Journal of Pharmaceutical Innovation (2019) 14:382–390
https://doi.org/10.1007/s12247-018-9361-x

ORIGINAL ARTICLE

Ionic Liquid Forms of Carvedilol: Preparation, Characterization, and Solubility Studies

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Published online: 12 November 2018
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Abstract

Purpose Pharmaceutically active compounds (API) in solid form have several disadvantages which may include polymorphism, poor solubility, and low bioavailability. To overcome these issues, API-based ionic liquids have been proposed to solve this problem.

Methods Solvent evaporation method was selected to prepare ionic liquid forms of CVD. A binary mixture of CVD with citric acid, tartaric acid, and saccharin in 1:1 M ratio was dissolved in 5 ml of methanol then they left 4 days for solvent evaporation. The solubility of CVD and prepared ionic liquids were measured in different media.

Results A viscous yellow liquid in all cases was obtained. More than three-unit differences between pK_a of CVD and studied compounds and characterization by different instrumental analysis methods confirmed the formation of an ionic liquid form of CVD and the prepared ionic liquids could significantly change the solubility of CVD.

Conclusion Overall, ionic liquids of CVD could be used for overcoming the disadvantages of its solid form and increasing CVD solubility. However, pH, type, and concentration of dissolution medium and the solubility of counter-ions are critical issues which they should be considered in evaluating solubility of CVD and its ionic liquid forms.

Keywords Carvedilol · Ionic liquid · Solubility

Introduction

Solubility is one of the common physicochemical properties of active pharmaceutical ingredient (API) which it is an essential point in the evaluation of drug candidates in drug discovery and development and preparation of new formulations [1, 2]. Various methods for solubilization of API have been proposed such as cosolvency [3], using complexing agents [4], surfactants [5], nanosizing [6], and crystal engineering [7]. However, salt formation is a classic method for solubilization of drug molecules. It is applicable for ionizable drugs whenever a three-unit difference was observed between pK_a of base and acid [8]. Several analytical techniques could provide valuable information for salt formation such as Fourier transform infrared spectrophotometer (FT-IR), differential scanning calorimetry (DSC), powder X-ray diffraction and single X-ray crystallography [9, 10].

Ionic liquids (salt in the liquid state) usually with a melting point less than 100 °C are considered as a new solvent instead of classic organic solvent. They have some advantages from the green chemistry viewpoint and they are applied in different aspect of chemical and pharmaceutical sciences for extraction and analysis of pharmaceutical substances [11], synthesis [12], as an antibiotic agent [13], and it was used for drug delivery such as improving the skin permeation [14]. Moreover, ionic liquids were used as a solvent for the solubilization of medicines [15–17]. Recently, the salt formation of active pharmaceutical ingredient (API) in liquid state which it is named as API-ionic liquids has been considered as a new technique to improve the solubility of medicines [18, 19]. Different API-based ionic liquids such as lidocaine with etodolac [20], sulfasalazine with choline [21], some non-steroidal anti-inflammatory drugs (NSAIDs)

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12247-018-9361-x) contains supplementary material, which is available to authorized users.

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with tetrabutyl phosphate [22], and amantadine with benzoic acid [23] were prepared and a significant increase in their solubility has been reported which they may have an impact on the oral bioavailability. Moreover, solid state stability of API is one of the common problems in the pharmaceutical industry which this technique avoids polymorphic transformation [24], although the chemical stability is more considered in liquid forms.

Carvedilol (CVD) is a very slightly soluble basic compound with $pK_a = 7.8$ corresponds to the secondary amine group in the structure of CVD which it could be ionized in acidic media. The acidic carbazole group in CVD's structure is in the unionized form in biological pH [25]. CVD is a non-selective β and α_1 blocker that is used in the management of various cardiovascular diseases such as hypertension, angina pectoris, and congestive heart failure. It also has antioxidant effects and more promising therapeutic applications such as liver cirrhosis [26]. Based on the reported data in the literature [38], CVD is not susceptible to acidic, basic, thermal, and UV–vis light stress conditions [27].

CVD is a drug with low oral bioavailability (25%) and from a biopharmaceutical classification point of view is a class II drug (low solubility and high permeability) [25]. Although first pass metabolism is another possible for its low bioavailability [28], so an increased solubility and dissolution rate for CVD is a useful strategy to improve its bioavailability [29]. Various plans such as preparation of solid salts [30], complexing agents [31], using of nanofibers [32], nanomicelle formulation [33], solid dispersion [34], and preparation of amorphous and coamorphous forms [35, 36] were applied to improve solubility and dissolution rate of CVD. Citric acid (CA), tartaric acid (TA), and saccharin (SAC) are common acceptable pharmaceutical excipients to change the physicochemical properties of drugs. CA and TA belong to "generally regarded as safe" (GRAS) list [37] and SAC approved by FDA for use in food as a non-nutritive sweetener [38]. In previous work, ionic liquid forms of ketoconazole with CA and TA have been prepared and the physicochemical properties, i.e., solubility, was studied [39]. SAC also is a common counter-ions to prepare API-based ionic liquids with basic compounds such as bupivacaine and pyridostigmine [40].

In this study, ionic liquids of CVD with CA, TA, and SAC have been prepared by solvent evaporation method and salt formation have been confirmed by different instrumental analysis method. The apparent solubility of CVD and their ionic liquid forms has been determined in different media, i.e., various concentrations of HCl, acetate buffer solution (pH = 4.8), and phosphate buffer solution (pH = 6.8) at 37 °C.

Method and Materials

Crystalline form of carvedilol (Form II) (Damavand Darou Co, Damghan, Iran) with a melting point of 115 °C [27], CA (in monohydrate form), TA, SAC, methanol, sodium hydroxide, hydrochloric acid (HCl, 12 M), and sodium acetate were purchased from Merck (Darmstadt, Germany). Disodium hydrogen phosphate and sodium dihydrogen phosphate were supplied from Barcelona, Spain. All of the materials were analytical grade. Lab-made distilled water was used for the preparation of the solutions.

Preparation of CVD-Based Ionic Liquids

Solvent evaporation method was applied to prepare ionic liquids of CVD. Equimolar (1:1, millimolar) of CVD with CA (in monohydrate form), TA, and SAC were dissolved by sonication in 5 ml of methanol (a mutual solvent), separately, until a clear solution appeared, then it was left for 4 days at room temperature for solvent evaporation.

Characterization of CVD-CA, CVD-TA, and CVD-SAC by Different Instrumental Analysis Methods

The thermal properties of CVD, CA, TA, and SAC (crystalline solid) were assessed, using differential scanning calorimetry (DSC) (PerkinElmer, USA) from 30–240 °C, and CVD-CA, CVD-TA, and CVD-SAC (liquid compounds) were studied from − 120 to 240 °C.

The samples were studied by Fourier transform infrared spectrophotometer (FT-IR) to evaluate the potential interaction between the studied compounds. Sodium chloride aperture plate and sandwiching it under another aperture plate were used to get FT-IR spectrum of the prepared ionic liquids. Moreover, the ionization of counter-ions (CA, TA and SAC) was checked by H-NMR-400 MHz (Bruker, USA).

Apparent Solubility Determination of CVD and Prepared Ionic Liquids in Different Media

The apparent solubility of CVD and the prepared ionic liquids were determined in phosphate solution (pH = 6.8, 0.1 M), acetate solution (pH = 4.8, 0.1 M), and three different concentrations of HCl (0.2, 0.1 and 0.01 M) at 37 °C using the shake-flask method. For simulation of intestinal fluid, phosphate buffer solution (pH = 6.8, 0.1 M) was prepared by an appropriate amount of disodium hydrogen phosphate and sodium dihydrogen phosphate (0.40 g and 0.86 g in 100 mL, respectively) and the pH of solution was adjusted by sodium hydroxide (1 M). Solubility evaluation of CVD was performed in two different acidic media, i.e., acetate buffer solution (pH = 4.8, 0.1 M) and different concentration of HCl (0.2, 0.1 and 0.01 M). Acetate buffer solution was prepared by dissolving an appropriate quantity of sodium acetate (0.82 g in 100 mL) and the pH of solution was adjusted by HCl (1 M). Various concentration of HCl because of previous reports about a significant effect of HCl concentration on CVD's solubility [25,

27] was prepared by diluting of the stock solution of HCl (12 M) by distilled water.

An excess amount of CVD and its ionic liquid forms (15–60 mg equivalent of CVD) on a tiny aluminum paper were added to an Erlenmeyer flask containing 25 ml of each medium. The solutions were sonicated for 15 min until the ionic liquid was dispersed in the dissolution medium. Then, the solutions were put in a shaker-incubator equipped with a temperature controlling system (Heidolph, Schwabach, Germany) and were maintained at 37 °C (The speed of the shaker was set at 150 rpm). After 48 h, an appropriate amount of solution was sampled by syringe and it was filtrated by a funnel and filter paper. The CVD's absorbance in clear solution was determined using a UV-spectrophotometer (Shimadzu, Tokyo, Japan) at 332 nm. In this wavelength, the applied counter-ions (CA, TA and SAC) have no significant absorbance in the studied media. The concentration was calculated based on the plotted calibration curve in each medium by standard solutions of CVD (linear range 10–200 mg/L and $R^2 = 0.999$). The solutions were diluted to maintain linearity whenever they had an absorbance out of calibration range. One-way analysis of variance (ANOVA) was applied to compare solubility of CVD and its ionic liquid forms in different media by the SPSS 17.

Results and Discussion

Characterization of CVD's Ionic Liquids

Figure 1 shows the prepared ionic liquid of CVD, CVD with CA, TA, and SAC (white crystalline materials) converted to a viscous yellow liquid after dissolving them in 1:1 M ratio in methanol and complete solvent evaporation after 4 days. Formation of a colorful compound has been reported for API-based ionic liquids in the literature [41, 42]. This method was used in the preparation of different ionic liquid forms of some drugs such as ketoconazole with TA and CA [39] and sulfasalazine and acyclovir with choline [43].

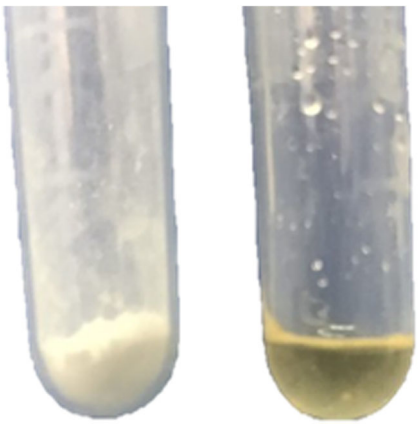


Fig. 1 Photographs of solid powder of CVD (left) and the prepared ionic liquid (right)

The DSC thermograms of CVD, CA, TA, and their ionic liquid forms have been demonstrated in Fig. 2. They show that CVD and studied acidic compounds are crystalline and they have a distinct endothermic peak corresponding to the melting of solid forms. The DSC curve of CA exhibits a broad endotherm which it indicates hydrate form of CA, while prepared ionic liquids have no typical endothermic melting peak. A small broad endothermic peak at 80 °C may be related to residual solvent in the prepared ionic liquids. Ionic liquids usually have a melting point less than 100 °C such as the prepared ionic liquid of benzalkonium and ibuprofen [19]. However, no melting point was observed in the prepared ionic liquid of ampicillin with trihexyltetradecylphosphonium [44] and ketoconazole with CA and TA [39].

Conversion of a solid material to liquid form is possible because of absorption of moisture from the atmosphere (deliquescence process). However, the preliminary study confirmed that studied compounds do not convert to liquid form in the absence of counter-ions. In addition, CVD is a non-hygroscopic compound and solid state and solution-phase stability studies confirmed its stability in different conditions [27]. The previous study on hygroscopic properties of carboxylic acids did not show that the deliquescence phenomenon for CA and TA even when the relative humidity is 90% [45]. Moreover, one of the possible reasons for the obtained liquid form is the salt formation in the liquid state or ionic liquid based on the approximately three-unit difference between pK_a of acid and base [8]. According to the collected data in Table 1 [27, 46], CVD is basic compound with a pK_a of 7.8 for amine functional group and the first pK_a for carboxylic acids of CA and TA are 3.09 and 2.95, respectively, and SAC is a stronger acidic compound with pK_a of 1.31. More than a three-unit difference between the pK_a of CVD with studied acidic compounds could indicate the salt formation between them. Therefore, one of the carboxylic acids of CA, TA, and benzothiazole ring of SAC could be involved in an ionic bond with the amine group of CVD.

Moreover, FT-IR was used to confirm ionic bond formation between CVD and studied acidic compounds (Fig. 3 and Fig. S1 in supplementary information) for prepared ionic liquids. Asymmetrical stretching for carboxylate functional groups (COO^-) in 1595 cm^{-1} and 1597 cm^{-1} for CA and TA was observed in FT-IR spectra of CVD-CA and CVD-TA, respectively. A strong asymmetrical band below 1600 cm^{-1} can indicate to the carboxylate functional group and the salt formation between the studied compounds [30].

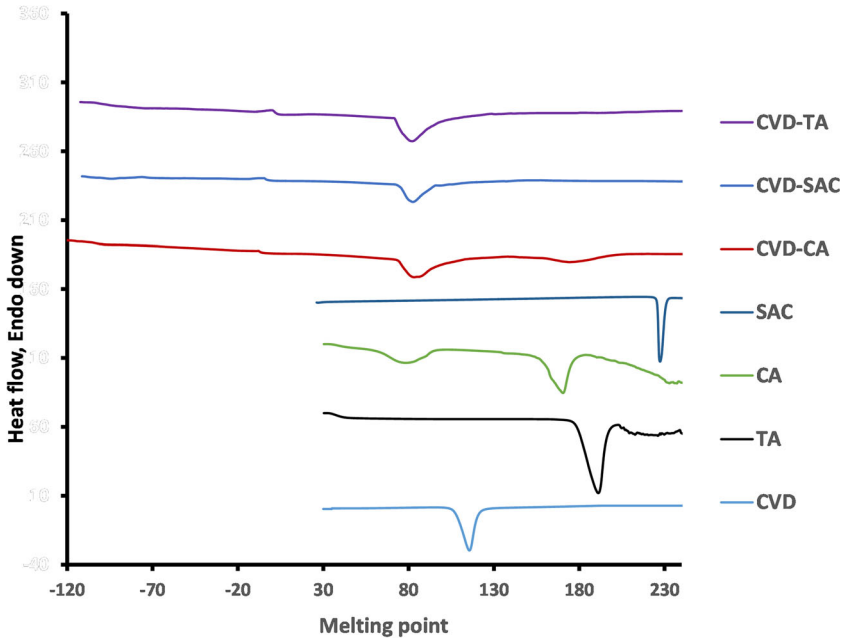
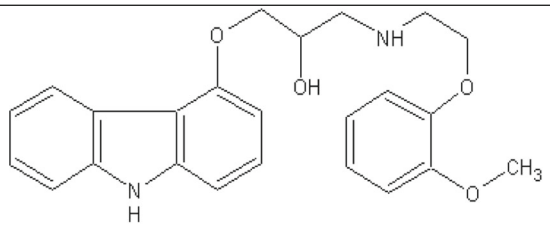
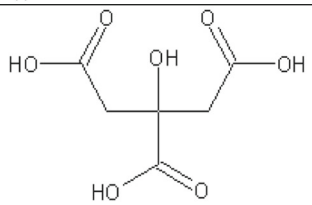
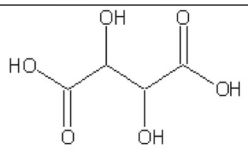
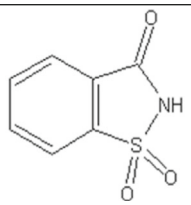


Fig. 2 DSC thermograms of CVD, CA, TA, SAC, CVD-CA, CVD-TA, and CVD-SAC

A good indication for CVD-SAC salt formation is obtained from the bathochromic shift in the carbonyl stretching frequency from 1720 cm^{-1} in SAC to around 1641 cm^{-1} in the prepared CVD-SAC salt form [47] (CVD has no carbonyl functional group and typical peak in this region [27]).

Table 1 Structure, pK_a, and melting point of CVD, CA, TA, and SAC

Drug	Structure	pK_a	Melting point
Carvedilol (CVD)		7.8	115 °C
Citric acid (CA)		3.09, 4.75, 6.41	153 °C
Tartaric acid (TA)		2.95, 4.25	171 °C
Saccharin (SAC)		1.31	230 °C

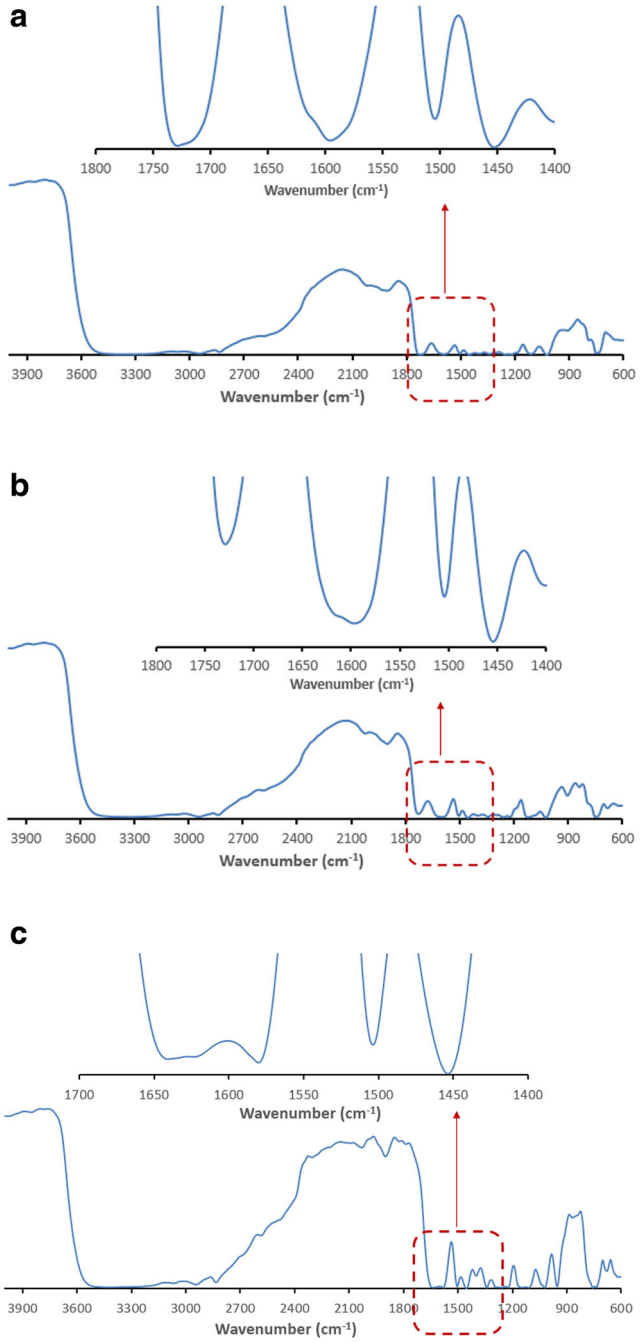


Fig. 3 FT-IR spectra of **a** CVD-CA, **b** CVD-TA, and **c** CVD-SAC. The characteristic peaks highlighted with asterisk

Ionic bond formation (salt) was verified by 1H-NMR spectrum. According to the simulated NMR spectra of CA, TA, and SAC by ACD-ilab software [48], hydroxyl functional groups of CA and TA have a single peak at ~ 10 ppm which is upfield to ~ 6 ppm in ionized from whenever the first carboxylic acid was converted to carboxylate (COO^-). In SAC, the disappearance of a single peak at 8.1 ppm confirms ionization of 1,2-benzisothiazole ring. CVD has no peak in the studied regions.

Similar spectra (Fig. S2 in supplementary information) of CVD-CA and CVD-TA show the appearance of a peak at ~ 6 ppm. It established the ionization of the first carboxylic acid of CA and TA and the salt formation. In CVD-SAC, disappearance of a single peak at 8.1 ppm of SAC in ionized form confirms ionization of 1,2-benzisothiazole ring.

Apparent Solubility of CVD and Prepared Ionic Liquids in Different Media

HCl with different concentrations, i.e., 0.2 M by USP pharmacopeia [49] and 0.1 M by FDA [50], was applied to simulate stomach acidic condition as dissolution medium for CVD. Therefore, the solubility of CVD in this study was investigated at different concentrations of HCl. Moreover, acetate buffer (pH = 4.8, 0.1 M) recommended dissolution media by Japanese Pharmacopeia for CVD [51], and phosphate buffer (pH = 6.8, 0.1 M) solution to simulate intestinal condition were used to evaluate the solubility of CVD and prepared ionic liquids. The results of CVD's solubility in different dissolution media were shown in Fig. 4. The solubility in acetate buffer is higher than phosphate buffer solution due to the more ionization of CVD in pH = 4.8 (100%) in compared with pH = 6.8 (90%) and formation of CVD acetate salt that has significantly higher solubility than the respective phosphate [31].

CVD is a basic compound ($pK_a = 7.8$) and is not susceptible to acidic and basic conditions [31] and it is converted to ionized form (100%) in pH < 5; however, a substantial difference was observed between solubility of CVD in acetate buffer (pH = 4.8, 0.1 M) and HCl in different concentrations. There is an inverse relation between HCl concentration and CVD's solubility because of formation of chloride salt and the common ion effect which it can significantly decrease the solubility of CVD [31]. Moreover, the solubility value in acetate buffer is significantly less than solubility in HCl 0.01 M because of adjusting pH by HCl and available chloride ions in solution (~ 0.1 M).

Figures 5 and 6 illustrated the solubility of CVD's ionic liquids, in phosphate buffer (pH = 6.8, 0.1 M, composed of NaH_2PO_4 and Na_2HPO_4) and acetate buffer solutions (pH = 4.8, 0.1 M which pH adjusted with HCl and the chloride concentration was ~ 0.1 M), respectively. pH of final solutions was unchanged (± 0.1) because of the appropriate concentration of buffer solution to maintain the pH in a constant value. CVD in ionic liquid forms showed a significantly improving in solubility values in acetate buffer (pH = 4.8, 0.1 M) and phosphate buffer (pH = 6.8, 0.1 M) solutions. A similar pattern has been observed in evaluating ketoconazole's solubility in the ionic liquid form in phosphate buffer solution (0.1 M, pH = 6.8) [39]. Salification and liquefaction could be a possible mechanism for solubilization of CVD in ionic liquid forms. However, this increase in solubility of the ionic liquid

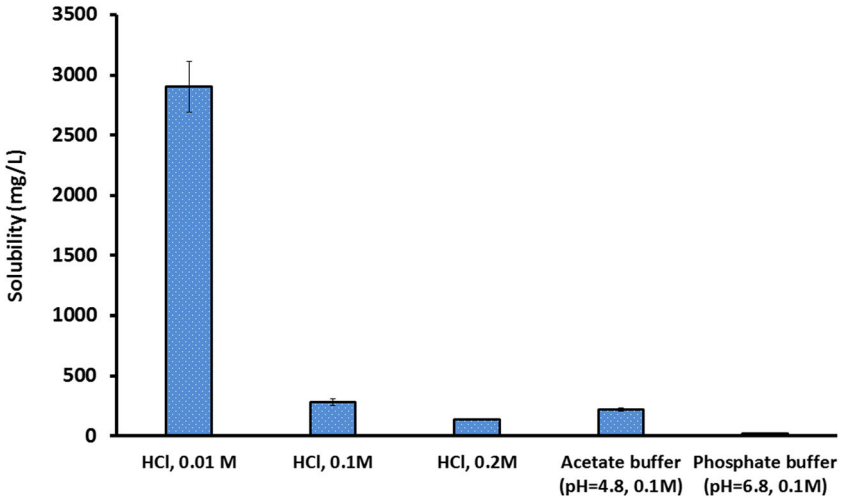


Fig. 4 Solubility of CVD in HCl (0.2, 0.1 and 0.01 M), acetate buffer (pH = 4.8, 0.1 M) and phosphate buffer (pH = 6.8, 0.1 M) at 37 °C

forms of CVD with CA and TA is considerably higher than CVD-SAC. CVD is practically insoluble in water and while CA and TA are freely soluble and SAC is slightly soluble [52]. Less soluble counter-ions can slightly change the solubility of drug substances [53]. In addition, salt formation with lipophilic compounds could convert them to relatively less soluble forms for development of extended release formulation [54].

Furthermore, the solubility of prepared ionic liquids (CVD-CA, CVD-TA) was investigated in different concentrations of HCl (Fig. 7). Preliminary observations showed that the spectrum of CVD in solubility determination of CVD-SAC in acidic condition was considerably changed due to the probability of instability. Therefore, it was excluded from the experiment. Unlike CVD, the ionization percentage of CA, TA, and SAC based on Henderson-Hasselbalch equation was affected by a change in pH of the solution. CVD remains 100% ionized in acidic condition and we did not expect any significant change in the solubility of CVD in ionic liquid form, while the solubility of CVD in ionic liquid form with CA and TA is less than CVD. This observation could be related to pH of the final solution. This value for CVD's ionic liquids with CA and TA in HCl 0.2 M is 2.5–3. According to the pK_a of CA and TA (Table 1), they are partially unionized (> 50%) in this medium and CVD's solubility in the ionic liquid form is less than CVD. Unlike the solubility in HCl, it increases in acetate buffer solution, (pH = 4.8, Fig. 5), since the counter-ions are in the ionized state (> 90%). Moreover, based on the previous study by Hamed et al. [25], decrease in CVD solubility in ionic liquid forms could be related to the high ionic strength of the solution. Ionic liquids can produce higher ionic strength in solution medium and it is a possible reason for reducing solubility in acidic medium whenever CVD is fully ionized.

A similar pattern is observed in solubility studies of CVD and corresponding ionic liquid forms in HCl 0.1 M and 0.01 M. However, solubility in HCl 0.01 M was considerably improved in compared with HCl 0.1 and 0.2 M. It could be associated with the low concentration of chloride ion. The maximum solubility in different concentrations of HCl was observed in CVD, because of the ionic strength of CVD in solution is less than CVD's ionic liquids (both of them are in fully ionized form in pH < 5).

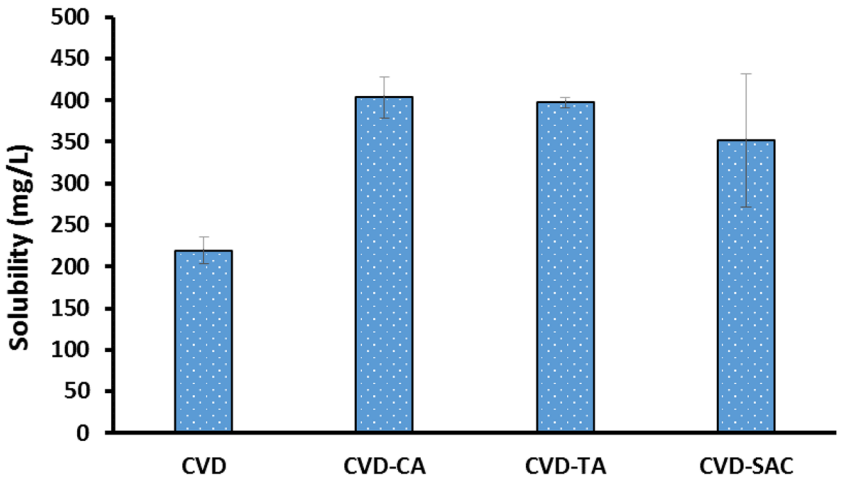


Fig. 5 Solubility of CVD's ionic liquids in acetate buffer (pH = 4.8, 0.1 M) at 37 °C

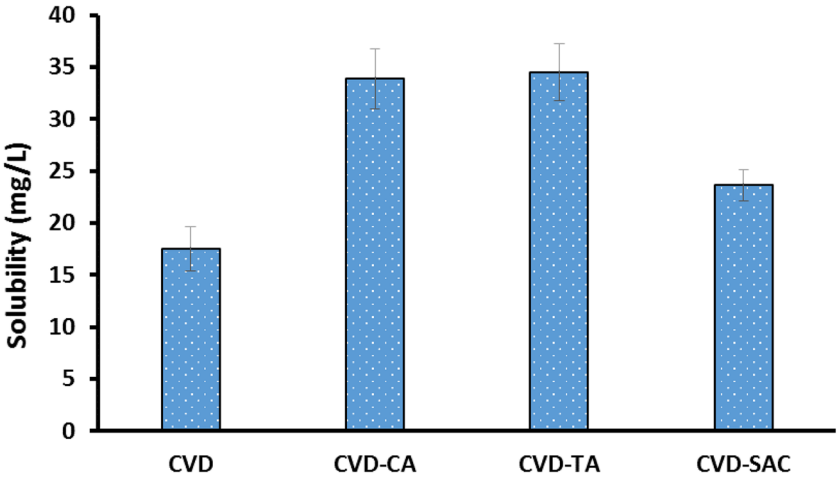


Fig. 6 Solubility of CVD's ionic liquids in phosphate buffer (pH = 6.8, 0.1 M) at 37 °C

Statistical analysis to compare the solubility of CVD and its ionic liquids forms shows a significantly statistical difference in all studied cases at different media ($p < 0.01$). Details of one-way ANOVA analysis have been shown in Table S1 (supplementary information).

These data are in agreement with previous studies [25, 27, 31] that pH of the solution, type and concentration of dissolution medium, and ionic strength of medium are critical parameters in evaluating CVD's solubility. Moreover, the solubility of counter-ions and the percentage of ionization are crucial and it can influence the solubility. These data show that the CVD's solubility is a complex phenomenon and the percentage of ionization, type, concentration, and ionic strength of dissolution media and solubility of counter-ions are essential issues in the assessment of API-based ionic liquids of CVD. Also, the phase behavior of the ionic liquids needs to be looked at more rigorously in future studies because of the residual eutectic mixture may no longer be at its stoichiometric composition.

Conclusion

Preparation of API-based ionic liquid form of drugs is one of the interesting issues to address physicochemical properties of drugs. CVD's ionic liquids with different acidic compounds, i.e., CA, TA, and SAC, were applied to salt formation and liquefaction of CVD. It can significantly improve CVD's solubility. However, pH of the solution, ionization and solubility of counter-ions, and type, concentration, and ionic strength of dissolution media can affect the solubility and it should be considered in evaluating CVD's physicochemical properties in similar studies.

Acknowledgments This article is a part of the results of S.S's Pharm.D thesis No. 3965 registered at Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran. The authors would like to give special thanks to East Azarbaijan Sciences and Technology Park for providing DSC thermograms. We appreciate the editor and reviewers of this manuscript for editing and their valuable comments.

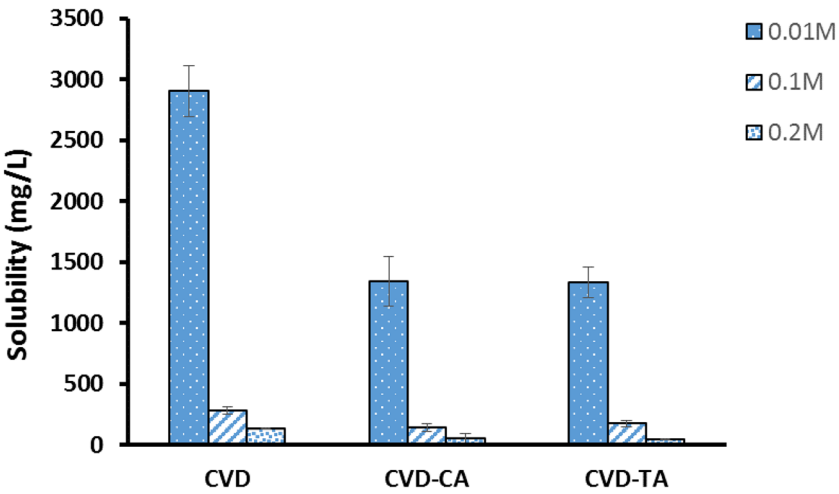


Fig. 7 Solubility of CVD's ionic liquids in HCl (0.2, 0.1 and 0.01 M) at 37 °C

Funding Information A.S. thanks the Ministry of Health and Medical Education (grant for young assistant professors), Tehran, Iran, for financial support.

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