Original Article

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Application of Chemometrics in determination of the effects of ionic and non-ionic surfactants on acid dissociation constant (pKa) of Meloxicam using spectrophotometric method

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ABSTRACT

The purpose of this study was to determine the acid dissociation constants (pKa) of meloxicam in the presence of various surfactants including sodium lauryl sulfate (SLS) as an anionic surfactant, cetyltrimethylammonium bromide (CTAB) as a cationic surfactant and Triton® TX-100 (TX-100) as a non-ionic surfactant in different pre-determined concentrations. The related pKa was determined spectrophotometrically at a constant ionic strength of 0.1 M at 250C. In order to investigate the effect of solvent on pKa of meloxicam, the pKa was also determined in different concentrations of ethanol, separately. The acid dissociation constant of all appropriate species were calculated using chemometric methods. In this study, DATAN® software was applied for analysis and interpretation of data. The acid dissociation constants (i.e. pKa) for meloxicam as poorly soluble drug were reported as 1.22±0.56 and 4.00±0.12 for pKa1 and pKa2, respectively. The obtained data showed that by increasing the concentration of SLS up to 0.05% (w/v), both the pKa1 and pKa2 of meloxicam were increased and to 2.67±0.054 and 5.73±0.029, respectively, while by increasing the concentration of CTAB, significant decrease was observed in pKa2 of meloxicam to 2.53±0.16. Different concentrations of TX-100 posed non-significant changes in pKa1 and pKa2. It was also reported that by increasing the concentration of ethanol as a co-solvent, both pKa1 and pKa2 of meloxicam were increased to 2.42±0.083and 5.81±0.23, respectively.

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Keywords
Acid dissociation constant (pKa), Meloxicam, Sodium lauryl sulfate (SLS), Cetyltrimethylammonium bromide (CTAB), Triton® X-100 (TX-100), Ethanol

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INTRODUCTION

Most of the therapeutic drugs are either weak acids or weak bases and some or all of the related molecules become ionized/ unionized in various biological fluids. The acid dissociation constant (pKa) of a molecule predicts the degree of ionization at a particular pH by using Henderson–Hasselbalch mathematical equation [1-2]. Therefore, determination of pKa values of therapeutic agents is considered to be an interesting issue in the drug

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developments, formulations and pharmacokinetic studies.

In the literature, there are various techniques available for determination of pKa including potantiometry [3], spectrophotometry [4], NMR [5], HPLC [6], Electrophoresis [7].

Chemometrics is a data-driven interdisciplinary science applied for solving diverse applications and considered as a way for statistical and mathematical interpretation of analytical data. By using chemometrics, the reliability of data obtained from the experimental procedures would be improved [8-9].

Some studies have reported the application of chemometrics as a tool for interpretation of the results in determination of pKa of various compounds [10-12]. In some reports, credible, reliable and valuable data for determination of pKa and other physico-chemical properties of a drug have been obtained by combination of experimental data and chemometrics [13-14].

Meloxicam (i.e. 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide) is considered as a non-steroidal anti-inflammatory drug (NSAID) with analgesic and fever killing effects to treat pain and/or inflammation in adults [15]. It is categorized as a widely used medicinal agent for treatment of osteoarthritis and rheumatoid arthritis [16]. Meloxicam is classified as one of the group II medicinal agents in biopharmaceutical classification system (BCS) which is identified by low solubility and high permeability, therefore the rate of intestinal absorption via oral administration is limited due to low aqueous solubility [17]. The chemical structure of meloxicam has been shown on Fig. 1.

In this study, a data analysis software was used to interpret the spectroscopic data for identifying the effects of sodium lauryl sulfate (SLS) as a anionic surfactant, cetyltrimethylammonium bromide (CTAB) as a cationic surfactant and Triton® X-100 (TX- 100) as a non-ionic surfactant on pKa values of meloxicam in aqueous media [18].

Surfactants are considered as amphiphilic molecules composed of hydrophilic or polar moieties known as head and also hydrophobic or non-polar moieties known as tail [19].Although, surfactants in low concentrations are absorbed into surfaces or interfaces and consequently pose significant role in reduction of the surface or interfacial free energy, but when they are dissolved at concentrations above their own critical micelle concentration (CMC), they form aggregates known as micelles. In a micelle formed in an aqueous media, the hydrophobic tails flock to the interior of the structure while the hydrophilic heads remain on the outer surface [20]. It is obvious that type, quality and intensity of interactions of surfactants with drug molecules are different above and below the CMC, therefore precise calculation of CMC point is assumed to be necessary for determination of interaction between surfactant and drug molecule.

The aim of this study was investigation of the effects of various concentrations of CTAB as a cationic, SLS as an anionic and TX-100 as a non-ionic surfactant on pKa of meloxicam. As aqueous solubility of a poorly soluble drug in constant pH is related to concentration of ionic and non-ionic dissociated species of the compound which is determined by acid dissociation constant, the alteration of pKa using surfactants can pose some effects on aqueous solubility of the compound.

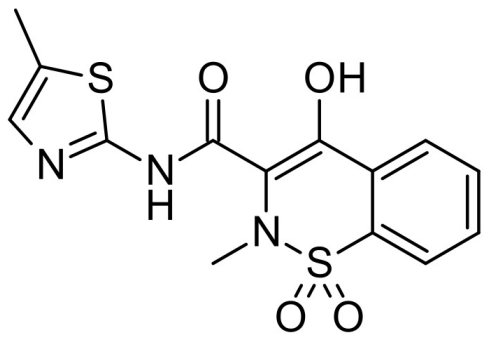


Figure 1. Chemical Structure of Meloxicam

MATERIALS AND METHODS

Material

Meloxicam, SLS, CTAB and TX-100 were provided from Sigma (Milwaukee, USA). Hydrochloric acid, sodium hydroxide, and potassium nitrate were supplied as pharmaceutical grade from Merck (Darmstadt, Germany). Hydrochloric acid and sodium hydroxide were then standardized and their normality was determined using titration with standard alkali solution and standard acid solution, respectively according to guidelines [21- 22]. The stock solutions of surfactants were prepared by dissolving appropriate amounts of substances in double distilled water. The authors have used freshly prepared doubled distilled water that was previously filtered through 0.22µm Milipore syringe filter in all cases. All other chemicals were of pharmaceutical grade and were used as received.

Instrumentation and software

A lambda 25 Perkin Elmer® spectrophotometer (Waltham, Massachusetts, USA) controlled by a computer and equipped with a 1-cm path length quartz cell was used for UV–Vis spectra acquisition. Spectra were acquired in the wavelength range of 200 to 500 nm. A PB-11 Sartorius® pH-meter (Gottingen, Germany) furnished with a combined glass-saturated calomel electrode was calibrated with two buffer solutions at a pH of 3.0 and 9.0.

For verifying the accuracy of pH measurements in the presence of surfactants, pre-determined concentrations of 0.001% (w/v), 0.01% (w/v), and 0.025 % (w/v) and 0.05% (w/v) from SDS, CTAB and TX-100 were added to the buffers and the pH was measured using pH-meter. Statistical analysis of data revealed that studied surfactants in the determined concentration did not cause any significant effect on the pH of buffer ($p< 0.05$) and therefore, the pH measurement system was considered to be accurate in the

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presence of surfactants.

All absorption spectra were acquired at five data points in each wavelength and transferred , in ASCII format, to an AMD 2000 XP (256 Mb RAM) computer for subsequent analysis using DATAN® package (Ver. 5.0, Multid Analyses AB, Goteborg, Sweden) .The specific conductance measurements were carried out by 856-Methrohm®conductometer equipped with a platinum electrode at 25°C.

Determination of the CMC

In order to determine CMC of various surfactants including SLS, CTAB and TX-100 in the presence of meloxicam (2.5×10-5 M) as a molecular probe, the experiments were carried out using different concentrations of each surfactant while conductivity and absorbance of meloxicam were also measured in each case. In order to keep the pH constant in the system, experiments were carried out in three different buffers with the adjusted pH values of 4.0, 7.0 and 9.0. The critical micelle concentrations (CMC) were determined from the plot of specific conductivity and absorbance versus concentration of the surfactant. All experiments were done on triplicate.

Spectrophotometric titrations

Acid- alkali titrations were performed for meloxicam (2.5×10-5 M) in pure water, and aqueous media containing various concentrations of SLS, CTAB and TX-100, separately. The related absorption spectra were determined by a titration set-up including a computer interfaced to a spectrophotometer. In this study, various and pre-determined concentrations of surfactants were used as 0.001% (w/v), 0.01% (w/v), 0.025% (w/v) and 0.05% (w/v). As it is assumed that surfactant in concentrations above CMC can prepare micellar structures which can interrupt the electrostatic interaction between the surfactant and drug, low amounts of surfactants were used and all of the concentrations were assured to be below the CMC of appropriate surfactants which had been calculated previously. The solution was transferred into the cuvette and the absorption spectra were recorded. Ionic strength was maintained at 0.1 M by adding appropriate amounts of KNO3. All measurements were carried out at a temperature of 25 ± 0.50C. Data was analyzed and interpreted chemometrically using the software.

Statistical analysis

All experiments were performed in triplicate and the related values were reported as Mean ± SD. In the case of comparison between several groups, statistical significance of differences were evaluated by one way analysis of variance (ANOVA) with appropriate post hoc tests while student's independent samples t-test was applied in the case of comparison between two groups. One sample t-test was used for comparison of a group with a constant, pre-determined value. The statistical analysis was performed using SPSS (V.19.0.0, IBM Statistics, New York, USA) and differences were considered significant when $p< 0.05$.

RESULTS

Determination of CMC

The CMC of three surfactants including SLS, CTAB and TX-100 were determined in the presence of meloxicam (2.5×10-5 M) as a molecular probe at various buffers which has been mentioned previously applying spectrophotometric and conductivity methods. Fig. 2 has shown the plot obtained from absorbance and conductivity measurements versus concentration of SLS for determining CMC of the surfactants in pH value of 4.0. The obtained data has been summarized in Table 1. As shown in the Table 1, no significant difference between CMC values obtained from either spectrophotometric method or conductivity method has been observed ($p< 0.05$).

Although the effects of formation of micelles on physicochemical properties of the drugs and also their interactions have been previously studied [23-25], but very few studies have been reported the CMC values of

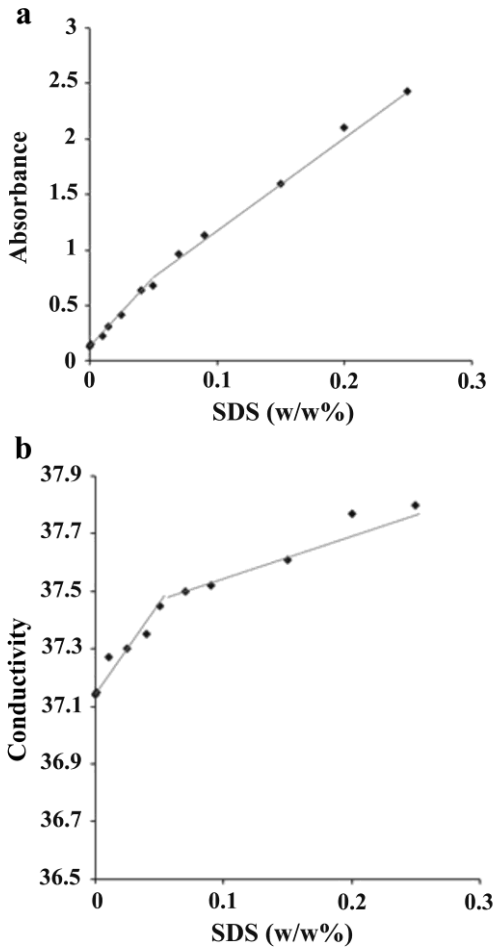


Figure 2. Plots obtained for determination of CMC of SLS in pH value of 4.0 using a. absorbance measurement and b. conductivity measurement

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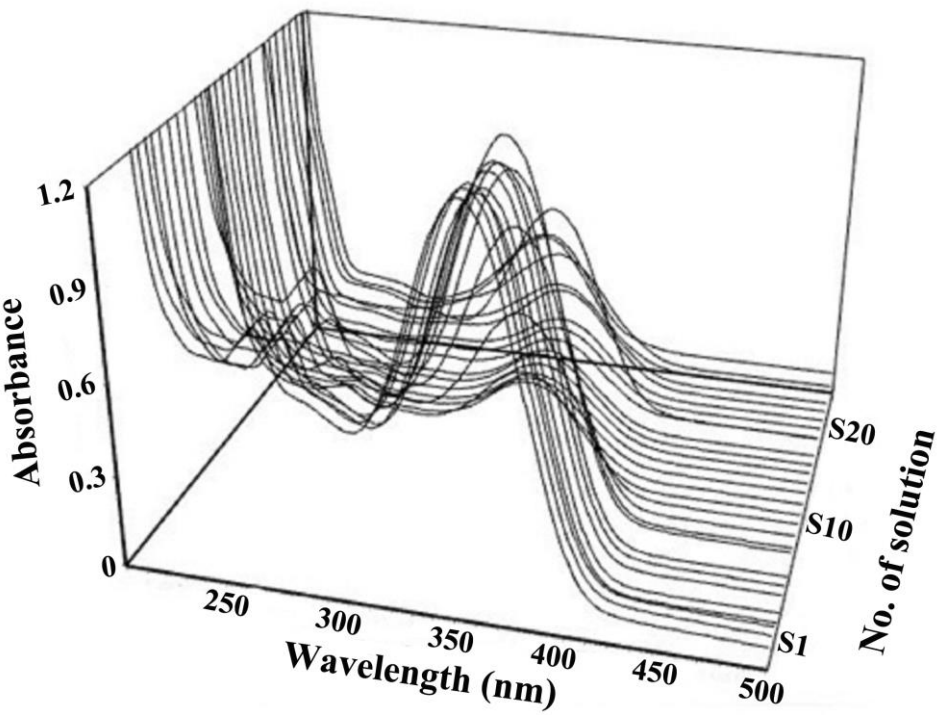


Figure 3. Absorption spectra of meloxicam in pure water at different pH values: (S1) 0.9, (S2) 1.2, (S3) 1.8, (S4) 2.3, (S5) 2.6, (S6) 2.9, (S7) 3.2, (S8) 3.8, (S9) 4.1, (S10) 4.8, (S11) 5.2, (S12) 6.0, (S13) 6.4, (S14) 6.7, (S15) 7.2, (S16) 7.8, (S17) 8.4, (S18) 8.8, (S19) 9.1, (S20) 9.6, (S21) 10.0, (S22) 10.3, (S23) 10.6, (S24) 11.1

surfactants in the presence of a poorly soluble drug as the molecular probe.

In this study, the changes in spectrophotochemical properties and electrical conductivity of meloxicam along with increase in surfactant concentration were used for determination of CMC.

Determination of acid dissociation constant (pKa) of meloxicam in different media

The absorption spectra of meloxicam (2.5×10^{-5} M) at constant ionic strength using KNO_3 (0.1 M) and various pH values in doubled distilled water in the wavelength range of 200–500 nm were recorded at 25^0C and the data has shown on Fig. 3. Obviously, spectrophotometric behavior of a molecule would be influenced by pH, other salutes (e.g. Surfactant), solvent and temperature. As shown on Fig. 3, increasing the pH value can decrease the porotonation of meloxicam as the weak base and consequently increases the displacement of protons from the molecule. This process causes bathochromic shift (i.e. change of spectral band position in the absorption spectrum of a molecule to a longer wavelength) in the absorption spectra of meloxicam.

In order to determine the influence of SLS, CTAB and TX-100 as the surfactants and also ethanol as the co-solvent on pKa of meloxicam, a series of experiments were performed at various concentrations of sur factants and also ethanol, as mentioned previously. The computer software was used to derive pKa val-ues from the data obtained by

Table 1. CMC determination of surfactants in buffers solutions (pH=3.00, 7.00, 9.00) at 25^0C and constant ionic strength (0.1 M KNO3) in the presence of meloxicam ($2.5*10^{-5}$ M) as a molecular probe (n=3)

Method		*CMC*		
		pH=4.00 (Mean±SD)	pH=7.00 (Mean±SD)	pH=9.00 (Mean±SD)
SLS% (W/V)	Spectrophotometry	0.10±0.043	0.11±0.071	0.10±0.056
	Conductometry	0.11±0.022	0.10±0.063	0.12±0.048
CTAB% (W/V)	Spectrophotometry	0.07±0.009	0.06±0.007	0.09±0.001
	Conductometry	0.07±0.004	0.05±0.003	0.08±0.004
TX-100% (W/V)	Spectrophotometry	0.07±0.013	0.09±0.006	0.10±0.032
	Conductometry	0.09±0.008	0.08±0.011	0.12±0.018

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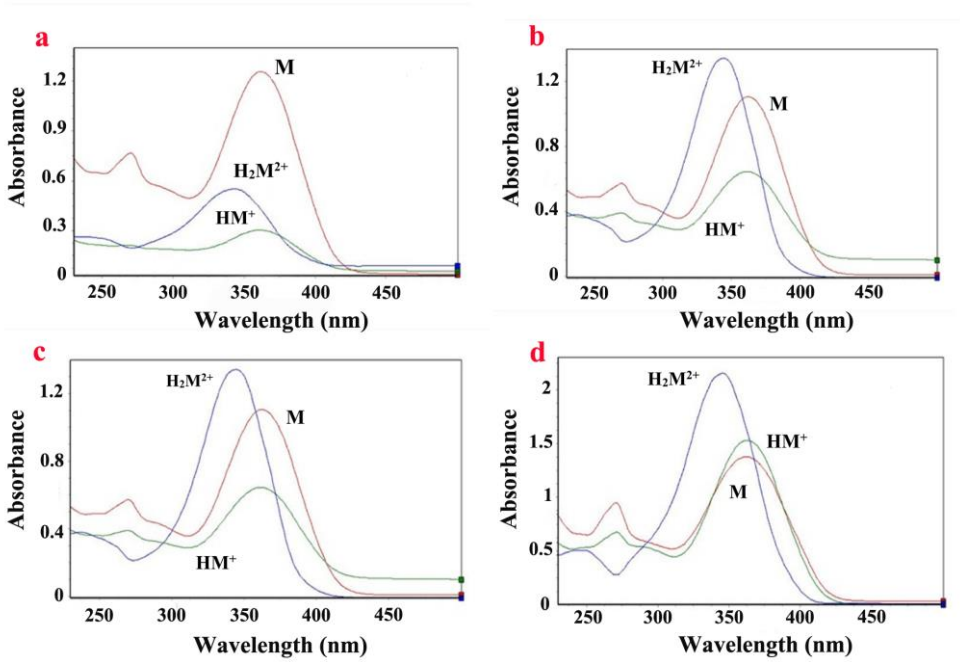


Figure 4. Absorption spectrum of dissociated species of meloxicam in a) pure water; b) SLS (0.05%); c) CTAB (0.05%); d) TX-100 (0.05%)

spectrophotometric titrations.

An important output of the software was providing absorption values for each species including protonated basic species (i.e. MH_2^{2+} or HM^+) and non-protonated acidic specie (i.e. M) obtained by deconvolution of the spectrophotometric spectra, at different wavelengths of the drug (Fig. 4).

These images were obtained among several recorded spectra that have been obtained at the time of separa- tion spectra that have been obtained at the time of separation of proton (i.e. H^+) from the drug.

As shown in Fig. 4 (a-d), the obvious differences in lambda-max wavelength and also absorbance intensity can be observed in the presence of various surfactants.

Other outputs of the software were included pKa values, the number of main components and the concentration distribution diagrams [18, 26].

In this study, the calculated values for pKa determination of meloxicam in pure water without presence of any surfactants were 1.22±0.56 and 4.00±0.12 for pKa_1 and pKa_2, respectively which is in accordance with previously published values for acid dissociation constant (pKa) of meloxicam as 1.1 and 4.2 for pKa_1 and pKa_2, respectively [27-28]. One statistical t-test analysis showed no significant difference between the values obtained in this study for pKa of meloxicam and the values reported previously ($p<0.05$).

DISCUSSION

In this study, the changes in spectrophotochemical properties and electrical conductivity of meloxicam along with increase in surfactant concentration were used for determination of CMC. As mentioned before statistical t-test analysis showed an insignificant difference between the pKas of meloxicam obtained in this study compared to these values reported previously ($p<0.05$). It is previously reported that pKa1 is related to enolic group of meloxicam while pKa2 is attributed to 2-pyridinyl group of the compound [27].

Earlier, different methods have been reported for determination of pKa of meloxicam. Although, there are some contradictory reports of pKa values for oxicams, but the pKa values of meloxicam obtained from UV-spectrophotometry are reported to be in accordance with those obtained from the solubility data.

Although, Luger et al., reported the values of 1.09 and 4.18 for pKa1 and pKa2 of meloxicam, respectively using pH-dependent UV-spectrophotometry [25], Tsai et al., have reported a single pKa value of 4.08 for meloxicam [29]. Bernhard et al., have attributed the pKa value of 5.46 to 2-pyridinyl group of meloxicam [30], while

Wiseman et al. assigned a pKa of 6.3 to 2-pyridinyl group of meloxicam [31].

In previous studies, conventional methods for determination of acid dissociation constant have been reported. In these studies, the risk of interference of experimental systematic errors in calculated acid dissociation constants would be probable, but mathematical analysis of the whole spectral domain using chemomertics can considerably reduce noise level.

The alteration of acid dissociation constant in the presence of various concentrations of surfactants is reflected in Table 2. As shown in the table, increasing concentration of SLS (as an anionic surfactant) can cause a significant increase in pKa1 of meloxicam from 1.22±0.061 in pure

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Table 2. Acid dissociation constants (pKa) of meloxicam in the presence of different concentration of surfactants at 25^{0}C and constant ionic strength (0.1 M KNO_3) (n=3)

	Conc. (% W/V)*	*pKa_1 (n=3) Mean±SD*	*pKa_2 (n=3) Mean±SD*
SLS	0.0001%	1.2±0.06	4.0±0.19
	0.0010%	1.3±0.05	4.4±0.22
	0.0100%	1.7±0.05	4.8±0.24
	0.0250%	2.2±0.06	5.2±0.26
	0.0500%	2.7±0.05	5.7±0.29
CTAB	0.0001%	1.2±0.06	4. 0±0.19
	0.0010%	1.3±0.03	3.7±0.23
	0.0100%	1.3±0.06	3.1±0.22
	0.0250%	1.4±0.08	2.8±0.22
	0.0500%	1.4±0.10	2.5±0.16
TX-100	0.0001%	1.2±0.06	4.0±0.19
	0.0010%	1.2±0.06	4.0±0.21
	0.0100%	1.3±0.08	4.0±0.16
	0.0250%	1.2±0.06	4.1±0.23
	0.0500%	1.2±0.05	4.1±0.14

*Conc: Concenteration

Table 3. Acid dissociation constants of meloxicam in different concentration of ethanol at 25^{0}C and constant ionic strength (0.1 M KNO_3) (n=3)

	pKa_1 (n=3) (Mean±SD)	*pKa_2 (n=3) (Mean±SD)*
0.00	1.22±0.061	4.00±0.19
20%(V/V)	1.54±0.145	4.02±0.21
40%(V/V)	1.87±0.075	4.17±0.24
60%(V/V)	2.16±0.022	4.74±0.25
80%(V/V)	2.42±0.083	5.81±0.23

water to 2.67±0.054 in the presence of SLS 0.05% (w/v) and its pKa2 from 4.00±0.19 in the pure water to 5.73±0.029 in the presence of SLS 0.05% (w/v) ($p<0.05$). As illustrated in the Table 2, increasing concentration of CTAB (as a cationic surfactant) poses a slight and insignificant increase of pKa1 of meloxicam from 1.22±0.061 to 1.43±0.098 ($p< 0.05$) but causes a significant decrease in pKa2 from 4.00±0.19 to 2.53 ±0.16 ($p<0.05$) . Meloxicam is considered as a poorly soluble drug and aqueous solubility of meloxicam is reported be as 0.0075 mg/ml. Therefore, intestinal absorption rate of the drug is limited due to low solubility in the gastrointestinal media. Previously, the effects of surfactants on water solubility have been widely studied.

We suggest that although surfactants can enhance the water solubility of poorly soluble compounds by reduction of surface tension as widely discussed by other studies, but in case of some ionic surfactants, other mechanisms are also involved for alteration of aqueous solubility. Here, it has been shown that SLS can increase both pKa1 and pKa2 values of meloxicam and consequently it increases the concentration of positively charged ionic species of the compound (i.e. MH22+ and MH+) which also enhances the aqueous solubility of meloxicam. Recognition of this mechanism could be useful for development of more bio-available and more efficient oral formulations of the meloxicam.

In the other hand, although CTAB as well as the other surfactants can cause an increase in aqueous solubility (by reduction of surface tension) but it can reduce the ionic species in the intestinal medium which is against the solubility improvement due to decrease in pKa values.

SLS as a negatively charged surfactant can pose electrostatic attraction with protonated form of meloxicam and therefore increases the concentration of positively charged species of meloxicam (i.e. MH_2^{2+} and MH^+) which in turn increases the acid dissociation constant of the compound while CTAB as the positively charged surfactant can pose electrostatic repulsion with protonated form of meloxicam followed by increase in concentration of non-ionic species (i.e. M) and therefore, the pKa of the drug is decreased.

As shown in Table 2, various concentrations of TX-100 is unable to make any significant changes in pKa_1 and $pKa_2$of meloxicam ($p< 0.05$).

It has been suggested that the electrostatic attraction or repulsion between surfactant and drug should be considered as a dominant mechanism for alteration in pKa of the drug.

The authors suggest that cationic or anionic surfactants may pose electrostatic interaction with drug substance and cause increase or decrease in concentration of non-ionized species of meloxicam (i.e. M), respectively while no electrostatic interaction could be considered between TX-100 as non-ionic surfactant with drug molecule. This would justify that in the presence of different concentrations of TX-100 no significant changes in acidity constant of meloxicam is observed.

The effects of ethanol as the co-solvent on acid dissociation constant (pKa) of meloxicam were also studied. As shown in Table 3, increasing the concentration of ethanol can cause significant increase in both pKa_1 and pKa_2 of meloxicam from 1.22±0.061 in pure water to 2.42±0.083 in 80% (v/v) of ethanol and from 4.00±0.19 in pure water to 5.81±0.23 in 80% (v/v) of ethanol ($p< 0.05$) respectively. The observed increase in acid dissociation constant can be justified by considering hydrogen bonding between ethanol and meloxicam which prevent formation of non-protonated species [32].

In this study, the acid dissociation constant (pKa) of meloxicam in various concentrations of three surfactants including SLS as an anionic surfactant, CTAB as a cationic surfactant and TX-100 as a non-ionic surfactant has been determined. The effects of various concentrations of ethanol as a co-solvent on pKa were also studied. The multi-wavelength spectrophotometric method interpreted with mathematical analysis of data had been applied for determination of pKa. Results showed that pKa values of meloxicam were influenced by increasing concentrations of SLS and CTAB while increase in concentration of TX-100 as a non-ionic surfactant had no significant effect on pKa of meloxicam. It was suggested that electrostatic interaction

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between ionic surfactant and dissociated species of the drug, is a dominant mechanism for alteration of pKa.

CONFLICT OF INTEREST

The authors declare that this research does not have any conflict of interest with anyone or any institute.

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