RESEARCH ARTICLE

Development of Acid-Neutralization and In Vitro Dissolution to Evaluate the Overall Quality of Compound Aluminum Hydroxide Tablets

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Abstract: Background: Compound Aluminum Hydroxide Tablets (CAHTs) are widely used in the Chinese domestic market, and strict quality control is required to ensure their clinical efficacy.

Purpose: In this study, we established a comprehensive strategy of acid-neutralization, in vitro dissolution and an assay of magnesium trisilicate to evaluate the overall quality and monitor the consistency of CAHTs.

Methods: The acid-neutralization profiles of 38 batches of CAHTs were generated using the dissolution and release method III (the cup method, the Chinese pharmacopeia) combined with potentiometric titration. To directly reflect the disintegration and release process of the preparation, we optimized the sample pretreatment method by omitting the grinding step to determine the profiles of complete tablets. In addition, in vitro dissolution was conducted in the hydrochloric acid medium at pH 1.0 by using the assay of magnesium trisilicate through a validated approach of Flame Atomic Absorption Spectrophotometry (FAAS) to evaluate the similarity of the dissolution profiles.

Results: Acid-neutralization tests showed that the quality of the samples from manufacturers B and F was poor. In vitro dissolution experiments showed that the samples from manufacturer A had the highest similarity with the reference preparation, which indicated their good quality consistency. Besides, the optimized acid-neutralization method had the advantage of simple operation and enabled direct characterization of pharmacodynamics in the quality consistency evaluation of antacids.

Conclusion: A successful synthetic evaluation strategy was established to assess the overall quality of CAHTs, which demonstrated that the improvement in the quality of this formulation is imperative.

Keywords: Compound aluminium hydroxide tablet, quality evaluation, acid-neutralization, in vitro dissolution, f2 similarity factor, flame atomic absorption spectrophotometry.

1. INTRODUCTION

Acid-related disorders are common diseases of the upper digestive tract which are closely related to acid attack [1]. The main clinical approaches to treat these diseases are antacids and acid inhibitors [2]. Antacids are weakly basic substances which can neutralize the gastric acid, thus inactivating pepsin and protecting the gastric parietal protein from being decomposed [3]. As one of the widely used over-the-counter antacids in China, Compound Aluminum Hydroxide Tablet (CAHT) is inexpensive and has the required effect suitable for stomach diseases such as hyperacidity, acid reflux and chronic gastritis. Each CAHT comprises 245 mg of aluminum hydroxide, 105 mg of magnesium trisilicate, and 0.0026 ml of Belladonna liquid extract. However, being a unique variety in the Chinese domestic market, CAHT lacks a reference preparation, which limits its prescription devel-
opment, preparation technology, and quality consistency evaluation. To solve this problem, we developed dynamic acid-neutralization profiles and in vitro dissolution profiles to evaluate the overall quality consistency of this medicine.

As a key quality attribute, acid-neutralization capacity guarantees that antacids are suitable to neutralize gastric acid and to maintain the pH of gastric juice between 3 and 5 [3]. National codes including the British Pharmacopoeia (BP) [4], the United States Pharmacopeia (USP) [5] and the Chinese Pharmacopeia (Ch. P) [6] have specified test items of neutralizing capacity based on the amount of hydrochloric acid consumed; in some cases, the pH value during the neutralizing process is also stipulated. However, these static methods typically do not provide the information that can be acquired from the dynamic acid-neutralization process, which simulates the physiological environment and forecasts in vivo pharmacokinetics; hence developing a dynamic method is of vital importance. Several representative approaches for constructing dynamic neutralization curves are mentioned in the literature. Shen et al. [7] studied the dynamic acid-neutralization process of aluminum hydroxide in three forms, the original powder, the granule and the tablet. Liu et al. established acid curve methods for hydrotalcite tablets and hydrotalcite chewable tablets [8] and evaluated the neutralizing capacity of CAHTs [9]. In our study, we determined the acid-neutralization profiles of 38 batches of samples in powder form from six manufacturers by using the dissolution and release method III (the cup method, the Ch. P) combined with potentiometric titration, and optimization was conducted to understand the pharmacodynamics based on the profiles of the complete tablets. We concluded that the acid-neutralization capacity of the samples from manufacturers B and F was relatively poor.

In vitro dissolution was employed as dissolution profiles have been proven helpful in predicting in vivo performance. Since an ideal antacid should not be absorbed in the gastrointestinal tract to avoid constipation and diarrhea [10]; therefore, the in vitro dissolution methodology we set up aimed to indirectly reflect the process of drug disintegration and release. Dissolution profiles of 38 batches of samples were generated methodically, and the $f_2$-factors were calculated. The results showed that the dissolution behavior of samples from each manufacturer was obviously different, and the samples from manufacturer A showed a higher similarity.

In conclusion, the first aim of our study was to develop and validate a robust and efficient FAAS method that will enable in vitro product performance assessment. The second aim was to establish an acid-neutralization method that could provide detailed quality information about the CAHTs. In general, the established synthetic evaluation strategy integrated the acid-neutralization process of tablets and powders, dissolution profiles and $f_2$ similarity factors, which is a powerful demonstration of comprehensive research on antacids.

2. MATERIALS AND METHODS

2.1. Drug Products and Reagents

A total of 38 batches of CAHTs were purchased from six manufacturers (manufacturers A-F). Hydrochloric acid (AR) was purchased from Nanjing Chemical Reagent Co., Ltd. (Jiangsu, China). Standard solutions of magnesium (100 µg/mL and 1000 µg/mL) were purchased from the National Institute of Metrology (China) and Guobiao Testing and Certification Co., Ltd. (Beijing, China), respectively. Ultrapure water was obtained from a SAS purification system (Millipore, USA).

2.2. Instruments and Materials

An RC806D dissolution tester from Tianda-Tianfa Pharmaceutical Testing Instrument Manufacturer (Tianjin, China) was used to determine the dissolution profiles (the paddle method, the Ch. P) and acid-neutralization profiles (the cup method, the Ch. P). Real-time pH curves were recorded using an 888 titrando potentiometric titrator (Metrohm, Switzerland) with a combined pH glass electrode (Metrohm, 6.0262.100). Magnesium trisilicate was quantified using an AA 7000 atomic absorption spectrometer (Shimadzu, Japan). A hollow cathode magnesium lamp from Shuguangming Scientific (Beijing, China) was employed as the radiation source.

2.3. Analysis Conditions

2.3.1. Assay of Magnesium Trisilicate

Magnesium trisilicate, a magnesium silicate hydrate with an indefinite composition (Mg$_2$Si$_2$O$_5$(OH)$_2$), is one of the active pharmaceutical ingredients of CAHT. The Ch. P prescribes only the lowest permitted content calculated using magnesium oxide (MgO) to quantify magnesium trisilicate. In this context, it is objective and logical to use the measured results to evaluate the dissolution performance of CAHTs. An assay of 38 batches of samples was performed according to the following procedures: Twenty tablets were accurately weighed, ground and homogenized to powder form. A quantity equivalent to one tablet was weighed into a 50 mL volumetric flask. Hydrochloric acid (5 mL) and an appropriate amount of ultrapure water were added to the volume. The solution was centrifuged for 5 min at 12000 rpm before filtration and was gradually diluted 2500 times. FAAS analysis was performed under the following conditions: background correction: D$_2$ lamp; detection wavelength: 285.2 nm; lamp current: 8mA; lighting method: BGC-D2; combustion head height: 7 mm; C$_2$H$_2$ flow rate: 1.8 L·min$^{-1}$; air flow rate: 15 L·min$^{-1}$ and slit width: 0.7 nm.

2.3.2. In Vitro Dissolution Test

The Ch. P apparatus II with eight dissolution vessels and paddles was used. The dissolution medium was hydrochloric acid (900mL, pH 1.0). The temperature of the dissolution medium was set at 37.0°C ± 0.5°C, and the rotation speed at 50 rpm. The sampling volume was 5 mL at 3, 5, 10, 15, 30, 45 and 60 min and an equal volume of medium was refilled immediately after sampling. All the test solutions were filtered through a 0.45 µm pore-size PES (hydrophilic) syringe filter (Pall, USA) and were diluted 50 times before FAAS analysis. The dissolution profiles were constructed based on the mean of six tablets (n=6).

2.3.3. Determination of Acid-neutralization Profiles

Acid-neutralization profiles were determined using the Ch. P dissolution apparatus III (the cup method) combined
with an automatic potentiometric titrator. The upper end of the combined pH-glass electrode was taped on the dissolution apparatus, and the lower end of the electrode with the glass film was inserted into the solution until the recording was completed. The finely ground powder was passed through an 80 mesh sieve (the Ch. P), and a quantity equivalent to two tablets was weighed into the dissolution cups. A total of 190 mL of water was preheated to 37 °C and an appropriate amount of it was added into the cup to disperse the powder evenly, then the remaining water and 10 mL of 1 mol/L hydrochloric acid titrant were added. The rotation speed was set at 200 rpm. Given that the grinding process may result in the loss of information imparted to the samples by granulation and tableting, the method optimization was mainly focused on the pretreatment steps: two tablets were put directly into the mixed solution of 10 mL 1 mol/L hydrochloric acid titrant and 190 mL water preheated to 37°C, after which the profiles were recorded.

### 3. RESULTS

#### 3.1. Analytical Method Validation

Two FAAS methods were developed successfully for quantifying the magnesium trisilicate in the CAHTs and for determining the magnesium dissolved at each sampling time based on the Ch. P General Chapters <9101> [11]. The validated parameters included linearity, specificity, accuracy (sample recovery), precision, repeatability, stability, limit of detection (LOD), limit of quantitation (LOQ) and membrane adsorption, as shown in Table 1.

#### 3.1.1. Linearity

To prepare for this study, a series of calibration solutions at 0.05, 0.10, 0.15, 0.20, 0.25 and 0.30 µg/mL covering the expected range of concentrations were prepared. The results indicated a good correlation between the absorbance and the magnesium concentration, with a coefficient (r) of more than 0.999.

#### 3.1.2. Accuracy

For assay of magnesium trisilicate, accuracy was determined by spiking standards to the preparation with known content 0.02413 g per tablet (calculated by magnesium oxide), measured according to the Ch. P titration method [6]. For in vitro dissolution, accuracy was evaluated by spiking standards to mixed blank excipient. Concentration levels ranged from 50% to 100% and were assessed in triplicate for all analytes.

#### 3.1.3. Specificity

Specificity is an essential part of method validation for assessing the interference from excipients or any other sources. The excipients containing corn starch, starch, sodium carboxymethyl starch, talc, magnesium stearate, pol-
Table 2. Assay of magnesium trisilicate of 38 batches of samples determined by FAAS method, calculated by magnesium oxide.

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Lot Number (Last Four Digits)</th>
<th>Content (g/tablet)</th>
<th>Manufacturer</th>
<th>Lot Number (Last Four Digits)</th>
<th>Content (g/tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
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<td>B</td>
<td>0601</td>
<td>0.02430</td>
</tr>
<tr>
<td></td>
<td>0836</td>
<td>0.02161</td>
<td></td>
<td>0906</td>
<td>0.02415</td>
</tr>
<tr>
<td></td>
<td>0937</td>
<td>0.02379</td>
<td></td>
<td>0905</td>
<td>0.02554</td>
</tr>
<tr>
<td></td>
<td>1217</td>
<td>0.02270</td>
<td></td>
<td>0902</td>
<td>0.02417</td>
</tr>
<tr>
<td></td>
<td>0821</td>
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<td></td>
<td>0900</td>
<td>0.02289</td>
</tr>
<tr>
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</tr>
<tr>
<td></td>
<td>0905</td>
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<td></td>
<td>0514</td>
<td>0.02407</td>
</tr>
<tr>
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<td></td>
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</tr>
<tr>
<td></td>
<td>1236</td>
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<td>C</td>
<td>0903</td>
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</tr>
<tr>
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<td></td>
<td>1003</td>
<td>0.02403</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>0704</td>
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</tr>
<tr>
<td></td>
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<td></td>
<td>0704</td>
<td>0.02683</td>
<td></td>
<td>0604</td>
<td>0.02535</td>
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<tr>
<td></td>
<td>0646</td>
<td>0.02595</td>
<td>F</td>
<td>5032</td>
<td>0.02446</td>
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</tbody>
</table>

sorbate 80, ethanol, menthol and microcrystalline cellulose used by six manufacturers were investigated for interference using FAAS method at a concentration of 1.5 µg/mL and 3.5 µg/mL, which covered the maximum possible injection concentration of a single excipient. The mixed blank excipients were also investigated and the results showed that the influence was negligible.

3.1.4. Precision and Repeatability

Precision and repeatability were validated by injecting six individual calibration solutions and six individual sample solutions at a concentration of 100.0%. The acquired results showed that the developed methods had adequate precision and repeatability.

3.1.5. Stability

Solution stability samples from six manufacturers (n=6) were analyzed at 0, 2, 4, 6, 8, 16 and 24 h, respectively. At the 24 h time point, the average absorbance of magnesium decreased to 99.30% for the assay of magnesium trisilicate and 98.47% for the in vitro dissolution of the initial values, respectively. The results showed that the solution remained stable for 24 h.

3.1.6. LOD and LOQ

The Limit of Detection (LOD) and the limit of quantification (LOQ) were calculated according to the Ch. P General Chapters <9101> [11] based on the standard deviation (σ) of the absorbance of the continuously injected blank solution, and the slope (S) of the calibration curve. The calculation formulas were as follows: LOQ=10 σ/S; LOD=3 σ/S.

3.1.7. Membrane Absorption

The membrane absorption experiment confirmed that the syringe filter used did not interfere with the determination of magnesium.

3.2. Quantification of Magnesium Trisilicate

As listed in Table 2, the quantification results showed that the content of magnesium trisilicate ranged from 0.0210 g to 0.0270 g per tablet (calculated by MgO). However, the maximum relative standard deviation (RSD) could reach up to 5.3% (n=19). The uneven content of the API revealed, from one aspect, the poor quality consistency. In addition, compared with the complexometric titration method in the Ch. P, which requires boiling twice [6] the FAAS method simplified the operation and reduced the error generated in the pretreatment.

3.3. Drawing Dissolution Profiles

The dissolution profiles in Fig. (1) show the cumulative percentages of magnesium released from the tablets as a function of time. The measured content of magnesium trisilicate, instead of the claimed dosage, was used to calculate the API released from the formulation at each sampling time point. Among the 38 batches of samples, 15 batches reached the level of 85% cumulative dissolution within 15 min. As
was stated by the guiding principles prescribed by the Center for Drug Evaluation of National Medical Products Administration (NMPA CDE, China) [12], these samples were considered similar without further mathematical evaluation [13]. In contrast, 7 batches did not reach the level of 85% within 60 min. Mean dissolution profiles were constructed using the average dissolution rate at each sampling time point. As shown in Figs. (2-6) mean dissolution profiles representing manufacturers A-F were distinct. These typical profiles obviously exhibited that the dissolution rates of the tablets from manufacturers B and E were slower than those of the rest. It is worth noting that the drug instruction of CAHTs emphasizes that this product needs to be chewed before swallowing; however, chewing does not guarantee complete comminution. Therefore, samples with slower dissolution rates may directly lead to an extended onset time in the gastrointestinal tract.

3.4. Comparison of Dissolution Profiles Using the \( f_2 \)-Factor

The dissolution profiles of the samples were mathematically compared with those of the reference. \( F_r \)-factor, also known as the similarity factor, is an independent mathematical method developed by Moore and Flanner [14], which is recommended by the United States Food and Drug Administration and the European Medicines Agency [15]. It indicates the extent of closeness between two profiles. An \( f_2 \)-value between 50 and 100 represents similar dissolution profiles. The calculation formula is as follows [16]:

\[
f_2 = 50 \times \log_{10} \left[ 1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{0.5} \times 100
\]

Where \( n \) is the number of time points, \( R_t \) and \( T_t \) are the dissolution value of the reference and test sample at time \( t \), respectively.

According to the CDE guidelines [17], reference preparation for dissolution is not recommended for CAHTs. We comparatively analyzed all the dissolution profiles to select an appropriate sample as the reference (last four digits: 1227), and four time points setting at 5, 10, 15, and 30 min were used to calculate the \( f_2 \)-factors. The results are presented in Table 3. Considering rapid dissolution, we counted that nearly 95% of the samples from manufacturer A were similar to the reference. However, the situation of manufacturers B, C, D, E, and F was not optimistic. The overall similarity of these manufacturers was less than 45%, indicating poor quality consistency.

3.5. Determination of Acid-Neutralization Profiles

The acid-neutralization profiles of the 38 batches of powdered samples are shown in Fig. (3A). The results obtained by the optimized method were shown in Fig. (3B), in which more profiles failed to reach a plateau, demonstrating enhanced discrimination. To clearly exhibit the details, we compared 7 batches of samples in Fig. (4) to highlight the advantages of the optimization. As we can see, the optimization procedure maximized the difference and separated the profiles successfully. The reason is that compared to tablets, powdered samples lost much information, including disintegration, release, and dissolution in the process of neutralizing hydrochloric acid. The inter-batch acid-neutralization profiles of the samples from manufacturer A-F are shown in Fig. (5), which clearly showed that the acid-neutralization rate of the samples from manufacturer B, C, E and F was relatively low, and the acid-neutralization capacity of the samples from manufacturer F was relatively weak because of the higher final acidity of the solution.

4. DISCUSSION

In this study, two evaluation systems were established to assess the quality of 38 batches of commercially available CAHTs. This section provides a detailed comparison between the two methods in the following four aspects.
Table 3. The calculated $f_2$ similarity factors of 38 batches of samples.

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Lot Number (Last Four Digits)</th>
<th>$f_2$-Factor</th>
<th>Manufacturer</th>
<th>Lot Number (Last Four Digits)</th>
<th>$f_2$-Factor</th>
</tr>
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<tr>
<td>A</td>
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<td>B</td>
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<td>30.8</td>
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<tr>
<td></td>
<td>0836</td>
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<td>5032</td>
<td>42.3</td>
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</table>

Fig. (3). Acid-neutralization profiles of 38 batches of samples. (A) Profiles of the powdered samples determined by the original method. (B) Profiles of the complete tablets obtained by the optimized method.
Fig. (4). Comparison of typical acid-neutralization profiles determined by two methods (powdered samples and complete tablets).

(Fig. 5). Contd…
Fig. (5). Inter-batch acid-neutralization profiles of manufacturer A-F determined with whole tablets.

Fig. (6). Average times of the samples from six manufacturers to reach pH 3.0. Determined by two acid-neutralization methods.

4.1. Time to Reach pH 3.0

Ayensu et al. [18] gave opinions that an ideal antacid should have a buffering capacity to maintain gastric pH above 3.5 for a considerable amount of time. Kerkhof et al. [19] characterized the pH profiles by the lag time, time to reach pH 3.0 and other parameters. We regarded the time to reach pH 3.0 as a critical indicator to evaluate the neutralizing capacity of antacids. A histogram (Fig. 6) showed a comparison of the average time between the two methods. Generally, samples from manufacturer A took less time to neutralize the solution acidity to pH 3.0. In contrast, samples from manufacturer B took over 40 min. We reasonably doubted that these CAHTs could not exert ideal anti-acid effects, possibly leading to prolonged illness and treatment failure. The results were also processed using the Kruskal-Wallis H test of the IBM SPSS Statistics software (version 22.0, IBM, Armonk, NY, USA). Considering a significance level of 0.05, the data showed significant differences ($\alpha=0.05$, $P<0.05$). Therefore, we concluded a changing quality of the samples between the batches and manufacturers. Besides, powders spent less time to reach pH 3.0 than tablets, and this difference in manufacturer E was even as long as 15 minutes. We can reasonably suspect that when the powder is used to evaluate the quality of antacids, a sample with poor neutralization capacity may be incorrectly evaluated as a good one.

4.2. Discrimination Capacity of the Profiles

To achieve a comprehensive assessment, the discrimination capacity of the established method should be ensured to
maximize the small difference in the samples. We conducted a comparison using 6 typical samples to show the details intuitively. Fig. (7) showed the results. The overlapped dissolution profiles could almost reach a platform, which indicated the weak distinguishing capacity. In contrast, the acid-neutralization profiles were highly distinguishable because each profile could be separated from the other; therefore, the quality difference could be judged comprehensively and objectively.

4.3. Quality Parameters of CAHT

Four quality parameters related to tablet properties were analyzed and discussed as were listed in Table 4. The average weight, thickness and hardness were calculated based on the average of twenty tablets which were randomly selected from each manufacturer. The friability was calculated according to the Ch. P General Chapters <0923> [20]. The results showed that the average weight of the samples from manufacturers D and E was relatively low, however, we thought that this difference was negligible according to the content of magnesium trisilicate. Similarly, both thickness and friability were not the key parameters which could result in the fluctuation in quality. As an important test item, hardness affects the disintegration and dissolution of the tablets. Although the hardness of the samples from manufacturers B, E and F was smaller than that of the others, which indicated that they might be easier to disintegrate, their profiles were not higher than the others. On the other hand, lower hardness indicated that they were more likely to break or wear during packaging and transportation, but also indicated that they were easier to be chewed by patients.

4.4. Advantages of Optimization

An ideal quality assessment method should be discriminative and suitable for multiple sample batches. Importantly, a method should be simplified to maximize its applicability. The optimized acid-neutralization method we established, which consisted of simple sample pretreatment steps and real-time determination, had the advantages of rapidity and simplicity. Besides, dissolution profiles were constructed by sampling at several time points, and a well-validated analytical method was required to ensure the reliability of the results. The stability of the sample needed to be investigated. In contrast, the acid-neutralization method reduced the workload while ensuring the reliability of the results. Compared to in vitro dissolution, this direct and in situ determination greatly improved the efficiency of the generation of analysis data.

Table 4. Quality parameters of CAHTs from six manufacturers.

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Average Weight (mg)</th>
<th>Thickness (mm)</th>
<th>Hardness (kg)</th>
<th>Friability (Weight Loss%)</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>456.39</td>
<td>3.22</td>
<td>12.34</td>
<td>0.044</td>
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<tr>
<td>B</td>
<td>453.78</td>
<td>3.38</td>
<td>7.70</td>
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<tr>
<td>C</td>
<td>422.48</td>
<td>3.65</td>
<td>11.57</td>
<td>0.134</td>
</tr>
<tr>
<td>D</td>
<td>402.14</td>
<td>3.49</td>
<td>11.12</td>
<td>0.591</td>
</tr>
<tr>
<td>E</td>
<td>405.91</td>
<td>3.48</td>
<td>9.88</td>
<td>0.145</td>
</tr>
<tr>
<td>F</td>
<td>435.83</td>
<td>3.25</td>
<td>7.53</td>
<td>0.115</td>
</tr>
</tbody>
</table>

Fig. (7). Comparison of seven batches of dissolution profiles and acid-neutralization profiles.
CONCLUSION

In this study, a comprehensive and innovative strategy combining assay of magnesium trisilicate, in vitro dissolution and acid-neutralization using both tablet and powder forms for the quality control of multi-batches of CAHTs was established. Two suitable and accessible FAAS methods were established and well-validated. The magnesium trisilicate assay was applied to 38 batches of samples to calculate the cumulative dissolution percentage, which revealed the uneven content of magnesium trisilicate in the samples from manufacturer A. Two evaluation systems, acid-neutralization profiles and dissolution profiles, were successfully used to assess the quality consistency. Optimization of acid-neutralization was performed based on the concept of evaluation and the convenience of experimental operation. The optimized method maximized the difference in each sample by directly determining the acid-neutralization profiles using complete tablets. Characterization of acid-neutralization profiles showed that the samples from manufacturer B took more time to reach pH 3.0, and those from manufacturer F had low neutralization ability, indicating their slow neutralizing rate and poor clinical efficacy. Moreover, in vitro dissolution was firstly reported to evaluate the quality of CAHTs. The dissolution profiles of the test samples were compared with that of the reference by f2 similarity factor. Compared with the reference, the overall similarity of the dissolution profiles from manufacturers B, C, D, E and F was relatively low. Finally, four quality parameters, including the average weight, thickness, hardness and friability, were analyzed. However, none of them were considered as key factors affecting the profiles. In conclusion, this study demonstrated that both acid-neutralization and in vitro dissolution can be useful for assessing the quality consistency and monitoring lot-to-lot changes of CAHTs. We also believe that our study offered a scientific, practical and comprehensive analytical strategy to guide the development of antacids.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No animals/humans were used for studies that are the basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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