PHARMACY

THE DIRECT TITRATION OF SOME SULFONAMIDES IN TABLETS

BY

TAN SIP IE & POEY SENG BOUW *)

Ringkasan.

Telah dilakukan peniteran beberapa sulfonamida jang banjak dipakai di Indonesia, jakni sulfadiazine, sulfamerazine, sulfamezathine dan sulfisomidine ("Elkosin").

Tjara jang dipakai adalah suatu modifikasi mengenai indikatornja dari tjara van Arkel & Woute jang sudah dimasukkan dalam Farmakope Belanda Ed. VI. Dengan tjara modifikasi kami ini perubahan warna pada titik achir titrasi, teristimewa pada penentuan langsung dari tablet'-nja adalah lebih djelas, sehingga dapat digunakan untuk penentuan' routine dari tablet' sulfa, meskipun hasil jang diperoleh pada umumnja ada sedikit lebih tinggi dari semestinja.

Sebagai kontrole dilakukan djuga peniteran setjara nitrimetrik.

The quantitative determinations of sulfonamides can be done by various ways. Among the nowadays used methods are the bromometric method (1, 2, 3, 4), nitrite method, official in some pharmacopoeias (4, 5, 6, 7), argentometrically (8), which is also official for some sulfonamides in the Swiss Pharmacopoeia, and by titration in non-aqueous solvents as a base (9, 10) as well as an acid (11, 12, 13, 14).

Beside above mentioned techniques, the sulfonamides can also be estimated by several physical methods, f.i. spectrophotometrically (15), etc.

As we know the bromometric assay depends on several factors including the duration of the bromination, the acidity of the solutions, the excess of the bromine used, etc.

The nitrite method is according to our opinion not so convenient in the performance. It is also the case with the argentometric method, especially for the direct titrations of tablets. When the formulation contains stearic acid, it gives precipitations with silver nitrate (16).

Van Arkel & Woute (17) has titrated some sulfonamides using neutral aceton as solvent and a solution of sodium hydroxide in water as titrant. This method is now adapted in the Dutch Pharmacopoeia Ed. VI using a mixture of thymolblue and phenolphthalein as indicator. This procedure generally gives satisfactory results for most of the pure sulfonamides.

*) *From the Laboratory of Pharmaceutical Chemistry, Institute of Technology Bandung, Indonesia.*

However, for direct titrations in tablets the color change at the end point of the titrations is not so convenient.

By changing the indicator mixture we have made this method applicable to direct routine analysis of some sulfonamides in tablets. As indicator we use a mixture of a yellow dye-stuff, phenolphthalein and methylene blue.

EXPERIMENTAL

Apparatus.

50-ml. burette, graduated in O.1 ml.;
electromagnetic stirrer;
Beckman Zeromatic pH meter with glass and calomel electrodes.

Reagents and Solutions.

Aceton B.P.;
Yellow dye-stuff solution: 1 Gm. "Citroengeel" (K 1460 Naarden) dissolved in 100 ml. dilute alcohol. The solution should be filtered after preparing.
Phenolphthalein solution: 100 mg. phenolphthalein dissolved in 100 ml. dilute alcohol;
Methylene Blue solution: 50 mg. methylene blue dissolved in 100 ml. strong alcohol;
Sodium Hydroxide solution: ± 0.1 N; ± 4 Gm. sodium hydroxide purified grade dissolved in 1000 ml. distilled water and standardized against oxalic acid.

Procedure.

a. Pure Sulfonamide.

Weigh accurately a sample of about 250 mg. into a 100-ml. Erlenmeyer flask and dissolve it in 10 ml. neutral aceton. Add 2 drops of yellow dye solution, 5 drops phenolphthalein solution and 1 drop methylene blue solution. Titrate with sodium hydroxide solution using as the end point the color change from yellow green to pinkish purple.

b. Sulfonamide Tablets.

Weigh and powder at least 10 tablets. Place and accurately weighed sample equivalent to about 250 mg of the sulfonamide in a 100-ml. Erlenmeyer flask, add 10 ml. of neutral aceton. Proceed by the method for pure sulfonamide beginning at "Add 2 drops of yellow dye solution, ..."

To verify this recommended method we also estimated the sulfonamides by the nitrite methods as described in the U.S. Pharmacopoeia.

RESULTS

Table I.

COMPARISON OF RECOMMENDED METHOD WITH NITRITE METHOD

Form	Per cent recovery	
	method Recommended	Nitrite method
A. *Pure*		
Sulfadiazine	100.6 100.7	100.0 99.9
Sulfamerazine	100.5 100.3	100.3 100.0
Sulfamezathine	100.2 100.0	100.7 100.6
Sulfisomidine ("Elkosin")	100.6 100.9	99.9 100.1
B. *Self-compound Tablets*		
Sulfadiazine	100.6 100.1	100.4 100.2
Sulfamerazine	100.7 100.8	99.8 100.2
Sulfamezathine	100.2 100.7	100.3 100.4
Sulfisomidine ("Elkosin")	100.8 100.9	100.4 100.2

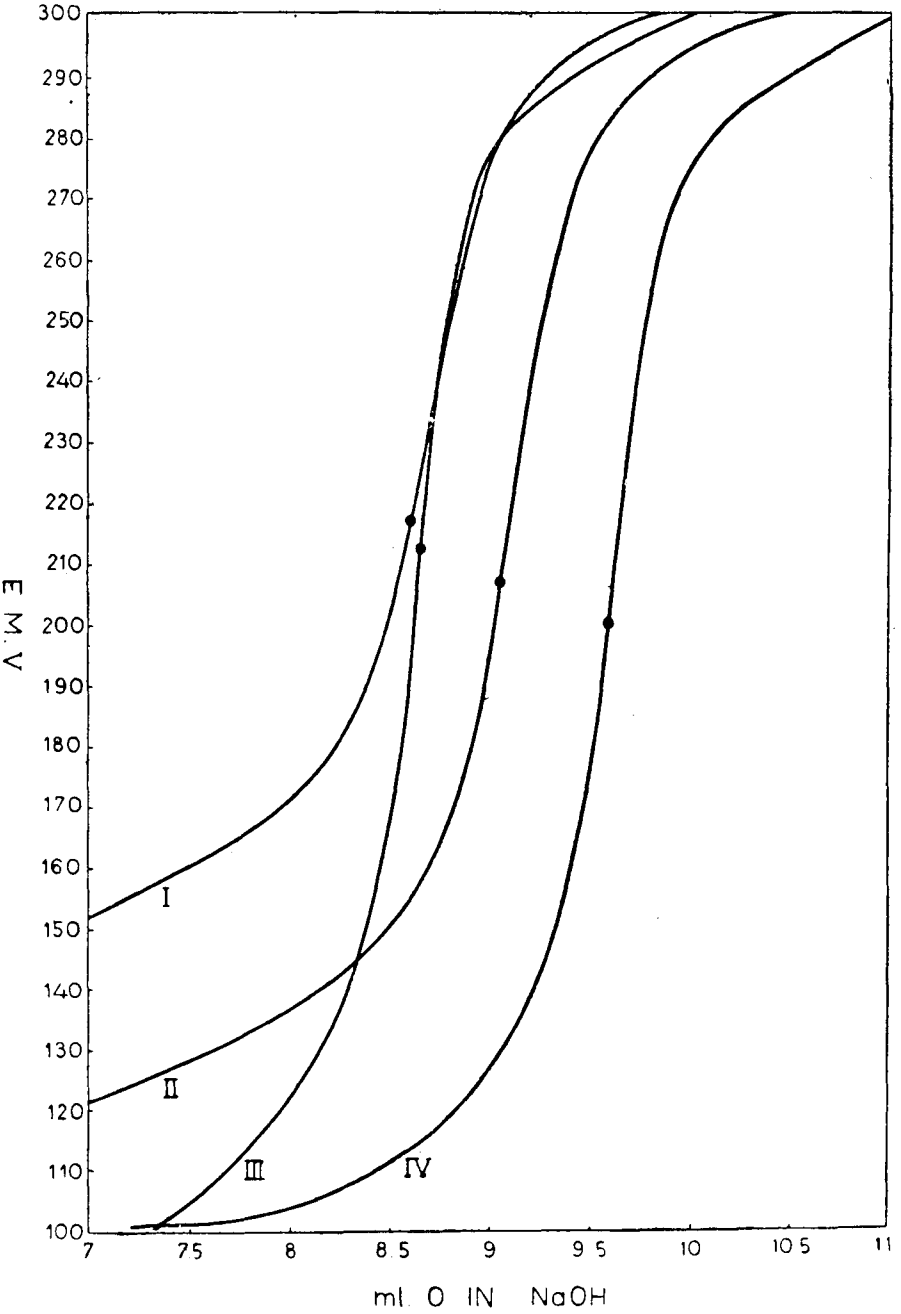
Table II.

RESULTS OF DIRECT TITRATIONS OF SULFONAMIDE TABLETS, COMMERCIALLY AVAILABLE FROM DIFFERENT MANUFACTURES

Sample		Weight (mg.) per tablet indicated on label	Recovery (mg.)	
			Recommended method	Nitrite method
Sulfadiazine :	Factory A	500	506.5 507.3	499.0 502.3
	Factory B	500	484.8 484.9	478.1 480.7
Sulfamerazine :	Factory C	500	494.0 495.7	492.5 490.0
	Factory D	500	475.2 472.8	468.6 468.1
Sulfamezathine :	Factory E	500	489.8 491.2	490.4 491.6
	Factory F	500	388.4 386.0	386.0 385.5
Sulfisomidine : *("Elkosin")*	Factory G	500	481.4 480.7	480.4 480.2
	Factory H	500	512.9 511.3	494.9 493.8

DISCUSSION

Fig. I



I = sulfamezathine
II = sulfamerazine
III = sulfisomidine
IV = sulfadiazine

Before carrying out this titration visually, the end point of the indicator mixture was checked potentiometrically using a glass-calomel electrode combination.

Figure I shows the titration curves of the sulfonamides. It illustrates a more or less agreement that was obtained between the potentiometric and visual end points. It is worth mentioning that the curve of sulfisomidine shows relatively a sharp interval in comparing with the other sulfonamides.

The results, obtained visually, are generally higher than they must be. However, regarding the simplicity, rapidity and the sharp color change at the end point of the titration, and concerning the content of the sulfonamides in each tablet by the standard of most of the pharmacopoeias may vary between 95 — 105%, so according to our opinion this method can be applied to the direct titration of sulfonamide tablets in routine analysis.

The self-compound tablets have the following formula :

Sulfa drug	500 mg.
Talcum	31.2 mg.
Lactose	46.9 mg.
Starch	46.9 mg.

In the titrations of the tablets it is better to crush the tablets as fine as possible, followed by sieving through a fine sieve.

If the aceton used in this titration is not neutral against the used indicator mixture, so a blank titration of the solvent itself is necessary.

The yellow dye-stuff used in this method is available everywhere in Indonesia. It is shown that this dye-stuff is not influenced upon addition of acid or alcali as is the case with the methylene blue. The addition of methylene blue and the yellow dye is to produce a yellow green color, so that the color change at the end point is now from yellow green to pinkish purple instead of from colorless to pink as if phenolphthalein alone is used. Besides, by adding the 2 dyes the transition point of phenolphthalein is shifted to a higher range, namely at pH $\pm$ 10.5 as was checked by a Beckman pH meter model H 2.

Sulfaguanidine and sulfanilamide can not be estimated by this method as they are too weak. Sulfanilamide can be titrated as acid only when dissolved in butylamine as solvent and sodium methoxide as titrant using azoviolet as indicator (13).

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