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Factors Contributing to Solubility Synergism of Some Basic Drugs with β-Cyclodextrin in Ternary Molecular Complexes

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Abstract

Ternary complexes exploiting solubility synergism (SSn) between basic drugs and β-cyclodextrin (β-CD) in the presence of an organic hydoxy acid have been reported to provide the pharmaceutical technology with highly soluble ternary complexes, even with the least soluble β-CD. In this work, phase solubility techniques were used to study factors affecting SSn in aqueous solution, which may help in understanding the mechanism involved in ternary complex formation in solution, under equilibrium conditions. The equilibrium solubility of both β-CD and each of 8 structurally unrelated drugs were measured in tandem in the presence of different acid types at low and high pHs, and at different time intervals over a period of 1–40 days. The results indicate that SSn is evident regardless of acid type (organic and inorganic) at low pH, but the extent of SSn is acid type dependant and is limited by the drug salt solubility product constant (pK_{sp}). Among different drugs, no apparent trend exists between drug salt solubility and the extent of SSn, but lowering drug salt solubility by increasing pH depresses SSn. The results also reveal no apparent trend between the magnitude of the complex formation constant (K_{ij}) and SSn. For example, drugs of low K_{ij} values such as astemizole, cisapride and sildenafil do not show any SSn, yet ketotifen and pizotifen, which also have low K_{ij} values, exhibit substantial SSn. However, the solublizing power of β-CD represented by the slope of phase solubility diagram can be used as a marker for SSn (slopes exceeding 0.4 induce SSn).

Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides composed of 6–8 dextrose units joined through 1–4 α-D bonds. They are classified according to the number of dextrose units, where α-, β- and γ-CDs contain 6, 7, and 8 units, respectively. They vary in their water solubility, where γ-CD is the most soluble (23.2 gm/100 ml), α-CD (14.5 gm/100 ml), while β-CD is the least soluble (1.85 gm/100 ml) at 25 °C [1].

It was reported that pH adjustment and addition of a suitable additive such as an acid, a base or a polymer in the presence of CDs significantly improve drug solubility [2–13]. This combination was used to achieve the target drug solubility for solution preparations and to improve the release of drug from solid formulations. Badwan *et al.* [14] patented a system comprising a basic drug, an acid and β-CD, where the solubility of different drug substrates used were dramatically enhanced. Most of these studies were oriented towards formulation aspects such as liquid preparations using concentrations of CDs not exceeding their optimal solubility.

Phase solubility diagrams were used to investigate complexation of CDs with various substrates, some of which led to the observation that an increase of the amount of ligand in excess of its maximum solubility was concomitantly accompanied with a corresponding increase in the substrate solubility. Cabral *et al.* [15] were first to give an indicative remark about the increase in solubility of β-CD beyond its solubility limit when complexing with the amphoteric drug salbutamol in a binary system. Subsequent studies suggested preparation of different highly soluble complexes for basic drugs in the presence of organic and inorganic acids involving ternary complexes [16–18]. These ternary complexes offered high solubility rates and produced saturated solutions that remain stable for several days [19]. This dramatic increase in the solubility of both ligand and substrate in the presence of a third component such as an acid in ternary systems can be expressed as solubility synergism (SSn). This opened great opportunities in complexation techniques to be used in pharmaceutical formulation and many workers dealt with this approach.

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Further examination of these systems led to the following criteria governing drug/β-CD SSn in multicomponent systems [19]: (a) the substrate solubility must be lower than 0.1 mg/ml and should be improved by salt formation with the hydroxy acid (citric, tartaric, ascorbic acids etc); (b) the substrate must tightly fit into the CD cavity yielding a complex formation constant of at least 1000 M^{-1}; (c) the substrate must have a fairly basic character ($pK_a \geq 5$) and the functional group responsible for such basicity must be located away from the part designated for inclusion, in such a way that either the charge does not compromise the complexing ability, and the counter ion is able to interact with the hydroxyl groups of the wider external rim of CD.

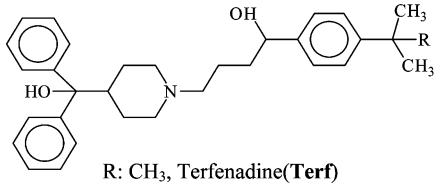
This report examines factors that may determine the extent of SSn of β-CD with some selected structurally unrelated drugs in aqueous acid solutions, including organic and inorganic acid types, pH, the value of drug/β-CD complex formation constant, inherent drug salt solubility and drug salt surface activity. This may help in understanding the mechanism involved in basic drug/β-CD systems and the establishment of possible markers for SSn.

Experimental

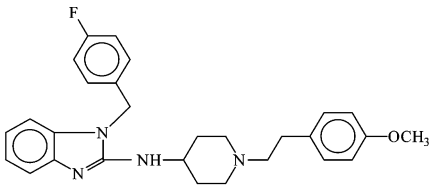
Materials

All drugs were provided by the Jordanian Pharmaceutical Manufacturing Company (JPM). Their purity was as follows: Terfenadine (Terf) of 99.9%, fexofenadine (Fexo).HCl of 100.1%, cisapride (Cisp) of 99.2%, sildenafil (Sild).citrate of 100.3%, dipyridamole (Dipy) of 99.0%, ketotifen (Keto).fumarate of 99.3%, pizotifen (Pizo).malate of 100.1%, astemizole (Astm) of 100.4% and β-CD of 99.0%. The neutral forms of drugs were prepared by neutralisation with 0.1 M NaOH solution. Drug.citrate salts were prepared by shaking an equimolar of neutral drug and citric acid in a sufficient amount of water, followed by filtration and drying at 40 °C. In case of Terf, different salts were prepared using citric, H_3PO_4, or HCl acid. The purity of neutral drugs and their citrate salts was determined by acid–base titration and spectrophotometry and found to be more than 98%. Different Terf salts/β-CD complexes were also prepared by dissolving mixtures of Terf and β-CD (3.8 mmol: 7.6 mmol) in 50 ml of water containing 3.8 mmol of citric acid, H_3PO_4, or HCl. The solutions obtained were kept at 5 °C for 2 days, then the precipitates were filtered, dried and then assayed for drug, acid, β-CD and water contents.

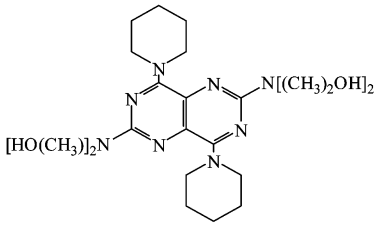
Different aqueous acid solutions were used for phase solubility studies including 0.05 M citrate buffer of different pHs ranging from 3.0 to 8.2, 0.5 M acetate and 0.05 M phosphate, nitrate, sulphate and hydrochloride solutions of low pHs (3.0–3.5). These solutions were obtained by preparing 0.05 M of the acid, followed by adjusting the pH with diluted NaOH solution. After equilibrium, further adjustment to the desired pH was conducted with the addition of few drops of the corresponding acid through a micropipette.



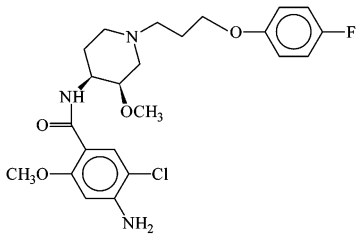
R: CH_3, Terfenadine(**Terf**)
R: COOH, Fexofenadine(**Fexo**)



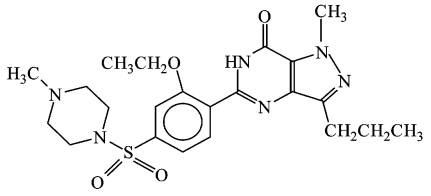
Astemizole(**Astm**)



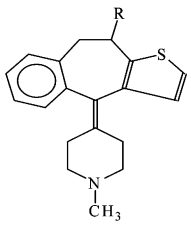
Dipyridamole (**Dipy**)



Cisapride (**Cisp**)



Sildenafil (**Sild**)



R = H, Pizotifen (**Pizo**)
R = O (double bond), Ketotifen (**Keto**)

Instrumentation

UV/Visible spectrophotometer (Du-650i, Beckman/ USA). Thermostatic shaker (1086, GFL/Germany). pH-meter (3030, Jenway/ UK). Dunoy ring interfacial tensiometer (K8, Kruss/ Germany). Polarometer with sodium-D line (589 nm) (Polartronic D, Schmidt & Haensch/ Germany). Halogen moisture analyzer (HR 73, Mettler/ Switzerland).

Analytical methods

The drug concentration was determined spectrophotometrically by measuring the first derivative amplitudes at 270 nm for Terf, Fexo and Pizo, at 320 nm for Keto and Cisp, and at 278, 285 and 311 nm for Dipy, Astm and Sild, respectively.

The β-CD concentration was determined by optical rotation (α) measurements on a Polartronic D at 25 °C using a 1-dm cell [20]. For calibration standards, stock solutions of drug molecules were prepared by dissolving predetermined amounts (25–200 mg) in 100 ml of ethanol or methanol to be diluted further with 1% citric acid. Solutions of β-CD were prepared by dissolving predetermined amounts of β-CD (0.05–2.0 g) in 100 ml of 1% citric acid. The method could be utilised with an excellent accuracy since all drugs used were either optically inactive or racemic isomers, and it proved linear with a correlation coefficient (R^2) of 0.9999.

Phase solubility studies

Solubility studies were performed as described by Higuchi and Connors [21]. Excess amounts of drug (0.5–2 g) were added to 50 ml of the desired media, where β-CD was added in amounts far in excess of its optimal solubility in water (18 mM at 30 °C) to reach about 150 mM. The samples were mechanically shaken in a thermostatic bath shaker (~200 rpm), an aliquot was centrifuged (when necessary) and filtered using a 0.45-μm filter (cellulose acetate or cellulose nitrate, Advantec MFS Inc., Duplin, USA). The concentrations of both drug and β-CD were measured at time intervals ranging from 1 to 40 days of thermostatic mechanical shaking to reach equilibrium and to ascertain that SSn and not supersaturation is taking place. The drug and β-CD assays were conducted as indicated in the "Analytical methods" described above. Moreover, the complex formation constants were estimated through linear and nonlinear regression as described elsewhere [22–24].

pH solubility profile of drugs and β-CD

Excess amounts of drug or β-CD were added to 50 ml of 0.05 M citrate buffers of different pHs ranging from pH 2 to 12. The samples were mechanically shaken in a thermostatic bath shaker (~200 rpm), to attain equilibrium an aliquot was centrifuged (when necessary) and filtered using a 0.45-μm filter (cellulose acetate or cellulose nitrate, Advantec MFS Inc., Duplin, USA). The assays of drug and β-CD were conducted using the analytical methods described above. To obtain the drug, acid–base ionisation constants (pK_a) and the solubility product constants (pK_{sp}) of the drug salts, nonlinear regression of the experimental data of the inherent drug solubility (S_o) against pH was carried out using the Marquardt–Levenberg finite difference algorithm utilised by the SPSS 10.0 for Windows Statistical Package (SPSS Inc., 233 S. Wacker Drive, Chicago, Illinois) linked to Microsoft Excel for data plotting.

Surface tension measurement

Saturated solutions of the drug used were prepared by shaking excess amounts of the free base in 50 ml of 0.05 M citric acid solution, followed by filtration using a 0.45-μm filter (cellulose acetate). Surface tension measurements of the stock solutions and several more dilute solutions were obtained at 25.0 ± 0.1 °C. A 20 ml portion of the solution was placed in a cleaned glass dish. The Pt-Ir ring, which was previously cleaned with alcohol followed by successive washing with water, was allowed to touch the solution surface, left to attain thermal equilibrium with the thermostatted solution, and the surface tension subsequently read and recorded.

Results and discussion

SSn of multicomponent inclusion complexes consisting of some basic drugs and β-CD in the presence of different acids was investigated using phase solubility techniques. The influence of different factors including acid type, pH and, complex formation constant and surface activity on the extent of drug/β-CD SSn are separately discussed below.

Effect of acid type on solubility synergism

Due to the simultaneous solubility enhancement of drug and β-CD as obtained from phase solubility diagrams (PSDs), only the maximum solubility enhancement of β-CD, expressed as $[\beta\text{-CD}]_{max}$, was used as a marker for SSn.

The effect of acid type (organic and inorganic) on SSn was examined through measured PSDs for the Terf/β-CD system in 0.05 M citrate, phosphate, nitrate, sulphate, hydrochloride and 0.5 M acetate solutions at low pH (3.0–3.5), which are shown in Figure 1. The equilibrium $[\beta\text{-CD}]_{max}$ values were found to be 74, 66, 65, 60, 47 and 39 mM, respectively (Table 1). Since the solubility of β-CD in water (18 mM at 30 °C) was not affected by the addition of inorganic acids [25], and only increased to 30 mM in 0.05 M citrate buffer of pH 3.4 at 30 °C (Figure 2), it is evident that both organic and inorganic acids induce SSn but its extent is acid type dependant (e.g., limited by the solubility product constants (pK_{sp}) of either the drug salt or the corresponding complex). For example, Terf.citrate ($(TerfH^+)_2.citrate^{2-}$), phosphate

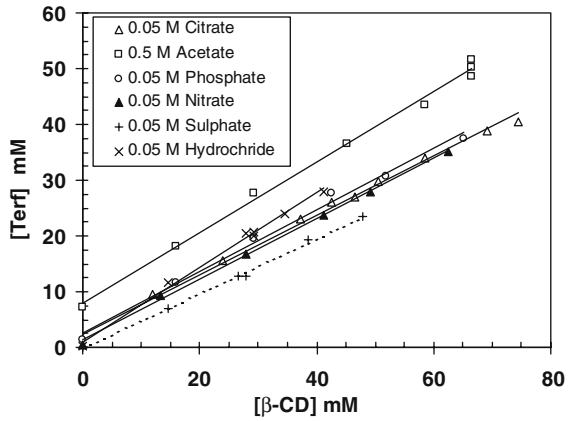


Figure 1. Phase solubility diagrams of the Terf/β-CD system in 0.05 M citrate, phosphate, nitrate, sulphate, hydrochloride and 0.50 M acetate solutions of low pHs (3.0–3.5) at 30 °C.

Table 1. Data on the solubility synergism of Terf/β-CD systems obtained in the presence of different acid types at low pHs (3.0–3.5) and 30 °C

Media	pH	S_o (mM)	Slope	K_{11}; K_{12} (M^{-1})	$[\beta\text{-CD}]_{max}$ (mM)
0.05 M Citrate	3.4	1.7	0.54	9000; 460	74
0.5 M Acetate	3.4	7.3	0.62	200; 109	66
0.05 M Phosphate	3.3	1.4	0.57	1100; 540	65
0.05 M Nitrate	3.5	0.5	0.55	1900; 600	60
0.05 M Sulphate	3.0	0.05	0.49	20,000	47
0.05 M Hydrochloride	3.2	0.3	0.67	6000; 130	39

(TerfH^+.$H_2PO_4^-$) and hydrochloride (TerfH^+.Cl^-) salts have solubilities of 0.77, 1.81 and 3.35 mM in water, respectively, while their corresponding complexes exhibit a different order of solubility (38.9, 45.1, and 14.2 mM, respectively). A similar trend in solubility was observed earlier for different salts of ziprasidone and their complexes including tartarate, mesylate, esylate and napsylate [4]. Thus differences in the aqueous solubilities of drug salts and/or drug salt/β-CD complexes expressed by pK_{sp} most probably induce different extents of SSn. Therefore, organic acids, mainly hydroxycarboxylic acids [16, 17, 19], appear to induce higher SSn due to a relatively higher pK_{sp} values.

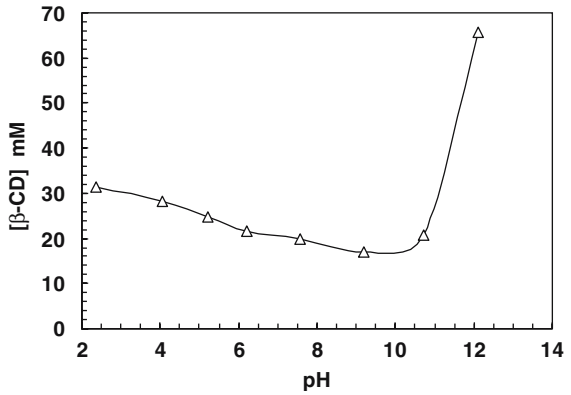


Figure 2. pH solubility profile of β-CD in 0.05 M citrate buffer at 30 °C.

Effect of pH on solubility synergism

Figure 3a shows PSDs for all drugs obtained in 0.05 M citrate buffers at low pHs (3.0–4.2), where they all exist as protonated drug species. Meanwhile, since Keto showed high solubility both in the absence or presence of β-CD, its PSDs were constructed at a higher pH of 5.6. Also, since the complex formation constant (K_{11}) of Keto obtained from a normal PSD was found almost zero due the relatively high solubility of Keto in the absence of β-CD, an inverted PSD was constructed by measuring the solubility of β-CD as a function of Keto concentration (Figure 3b). The results indicate that the salts of Keto, Fexo, Pizo, Terf, and Dipy induce SSn (Table 2). In contrast, Astm, Cisp and Sild do not lead to any SSn since $[\beta\text{-CD}]_{max}$ was lower than the solubility of β-CD in 0.05 M citrate buffer at 30 °C (30 mM).

Figure 4 shows PSDs for all drugs obtained in 0.05 M citrate buffers at higher pHs (5.1–8.2), where they still exist as protonated species. The results indicate that Fexo, Keto, Pizo and Terf induce SSn, but to a

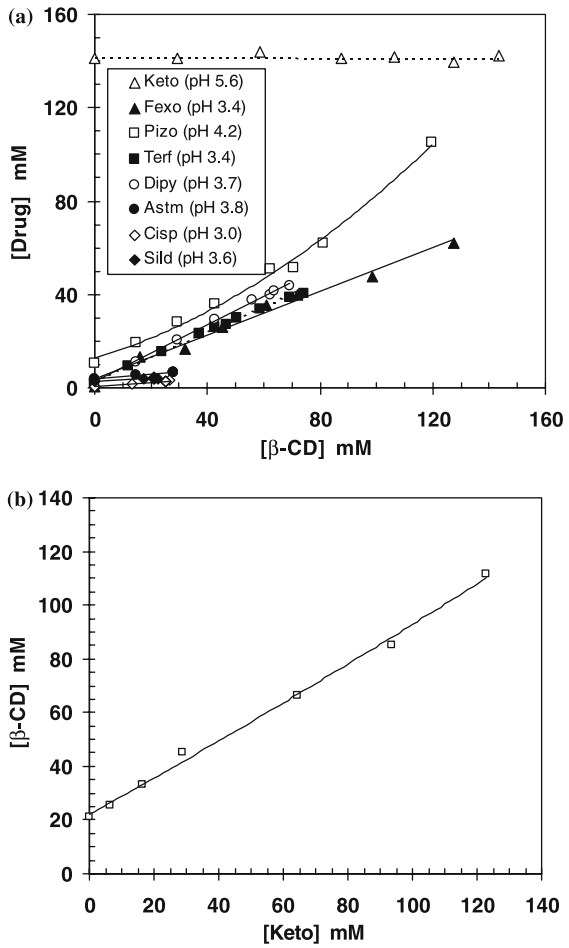


Figure 3. Phase solubility diagrams of (a) the drug/β-CD systems in 0.05 M citrate buffer of low pH (3.0–4.2) and (b) inverted phase solubility diagram of Keto/β-CD system in 0.05 M citrate buffer of pH 5.6 at 30 °C.

Table 2. Data on the solubility synergism of drug/β-CD systems obtained in 0.05 M citrate buffers at 30 °C

Drug	pH	S_o (mM)	Slope	K_{11}; K_{12} (M^{-1})	$[\beta\text{-CD}]_{max}$ (mM)	Solubility synergism
Keto	5.6	141	0.00	0	144	Present
	5.6[a]	–	0.71	120	110	Present
	6.6	4.8	0.84	442	80	Present
Fexo	4.0	0.4	0.47	7000; 730	128	Present
	7.0	0.9	0.52	1200; 47	128	Present
Pizo	4.2	10.6	0.75	155	120	Present
	6.4	1.9	0.64	900	55	Present
Terf	3.4	1.7	0.54	9000; 460	74	Present
	6.1	0.04	0.50	25,000; 200	45	Present
Dipy	3.7	3.2	0.60	730; 100	69	Present
	5.2	0.07	0.05	780	23	Absent
Astm	3.8	3.7	0.11	33	28	Absent
	5.8	0.7	0.13	220	25	Absent
Cisp	3.0	0.4	0.10	110; 70	27	Absent
	5.1	0.1	0.02	110; 50	27	Absent
Sild	3.6	2.7	0.07	26	23	Absent
	8.2	0.02	0.003	140	19	Absent

[a] Data obtained from inverted phase solubility diagram.

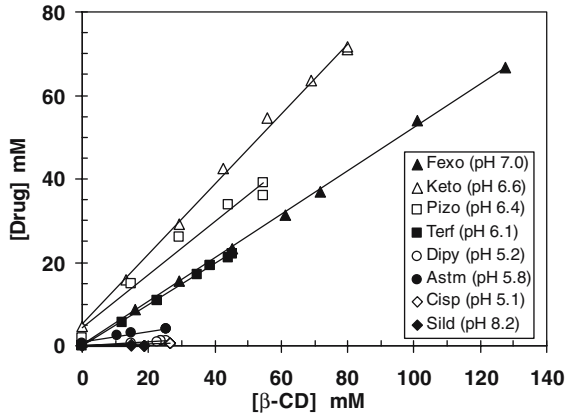


Figure 4. Phase solubility diagrams of the drug/β-CD systems in 0.05 M citrate buffer of higher pH (5.1–8.2) at 30 °C.

relatively lower extent than at low pHs. Dipy, Astm, Cisp and Sild do not show any substantial SSn.

Figure 5 depicts PSDs for drug.citrate salts against β-CD concentration obtained in unbuffered water where the pH was consistently less than 5.5. The results show the same trend obtained in citrate buffer at low pH.

Aside from Fexo, it is observed that for each individual drug, the higher the solubility of the drug salt species (S_o), the higher is the SSn (Table 2). This is also corroborated by a lower extent of SSn as pH increases (e.g. lower S_o). For example, the solubilities of Pizo at pHs 4.2 and 6.4 were 10.6 and 1.9 mM, respectively, while the corresponding $[\beta\text{-CD}]_{max}$ were 120 and 55 mM. It is generally observed that drug/β-CD systems having PSDs with slopes exceeding 0.4 exhibit high mutual solubility enhancement of drug and β-CD (Tables 1 and 2). Other drug/β-CD systems having slope

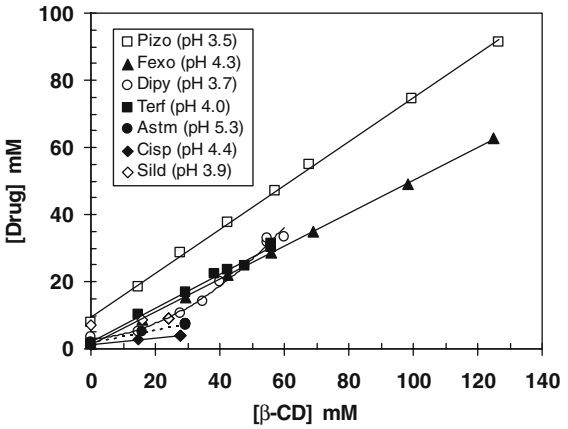


Figure 5. Phase solubility diagrams of the drug.citrate salt/β-CD systems in unbuffered water at 30 °C.

less than 0.2 show no SSn as in the case of Astm, Cisp and Sild. It has been reported [19] that to induce SSn, the substrate must tightly fit into the CD cavity yielding a complex formation constant of at least 1000 M^{-1}. In the present work, drugs with low complex formation constants induced high SSn. For example, Keto, Pizo and Dipy have relatively low complex formation constants at low pH (K_{11} = 120, 155 and 730 M^{-1}, respectively), but they induced high SSn where the corresponding $[\beta\text{-CD}]_{max}$ were 110, 120 and 69 mM, respectively. This indicates that the complex formation constant is not an index for SSn; but the slope of PSD may provide a better marker.

A further exploration of the source of the variation among the different drug salts in inducing SSn with β-CD in terms of drug salt solubility (S_o) or complex formation constant (K_{11} or K_{12}) revealed no apparent trends (Table 2).

Surface activity of drug salts

In an attempt to look for other sources of SSn, the surface activity of drug salts was investigated. All drug salts listed in Table 2 proved to be surface active since there was a significant decrease in the surface tension (γ) of drug salt solutions with an increase in drug salt concentration up to the drug salt saturation limit. This indicated that no correlation between surface activity and SSn exists, especially since those drug salts that do not induce SSn were also found to be surface active.

In addition to the requirements stated earlier [19] for exploitation of SSn in multicomponent complexation technology and in light of the current work, the following findings were obtained: (a) drug salt formation is essential to induce SSn with β-CD regardless of the acid type (organic or inorganic) and is limited by the K_{sp} value of the drug salt and/or that the corresponding β-CD complex salt, (b) the requirement that the solubility of drug in water should be less than 0.1 mg/ml and is improved by salt formation is valid for basic drugs (Table 3), but is not essential for amphoteric drugs such

Table 3. Solubilities of neutral drug species in unbuffered water, and estimates of drug acid–base ionisation constants (pK_a) and drug salt solubility product constants (pK_{sp}) which were obtained from pH solubility profiles in 0.05 M citrate buffer at 30 °C

Drug	S_o (mg/ml)	pK_{a1}, pK_{a2}	pK_{sp}	Acidity in water
Terf	0.013	9.5 (piperidine)	10.6	Basic
Fexo	0.16	4.2 (carboxylic), 9.6 (piperidine)	9.9	Zwitter ion
Pizo	0.012	8.9 (piperidine)	1.5	Basic
Keto	0.025	8.4 (piperidine)	–	Basic
Cisp	0.002	2.0, 8.7 (piperidine)	2.9	Basic
Sild	0.011	7.0 (piperazine), 9.8 (amide)	1.6	Basic
Dipy	0.012	2.7 (aromatic amine), 6.4 (fused nitrogen)	0.5	Basic
Astm	0.003	5.0 (fused nitrogen), 7.5 (piperidine)	6.2	Basic

as Fexo; (c) The value of the complex formation constant cannot be an index to predict SSn, while the slope of PSD is more representative (e.g. slope of more than 0.4 and complex formation constant more than 100 M^{-1} are requirements for SSn).

Conclusion

The results of equilibrium solubility measurements of both drug substrates and β-CD, which obtained under controlled conditions of pH indicate that SSn of basic drugs/β-CD systems is pH dependent and is more evident at low pH, where drug salts and their complexes are more soluble. The extent of SSn is acid type dependant extending to inorganic acids (e.g., H_3PO_4, HNO_3, H_2SO_4, and HCl); the only limitation on the choice of the acid is the drug salt solubility product constant pK_{sp} and/or the drug salt/β-CD complex pK_{sp}. Drug salt surface activity is not a marker for drug/β-CD SSn. Using the magnitude of the slope of PSD rather than the complex formation constant as a marker to predict SSn is more representative.

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