Novel Application of Hydrotropic Solubilization in the Analysis of Some NSAIDs and their Solid Dosage Forms

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Quantitative analysis of poorly water-soluble drugs involves use of various organic solvents. Major drawbacks of organic solvents include high cost, volatility and toxicity. Safety of analyzer is affected by toxicity of the solvent used. Sodium benzoate is one of the widely used hydrotropic agents and has demonstrated the enhancement in aqueous solubilities of a large number of poorly water-soluble drugs. In the present investigation 2 M sodium benzoate solution has been used as hydrotropic solubilizing agent for three poorly water-soluble, non-steroidal antiinflammatory drugs ibuprofen, flurbiprofen and naproxen. There were more than 80, 110 and 120 fold enhancements in the solubilities of ibuprofen, flurbiprofen and naproxen, respectively in 2 M sodium benzoate solution as compared to solubilities in distilled water. Therefore, 2 M sodium benzoate solution was employed to solubilize these drugs to carryout their titrimetric analyses. These drugs have been analyzed successfully in basic drug samples and in solid dosage forms. Proposed method is new, simple, economic, safe, rapid, accurate and reproducible. The results of analysis obtained by the proposed methods compared well with those obtained by corresponding pharmacopoeial methods. Recovery studies and statistical data proved the accuracy, reproducibility and the precision of the proposed methods. Presence of sodium benzoate did not interfere in analysis.

Several methods have been reported in the literature to enhance the aqueous solubilities of poorly water-soluble drugs. Hydrotropic solubilization is one of them. Hydrotropy is a solubilization phenomenon whereby addition of large amounts of a second solute results in an increase in the aqueous solubility of another solute. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate and sodium acetate have been observed to enhance the aqueous solubilities of many poorly water-soluble drugs[1-19]. Maheshwari has analyzed various poorly water-soluble drugs ketoprofen[1], salicylic acid[1], aceclofenac[2] and frusemide[3] by titrimetric analysis by use of sodium benzoate solution as solubilizing agent. Maheshwari *et al.* have used sodium benzoate as hydrotropic solubilizing agent to estimate various poorly water-soluble drugs ofloxacin[4], norfloxacin[5], nalidixic acid[5], metronidazole[5] and tinidazole[5] by spectrophotometric analysis and aspirin[6] by titrimetic analysis.

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Various organic solvents used to solubilize the poorly water-soluble drugs to facilitate the acid-base titrations include methanol, ethanol, chloroform, dimethyl formamide and acetone. Most of the organic solvents are costly and toxic. Above account prompted us to investigate the use of sodium benzoate solution (2 M) in place of organic solvents for the purpose of solubilization to facilitate the titrimetric analysis of the poorly water- soluble NSAIDs, ibuprofen [(RS)2-(4-isobutylphenyl) propionic acid], flurbiprofen [(RS)2-(2-flubrobiphenyl-4-yl) propionic acid] and naproxen [(RS)6-methoxy-a-methyl-2-naphthalene acetic acid] with sodium hydroxide solution.

MATERIALS AND METHODS

A Shimadzu UV/Vis recording spectrophotometer (Model–UV 160 A) with 1 cm matched silica cells was employed for spectrophotometric analysis. The basic drug samples of ibuprofen, flurbiprofen and naproxen were generously supplied by M/s Alkem Laboratories Limited, Mumbai (India). Tablets of ibuprofen, Brufen (Knoll Pharmaceuticals Ltd.,) and Ibugesic (Cipla Ltd.), tablets of

flurbiprofen, Froben and Froben–SR (RPG Life Sci. Ltd.) and naproxen, Naprosyn (RPG Life Sci. Ltd.) and Xenar-CR (Elder Health Care Ltd.) were procured from local drug stores. Other chemicals and solvents were of analytical grade.

Preliminary solubility studies of ibuprofen, flurbiprofen and naproxen:

Solubilities of ibuprofen, flurbiprofen and naproxen were determined at 28±1°. An excess amount of drug was added to screw capped 30 ml glass vials containing different aqueous systems viz. distilled water, buffer (pH 8.2) and 2 M sodium benzoate solution. The vials were shaken mechanically for 12 h at 28±1° in orbital flask shaker (Khera Instrument Pvt. Ltd., India). These solutions were allowed to equilibrate for next 24 h and then centrifuged for 5 min at 2000 rpm (Remi, India).The supernatant of each vial was filtered through Whatman filter paper no. 41 and filtrates were analyzed for drug contents to determine the solubilities.

Analysis of ibuprofen drug sample by the proposed method:

Accurately weighed (400 mg) ibuprofen drug sample was transferred to a conical flask. The flask was shaken for 5 min after adding 100 ml of 2 M sodium benzoate solution (to solubilize the drug). Titration was performed with 0.1 M sodium hydroxide solution using 0.2 ml of phenolphthalein solution as indicator. Blank determination was carried out and necessary correction was done to calculate the drug content (Table 1).

Analysis of ibuprofen drug sample by the method of Indian Pharmacopoeia (1996)[20]:

Accurately weighed (400 mg) ibuprofen drug sample was dissolved in 100 ml of ethanol (95%) and titrated with 0.1 M sodium hydroxide solution using 0.2 ml of phenolphthalein solution as indicator. Blank determination was performed and necessary correction was made to calculate the drug content (Table 1).

Analysis of flurbiprofen drug sample by the proposed method:

Accurately weighed (500 mg) flurbiprofen drug sample was transferred to a conical flask. The flask was shaken for 5 min after adding 50 ml of 2 M sodium benzoate solution (to solubilize the drug). Titration was performed with 0.1 M sodium hydroxide using phenolphthalein solution as indicator. Blank determination was carried out and necessary correction was made to calculate the drug content (Table 1).

Analysis of flurbiprofen drug sample by the method of Indian Pharmacopoeia (1996)[21]:

Accurately weighed (500 mg) flurbiprofen drug sample was dissolved in 100 ml of ethanol (95%) previously neutralized to phenolphthalein solution as indicator and titrated with 0.1 M sodium hydroxide solution and drug content was calculated (Table 1).

Analysis of naproxen drug sample by the proposed method:

Accurately weighed (200 mg) naproxen drug sample was transferred to a conical flask. After adding 50 ml of 2 M sodium benzoate solution, the flask was shaken for 5 min for complete solubilization of drug. Titration was performed with 0.1 M sodium hydroxide solution using 1 ml of phenolphthalein solution as indicator. Blank determination was carried out and necessary correction was made to calculate the drug content (Table 1).

Analysis of naproxen using the method of British Pharmacopoeia (2002)[22]:

Accurately weighed (200 mg) naproxen drug sample was dissolved in a mixture of 25 ml of distilled water and 75 ml of methanol and titrated with 0.1 M sodium hydroxide solution using 1 ml of phenolphthalein solution as indicator. Blank determination was carried out and necessary correction was made to calculate the drug content (Table 1).

TABLE 1: ANALYSIS DATA OF BULK DRUG SAMPLES OF IBUPROFEN, FLURBIPROFEN AND NAPROXEN

Drug	Amount of drug taken (mg)	Method of analysis	Amount estimated[a] (mg) (mean±SD)	% Coeff. of variation	Standard error
Ibuprofen	400	PM[b]	398.9±0.63	0.63	0.36
	400	IP[c]	398.3±0.70	0.70	0.40
Flurbiprofen	500	PM[b]	496.2±1.13	1.14	0.65
	500	IP[c]	496.1±1.46	1.47	0.84
Naproxen	200	PM[b]	198.4±0.59	0.59	0.34
	200	BP[d]	197.7±0.77	0.78	0.44

[a]Mean (n=3), [b]Proposed method, [c]Method of IP (1996), [d]Method of BP (2002)

Analysis of ibuprofen tablets by the proposed method:

Twenty tablets of ibuprofen were weighed and powdered. Powder equivalent to 500 mg of ibuprofen was accurately weighed and transferred to a conical flask. After adding 100 ml of 2 M sodium benzoate solution, the flask was shaken for 10 min (to solubilize the drug). Titration was performed with 0.1 M sodium hydroxide solution using phenolphthalein solution as indicator. Blank determination was carried out and necessary correction was made to calculate the drug content (Table 2). For recovery studies, same procedure was repeated using 40 mg and 60 mg of ibuprofen drug as the spiked drug together with the tablet powder equivalent to 500 mg of ibuprofen. The results of analysis are presented in Table 3.

Analysis of ibuprofen tablets by the method of Indian Pharmacopoeia (1996)[20]:

Tablet powder equivalent to 500 mg of ibuprofen was accurately weighed and extracted with 60 ml of chloroform for 15 min and filtered. Residue was washed with three quantities each of 10 ml of chloroform.

TABLE 2: ANALYSIS DATA OF TABLET FORMULATIONS WITH STATISTICAL EVALUATION

Drug	T.F.[a]	Label claim (mg/tablet)	Method of analysis	% Label claim estimated[b] (mean±SD)	% Coeff. of variation	Standard error
Ibuprofen	I	400	PM[c]	99.52±1.25	1.26	0.72
		400	IP[d]	98.37±1.47	1.49	0.85
	II	400	PM[c]	99.22±0.62	0.63	0.36
		400	IP[d]	99.06±0.79	0.80	0.46
Flurbiprofen	III	100	PM[c]	99.03±0.76	0.77	0.44
		100	IP[d]	98.96±1.03	1.04	0.59
	IV	200	PM[c]	99.21±0.83	0.84	0.48
		200	IP[d]	98.85±0.53	0.54	0.31
Naproxen	V	250	PM[c]	99.34±1.14	1.15	0.66
		250	BP[e]	99.45±1.54	1.55	0.89
	VI	750	PM[c]	99.18±0.88	0.89	0.51
		750	BP[e]	99.11±0.72	0.73	0.42

[a]Tablet formulation, [b]Mean (n=3),. [c]Proposed method, [d]Method of IP (1996), [e]Method of BP (2002), I- Brufen (Knoll Pharmaceuticals Ltd.), II- Ibugesic (Cipla Ltd.), III-Froben, IV- Froben-SR, V-Naprosyn (RPG Life Sci. Ltd.), VI- Xenar-CR (Elder Health Care Ltd.)

TABLE 3: RESULTS OF RECOVERY STUDIES OF TABLET FORMULATIONS WITH STATISTICAL EVALUATION

Drug	T.F.[a]	Drug in preanalyzed tablet powder (mg)	Amount of drug (mg)	Method of analysis	% Recovery estimated[b] (mean±SD)	% Coeff. of variation	Standard error
Z	I	500	40	PM[c]	99.21±0.83	0.84	0.48
		500	40	IP[d]	98.37±'1.47	0.49	0.85
		500	60	PM[c]	99.09±0.92	0.93	0.53
		500	60	IP[d]	98.83±1.35	1.36	0.78
	II	500	40	PM[c]	99.11±0.72	0.73	0.42
		500	40	IP[d]	98.93±0.67	0.70	0.39
		500	60	PM[c]	99.45±0.54	0.55	0.31
		500	60	IP[d]	98.85±0.53	0.54	0.31
Y	III	400	30	PM[c]	99.03±0.76	0.77	0.44
		100	10	IP[d]	99.20±1.43	1.44	0.83
		400	50	PM[c]	98.37±0.47	0.48	0.27
		100	20	IP[d]	99.09±0.92	0.93	0.53
	IV	400	30	PM[c]	99.31±0.88	0.89	0.51
		100	10	IP[d]	98.83±1.34	1.36	0.77
		400	50	PM[c]	98.93±0.69	0.69	0.40
		100	20	IP[d]	99.11±0.72	0.73	0.42
X	V	400	30	PM[c]	98.96±0.73	0.74	0.42
		50	10	BP[e]	99.18±0.88	0.89	0.51
		400	50	PM[c]	98.22±1.38	1.41	0.80
		50	20	BP[e]	98.61±0.73	0.74	0.42
	VI	400	30	PM[c]	99.22±0.61	0.61	0.35
		50	10	BP[e]	98.77±0.58	0.59	0.33
		400	50	PM[c]	98.37±0.82	0.83	0.47
		50	20	BP[e]	99.30±0.49	0.49	0.28

[a]Tablet formulation, [b]Mean (n=3),. [c]Proposed method, [d]Method of IP (1996), [e]Method of BP (2002), X-ibuprofen, Y-flurbiprofen, Z-naproxen, I- Brufen (Knoll Pharmaceuticals Ltd.), II- Ibugesic (Cipla Ltd.), III-Froben, IV- Froben-SR, V-Naprosyn (RPG Life Sci. Ltd.), VI- Xenar-CR (Elder Health Care Ltd.)

Chloroform was evaporated in a current of air. Residue was dissolved in 100 ml of ethanol (95%) previously neutralized to phenolphthalein solution and titrated with 0.1 M sodium hydroxide solution. Drug content was calculated (Table 2). For recovery studies, same procedure was repeated using 40 mg and 60 mg of ibuprofen drug as the spiked drug together with the tablet powder equivalent to 500 mg of ibuprofen and the results of analysis are presented in Table 3.

Analysis of flurbiprofen tablets by the proposed method:

Twenty tablets of flurbiprofen were weighed and powdered. Powder equivalent to 400 mg flurbiprofen was accurately weighed and transferred to a conical flask. After adding 100 ml of 2 M sodium benzoate solution the flask was shaken for 5 min for solubilization of the drug. Titration was performed using 0.1 M sodium hydroxide solution using phenolphthalein solution as the indicator. Blank determination was carried out and necessary correction was made to calculate the drug content (Table 2). For recovery studies, same method was repeated using 30 mg and 50 mg flurbiprofen drug as the spiked drug together with the tablet powder equivalent to 400 mg of flurbiprofen. The results of analysis are presented in Table 3.

Analysis of flurbiprofen tablets by the method of Indian Pharmacopoeia (1996)[21]:

Tablet powder equivalent to 100 mg drug was shaken with 60 ml of 0.1 M sodium hydroxide solution for 5 min and diluted to 100 ml with 0.1 M sodium hydroxide solution. After filtration, 10 ml of the filtrate was diluted to 100 ml with 0.1 M sodium hydroxide solution. Absorbance of this solution was noted at 247 nm by spectrophotometer (Model-UV 160 A). Drug content was calculated taking 802 as the value of A (1%, 1 cm) at 247 nm (Table 2). For recovery studies same method was repeated using 10 and 20 mg of flurbiprofen drug sample as the spiked drug together with the tablet powder equivalent to 100 mg of flurbiprofen. Results of analysis are presented in Table 3.

Analysis of naproxen tablets by the proposed method:

Twenty tablets of naproxen were weighed and powdered. Powder equivalent to 400 mg naproxen was accurately weighed and transferred to a conical flask. After adding 100 ml of 2 M sodium benzoate solution, the flask was shaken for 5 min for solubilization of the drug. Titration was performed using 0.1 M sodium hydroxide solution with phenolphthalein solution as indicator. Blank determination was carried out and necessary correction was made to calculate the drug content (Table 2). Recovery studies were conducted repeating the operation using 30 mg and 50 mg naproxen drug sample as the spiked drug together with the tablet powder equivalent to 400 mg of naproxen. Results of analysis are shown in Table 3.

Analysis of naproxen tablets by the method of British Pharmacopoeia (2002)[23]:

Tablet powder equivalent to 50 mg of naproxen was shaken with 70 ml of methanol for 30 min. Sufficient methanol was added to produce 100 ml. After filtration, 10 ml filtrate was diluted to 50 ml with methanol. Absorbance of this solution was measured at 331 nm using spectrophotometer. Drug content was calculated (Table 2) from the absorbance obtained by repeating the operation using a 0.01% w/v solution of naproxen drug sample in methanol. Same procedure was repeated for recovery studies using 10 mg and 20 mg naproxen as the spiked drug together with the tablet powder equivalent to 50 mg of naproxen. Results of analysis are presented in Table 3.

RESULTS AND DISCUSSION

By performing the solubility studies, it was found that enhancements in aqueous solubilities of ibuprofen, flurbiprofen and naproxen in 2 M sodium benzoate solution were more than 80, 110 and 120 fold, respectively as compared to their solubilities in distilled water. There was negligible effect on solubilities of these drugs in buffer of pH 8.2 and such enhancements in solubilities of these drugs in 2 M sodium benzoate solution could therefore be attributed to hydrotropic solubilization phenomenon and not due to change in pH. Hence, it was thought worthwhile to solubilize these drugs in 2 M sodium benzoate solution to carryout titrimetric analysis precluding the use of organic solvents.

Table 1 shows that amounts of ibuprofen estimated in the drug sample were 398.9±0.63 and 398.3±0.70 mg by the proposed and pharmacopocial methods, respectively. Similarly, the amounts of flurbiprofen estimated in the bulk drug sample were 496.2±1.13 and 496.1±1.46 mg by the proposed and pharmacopoeial methods, respectively. In case of naproxen bulk drug sample, the amounts estimated by proposed and pharmacopoeial methods were 198.4±0.59 and 197.70±0.77 mg, respectively. The amounts of the drugs estimated by

both the proposed and pharmacopoeial methods are very close to each other and comparable indicating the accuracy of the proposed methods of analysis. Validation of the proposed methods is further confirmed by the low values of standard deviation, percent coefficient of variation and standard error. Table 2 shows the results of analysis of tablet formulations. Percent label claims of ibuprofen tablets formulations estimated by the proposed and pharmacopoeial methods ranged between 98.37±0.47 and 99.52±0.25. Similarly percent label claims of flurbiprofen tablet formulations estimated by the proposed and pharmacopoeial methods ranged between 98.85±0.53 and 99.21±0.83. In case of naproxen tablet formulations, the values of percent label claims estimated by the proposed and pharmacopoeial methods ranged between 99.11±0.72 and 99.45±0.54. Thus, the percent label claims of ibuprofen, flurbiprofen and naproxen tablet formulations estimated by the proposed and pharmacopoeial methods are very comparable and close to 100 indicating the accuracy of the proposed methods. Validation of the proposed methods of analysis is confirmed statistically by low values of standard deviation, percent coefficient of variation and standard error.

Recovery studies (Table 3) were also carried out by spiking the previously analyzed fine powders of tablet formulations at two levels to further ascertain the accuracy and precision of the proposed methods. The values of percent recoveries estimated by the proposed methods compared very well with the values obtained by the corresponding pharmacopoeial methods. The percent recovery values are close to 100 and the values of statistical parameters viz. standard deviation, percent coefficient of variation and standard error are significantly low. Thus, the proposed methods of analysis are very well validated.

Indian Pharmacopoeial method for the analysis of ibuprofen drug sample involved the use of alcohol for dissolution of drug to carryout the titration with sodium hydroxide solution. Similarly Indian Pharmacopoeial method for the analysis of ibuprofen tablets requires extraction of ibuprofen by chloroform. Chloroform is removed by air-drying which is responsible for pollution and toxicity and it is a costlier solvent too. Residue is re-dissolved in alcohol to carryout titration. Official methods for the analysis of flurbiprofen and naproxen drug samples involve the use of alcohol and methanol, respectively. Methanol is also a toxic solvent. Method of British Pharmacopoeia for the analysis of naproxen tablets involves the use of methanol. However, in the proposed methods 2 M sodium benzoate solution has been used as hydrotropic solubilizing agent for solubilization of drugs to carryout titrations with sodium hydroxide solution. There is no involvement of organic solvents. The proposed methods are comparable to official methods and have been validated with statistical evaluation. Also a sophisticated instrument is not required in analysis of flurbiprofen and naproxen tablet by proposed methods. The commonly used excipients in the formulation of tablets and the hydrotropic agent, sodium benzoate did not interfere in the analysis of tablets.

Thus, it may be concluded that the proposed methods of analysis are new, simple, cost-effective, environmentally friendly, safe, accurate and reproducible. Decided advantage is that organic solvents are precluded but not at the expense of accuracy. Certainly there is further scope of 2 M sodium benzoate solution as solubilizing agent for the titrimetric analysis of other poorly water-soluble drugs. The proposed method is worth adopting in the respective pharmacopoeias.

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