE 6: A: Mixture contour plot of percentage transmission, B: Mixture surface plot of percentage transmission

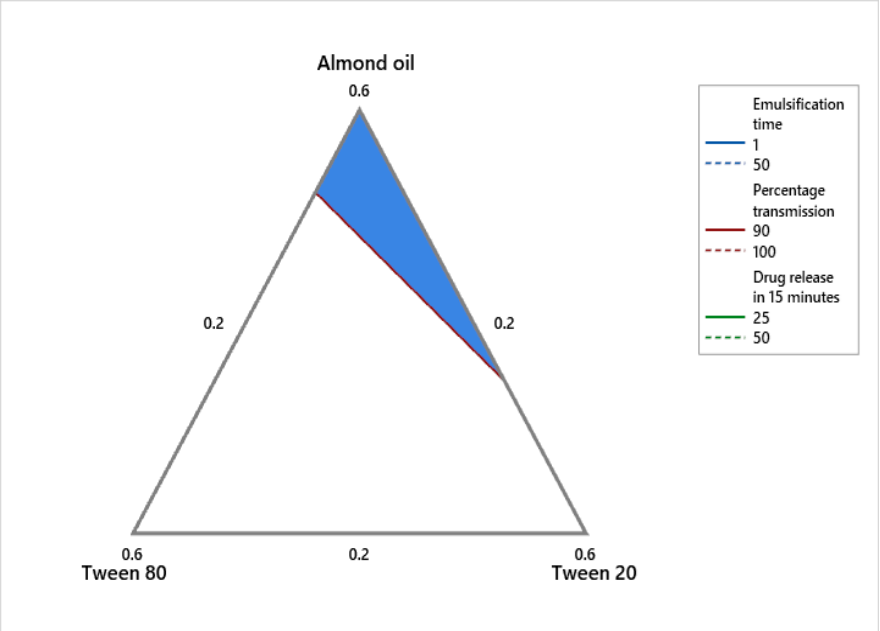

Figure 7: Overlay plot of emulsification time, percentage transmission and drug release in 15 minutes

Table 4: Emulsification time, Percentage transmission and Drug release in 15 minutes of prepared design formulations

Formulation code	Emulsification time (seconds)	Percentage transmission (%)	Drug release in 15 minutes (%)
FD1	34 ± 2	90.47 ± 0.11	32.26 ± 0.33
FD2	10 ± 1	96.28 ± 0.27	47.82 ± 0.41
FD3	30 ± 1	94.21 ± 0.32	43.20 ± 0.57
FD4	8 ± 1	97.72 ± 0.49	50.31 ± 0.25
FD5	24 ± 1	90.21 ± 0.31	44.21 ± 0.32
FD6	20 ± 2	88.34 ± 0.24	30.20 ± 0.39
FD7	36 ± 1	89.26 ± 0.53	34.26 ± 0.42

Table 5: Model summary

Parameter	S	R-sq	R-sq(adj)	PRESS	R-sq(pred)
Emulsification time	5.05776	86.23%	79.34%	243.101	67.27%
Percentage transmission	2.12347	77.86%	66.80%	35.6613	56.23%
Drug release in 15 minutes	3.74493	85.38%	78.06%	142.365	62.89%

3.4 Characterization of self emulsifying drug delivery system of aceclofenac

3.4.1 Emulsification time

It was observed that all the formulations containing got spontaneously dispersed as soon as they got released from the hard gelatin capsule. The time taken for complete emulsification is minimum for formulation F2 and maximum for formulation F1 as shown in Table 6. Formulation F1 consists of a total of 50% of surfactant concentration and 50% of oil concentration; formulation F2 consists of a total of 70% of surfactant concentration and 30% of oil concentration. This indicates that formulations containing high proportion of oil require slightly more time for emulsification[39][19]. The emulsification time for different formulations follows the order F2< F4< F5< F3< F6< F7< F1. This indicates that high surfactant concentration leads to quick dispersion. Also, it was observed that all the formulations got dispersed within one minute, which indicates good dispersibility of the formulations.

3.4.2 Percentage transmission

The percentage transmission of all the prepared formulations is shown in Table 6. It has been observed that the percentage transmission is highest for formulation F2 and lowest for formulation F1. The percentage transmission for all the formulations follows the order F1 < F3 < F6 < F4 < F7 < F5 < F2. The results show that maximum transparency is found when surfactant concentration is 70% and oil proportion is 30%. This may be due to the fact that given quantity of drug gets solubilized completely in 30% oil and 70% (when Tween 80 is 40% and Tween 20 is 30% in Smix) surfactant mixture (Smix) and the same mixture is able to form very fine dispersion. Also it has been observed that when the oil proportion is higher as compared to Smix then the transparency decreases as in case of formulation F15. However it is observed that the transparency of all the formulations was above 90% which is an indicative of good micro emulsification[40].

3.4.3 pH

The pH values of all the formulations were found to be in the range of 7.3± 0.62 to 7.4± 0.53 and do not change upon dilution. This indicates that pH of all the formulations is near to physiological pH of 7.4[41]. The pH values of the prepared formulations are shown in Table 6.

Table 6: Emulsification time of prepared SEDDS formulations

Formulation code	Emulsification time (seconds) (mean ± SD, n=3)	Percentage transmission (%) (mean ± SD, n=3)	pH	Refractive index
F1	33 ± 1	92.31 ± 0.38	7.3 ± 0.62	1.41 ± 0.30
F2	13 ± 2	98.62 ± 0.43	7.3 ± 0.47	1.36 ± 0.30
F3	24 ± 1	94.44 ± 0.27	7.4 ± 0.53	1.39 ± 0.40
F4	14 ± 2	95.57 ± 0.26	7.3 ± 0.47	1.37 ± 0.50
F5	18 ± 1	96.43 ± 0.39	7.3 ± 0.61	1.38 ± 0.30
F6	26 ± 2	95.41 ± 0.47	7.3 ± 0.56	1.42 ± 0.40
F7	29 ± 1	95.64 ± 0.53	7.3 ± 0.38	1.38 ± 0.30

3.4.4 Globule size, polydispersity index and zeta potential analysis

Globule size is an important parameter which determines the competency of self emulsifying system. Finer globule size results in better performance of self emulsifying systems and can lead to achieve good bioavailability. The globule size of the optimized formulation, F2 was found to be 68.95 ± 1.294nm (mean ± SD, n=3) and the polydispersity index was found to be 0.566 ± 0.021 (mean ± SD, n=3). The globule size indicates that the self emulsifying preconcentrate is capable of forming a fine microemulsion upon dilution[42]. The polydispersity index indicates that the formed microemulsion is homogeneous[43]. The size distribution by intensity of the optimized formulation is shown in Figure 8. The apparent zeta potential of the optimized formulation F2 was found to be -15.30 ± 2.08 mV as shown in Figure 9, which indicates that the formed microemulsion possess high stability[44].

Results

		Size (d.n...	% Intensity:	St Dev (d.n...
Z-Average (d.nm):	69.13	Peak 1:	43.07	46.6	16.54
PdI:	0.588	Peak 2:	174.9	40.8	88.54
Intercept:	0.975	Peak 3:	3474	12.6	1390
Result quality	Good				

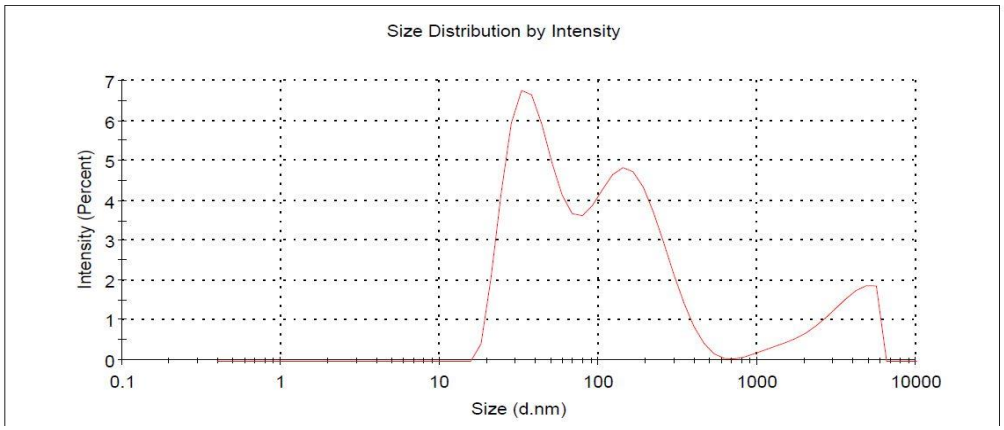

Figure 8: Size distribution by intensity of optimized self-emulsifying system of aceclofenac, average reading (n=3)

Results

		Mean (mV)	Area (%)	St Dev (mV)
Zeta Potential (mV):	-15.3	Peak 1:	-15.2	100.0	7.66
Zeta Deviation (mV):	7.34	Peak 2:	0.00	0.0	0.00
Conductivity (mS/cm):	0.564	Peak 3:	0.00	0.0	0.00
Result quality	Good				

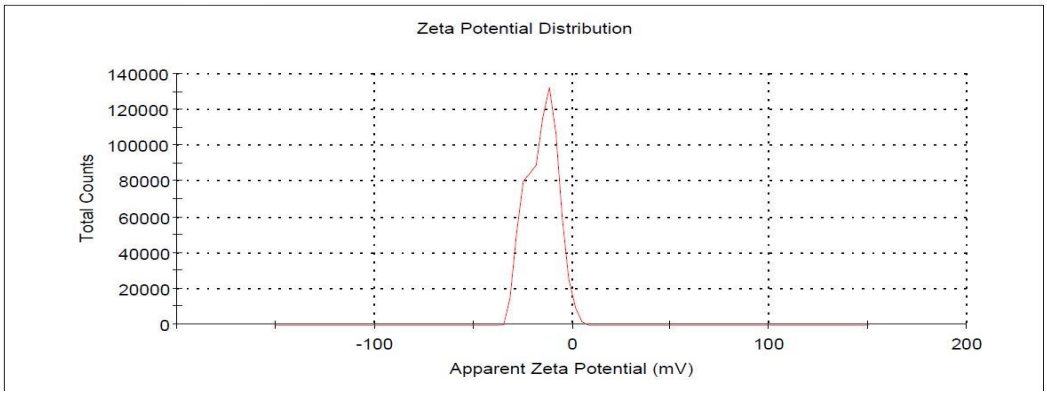

Figure 9: Apparent zeta potential (average) of optimized self-emulsifying system of aceclofenac (n = 3)

3.4.4 Rheology

The viscosity values of different formulations are presented in Table 7 and the graphical representation is shown in Figure 10. The viscosity values in general indicate that the formulations which contain high oil proportion and high Tween 80 concentration have high viscosity values. The viscosity values follows the order F4 < F2 < F7 < F6 < F3 < F5 < F1. Formulation F1 has the highest viscosity values at 20, 60 and 100 rpm and it contains 50% of almond oil and 30% of Tween 80 and 20% of Tween 20. Formulation F18 has lowest viscosity value at 20, 60, 100 rpm and it contains 20% of almond oil and 40% of Tween 80 and 40% of Tween 20. This indicates that increase in concentration of oil leads to increase in viscosity along with high concentration of surfactants[45]. Also it has been observed that as the rotations per minute increases, viscosity decreases which indicates that the prepared formulations are shear thinning systems which ensures the ease of handling[46].

Table 7: Viscosity of prepared SEDDS preconcentrates

Rpm	Viscosity ± Standard deviation (cP)		
	20	**60**	**100**
F1	467 ± 3.6	343 ± 4.4	258 ± 3.8
F2	361 ± 4.5	328 ± 5.2	231 ± 3.2
F3	391 ± 3.3	338 ± 3.6	238 ± 4.3
F4	344 ± 4.7	321 ± 4.5	211 ± 4.5
F5	424 ± 5.3	380 ± 3.7	246 ± 3.6
F6	382 ± 4.2	337 ± 4.6	241 ±3.7
F7	379 ± 3.4	329 ± 3.5	224 ± 4.3

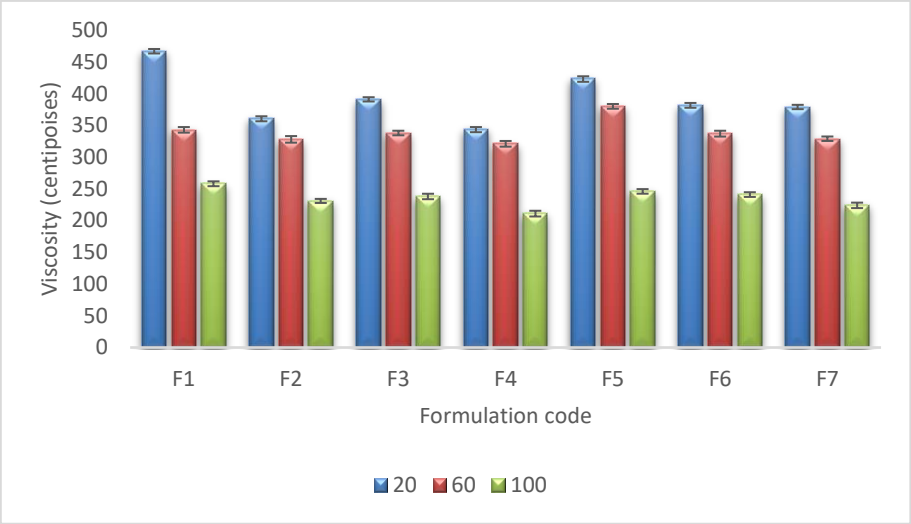

Figure 10: Viscosity of prepared SEDDS preconcentrates

3.4.5 Refractive index

All the self-emulsifying formulations were found to have refractive index in the range of 1.36 to 1.42, which is close to the refractive index of water 1.33. This result indicates that all the formulations were isotropic in nature[30]. The refractive index of different self emulsifying formulations is shown in Table 6.

3.4.6 Tyndall effect

The laser light scattering through all the formulations was observed. It was observed that the laser light illuminated most clearly through formulation F2, which indicates formation of oil in water microemulsion as shown in Figure 11[47].

Figure 11: Laser light scattering through F16

3.4.7 Drug content

The drug content of all the prepared formulations was found to be above 90%. The highest drug content was found in case of formulation F2 i.e. 99.83%. The drug content of prepared self emulsifying drug delivery systems is shown in Table 8.

Table 8: Drug content of the prepared SEDDS formulations

Formulation code	Drug content= Practical content/ Theoretical × 100 (%)
F1	92.37±0.33
F2	99.83±0.27
F3	95.52±0.31
F4	95.11±0.29
F5	96.82±0.49
F6	98.68±0.57
F7	94.72±0.38

3.4.8 In vitro dissolution study

The dissolution profile of aceclofenac from various self emulsifying formulations was determined and compared with dissolution of plain aceclofenac in phosphate buffer pH 6.8, acetate buffer solution pH 4.5, 0.1 M hydrochloric acid solution pH 1.5. In 60 minutes the drug released from the developed aceclofenac formulations F1, F2, F3, F4, F5, F6, F7 was found to be highest in phosphate buffer pH 6.8, the same trend is also observed at the end of 240 minutes. The drug release was found to be 1.01-1.18 times higher at pH 6.8 as compared to pH 1.5 which indicates that with increase in pH drug release increases. The dissolution rate of aceclofenac from the plain drug was found to be quite low as compared to developed formulations. The drug release was found to be highest from formulation F2 and follows the order F1< F2<F3< F4< F5< F6< F7 at pH 6.8. The dissolution data from phosphate buffer pH 6.8, acetate buffer solution pH 4.5, 0.1 M hydrochloric acid solution pH 1.5 is presented in Table 9, Table 10 and Table 11 respectively. The graphical representation is shown in Figure 12, Figure 13 and Figure 14 respectively.

Table 9: In vitro release of aceclofenac from prepared self-emulsifying pre-concentrates in 0.1 M hydrochloric acid solution (pH 1.5)

Time (minutes)	%Cumulative Drug Release*								
	5	15	30	45	60	90	120	180	240
Formulation code									
F1	15.21±0.5	20.42±0.4	54.80±0.4	62.90±0.6	81.91±0.3	81.62±0.3	82.21±0.5	81.71±0.4	81.71±0.5
F2	15.87±0.4	22.22±0.4	54.61±0.3	70.60±0.4	82.41±0.3	82.41±0.5	83.62±0.4	83.66±0.5	83.53±0.3
F3	16.81±0.3	31.21±0.5	55.90±0.3	71.40±0.5	90.31±0.4	92.53±0.4	92.51±0.5	92.62±0.3	92.51±0.3
F4	16.36±0.5	20.51±0.6	45.43±0.4	60.70±0.3	73.80±0.5	73.60±0.5	74.11±0.4	73.52±0.4	73.52±0.5
F5	15.80±0.3	20.31±0.4	50.44±0.5	57.90±0.5	78.91±0.4	78.34±0.5	78.64±0.3	78.91±0.4	78.88±0.3
F6	16.78±0.4	20.81±0.5	50.98±0.6	60.80±0.6	79.90±0.5	79.91±0.4	79.88±0.5	79.90±0.4	79.89±0.4
F7	14.99±0.4	21.47±0.4	54.88±0.5	62.88±0.4	80.87±0.3	80.62±0.4	81.76±0.5	81.66±0.4	81.52±0.5
Plain Aceclofenac	9.71±0.3	12.22±0.4	16.43±0.3	22.40±0.4	38.64±0.3	38.64±0.3	39.21±0.3	39.32±0.3	39.28±0.3

*Data indicate mean±SD (n=3)

Table 10: In vitro release of aceclofenac from prepared self-emulsifying pre-concentratesin acetate buffer solution (pH 4.5)

Time (minutes)	%Cumulative Drug Release*								
	5	15	30	45	60	90	120	180	240
Formulation code									
F1	15.20±0.4	21.30±0.2	56.80±0.5	68.40±0.4	84.43±0.4	84.33±0.4	84.71±0.3	84.68±0.4	84.41±0.3
F2	16.32±0.2	21.50±0.4	62.70±0.4	71.30±0.3	85.70±0.5	85.74±0.2	86.47±0.5	85.73±0.4	85.70±0.3
F3	19.50±0.6	34.50±0.3	60.70±0.6	75.22±0.6	90.54±0.4	90.54±0.2	91.65±0.4	90.73±0.5	90.71±0.4
F4	17.19±0.4	22.16±0.4	49.90±0.3	62.32±0.5	75.21±0.3	75.64±0.3	75.48±0.3	75.71±0.6	75.71±0.3
F5	18.38±0.4	22.30±0.6	53.40±0.5	60.23±0.4	81.24±0.6	82.54±0.3	82.43±0.3	82.24±0.3	82.24±0.5
F6	18.41±0.3	23.32±0.3	54.42±0.5	64.36±0.2	80.89±0.3	80.89±0.3	81.46±0.2	81.32±0.4	81.46±0.4
F7	15.55±0.4	20.85±0.5	57.21±0.4	66.71±0.4	84.79±0.5	84.79±0.3	84.79±0.3	84.79±0.4	84.79±0.5
Plain Aceclofenac	15.40±0.5	23.71±0.4	30.43±0.3	37.97±0.6	42.53±0.3	43.66±0.3	42.68±0.4	43.71±0.3	42.72±0.5

*Data indicate mean±SD (n=3)

Table 11: In vitro release of aceclofenac from prepared self-emulsifying pre-concentrates in phosphate buffer solution (pH 6.8)

Time (minutes) / Formulation code	%Cumulative Drug Release*								
	5	15	30	45	60	90	120	180	240
F1	15.29±0.4	38.41±0.3	55.28±0.5	63.41±0.4	79.43±0.5	81.31±0.3	82.34±0.5	80.92±0.3	82.27±0.5
F2	26.41±0.4	49.38±0.4	70.81±0.6	85.42±0.4	96.43±0.3	96.31±0.4	97.48±0.3	98.76±0.4	98.76±0.4
F3	17.43±0.5	34.23±0.4	51.91±0.4	69.31±0.3	82.88±0.5	83.29±0.4	85.54±0.3	85.54±0.4	85.54±0.5
F4	20.31±0.3	33.43±0.4	54.29±0.5	77.36±0.3	87.29±0.4	87.31±0.4	90.82±0.4	91.53±0.5	91.53±0.4
F5	21.88±0.4	39.71±0.5	61.29±0.4	76.48±0.5	90.76±0.4	93.18±0.6	93.34±0.4	93.78±0.5	93.78±0.4
F6	21.53±0.3	43.29±0.4	68.31±0.4	80.28±0.5	94.31±0.4	95.21±0.4	95.33±0.3	94.27±0.5	95.49±0.4
F7	19.97±0.3	36.28±0.4	58.46±0.5	71.84±0.3	89.31±0.4	89.31±0.6	90.28±0.5	89.46±0.3	90.21±0.3
Plain Aceclofenac	18.22±0.5	26.10±0.4	36.20±0.3	58.28±0.6	58.28±0.4	58.28±0.4	58.28±0.6	58.28±0.5	58.28±0.4

*Data indicate mean±SD (n=3)

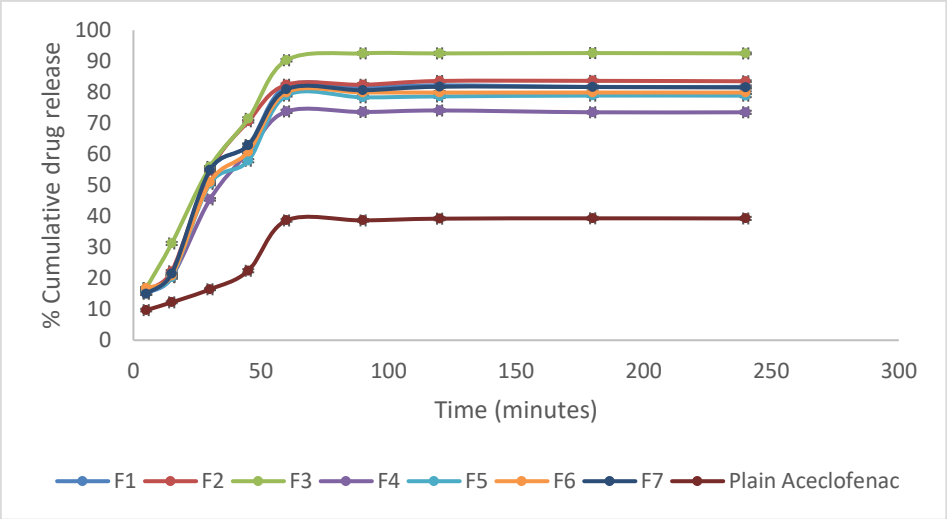

Figure 12: Percentage cumulative drug release of aceclofenac from the prepared formulations and plain drug in 0.1 M hydrochloric acid solution (pH 1.5)

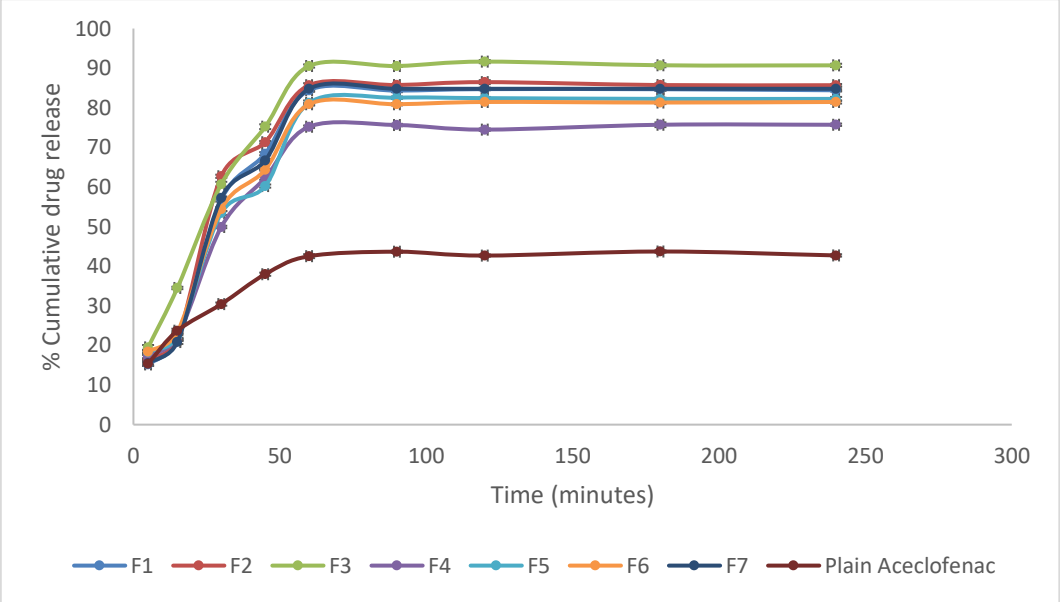

Figure 13: Percentage cumulative drug release of aceclofenac from the prepared formulations and plain drug in acetate buffer solution (pH 4.5)

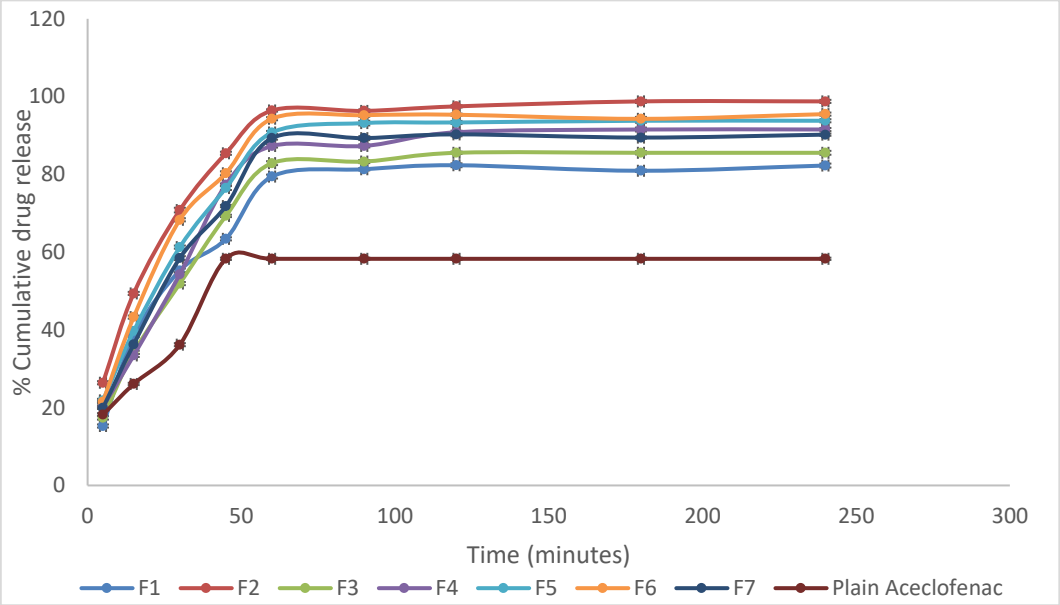

Figure 14: Percentage cumulative drug release of aceclofenac from the prepared formulations and plain drug in phosphate buffer solution (pH 6.8)

4. Conclusion

The effect of difference in chain length of different non-ionic surfactants of Tween series has been investigated on self emulsifying efficiency of aceclofenac SEDDS. Homologous Tween surfactants mixtures with varying chain length were selected for the pseudoternary diagram study, indicated that the largest self emulsifying region is observed for Tween 80 and Tween 20 combination with chain length difference of six; as larger the difference between the chain length more stable micellization will occur by incorporation of smaller chain length surfactants between larger chain length surfactants, resulting in compact packing and protection of hydrophobic core from outside aqueous environment resulting in formation of stabilized and fine microemulsion[48]. Optimization was done using Simplex lattice design on the basis of emulsification time, percentage transmission and drug release in 15 minutes. Seven SEDDS formulations were prepared using overlay plot and pseudoternary diagram and then evaluated. The stability of optimized microemulsion so formed is also found good with a zeta potential value of -15.30 mV.

Acknowledgement: We acknowledge Head of Department, Department of Pharmaceutical Sciences, Mohanlal Sukhadia University, Udaipur for providing facilities.

Conflicts of interest: None

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Balakumar K, Raghavan CV, Selvan NT, Rahman SMH. Self emulsifying drug delivery system : Optimization and its prototype for various compositions of oils , surfactants and. JOPR J Pharm Res [Internet]. 2013;6(5):510–4. Available from: http://dx.doi.org/10.1016/j.jopr.2013.04.031
2. Bernkop-schnürch A, Jalil A. NU. J Control Release [Internet]. 2017; Available from: http://dx.doi.org/10.1016/j.jconrel.2017.12.027
3. Echeverry SM, Rey D, Valderrama IH, Araujo BV de, Aragón DM. Development of a self-emulsifying drug delivery system (SEDDS) to improve the hypoglycemic activity of Passiflora ligularis leaves extract. J Drug Deliv Sci Technol. 2021;64(January).
4. Bnyan R, Khan I, Ehtezazi T, Saleem I, Gordon S, O'Neill F, et al. Surfactant Effects on Lipid-Based Vesicles Properties. J Pharm Sci [Internet]. 2018;107(5):1237–46. Available from: https://doi.org/10.1016/j.xphs.2018.01.005

5. Schreier S, Malheiros SVP, De Paula E. Surface active drugs: Self-association and interaction with membranes and surfactants. Physicochemical and biological aspects. Biochim Biophys Acta - Biomembr. 2000;1508(1–2):210–34.
6. Schulz PC, Rodríguez JL, Minardi RM, Sierra MB, Morini MA. Are the mixtures of homologous surfactants ideal? J Colloid Interface Sci. 2006;303(1):264–71.
7. Groth C, Nydén M, Holmberg K, Kanicky JR, Shah DO. Kinetics of the self-assembly of gemini surfactants. J Surfactants Deterg. 2004;7(3):247–55.
8. Mahdi ES, Sakeena MH, Abdulkarim MF, Abdullah GZ, Sattar MA, Noor AM. Effect of surfactant and surfactant blends on pseudoternary phase diagram behavior of newly synthesized palm kernel oil esters. Drug Des Devel Ther. 2011;5:311–23.
9. Szymczyk K, Zdziennicka A, Jańczuk B. Adsorption and Aggregation Properties of Some Polysorbates at Different Temperatures. J Solution Chem [Internet]. 2018;47(11):1824–40. Available from: https://doi.org/10.1007/s10953-018-0823-z
10. Zhang H, Feng F, Li J, Zhan X, Wei H, Li H, et al. Formulation of food-grade microemulsions with glycerol monolaurate: Effects of short-chain alcohols, polyols, salts and nonionic surfactants. Eur Food Res Technol. 2008;226(3):613–9.
11. Chai JL, Liu N, Bai TT, Zhang HM, Liu NN, Wang D. Compositions and Physicochemical Properties of Tween Type Surfactants-Based Microemulsions. J Dispers Sci Technol. 2014;35(3):441–7.
12. Maulvi FA, Desai AR, Choksi HH, Patil RJ, Ranch KM, Vyas BA, et al. Effect of surfactant chain length on drug release kinetics from microemulsion-laden contact lenses. Int J Pharm [Internet]. 2017;524(1–2):193–204. Available from: http://dx.doi.org/10.1016/j.ijpharm.2017.03.083
13. Chouhan S, Chauhan LS. Effect Of Surfactant Chain Length On Emulsification Dynamics Of Self Emulsifying Formulation Of Poorly Soluble Drug. Curr Drug Deliv. 2021;18:1–15.
14. Yan B, Ma Y, Guo J, Wang Y. Self-microemulsifying delivery system for improving bioavailability of water insoluble drugs. J Nanoparticle Res. 2020;22(1).
15. Yang JH, Suk KS, Lee BH, Jung WC, Kang YM, Kim JH, et al. Efficacy and safety of different aceclofenac treatments for chronic lower back pain: Prospective, randomized, single center, open-label clinical trials. Yonsei Med J. 2017;58(3):637–43.
16. Liu Y, Liu M, Yan H, Liu H, Liu J, Zhao Y, et al. Enhanced solubility of bisdemethoxycurcumin by interaction with Tween surfactants: Spectroscopic and coarse-grained molecular dynamics simulation studies. J Mol Liq [Internet]. 2021;323:115073. Available from: https://doi.org/10.1016/j.molliq.2020.115073
17. Jianxian C, Saleem K, Ijaz M, Ur-Rehman M, Murtaza G, Asim MH. Development and in vitro evaluation of gastro-protective aceclofenac-loaded self-emulsifying drug delivery system. Int J Nanomedicine. 2020;15:5217–26.
18. Atef E, Belmonte AA. Formulation and in vitro and in vivo characterization of a phenytoin self-emulsifying drug delivery system (SEDDS). Eur J Pharm Sci. 2008;35(4):257–63.
19. Balakrishnan P, Lee BJ, Oh DH, Kim JO, Lee YI, Kim DD, et al. Enhanced oral bioavailability of Coenzyme Q10 by self-emulsifying drug delivery systems. Int J Pharm. 2009;374(1–2):66–72.
20. Prajapat MD, Patel NJ, Bariya A, Patel SS, Butani SB. Formulation and evaluation of self-emulsifying drug delivery system for nimodipine, a BCS class II drug. J Drug Deliv Sci Technol [Internet]. 2017;39(October 2018):59–68. Available from: http://dx.doi.org/10.1016/j.jddst.2017.02.002
21. Das SS, Singh A, Kar S, Ghosh R, Pal M, Fatima M, et al. Application of QbD Framework for Development of Self-Emulsifying Drug Delivery Systems [Internet]. Pharmaceutical Quality by Design. Elsevier Inc.; 2019. 297–350 p. Available from: http://dx.doi.org/10.1016/B978-0-12-815799-2.00015-0
22. Hosny KM, Al Nahyah KS, Alhakamy NA. Self-Nanoemulsion Loaded with a Combination of Isotretinoin, an Anti-Acne Drug, and Quercetin: Preparation, Optimization, and In Vivo Assessment. Pharmaceutics. 2020;13(1):46.
23. Salawi A. Self-emulsifying drug delivery systems: a novel approach to deliver drugs. Drug Deliv [Internet]. 2022;29(1):1811–23. Available from: https://doi.org/10.1080/10717544.2022.2083724
24. Utami D, Meliana Y, Helmiyati, Budianto E. In-Vitro Dissolution and Characterization of Self-Emulsifying Drug Delivery System of Artemisinin for Oral Delivery. J Phys Conf Ser. 2021;
25. Zewail MB, El-Gizawy SA, Osman MA, Haggag YA. Preparation and In vitro characterization of a novel self-nano emulsifying drug delivery system for a fixed-dose combination of candesartan cilexetil and hydrochlorothiazide. J Drug Deliv Sci Technol [Internet].2021;61(November 2020):102320.
26. Bennett-Lenane H, Jørgensen JR, Koehl NJ, Henze LJ, O'Shea JP, Müllertz A, et al. Exploring porcine gastric and intestinal fluids using microscopic and solubility estimates: Impact of placebo self-

emulsifying drug delivery system administration to inform bio-predictive in vitro tools. Eur J Pharm Sci. 2021;161(February).
27. Shewaiter MA, Hammady TM, El-Gindy A, Hammadi SH, Gad S. Formulation and characterization of leflunomide/diclofenac sodium microemulsion base-gel for the transdermal treatment of inflammatory joint diseases. J Drug Deliv Sci Technol [Internet]. 2021;61(July):102110. Available from: https://doi.org/10.1016/j.jddst.2020.102110
28. Ansari MJ, Alnakhli M, Al-Otaibi T, Meanazel O Al, Anwer MK, Ahmed MM, et al. Formulation and evaluation of self-nanoemulsifying drug delivery system of brigatinib: Improvement of solubility, in vitro release, ex-vivo permeation and anticancer activity. J Drug Deliv Sci Technol [Internet]. 2020;102204. Available from: https://doi.org/10.1016/j.jddst.2020.102204
29. Manish Upadhyay, Vijay Ghori, M.M. Soniwala. Design And Optimization of Midazolam Loaded Microemulsion Using Quality by Design (Qbd) Assisted Statistical Modelling. J Pharm Negat Results. 2022;13(9):765–76.
30. Bhattacharya S. Double w/o/w self-nano emulsifying drug delivery system of imatinib mesylate for colon cancer treatment. J Mol Liq [Internet]. 2021;341:117368. Available from: https://doi.org/10.1016/j.molliq.2021.117368
31. Gibaud S, Attivi D. Microemulsions for oral administration and their therapeutic applications. Expert Opin Drug Deliv. 2012;9(8):937–51.
32. Geethanjali K, Vaiyana RC. Formulation and evaluation of self nano-emulsifying drug delivery system of ezetimibe for dissolution rate enhancement. Int J Res Pharm Sci. 2020;11(2):1294–301.
33. Cao M, Zhan M, Wang Z, Wang Z, Li XM, Miao M. Development of an orally bioavailable isoliquiritigenin self-nanoemulsifying drug delivery system to effectively treat ovalbumin-induced asthma. Int J Nanomedicine. 2020;15:8945–61.
34. Banik S, Halder S, Sato H, Onoue S. Self-emulsifying drug delivery system of (R)-α-lipoic acid to improve its stability and oral absorption. Biopharm Drug Dispos. 2021;42(5):226–33.
35. Batool A, Arshad R, Razzaq S, Nousheen K, Kiani MH, Shahnaz G. Formulation and evaluation of hyaluronic acid-based mucoadhesive self nanoemulsifying drug delivery system (SNEDDS) of tamoxifen for targeting breast cancer. Int J Biol Macromol [Internet]. 2020;152:503–15.
36. Dizdarević A, Marić M, Shahzadi I, Ari Efiana N, Matuszczak B, Bernkop-Schnürch A. Imine bond formation as a tool for incorporation of amikacin in self-emulsifying drug delivery systems (SEDDS). Eur J Pharm Biopharm. 2021;162(February):82–91.
37. Abdulkarim M, Sharma PK, Gumbleton M. Self-emulsifying drug delivery system: Mucus permeation and innovative quantification technologies. Adv Drug Deliv Rev [Internet]. 2019;142:62–74. Available from: https://doi.org/10.1016/j.addr.2019.04.001
38. De M, Bhattacharya SC, Moulik SP, Panda AK. Interfacial composition, structural and thermodynamic parameters of water/(surfactant+n-butanol)/n-heptane water-in-oil microemulsion formation in relation to the surfactant chain length. J Surfactants Deterg. 2010;13(4):475–84.
39. Laddha P, Suthar V, Butani S. Development and optimization of self microemulsifying drug delivery of domperidone. Brazilian J Pharm Sci. 2014;50(1):91–100.
40. Rasoanirina BNV, Lassoued MA, Kamoun A, Bahloul B, Miladi K, Sfar S. Voriconazole-loaded self-nanoemulsifying drug delivery system (SNEDDS) to improve transcorneal permeability. Pharm Dev Technol [Internet]. 2020;25(6):694–703. Available from: http://dx.doi.org/10.1080/10837450.2020.1731532
41. Zhang X, Meng L, Lu Q, Fei Z, Dyson PJ. Targeted delivery and controlled release of doxorubicin to cancer cells using modified single wall carbon nanotubes. Biomaterials [Internet]. 2009;30(30):6041–7.
42. Lupo N, Jalil A, Nazir I, Gust R, Bernkop-Schnürch A. In vitro evaluation of intravesical mucoadhesive self-emulsifying drug delivery systems. Int J Pharm [Internet]. 2019;564(January):180–7. Available from: https://doi.org/10.1016/j.ijpharm.2019.04.035
43. Izham MNM, Hussin Y, Aziz MNM, Yeap SK, Rahman HS, Masarudin MJ, et al. Preparation and characterization of self nano-emulsifying drug delivery system loaded with citraland its antiproliferative effect on colorectal cells in vitro. Nanomaterials. 2019;9(7).
44. Wolf JD, Kurpiers M, Götz RX, Zaichik S, Hupfauf A, Baecker D, et al. Phosphorylated PEG-emulsifier: Powerful tool for development of zeta potential changing self-emulsifying drug delivery systems (SEDDS). Eur J Pharm Biopharm [Internet]. 2020;150(March):77–86. Available from: https://doi.org/10.1016/j.ejpb.2020.03.004
45. Madan JR, Patil K, Awasthi R, Dua K. Formulation and evaluation of solid self-microemulsifying drug delivery system for azilsartan medoxomil. Int J Polym Mater Polym Biomater [Internet].

2021;70(2):100–16. Available from: https://doi.org/10.1080/00914037.2019.1695206
46. Gao Y, Lei Y, Wu Y, Liang H, Li J, Pei Y, et al. Beeswax: A potential self-emulsifying agent for the construction of thermal-sensitive food W/O emulsion. Food Chem [Internet]. 2021;349(January):129203.
47. Fan Q, Zhao R, Yi M, Qi P, Chai C, Ying H, et al. Ti3C2-MXene composite films functionalized with polypyrrole and ionic liquid-based microemulsion particles for supercapacitor applications. Chem Eng J [Internet]. 2021;428(May 2021):131107. Available from: https://doi.org/10.1016/j.cej.2021.131107
48. Trawińska A, Hallmann E, Mędrzycka K. The effect of alkyl chain length on synergistic effects in micellization and surface tension reduction in nonionic gemini (S-10) and anionic surfactants mixtures. Colloids Surfaces A Physicochem Eng Asp [Internet]. 2016;506:114–26. Available from: http://dx.doi.org/10.1016/j.colsurfa.2016.06.001