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Original Article

AN ELECTROMETRIC METHOD FOR THE DETERMINATION OF IMPACT OF DMSO-WATER MIXTURES ON pKa VALUES OF SALICYLIC ACID DERIVATIVES

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ABSTRACT

Objective: The main objective of this present study is to conduct an experiment to analyze the variation of protonation-deprotonation equilibria with regards to the dielectric constants of an organic medium, influence of errors on protonation constants and effect of pH on the percentage of species.

Methods: The present investigation was carried out by using pH meter at a temperature of 303 K and ionic strength of 0.16 mol dm^{-3} in Dimethyl sulfoxide (DMSO)-water mixtures. The processing of data was done by using Gran plot titration. The advanced principles of mathematics and fuzzy logic have been employed to correlate chemical problems, known as chemometrics. To obtain best-fit chemical models, a modelling strategy such as SCPHD is used and a computer program MINIQUAD 75 is also employed for the refinement of results.

Results: In the present study, we found the influence of dielectric constants of a medium Dimethyl sulfoxide (DMSO)-water on protonation constants of 5-Sulfosalicylic acid and 5-Hydroxysalicylic acid has been studied. The species distribution diagrams were presented and understood the effect of pH on the percentage of species. The obtained skewness values are ranging from 0.11-0.36 and–0.56-0.38, for 5-Sulfosalicylic acid (5-SSA) and 5-Hydroxysalicylic acid (5-HSA), respectively, which describes the distribution curves are right skewed and left skewed. The kurtosis values are ranging from 2.12-3.56, which indicates the peak of the distribution curve exhibits both platykurtic and leptokurtic pattern. The changes in the concentrations of some influential parameters such as log F, acid, alkali, volume of titrands, ligand causes variation of stability constants and the order of the effect of influential parameters on stability constants are as alkali>acid>ligand>volume of titrand>log F.

Conclusion: It is observed that the significant influence of co-solvent Dimethyl sulfoxide (DMSO)-Water mixtures on the protonation constants of ligands also studied how some factors such as changes in concentrations of ligand, acid, base log F and volume of the solution have influence on the protonation constants.

Keywords: Acid-base equilibria, 5-Sulfosalicylic acid, 5-Hydroxysalicylic acid, Dimethyl sulfoxide, Protonation constant and dielectric constant

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INTRODUCTION

The solubility and the bioavailability of a drug affect the therapeutic efficacy of the drug when released from its dosage form. Solubility is one of the major parameters to attain the desired plasma drug concentration. The poor solubility of the drug may result in limited absorption, further leading to the decrease in bioavailability [1]. Measurement of drug concentration in biological fluids, such as blood or urine, following drug administration, is considered a direct and efficient method for the determination of systemic drug bioavailability [2]. Drug disposition means the change in the position of drug molecules after administration into the system. As per the pharmacological view: Drug is a substance which can cause positive or negative effect to the system. But in actual, a drug is a chemical substance comprised with a definite chemical structure when a chemical substance goes into a system which itself is governed by the pH-partition hypothesis. The disposition of drug molecules involves administration, distribution, metabolism, excretion and toxicity (ADMET) [3]; every drug has its beneficial pharmacological activity as well as unavoidable side effects [4]. Drug discovery is a method and time-thorough process which is aimed at developing new drug candidates [5].

Salicylic acid derivatives like 5-SSA and 5-HSA have numerous applications in drug designing [6-9]. The dielectric constant is a macroscopic property which plays a significant role in the solution properties of the reaction medium. It is a useful technique in characterizing molecular ordering in solutions and the value of the dielectric constant is strongly related to the chemical structure of a molecule and to its intermolecular interactions. The dielectric constant is one of the characteristics of liquid. The proton-ligand and metal-ligand stability constants are strongly affected by the dielectric constant of the medium because of the fact that at least one of the constituents is charged and the other is either changed or has a dipole. Variations in the relative strengths of acids and bases with changing solvents should be a function of the charge, the radius of the ion and the dielectric constants of the medium. DMSO is most commonly used in biochemistry. It is a polar solvent can dissolve many compounds in it, which property makes DMSO to have a number of applications in drug designing and synthesis [10].

The speciation analysis of harmful and necessary metal ion complexes helps clarify the role of biologically active site cavities and drug residue interacting with the metal ion. Number of studies has been performed on chemical speciation in aqueous media under the same conditions as in natural systems. These are used as models for the systems that exist in natural water and biofluids. Nevertheless, Biosystems are linked to low dielectric mediums of varying magnitudes, and metabolic reactions are carried out in rigid compartments. The binary mixtures of dipolar aprotic and protic solvents have current interest in biological, chemical, pharmaceutical, technological and laboratory applications because mixed solvents manifest physicochemical properties as compared to those of pure constituents of the mixture amongst the physicochemical properties, dielectric constant of the mixed solvents, which is sensitive to molecular interactions specially H-bond formation, enhances or controls most of the applications, and hence precise the dielectric characterization is important. The study of chemical speciation plays a very important role to understand nutrition, human biology and toxicology, which will also helpful to understand the nature of an element in the sample [11]. One of the most important parameter in pharmaceutical is acid dissociation constants, ionization of functional groups with respective to pH; they are very useful in understanding the properties of new drug substances.

The present study deals with the dissociation and salvation processes in solutions of drugs and is important to elucidate the connection between

chemical ability and biological activity; salicylates are used as food preservatives. In addition, salicylic acid and its derivatives have been widely used in medicine and analytical chemistry. This medium has been chosen to study the acid-base equilibria to mimic the physiological conditions where the concept of equivalent solution dielectric constant for active site cavities of protein or drug is applicable. In the present investigation, we have studied the protonation constants of both the ligands 5-SSA and 5-HSA in various mixtures of DMSO-water and to study the effect of dielectric constants on protonation constants through acid-base titrations. Speciation profoundly influences both the toxicity and bioavailability of an element. The data obtained would be useful to those who are working in biomedicine.

MATERIALS AND METHODS

The chemicals required to carry out this present investigation is 5-SSA (TCI, India) and 5-HSA (TCI, India). Both the ligand solutions were prepared for 0.05M; this is done by dissolving the substance in distilled water. The dissolution of the ligand substances can be increased by adding little amount of hydrochloric acid (Qualigens, India); here, the acid concentration maintains the ligand solution at 0.05M. The ionic strength of the system was maintained at 0.16 mol L^{-1} using pure sodium chloride (Qualigens, India). Carbonate-free sodium hydroxide (Qualigens, India) solution and hydrochloric acid solutions are prepared for acid-base titrations by maintaining their concentrations at 0.4 mol L^{-1} and 0.2 mol $L^{-1,}$ respectively.

Alkalimetric titrations

An Equiptronics-made EQ614 A model pH meter was used to carry out the titrations in the present study. Before using the instrument, it was calibrated by using two standard solutions i.e. Borax and Potassium hydrogen phthalate, all the titrations are carried out at 303.0 K. The electrode was calibrated by keeping it the percentage of DMSO-water mixtures in which the study has to be carried out, the process is call the equilibrium process of the electrode. The process of keeping electrode in the DMSO-water mixtures has to be continued to all the mixtures under which the study was done. For better results from the electrode, the equilibrium process has to be done by allowing the electrode at least a week days before the titration. The data were analyzed using a one-way classification in order to determine the errors [12, 13]. The method Gran plot is used to calculate the concentrations of base and acid [14, 15]. The acid-base titrations are carried out at various compositions of DMSO-water mixtures; in the present investigation, the DSMO-Water mixtures are having the composition of 0.0-60.0% v/v, The amounts of 5-SSA and 5-HSA in the titrands ranging from 0.25-0, 50 mmol. The total initial concentrations of ingredients are given in table 1.

Table 1: Total initial concentrations of ingredients (in mmol) in proton-ligand titrations

DMSO% (v/v)	TL0	
	5-SSA	5-HSA
0.0	0.2499	0.2449
	0.3748	0.3673
	0.4998	0.4898
10	0.2493	0.2493
	0.3740	0.3740
	0.4987	0.4987
20	0.2445	0.2488
	0.3667	0.3732
	0.4890	0.4977
30	0.2442	0.2510
	0.3663	0.3765
	0.4885	0.5021
40	0.2505	0.2483
	0.3757	0.3724
	0.5010	0.4966
50	0.2494	0.2437
	0.3667	0.3656
	0.4989	0.4875
60	0.2439	0.2499
	0.3659	0.3748
	0.4879	0.4998

Modeling strategy

One of the best computer programs like SCPHD is used in the present study to determine the stability constant values [16] and correction factor, and also another computer program MINIQUAD75 has been employed to refine the obtained data [17, 18]. In the present study, we studied the influence of various compositions of DMSO-water mixtures on the protonation constant values.

RESULTS AND DISCUSSION

In generally the biochemical processes will occurs at a pH 7.0, i.e. neutral medium. The physiological pH is 7.2 to 7.4. Normal biochemical processes occur in aqueous solutions at about neutral pH. Physiological pH is about 7.2 to 7.4. The relation between secondary formation function and equilibrium constants can be understood with the equation below.

$$\bar{n}_H = \frac{\beta_{011} * FH_i + 2 * \beta_{012} * FH_i^2}{1 + \beta_{011} * FH_i + 2 * \beta_{012} * FH_i^2}$$

Where $\beta_{011} = K_1^H$ and $\beta_{012} = K_1^H * K_2^H$ and FH_i is the free hydrogen ion concentration. It is very useful to study the dimeric species and equilibria using secondary formation functions. The formation functions/can be defined as one mole of ligand and it is bounded with the average number of protons, one mole of ligand, which consumes the average number of moles of alkali (a). The number of dissociable protons of the ligand, total concentration, total acid concentration and the concentration of hydroxide ions can be calculated using a computer program called SCPHD, which is used in our present study. The equation employed to calculate the above said can be given as $\bar{n}_{Hi} = (NDP_i + TLE_i + E_i + OH_i - ALK_i - FH_i)/TLE_i$ It is very clear that there should be an overlap in a curve drawn between $\bar{n}_H$ versus pH, which indicates that the absence of formation of dimeric species. The overlapping of curves are observed in the case of the 5-SSA and 5-HSA, it confirms that there are no dimeric species are formed (fig. 1). A computer program MINIQUAD75 has been employed to simulate all the titration curves.

The half-integral values for the two ligands are 0.5 and 1.0, which says that both ligands have two protonation-deprotonation equilibria in the pH range of the present investigation. The number of associable and dissociable protons of a ligand can be understood with help of fig. 2, which is plotted between and pH, where a number of associable protons. From the fig. 2, it is confirmed that the two ligands has 3 dissociable protons as the maximum value of a is+3 for both ligands.

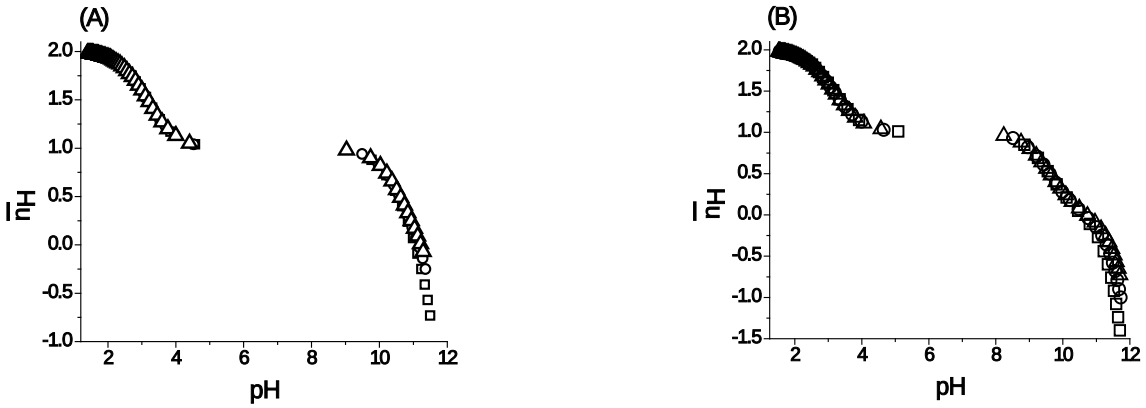

Fig. 1: Plots of $\bar{n}H$ /versus pH in 30% v/v DMSO-water mixture: (A) 5-SSA and (B) 5-HSA, (□) 0.25 (○) 0.38 (Δ) 0.50 mmol

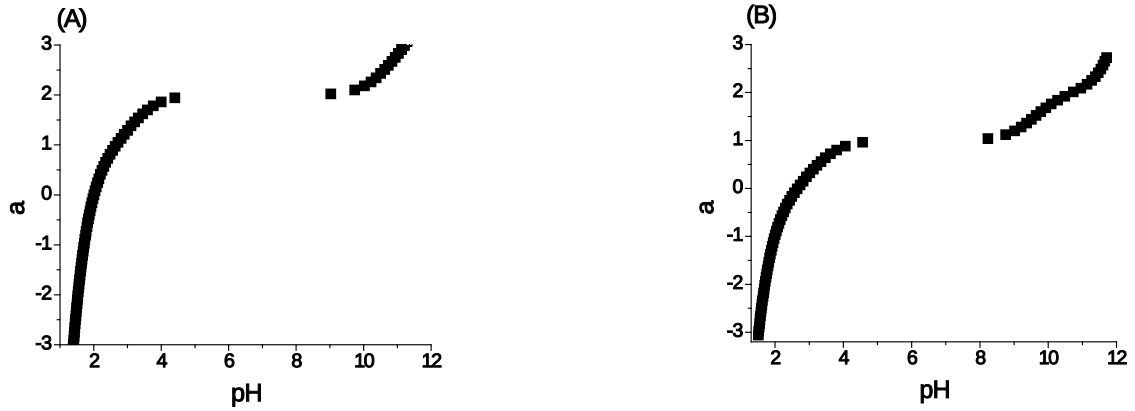

Fig. 2: Variation of a with pH in 40% v/v DMSO-water mixture: (A) 5-SSA (B) 5-HAS

The statistical parameters were calculated in the present study for the best-fit models; the calculated parameters, such as formation constants log β_i, Ucorr, skewness, kurtosis, R-Factor and Chi-square, were present in the table 2. The standard deviation values for log β are very low, which indicates the experimental data represents the model.

Residual analysis

The statistical data obtained in the present study are smaller than the tabular values. The *χ2* values are ranging from 1.21-6.88 and skewness values are ranging from-0.56-0.36 for 5-SSA and 5-HSA. The kurtosis values obtained in the present investigation for both 5-SSA and 5-HSA shows platykurtic. The obtained R-factor values also suggest that the present model is acceptable.

Effect of systematic errors in concentrations on best fit model

Effect of errors in the concentrations of acid, base, ligand is very useful as they show deviations in the protonation constant values but MINIQUAD75 does not have an in-built provision for the assessment of errors. To obtain a best fit chemical model, a critical evaluation has to be done by introducing pessimistic errors in the ingredients and checked for the variation in the protonation constant vales along with standard deviation. The changes in the protonation constants of both ligands are presented in the below table 3. It is observed that there are errors in their constants majorly due to change in the concentrations of acid and alkali; the rest of the ingredients shows very less influence.

Table 2: Best-fit chemical models of acido-basic equilibria of 5-SSA and 5-HSA in DMSO-water mixtures

% v/v DMSO	Log β_1(SD)	Log β_2(SD)	NP	Ucorr	Skewness	Kurtosis	χ^2	R-Factor
5-Sulfosalicylic acid (pH range 1.70-11.30)								
0.00	10.92(2)	13.23(1)	91	7.65	0.14	3.03	6.66	0.0166
10.0	10.86(1)	13.35(1)	82	21.52	0.11	2.68	8.91	0.0421
20.0	10.89(2)	13.70(3)	79	36.17	0.16	3.01	7.65	0.0256
30.0	10.72(3)	13.85(2)	69	42.24	0.18	2.97	5.45	0.0102
40.0	10.68(5)	13.91(4)	65	17.89	0.36	2.86	1.21	0.0213
50.0	10.54(2)	13.82(5)	58	57.14	0.16	2.64	2.35	0.0547
60.0	10.66(2)	14.02(78)	45	46.72	0.31	2.12	1.86	0.0279
5-Hydroxysalicylic acid (pH range 1.70-11.30)								
0.00	10.23(1)	13.05(1)	135	6.53	-0.56	2.90	6.88	0.0110
10.0	9.80(1)	12.89(2)	89	11.59	0.38	3.12	5.42	0.0679
20.0	9.69(4)	12.82(4)	75	29.12	-0.14	2.89	3.19	0.0456
30.0	9.70(3)	13.02(5)	67	38.61	-0.16	3.34	3.98	0.0278
40.0	9.57(1)	12.93(6)	58	66.14	0.24	2.78	2.81	0.0156
50.0	9.50(2)	12.98(6)	49	54.98	0.09	3.46	7.24	0.0118
60.0	9.52(1)	13.23(4)	38	47.09	0.26	2.57	2.76	0.0135

U_{corr}= U/(NP-m) X 10^8; NP = Number of points; SD = Standard deviation

Table 3: Effect of errors in influential parameters on the protonation constants in 10% v/v DMSO-water mixture

Ingredient	% Error	Log β_{mlh} (SD)			
		5-SSA		5-HSA	
	0	LH_2^-	LH^{2-}	LH_3	LH_2^-
		10.86(1)	13.35(1)	9.80(1)	12.89(2)
Alkali	+5	11.01(2)	14.01(1)	10.01(1)	13.12(2)
	+2	10.98(2)	13.78(1)	10.17(1)	13.29(2)
	-5	11.14(1)	13.96(1)	10.15(1)	13.35(2)
	-2	11.24(1)	13.01(1)	10.21(1)	13.10(2)
Acid	+5	11.75(1)	13.89(1)	10.20(1)	13.21(2)
	+2	11.56(2)	13.90(1)	10.35(1)	13.19(2)
	-5	11.23(1)	14.01(1)	10.15(1)	13.46(2)
	-2	10.37(1)	14.14(1)	10.68(1)	13.37(2)
Ligand	+5	10.75(1)	13.11(1)	9.89(1)	12.82(2)
	+2	10.69(1)	13.47(1)	9.70(1)	12.79(2)
	-5	10.79(1)	13.52(1)	9.85(1)	12.95(2)
	-2	10.59(1)	13.58(1)	9.78(1)	12.91(2)
Log F	+5	10.82(1)	13.41(1)	9.86(1)	12.86(2)
	+2	10.73(1)	13.56(1)	9.88(1)	12.81(2)
	-5	10.71(1)	13.25(1)	9.78(1)	12.92(2)
	-2	10.75(1)	13.38(1)	9.89(1)	12.94(2)
Volume	+5	10.79(2)	13.53(1)	9.89(1)	12.79(2)
	+2	10.74(1)	13.55(1)	9.87(1)	12.83(2)
	-5	10.89(1)	13.29(1)	9.76(1)	12.86(2)
	-2	10.81(2)	13.30(1)	9.81(1)	12.93(2)

Effect of the dielectric constant of the medium

The dielectric constant is an important property of any solvent; the polarity of the solvent affects the stability constants. The dielectric constant of a solvent and the electrostatic forces between ions and solution directly shows their impact on acid and base strength characteristics. According to previous [19, 20] studies and Born's [21, 22] equation, electrostatic contacts affect the dielectric constant of the system. The effect of dielectric constants on stability constants can be observed in fig. 3. The linear variation in the protonation constants of 5-SSA and 5-HSA shows the dominance of electrostatic interactions.

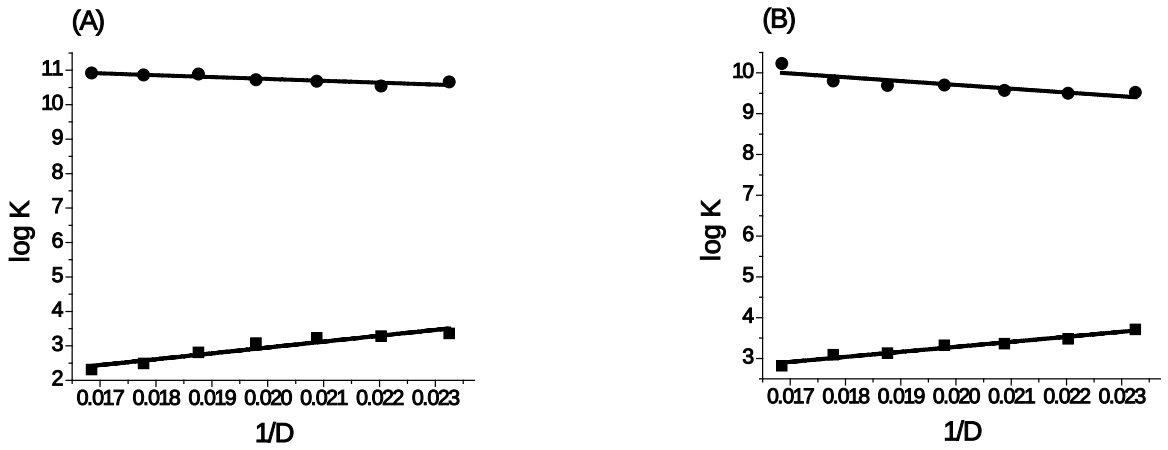

Fig. 3: Variation of stepwise protonation constants (log K) with reciprocal of dielectric constants in DMSO-water mixture, (A) 5-SSA, and (B) 5-HSA (■) log K_1 (●) log K_2

Distribution diagrams

The typical distribution plots produced by DISPLOT [23-27], 5-Sulfosalicylic acid has three dissociable protons, one among three has low protonation constant value and will dissociate at a pH lower than 2.0 and unable to see due to the glass membrane electrode sensitivity, the existence of the ligand will be as LH_2^-,LH^{2-}, and $L3^-$. In the same way 5-Hydroxysalicylic acid has three dissociable protons, one among the three has high protonation constant and will dissociate at a pH 12.0, this range of pH makes the glass electrode unable to detect the protonation as the sensitivity is high at the pH. The existence of 5-HSA will be as LH_3 at low pH and LH_2^- and LH^{2-}.

From fig. 4(A), it is observed that the ligand 5-SSA in the form of as LH_2^-shows 98% of species up to the pH 2.0, as the pH is increasing the deprotonation of LH_2^-takes place and the percentage of species slowly falling down and possess very less percentage of species at the pH 8.0. Percentage of species of LH^{2-}starts increasing with pH and exhibits 98% of species at the pH 7.0. As the pH is increasing further, the percentage of species falling down and produce very less percentage at the pH 11.0. The other form of 5-SSA ligand i.e. L^{3-} increases with pH and possess high percentage of species at a pH 11.0.

Now, the LH_3 form of 5-HSA possess high percentage of species at a pH 2.0 and the percentage starts falling down with respective to increase in the pH. The LH_2^- form of 5-HSA possess maximum percentage of species at pH 7.0 and the percentage gradually decreasing with increase in the pH. Another form of the ligand i.e. LH^{2-}gradually increases with increases with increase in the pH and exhibits highest percentage of species at pH 11.0. This is observed in the fig. 4(B). The effect of pH on the percentage of species of both ligands was studied in between the pH range 1.7-11.5.

The protonation-deprotonationequilibria of both the ligands 5-SSA and 5-HSA were shown in the fig. 5.

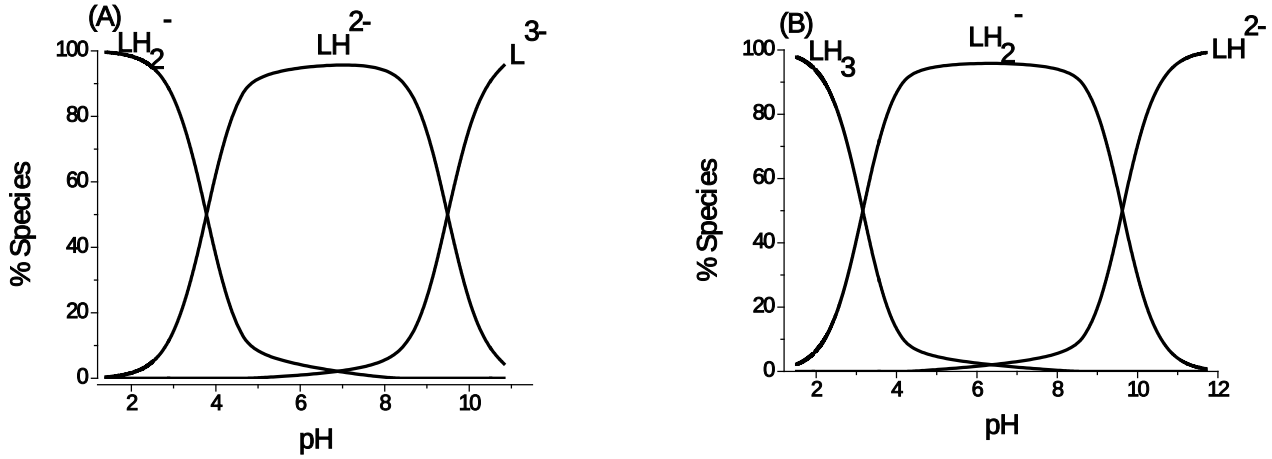

Fig. 4: Species distribution diagrams of (A) 5-SSA and (B) 5-HSA in 20% v/v DMSO-water mixture

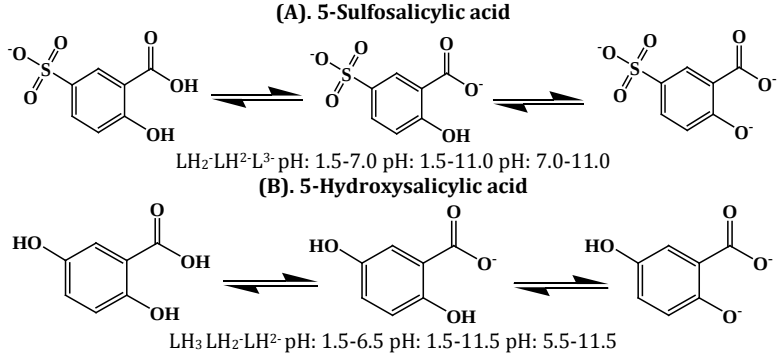

Fig. 5: Protonation-deprotonation equilibria of 5-SSA (A) and 5-HSA (B)

CONCLUSION

The half-integral values of both ligands confirm that they have three dissociable protons, 5-SSA has three dissociable protons and exists as LH_2^-, LH^{2-} and L^{3-} and 5-HSA has three dissociable protons and they exist as LH_3, LH_2^- and LH^2. The kurtosis values says that the system possess platykurtic. The skewness values of both the ligands ranging from 0.56-0.36 and the $\chi 2$ values are ranging from 1.21-6.88. The curve drawn between/versus pH indicates the absence of dimeric species. The changes in the concentration of alkali and acid shows major influence on protonation constants of both the ligands than the other ingredients such as ligand, log F and volume. The linear variation in the protonation constants of 5-SSA and 5-HSA due to the effect of dielectric constants of DMSO-water mixtures shows the dominance of electrostatic forces.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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