

The Effect of Residual Water on Antacid Properties of Sucralfate Gel Dried by Microwaves

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ABSTRACT

The aim of this work was to study the acid neutralization characteristics of microwave-dried sucralfate gel in relation to the water content and physical structure of the substance. Several dried sucralfate gels were compared with humid sucralfate gel and sucralfate nongel powder in terms of neutralization rate and buffering capacity. Humid sucralfate gel and microwave-dried gel exhibited antacid effectiveness. In particular, the neutralization rate of dried gel powders was inversely related to the water content: as the water content of dried powders decreased, the acid reaction rate linearly increased. The relationship was due to the different morphology of dried sucralfate gels. In fact, the porosity of the dried samples increased with the water reduction. However, the acid neutralization equivalent revealed that the dried sucralfate gel became more resistant to acid attack in the case of water content below 42%. Then, the microwave drying procedure had the opposite effect on the reactivity of the aluminum hydroxide component of dried sucralfate gel powders, since the rate of the reaction increased whereas the buffering capacity decreased as the amount of water was reduced.

KEYWORDS: sucralfate gel, antacid effectiveness, microwave drying, water content, Rossett-Rice test.

INTRODUCTION

The active pharmaceutical ingredient sucralfate is available in 2 physical forms for dosage form manufacturing: humid sucralfate gel and sucralfate nongel powder. At present, the humid gel is employed for the preparation of suspensions and exhibits better antiulcer activity than does the nongel product.^{1,2}

The sucralfate molecule contains ~19% aluminum, mainly in the form of aluminum hydroxide, which is a reference

product for antacid activity.³ Despite its aluminum hydroxide content, sucralfate is not classified an antacid product. However, owing to its favorable particle size distribution, humid sucralfate gel shows higher neutralization rate than nongel powder, suggesting a potential use in antacid products.⁴ Previous studies have demonstrated that the drying process could irreversibly affect the properties of humid sucralfate gel depending on the residual water content. We found that the dried sucralfate gel powders prepared from humid sucralfate gel in appropriate drying conditions could maintain the gel characteristics.^{5,6} It would be of therapeutic relevance to explore the suitability of these dried sucralfate gel powders for the preparation of antacid solid dosage forms. In fact, the antigastitis activity of sucralfate gel would be synergistically coupled with the acid-neutralizing capacity.

The aim of the present work was to study the acid neutralization characteristics of microwave-dried sucralfate gel samples. The reaction rate toward acid and the buffering capacity were evaluated for dried sucralfate gel powders with different residual water content. The dried sucralfate gels were compared in terms of antacid activity with humid sucralfate gel and sucralfate nongel powder.

MATERIALS AND METHODS

Materials

Humid sucralfate gel (batch 7/99, water content 77% wt/wt, Euticals SpA, Lodi, Italy) was kindly donated by Lisapharma SpA (Erba, Como, Italy). The quality of sucralfate nongel powder used was USP24 Sucralfate monograph (batch K11648135, Merck, Darmstadt, Germany).

Methods

Dried Sucralfate Gel Preparation and Characterization

Dried sucralfate gels were prepared using a conventional microwave oven (Perfecto De Longhi, Treviso, Italy), as previously described.⁵ Briefly, 200 g of humid sucralfate gel were layered on the circular dish of the oven (diameter 27.5 cm). Microwave power of 800 W (on-off ratio: 24 seconds "on," 6 seconds "off") was applied for the

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selected drying time. The microwave-dried sucralfate gel lumps were comminuted using an oscillating granulator with 1.5 mm net (Erweka AR 400, Heusenstamm, Germany). The powder obtained was calibrated through ASTM International sieves collecting the fraction retained between 850 and 150 μm . Particle size distribution in this interval was determined by sieving.

The residual water content of dried sucralfate gels was measured according to USP24 Water Determination, METHOD I (Trimetric) Method Ia (Direct Titration). The aluminum content was measured according to the USP24 Sucralfate monograph. Particle morphology was analyzed by scanning electron microscopy employing a Jeol 6400 microscope (Jeol, Tokyo, Japan), upon deposition of a 200 to 400 Å carbon layer on top of the sample. The analysis was conducted at 15 kV, and the magnification was $\times 200$. The true density of the samples was measured with a helium pycnometer (Micromeritics, Norcross, GA). The porosity of the tapped powder bed was calculated from the apparent volume measured in accordance with the European Pharmacopoeia 4.0.

For the determination of the antacid properties, 3 classical antacid tests were performed on samples containing 1 g of sucralfate—that is, the sucralfate minimum labeled dosage. Dried powders calibrated in the range between 150 to 850 μm were used. Humid sucralfate gel and sucralfate nongel were used as received.

The preliminary antacid test was performed according to USP23. Briefly, an accurately weighed sample equivalent to 1 g of sucralfate was placed in a 100 mL beaker. Water ($25 \pm 3^\circ\text{C}$) was added to a volume of 40 mL and mixed with a magnetic stirrer at 300 rpm for about 1 minute. Then,

10 mL of 0.5N HCl was added under continuous stirring. The pH of the suspension was recorded over time.

The acid neutralization equivalent was tested according to the USP24 Sucralfate monograph. Briefly, an accurately weighed sample equivalent to 250 mg of sucralfate was added to 100 mL of 0.1N hydrochloric acid in a stirred bottle for 1 hour at 37°C . The solution was titrated with 0.1N NaOH to determine the acid equivalent neutralized.

In the acid neutralizing dynamic test (Rossett-Rice test),⁷ 30 mL of 0.1N HCl, 70 mL of water, and an amount of sample equivalent to 1 g of sucralfate were introduced into the reaction beaker under continuous magnetic stirring. Then, 0.1N hydrochloric acid was continuously added at a rate of 2 mL/min, and the pH changes were recorded as a function of time.

RESULTS AND DISCUSSION

In a previous paper,⁵ dried sucralfate gel samples with residual water content ranging from 77% to 3% (wt/wt) (Table 1) were prepared from humid sucralfate gel, by setting different microwave drying times. We showed that for dried sucralfate gels containing more than 42% water, water was present in both the free and the bound states. In contrast, only bound water could be detected in dried sucralfate gel samples containing less than 42% water.

Sucralfate is not considered an antacid product since its reaction rate toward acid is slowed by the formation of a sticky paste on the particles upon contact with acids.⁸ For this reason, the acid reactivity of sucralfate gel samples was at first evaluated by performing the USP23 Preliminary antacid test. This test allows the evaluation of the reaction

Table 1. Residual Water Content, mEq of Hydrochloric Acid Consumed per 1 g, True Density, Tapped Density, Porosity, and Sieve Diameter of the Sucralfate Gel Samples*

Water Content (% wt/wt)	mEq/g	True Density (g/cm^3)	Tapped Density (g/cm^3)	Porosity (%)	$d_{\text{sieve } 50}$ (μm)
3 ± 0.3	16.8 ± 0.1	—	—	—	—
9 ± 0.7	16.9 ± 0.1	2.145	0.76	64.8	458
17 ± 0.6	16.1 ± 0.1	2.016	0.72	64.1	487
21 ± 0.1	16.9 ± 0.2	1.920	0.76	60.5	460
34 ± 1.3	17.0 ± 0.3	1.725	0.72	57.9	464
42 ± 1.3	19.9 ± 0.1	1.646	0.79	56.9	471
50 ± 2.1	20.5 ± 0.2	1.479	0.80	46.0	460
57 ± 2.0	21.7 ± 0.4	—	—	—	—
$77 \pm 0.8^\ddagger$	22.1 ± 0.2	—	—	—	—
$11 \pm 2.3^\ddagger$	15.3 ± 0.2	—	—	—	—

*Mean \pm SD; n = 3. — indicates that values were not determined.

[†]Sucralfate humid gel.

[‡]Sucralfate nongel powder.

rate of the sample toward acid. For a product to be considered an antacid, the labeled dose must raise the pH of the acid solution to a value of 3.5 or higher in 10 minutes. The test was performed on 1 g of sucralfate—that is, the labeled dosage for ulcer therapy. The weighed amount of sucralfate powder to be tested was calculated on the sample aluminum content, considering 190 mg of aluminum equivalent to 1 g of sucralfate. Sucralfate nongel powder was taken as the reference product for comparison purposes.

Figure 1 shows the acid neutralization profiles of the dried sucralfate gel samples during the preliminary antacid test. Figure 1a shows the results obtained with samples having a residual water content below 42% (wt/wt)—that is, containing only bound water. The neutralization profiles of dried sucralfate gel samples containing also free water—that

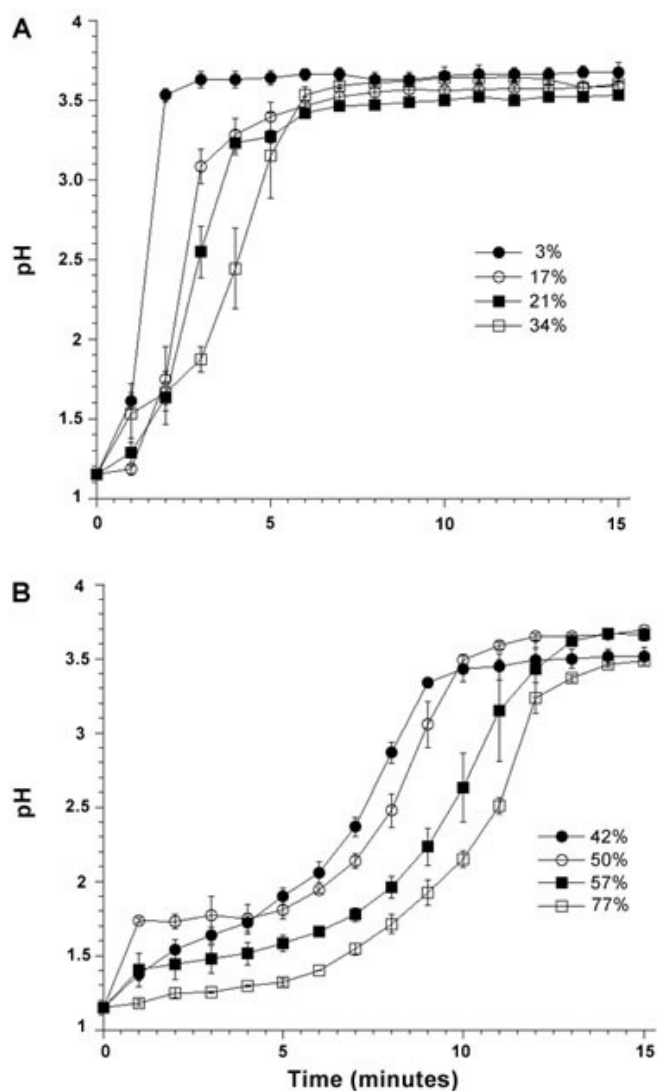


Figure 1. Acid neutralization profiles of the dried sucralfate gel samples during the preliminary antacid test: (a) water content lower than 42% (wt/wt); (b) water content equal to or higher than 42% (wt/wt) (mean \pm SEM; $n = 3$).

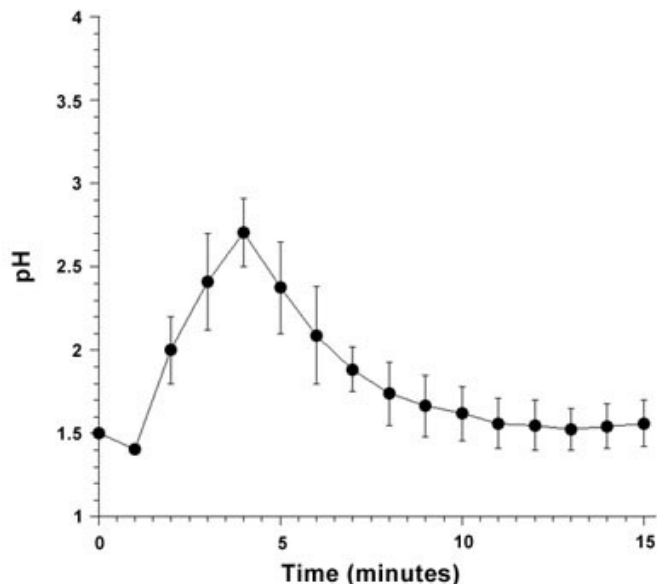


Figure 2. Acid neutralization profile of sucralfate nongel powder (mean \pm SEM; $n = 3$).

is, having a total water content equal to or above 42%—are shown in Figure 1b. Sucralfate nongel powder was also tested for comparison purposes; the profile is shown in Figure 2.

The acid neutralization profiles of dried sucralfate gel samples revealed that the reaction rate depended on the residual water content. In fact, all sucralfate gel samples (humid gel included) were able to reach the limit pH value of 3.5, but at different rates. The most dried gels (ie, those containing only bound water) took from 1 to 6 minutes to reach this pH value, with differences between them depending on water content (Figure 1a). In contrast, in the samples containing free water also, the time required to reach pH 3.5 became longer (eg, 14 minutes was the value measured for humid sucralfate gel) (Figure 1b). Hence, the rate of acid neutralization slowed down as the total water content of sucralfate gel increased. According to this preliminary test, only dried sucralfate gels containing an amount of water equal to or lower than 42% could be classified as antacid products at the dose of 1 g. Dried sucralfate gel samples containing bound and free water (ie, total water content $> 42\%$) and sucralfate nongel powder could not be defined as antacid products unless they are employed at higher doses.

The neutralization curves of Figure 1 were fitted to the Weibull function⁹ to calculate the time parameter (τ_d), which is the characteristic time of the overall rate of neutralization. The time parameter is inversely related to the acid neutralization rate. In Figure 3, τ_d values were plotted against water content and fitted to a straight line. A significant linear correlation was obtained, indicating that the

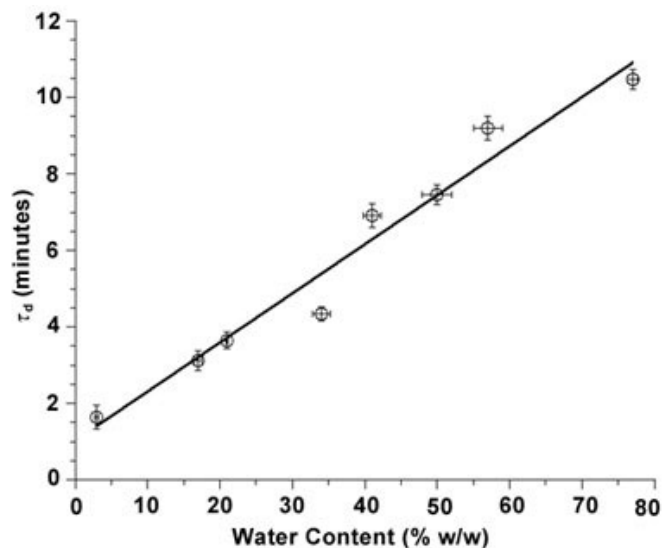


Figure 3. Time parameter of Weibull function applied to the acid neutralization profiles plotted versus the water content of dried sucralfate gel samples (mean \pm SD). Line equation: $y = 1.0286x + 1.12847x$; $R^2 = 0.96373$.

reaction rate of dried sucralfate gels with hydrochloric acid was inversely dependent on water content.

Given that humid sucralfate gel and its dried products showed a preliminary antacid activity, their buffering capacity toward acid needed to be evaluated to complete the characterization. In fact, an antacid product requires not only a rapid acid reaction (neutralization rate) but also a durable effect (buffering capacity). Thus, the acid neutralization equivalent according to the USP24 Sucralfate monograph was measured (Table 1). The pharmacopoeia requirement is that 1 g of sucralfate neutralizes at least 12 mEq of acid in 1 hour. Microwave dried gel samples with less than 42% (wt/wt) water content exhibited roughly similar acid neutralization equivalent values—that is, between 16.1 and 17.0 mEq/g. With more humid products also containing free water, the acid neutralization values were generally higher than 19.9 mEq/g, reaching 22.1 mEq/g for the sucralfate humid gel raw material (77% water content). A significant difference (t probability < 0.0001) was calculated between the samples 34% and 50%—that is, the samples encompassing the critical value of water identifying the limit

of free water (42%). This suggests that the bound water removal had a negative effect on the acid neutralization capacity of sucralfate gel. The reduction of buffering capacity of gel samples during the bound water removal indicated that microwave drying somewhat affected sucralfate gel structure. A similar effect has already been observed with aluminum hydroxide samples, where differences in reaction rate and buffering capacity were measured between the freshly precipitated and the dried products.^{10,11} A negative influence of the drying procedure on sucralfate gel structure had been measured through the reduction in the self-suspending capacity of humid gel after drying, in particular when the dried samples contained less than 42% water.⁵ Finally, concerning the buffering capacity, the sucralfate nongel powder behaved like most dried gel samples.

The relationship between the acid reactivity and the residual water content of sucralfate gel powders indicated a direct role of residual water on the reaction between acid solution and sucralfate gel particles. The particles of powders produced by microwave drying were quite porous, and the total porosity of their powder beds increased as the bound water was removed, as shown in Table 1. The scanning electron microscopy microphotographs of particles from different samples containing 50%, 21%, and 9% water exhibit differences in the surface structure likely due to the removal of water (Figure 4). The drying process produced a network of cracks of varying size on the particle surface. No cracks were visible in the sample that had residual water higher than 42% (wt/wt) (Figure 4a). The number of cracks was very high for the sample with the lowest water content (9%) (Figure 4c) in comparison with the sample at 21% (Figure 4b). The sharp edges of the particles in Figures 4b and 4c clearly indicate that the cracks or lines of fracture existed prior to the scanning electron microscopy analysis, thus eliminating the possibility that the sputtering process involved in scanning electron microscopy could have caused the cracks. Thus, when the acid solution came into contact with these particles, the more porous materials were more easily penetrated and thus showed an increased neutralization rate.¹² However, this interpretation does not fit with the lower reaction rate of the humid gel samples, where the product would be expected to have the highest

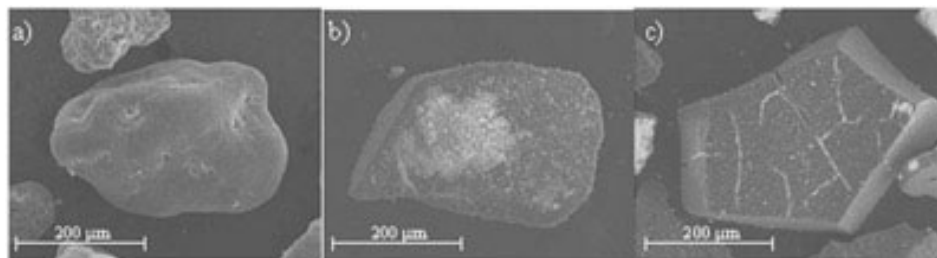


Figure 4. SEM microphotographs of sucralfate gel particles after drying process (magnification 200 \times); water content: (a) 50% (wt/wt); (b) 21% (wt/wt); (c) 9% (wt/wt).

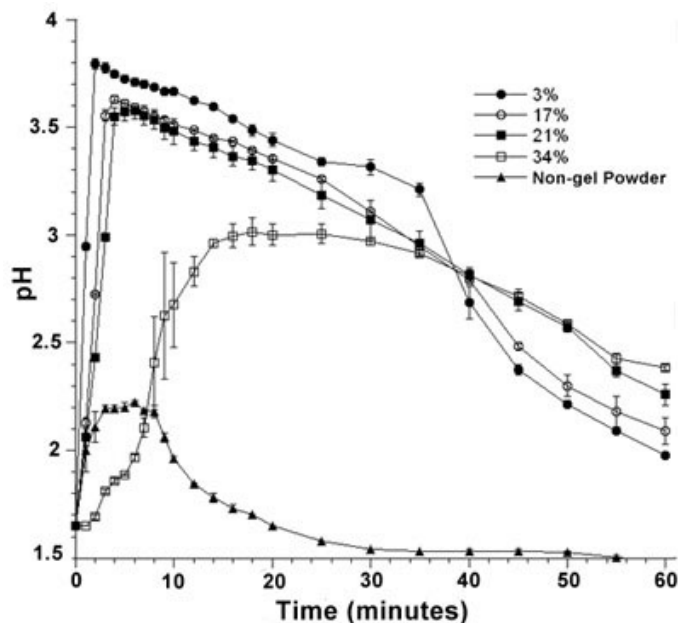


Figure 5. pH variation during Rossett-Rice test of sucralfate gel samples containing less than 42% (wt/wt) of water compared with the sucralfate nongel (mean \pm SEM; $n = 3$).

surface area since it has a micronized particle size.¹³ It could be speculated that, in the humid gel that contains an increasingly great amount of water, the presence of coordinated water inside the particle would delay the diffusion of hydrogen ions and hence their reaction with the solid surface. In contrast, with the most dried products, direct contact between the acid and the solid surface could be envisaged. If this was the case, the direct contact between acid and solid could explain the higher reaction rate of the most dried sucralfate gel samples, despite their lower buffering capacity.

As the water content decreased, the neutralization rate toward acid increased but the buffering capacity was reduced. To better understand this antacid behavior of sucralfate gel samples, the Rossett-Rice dynamic antacid test was performed. In this test, which simulates the continuous acid secretion in the gastric environment, the antacid performance of the product depends on both neutralization rate and buffering capacity. A product can be considered an antacid if the labeled dose reaches pH 3.0 in 10 minutes and remains above this value for 1 hour under continuous addition of acid. Figure 5 shows the pH variation as a function of time for the most dried sucralfate gel samples and the sucralfate nongel powder in the conditions of the Rossett-Rice test. The results indicated that only the most dried samples of sucralfate gel (ie, those containing 3%, 17%, and 21% of water) were close to satisfying the Rossett-Rice test specifications. The buffering capacity of 1 g of sucralfate gel was not sufficiently high to sustain pH 3.0 for 1 hour. Hence, the sucralfate dried gel products containing

less than 42% (wt/wt) water may have a potential use in antacid therapy according to the Rossett-Rice test at a dose higher than 1 g. The sucralfate nongel sampler was incapable of reaching the pH value of 3.5.

CONCLUSION

The present study demonstrated that dried sucralfate gel reacted faster toward acid than did humid gel, likely because of direct contact between dried samples and the acid solution. In fact, as the water content decreased, the reaction rate with hydrochloric acid linearly increased. However, the acid neutralization equivalent revealed that the dried sucralfate gel became more resistant to acid attack when water content was below 42%. Then, the microwave drying procedure had the opposite effect on the reactivity of the aluminum hydroxide component of dried sucralfate gel powders, since the rate of the reaction increased whereas the buffering capacity decreased.

In conclusion, sucralfate gel exhibits promising antacid properties in comparison to sucralfate nongel. The antacid characteristics of dried sucralfate gel powders were strongly dependent on their water content. The dried samples containing only bound water (less than 42% of water), despite an evident reduction of buffering capacity due to drying, could be proposed as antacid products according to the USP23 Antacid effectiveness test.

However, the Rossett-Rice dynamic test conditions can be fulfilled by sucralfate gel only at doses higher than the labeled dose for antiulcer activity. The advantage of having an antacid effect coupled with antiulcer activity seems achievable with dried sucralfate gel powders.

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