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Estimation of Drug-Protein Binding Parameters using Amino Acids as Low Molar Mass Model Compounds: A Review

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In drug development, the interactions between drugs and proteins are vital because they determine efficacy. However, due to the complex configurational and conformational structures of native globular protein molecules, it is difficult to understand their structural features. It is known that hydrophilic and hydrophobic groups as well as dipolar water interactions play a crucial role in the stability and structural properties of proteins as most biochemical and physiological processes occur in the aqueous medium. Such interactions may be understood via thermodynamic properties such as partial molar volume and compressibility. Thus, amino acids, simple monomer building blocks that mimic aspects of proteins, are used by researchers as model compounds to understand protein-drug interactions and protein hydration. This review surveys the thermodynamic properties of amino acids in drug solutions at various temperatures as they are crucial in interpreting the hydration of peptides and proteins. Past studies of amino acids in aqueous drug solutions at different temperatures are also discussed and summarised.

Key words: Amino acid; aqueous solution; drug, molecular interaction; physicochemical properties

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Studies of interactions between drugs and proteins are often complicated due to the intricacy of the configurational and conformational structures of native globular protein molecules. Hence, the various structural features of proteins can be difficult to recognise [1]. Hydrophilic and hydrophobic groups in proteins as well as dipolar water interactions play important roles in the stability and structural properties of proteins because biochemical and physiological processes occur in water [2]. Such non-covalent interactions are heavily influenced by solute molecules and the surrounding solvent that may be described by thermodynamic properties such as partial molar volume and partial molar compressibility [3].

To study protein interactions and hydration behaviour, amino acids are used as model compounds that mimic aspects of proteins [4]. Consequently, there has been a rise in popularity of physicochemical studies of amino acids in the presence of drugs as these can help us understand how drugs function and how they alter proteins [5]. However, it is difficult for researchers to fully utilise the data available as previous studies were varied in terms of amino acids, drugs, methods and data interpretation. For instance, some studies were performed at 30 ^{o}C (303.15 K) [5], rendering the data inapplicable to human physiological processes which occur at 37^{o}C (310.15 K). Any discrepancy in the results may also remain undiscovered if the existing data are not sorted and grouped accordingly. Hence in the following section we will summarise past studies on drug-amino acid interactions.

The main objective of this review is to survey the thermodynamic parameters of amino acids in drug solutions at various temperatures as they are important in interpreting the hydration of peptides and proteins. The effects of drug molecules on the viscometric and volumetric properties of amino acids in the aqueous system are also discussed in terms of their kosmotropic ('structure-making') effects on the hydration of amino acids. Journal finders such as Science Direct, Scopus, Springer, Google Scholar and Directory of Open Access Journals (DOAJ) were used with keywords such as 'amino acid-drug interaction', 'viscometric study', 'volumetric study', 'sound velocity study', and 'physicochemical and thermodynamic properties. The preferred parameters in each study namely volumetry (standard partial molar volume (V_{φ}^{0}), Hepler hydrophobicity criteria ($\delta V_{\varphi}^{0}/\delta T)_{P}$), viscometry (B-coefficient), sound velocity (partial molar adiabatic compressibility ($K^{o}_{\varphi,s}$)), spectrophotometric properties

(binding constants (K_a)), conductometry (molar conductance (Λ)), refractometry (higher molar refraction (R_M)) and calorimetry (molar enthalpy of dilution ($\Delta_{dil}H^0$)) are also discussed in this review.

1. Drug-Amino Acid Interactions

For drug-amino acid interactions, numerous experimental studies with various methods have been reported, and a summary of these are provided in Table 1. The methods used to determine the thermodynamic and physicochemical properties of the two molecules in water varied according to the goals of the studies, whether to determine a specific molecular interaction or the driving forces present therein, or both. Several methods were used in parallel to ensure the results were consistent. The methods commonly employed were volumetry, viscometry, or acoustics, followed by spectroscopy (Figure 1).

From our literature survey [15], 20 amino acids were used, either singly or in combination, for the drug-amino acid interaction studies. These were non-polar glycine, alanine, leucine, isoleucine, phenylalanine, valine, methionine and proline, polar uncharged serine, asparagine, glutamine and cysteine, polar positive arginine, histidine, lysine, polar negative aspartic acid and glutamic acid. In human blood plasma, these are present in large quantities as free amino acids. In addition, amino acids as monomers of proteins are naturally present in human serum albumin, blood cells and active sites of receptor proteins [6]. Hence, data obtained from drug-amino acid interaction studies may represent drug-protein interactions.

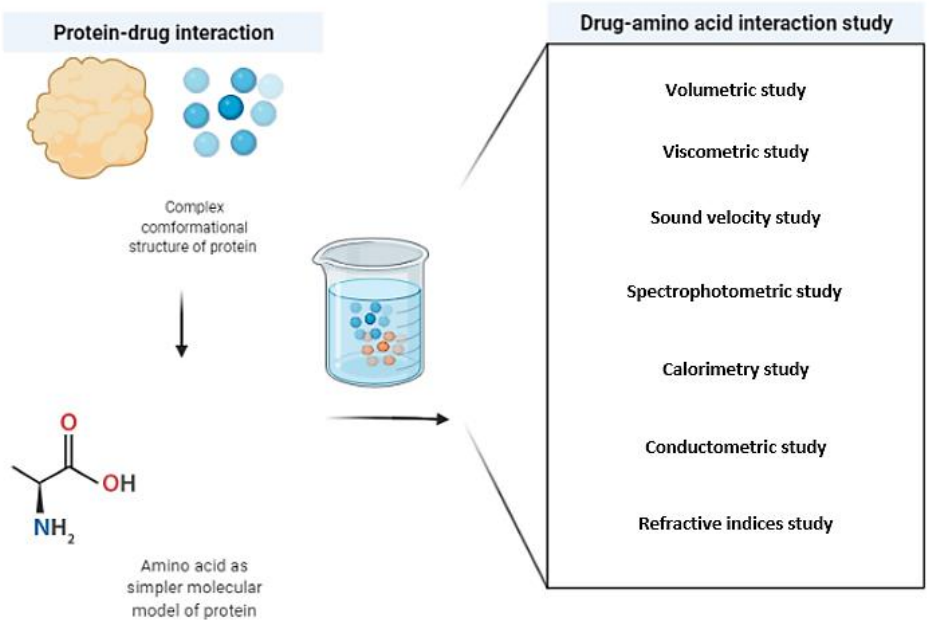

Figure 1. Studies on drug-amino acid interactions in aqueous solution as a model of protein-drug interactions.

Table 1. A summary of drug-amino acid interaction studies (HCl, hydrochloride; NSAID, nonsteroidal anti-inflammatory drug)

No	Drug	Amino acid	Method Used/Parameter measured)	Reference
1	Acetylsalicylic acid	Glycine, L-serine, L-proline, L-asparagine monohydrate and L-arginine	Ultrasonic speed, Density (303.15, 308.15 or 313.15 K)	[6]
2	Amikacin sulphate	Glycine and methionine	Density, Viscosity (293.15, 298.15, 303.15, 308.15 and 313.15 K)	[7]
3	Amoxicillin (antibiotic)	Glycine, L-alanine, L-valine, L-leucine	Ultrasonic speed, Density (305.15, 310.15 and 315.15 K)	[8]

4	Ampicillin sodium (antibiotic)	L-histidine	Density, Viscosity, Ultrasonic speed (293.15, 298.15, 303.15, 308.15 and 313.15 K)	[9]
5	Ampicillin	Glycine, glycylglycine, glycylleucine	Ultrasonic speed, Density (305.15, 310.15 and 315.15 K)	[10]
6	Benzalkonium chloride	Glycine, L-alanine, L-valine, L-leucine, glycylglycine, glycyl-L-valine, glycyl-L-leucine	UV-vis spectroscopy, Fluorescence spectroscopy, Density, Conductivity (293.15, 298.15, 303.15, 308.15 and 313.15 K)	[11]
7	Betaine HCl	L-arginine and L-histidine	Ultrasonic speed, Density, Viscosity (293.15, 298.15, 303.15, 308.15, 313.15 and 318.15 K)	[12]
8	Ciprofloxacin HCl	Glycine, and L-isoleucine	UV–vis spectroscopy, Ultrasonic speed, Density, Enthalpy (288.15, 293.15, 298.15, 303.15, 308.15, 313.15, 318.15 and 323.15 K)	[13]
9	Chloramphenicol	L-leucine and glycyl-L-leucine	Ultrasonic speed, Density (288.15, 298.15, 308.15, and 318.15 K)	[14]
10	Diclofenac sodium salt (NSAID)	Glycine, L-proline	Ultrasonic speed, Density (293.15, 298.15, 303.15, 308.15 and 313.15 K)	[15]
11	Dolonex (NSAID)	L-Alanine and L-Valine	Ultrasonic speed, Density (293.15, 298.15, 303.15, 308.15 and 313.15 K)	[16]
12	Dopamine HCl	Aspartic acid and glutamic acid	Density, Viscosity, Conductivity, UV-vis spectroscopy, Nuclear Magnetic Resonance spectroscopy and Raman spectroscopy (293.15, 303.15, and 313.15 K)	[17]
13	Furosemide (loop diuretic)	Glycine, DL-alanine	Density, Ultrasonic speed, Viscosity (293.15, 298.15, 303.15, 308.15, and 313.15 K)	[18]
14	Furosemide	Glycine and DL-alanine	Density, Ultrasonic speed, Viscosity, UV-vis spectroscopy (293.15, 298.15, 303.15, 308.15, and 313.15 K)	[19]
15	Gentamicin sulphate (antibiotic)	L-asparagine, L-glutamine	Density, Ultrasonic speed, Viscosity (293.15, 298.15, 303.15, 308.15, 313.15 and 318.15 K)	[20]
16	Glycyl dipeptides	Glycine, L-alanine, L-valine, L-leucine, Glycylglycine, Glycyl-L-valine and Glycyl-L-leucine	Density, UV–vis spectroscopy (293.15, 298.15, 303.15 and 308.15 K)	[21]
17	Isoniazid (antibiotic)	Glycine, L-alanine, L-valine and L-isoleucine	Density, Ultrasonic speed, Viscosity (293.15, 298.15, 303.15, 308.15, 313.15 and 318.15 K)	[22]
18	Ketorolac tromethamine	L-histidine	Density, Ultrasonic speed and Viscosity (293.15, 298.15, 303.15, and 308.15 K)	[23]

19	Ketorolac tromethamine (NSAID)	L-arginine	Density, Ultrasonic speed, Viscosity (293.15, 298.15, 303.15, 308.15 and 313.15 K)	[24]
20	Levofloxacin (antibiotic)	Glycine, L-alanine and L-valine	Density, Ultrasonic speed (288.15, 293.15, 298.15, 303.15 and 308.15 K)	[25]
21	Metoclopramide	Glycine, D-alanine, L-cystine and L-histidine	Density, Viscosity, Refractive index (303.15 K)	[26]
22	Metformin HCl	Glycine, DL-α-alanine, DL-α-valine, and DL-α-leucine	Density, Viscosity (308.15, 313.15 and 318.15 K)	[27]
23	Metformin HCl	L-glutamine and L-histidine	Ultrasonic speed, Density, Viscosity (298.15, 303.15, 308.15, and 313.15 K)	[28]
24	Metformin HCl	L-Phenylalanine	Density, Viscosity (298.15, 303.15, 308.15, 313.15 and 318.15 K)	[4]
25	Metformin HCl (antidiabetic and antihypergly-cemic agent)	L-Proline	Density (298.15, 303.15, 308.15, 313.15 and 318.15 K)	[29]
26	Pentoxifylline (Hemorrheologic agent)	Glycine, L-alanine, L-valine, Glycylglycine, and Glycylglycylglycine	Density (293.15, 298.15, 303.15, and 308.15 K)	[30]
27	Procainamide HCl (Antiarrhythmic)	L-alanine and L-valine	Density and Ultrasonic speed (298.15, 308.15 and 318.15 K)	[31]
28	NTPH (nortriptyline HCl)	Glycine, L-alanine and L-valine	Density and Ultrasonic speed, FTIR (288.15 K, 293.15 K, 298.15 K, 303.15 K and 308.15 K)	[32]
29	Paracetamol	Alanine	Ultrasonic speed (298.15, 303.15, 308.15, 313.15 and 318.15 K)	[33]
30	Semicarbazide HCl	Glycine, L-alanine, L-valine and L-isoleucine	Density, Ultrasonic speed, Viscosity (303.15, 308.15, 313.15 and 318.15 K)	[34]
31	Semicarbazide HCl	L-arginine and L-histidine	Density, Ultrasonic speed, Viscosity (293.15, 298.15, 303.15, 308.15, 313.15 and 318.15 K)	[35]
32	Streptomycin sulfate (antibiotic)	Glycine, L-alanine, L-valine, L-isoleucine	Density, Ultrasonic speed, Viscosity (293.15, 298.15, 303.15, 308.15, 313.15, and 318.15 K)	[36]
33	Streptomycin sulphate	L-asparagine/L-glutamine	Density, Ultrasonic speed, Viscosity (293.15, 298.15, 303.15, 308.15, 313.15 and 318.15 K)	[37]
34	Sulfanilamide, sulfanilic acid, and sulfosalicylic acid dihydrate	Glycine	Density (288.15, 298.15, and 308.15 K)	[38]

2. Parameters Studied

2.1 Volumetric Studies

By measuring density values, volumetric parameters may be calculated. The density data of a solution system at various temperatures and concentrations may be used to determine several volumetric properties. The common parameters derived from density data include apparent molar volume/partial molar volume (V_φ) (some use molal instead of molar), standard partial molar volume (V_φ^0), transfer volume (ΔV_φ^0) and the second derivative of infinite dilution of partial molar volume with respect to temperature ($\delta^2 V_\varphi^0/ \delta T^2$), which have proven useful in elucidating structural interactions that occur in solution [4,7].

The partial molar volumes of a solute at infinite dilution are known as standard partial molar volume or limiting partial molar volume. At infinite dilution, the solute-solute interaction is believed to be minimal, hence the temperature-dependant standard partial molar volume provides insight into the solute-solvent interactions. Experimental density values can be used to obtain the apparent molar volume (V_φ, $m^3 \cdot mol^{-1}$) via the following equation [8],

$$V_\varphi = M/\rho - (\rho-\rho_0)/m\rho_0\rho \quad (1)$$

where ρ is the density of the solution, ρ_0 is the density of water in $kg.m^{-3}$, m is the molality of the solution in $mol.kg^{-1}$ and M is the molar mass of the solute in $kg.mol^{-1}$.

The standard partial molar volume is obtained from the extrapolation of V_φ to an infinite dilution using the following linear equation [10]:

$$V_\varphi = V_\varphi^0 + S_v m \quad (2)$$

where m is the concentration of solute (amino acid) in $mol.kg^{-1}$ and S_v is the slope indicating solute-solute interactions (also known as the volumetric pairwise interaction coefficient v_{AA}) [11].

Values of the partial molar volume are dependent on the temperature and concentration of the drug solution [10]. Additionally, Singla *et al*. discovered that the partial molar volume also increased with the number of alkyl groups present in amino acids from glycine to leucine, at all temperatures [12].

The standard partial molar volume, also known as the limiting value of the apparent molar volume of the solute V_φ^0, is the change in volume when 1 mol of solute is added to an infinite amount of solvent. This parameter is useful to investigate solute-solvent interactions in solutions where solute-solute interactions are not present [13].

To avoid oversimplification when interpreting V_φ^0, Wawer *et al*. suggested the use of the following equation [13],

$$RC_v = [(V_\varphi - V_\varphi^0)/V_\varphi^0] \, 100\% \quad (3)$$

where RC_v is the relative deviation of apparent molar volume from its limiting (standard) value which also indirectly compares S_v versus V_φ^0:

$$RC_v = [(mS_v/ V_\varphi^0)]100\% \quad (4)$$

Gupta *et al*. obtained comparable values of RC_v for L-arginine/L-histidine in water and in aqueous semicarbazide hydrochloride solutions. These findings support their conclusion regarding the presence of weak solute-solute interactions (at infinite dilution) in the solution system using Mason's equation [14].

The V_φ^0 data also elucidate the hydration properties, solute hydrophobicity and solute-solvent interaction. Meanwhile, the derivative with temperature indicates the hydrophobicity of the solute (also known as Hepler hydrophobicity criteria): if $(\delta V_\varphi^0/ \delta T)_P>0$ and $(\delta^2 V_\varphi^0/\delta T^2)_P<0$, the solute is hydrophilic, where $(\delta V_\varphi^0/\delta T)_P$ is actually the partial molar expansibility, and if $(\delta V_\varphi^0/ \delta T)_P<0$ and $(\delta^2 V_\varphi^0/ \delta T^2)_P>0$, the solute is hydrophobic [15].

As for the second derivative of infinite dilution of partial molar volume with respect to temperature ($\delta^2 V_\varphi^0/ \delta T^2$), most amino acid-drug ternary systems showed positive values (hydrophobic solute) indicating structural promoter behaviour in drugs such as furosemide, gentamicin sulphate, metformin HCl, and ketorolac tromethamine [16-19]. However, there are exceptions when the saturation point is reached, e.g., with amoxicillin where the value became negative at high concentrations of the amino acid or drug (at 0.2 $mol.kg^{-1}$ or when interacted with L-leucine at higher amoxicillin concentration) [20]. Meanwhile, there are also amino acids that produced negative values when interacting in a solution system with certain drugs such as pentoxifylline, levofloxacin, NTPH (nortriptyline HCl), procainamide HCl, dolonex and diclofenac sodium salt (DSS), suggesting structure-breaking behaviour [21].

The degree of hydration in water is indicated by the hydration number n_H (solvation number n_s, in molecules of water per molecule of solute). On the other hand, the effect of hydration may be evaluated using the electrostriction partial molal volume $V_\varphi^{0}{}_{(elec)}$ from the

experimentally measured V_φ^0 values as,

$$V_{\varphi}^{0}{}_{(elec)} = V_{\varphi}^{0} - V_{\varphi}^{0}{}_{(int)} \quad (5)$$

where $V_{\varphi}^{0}{}_{(int)}$, the intrinsic partial molal volume is calculated using the following expression,

$$V_{\varphi}^{0}{}_{(int)} = (0.7/0.634) \times V_{\varphi}^{0}{}_{(cryst)} \quad (6)$$

where

$$V_{\varphi}^{0}{}_{(cryst)} = (M/\rho_{(cryst)}) \quad (7)$$

with M and ρ being the molecular weight and density of the amino acids, respectively. The value 0.7 is the packing density for molecules in the organic crystal and 0.634 is the packing density for randomly packed spheres in equation (4). The decrease in volume due to electrostriction can be related to the number of water molecules hydrated to the amino acids n_H and is estimated using the following relation [15,22],

$$n_H = V_{\varphi}^{0}{}_{(elec)} / (V_E^0 - V_B^0) \quad (8)$$

where V_E^0 is the molal volume of the electrostricted water and V_B^0 is the molal volume of bulk water at T = 308.15 K.

$$(V_E^0 - V_B^0) = -4 \text{ cm}^2.\text{mol} \quad (9)$$

This value of $(V_E^0 - V_B^0)$ has been retained for other studied temperatures following the work of Lark *et al* [23].

The hydration number generally increases with the size of the amino acid in water [15]. However, for the amino acid in a drug solution, the hydration number depends on the drug. Rajagopal and colleagues studied the interaction between metformin HCl with L-phenylalanine, L-proline and L-threonine, and found the hydration number decreased with an increase in drug concentration and temperature as metformin HCl had a dehydration effect [4,18,24].

The hydration number represents the volume behaviour of a solute at infinite dilution which provides information regarding solute-solvent interactions, where positive values indicate the presence of solute-solvent interactions and the magnitude signifies the strength of these interactions. The literature shows positive values of partial molar volume which are dependent on the temperature and concentration of the drug solution. All amino acids in the studies we reviewed showed positive values and had positive linear relationships with drug concentration and temperature [10]. Additionally, a study by Singla *et al*. showed that the partial molar volume was enhanced with an increase in the number of alkyl groups present in amino acids from glycine to leucine at all temperatures [12].

The V_φ^0 values in water and in aqueous drug solutions from equation (2) were used to calculate the partial molar volume of transfer at infinite dilution using the equation:

$$\Delta V\varphi^0 = V\varphi^0 \text{ (amino acids in aqueous drug solution)} - V\varphi^0 \text{ (amino acids in water)} \quad (10)$$

As solute-solute interactions are absent at infinite dilution, the observed ΔV_φ^0 are assumed to be due to the solute-solvent interaction. The amino acid-drug interactions can be rationalised by the cosphere overlap model developed by Friedman and Krishnan, where the interactions are classified as: (1) (ion+hydrophilic) interactions (between zwitterionic centres of amino acids and polar groups of the drug; (2) (hydrophilic+hydrophilic) interactions (between polar groups of amino acids and polar groups of the drug); (3) (ion+hydrophobic) interactions (between zwitterionic centres of amino acids and nonpolar groups of the drug); and (4) (hydrophobic+hydrophobic) interactions (between non-polar groups of amino acids and non-polar groups of the drug) [4].

According to the cosphere overlap model, (ion+hydrophobic) interactions and (hydrophobic+hydrophobic) interactions contribute negatively, whereas (ion+hydrophilic) and (hydrophilic+hydrophilic) interactions contribute positively to the ΔV_φ^0 values [4]. For transfer volumes (ΔV_φ^0) of amino acids, most studies showed positive values indicating a specific contribution to the transfer volumes of amino acids from water to aqueous drug solutions. However, the trend varied with the drug they interacted with, for example the most frequent amino acid studied, glycine, showed positive values that increased with the concentrations of the amino acid (interaction with metformin HCl) and the drug (interaction with amoxicillin) [12,25]. The two studies that gave negative values were L-phenylalanine with metformin HCl, and glycine and L-proline with diclofenac sodium salt (DSS), where interactions with DSS showed decreasing negative values with an increase in temperature [21].

2.2. Viscometric Studies

To determine viscometric parameters, experimental viscosity (η) values for amino acids in pure water and aqueous solutions of drugs at different temperatures are measured. Data are then analysed using the Jones-Dole empirical equation [15, 26, 39-41]:

$$\eta/\eta_0 = 1 + AC^{1/2} + BC + DC^2 \quad (11)$$

which is usually simplified to

$$\eta_r = 1 + AC^{1/2} + BC \quad (12)$$

where n_r ($=\eta/\eta_0$) is the relative viscosity of the solution, η and η_0 are the viscosities of the solution and the solvent, respectively, C is the molar concentration (evaluated from molal concentration 'm' using the standard relation), A is the Falkenhagen coefficient that reflects solute-solute interactions that can be estimated theoretically but are typically negligible for non-electrolytes, and which in amino acid solutions are often omitted, while B is the viscosity coefficient that reflects solute-solvent interactions [1]. The D coefficients from the original equation which represent solute-solute and solute-solvent interactions are omitted here, although they are necessary at higher concentrations. As the goal is to obtain information about solute-solvent interactions in ternary systems rather than solute-solute interactions, many researchers use the relative viscosity data η_r in the modified equation [4],

$$\eta_r = 1 + BC \quad (13)$$

Thus, in studies of amino acid-drug interactions, the measured relative viscosity is used to obtain information on B only (solute-solvent interactions) rather than A (solute-solute).

Generally, positive B-coefficients indicate kosmotropes (structure-making) since strongly hydrated solutes exhibit a larger change in viscosity with concentration, while a negative value shows chaotropic (structure-breaking) behaviour for weakly hydrated solutes. However, Zhao suggested that the B-coefficients may not be indicative especially for large hydrophobic solutes [15]. In fact, amino acids in this review have relatively large B-coefficients, but not all of them are kosmotropic. The magnitude of a B-coefficient is also reflective of the strength of solute-solvent interactions. In a study by Chauhan *et al*., solute-solvent interactions in metformin HCl seem to be more effective in the presence of L-histidine, as reflected by its higher B-coefficient, compared to L-glutamine [1].

Many researchers prefer the first derivative of the B-coefficient with temperature. This is because dB/dT is more indicative in measuring the structure-making or breaking ability than the B-coefficient. As per the literature, when dB/dT is negative, the solute is kosmotropic but when dB/dT is positive, it is chaotropic. The values of dB/dT are established based on Eyring's theory of viscosity, where a negative dB/dT value corresponds to the energy of activation for viscous flow being greater for the solution than for the pure solvent.

Meanwhile, the viscometric properties of glycine were also studied in other aqueous drug solutions such as amikacin sulphate, furosemide, aqueous-streptomycin sulphate, and aqueous isoniazid solution [16,27-29]. In a study by Chauhan *et al*. on glycine and DL-alanine, the positive viscosity B-coefficient and negative dB/dT value showed their structure-making tendencies in aqueous furosemide [16].

In two separate studies by Nain *et al*. and Gupta *et al*., homologous glycine, L-alanine, L-valine and L-isoleucine in aqueous-streptomycin sulfate solution and aqueous isoniazid showed positive B-coefficients that increased with temperature. This signified strong solute-solvent interactions, where the amino acids act as structure-breakers in the ternary solutions [28].

A study by Gupta *et al*. for gentamicin sulphate in L-asparagine and L-glutamine solutions showed positive B-coefficient values that decreased with an increase in temperature. This signified a structure-making effect of the solute on the solvent [17]. Another study by Sawhney *et al*. on dolonex in aqueous solutions of L-alanine and L-valine showed positive viscosity B-coefficients [30]. In fact, similar results of the structure-breaking ability of these two amino acids were found in the literature [28,31].

In a study by Sawhney *et al*., L-arginine in an aqueous solution of ketorolac tromethamine showed negative dB/dT values indicating the amino acid was kosmotropic. This was later confirmed by Gupta *et al.* [14].

2.2.1. Thermodynamics of Viscous Flow

Viscosity data such as activation factors, Gibbs energies of activation per mole of solute and free energies of activation per mole of solvent were calculated according to Eyring transition state theory [32]. According to this theory, the B-coefficient could be stated by the following equation,

$$B = [(V_1^o - V_2^o) + V_1^o (\Delta\mu_2^{o\#} - \Delta\mu_1^{o\#}) / RT]/1000 \quad (14)$$

where V_1^o is the apparent molar volume of the mixed solvent (aqueous amino acids) and V_2^o ($=V_\varphi^o$) is the limiting apparent molar volume of the solute at infinite dilution, respectively. The free energy of activation per mole of solvent ($\Delta\mu_1^{o\#}$) may be obtained by applying the Eyring viscosity relation [32]:

$$\Delta\mu_1^{o\#} = RT \ln (\eta V_1^o/hN) \quad (15)$$

where h and N are the Planck's constant and Avogadro number respectively, and equation (14) rearranges to give the free energy of activation per mole of the solute, $\Delta\mu_2^{o\#}$.

$$\Delta\mu_2^{o\#} = \Delta\mu_1^{o\#} + (RT/ V_1^o [1000B – (V_1^o – V_2^o)]) \quad (16)$$

The entropy, ΔS^o, and enthalpy, ΔH^o, of activation of viscous flow are calculated using the following relations [29]:

$$\Delta H^o = \Delta\mu_2^{o\#} + T\Delta S^o \quad (17)$$

$$\Delta S^o = -d (\Delta\mu_2^{o\#} /dT) \quad (18)$$

The ΔS^o values are obtained from the negative slopes of the plots of $\Delta\mu_2^{o\#}$ versus T using a least-squares treatment.

Within the range of our literature review, most amino acids when interacted with a drug gave positive values of $\Delta\mu_2^{0*}$ which were larger than $\Delta\mu_1^{0*}$, indicating the structure-making ability of the amino acid in an aqueous drug solution. However, the pattern varied where the magnitude decreased with an increase in the concentration of the drug (furosemide, metformin HCl, ketorolac tromethamine) and temperature (ketorolac tromethamine, gentamicin sulphate, metformin HCl), but increased with the concentration/complexity of the amino acid (gentamicin sulphate, furosemide). For metformin HCl, increasing values with drug concentration were seen in interactions with L-histidine and L-glutamine [1,4,19,25,29,33].

2.3. Sound Velocity Studies

Partial molar adiabatic compressibility ($K^o_{\varphi,s}$) and partial molar adiabatic compressibility of transfer ($\Delta K^o_{\varphi,s}$) are common parameters determined in a sound velocity study. Values of $K^o_{\varphi,s}$ are obtained using linear regression, and the magnitude of $K^0_{\varphi,s}$ indicates solute–solvent interactions as solute-solute interactions are negligible at infinite dilution [34].

Equations to obtain these acoustic parameters are similar to volumetric equations and often the parameters of these two studies are calculated and analysed simultaneously for convenience [16,28,29]. The equations are as follows:

$$K_{\varphi,s} = [1000(K_s\rho_o - K_s^o\rho)/ m\rho\rho_o] + (K_sM/\rho) \quad (19)$$

where M is the molality of the solute (amino acid), ρ and ρ_o are the densities of the solution and the solvent (water or aqueous drug) respectively, calculated using the relation,

$$K_s = 1/u^2\rho \quad (20)$$

where u is the acoustic velocity and ρ is the density of the solution.

The limiting apparent molar compressibility can be obtained with

$$K_{\varphi,s} = K^o_{\varphi,s} + S_km \quad (21)$$

where the intercept is free from the interaction between solutes and therefore reveals the solute-solvent interactions, whereas the linear regression slope parameter, S_k is a measure of solute-solute/ion-ion interactions. Such interactions are dependent on the charge, and the nature of the solute and solvent, where negative values indicate water molecules surrounding charged groups of amino acid molecules, which provide greater resistance to compression than water molecules present in the bulk of the solution, while positive values indicate that the solution is more compressible [35]. The partial molar adiabatic compressibility of transfer of each amino acid from water to drugs at infinite dilution is calculated using the equation [35],

$$\Delta K^0_{\varphi,s} = K^0_{\varphi,s} \text{ (in aqueous drug solution)} - K^0_{\varphi,s} \text{ (in water)} \quad (22)$$

The $K^0_{\varphi,s}$ values for glycine, L-alanine, L-valine, L-leucine, L-proline, L-histidine, L-serine, L-asparagine, L-arginine, and L-glutamine in aqueous solutions of drugs are negative, and they become less negative with an increase in temperature and drug concentration, except for L-arginine in acetyl salicylic acid (ASA), where $K^0_{\varphi,s}$ values become less negative with increasing drug concentration and temperature [12,16,17,19,21, 29,31,36-38]. In the amino acid-drug solution system where $K^0_{\varphi,s}$ values become less negative with an increase in temperature, the electrostriction is reduced and some water molecules are released to the bulk [42]. Negative values of $K^0_{\varphi,s}$ for all the systems indicate the existence of solute-solvent interactions. Meanwhile, $\Delta K^0_{\varphi,s}$ values were positive for the amino acids and increased with drug concentration. The mostly positive values of $\Delta K^0_{\varphi,s}$ indicate the dominance of interactions between the zwitterionic centres of the amino acid and drug, leading to the structure-making tendency of the ions. With increasing drug concentration, electrostriction diminishes, enhancing the structure-making tendency of ions. As a result, the electrostricted water is much less compressible than the bulk water [12].

2.4. Spectrophotometric Studies

For spectrophotometric studies on drug-amino acid interactions, UV-Vis, FTIR, Raman, nuclear magnetic resonance (NMR) and fluorescence spectroscopy are methods commonly applied. The absorption spectra obtained are dependent on the concentration of the studied solution system.

To understand the intermolecular interactions that occur in the ternary system, UV-Vis spectroscopy

provides additional data, analysing the absorbance of aqueous solutions of amino acids with different concentrations of drugs [33]. Some of the drugs that have been studied with amino acids are dopamine HCl, ciprofloxacin HCl, glycyl dipeptides, benzalkonium chloride and furosemide.

From UV-Vis measurements, association or binding constants (K_a or K_b) may be calculated. The association constants (K_a) and thermodynamic parameters of the amino acid + drug system may be calculated using the modified Benesi-Hildebrand equation [43]:

$$1/A\text{-}A_0 = (1/\Delta\varepsilon[AA]\,K_a)\,(1/[D]) + (1/\Delta\varepsilon\,[AA]) \qquad (23)$$

where [D] and [AA] represent drug and amino acid concentrations, respectively, while $\Delta\varepsilon$ signifies the difference in the molar extinction coefficient between the free and drug-bound amino acids. The change in absorption caused by addition of the drug is represented by $A\text{-}A_0$. The value of K_a can be obtained by dividing the y-intercept by the slope of the straight line of the double reciprocal plot. For further evaluation, free energy change ΔG may be determined through the relation:

$$\Delta G = -RT \ln K_a \qquad (24)$$

In the study by Yasmin *et al*., the association constant for glutamine+dopamine HCl was found to be higher than that of asparagine+dopamine HCl, suggesting that the former system had a higher degree of interaction. Both structures had negative ΔG values, indicating that complex formation was possible [43].

Meanwhile, in domiphen bromide the obtained K_b values in the presence of four amino acids (glycine, L-alanine, L-valine, L-leucine) were found to be 48.17 ± 0.06, 49.98 ± 0.06, 50.89 ± 0.06 and 51.45 ± 0.07 $m^3.mol^{-1}$ and 52.77 ± 0.05, 53.00 ± 0.03 and 55.63 ± 0.04 $m^3.mol^{-1}$, respectively. The experimental results show that the strength of the binding affinity between the amino acids and domiphen bromide follows the order L-leucine > L-valine > L-alanine > glycine [44].

The spectral pattern of the drug as it transitioned from its free state to its bound state with the amino acids was also observed. The changes indicate the strength of the interactions occurring in the solution process. There are four types of shifts in the UV-Vis spectrum: the bathochromic shift (also known as red shift), hypsochromic shift (blue shift), hyperchromic shift and hypochromic shift (Figure 2).

Beri *et al*. studied the ciprofloxacin HCl drug system with glycine and isoleucine. The significance of the hydrophilic-hydrophilic/ionic interactions is shown by the hyperchromic shift in the absorption spectra of ciprofloxacin HCl in glycine and isoleucine. The blue shift in the wavelength of ciprofloxacin HCl in the presence of isoleucine was due to the greater degree of interaction, compared to the ciprofloxacin HCl-glycine system which experienced a red shift [45].

For the study involving dopamine HCl with L-aspartic acid and L-glutamic acid, a red shift was observed in both systems. The absorption maximum was enhanced with an increase in the concentration of dopamine HCl [43].

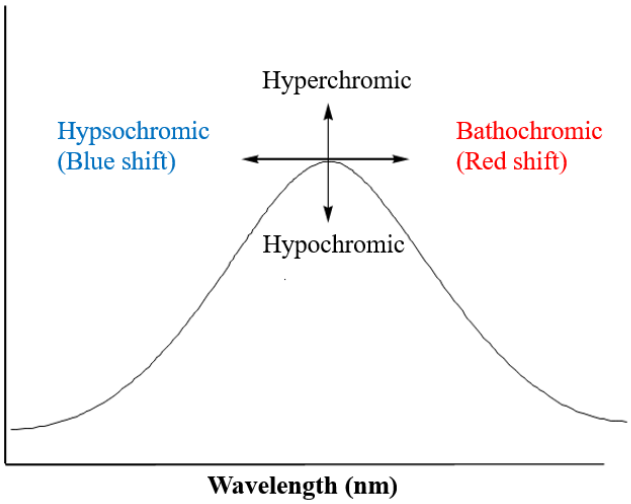

Figure 2. Types of shifts in a UV-Vis spectrum.

Yan *et al*. in their study on benzalkonium chloride with amino acids glycine, L-alanine, L-valine and L-leucine, reported a hyperchromic shift in the UV-Vis absorption spectra. It was concluded that lengthening the side chain of small biomolecules strengthened the interactions between amino acids and benzalkonium chloride molecules [46].

FTIR was used in a study on glycine, L-alanine and L-valine in an aqueous solution of nortriptyline HCl [47] to support the volumetric and acoustic data obtained. The spectra of the pure drug nortriptyline HCl, its aqueous solution and aqueous solution mixed with amino acids were investigated. Based on the findings, it was determined that the shift in wavenumber with changes in amino acid and nortriptyline HCl concentration indicated some form of structural change, which confirmed previous findings.

Raman spectroscopy is a vibrational spectroscopy that can be used to view intermolecular interactions in detail. Excitation wavelengths in the visible spectrum are used to collect Raman spectra. In the study by Yasmin *et al*. for dopamine HCl with aspartic acid and L-glutamic acid, it was concluded that the solute-solvent interaction increased from L-aspartic acid to L-glutamic acid [43].

Fluorescence spectroscopy via a steady-state fluorescence quenching method was used to assess the aggregated amount of benzalkonium chloride in water and aqueous solutions in the presence of glycine, L-alanine, L-valine and L-leucine [48]. The following equation can be used to calculate the drug's aggregation number, N_{agg}, in the presence and absence of amino acids using the steady-state fluorescence quenching method:

$$\ln (I_0/I) = N_{agg} [CPC]/(S_T - cmc) \quad (25)$$

where I_0 and I represent fluorescence intensity before and after the quencher addition, while [CPC] and S_T are the concentrations of cetylpyridinium chloride and total drug, respectively. The N_{agg} values were obtained from the linear relation of ln (I_0/I) against [CPC]. The packing parameter was also determined to predict micellar aggregate shape using the equation,

$$P = v_c/(a_0 I_c) \quad (26)$$

where I_c and v_c represent the length and volume of the hydrocarbon tail of the benzalkonium chloride molecule in the micellar core, respectively. A_0 is the surface area of the head group of a micelle. I_c and v_c are estimated from the Tanford equations,

$$v_c = (27.4 + 26.9n)Å^3 \quad (27)$$

$$I_c = (1.5 + 1.265n)Å \quad (28)$$

where n denotes the number of carbon atoms in the alkyl chain of benzalkonium chloride. The radius (r) and a_0 of a micelle are estimated by $r = [3v_c N_{agg}/ (4\pi)]^{1/3}$ and $a_0 = 3v_c/r$.

The molecular weight (MW) of a benzalkonium chloride micelle is related to its hydrodynamic radius (R_h) and leads to the following equation,

$$MW = -9.855R_h^2 + 50.79R_h - 30.04 \quad (29)$$

where the units of MW and R_h are kilodaltons (kDa) and nanometers, respectively.

The addition of amino acids to a drug solution has been found to reduce the size of micelle aggregates. The distribution of benzalkonium chloride monomers and the surface charge density of the micelle are affected by the complex interactions of amino acids with water. The micelle's surface area, and therefore its aggregate size, will be altered.

Nuclear magnetic resonance (NMR) is used in drug solution systems with amino acids to analyse the changes in the electronic environment around the various protons of a drug molecule in the presence of amino acids. The electron density in the immediate surroundings influences the chemical changes of the amino acids and the substance under investigation.

In the study of dopamine HCl with aspartic acid and glutamic acid, intermolecular hydrogen bonding between the benzene ring and NH_2 (in dopamine HCl) was observed, resulting in a decrease in electron density around the benzene ring [43]. Potential contributing factors include intermolecular H-bonding interactions between amino acids and dopamine HCl, and hydrophobic interactions.

2.5. Calorimetry Studies

Calorimetry studies are mostly done in protein-ligand binding using two methods, DSC (differential scanning calorimetry) and ITC (isothermal titration calorimetry). In DSC, the binding of the ligand to proteins is observed as an increase in the melting temperature of the proteins, whereas ITC directly measures the heat associated with ligand binding [49,50]. Nevertheless, there has been one application of ITC in an interaction study of ciprofloxacin HCl with glycine and L-isoleucine [45].

ITC is used to determine the dilution enthalpy, q, for ciprofloxacin HCl in water and in aqueous solutions of glycine and L-isoleucine. The q values for the solute (drug) were observed to be positive in water and in the presence of cosolutes (amino acids). These values

decreased as the concentration of solute or drug (m_A) increased, but rose with the concentration of cosolute or amino acid (m_B). Fitting the q and m_A data to the following equation with constants S_{w1}, S_{w2}, and S_{w3} yields the normal molar enthalpy of dilution $\Delta_{dil}H^0$,

$$q = \Delta_{dil}H^0 + m_A S_{w1} + m_A^2 S_{w2} + m_A^3 S_{w3} \quad (30)$$

The standard molar enthalpy of transfer $\Delta_{tr}\Delta_{dil}H^0$ for the ciprofloxacin HCl from water to aqueous solutions of glycine/L-isoleucine was also determined as follows,

$$\Delta_{tr}\Delta_{dil}H^0 = \Delta_{dil}H^0 \text{ (in aqueous solutions of glycine/ L-isoleucine)} - \Delta_{dil}H^0 \text{ (in water)} \quad (31)$$

A low m_B value results in a negative $\Delta_{tr}\Delta_{dil}H^0$ value for ciprofloxacin HCl, whereas a high m_B value results in a positive value. Negative transfer values at low m_B indicate dominant hydrophilic/hydrophilic ionic interactions, whereas positive $\Delta_{tr}\Delta_{dil}H^0$ values at high m_B imply that the dehydration effect of cosolutes is dominant over hydrophilic/hydrophilic ionic interactions.

2.6. Conductometric Studies

The ability of a substance to conduct electricity is determined by the ionic content of its solution. The most cost-effective and efficient method of determining the ionic content of a solution is to calculate its conductivity. Along with viscosity, conductivity can be used to determine the composition of an electrolyte solution [51]. Conductometry has been applied in several studies involving solubility enhancement, e.g., atorvastatin and simvastatin in the presence of arginine, albendazole in nicotinamide, inclusion complexation of drugs in cyclodextrins and gluten by arginine [52-55]. Yasmin *et al*. [43] performed a conductometric study on aspartic acid and glutamic acid in a dopamine HCl aqueous solution.

Molar conductance (Λ, Sm cm^{-1}) can be calculated using the following equation,

$$\Lambda = 1000\kappa/C \quad (32)$$

where C is the molar concentration and κ is the measured specific conductance of the studied systems.

In dopamine HCl - amino acid solutions, a decreasing trend of Λ values was observed. This may be attributed to factors such as: (i) interactions caused by the hydrophobic effect with both hydrocarbon chains of amino acids and alkyl chains of the drug molecule itself; (ii) changes in the chemical structure of dopamine as the temperature rises, where dopamine undergoes aerial oxidation, which causes the molecule to change from a benzenoid to a quinone structure; and (iii) dopamine-to-quinone (DQ), which is less reactive than a benzenoid, enabling the intermolecular hydrogen bonding interaction ($-NH_3^+$—COO^-) between dopamine (—NH_2.HCl) and amino acid (-COOH) [43].

2.7. Refractive Index Studies

The refractive index (n_D) is a physicochemical property of a substance, which reveals the magnitude of its molecular interactions in solution. It is defined as the c_o/c ratio, where c_o is the speed of light in vacuum and c indicates the speed of light in the medium. The refractive index of a compound determines its ability to refract light as it passes from one medium to another. A high refractive index compound indicates that more light is refracted while higher molar refraction (R_M) values suggest that more interactions are taking place.

This approach has been used in many studies on interactions of molecules, such as diclofenac sodium, cetirizine, and doxycycline, and binary mixtures of esters and alcohols (diethyl succinate, or ethyl octanoate + isobutanol, or isopentanol) [56-59]. For drug-amino acid interactions, studies have been conducted on metoclopramide-glycine/D-alanine/L-cystine/L-histidine aqueous systems and on aspartic acid and glutamic acid in an aqueous solution of dopamine HCl [60]. In the study, the refractive index of aqueous solutions of the drug in amino acid at 303.15 K increased with drug concentration for all the amino acid systems studied, showing that the refractive index was dependent on concentration. However, no other indication was discussed.

The dependency of refractive index on drug concentration in aqueous amino acids has been studied using the $n_D = Kc +$ equation and n_D^0 from the plot of n versus c, where the refractive index at infinite dilution (n_D^0) is the intercept of n_D^0, while the constant K was the slope of the plot. Meanwhile, the Lorentz-Lorenz relation is used to calculate the molar refraction R_M. This value is a measure of the capacity of molecular orbitals to be impaired under an electrical field applied, as the value is directly proportional to molecular polarizability,

$$R_M = \{(n^-_D - 1)/(n^2_D + 2)\} (M/\rho) \quad (33)$$

where R_M, n_D, M and ρ are the molar refraction, refractive index, molar mass and density of the solution, respectively.

In the study by Yasmin *et al*., the dopamine solution reacted more with glutamic acid than with aspartic acid. This was due to higher values of R_M, which suggested a greater extent of interactions [44].

CONCLUSION

Based on the literature, there are currently a small number of studies on drug-amino acid interactions available compared to amino acids in water, ion-amino acid, and organic solute-amino acid interactions. Hence, more studies are required to better understand drug-amino acid interactions. The volumetric, viscometric, sound velocity, spectrophotometric, conductometric, refractometric and calorimetric studies of drug-amino acid solution systems discussed in this review may help interpret the behaviour of peptides and proteins in aqueous drug solutions.

This information will shed light on why amino acids can be structure-makers or breakers in certain drugs, and why some drugs produce hydration or dehydration effects on amino acids. Although determination of the thermodynamic properties of drug-amino acid interactions is seemingly simple and straightforward, one needs to be careful when making assumptions to apply constants in some of the equations used. Most importantly, one should not oversimplify the interpretation of the data acquired. The best strategy is to confirm the results using multiple study parameters for higher accuracy.

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