Effect of Solvent on pka Determination of Nonsteroidal Antiinflammatory drugs

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The variation in the pKa values was observed in presence of different solvents used to improve sample solubility. Quantitative expression has been developed to estimate pKa values of a specific compound. The information may be useful for the pKa estimation of other compounds.

CONSIDERING the importance of pKa value of a drug molecules[1], several methods for its determination have been reported in the literature[2]. Out of the these, the potentiometric method is preferred due to its convenience, simplicity and accuracy. The technique is elaborated by Albert and Serjeant[3]. The literature review reveals that pKa determination of poorly water soluble drugs by potentiometry is difficult and therefore water miscible organic solvents are recommended to improve solubility of samples[4-7].

Ibuprofen, ketoprofen and flurbiprofen were recrystalized and checked for possible impurities through HPLC profile, Ethanol, dimethyl formamide and propylene glycol were purified by distillation process. The potentiometric titrations of these profens were conducted on 50 mg of sample in 40 ml solvent blend using carbonate free 0.005 M sodium hydroxide solution under nitrogen atmosphere using Mettler DL21 Autotitrator and DG111SC electrode. The burette capacity was 10 ml and resolution was 0.005 ml. The pKa values were obtained as pH at half neutralization by setting the data acquisition in t/20 sec mode which was optimized during pilot experiments.

Experimental and estimated pKa values of drugs in different solvent blends are compiled in table 1. To establish the effect of solvent medium on the pKa a graph has been constructed between experimentally observed pKa and solvent content. This relationship was found to be linear in the experimental range of solvent percentage in between 30 to 70. Lower percentage of solvent was not sufficient to dissolve the material and higher percentage of solvent yielded drifts in pH measurements. In case of ethanol and dimethyl formamide measurements have been made but higher percentages were not necessary. In case of propylene glycol, increased viscosity at its higher percentage was found to be the major problem. A linear relationship (Fig. 1) was observed in between experimental pKa and percentage of solvent. The linear relationships of pKa of profens in various solvent systems was obtained using linear regression analysis. The regression equations are as following:

Ibuprofen:

Dimethyl formamide	:	pKa=0.0483 (% of DMF) + 4.2408 (R^2=0.9886)
Ethanol	:	pKa=0.0364 (% of Ethanol) + 4.4581 (R^2=0.9977)
Propylene glycol	:	pKa=0.02441 (% of PG) + 4.4015 (R^2=0.9769)

Ketoprofen:

Dimethyl Formamide	:	pKa=0.0497 (% of DMF) + 3.7044 (R^2=0.9839)
Ethanol	:	pKa=0.0357 (% of Ethanol) + 4.1024 (R^2=0.9851)
Propylene glycol	:	pKa=0.0192 (% of PG) + 4.3458 (R^2=0.9901)

Flurbiprofen:

Dimethyl formamide	:	pKa=0.0453 (% of DMF) + 3.8936 (R^2=0.9937)
Ethanol	:	pKa=0.0292 (% of Ethanol) +4.4319 (R^2=0.9774)
Propylene glycol	:	pKa=0.021 (% of PG) + 4.2553 (R^2=0.9815)

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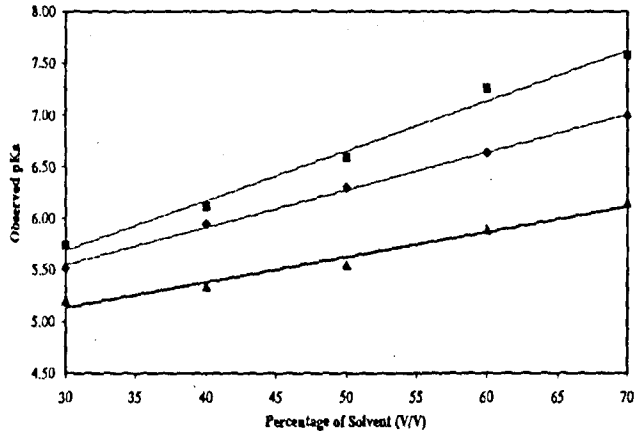
Table 1: Experimental values of pKa of various profens in solvent blends used in potentiometric titration.

Drug	% of solvent	pKa in		
		Alcohal	DMF	PG
Ibuprofen	70	6.990	7.576	6.148
	60	6.639	7.260	5.885
	50	6.302	6.591	5.546
	40	5.946	6.112	5.334
	30	5.516	5.736	5.202
Ketoprofen	70	6.575	7.284	5.718
	60	6.299	6.644	5.480
	50	5.924	6.036	5.270
	40	5.423	5.724	5.150
	30	5.226	5.259	4.921
Flurbiprofen	70	6.551	7.058	5.716
	60	6.078	6.616	5.516
	50	5.879	6.201	5.312
	40	5.653	5.610	5.171
	30	5.302	5.298	4.834

Fig. 1: pKa of ibuprofen in different solvents



The regression relation ships are y = 0.0483 x + 4.241, R2 = 0.9886 for DMF (▪), y = 0.0364 x + 4.4581, R2 = 0.9977 for alcohol (♦) and y = 0.0244 x + 4.4015, R2 = 0.9769 for PG (·)

The slope of regression lines provides the insight about the medium effect. Larger values of slope in case of DMF indicates the presence of very high intermolecular forces, the property responsible for solubility enhancement of sample. The extrapolation of regression line does not yield constant extrapolated pKa in pure water, hence the validity of this method may be questionable. The regression line along with propylene glycol has minimum slope and best linearity indicating its suitability. The relatively low solubility enhancement property of propylene glycol may be a constraint. In conclusion, while water miscible solvents are used in pKa determination, extrapolated values must be used with caution in data analysis.

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