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Metoclopramide determination by amperometric and potentiometric titrations—application to some pharmaceutical preparations

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Summary

A method for the determination of metoclopramide in pharmaceutical preparations by titration with standardized sodium nitrite solution using double-pin platinum and combined platinum ring electrodes was developed and compared with the Br. Pharm. current methods. The amount of acid used to catalyze the diazotization is a decisive factor in determining amounts less than 10 mg. When amounts of about 300 mg were used the acid strength had no significant effect. Generally, additives used in pharmaceutical preparations were found not to interfere with the assay technique. The method was applied to bulk drug, tablets, tablets' content uniformity, syrups, solutions and injections, and was found to be fast, simple, reproducible and applicable for automation.

Introduction

Metoclopramide (4-amino-5-chloro-N-(2-diethyl aminoethyl)-2-methoxybenzamide) is used medicinally to increase gastric motility, accelerate gastric emptying, to treat irradiation sickness and to prevent post-operative vomiting (Martindale, 1982). Recently, it has been demonstrated that high doses of metoclopramide are also successful in the prevention of nausea and vomiting accompanying cytotoxic chemotherapy (Gralla et al., 1980).

Different methods have been used for the assay of metoclopramide. Such methods are based on the absorbance measurement in UV, colorimetery following diazotization, non-aqueous titration (Pitel and Luce 1965) or spectrofluorometry (Baeyens and De Moerloose 1978). In addition, the identification and quantitative determination of some substituted benzamides in various pharmaceutical dosage forms are carried out by high-pressure liquid chromatography (Verbiese-Genard et al., 1979).

Metoclopramide is the subject of a British Pharmacopoeia (B.P.) monograph which adopts the non-aqueous titration against perchloric acid as the official assay for the bulk drug (British Pharmacopoeia, 1980a). The utilization of the non-aqueous titration method in dosage form analysis has proven inadequate due to interferences from additives. The B.P. adopts a spectrophotometric method for tablets depending on dispersing the tablet content in hydrochloric acid and heating at 70°C for 15 min. The solution is rendered alkaline, extracted with chloroform and the

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absorbance is read at a maximum of 305 nm (B.P., 1980b). The B.P. method is tedious and time-consuming, consequently this report describes a fast method developed for the determination of metoclopramide in bulk and in different dosage forms that can be applied for tablet content uniformity testing.

Materials

Reagents

Sodium nitrite (99%, Merck) solutions were standardized against sulphanilic acid (99.0%, Merck). Hydrochloric acid 37% w/w (Riedel-de Haën). Perchloric acid (72%, Merck) in glacial acetic acid was prepared and standardized as described in the pharmacopoeial monograph (B.P., 1980c).

Metoclopramide hydrochloride was of B.P. quality.

Dosage form samples

The same batch of each metoclopramide dosage form was obtained locally. The following brands were used in the present study as shown in "Table of Brands".

Instruments

An automatic microprocessor titrator (Mettler DL 40 RC) connected to alphanumeric printer and recorder is used. The automatic titrator is programmed to titrate in different titration modes depending on the reaction nature. The chosen mode is the equilibrium titration in which the titrant is added in constant selectable volume increments. The time sequence of the various volume increments is controlled in such a manner that electrode potential has reached a defined equilibrium condition before any new additions are made. This results in an automatic adaptation of the titration to the reaction speed and to the response time of the electrode. The electrodes used are a double-pin platinum electrode (Mettler DM 142) and a combined platinum ring electrode (Mettler DM 140). When the double-pin platinum electrode is used, a polarization current adaptor is fixed into the automatic titrator (Mettler DK 102). For non-aqueous titration a special glass electrode is used (Mettler DG 112).

For absorbance measurements a Perkin Elmer 550 model spectrophotometer is used.

Methods

Bulk material. 300 mg of metoclopramide were dissolved in 50 ml of 4 M hydrochloric acid solution in the automatic titrator cup. The solution was stirred for 1 min and titrated against 0.1 M sodium nitrite. The end-point was detected by the combined platinum ring electrode and the double-pin platinum electrode.

Tablets. 20 tablets of known weight were powdered and the equivalent of 10 mg of anhydrous metoclopramide hydrochloride was placed in the automatic titrator cup and dispersed in 50 ml of 4 M hydrochloric acid solution. The cup contents were stirred for 2 min and titrated against 0.01 M sodium nitrite. The titrant was added in 0.025 ml portions and the end-point was

TABLE OF BRANDS

Brand	Origin	Dosage forms	Strength
Product (A) Pylomid	The Jordanian Pharmaceutical Manufacturing Co., Naur, Jordan	Tablets Syrups Solutions (drops)	10 mg 1 mg/ml 2.5 mg/ml
Product (B) Plasil	The Gruppo Lepetit, Italy	Tablets Syrups Solutions (drops)	10 mg 1 mg/ml 4 mg/ml
Product (C) Primperan	Laboratories Delagrange, France	Tablets Syrups Solutions (drops) Injections	10 mg 1 mg/ml 2.5 mg/ml 10 mg/2 ml

detected as described in the bulk drug determination.

Content uniformity. The whole tablet was placed in the titration cup and dispersed in 50 ml of 4 M hydrochloric acid solution. A few drops of water were added prior to acid addition in order to disintegrate the tablet. The titration course was followed as for tablets.

Syrups, solutions and injection. A sample which contained the equivalent of 10 mg of anhydrous metoclopramide hydrochloride was placed in the titration cup with 17 ml of 37% w/w hydrochloric acid and the volume was completed to 50 ml with water in order to obtain a final concentration of 4 M hydrochloric acid solution. The titration course was followed as for tablets.

Calculations

The amount of anhydrous metoclopramide hydrochloride in bulk drug and all dosage forms are determined according to the formula:

$$X = V \times M \times f \times M.wt.$$

where X = weight of anhydrous metoclopramide hydrochloride (mg in sample); V = volume of sodium nitrite solution (ml); M = molarity of sodium nitrite solution used; f = titration factor of sodium nitrite solution standardized against sulphanilic acid; M.wt. = molecular weight of anhydrous metoclopramide hydrochloride.

Official assay methods for bulk drug and tablets

The methods were followed as described in the current British Pharmacopoeia (B.P., 1980a and b).

Results and Discussion

The present method is based on the classical reaction of sodium nitrite with an aromatic amine in the presence of acids (Siggia, 1967). A typical curve of metoclopramide titration against sodium nitrite in the presence of hydrochloric acid is illustrated in Fig. 1. The addition of sodium nitrite to the metoclopramide solution causes a sudden increase in the electrode potential. The potential decreases slowly until all the added amount of sodium nitrite is consumed and equilibrium is reached. This behaviour is due to the fast response

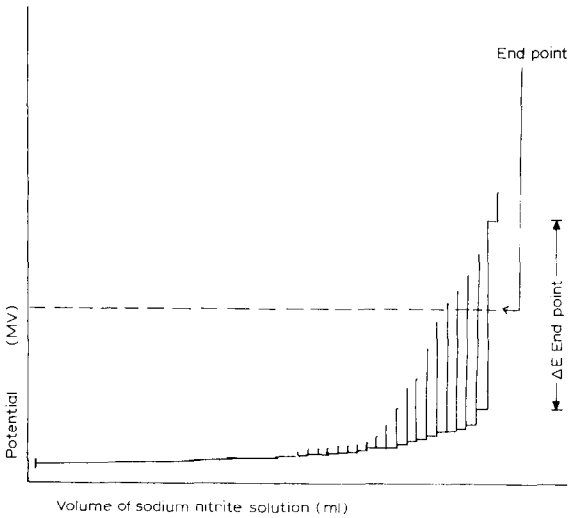

Fig. 1. Titration curve of metoclopramide hydrochloride against standard solution of sodium nitrite in the presence of hydrochloric acid.

of the electrode to the oxidation reduction system of the titrant, and to the slow reaction between the sodium nitrite and metoclopramide. It was noticed that the combined platinum electrode for redox

TABLE 1

THE EFFECT OF ACID STRENGTH ON THE CONTENT OF METOCLOPRAMIDE HYDROCHLORIDE IN BULK DRUG USING THE RECOMMENDED B.P. WEIGHT (300 mg)

Sample no.	Molarity of acid used	% Metoclopramide hydrochloride
1	0.2352	100.07
2	0.4705	100.42
3	0.7058	100.32
4	0.9411	100.77
5	1.1764	99.78
6	1.4117	100.14
7	1.6470	100.17
8	1.8823	100.14
9	2.1176	100.37
10	2.3529	100.14
11	2.3529	99.51
12	4.7058	100.37
13	4.7058	100.37
14	7.0588	99.93
15	7.0588	100.41
Mean		100.19
Standard deviation		±0.30

TABLE 2

THE EFFECT OF ACID STRENGTH ON THE CONTENT OF METOCLOPRAMIDE HYDROCHLORIDE WHEN 10 mg SAMPLES WERE TITRATED

Sample no.	Molarity of acid used	% Metoclopramide hydrochloride
1	1.1765	113.81
2	1.1765	111.04
3	2.3529	102.55
4	2.3529	105.52
5	2.3529	104.40
6	3.5294	102.09
7	4.0000	100.47
8	4.0000	100.47
9	4.7058	100.42
10	4.7058	100.42
11	5.8823	88.09
12	5.8823	93.37
13	7.0588	95.13
14	7.0588	89.17
15	8.2353	erratic behaviour and
16	9.4117	irreproducible results

titration yielded a better reproducibility in the titration.

The acid strength was found to be the most important factor in the process of the reaction. In order to study the effect of the variation in hydrochloric acid concentration on the sharpness and precision of the end-point, different molarities of hydrochloric acid solution ranging from 0.2–9.0 M were used. When 300 mg of metoclopramide were titrated with 0.1 M sodium nitrite solution, the strength of the acid added was indifferent as shown in Table 1. The standard deviation indicated the insignificant effect of acid strength influencing the accuracy of the method. On the contrary, the acid strength had a pronounced effect on the detection of the end-point when 10 mg of metoclopramide were used, as is evident from Table 2. The optimum concentration of the acid is between 3.7 and 4.7 M of hydrochloric acid solution as shown in Table 3. It is worth mentioning that low concentration of acid used caused a false higher content of the active material compared to the actual amount. This is manifested by the splitting of millivolts range which accompanied the end-point into smaller fractions. The addition of high acid strength results in a false lower content of metoclopramide and the electrodes show an erratic behaviour during the course of titration. Attempts to compare the present method with the B.P. current method for the determination of bulk drug was

TABLE 3

THE OPTIMUM ACID STRENGTH AND ITS EFFECT ON THE METOCLOPRAMIDE HYDROCHLORIDE PERCENTAGE CONTENT WHEN 10 mg SAMPLES WERE USED

Sample No.	Molarity of acid used	% Metoclopramide Hydrochloride
1	3.7647	100.37
2	3.8823	100.42
3	4.0000	99.70
4	4.1176	99.70
5	4.2352	100.42
6	4.3529	99.72
7	4.4705	98.66
8	4.5882	97.78
9	4.7058	99.54
Mean		99.59
Standard deviation		±0.87

TABLE 4

COMPARISON BETWEEN B.P. METHOD AND THE PRESENT REPORTED METHOD FOR BULK DRUG DETERMINATION USING THE RECOMMENDED BP WEIGHT (300 mg)

Sample no.	% Content by diazotization method	% Content by non-aqueous titration
1	99.50	99.66
2	99.50	99.65
3	100.00	99.95
4	99.50	100.12
5	99.86	100.01
6	99.50	99.76
7	99.48	99.91
8	99.39	99.86
9	99.50	99.96
10	99.50	99.97
Mean	99.57	99.88
Standard deviation	±0.19	±0.15

TABLE 5

A COMPARISON BETWEEN THE REPORTED AND THE B.P. METHOD FOR 20 TABLETS, EACH CONTAINING THE EQUIVALENT OF 10 mg ANHYDROUS METOCLOPRAMIDE HYDROCHLORIDE

Sample no.	Diazotization Method	B.P. Method
	mg of metoclopramide hydrochloride	mg of metoclopramide hydrochloride
1	10.40	10.37
2	10.40	10.30
3	10.33	10.10
4	10.33	10.30
5	10.40	10.20
6	10.33	10.00
7	10.22	10.10
8	10.13	10.15
9	10.31	10.45
Mean	10.32	10.22
Standard deviation	±0.09	±0.15

found to have no significant difference as shown in Table 4. In order to test the suitability of the method in detecting low concentration in solid mixtures, amounts ranging between 0.4 and 10 mg of the drug were incorporated in a synthetic mixture containing starch, calcium hydrogen phosphate, lactose and magnesium stearate. Samples equivalent to the weight of one tablet of product A (230 mg) were titrated. Metoclopramide was recovered and the additives showed no interference with the method of determination. Consequently, the present method was used for routine analysis of tablets and compared with the B.P. method as shown in Table 5. Three brands of metoclopramide tablets each containing 10 mg were assayed for their content uniformity. Their active drug content is shown in Table 6. The analysis was carried out irrespective of the individual tablet

TABLE 6

A COMPARISON BETWEEN THE CONTENT UNIFORMITY OF DIFFERENT LOCAL BRANDS OF METOCLOPRAMIDE USING THE PRESENT METHOD

Sample no.	Product A (%)	Product B (%)	Product C (%)
1	103.81	97.57	98.76
2	107.96	108.77	103.26
3	104.09	98.85	101.95
4	99.67	100.43	102.03
5	104.09	98.60	98.70
6	103.55	96.11	100.10
7	107.36	105.37	101.53
8	106.08	100.01	97.78
9	103.07	96.51	94.73
10	104.35	107.30	99.73
Mean	104.40	100.95	99.86
Standard deviation	±2.35	±4.55	±2.51

TABLE 7

THE PERCENTAGE CONTENT OF METOCLOPRAMIDE HYDROCHLORIDE IN SYRUPS CALCULATED WITH REFERENCE TO THE LABELLED AMOUNT

Sample no.	Product A (%)	Product B (%)
1	99.21	99.11
2	99.21	99.21
3	100.88	101.41
4	99.21	101.59
5	100.74	101.28
6	99.28	100.89
7	99.85	100.44
8	99.74	100.89
9	99.55	99.07
10	99.97	100.89
Mean	99.76	100.48
Standard deviation	±0.62	±0.98

TABLE 8

THE PERCENTAGE CONTENT OF METOCLOPRAMIDE HYDROCHLORIDE IN SOLUTIONS CALCULATED WITH REFERENCE TO THE LABELLED AMOUNT

Sample no.	Product A (%)	Product B (%)	Product C (%)
1	98.64	102.56	96.15
2	98.75	102.56	96.13
3	98.85	102.61	95.31
4	98.09	102.39	96.02
5	98.50	102.69	96.88
6	98.36	102.99	95.31
7	99.15	101.94	96.41
8	98.71	101.41	95.27
9	98.59	103.37	95.82
10	98.71	–	96.15
Mean	98.63	102.50	95.95
Standard deviation	±0.29	±0.57	±0.53

TABLE 9

THE PERCENTAGE CONTENT OF METOCLOPRAMIDE HYDROCHLORIDE IN INJECTIONS CALCULATED WITH REFERENCE TO THE LABELLED AMOUNT

Sample no.	Product C (%)
1	94.68
2	94.47
3	96.15
4	96.15
5	94.47
6	96.15
7	96.15
8	96.15
9	96.15
10	94.46
Mean	95.50
Standard deviation	±0.84

weight. Each analysis was executed in 8 min. However, when syrups were assayed, the method proved suitable for products A and B as shown in Table 7 but failed to determine the metoclopramide content in product C. When the constituents of the latter formulation were screened, it was found that it contained 20 mg of sodium cyclamate which is liable to diazotize. The presence of such material in preparations limits the application of the method. The method was applied to three solution brands and one injection brand; the results are presented in Tables 8 and 9, respectively.

The advantage of using automatic diazotization titration is to minimize errors resulting from indicator usage, delivery volume, poor end-point and nitrous oxide loss. In conclusion, the method saves time and has a better reproducibility for tablets than the B.P. method. Such advantages make the method an attractive choice for automation of analyses.

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