Solubility enhancement of ibuprofen in oral liquid preparations using basic amino acids as counter ions

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ABSTRACT

Background: The recent advance in combinatorial chemistry to find new drug candidates has increased the number of compounds having low solubility profile, which makes them more difficult and less desirable for further dosage form development. Salt formation is one of the most common and preferred method for increasing the aqueous solubility of poor soluble drugs. Basic amino acids are considered fairly strong bases with the advantages of self-buffering in the formulation as well as producing salts that have pleasant tastes and less likely to be affected by the common-ion effect.

Objective: The main aim of the project will focus on the development of a universal solubilising vehicle for the formulation of insoluble acidic drug candidates as liquid preparations through salt formation by using acidic amino acids as counter ions.

Materials and Methods: Ibuprofen was chosen as a drug candidate and reacted with two different basic amino acids (lysine and arginine). Phase solubility diagram was obtained by measuring the solubility of ibuprofen free acid with different concentrations of basic amino acid (lysine and arginine) by UV spectrophotometer. The amino acid solutions pH was measured using pH meter. The stability of the prepared salts in in the presence of other solvents such as ethanol and glycerin and other salts such as potassium chloride was monitored by measuring the solubility of the drug over time.

Results: Increasing the concentrations of both arginine and lysine resulted in increasing pH of the solution and consecutively improving the solubility of ibuprofen by 1371 and 242 fold, respectively. The prepared salts showed high stablity in the presence of ethanol, glycerin and potassium chloride over a period of 6 months.

Conclusion: salt formation is very effective method in solubility enhancement provided that the appropriate counter-ion with the correct concentration and pH condition is used.

Keywords: *amino acid, solubility, salt formation*

INTRODUCTION

The recent advance in combinatorial chemistry to find new chemical candidates and the increased focus on the specificity of the drug on the expense of its "drugability" has increased the number of compounds with low solubility profile. This makes these drugs difficult and less desirable for further dosage form development [1]. This shift has increased the need for methods to improve and enhance the solubility of these synthesized compounds especially in the formulation of liquid preparations [2].

Many formulation strategies have been utilized to increase drug solubility such as reduction of the particle size, using co-solvents and surfactant, pH modification, lipid formulation and complexation. However these strategies have their own limitations and disadvantages of being inadequate, relatively expensive, having quite complicated formulation process and problematic quality control [3-6].

Salt formation is one of the most common and preferred method for increasing the aqueous solubility of poor soluble drugs; it is very effective, simple, less expensive method that is well accepted from regularities [7, 8]. The choice of the counter-ions is very important in determining various physiochemical and biopharmaceutical properties of the salt. The need of stronger basic counter-ions has increased over the year due to the continuous rise in the number of weakly acidic poor water soluble drugs [2].

Basic amino acids (lysine and arginine) are considered fairly strong bases (Figure 1) with the advantages of producing less basicity in the formulation, self-buffering action [9] as well as producing salts that have pleasant tastes which is a property that is especially useful in the case of oral liquid formulation [10, 11]. They are also less likely to be affected by the common ion effect, which has a major negative impact on the solubility of sodium and potassium salts in the presence of gastric and intestinal sodium/potassium ion [12] (the potassium salt of ibuprofen is extremely hygroscopic and has never been used in commercial tablets) [13]. ElShaer et al. has demonstrated that the solubility of trimethoprim has increased significantly when combined with glutamic and aspartic acid due to the formation of novel salts with a self-buffering capacity forming a suitable pH for the solubility of the salt during dissolution [14].
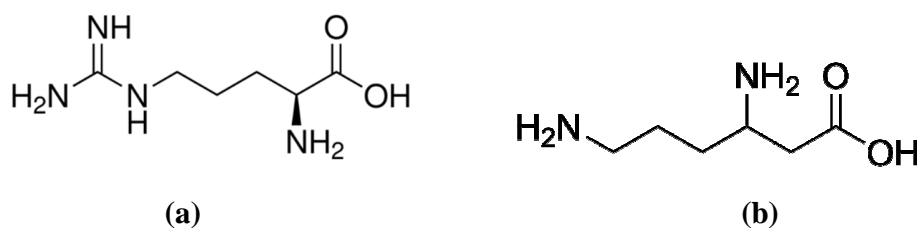
Figure 1. Arginine (a) and lysine (b) chemical structures.

The main aim of the project is to focus on the development of a universal solubilising vehicle for the formulation of an acidic drug candidate as liquid preparation through salt formation by using basic amino acids (lysine and arginine) as counter ions. Ibuprofen (Figure 2) was chosen as the model drug, which is a relatively weak acid (pKa 4.4) that has low water solubility (21 µg/ml) [15]. Ibuprofen is classified as a Class II drug according to the present Biopharmaceutical Classification System (BCS). Ibuprofen shows pH-dependent solubility. It is insoluble in acidic medium and its solubility increases only above a pH of 6.5 [16].

Another objective is to determine the stability of the liquid preparation and its compatibility with other co-solvents such as ethanol and glycerin and investigating the effect of common ions such as potassium chloride on solubility.
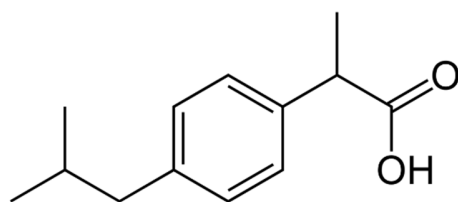

Figure 2. Ibuprofen chemical structure.

MATERIALS AND METHODS

Materials

L-lysine and L-arginine were bought from sigma Aldrich, UK. Ibuprofen was purchased from Samarra Drug Industries (SDI), Samarra, Iraq. KCL was purchased from Riedel-deHaën, Germany. Ethanol was purchased from J.T. Baker, Netherlands. Glycerine was purchased from Biosolve, France.

Methods

Analytical Technique

The amount of ibuprofen solubilized in the solution samples was measured using UV spectrophotometer (Model SPUV-26, SCO tech) at 224 nm. A linear calibration curve was obtained at concentrations ranging between 1–50 μg/mL (R^2 of 0.998, slope of 0.065, and intercept of 0.005)

Phase Solubility Diagram

Phase solubility diagram was obtained by monitoring the solubility of ibuprofen free acid with different concentrations of basic amino acid (L-lysine and L-arginine). Excess ibuprofen was transferred into capped plain tubes that contain different concentrations of the amino acid solutions and shaken at room temperature by water bath shaker (Schutzart DIN EN 60529, Memmert) for 24 hr. The tube content was filtered after equilibrium by 0.45 µm filters and analysed by UV spectrophotometer to obtain ibuprofen concentration. The amino acid solutions pH were measured using (WTW InoLab pH 720) pH meter.

Solubility study

An excess equimolar amount of ibuprofen with the amino acid (arginine and lysine) were transferred to capped tubes with 10 mL of distilled water and agitated at room temperature for 24 hr until equilibrium was reached. The tube content was filtered by 0.45 μm filters and the concentration was measured by UV spectrophotometer after suitable dilution.

Stability and compatibility studies

Equimolar amount of ibuprofen with the amino acid (L-lysine and L-arginine) were solubilized in water, then the solutions were mixed and agitated until equilibrium was achieved after 24 hr at room temperature. The filtrate was transferred into separate tubes with the addition of ethanol 10%, glycerin 10%, and potassium chloride 1% to each tube separately (with the exception of one tube).

Samples are taken from these solutions and filtered, then the solubility of the drug in the filtrate is measured by UV spectrophotometer at different time intervals of 0, 1, 2, 3, 4, 5, 6 months.

Statistical Analysis

Data analysis was performed by GraphPad Prism V 5.01 software. The results were described as mean ± SEM. One way ANOVA followed by Tukey post-test was performed for comparison. Probability values of (P <0.05) was regarded as significant statistically. P value with one star (*) represents significance and P value with more stars represents higher significance.

RESULTS AND DISCUSSION

Phase Solubility Diagram

A solubility phase diagram was created between ibuprofen and two basic amino acids; arginine and lysine as described by ElShaer et al [17]. Figure 3 reveals that increasing the concentrations of cationic amino acid results in increasing the pH of the solution and as a result increasing the solubility of ibuprofen, especially at high concentrations of the amino acids. Ibuprofen solubility increased from 22 ± 5.2 μg/mL to 1172 ± 82.7 μg/mL when arginine concentration increased from 10 μg/mL to 1000 μg/mL. There is an empirical rule which state that the difference in pKa between the base and the acid should be more than 2 pH units for a stable ionic bond and salt formation to occur [18]. Arginine has a basic (-NH$_2$) side chain (guanidinium group) with a pKa of 13.8 which is more than 9 units higher than the pKa of ibuprofen (pka 4.4) [19]. Therefore, ibuprofen can possibly act as a strong acid in the

solution of arginine with the capabality of protonating the -NH$_2$ basic group of arginine. A linear relationship (R2 = 0.992) between ibuprofen solubility and arginine concentration was revealed which indicates that ibuprofen was completely ionization in arginine solution suggesting the possibility of salt formation. In spite of the slightly lower pka of the basic (-NH$_2$) side chain (ζ-aminium group) of lysine (pKa = 10.9) a similar pattern in solubility enhacement was obtained probably due to ibuprofen ionization in solution. Ibuprofen solubility increased from 15 ± 6.8 μg/mL to 414 ± 67.3 μg/mL when the concentration of lysine increased from 10 μg/mL to 1000 μg/mL.
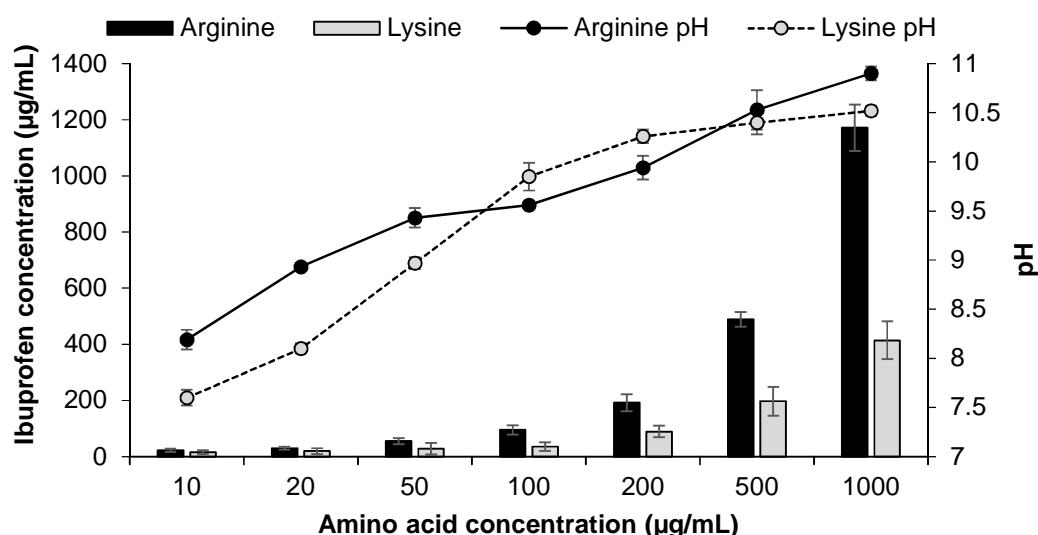

Figure 3. Phase solubility diagram of ibuprofen in different arginine and lysine concentrations at different pH (n = 3).

Solubility study:

In the case of liquid formulation; dissolution rate, crystal form, flow properties and hygroscopicity are less important factors to consider in the choice of counter-ion and the salt form since all of differences in these properties will disappear as soon as the drug is in solution [20]. The main important parameter that is required in salts that are intended to be formulated as pharmaceutical solutions is their solubility in the formulation.

Liquid formulations require higher aqueous drug solubility to achieve sufficient drug concentration; therefore, certain salts may show a good dissolution rate that is important in the case of solid drug formulation, but may not necessarily exhibit enough aqueous solubility for the formulation of an acceptable stable liquid preparation.

Solubility studies showed that the saturated solubility of ibuprofen free acid was 0.062 ± 0.024 mg/mL in water. Arginine and lysine increased ibuprofen solubility by 1371 and 242 fold, respectively compared to the free drug. The solubility of ibuprofen in arginine and lysine solution was about 85 ± 8.9 mg/mL and 14 ± 3.7 mg/mL respectively (Figure 4). The higher solubility in arginine solution compared to lysine may be due to the higher pKa of arginine guanidinium group (13.8) versus the pka of lysine ζ-aminium group (10.9).
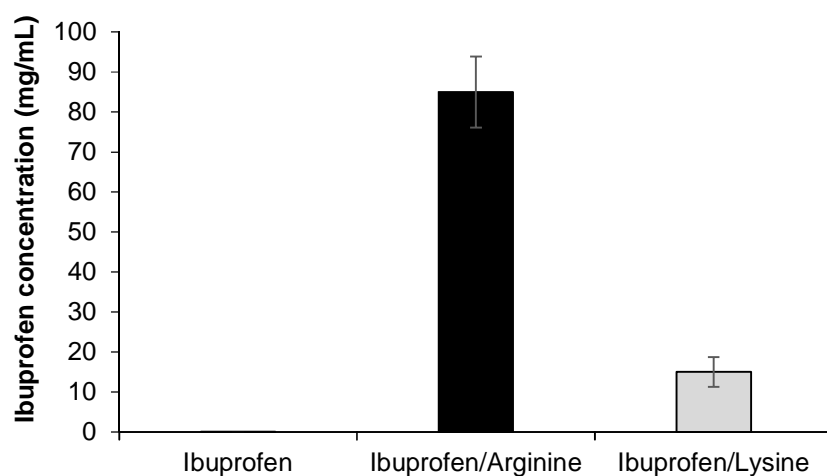

Figure 4. Solubility of ibuprofen alone and in the presence of arginine and lysine mean ± SD (n = 3).

Stability and compatibility studies

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Precipitation of the drug to its free form is a frequent problem in liquid dosage form. The salt solubility was determined alone and in the presence of ethanol and glycerol over time to determine the extent of precipitation and chemical stability of the liquid formulation in storage condition. Ethanol and glycerol are polar organic solvents that are frequently used in oral liquid dosage forms to dissolve many water-insoluble excipients like flavoring agents and antimicrobial preservatives [21]. Organic solvents can negatively affect the solubility of the drug salt through by reducing its ionization, or decreasing solubility of the salt form [2, 22]. Organic solvent can also cause a shift in both pH_{max} and the pKa of the weakly acidic drug [23, 24].

Another important factor to investigate is the effect of counter ion on the salt solubility. Even if the counter-ion that is used is different from the potassium/sodium ion in the physiological media, Li et al. shows that the non-hydrochloride salts of haloperidol (phosphate and mesylate salts) can be converted to the less soluble hydrochloride (HCl) salt if enough chloride ion is found in the dissolution medium [12]. Although this problem is more pronounced in solid dosage form during dissolution and less of a concern in the case of liquid formulation, it is worth to know whether this conversion from the non-potassium to the potassium salt occur or have a significant negative impact on the solubility of the salt.

The results (expressed as percentage of the drug over time) in Figure 5 showed high stability of ibuprofen in arginine and lysine solution alone and in the presence of ethanol, glycerol. In all solutions, ibuprofen percentage did not decrease below 98% over a period of 6 months, which show high physical and chemical stability and compatibility of ibuprofen with the other organic solvents. The high stability of the salt in ethanol and glycerol can be attributed to the complete ionization of ibuprofen due to the large difference

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between pKa of ibuprofen and the pKa of arginine and lysine. Therefore, shifting pka of the drug will not have a significant effect on salt solubiliy. In addition, the negative effects of these organic solvents on salt solubility may be negated by their positive effect in increasing the solubility of unionized drug, lowering pH_{max} and favoring salt formation [23]. The results also showed that there is no significant effect of potassium ion (1%) on ibuprofen solubility, which indicate that the amino acid salt is very stable against conversion to other salt form (potassium salt), and hence the effect of common ion is not expected to influence the solubility of the drug in the gastrointestinal tract [25].
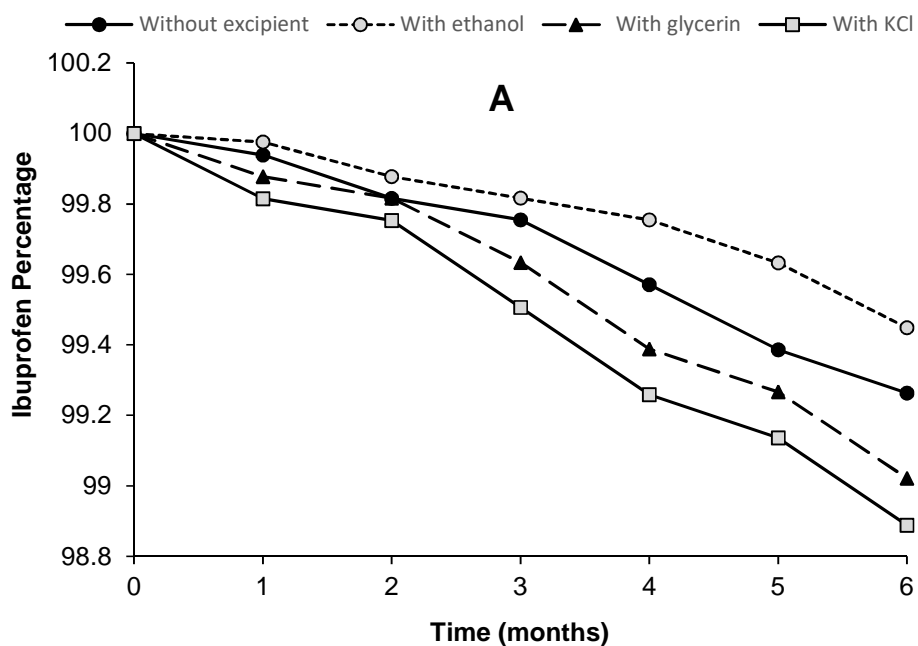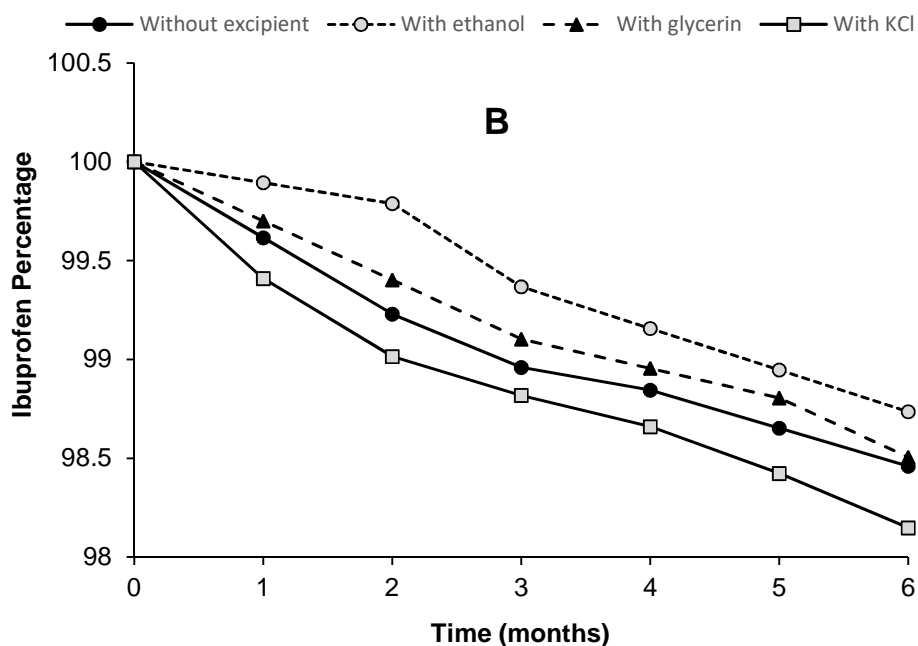
Figure 5. Ibuprofen percentage over time alone and in the presence of ethanol, glycerol, KCl in (A) arginine solution and (B) lysine solution (n = 3).

CONCLUSION

Salt formation is very effective method in solubility enhancement provided that the appropriate counter-ion with the correct concentration and pH condition is used. Future work will focus on the physical and chemical characterization of the salt and testing its pharmacological effect in rats.

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