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Non-aqueous potentiometric determination of drugs mefenamic acid and paracetamol-mefenamic acid in single and double component pharmaceuticals

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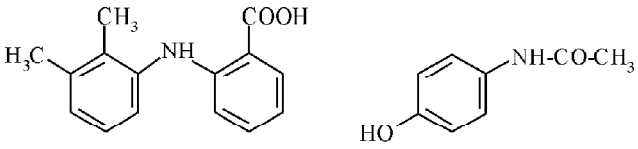
The non-aqueous potentiometric determination of drugs mefenamic acid and paracetamol-mefenamic acid has been worked out. These drugs are widely used in medicines either as a single component or in combination of two. The effect of solvent and concentration on determination of drug mefenamic acid along with its determination in single component tablets and paracetamol containing double component tablets has been studied using the solvent isopropanol and titrant KOH in isopropanol. The acidic drugs paracetamol-mefenamic acid were simultaneously determined in double component tablets by differentiating potentiometric titrations. Titrations were carried out using a pair of glass and saturated calomel electrodes. This method was found to be quite simple, efficient, precise and convenient for assay of single and double component tablets. The results obtained are comparable to those obtained by Indian Pharmacopoeia (IP) method.

Keywords: Non-aqueous, potentiometric, mefenamic acid, paracetamol-mefenamic acid.

Introduction

The non-aqueous potentiometric determination of various pharmaceutical drugs has been reported earlier using different electrode pairs[1]. Several methods have been reported for the determination of drug mefenamic acid in single component form and majority of these are spectrophotometric[2]. However, these methods are very much non-selective and time consuming. The estimation of drug mefenamic acid by colorimetry, voltammetry, potentiometry and polorography was reported earlier[3]. It has been also analyzed by atomic absorption spectrometry, gas liquid chromatography and capillary electrophoresis technique[4].

Different methods have been suggested for the determination of drugs in double or triple component dosage form and mostly involved the separation of components followed by their estimation using suitable method[5]. Pharmacopoeias include the methods for determination of drugs in combination[6]. Literature is enriched with spectrophotometric determination of drugs paracetamol-mefenamic acid in double component form[7]. These drugs in combinations were analyzed by reversed phase ultra performance liquid chromatography, high performance thin layer chromatography and ^{1}H NMR spectroscopy[8]. Although different methods have been evaluated and utilized for the determination of drugs, however, very little work is available on the direct estimation of drugs by non-aqueous potentiometric titrations. As the drugs mefenamic acid and paracetamol are distinctly acidic, could not be titrated directly with aqueous alkali due to their easy hydrolysis. The basic titrant KOH in isopropanol is also superior to the alkoxide solvents which are more susceptible to the atmospheric moisture and CO_2.



The present communication deals with the non-aqueous potentiometric determination of drugs mefenamic acid and paracetamol-mefenamic acid in single and double component pharmaceuticals. The effect of solvent and concentration on potentiometric analysis of drug mefenamic acid has been also studied. In double component tablets, determination of one component in presence of other was carried out without any prior separation. In all non-aqueous potentiometric titrations, isopropanol was used as the solvent and KOH in isopropanol as the titrant. Present work is aimed at finding out simple analysis procedure for common drugs

which will help the analysis of raw materials and products for quick check of spurious drugs that are feared to penetrate the markets.

Results and discussion

Effect of solvent and concentration on non-aqueous potentiometric determination of drug mefenamic acid:

In the study of effect of solvent on non-aqueous potentiometric determination of drug mefenamic acid, accuracy of results in determination of drug mefenamic acid by using different types of solvents was checked. The required volumes of stock solutions of drug mefenamic acid in different solvents were diluted to 20 ml and then titrated separately with KOH in isopropanol. It was observed that, accuracy of result in determination of drug mefenamic acid using solvent isopropanol is much more as compared to other solvents with minimum % error (Table 1). The potentiometric break obtained using solvent dimethyl formamide is smoother as compared to acetone and methanol. The potentiometric break obtained using solvent isopropanol is much more pronounced and prominent with maximum potential difference near equivalence point (Fig. 1). As compared to acetone, methanol and dimethyl formamide, the dielectric constant of solvent isopropanol is smaller and it permitted a large change in solvated proton concentration near end point. Solvent isopropanol can be purified and made anhydrous very easily as compared to other solvents.

Table 1. Effect of solvent on non-aqueous potentiometric determination of drug mefenamic acid

Solvent	Weight titrated (mg) (±0.5%)	Weight found (mg)	Error (%)
Acetone	4.824	4.806	–0.37
Methanol	4.824	4.782	–0.87
Dimethyl formamide	4.824	4.858	+0.70
Isopropanol	4.824	4.865	+0.84

For the study of effect of concentration on non-aqueous potentiometric determination of drug mefenamic acid and to determine suitable concentration range that gives best results, different volumes of the stock solution of drug mefenamic acid were diluted to 20 ml with isopropanol and titrated separately with KOH in isopropanol. It was observed that, non-aqueous potentiometric titration method gave an accuracy of ±1% for the entire range of 2.412 to 24.120 mg.

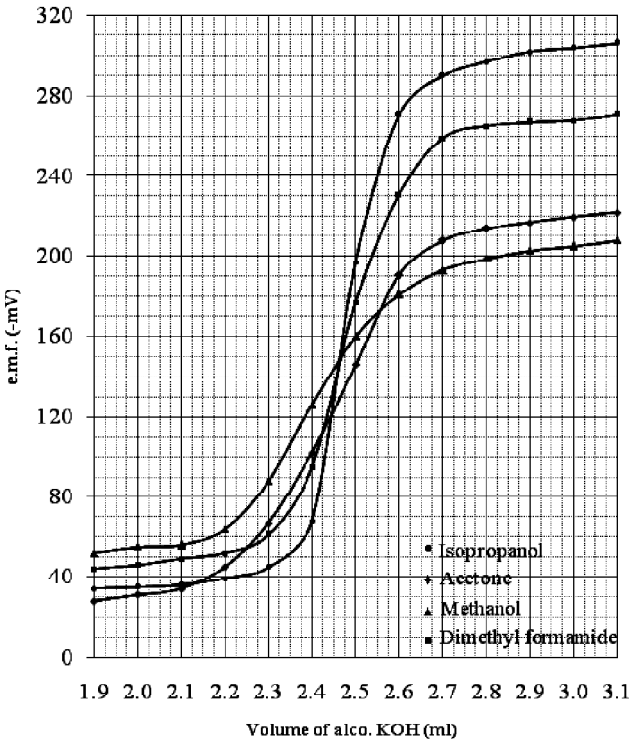


Fig. 1. Effect of solvent on non-aqueous potentiometric determination of drug mefenamic acid.

The results obtained are much better and accurate as compared to other methods with both positive as well as negative errors (Table 2). The present method of determination gave much more pronounced potentiometric breaks (Fig. 2) and found to be better than the method given in pharmacopoeias. The values of mean, mean deviation and standard deviation of study of effect of concentration on poten-

Table 2. Effect of concentration on non-aqueous potentiometric determination of drug mefenamic acid

Weight titrated (mg)	Weight found (mg)	Error (%)
2.412	2.434	+0.91
4.824	4.856	+0.66
7.236	7.182	–0.74
9.648	9.597	–0.52
12.060	12.092	+0.26
14.472	14.590	+0.81
16.884	16.786	–0.58
19.296	19.321	+0.12
21.708	21.728	+0.09
24.120	24.065	–0.22

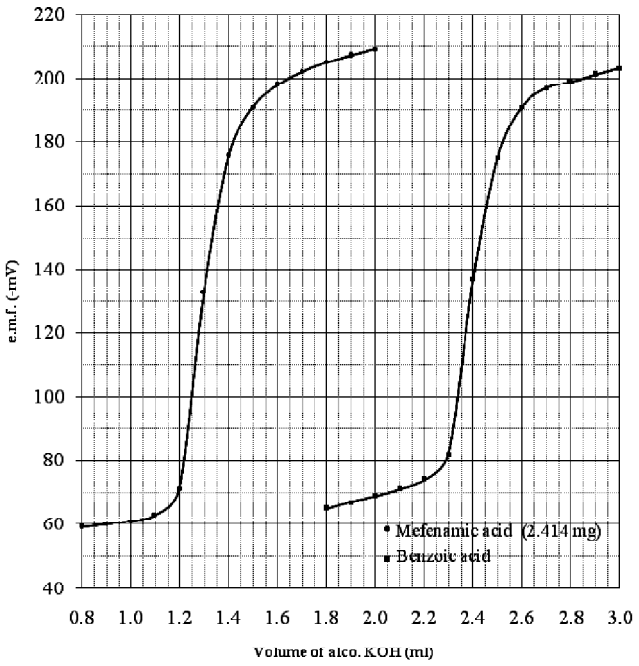


Fig. 2. Effect of concentration on non-aqueous potentiometric determination of drug mefenamic acid.

tiometric determination of drug mefenamic acid are 13.266, 6.030, 7.302 for weight titrated, 13.265, 6.032, 7.294 for weight found and 0.079, 0.475, 0.590 for % error respectively.

Determination of drugs mefenamic acid and paracetamol-mefenamic acid in single and double component tablets:

Ten single component tablets of the same batch containing drug mefenamic acid were powdered. The required quantity of powder was accurately weighed, extracted with isopropanol and then volume was made to 100 ml. An aliquot of 10 ml of this solution was diluted with isopropanol to 20 ml and it was then titrated with KOH in isopropanol using potentiometer. The quantity of drug mefenamic acid present in one tablet was calculated. Titrant was standardized using benzoic acid in isopropanol by potentiometric titration. Similarly, the quantity of drug paracetamol-mefenamic acid present in titrated amount of double component tablet was determined. The same tablets were determined by IP method. The results obtained for four different brands of single and double component tablets showed that, the present non-aqueous potentiometric titration method gives fairly accurate and comparable results to those obtained by IP method (Tables 3 and 4).

Table 3. Determination of drug mefenamic acid in single component tablets

Sample	Label claim	Weight found (mg)	
	(mg)	IP method	Present method
A1	100.0	100.83	100.21
A2	100.0	101.08	100.56
A3	250.0	248.42	250.08
A4	500.0	497.80	498.63

The present method is free from indicator error and interferences, it is simple, quite better and accurate than the methods reported in literature. The acidic drugs get hydrolyzed in presence of aqueous alkali but this is avoided in non-aqueous medium. According to US Pharmacopoeia procedure, alcoholic solution of the acidic drugs can be titrated with aqueous alkali but such titrations must be performed quickly so as to minimize hydrolysis. The present method has no such limitations. Commonly the additives present in pharmaceutical tablets are calcium carbonate, sugars, gum etc. These are insoluble in isopropanol and do not affect the results. The solvent isopropanol can be used as a good differentiating solvent. The potentiometric breaks obtained using solvent isopropanol are quite pronounced and prominent with minimum error (Fig. 3). The dielectric constant of isopropanol is smaller and it can be purified and made anhydrous very easily. The solvent isopropanol permitted a large

Table 4. Determination of drug paracetamol-mefenamic acid in double component tablets

Sample	Label claim (mg)		Weight found (mg)			
			IP method		Present method	
	Paracetamol	Mefenamic acid	Paracetamol	Mefenamic acid	Paracetamol	Mefenamic acid
B1	125.0	50.0	124.20	49.63	124.85	50.03
B2	500.0	250.0	502.18	247.12	500.55	248.97
B3	500.0	250.0	502.08	250.71	499.31	250.11
B4	500.0	500.0	497.72	502.14	498.64	500.86

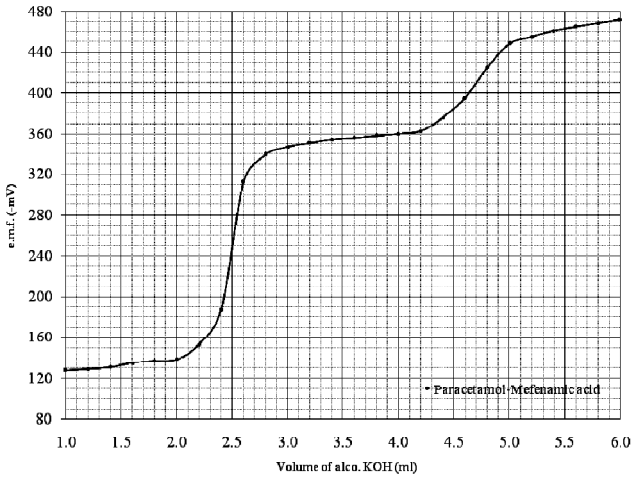


Fig. 3. Determination of drug paracetamol-mefenamic acid in double component tablets.

change in solvated proton concentration near the end point. This method is simple than the other methods in which the components are separated and estimated by chromatographic, spectrophotometric or other techniques.

Experimental

All potentiometric titrations were carried out by using digital potentiometer (Equiptronics, EQ-602). Glass electrode was used as an indicator electrode whereas saturated calomel electrode as a reference. Weighing were done by using Precisa-310M (±0.001 g) electronic balance. All chemicals as well as solvents used were of AR grade. Solvents were purified and made anhydrous following standard methods. Care was taken to protect the titrant from atmospheric moisture and CO_2. The drugs mefenamic acid and paracetamol-mefenamic acid utilized for present investigation were obtained from pharmaceutical laboratories. These drugs are of pharmaceutical nature and included in pharmacopoeias[6].

Effect of solvent and concentration on non-aqueous potentiometric determination of drug mefenamic acid:

To perform the study of effect of solvent on non-aqueous potentiometric determination of drug mefenamic acid, its stock solutions (2.412 mg/ml, ±0.5%) have been prepared by dissolving it in solvents acetone, methanol, dimethyl formamide and isopropanol. Using the same solvents, 2 ml of these solutions were then diluted to 20 ml and separately titrated with KOH in isopropanol using a pair of glass and saturated calomel electrodes.

To do the study of effect of concentration, stock solution of drug mefenamic acid (2.412 mg/ml) have been prepared by dissolving it in isopropanol. Different volumes of the stock solution (1 to 10 ml) were then diluted to 20 ml with isopropanol and separately titrated with KOH in isopropanol by adding titrant in the lots of 0.1 ml with continuous stirring using magnetic stirrer. After each addition, the potential developed across two electrodes was measured. To get the potential stabilized, waiting period of about 1 to 2 min was allowed. Addition of the titrant was continued till 0.3 to 0.5 ml excess of it was added. Near the end point readings were taken after each addition of 0.02 ml of titrant. End points were determined by plotting curves between the potential developed and the volume of titrant added.

Determination of drugs mefenamic acid and paracetamol-mefenamic acid in single and double component tablets:

For the determination of drug mefenamic acid present in single component tablets, ten tablets of the same batch were accurately weighed and powdered. The powder containing 100 mg of drug mefenamic acid was weighed accurately, treated with 50 ml of isopropanol and stirred vigorously to dissolve all the active components of the tablet. Binding agents and filler remained insoluble. The solution was then filtered, residue was washed with small portions of isopropanol three to four times and the volume of solution was made to 100 ml with isopropanol. An aliquot of 10 ml of this solution was diluted to 20 ml with isopropanol and using glass and saturated calomel electrodes titrated with 0.1 *M* of solution of KOH in isopropanol by potentiometric method. Titrant was standardized using 0.1 *M* benzoic acid in isopropanol by potentiometric titration. Similarly, the drug paracetamol-mefenamic acid present in double component tablets was determined. The end points were determined by plotting curves as described earlier and the amount of drugs present in titrated weights of tablet powder was calculated. The quantity of active component (drug) present in each tablet was calculated from the average weight of the tablet. The same tablets were then determined by method given in pharmacopoeias and results obtained were compared with present non-aqueous potentiometric titration method.

Conclusion

The method of determination of drugs mefenamic acid and paracetamol-mefenamic acid by non-aqueous potentio-

metric titration is simple, efficient, precise and gave better results. It can be used even in common laboratories without use of any sophisticated instrument. The solvent isopropanol was found to be excellent for all titrations. The basic titrant, KOH in isopropanol was superior to the alkoxide solvents that are more susceptible to atmospheric moisture and CO_2. The potentiometric breaks obtained using calomel and glass electrode were quite larger.

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References

1. S. A. M. Abdulrahman and B. Kanakapura, *Chem. Ind. & Chem. Engg. Q*, 2011, **17(2)**, 173; V. R. Patil and P. P. Deohate, *J. Indian Chem. Soc.*, 2013, **90**, 1379; V. R. Patil and P. P. Deohate, *J. Indian Chem. Soc.*, 2014, **91**, 647; M. Khateeb, B. Elias and H. Alksair, *J. Electrochem. Sci. Engg.*, 2016, **6(4)**, 277; E. Y. Z. Frag, G. G. Mohamed, M. M. Khalil and M. M. A. Hwehy, *Int. J. Anal. Chem.*, 2011, **2011**, 1; P. P. Deohate, *J. Indian Chem. Soc.*, 2018, **95**, 559; A. Raza, *J. Anal. Chem.*, 2008, **63(3)**, 244; R. V. Rele and R. H. Terse, *J. Chem. Pharm. Res.*, 2011, **3(3)**, 1.
2. N. A. Alarfaj, S. A. Altamimi and L. Z. Almarshady, *Asian J. Chem.*, 2009, **21(1)**, 217; G. Mathai, J. T. Moolayil, K. B. Jose and V. S. Sebastian, *Indian J. Pharm. Sci.*, 2010, **72(4)**, 525; H. Singh, R. Kumar and P. Singh, *Int. J. Pharm. & Pharm. Sci.*, 2011, **3(2)**, 237; Z. A. Kormosh, O. Y. Matviichuk and Y. R. Bazel, *J. Anal. Chem.*, 2014, **69(10)**, 960.
3. S. O. Idowu, S. C. Tambo, A. O. Adegoke and A. A. Olaniyi, *Trop. J. Pharm. Res.*, 2002, **1**, 15; L. Liu and J. Song, *Anal. Biochem.*, 2006, **354(1)**, 22; Z. Kormosh and O. Matviychuk, *Chin. Chem. Lett.*, 2013, **24(4)**, 315; J. F. Song and W. Guo, *Chin. J. Pharm.*, 1993, **24**, 24.
4. M. Y. Khuhawar, T. M. Jehangir and F. M. A. Rind, *J. Chem. Soc. Pak.*, 2001, **23**, 226; B. R. Dhumal, K. P. Bhusari, M. R. Tajne, M. H. Ghante and N. S. Jain, *J. Appl. Pharm. Sci.*, 2014, **4(12)**, 60; T. Perez-Ruiz, C. Martinez-Lozano, A. Sanz and E. Bravo, *J. Chromatogr. & Biomed. Sci. Appl.*, 1998, **708**, 249.
5. M. R. Rouini, A. Asadipour, Y. H. Ardakani and F. Aghdasi, *J. Chromatogr. B: Anal. Tech. Biomed. Life Sci.*, 2004, **800(1-2)**, 189; A. Goyal and I. Singhvi, *Indian J. Pharm. Sci.*, 2008, **70**, 108; Y. Jaiswal, G. Talele and S. Surana, *J. Liq. Chromatogr. & Rel. Techno.*, 2007, **30(8)**, 1115.
6. "British Pharmacopoeia", Her Majesty's stationary office, London, Vol. I and II, 2004; "Pharmacopoeia of India", Directorate of Publications, New Delhi, 2007; "United States Pharmacopoeia XX" and "National Formulatory XV", U.S. Pharmocopeal Convention, Rockville, 1980.
7. A. M. Karnik, V. P. Choudhari, S. Sharma, S. Murkute and V. Patole, *J. Pharm. Res. & Clin. Pract.*, 2012, **2(2)**, 43; W. A. A. Alballaa, A. A. A. Ali, O. A. A. Hamdi and A. M. Idris, *Dev. Anal. Chem.*, 2016, **3**, 12; E. Dinc, C. Ycesoy and F. Onur, *J. Pharm. Biomed. Anal.*, 2002, **28(6)**, 1091; S. Das, S. C. Sharma, S. K. Talwar and P. D. Sethi, *Analyst*, 1989, **114(1)**, 101; V. P. Choudhari, P. D. Bharande, S. G. Chate, S. N. Sharma and R. B. Singh, *Der Pharma Chemica*, 2012, **4(3)**, 935.
8. D. M. Basha and K. A. Reddy, *Int. J. Chem. Sci.*, 2014, **12(3)**, 1015; D. Shah, J. Rana, S. Baldania, U. Chhalotiya and K. Bhatt, *J. Planar Chromatogr. Modern TLC*, 2014, **27(1)**, 52; S. Hussain, M. Kifayatullah and R. Sekar, *Indian J. Chem. Tech.*, 2001, **8(3)**, 191; O. A. Mansour, M. F. Metwally, S. M. Sakr and M. I. Al-Ashmwi, *Spectr. Lett.*, 1990, **23**, 801.