Biomedical Letters ISSN 2410-955X DOI: https://doi.org/10.47262/BL/8.2.20220225

Research article
2022 | Volume 8 | issue 2 | Pages 170-176

ARTICLEINFO

Received
February 25, 2022
Revised
April 30, 2022
Accepted
June 13, 2022

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Keywords
Bending constant
Micelles
NSAIDs
Solubility
Sulindac

How to Cite
Ullah F, Ullah S, Khan MFA, Tareen FK, Khan NH. Enhancement in Aqueous solubility of Sulindac Medicine by Using Micellar Solution of Ionic and Non-ionic Surfactants. Biomedical Letters 2022; 8(2):170-176.

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Enhancement in aqueous solubility of sulindac medicine by using the micellar solution of ionic and non-ionic surfactants

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Abstract

In the science of pharmacology, solubility plays a crucial role in the efficacy and bioavailability of the drug. Utilizing solubility features to improve the bioavailability and pharmacological effect of diverse weakly soluble substances, is an arduous task for pharmaceutical experts and researchers. Particle size, surface area, physicochemical qualities, physical forms of drugs, solvents and surfactant usage are parameters that influence solubility. The objective of the current study was to enhance the solubility of the non-steroidal anti-inflammatory drug (NSAID): Sulindac. The micellar solutions method was employed with different surfactants to increase the efficiency. Both nonionic (Tween 20, 40, 60 and 80 with Brij 30, 35 and 56) and ionic (SDS, SDBS, CTAB, TTAB and DTAB) surfactants were investigated for their effect on drug solubility in aqueous solution. Various parameters of surfactant solutions such as aggregation number, micelle-water partition coefficient (K_M), molar solubilization ratio (MSR), Gibbs energy of solubilization (ΔG°_{s}), size of micelle and binding constant of the drug micelles were measured. Finding reveals that the use of mentioned surfactant is an excellent approach to enhancing the solubility of sulindac. Furthermore, the present work provides an understanding of the relation of aqueous solubility with aggregation number and structure of surfactants used.

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Introduction

Water solubility may be used to study a variety of factors, including molecule size, shape, intermolecular interactions, structure, and mechanism of pharmacological action. Physicochemical characteristics such as size, shape, surface area, solvent, physical form of the drug, pH, temperature, and surfactant type all affect drug solubility [1]. The balance of intermolecular forces between the drug and the solvent, as well as the change in entropy during salvation, all affect a medication's solubility in an aqueous solution [2]. There are several drug delivery systems available; however, the medicine must be solubilized before administration [3]. According to estimations around 40% of pharmaceutically active chemicals are insoluble in water and have a low bioavailability [4]. Pharmaceutical scientists and chemists have a difficult problem in improving the aqueous solubility of weakly water-soluble medicines. When we consider how to create an emulsion to increase the medication's water solubility, we see that the number of components necessary for drug delivery is rather little. This enhances their pharmacokinetics and pharmacodynamics [5][6]. As a result, scientists are altering the solvent's polarity/structure by the addition of various lipophilic compounds to enhance its medicinal dissolving capabilities. Aqueous formulations including a variety of surfactants are considered to be superior for dissolving a large proportion of medicine [7, 8]. Another advantage of using emulsions to increase the solubility and bioavailability of medications is that they are simple to manufacture on a large scale, have low toxicity, and remain longer in the circulatory system [9]. NSAIDs are primarily used to treat osteoarthritis and inflammation, as well as to inhibit the body from manufacturing prostaglandins [10]. Due to the risk of gastrointestinal (GI) harm, NSAIDs in the salt form are seldom used. NSAIDs have been associated with increased creatine levels, hypercalcemia, interstitial nephritis, and renal injury [11, 12]. Due to the adverse gastrointestinal (GI) and cardiovascular (CV) effects of nonsteroidal anti-inflammatory medications (NSAIDs), their use is limited [13]. Nonselective NSAIDs affect the kidneys, resulting in nephrotic syndrome, peripheral sickness, and necrosis, among other symptoms. They are particularly effective in decreasing antihypertensive effects, serum aldosterone elation, and sodium confinement [14, 15]. Nonsteroidal anti-inflammatory medicines (NSAIDs) usage increases blood pressure by 5mmHg, hence neutralizing aspirin's antiplatelet action. The use of nonsteroidal anti-inflammatory medicines (NSAIDs), such as coxibs and diclofenac, in excess doses, increases the risk of heart failure [16].

Sulindac belongs to NSAIDS and is a poorly aqueous soluble drug. Its poor aqueous solubility restricts its parenteral and topical application [17]. Equilibrium between micelle in micellar solution and solute describes the solubilization of the drug.

$$D_w + M \xrightarrow{K_m} D_m$$

Where, D_w, M and D_m represent aqueous solubility of drug, micelle, and drug solubility in the micelle phase respectively. Km is distribution co-efficient for the drug in the micelle phase and aqueous phase. So, the solubility of the drug can be calculated from

$$S_m = K_m S_o [M]$$

Where, S_m and S_o describe solubility of the unionized drug in micelle and aqueous phase respectively.

The goal of this study is to enhance the aqueous solubility of sulindac medicine by using micellar solutions of diverse ionic, nonionic, and zwitter ionic surfactants and to establish a relationship between solubility and surfactant aggregation number and structure. Physical characterization of the compounds, such as Zeta Sizer and UV spectroscopy is used to determine medication solubility.

Material and Method

Chemicals and reagents

Methanol (99%), Distilled water, Ethanol (99.8%), Sulphuric acid (97%) (BDH Laboratory USA), Sulindac (Wilson-Warrick pharmaceuticals Islamabad, Pakistan), Tween20, Tween40, Tween60, Tween80, Brij30, Brij35, Brij58 (Sigma-Aldrich, Germany), Dodecyl Trimethyl ammonium bromide (DTAB), Cetyltrimethylammonium bromide (CTAB), Tetradecyltrimethylammoniumbromide (TTAB), Sodium bicarbonate (98%) (Merck Schuchardt, Germany), Sodium dodecyl sulfate (SDS) and sodium dodecyl benzenesulfonate (SDBS) (Gattefosse, France).

Critical Micelle Concentration (CMC) of surfactants

Surface tension and critical micelle concentration (CMC) of all surfactants (SDS, SDBS, CTAB, TTAB, DTAB, Tween20, Tween40, Tween60, Tween80, Brij30, Brij35, and Brij58) were calculated at constant

temperature by an already calibrated tensiometer (**Fig. 1 A, B & C**) (**Fig. 2**).

Zeta sizer

Zeta sizer was operated to determine the size (micelle size) and stability of particles. For this purpose, 1ml deionized water was mixed with 10 ul of sample and vortexes followed by a zeta sizer.

Aggregation number

With help of the Debye equation, the aggregation number of surfactants was calculated.

$$\frac{k(C - C_{cmc})}{\Delta R_o} = \frac{1}{M} + 2B(C - C_{cmc})$$

Where, C and C_{cmc} are the total concentration of monomers and critical micelle concentration respectively. $\Delta R_\circ$ is excess Rayleigh ratio and B is second Virial coefficient and K is optical constant can be calculated as

$$K = \frac{4\pi^2 n^2 \left(\frac{dn}{dc}\right)^2}{N_A \lambda^4}$$

$$N_{agg} = \frac{Apprantmolecularweightofaggregate}{Molecularweightofcorrespondingsurfactant}$$

where, n is the refractive index of the solvent, dn/dc (change in refractive index with concentration) is the refractive index increment of the sample, NA is Avogadro's number and λ is the wavelength of the incident light. **Table 1** shows the aggregation number of surfactants.

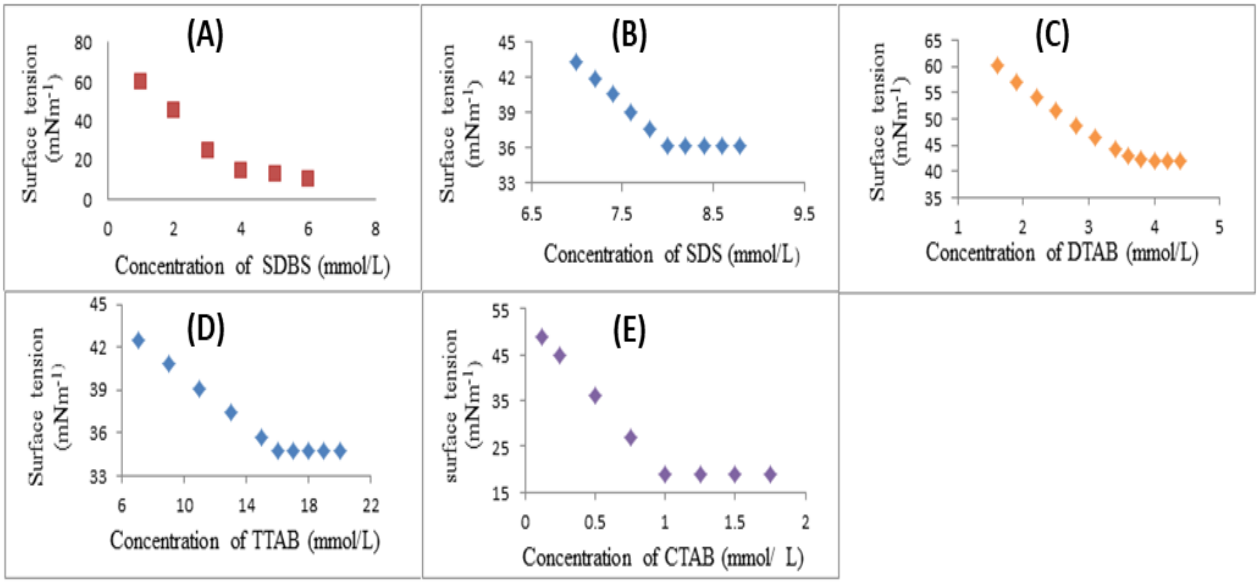

Fig.1: Critical micelle concentrations of (**A**) SDBS (**B**) SDS (**C**) DTAB (**D**) TTAB and (**E**) CTAB ionic surfactants as a function of surface tension

Table 1: Molar solubilization ratio (MSR), partition coefficient (KM) and equilibrium Gibbs (ΔG_o) energy change of drug

Surfactants	Cmc(mmol/L)	Aggregation number N_{agg}	MSR	$\log_{10} K_M$	ΔG_0 (KJ/mol)
SDS	8.2	60	0.24	3.91	-22.30
SDBS	1.83	50	0.34	4.03	-22.99
DTAB	14.7	77	0.28	3.96	-22.58
TTAB	3.81	78	0.42	3.45	-19.68
CTAB	1.00	93	0.40	4.03	-22.99
Tween20	0.064	67	0.41	4.09	-23.33
Tween40	0.029	90	0.46	4.12	-23.50
Tween60	0.002	68	0.60	4.20	-23.96
Tween80	0.011	60	0.62	4.21	-24.02
Brij30	0.035	103	0.29	3.98	-22.70
Brij35	0.050	42	0.21	3.86	-22.02
Brij56	0.046	139	0.44	4.11	-24.03

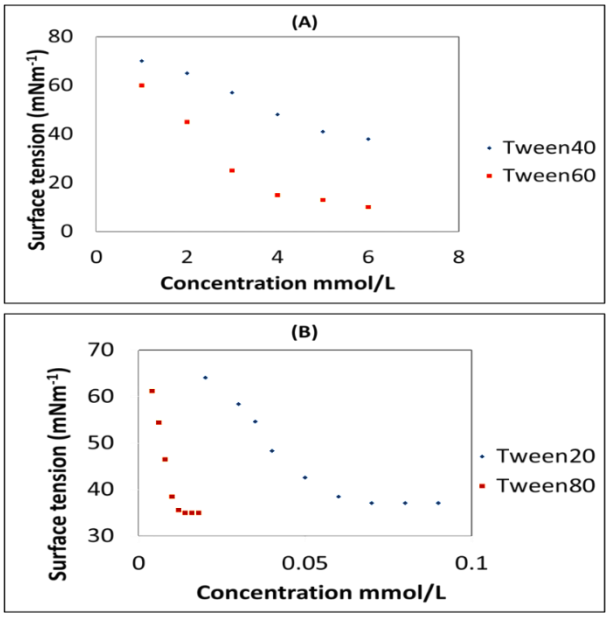

Fig. 2: Critical micelle concentration of (**A**) Tween40, Tween60 and (**B**) Tween20, Tween80 series as a function of surface tension

Solubility Measurement

A spectrometer was used to determine the solubility of sulindac. For this, a 1mL drug micellar solution was made in each surfactant individually and swirled at room temperature for 24 hours. Drug solutions were sealed with screw caps with Teflon-coated septa to prevent sample loss. Following that, aliquots were diluted to the desired concentration using the same surfactants solution of the same concentration using ultra-centrifugation. UV/Vis experiments were carried out with various surfactant solutions of the same concentration at a maximum wavelength (m) of 280 nm. Beer-Lambert law was used to determine the drug concentration.

Molar solubilization ratio (MSR)

The ability of micellar solution of different surfactants to solubilize the solubilization was measured by MSR. In the excess of solute, MSR was calculated by the following equation.

$$MSR = \frac{S_{t-S_{cmc}}}{C_{t-C_{cmc}}}$$

Where, C_t is the total concentration of surfactants (mmol/L), S_t is the solubility of drugs at a total concentration of surfactants, C_{cmc} is critical micelle concentration and S_{cmc} is drug solubility at C_{cmc}. The solubilization capability of the micellar solution was determined by the partition coefficient K_M.

$$K_M = \frac{X_M}{X_a}$$

Where, K_M is micelle partition coefficient and X_M and X_a are mole fraction of drug in micellar and aqueous solution respectively. X_M and X_a was calculated by MSR and molar volume of water ($V_{water} = 0.01805$ L/mole at 25°C) from equations

$$X_M = \frac{MSR}{1 + MSR}$$

$$X_a = S_{cmc} \times V_{water}$$

$$K_M = \frac{MSR}{(S_{cmc} \times V_{water})(1 + MSR)}$$

Thermodynamic properties such as Gibbs energy of solubilization (ΔG^o_s) that relate to the solubilization process, were also measured to understand the solubilization of drugs.

$$\Delta G^o_s = - RT \ln K_M$$

Where, R is the gas constant, T is the absolute temperature and K_M is the molar partition coefficient of the drug in the aqueous phase and micellar phase. ΔG^o_s for all system is negative and represent the favorable solubilization of the drug as shown in **Table 1**.

Results

Particle Size of Micelle

The size of the emulsion and its stability (zeta potential) evaluated using a zeta sizer demonstrate that the blank and drug-filled micelles are 174.0 nm and 181.8 nm, respectively. It also demonstrates that increasing size is related to drug encapsulation in the micelle. The zeta potential of the emulsion was measured to be -20.7 mV (**Fig. 4**).

Solubility of drug

The type of the tail and head groups, the length of the alkyl group, and the number of surfactant aggregations effects medication solubility [18] [19]. Increasing the concentration of emulsifying agents improved drug solubility, however the rise was sudden at cmc [14].

The solubility of the drug was determined up to 25 mmol/L micellar concentration of non-ionic (Tween20, Tween60, Tween40, Tween80, Brij30, Brij35 and Brij56) and ionic (SDS, TTAB, DTAB and CTAB) surfactants at room temperature and values are given in **Table 1**. In each case, solubility increase was noticeable as shown in **Fig. 5**. It has been observed that in the case of the Brij series (Brij30, Brij35 and Brij56) all surfactants have the same alkyl length due to the same number of carbon atom but aggregation number higher in Brij56 than Brij30, therefore, drug solubility increase order in this series was as Brij30<Brij35< Brij56 (**Fig. 3**).

But in anionic and cationic surfactants, solubility increase order was like SDS< SDBS and DTAB< TTAB< CTAB respectively. The solubility of the drug is higher in cationic surfactants as compared to anionic due to the high aggregation number in cationic surfactants.

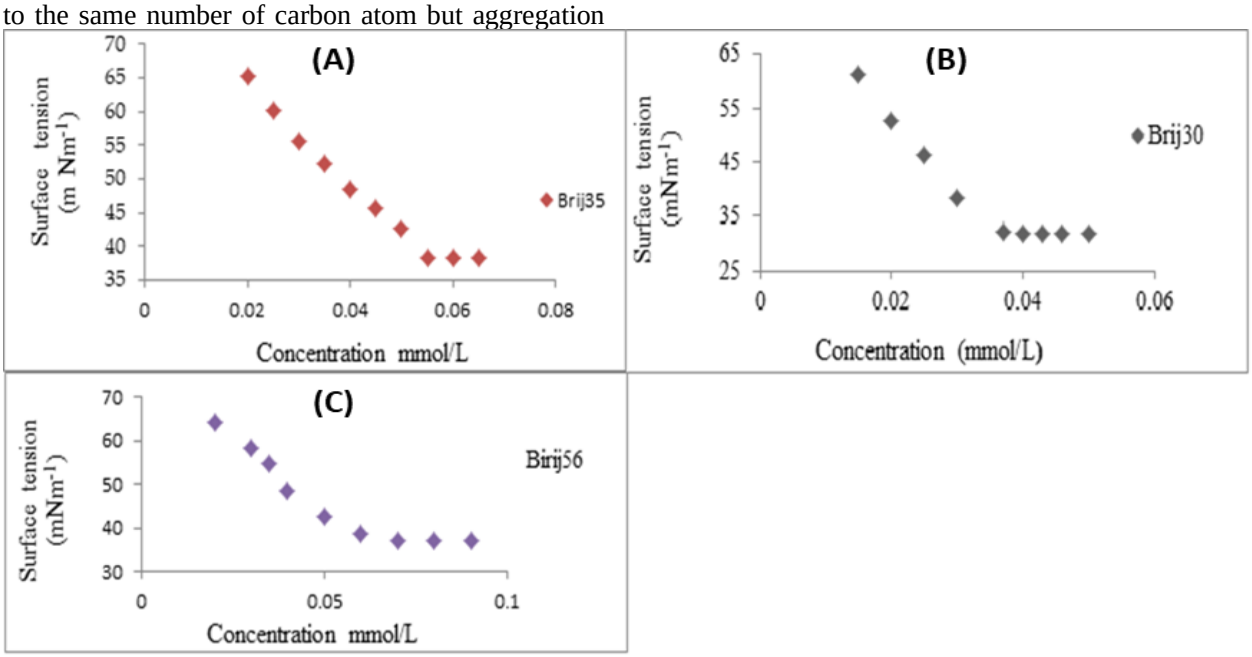

Fig. 3: Critical micelle concentrations of (**A**) Brij35 (**B**) Brij30 and (**C**) Brij56 series as a function of surface tension

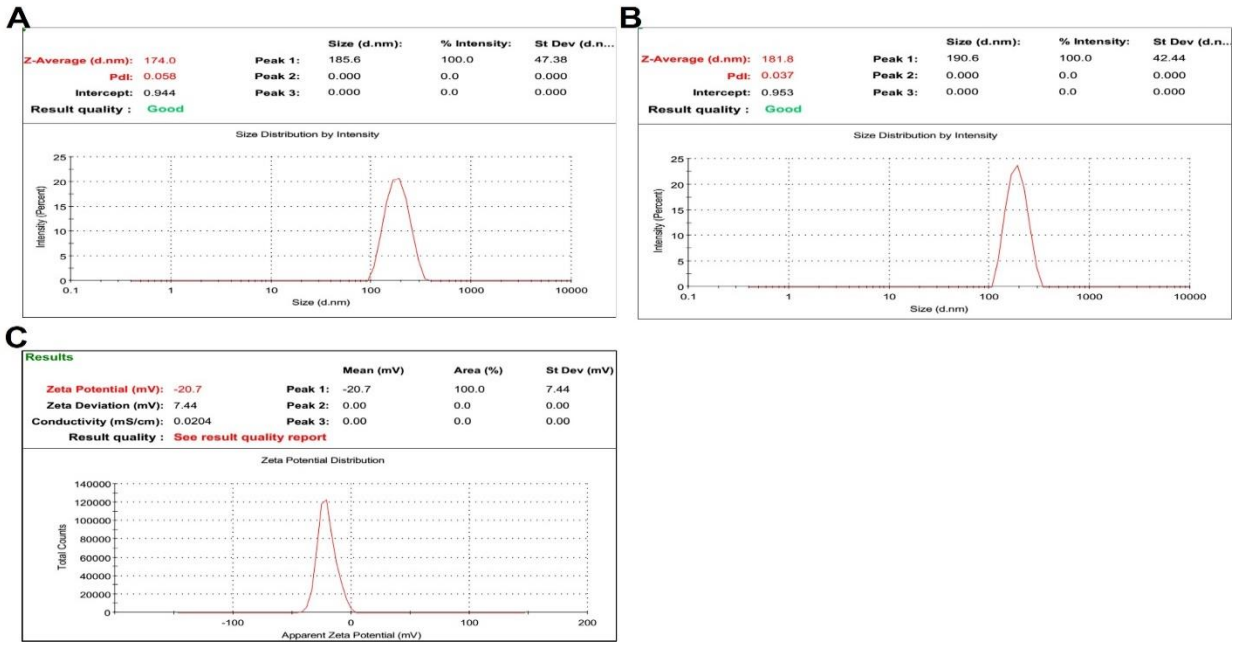

Fig.4: (**A**) Represent the particle size of the prepared blank micelle (**B**) Sulindac loaded micelle and (**C**) electrostatic stability of micelle

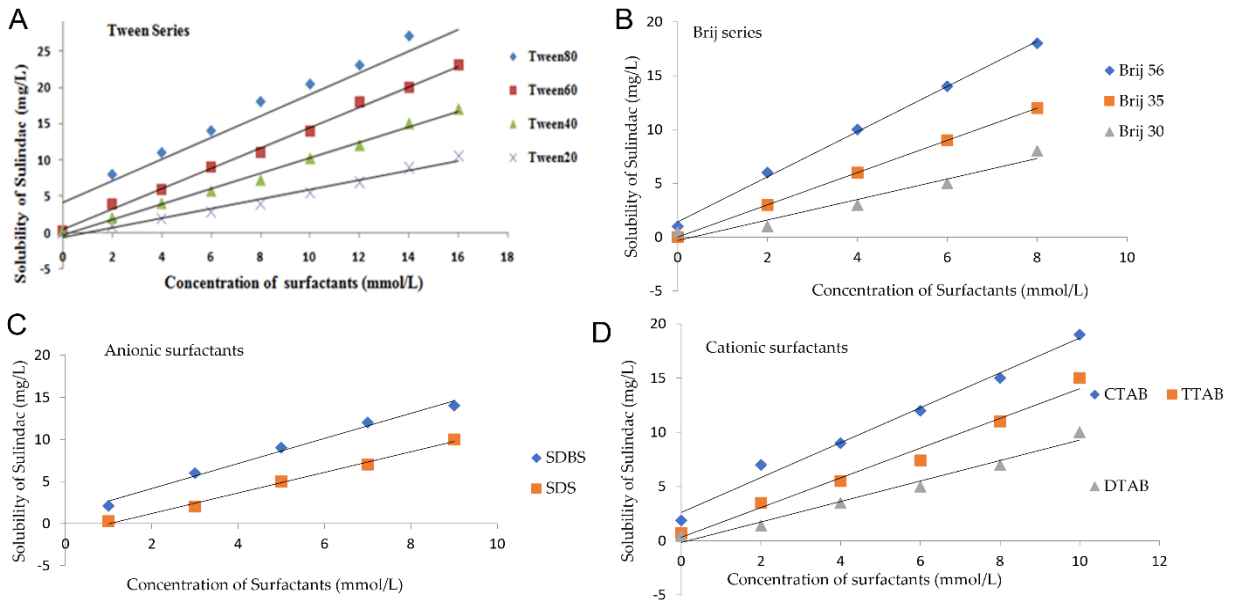

Fig. 5: (**A**) Enhancement of aqueous solubility of sulindac as a function of non-anionic (Brij series) surfactants (**B**) Brij series (**C**) anionic surfactants and (**D**) cationic surfactants at 25 ^{0}C

Bending constant of the drug

Bending constant values of sulindac, calculated by the formula are given in **Table 2.** It has been noted that Tween 80 has the highest value of 1.43 while Birj30 has the lowest value of 0.29.

Table 2: Bending constant (K1) and the number of solubilizate molecules per micelle (MS) of non-ionic surfactants.

Non-ionic Surfactants	Bending Constant ($K_1 \times 10^{-4}$/L)	M^S
Birj30	0.29	1.09
Birj35	0.24	7.1
Birj56	1.36	39.53
Tween20	0.88	33.125
Tween40	1.17	47.93
Tween60	1.32	57.03
Tween80	1.43	63.238

Discussion

With the help of Zeta Sizer stability of the emulsion was determined and the final emulsion has -20.7 mV Zeta Potential and represents high steric and electrostatic stability of emulsion as shown in figure 4. In the case of non-ionic surfactants, drug (NSAID, Ibuprofen) solubility increases from Tween20 (Tween20< Tween40< Tween60< Tween80) to Tween80 because the number of carbon units increases from Tween20 to Tween80 and due to this, hydrophobic nature of surfactants enhance from Tween20 to Tween80 as shown in above **Fig. 5A and B**.

In the case of the Brij series, Brij 56 has high solubility due to high aggregation number than Brij30. It is due to the different strength of carbon atoms, different aggregation number, and the different number of oxyethylene units in anionic and cationic surfactants therefore solubility of the drug increase SDS< SDBS and DTAB< TTAB< CTAB respectively as shown in above figures. Moreover, saturation and unsaturation of the alkyl chain in surfactants also play a vital role to solubilize the drug [15, 20, 21]. This variation in sulindac solubility is due to a difference in the number of oxyethylene units in the investigated nonionic surfactants, as well as a difference in the number of carbon atoms in the alkyl chain of the surfactants; additionally, the unsaturation in surfactants plays an important role in drug solubility in surfactant solutions.

In general, nonionic surfactants have elevated solubilization power as compared to cationic and anionic surfactants [16]. Pharmacologically, non-ionic surfactants are very important due to low bending with protein and show high solubilization power at a low cmc value. They also increase the bioavailability and efficiency of the drug. Their micelle also remains stable at large dilution with blood [22, 23].

Conclusions

In conclusion, we have learned that employing a combination of ionic and non-ionic series as

emulsifying agents may be a viable option for increasing sulindac solubility. Sulindac's solubility is controlled by factors such as its hydrophobic character, hydrophile-lipophile balance, alkyl chain length, and the amount of emulsifying agent's aggregation. Our findings show that using the specified surfactant is a great way to improve sulindac solubility, and it is a significant contribution to the literature on drug delivery systems to overcome solubility difficulties, which are a difficult chore for pharmaceutical firms. Furthermore, the current study sheds light on the relationship between aqueous solubility and the amount and structure of surfactants utilized.

Authors contribution

Study conception and design were done by Ullah F, Khan NH, data collection was done by Ullah F, Ullah S, Khan NH and analysis and interpretation of result were done by Khan MFA and Tareen FK and draft manuscript preparation was done by Ullah F.

Acknowledgment

This project "Enhance the Aqueous solubility of different Drugs" was funded by the Higher Education Commission of Pakistan (HEC).

Conflict of interest

The authors declare no conflict of interest.

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