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Research paper

An improved in vitro method for the evaluation of antacids with in vivo relevance ☆

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Abstract

An improved in vitro method for the evaluation of antacids for use with standard equipment is described. The method is a modification of an older method (RIGO method) and has in vivo relevance. The improved method uses USP dissolution test apparatus 2 with a stirring rate of 125 rpm in combination with a computerized automatic burette. The test solution is 250 ml 0.02 M HCl. A total of 20 min after addition of an antacid to the test solution titration starts at a constant speed of 2.0 ml/min 0.1 M HCl. The proposed acceptance criteria for a waiver for clinical studies are: pH after 4 min not less than 2.5 to ensure a rapid onset of effect, pH after 20 min not exceeding 7.0 to ensure that the pH in the stomach remains within physiological values, buffering capacity between pH 2.5 and 4.5 not less than 8 meq/dose and neutralizing capacity not less than 10 meq/dose to ensure sufficient efficacy within the physiological range. The improved method has been validated with respect to robustness to variations in sample preparation, repeatability and intermediate precision and has been cross-validated versus the RIGO method. The improved method has been found to be rather insensitive to variations in sample pretreatment and at least equivalent to the RIGO method.

Keywords: Antacids; In vitro/in vivo; Neutralizing capacity; Buffering capacity; USP dissolution test apparatus; Acceptance criteria

1. Introduction

The demonstration of efficacy and safety is a prerequisite for a medicinal product to obtain a marketing authorization and also to keep this marketing authorization after changes in the formulation and/or method of preparation. This also applies to antacids. The efficacy of antacids is based on a local effect in the stomach, so therapeutic equivalence between antacid products cannot be demonstrated with usual bio-equivalence testing. Consequently, clinical studies are needed to obtain a marketing authorization for new antacids with known active substances and to keep the marketing authorization of existing antacids after reformulation. The European Note for Guidance on locally acting products [1] provides for the possibility to use in vitro studies as a surrogate for clinical studies provided that the predictive power of the in vitro method has been demonstrated.

A large number of in vitro methods to determine antacid activity have been published over the last 40 years [2–32]. None of these methods has been commonly accepted as a surrogate for clinical studies, nor for routine quality control. The in vivo relevance of most of these methods has not been studied as they are intended for quality control only. The (modified) USP antacidacid neutralizing test [9,32] and the tests described by Sherill and Hagos [17,20] use a large excess of acid which is back titrated with alkali, both of which are unphysiological. Methods described by Guller, Kerkhof, Duffy, Walther, Prieto, Johnson, Verma, Plachy, Herrero and Lin [13,14,16,18,19,21,25,27,29,31] use static pH conditions. Again this is a non-physiological condition as the gastric pH will not be constant. Methods described by Rosset-Rice, Beekman, Schaub, Piper-Fenton, Furst, Engels, Fordtran, Smyth, Spivey, Johnson, Vatier, Boraie and Watts [2,8,12,15,21–24,26] start adding acid immediately after the sample is added to the test solution. By such procedures it is impossible to assess the short-term antacid activity, important for the relief of pain directly after swallowing.

Methods for which vivo relevance has been established are described by Vatier [23,28,33,34], Smyth [12] and Van Dop [11,35]. Vatier describes an artificial stomach/duode-

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num model that mimics not only gastric neutralization, but also variations in gastric and duodenal emptying fluxes and in the composition of the gastric juice, especially its protein content. The model uses three reservoirs representing the stomach and the proximal and distal duodenum. Vatiers model can be operated with different emptying fluxes. The model is however very complex and the necessary equipment is not readily available. Smyth describes a modified Beekman model. This is a dynamic model that continuously adds acid to the test solution under removal of the same volume of test solution, until the pH drops below 3.0. The method, however, starts with adding acid immediately after the sample. Van Dop describes a simple model (RIGO method) that uses no excess of acid, a lag time of 20 min before the addition of acid and continuous titration until pH 2.5. The method and its acceptance criteria have been used as a surrogate for clinical testing in The Netherlands for over two decades, thus showing its in vivo relevance. A disadvantage of the RIGO method is that it uses custom-built apparatus that is not commercially available.

The aim of this study was to develop an in vitro method with in vivo relevance fulfilling the following five requirements:

a) The method operates in the physiological pH range.
b) The method measures the short-term antacid activity.
c) The method measures the long-term antacid activity and the long-term buffering capacity.
d) The method measures the pH-changes that can be considered to take place in the stomach after swallowing the antacid product.
e) The method uses standard laboratory apparatus.

These requirements are met by the RIGO method, except for the last. The in vitro method will therefore be based on the RIGO method, however in an improved form.

2. Materials and methods

2.1. Improved method

USP dissolution test apparatus 2 was operated with a paddle speed of 125 rpm. The medium was 250 ml 0.02 M HCl at 37°C. The tip of a computerized automatic burette was immersed into the medium and the pH of the medium was monitored continuously. A total of 20 min after an antacid was added to the medium, the burette started with continuous titration at a constant speed of 2.0 ml/min 0.1 M HCl. The addition of HCl was stopped after 2 h or when pH 2.5 was reached. The antacid dose tested was the minimum dose for adults as described in the patient information leaflet. If the minimum dose was unknown, one unit of the available dosage form was used. Suspensions and gels were added directly. Tablets were pulverized in a mortar until the resulting powder had an homogeneous size by visual inspection and no particles float on the surface of the medium in the vessel (normal pulverization).

The total buffering capacity from pH 2.5 to 4.5 (BC_2) was calculated from Eq. (1):

$$BC_2 = (V_{tr-1} \times T_{tr}) \times (W_1/W_2) \quad (1)$$

V_{tr-1}: added volume of HCl from the burette between pH 2.5 and 4.5:
T_{tr}: titer of HCl in the burette;
W_1: weight of intact antacid;
W_2: weight of tested quantity antacid.

And the neutralizing capacity from pH 2.5 to 4.5 (NC) was calculated from Eq. (2):

$$NC = [(V_{HCl} \times T_{HCl}) + (V_{tr-2} \times T_{tr})] \times (W_1/W_2) \quad (2)$$

V_{HCl}: volume of HCl in the vessel;
T_{HCl}: titer of HCl in the vessel;
V_{tr-2}: added volume of HCl from the burette until pH = 2.5;
T_{tr}: titer of HCl in the burette;
W_1: weight of intact antacid;
W_2: weight of tested quantity antacid.

2.2. RIGO method

Sample size and sample pretreatment were identical to those of the improved method. An in-house glass vessel was filled with 50.0 ml 0.1 M HCl at 37°C. The medium was stirred with a custom built stirrer at a speed of 200 rpm. The outlet of an automatic burette was immersed into the medium and the pH was monitored continuously. A total of 20 min after the antacid was added the burette started with continuous titration at a constant speed of 2.0 ml/min 0.1 M HCl. The addition of HCl was stopped after 2 h or when pH 2.0 was reached. Full details are described by Van Dop [11].

2.3. Analytical validation

Intermediate precision was estimated by running Risp® tablets and Riopan® tablets through the improved method by two different technicians twice with a 3 months interval. Robustness was estimated by running Riopan® tablets through the improved method after breaking into quarters and normal and fine pulverization. Tablets were pulverized fine by crushing a normal pulverized powder in a mortar until a visually more fine homogeneous powder. Cross validation of the improved method versus the RIGO method was carried out by running Risp® tablets and Riopan® tablets through both methods and comparing the intermediate precision.

2.4. Setting acceptance criteria

Twenty-five antacids with a Marketing Authorization in The Netherlands were run through the improved method. Their trade names, composition and tested dose are

presented in Table 1. The proposed acceptance criteria as presented in Table 2 are based on their test results and the recommendations of the Health Care Insurance Council in The Netherlands [36].

2.5. Materials

The antacids were obtained from a wholesaler in The Netherlands (OPG). The antacids were stored at ambient

Table 1
Antacids tested with the improved method

Number	Brand name in NL	Composition	Dosage form	Tested dose
1	Maalox	Aluminii oxidum (anh) 200 mg Magnesii hydroxidum 400 mg	Tablet	One tablet
2	Alcasedine nieuwe formule	Aluminii oxidum 400 mg Magnesii trisilicas 400 mg	Tablet	One tablet
3	Ultacit	Hydrotalcitum (ln) 500 mg	Tablet	Two tablets
4	Riopan	Magaldratum (anh) 800 mg	Tablet	One tablet
5	Magnesiumhydroxide PCH	Magnesii hydroxidum (anh) 500 mg	Tablet	One tablet
6	Magnesiumperoxide 25% Gf	Magnesii peroxidum (ln) 500 mg	Tablet	One tablet
7	Magnesiumoxide Gf	Magnesii oxidum 500 mg	Tablet	One tablet
8	Rennie	Calcii carbonas (ln) 680 mg Magnesii subcarbonas 80 mg	Tablet	One tablet
9	Rennie deflatine	Calcii carbonas (ln) 680 mg Magnesii subcarbonas 80 mg Simeticonum 25 mg	Tablet	One tablet
10	Rennie Anijs	Calcii carbonas 680 mg Magnesii subcarbonas 80 mg	Tablet	One tablet
11	Maalox forte	Aluminii oxidum (ln) corr anhydricum 900 mg Magnesii hydroxidum 600 mg	Suspension	10 ml
12	Regla pH	Aluminii oxidum 66 mg/ml Magnesii hydroxidum 27.5 mg/ml	Suspension	4 ml
13	Antagel pH	Aluminii oxidum (anh) 40 mg/ml Magnesii hydroxidum 20 mg/ml	Suspension	10 ml
14	Muthesa N	Aluminii hydroxidum 61.4 mg/ml Magnesii hydroxidum 20.6 mg/ml	Suspension	10 ml
15	Ultacit	Hydrotalcitum (ln) 100 mg/ml	Suspension	10 ml
16	Riopan stickpack	Magaldratum (ln) corr. Anhydricum 800 mg	Suspension	One sachet
17	Risp	Aluminii oxidum 300 mg Magnesii oxidum 100 mg	Tablet	One tablet
18	Rigoletten	Aluminii 450 mg Magnesii hydroxidum 75 mg	Tablet	One tablet
19	Regla pH	Aluminii 450 mg	Tablet	One tablet
20	Gaviscon forte pepermunt	Acidum alginicum 500 mg Aluminii oxidum 100 mg Magnesii trisilicas 25 mg Natrii 170 mg	Chewable tablet	Two tablets
21	Gaviscon 250 citroen	Acidum alginicum (ln) 250 mg Aluminii oxidum 50 mg Magnesii trisilicas 12.5 mg Natrii 85 mg	Chewable tablet	Four tablets
22	Algicon	Aluminii 360 mg Kalii 100 mg Magnesii alginas 500 mg Magnesii carbonas 320 mg	Chewable tablet	Two tablets
23	Algicon, suspension	Magnesii alginas (ln) 50 mg/m; Magnesii carbonas 35 mg/ml Aluminii 28 mg/ml Calcii carbonas (ln) 15 mg/ml Kalii 10 mg/ml	Suspension	10 ml
24	Roteroblong, tablet	Bismuthi subnitras 300 mg Magnesii subcarbonas 400 mg Natrii 200 mg Rhamni frangulae 25 mg	Tablet	Two tablets
25	Neutroses, chewable tablet	Bismuthi subcarbonas 60 mg Calcii carbonas (ln) 270 mg Magnesii subcarbonas 114 mg Sal Vichy (ln) 8 mg	Chewable tablet	Two tablets

Table 2
Acceptance criteria with parameters to be tested: pH after 4 min ($pH_{4'}$), pH after 20 min ($pH_{20'}$), maximum buffering capacity per 0.5 pH unit in the range pH 2.5–4.5 ($BC_{0.5}$), total buffering capacity in the range pH 2.5–4.5 in meq acid (BC_2) and neutralizing capacity until pH 2.5 or until 120 min in meq acid (NC)

Method	$pH_{4'}$	$pH_{20'}$	$BC_{0.5}$	BC_2	NC
Improved	≥2.5	≤7.0	–	≥8.0	≥10
RIGO	≥2.5	≤6.0	≥2.0	–	≥10

temperature and humidity and tested within their expiry period. Information on batch numbers of the tested antacids, suppliers of the apparatus and source of reagents is available on request from the authors.

3. Results

The intermediate precision of the improved method and the RIGO method is presented in Table 3. Results for the robustness test of the improved method towards changes in sample pre-treatment are presented in Table 4. In Figs. 1–4 the results are shown for the antacids that were tested with the improved method. For comparison purpose, in Figs. 5–7 the results are shown of an older survey carried out in 1976 with the RIGO method using 34 antacids marketed in The Netherlands at that time [35].

4. Discussion

The therapeutic effect of antacids is related to a fast onset of activity, a sufficient buffering capacity in the physiological pH-range and a sufficiently long period of activity. The safety of antacids is related to a pH that does not reach unphysiologically high values. An in vitro method for antacids with in vivo relevance should cover these aspects. In addition the method should use standard laboratory equipment. The method described by Van Dop [11] (RIGO method) fulfills the four clinical aspects, but uses custom built apparatus. The in vivo relevance of the RIGO method and its acceptance criteria is supported by having served as a surrogate for clinical testing in The Netherlands for over two decades.

Our objective was to improve the RIGO method by using standard dissolution equipment. The USP dissolution test apparatus 2 was selected as it is commonly available and its suitability for the in vitro testing of antacids has been proven [27]. By changing the dissolution equipment, the volume and composition of the medium and the stirring speed had to be changed as well. The volume of the medium was increased to 250 ml, as this is the minimum volume to cover the paddle sufficiently. The molarity of the medium was reduced proportionally to maintain the same amount of acid in the vessel. The paddle stirring speed was reduced to 125 rpm because this speed is within the normal range and because a pilot study showed the best agreement in results between the improved and RIGO method The antacid dose tested was the minimum dose according the patient leaflet or if not known, one dosage unit. This approach is in line with the RIGO method [11] and the USP [32]. Consequently, the improved method emphasizes efficacy rather than safety.

Table 4
Influence of pulverization on the improved method using the test sample Riopan[a]

Pulverization	$pH_{4'}$[b]	rsd $pH_{4'}$	$pH^b_{20'}$	rsd $pH_{20'}$	NC[b]	rsd NC
Normal	4.1	0.78	6.2	1.2	23	1.0
1/4 tablets	3.8	6.2	6.2	3.3	24	0.7
Δ1/4 versus normal[c]		sig		ns		sig
Fine	4.1	0.81	6.6	3.4	25	2.2
Δ fine versus normal[c]		ns		ns		ns

[a] Tested parameters as in Table 2.
[b] Mean of six determinations.
[c] Significance of difference in precision between the manner of pulverization based on six determinations for each pulverization, one sided *F*-test ($P = 0.95$), sig (significant difference) or ns (non-significant difference).

Table 3
Intermediate precision of the improved method and cross validation of the improved method versus the RIGO method[a]

Method	Sample	Technician	$pH_{4'}$[b]	rsd $pH_{4'}$	$pH^b_{20'}$	rsd $pH_{20'}$	NC[b]	rsd NC
Improved	Risp	I	2.1	4.7	4.0	1.0	9.2	4.0
		II	2.1	4.8	4.1	0.60	9.3	6.7
RIGO	Risp	I	2.2	19	3.8	1.6	8.3	8.3
		II	2.7	23	3.8	0.82	8.3	8.4
Δ[c]				sig		ns		ns
Improved	Riopan	I	4.1	0.78	6.2	1.2	23	1.0
		II	4.1	0.96	6.5	1.6	24	1.7
RIGO	Riopan	I	4.3	1.8	6.6	0.8	23	1.9
		II	4.2	3.6	6.5	1.9	22	3.5
Δ[c]				sig		sig		ns

[a] Tested parameters as in Table 2.
[b] Mean of six determinations.
[c] Significance of difference in precision between new method and RIGO-method based on six determinations by two different technicians for each method, one sided *F*-test ($P = 0.95$), sig (significant difference) or ns (non-significant difference).

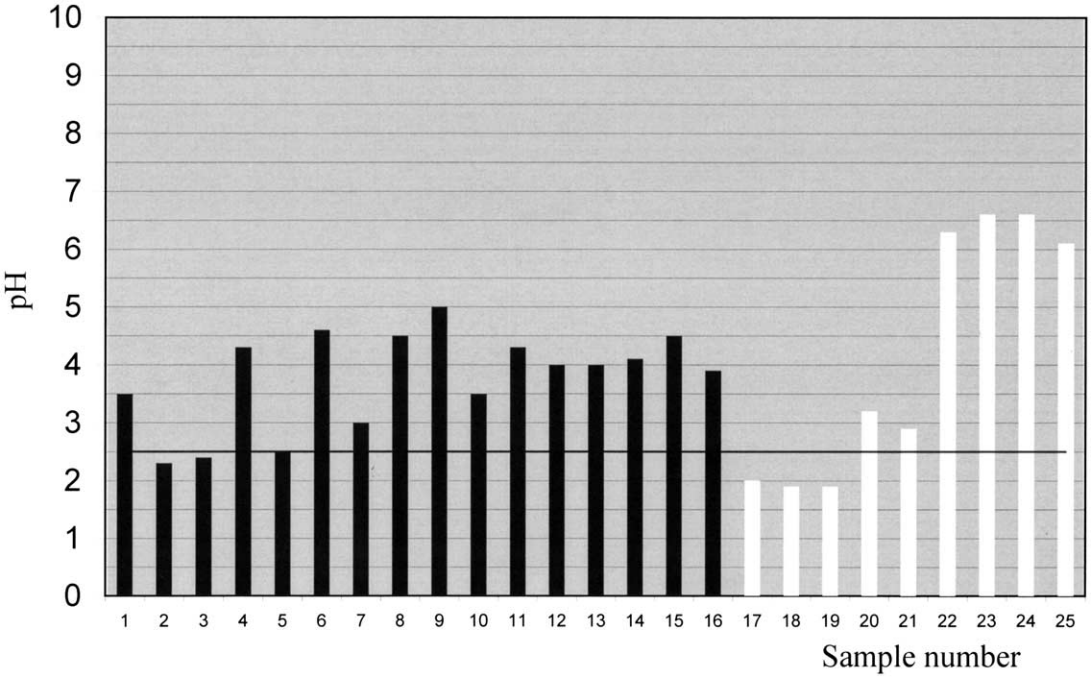

Fig. 1. Antacid properties of registered products. New method: $pH_{4'}$. Horizontal line: acceptance limit. White bars: antacids to be excluded. Black bars: others. See discussion.

The parameters measured by the improved method are nearly identical to those by the RIGO method The pH after 4 min ($pH_{4'}$) checks quick onset of activity, the pH after 20 min ($pH_{20'}$) checks unphysiologically high pHs and the total neutralizing capacity between pH 2.5 and 4.5 (NC) is an indication for the efficacy in the physiological range. The maximum buffering capacity over a range of 0.5 pH-unit in the range pH 2.5–4.5 ($BC_{0.5}$) has been replaced

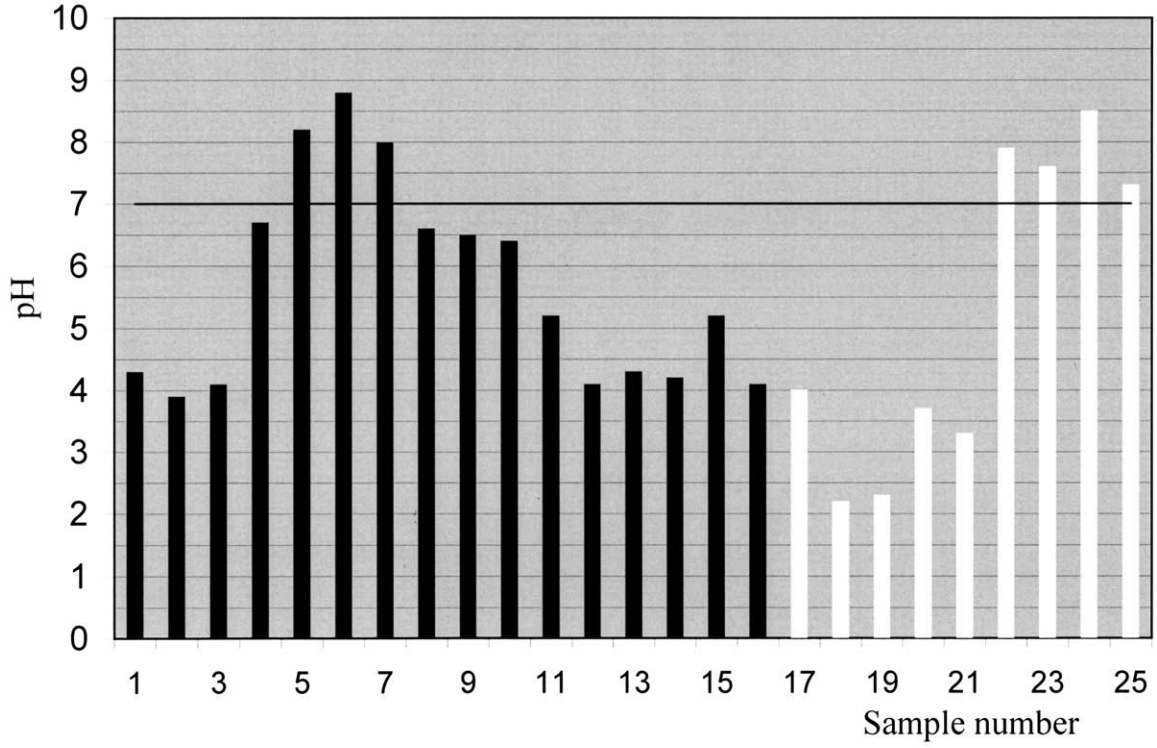

Fig. 2. Antacid properties of registered products. New method: $pH_{20'}$. Horizontal line: acceptance limit. White bars: antacids to be excluded. Black bars: others. See discussion.

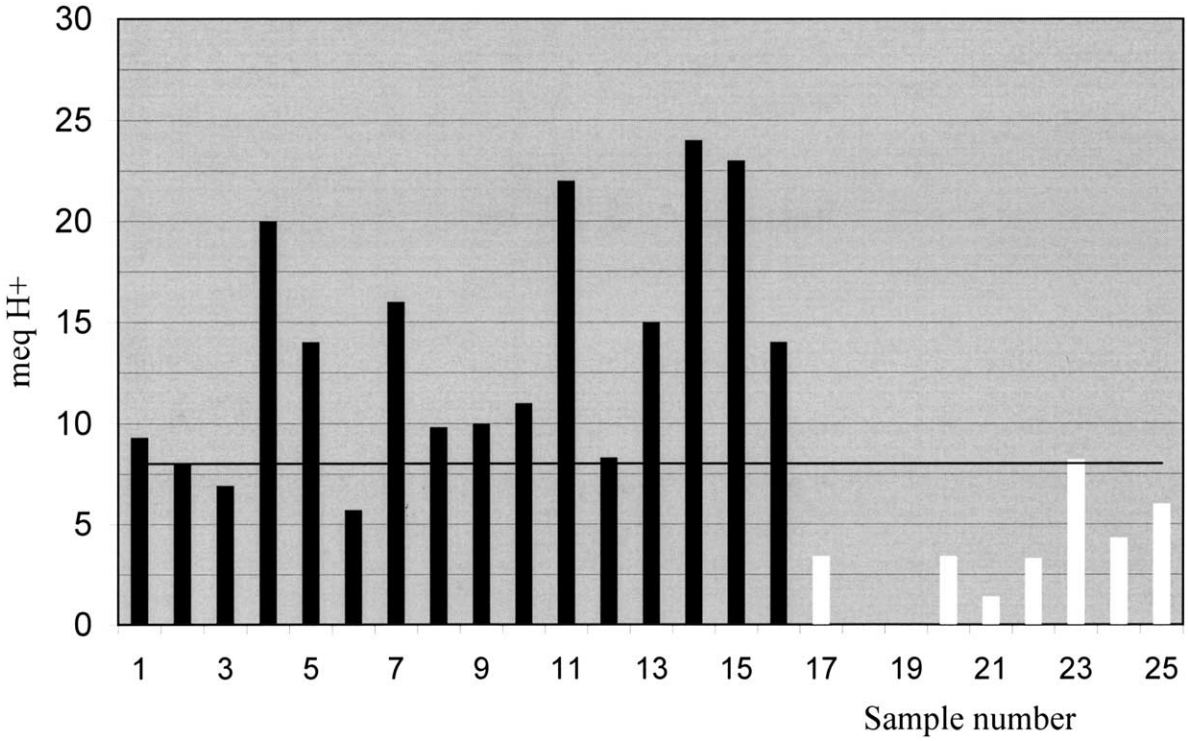

Fig. 3. Antacid properties of registered products. New method: BC_2. Horizontal line: acceptance limit. White bars: antacids to be excluded. Black bars: others. See discussion.

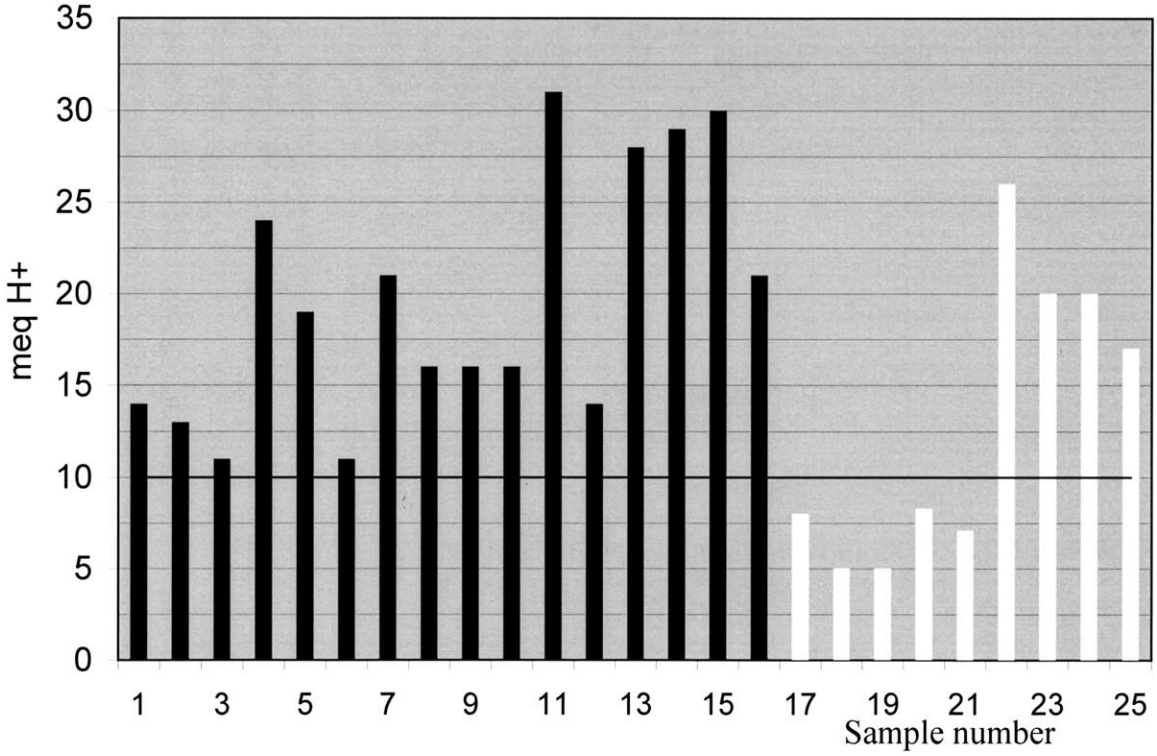

Fig. 4. Antacid properties of registered products. New method: NC. Horizontal line: acceptance limit. White bars: antacids to be excluded. Black bars: others. See discussion.

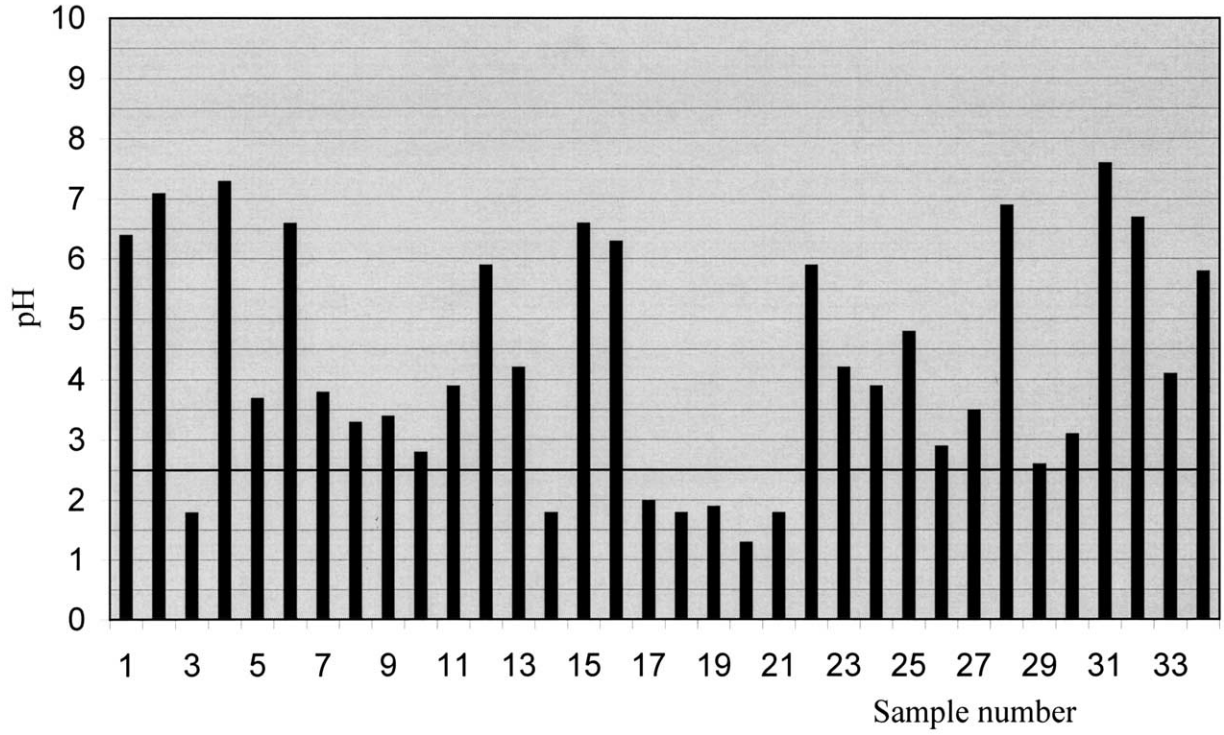

Fig. 5. Antacid properties of registered products in 1976. Data taken from [35]. RIGO method: $pH_{4'}$. Horizontal line: acceptance limit.

by total buffering capacity in the range pH 2.5–4.5 (BC_2), the latter being physiologically more relevant.

Cross validation of the improved method versus the RIGO method showed little difference. The intermediate precision of the improved method for $pH_{4'}$ is better than of the RIGO method. The highest variability is 6.7% for

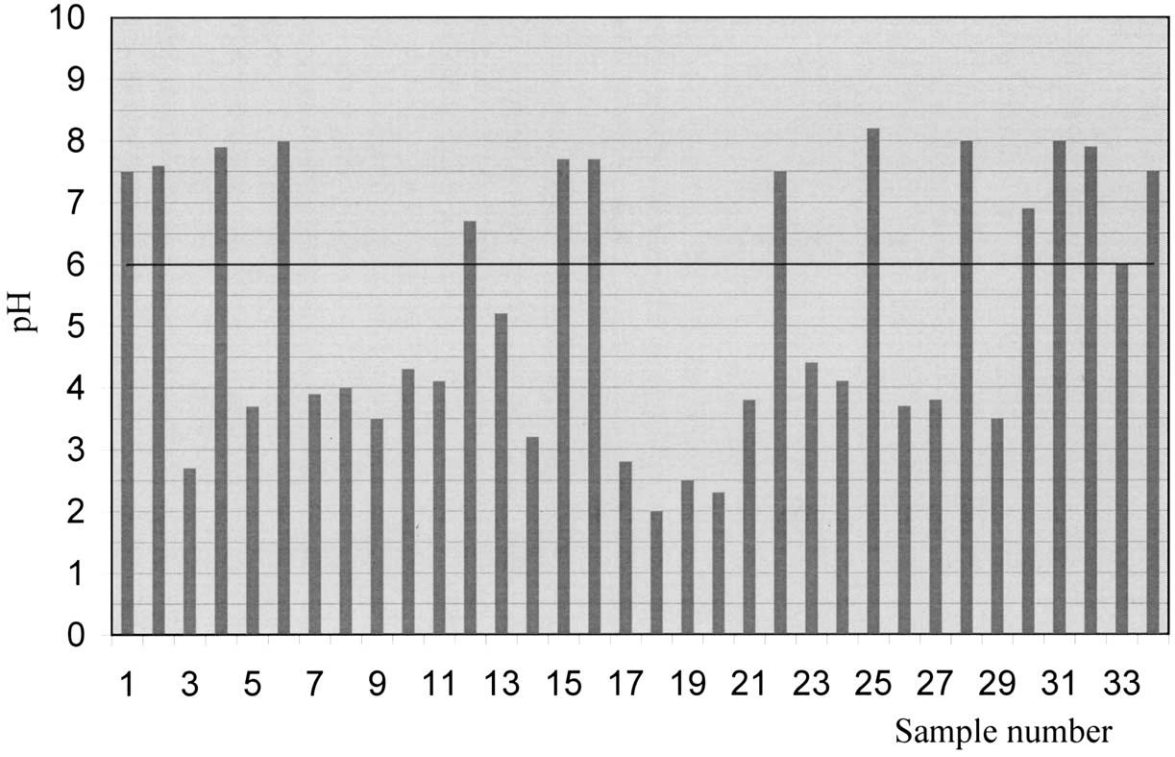

Fig. 6. Antacid properties of registered products in 1976. Data taken from [35]. RIGO method: $pH_{20'}$. Horizontal line: acceptance limit.

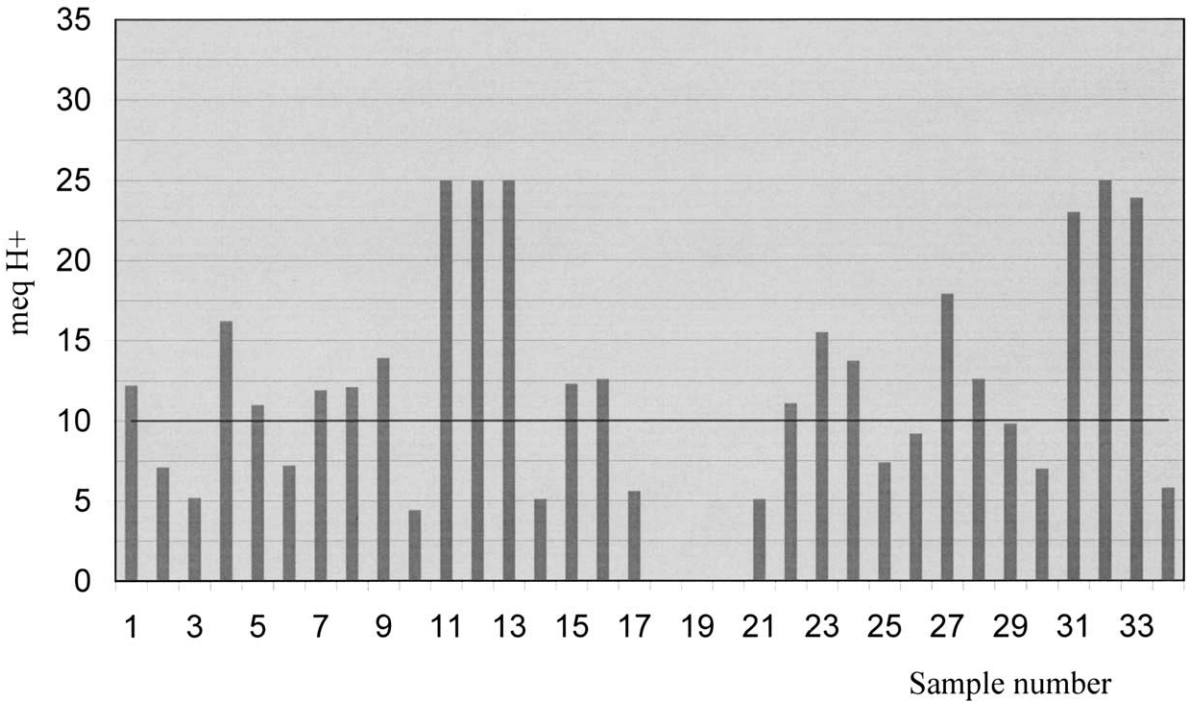

Fig. 7. Antacid properties of registered products in 1976. Data taken from [35]. RIGO method: NC. Horizontal line: acceptance limit.

NC for one product and one technician. This variability is acceptable in view of the goal of the improved method: a surrogate for clinical studies.

The robustness test for antacid sample pre-treatment revealed a small but significant difference between tablets broken in four quarters and normal pulverization at $pH_{4'}$ and NC. As most patients will break or chew their antacid tablets, normal pulverization was selected as sample pre-treatment. This is in line with most other tests [11,15,20,30]. The manner of pulverization is however not very critical as no significant differences were found between normal pulverization and very fine pulverization. The practicability of the improved method was demonstrated with the successful recent survey of the 25 antacids from Table 1.

The RIGO criteria needed re-evaluation for the improved method because both methods differ slightly and because the literature shows a trend to the use/need of more potent antacids [36]. In fact a lot of the antacids tested in 1976 are not marketed anymore or their composition has been changed. As the goal of the improved method was to develop a surrogate for clinical testing, the acceptance criteria for the improved method should be set too exclude all antacids that are not effective or not safe. The proposed criteria for the improved method and the former criteria for the RIGO method are presented in Table 2.

The Health Care Insurance Council in The Netherlands (CVZ) gives a negative prescription recommendation for the antacids 17–25 from Table 1. Risp® tablets, Rigoletten® tablets and Regla pH® tablets are considered to have poor neutralizing capacity, the different Gaviscon® and Algicon® products are regarded as anti-reflux drugs and not pure antacids and Neutroses® and Roteroblong® are considered to have an irrational composition [36]. Indeed, the proposed criteria for the improved method exclude all antacids with a negative prescription recommendation from the CVZ. The proposed criteria for the improved method include eleven of the 16 products with a positive recommendation from the CVZ and the results show that the method can indeed be applied to waive clinical studies.

The suitability of the proposed criteria for the improved method is further demonstrated by a strong correlation with the RIGO criteria. The criterion for $pH_{4'}$ is unchanged and about the same percentage of antacids in both studies is in compliance. The criterion for NC is also unchanged but is now met by a higher percentage of antacids, showing that stronger antacids are used presently. The criterion for $pH_{20'}$ is raised from pH 6.0 to 7.0 in line with the stronger antacid properties of recently tested antacids. This higher limit is considered acceptable as no adverse reactions have been reported for antacids with a $pH_{20'}$ in the range 6.0–7.0. The percent of marketed antacids outside the proposed criteria is now less than in the 1976 survey.

In conclusion, the improved method offers a simple procedure to determine the in vitro activity of antacids. The proposed acceptance criteria are predictive for the in vivo clinical efficacy and safety, hence the improved method can be used to waive clinical testing of new and reformulated antacids with known active substances. The acceptance criteria are rather tight; antacids not complying may be effective and safe but this needs to be demonstrated by clinical evidence.

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