The use of cosolvent pK_a assays for poorly soluble compounds

The ionisation constant or pK_a is a solution property of a compound. The formation of a precipitate during a pK_a acid/base titration therefore prevents the accurate measurement of pK_a. However, drug-like molecules are often poorly soluble in water. In these cases a cosolvent mixture comprising water and a water-miscible organic solvent can be used to enhance solubility. By performing titrations in several different solvent / water ratios, the pK_as of water-insoluble compounds can be derived using the well-known Yasuda-Shedlovsky extrapolation[1].

Experimental

The pK_as of a diverse set of 19 drug molecules were investigated using the Pion Fast UV pK_a method[2] under aqueous and methanol-water cosolvent conditions. Cosolvent assays consisted of three titrations in varying cosolvent ratios on the same sample aliquot. The methanol mixing ratio was varied from 50 – 30 % and pK_a results were obtained by Yasuda-Shedlovsky extrapolation. The compounds investigated were: amiloride, bendroflumethiazide, benzocaine, chlorzoxazone, diazepam, flumequin, fluoxetine, furosemide, hydrochlorothiazide, ketoprofen, naproxen, nortryptiline, papaverine, phenazopyridine, promethazine, quinine, terbutaline, tolmetin, and warfarin.

To illustrate the magnitude of solubility enhancement in cosolvent mixtures, the solubility of bendroflumethiazide, a weak acid, was investigated using the CheqSol method in the three cosolvent systems commonly used by Pion: methanol, dioxane, and methanol / dioxane / acetonitrile mix (MDM).

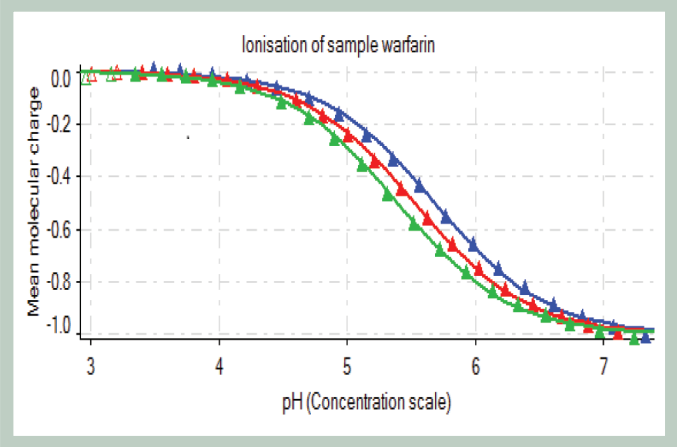

Figure 1. The Yasuda-Shedlovsky method utilises the apparent shift in pK_a when compounds are titrated in nonaqueous media. The figure shows the ionisation graphs for the acidic compound warfarin. The graphs move towards higher pH with increasing volumes of methanol.

Results

pK_a

Results obtained by Yasuda-Shedlovsky extrapolation from methanol / water mixtures were found to show excellent agreement with those obtained under aqueous conditions (R^2 = 0.998). This illustrates that high quality pK_a results can be obtained by extrapolation.

In general, acidic pK_as were found to increase as the cosolvent ratio increased. Basic pK_as were found to decrease as the cosolvent ratio increased. This is illustrated in Figure 2. Increasing the cosolvent ratio lowers the dielectric constant of the medium. This stabilizes the neutral species relative to the ionized species. This effect may be used to help assign pK_a types, if these are not apparent from the structural formula of the compound.

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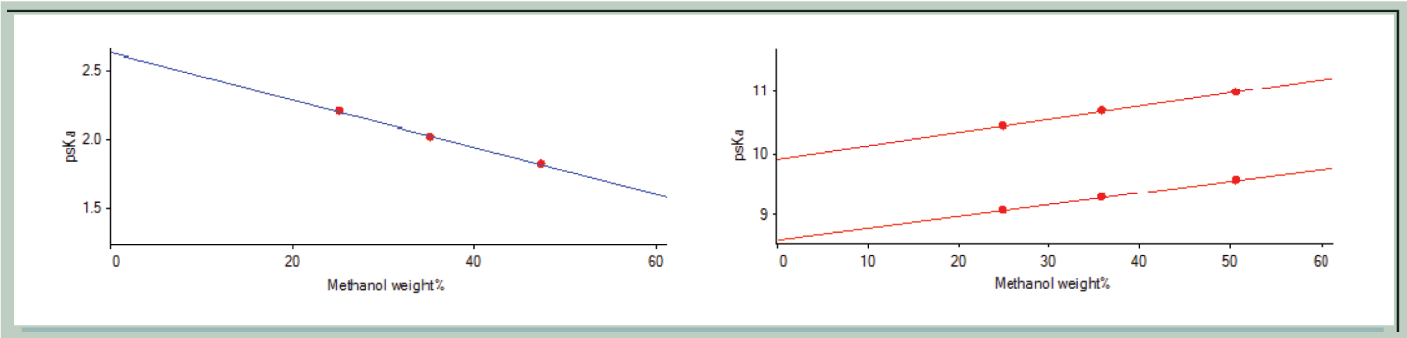

Figure 2: Variation in apparent pK_a with methanol ratio for benzocaine, a weak base (left) and hydrochlorothiazide, a weak acid (right). In general, base pK_as decrease and acid pK_as increase with increasing solvent ratio.

Solubility

The aqueous intrinsic solubility of bendroflumethiazide, expressed as logS, was found to be -4.31(5). Table 1 lists the intrinsic solubility of this compound in various ratios of methanol-water, dioxane-water and MDM-water. These data show that the presence of a cosolvent can result in a very large improvement in solubility. The presence of 50% MDM produced more than a 100-fold increase in solubility. A similar enhancement was observed in 50% methanol. Dioxane produced a considerably smaller effect.

	Solubility at wt % solvent (LogS)			
Cosolvent system	**20**	**20**	**40**	**50**
Methanol	**-3.65**	**-3.14**	**-2.64**	**-2.13**
Dioxane	**-3.71**	**-3.51**	**-3.30**	**-3.10**
MDM	**-3.74**	**-3.18**	**-2.62**	**-2.06**

Table 1. The intrinsic solubility of bendroflumethiazide with methanol weight percent.

(pK_a) Results obtained by Yasuda-Shedlovsky extrapolation from methanol / water mixtures were found to show excellent agreement with those obtained under aqueous conditions.

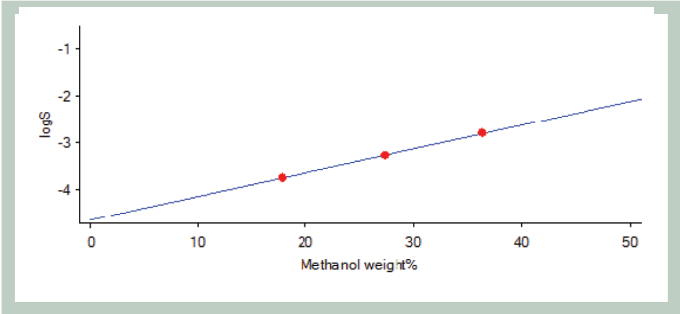

Figure 3. variation of the intrinsic solubility of bendroflumethiazide with methanol weight percent

Conclusion

pK_a results for a test set of 19 compounds extrapolated from cosolvent data showed excellent agreement with aqueous values (R^2 = 0.998). Drug-like compounds may be orders of magnitude more soluble in cosolvent mixtures than in water. Bendroflumethiazide was found to be more than 100 times more soluble in 50% MDM than in water alone.

References

[1] Avdeef, A., Box, K., Takács-Novák, K. Int. J. Pharm., **2001**, 151, 235 - 248

[2] Pion Application Note 2