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Effect of Residual Water Content on the Physico-Chemical Properties of Sucralfate Dried Gel Obtained by Microwave Drying

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ABSTRACT The purpose of this study was to investigate the physico-chemical characteristics of sucralfate humid gel dried by microwaves, in relation to the residual water content. Differential scanning calorimetry (DSC) allowed for the determination of the water state in sucralfate samples. Fourier-transform infrared (FT-IR) spectroscopy was used to monitor the changes in sucralfate gel structure induced by the microwave drying. A boundary value of total water content for sucralfate gel samples was found at 42% (w/w). Below this value only bound water was present, whereas above this value, the increase in total water was due to free water. In the physical form of gel, the strength of the coordination between sulfate anions and the positively charged aluminum hydroxide was dependent on the residual water content. The study of the sedimentation behavior of water suspensions prepared with dried sucralfate allowed for the evaluation of the retention of gel properties. We found that the microwave drying process affected the sedimentation of sucralfate dried gel suspensions independent of the residual water content: when suspensions were prepared from sucralfate dried gel powders containing more than 42% (w/w) of residual water, the sedimentation ratio was higher than 0.9. The nongel powder suspension showed a sedimentation ratio of 0.68±0.02, whereas the sucralfate humid gel suspension did not sediment.

KEYWORDS Sucralfate dried gel, Microwave drying, Bound water, Aluminum octasulfate, Sedimentation

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INTRODUCTION

Sucralfate is a complex of aluminum sucrose octasulfate dispersed in an aluminum hydroxide matrix (Higo et al., 2004a; Ishimori, 1995; Nagashima, 1981a). Its anti-ulcer and cytoprotective actions were attributed to the capability of forming a bioadhesive paste with gastric acid, sticking to the ulcerated GI mucosa (Higo et al., 2004b; Nagashima, 1981b). Two physical forms of sucralfate are available for dosage form manufacturing, namely dry powder and humid gel, the latter containing between 50% and 80% (w/w) of water (Caramella et al., 1988, 1995). The humid gel exhibits colloidal properties allowing for the preparation of self-suspending suspensions with thixotropic behavior (Rossi et al., 1992). Sucralfate gel revealed strong adhesion to mucosa without acid intervention (Hardy et al., 1993; Vaira et al., 1993). Several clinical trials demonstrated that the gel form halved the therapeutic dose of sucralfate (Girola & Ventura, 1992).

Sucralfate has structural analogies with aluminum hydroxide. The freshly precipitated humid aluminum hydroxide is more reactive towards acids and more stable to settling (Nail et al., 1976a, 1976b; Serna et al., 1977). It has also been shown that sucralfate humid gel retains its colloidal and bioadhesion properties only if stored as a moist solid (Colombo, 1995). Consequently, the manufacture of sucralfate solid dosage forms such as tablets is impeded, since conventional drying irreversibly affects the gel characteristics. A previous study showed that a microwave-based drying procedure allowed for the preparation of sucralfate gel powders that retained in part the humid gel characteristics, as shown with rheology measurements and with an in vitro bioadhesion test (Maggi et al., 2000). In particular, microwave drying of sucralfate humid gel in the presence of mannitol as gel protector improved the capability of the dried powders to reconstitute the gel form of sucralfate when dispersed in water.

Since in the above-mentioned study the effect of residual water content of sucralfate dried gel was not considered, the aim of the present work was to study the physico-chemical characteristics of sucralfate dried gel powders obtained by microwave drying without mannitol as gel protector, in relation to the residual water content. Water state by DSC, gel structure by FT-IR spectroscopy, and particle size were the properties investigated to identify the modifications induced by the microwave drying process. Instead of rheology, the more accessible measurement of the sedimentation ratio of sucralfate dried gel suspensions was performed. The sedimentation ratio allowed for the evaluation of the modifications induced by drying, when compared with the ability of sucralfate humid gel to produce unsettling suspensions in water.

MATERIALS AND METHODS

Materials

Three different batches of sucralfate humid gel raw material supplied by the two existing official suppliers were used. The quality of raw materials, in particular particle size and rheology, complied with the Drug Master File requirements for sucralfate gel commercial suspensions. The batches and suppliers were: batch 07/99, water content 77% (w/w) (Euticals S.p.A., I-Lodi); batch 997930, water content 78% (w/w), and batch 01090312, water content 79% (w/w) (Giulini Chemie GmbH, D-Ludwighafen).

Sucralfate powder USP24 was supplied by Merck (D-Darmstadt).

Methods

Sucralfate Dried Gel Preparation and Characterization

Sucralfate dried gel powders were prepared by means of a 16-liter-capacity microwave oven (Perfecto® De Longhi, I-Treviso). Two hundred grams of humid gel were deposited on the oven rotating plate (diameter, 27.5 cm). Microwave power of 800 W was applied with an irradiation period of 24 seconds "on" and 6 seconds "off" for the fixed drying time. The clumps of sucralfate dried gel obtained were forced through a sieve having a mesh size of 1.5 mm.

Residual water content was determined either by direct titration (Trimetric Method Ia, USP24) or by loss on drying in accordance with the Japanese Pharmacopoeia XIV (sample 1 g, 3 hours, 105°C). No significant difference was found between the two methods. Sucrose octasulfate (SOS) content was measured according to USP24 sucralfate monograph.

The water state in each sucralfate sample (humid gel, dried gels, and nongel powder) was determined by differential scanning calorimetry (Bouwstra et al., 1995; McCrystal et al., 1999; Zografi, 1988). The thermal analysis was carried out on Indium calibrated Mettler 821eSTARe DSC system apparatus (Mettler Toledo, CH-Greifensee). Samples of about 10 mg were weighed on a microbalance (MT5, Mettler Toledo, CH-Greifensee) in aluminum pans that were then hermetically sealed and pierced. DSC traces were recorded under nitrogen atmosphere according to the following procedure: samples were cooled down from

+25°C to −20°C, kept at −20°C for 15 minutes to ensure the complete crystallization of water, and then gradually heated from −20°C to +25°C. The heating and cooling rates were kept at 2°C/min during the entire analysis. Assuming that the melting enthalpy was directly correlated to the amount of unbound water (i.e., free water) in the sample, the percentage of free water was calculated from the melting enthalpy value, taking as reference the melting enthalpy of a known amount of pure water. The amount of bound water was then calculated by subtracting the free water from the total water content previously measured by direct titration.

Horizontal attenuated total reflectance Fourier-transform infrared (HATR-FTIR) spectroscopy was used to obtain spectra of sucralfate humid gel (FT/IR-300 E Jasco spectrometer, Jasco, Tokyo, Japan). An ATR-crystal (ZnSe, dimension 7 × 1 cm, incident angle 45°) enabled horizontal positioning of humid gel samples. Spectra were acquired at a resolution of 4 cm^{-1} in the region between 400–4000 cm^{-1} and then Fourier-transformed against background interferogram. Spectra were analyzed using the SpectraManager software (Jasco, Tokyo, Japan).

Spectra of powdered sucralfate samples (both dried gel and nongel powders) were recorded on the same FT/IR spectrometer, employing the method of potassium bromide pellets. Each spectrum was acquired in the above-described conditions.

Suspension Preparation and Characterization

Twenty percent (w/v) aqueous suspensions of sucralfate were prepared by means of an Ultra-Turrax® homogenizer (TP18/10N, Ika-Werk, D-Staufen) equipped with a 10-mm, 10 N head rotating at 11,000 rpm for 15 minutes. Each suspension was then poured into a stoppered 50-mL graduated cylinder and stored at room temperature. The ultimate height of the sediment (H_u) was measured on the sixth day, in order to calculate the sedimentation ratio H_u/H_o (initial height of suspension, H_o) (Biró et al., 2000).

At the end of the sedimentation experiment, the particle size distribution of sucralfate gel, dried gels, and nongel suspensions was determined by laser diffraction (Malvern Series 2600, Malvern Instruments Ltd., Malvern, UK) upon dispersion of one drop of suspension into 80 mL of distilled water. In addition, after diluting a small amount of the suspension with glycerol, optical microscopy analysis in accordance with the British Standard guidelines was also performed using a microscope equipped with a 100/1.25 objective and 10 × ocular (Nikon Labophot, Tokyo, Japan).

Statistical Analysis

All data are reported as the mean ± the standard deviation. Statistical analysis was based on the unpaired Student's test (two-tailed). Significance was accepted at $p<0.05$.

Curve fitting was done with KaleidaGraph® software (Version 3.6) running on a Macintosh PowerBook G4 laptop. The sedimentation ratio values of all individual experimental data were fitted vs. water content using the Rosin-Rammler-Sperling-Bennett-Weibull distribution function. A nonlinear regression analysis was performed.

RESULTS AND DISCUSSION

Effect of Drying Time on Sucralfate Gel Properties

Samples of sucralfate dried gel with different residual water contents were prepared by varying the time of microwave drying of sucralfate humid gel raw material (77% w/w initial water content). The dependence of the residual water content of sucralfate dried gel samples (measured by direct titration) from the drying time is illustrated in Fig. 1. The reduction

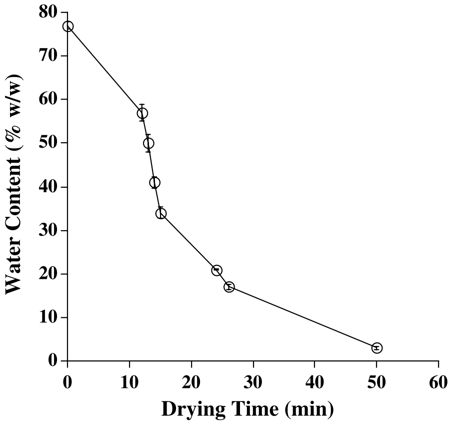

FIGURE 1 Residual Water Content of Sucralfate Dried Gel Samples as a Function of Drying time (Euticals Batch 07/99). Bars Represent the Standard Deviation of the Mean (n = 3).

of the water content of dried gels was nonlinear with the drying time. Drying was initially quick, until the residual water was about 40–30% (w/w), whereas below this value the rate of water loss slowed down. By continuing the drying for up to 50 minutes, residual water content of 3% (w/w) was obtained, although the dried gel appeared somewhat burnt.

The SOS content of dried gels was determined. The drying procedure generally did not degrade SOS, except when drying was prolonged to 50 minutes: in this case, the sample containing 3% (w/w) water showed a 10% loss in SOS content.

The physico-chemical characteristics of microwave dried sucralfate gel were studied. Preliminarily, we assessed the water state in each sucralfate sample (humid gel, dried gels, and nongel powder) by DSC. Figure 2 shows an example of a DSC scan of a sample of sucralfate dried gel having total water content of 57% (w/w). The time scale of the scan is indicated in the figure caption. Assuming that the calorimetric behavior of the free water in sucralfate gel is equivalent to that of pure bulk water, it was possible to determine the free water content by thermal analysis. In fact, the exothermic peak corresponding to water crystallization occurring during the isothermal freezing process at −20°C was followed by an endothermic peak corresponding to the melting event (onset −1.2°C, peak 1.1°C). From the melting enthalpy of a known amount of pure water and the melting enthalpy of the water contained in the sample, the percentage of free water in sucralfate gel was calculated.

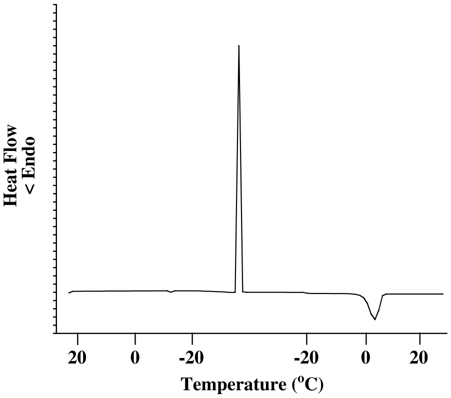

FIGURE 2 **DSC Scan of Sucralfate Dried Gel (Euticals Batch 07/99) Having 57% (w/w) Residual Water Content (Melting Enthalpy of Water Peak=1396.56 mJ; Sample Weight 15.275 mg; Samples Were Cooled Down from +25°C to −20°C, Kept at −20°C for 15 Minutes, and Then Gradually Heated from −20°C to +25°C. Heating and Cooling Rates were 2°C/min).**

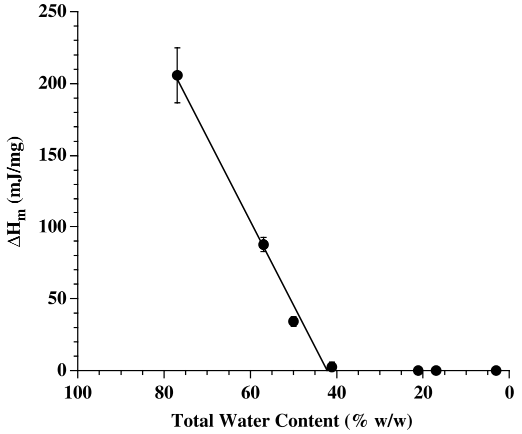

FIGURE 3 **Relationship Between the Melting Enthalpy of Sucralfate Gel Samples, Expressed as mJ per mg of Sample, and the Total Water Content. Bars Represent the Standard Deviation of the Mean (n=3). Below 42% (w/w), the Melting Enthalpy Values were Zero. The Regression Line Equation was: $y = -244.09 + 5.8087x$; $R = 0.99543$.**

The total water content of sucralfate humid gel, measured by direct titration, decreased with drying (see Fig. 1). In parallel, the melting enthalpy of water in sucralfate gel samples decreased, indicating a reduction of the free water content. In Fig. 3 the melting enthalpy of free water is plotted against the total water content of the sample. A linear decrease of melting enthalpy with total water content is observed, and the fitted straight-line intercepts the x axis in correspondence with a total water content of 42% (w/w). Since at 42% (w/w) of total water the melting enthalpy was zero, this percentage represented the threshold value, below which the sucralfate gel samples contained only bound water. This water corresponded to the nonfreezable bound water, which did not undergo a detectable phase transition (crystallization/fusion) during thermal analysis; these water molecules can be considered as being either adsorbed water or water of constitution (McCrystal et al., 1999). In the sucralfate non-gel powder, the total water content (11% w/w) was only bound water, since in the DSC trace no melting enthalpy was measured.

The infrared (IR) spectra of sucralfate non-gel and sucralfate humid gel are shown in Fig. 4. The spectrum of sucralfate non-gel shows absorption bands around 3500 cm^{-1} (stretching O-H) and 1650 cm^{-1} (bending O-H) due to hydroxyl groups. Sulfate anion exhibits the asymmetric stretching band at 1260 cm^{-1} and, in the region around 1000 cm^{-1}, the symmetric stretching (S-O) band shows a splitting with maximum absorption at 900, 1000, and 1100 cm^{-1}. This splitting

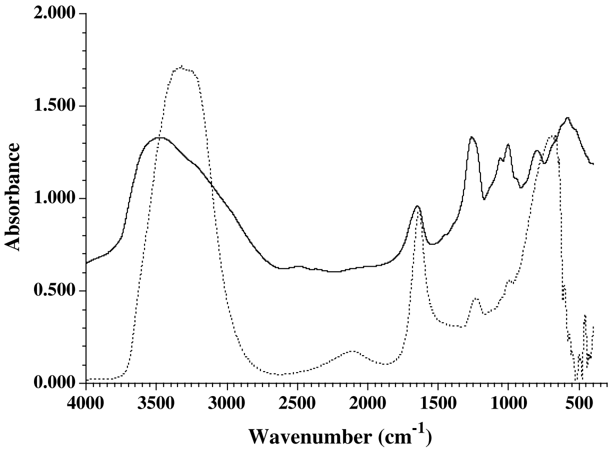

FIGURE 4 **Fourier Transformed IR Absorption Spectra of Sucralfate Non-Gel (——) and Sucralfate Humid Gel (·········) (Euticals 07/99).**

of the sulfate band was related to the interaction between the sulfate anion and the positively charged aluminum (Serna et al., 1977).

When comparing the two spectra, even though it was possible to recognize the same bands, a few differences were observed for the gel product. In particular, in the sucralfate gel spectrum the OH stretching band shifted from 3500 to 3330 cm^{-1} and the peak was narrower. Moreover, the magnitude of the splitting observed for the sulfate anion in the region around 1000 cm^{-1} was significantly lower and reduced to a barely perceptible shoulder. Finally, a strong absorption band at 700 cm^{-1} appeared. The narrow absorption band of hydroxyl groups at 3330 cm^{-1} could be explained by considering the very high water content of sucralfate humid gel. The limited splitting of the band at 1000 cm^{-1} was also related to the presence of water in the structure, which might reduce the interaction between aluminum hydroxide and sulfate anion. Serna et al. (1977) described a similar interaction between sulfate anion and aluminum hydroxide. In the absence of water, a strong interaction was observed in the sulfate-containing aluminum hydroxide gel. This interaction became less strong when molecules of water were present in the same environment, since water was able to compete with sulfate anions for coordination with the Al atom. Based on this hypothesis, although sucralfate non-gel and sucralfate humid gel have identical chemical structure, the great difference in their water content may affect the interaction between sulfate anions and Al atoms. In particular, the interaction would become stronger, thus better detectable, in the case of sucralfate non-gel.

Further spectroscopic analysis was performed on the microwave dried sucralfate gels. After drying the sucralfate humid gel raw material, no significant difference was observed when comparing the IR spectra of sucralfate dried gels with that of sucralfate non-gel powder (data not shown). In fact, the magnitude of the splitting of the sulfate anion band was similar for both powdered samples, supporting the hypothesis of a stronger interaction of the sulfate anion with the positively charged aluminum under dry conditions. However, a shift of the hydroxyl group absorption band (stretching modes) from 3330 cm^{-1} to higher wavenumbers with the decrease of the water content was observed. To examine this shift better, the wavenumbers corresponding to the OH stretching bands were plotted against the water content of each dried gel sample. The graph is shown in Fig. 5. The gel samples having a water content lower than 42% (w/w) (i.e., containing only bound water) did not show significantly different wavenumbers for OH absorption band ($\approx$3450 cm^{-1}).

Furthermore, these values were not significantly different from the band relevant to sucralfate non-gel ($\approx$3470 cm^{-1}), whose water content was 11% (w/w) (see Fig. 5). When the free water increased, the wavenumber values quickly decreased to the minimum value of 3330 cm^{-1} seen for humid gel.

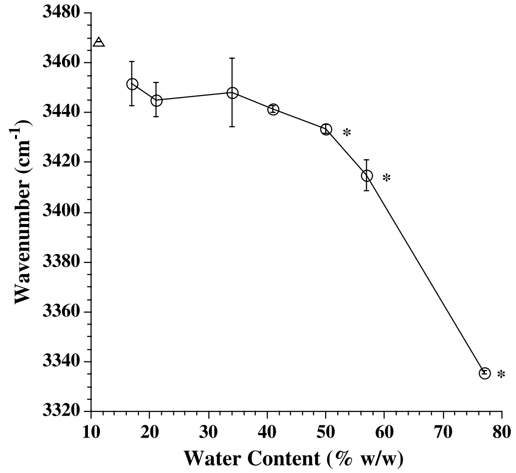

FIGURE 5 **Infrared OH Stretching Band Wavenumber as a Function of the Water Content of Sucralfate Gel Samples (○) (Euticals 07/99) and Sucralfate Non-Gel (△). Bars Represent the Standard Deviation of the Mean ($n=3$). The Asterisks Indicate Statistically Significant Difference from the Previous Value ($p<0.05$).**

Therefore, the positioning of the OH stretching band at higher wavenumbers seen for the sucralfate gel samples at the lowest water content reflected the decrease in the free water content. As previously described, the presence of free water determined the existence of a nonspecific coordination within sucralfate gel structure in moist conditions, which may explain this shift in the IR spectra.

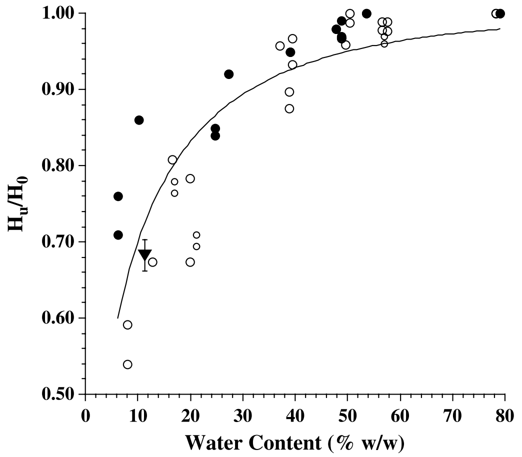

FIGURE 6 **Sedimentation Ratio vs. Water Content for Suspensions Made from Dried Gel Samples Obtained from Several Batches of Sucralfate Humid Gel Raw Material: Giulini 997930 (○); Giulini 01090312 (●); Euticals 07/99 (○); Weibull Curve Parameters: $\alpha=7.21\pm0.91$; $\beta=0.57\pm0.06$; $\chi^2=0.18$; $R^2=0.74$. The Point (▼) Indicates the Sedimentation Ratio of Sucralfate Non-gel Suspension (Mean ± Standard Deviation, n=3).**

Sedimentation of Sucralfate Suspensions

The sedimentation behavior was studied on water suspensions containing 20% (w/v) of sucralfate prepared from the microwave-dried powders obtained from all three batches of sucralfate humid gel raw material. This approach was motivated by the interest in evaluating the variability associated with three batches of the same raw material. Several samples of sucralfate dried gel were prepared having loss on drying values in the range between 79% and 6% (w/w). All suspensions were prepared under standardized mixing conditions.

It is known that sucralfate humid gel does not require the use of suspending agents for preparing a stable and elegant suspension (Caramella et al., 1989); in fact, the gel particles in water lead to structured sediment and the suspension exhibits self-suspending behavior. Thus, we considered the sedimentation of sucralfate dried gel suspensions as an indicator of the maintenance of the gel structure after drying. The settling of both sucralfate humid gel and sucralfate non-gel suspensions was chosen as references for the sedimentation behavior. In the case of the suspension prepared from sucralfate humid gel, practically no sedimentation was observed. Owing to particle–particle interactions, the dispersed phase produced a rigid structured suspension on resting that was reversed to fluid suspension by shaking. This behavior was attributed to the colloidal properties of the humid gel, explaining its peculiar thixotropic rheology. In contrast, the sedimentation of the suspension containing the non-gel powder was very fast, showing turbid supernatant and nonstructured sediment.

To evaluate the effect of drying on settling, the sedimentation ratio values of suspensions prepared from different sucralfate dried gels were plotted vs. the residual water content (Fig. 6). In order to describe the trend and dispersion of the results obtained, the Weibull equation was preferred among other more general models since the curve parameters have a clearly assigned meaning (Langenbucher, 1976). In its most convenient form the equation is written as

$$SR = 1 - \exp\left\{-\left(\frac{x}{\alpha}\right)^{\beta}\right\}$$

where x denotes the water content (% w/w) and SR the sedimentation ratio (H_u/H_0). In addition, α corresponds to the water content value at which the 63.2% of the sedimentation ratio is reached, and β is a curve shape parameter. The R^2 value, the χ^2 value (i.e., the sum of the squared error between the original data and the calculated curve fit), and the equation parameters of the fitting with their respective errors are reported in the Fig. 6 caption. The calculated curve fitted the experimental data quite well. The fitted line shows that the sucralfate dried gel suspensions are very stable when prepared from dried gel powders containing more than 42% (w/w) water ($H_u/H_0>0.9$). Afterwards, below 42% (w/w) the sedimentation ratio markedly decreases with the residual water content of the dried gels. At 42% (w/w) the sedimentation ratio estimated from the Weibull parameters was 0.93 (range 0.90–0.96). Therefore, we were able to assess that the elimination of free water in sucralfate humid gel slightly changed the sedimentation ratio of the dried gel powder suspensions; in contrast, the removal of bound water, obtained by prolonging the drying time, was responsible for a rapid decrease in suspension stability. The sedimentation ratio of the suspension made from sucralfate USP24, taken as a reference for the non-gel form, was close to that of the most dried gel samples (see Fig. 6).

In summary, the microwave drying partially affected the colloidal structure of sucralfate gel. The effect of drying on the disappearance of the gel characteristics was very intense when the bound water was removed. However, it has been shown that a mixture of sucralfate gel and a protective agent, such as mannitol, was able to maintain the gel structure during drying, even when the residual water was reduced below 42% (w/w) (Maggi et al., 2000).

Given the relevance of particle size to the sedimentation rate, the particle size distribution of representative sucralfate suspensions tested for sedimentation was checked by both laser diffraction and microscopic examination. In particular, microscopy was performed to detect particle agglomerates. The particle size distribution of sucralfate humid gel and sucralfate dried gels containing 49% and 10% (w/w) of water, respectively, are reproduced in Fig. 7, as well as the size distribution of sucralfate non-gel. The particle size distribution of gel samples showed an increased presence of large particles due to water reduction; the sample containing 10% (w/w) residual water exhibited a bimodal size distribution, more evident than the one presented by the sucralfate non-gel. The actual numbers of particle size distribution are reported in the figure caption.

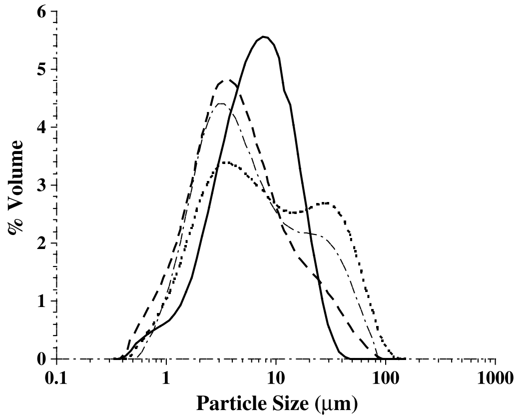

FIGURE 7 **Particle Size Distribution of Sucralfate Humid Gel (–·–·–·) ($d_{v,50}$=6.6 μm; $d_{v,10}$=2.0 μm; $d_{v,90}$=16.6 μm) (Giulini 01090312); Sucralfate Dried Gels Containing 49% (– – –) ($d_{v,50}$=4.2 μm; $d_{v,10}$=1.3 μm; $d_{v,90}$=19.3 μm) and 10% (w/w) Water (———) ($d_{v,50}$=7.2 μm; $d_{v,10}$=1.6 μm; $d_{v,90}$=41.8 μm), Respectively; Sucralfate Non-Gel Containing 11% (w/w) Water (·········) ($d_{v,50}$=5.1 μm; $d_{v,10}$=1.6 μm; $d_{v,90}$=30.9 μm).**

On microscopy, the suspensions presented a very high number of particles with a projection diameter lower than 1.0 μm. The presence of these particles might account for the self-suspending properties of sucralfate gel. Microscopic examination also confirmed the presence of large clusters of particles in the sucralfate dried gels with water content below 42% (w/w). Therefore, the drying process affected the gel form of sucralfate humid gel, also by modifying the particle size distribution through aggregate formation, an effect that could be related to the sedimentation behavior observed.

CONCLUSIONS

The capability of sucralfate gel to bind water presented a maximum value of 42% (w/w). Below this value, only bound water was present within the sucralfate gel molecule, whereas when the total water content was higher than 42% (w/w), free water was present in the sample.

Water plays a relevant role in determining the characteristics of sucralfate gel; in particular, the coordination of the water molecules by sucralfate and the interactions between sulfate anions and aluminum within sucralfate gel are dependent on the water content. FT-IR spectroscopic analysis illustrated the role of free water within the sucralfate gel structure: the OH band shift observed supported the hypothesis of the involvement of the water molecule within the sucralfate gel structure. The splitting of the sulfate anion band confirmed the existence in the humid gel of a nonspecific coordination between the positively charged aluminum and the sulfate anion.

The present study demonstrates that the microwave drying process largely affected the characteristics of sucralfate humid gel when the bound water was removed. This was shown by the reduction of the self-suspending capability and by the modification of particle size distribution of sucralfate suspensions. The water content of 42% (w/w) represents a threshold value for the stability of sucralfate gel suspensions: above 42% (w/w) of residual water the sedimentation ratio remained higher than 0.9, whereas below 42% (w/w), the ratio steeply decreased towards 0.68, i.e., the value of sedimentation ratio of sucralfate non-gel.

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