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Effect of Drying Methods on Retention of Moist Sucralfate Gel Properties

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ABSTRACT The aim of this work was to find a drying procedure for moist sucralfate gel capable of producing dried sucralfate gel that retains the original gel properties of bioadhesion, rheology, and micromeritics. Spray-drying and microwave-drying procedures were employed. Mannitol was used as a gel-protective substance during the drying processes. The spray drying of moist sucralfate gel gave rise to a powder whose water suspensions showed significantly reduced viscosity. The bioadhesion of spray-dried sucralfate gel was strongly reduced by drying. When mannitol was used as a gel protector, the spray-dried sucralfate in part maintained the original bioadhesion of moist sucralfate gel. The preparation of a dried sucralfate gel retaining the bioadhesion characteristics, avoiding the use of mannitol, was made possible using the microwave-drying procedure. The microwave-dried product possesses a granular morphology suitable for direct compression because it is a free flowing and strongly coherent granular powder.

KEYWORDS: Dried Sucralfate Gel, Spray Drying, Microwave, Bioadhesion.

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INTRODUCTION

Sucralfate, a basic aluminum salt of sucrose octasulphate, is a safe and effective drug for the treatment of gastroduodenal ulcers. After contact with hydrochloric acid, sucralfate gives rise to a sticky paste capable of coating and protecting gastric mucosa from pepsin and gastric juice insults [1-3]. Recent studies have demonstrated cytoprotection mechanisms of sucralfate, which include the stimulation of bicarbonate secretion, mucus production, and prostaglandin release [4]. Because the mechanism of action of sucralfate is based on the coating of ulcerated mucosa, it is of great importance for the drug to display a large, specific surface area. For this reason, the most useful dosage forms are suspensions, but many attempts to produce stable sucralfate suspensions have failed because the commonly used suspending agents are precipitated by sucralfate [5].

A new physical form of sucralfate, having the aspect of a moist solid containing more than 70% wt/wt of water, has been discovered [6]. The new form exhibited characteristics similar to colloidal clays and was named sucralfate gel [7]. Sucralfate gel possesses self-suspending properties and, therefore, the preparation of a stable and innovative sucralfate suspension without any suspending agent was made possible. Numerous clinical trials discovered that the suspension of sucralfate gel strongly adhered to gastric mucosa and had superior therapeutic efficacy compared to the previously existing sucralfate suspensions [8,9]. In fact, using sucralfate gel suspension, the daily dosage of sucralfate has been halved.

Low particle size, rheological behavior, and strong bioadhesion characterize the gel form of sucralfate. However, sucralfate gel raw material has to be stored as a moist solid because most drying procedures, such as oven drying or freeze drying, give rise to dried powders no longer exhibiting the self-suspending and bioadhesion properties [10]. For this reason, until now sucralfate gel has been exclusively administered in a liquid dosage form (eg, suspension). A dry form of sucralfate gel that retains the properties of moist gel is still lacking. A dry form would allow the manufacturing of solid dosage forms, with evident advantages for the microbial stability of the product.

Therefore, the aim of this work was to discover a drying procedure for producing dried sucralfate gel that retains the gel properties and bioadhesion of moist sucralfate gel.

Spray-drying and microwave-drying processes were employed, and mannitol was used as gel protector. The effects of drying processes on sucralfate gel characteristics were studied by resuspending the dried sucralfate gel in water and comparing the physical, chemical, and bioadhesion properties before and after drying.

MATERIALS AND METHODS

Suspensions Preparation

Sucralfate moist gel (Batch 23/95, Euticals, Lodi, Italy), sucralfate amorphous powder (Batch 11648139, Merck, Darmstadt, Germany), and mannitol (USP 24) were used to prepare the following aqueous suspensions: sucralfate gel 20% wt/vol; sucralfate gel 20% wt/vol containing mannitol in ratio 1:1 by weight to sucralfate; and sucralfate amorphous powder 20% wt/vol. All suspensions were homogenized for 15 minutes using an Ultra Turrax homogenizer (Janke & Kunkle GMBG & Company, Staufen, Germany) equipped with the head ATX2 rotating at 500 rpm.

Drying Procedures

The drying conditions were selected in order to have residual water content in the range between 10% and 15%.

Spray drying of sucralfate gel was performed with a mini spray dryer (Buchi model 191, Flawil, Switzerland) in the following conditions: inlet temperature 130°C; outlet temperature 70°C; pump speed 6.5 mL/min; and nozzle diameter 1 mm. The feeding materials were the above-reported aqueous suspensions diluted 1:1 by volume with deionized water and homogenized as before for 5 minutes.

The microwave drying process was performed with a microwave oven (Perfecto, De Longhi, Italy). Two hundred grams of suspension was layered at 0.3 g/cm^2 on the circular dish of the oven. Sucralfate gel suspension with mannitol was diluted 1:0.5 by volume with deionized water and homogenized, as before, for 5 minutes. Microwave power of 800 W (on-off ratio: 24 seconds "on," 6 seconds "off") was applied for a drying time of 20 minutes. The microwave-dried sucralfate gel consisted of large lumps of granular material that was calibrated using an oscillating granulator with 1 mm net (Erweka AR 400, Heusenstamm, Germany).

Starting from the same raw material, 3 batches of both spray-dried and microwave-dried sucralfate gel were prepared and the powders were stored in tight glass containers.

Characterization of Dried Products

The water content of powders was determined using the Karl Fisher method (Trimetric Method 1a, USP24).

Particle size distributions of sucralfate amorphous powder and spray-dried powder were determined by laser light diffraction (Mastersizer X, Ver. 1.2, Malvern, United Kingdom) after dispersion in chloroform. The measurements were taken with a 45 mm lens, detecting particles from 0.05 to 80 µm. Particle size of microwave-dried products was determined by sieve analysis.

Bulk and tapped densities were measured on 100 g of powder using a 250 mL glass cylinder. Carr's Flowability Index (CI) [11] was calculated according to the following relationship:

$$CI = ?_t - ?_b / ?_t \times 100,$$

where $?_t$ is the tapped density and $?_b$ is the bulk density.

Characterization of Suspensions

Dried sucralfate gel powders were suspended in water and homogenized in the same conditions previously described to obtain suspensions containing 20% wt/vol of sucralfate. To allow the complete hydration of the dried gel powders, the suspensions were prepared 24 hours before measuring.

The particle volume diameter of these suspensions was measured by laser light diffraction in the same conditions as described before; d_v50 (50% of the particle population having a volume diameter equal or below the value) and d_v90 were determined.

The rheology of suspensions was evaluated at room temperature determining flow curves of shear stress (Pa) versus shear rate (s^{-1}). Both up and down curves were recorded using a Carrimed CSL 100 Rheometer (Carri-Med Ltd, Dorking, Surrey, United Kingdom) equipped with 6 cm diameter flat plates (Serial No. 71127)(Carri-Med Ltd, Dorking, Surrey, UK). The "control shear stress" program of the rheometer was considered as the most suitable for yield stress value determination because the material was not forced to move. A maximum stress value of 100 Pa, divided in 200 equal steps in 1 minute, was programmed. A distance between the parallel plates of 100 µm was selected to accommodate 1 mL of suspension in the gap. The equilibration time before each measurement was 3 minutes. No evaporation of the sample was observed during the experimentation time. The limiting viscosity (up-curve slope in the linear tract) and the static yield value (y-intercept of up curve) were calculated.

The bioadhesion properties of sucralfate gel suspensions, before and after drying, were tested with the apparatus shown in **Figure 1**, using samples of pig gastric mucosa obtained from a local slaughter house. The mucosa, collected immediately after the animal sacrifice, was cut in appropriate pieces (4 x 4 cm) and washed with saline solution. The sample was clamped between a glass slide and a rectangular Plexiglas® frame (7.5 x 11.5 cm) leaving a squared window with a mucosa-exposed area of 6.76 cm^2 (2.6 x 2.6 cm). The device with the immobilized mucosa was washed for 5 minutes in distilled water at 37° C, using a tablet disintegration apparatus (Erweka ZT2, Heusenstamm, Germany) that allowed the sample to be reciprocating vertically immersed in the bath 32 times per minute (traveling distance 5 cm). After washing, the device was laid horizontally in a moisture-saturated environment and the exposed mucosa was carefully covered with 100 mg of sucralfate, as 20% wt/vol suspension. The sucralfate-coated mucosa in the device was left to equilibrate for 20 minutes.

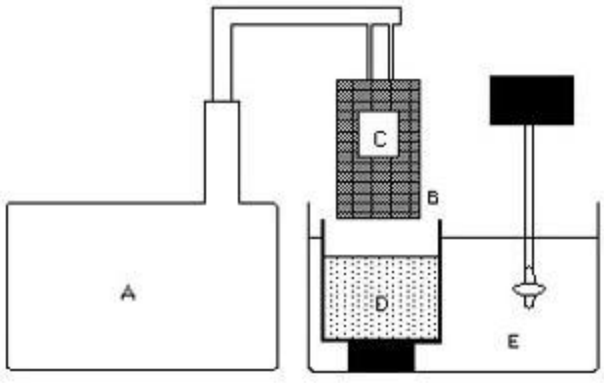

Figure 1. Apparatus used for the bioadhesion experiments: (a) tablet disintegration apparatus; (b) glass support; (c) pig gastric mucosa; (d) rinsing solvent; (e) 37°C bath.

By means of a video camera (CCD Panasonic F 15, Milan, Italy), a picture of the coated mucosa was registered at time zero. Then, the device was mounted vertically on the disintegration apparatus shaft and rinsed according to the previously described procedure. At regular time intervals, the device was withdrawn and a picture was taken with the video camera. All pictures were analyzed with an image analysis program (Image NIH 1.60, Bethesda, MD) to determine the area of mucosa that remained coated during the rinsing operation. The portions of mucosa still covered by sucralfate, at increasing time intervals during rinsing, were electronically selected for area measurement. The ratio between the values measured during rinsing and the area at time 0 (6.76 cm^2) allowed the determination of the percentage of mucosa still covered by sucralfate. This value was taken as a measure of the bioadhesiveness of the preparation. The measures were repeated 3 times.

The acid neutralization equivalent of sucralfate preparations (mean ± SEM) was determined according to USP 24. Three assays were performed.

RESULTS AND DISCUSSION

Micromeritics of Dried Sucralfate Gel

The micromeritics of sucralfate amorphous powder and dried sucralfate gel powders was checked. Sucralfate amorphous powder had a mean geometric diameter of 130.9 µm and a geometric standard deviation of 1.7. For the spray-dried product, this value was 8.2 µm, with a geometric standard deviation of 1.9. The microwave-dried product, which had a granular aspect, showed a size (d_g = 663 µm; ? $_g$ = 1.6) dependent on the net used for calibrating the lumps of product recovered after drying.

Packing properties of powders were also measured. The results, expressed as bulk density, tapped density, and Carr's Index are reproduced in **Table 1**. The microwave-dried products show favorable packing and flow properties, as indicated by the bulk density and Carr's Index values. Using microwave-dried sucralfate gel containing mannitol, tablets were easy manufactured by direct compression.

Table 1. Packing Properties of Sucralfate Products Used (mean ±SD)

	Bulk density(g/mL)	Tapped density(g/mL)	Carr's Index
Sucralfate Powder	0.790 ± 0.003	0.875 ± 0.010	9.7
Spray-dried Sucralfate Gel	0.424 ± 0.010	0.628 ± 0.003	32.8
Microwave-dried Sucralfate Gel	0.787 ± 0.007	0.864 ± 0.002	8.9
Spray-dried Sucralfate Gel:Mannitol, 1:1	0.402 ± 0.010	0.653 ± 0.013	38.4
Microwave-dried Sucralfate Gel:Mannitol, 1:1	0.756 ± 0.013	0.832 ± 0.001	9.1

One of the peculiar properties of moist sucralfate gel characterizing the colloidal behavior is the particle size of its water suspension; therefore, particle size distribution of the dried powders after dispersion in water was also measured. To avoid differences resulting from the sample preparation, the technique employed for dispersing the powder in water was standardized, and the suspensions were stored for 24 hours before size determination to guarantee complete hydration.

Particle size distributions of spray-dried and microwave-dried sucralfate gels, dispersed in water, were compared with sucralfate gel suspension before drying (**Table 2**). As a reference, a water dispersion of sucralfate amorphous powder was also checked. The mean size of sucralfate amorphous powder dispersed in water was 1 order of magnitude lower than the previously mentioned value obtained in organic solvent, meaning that sucralfate amorphous powder was probably composed of agglomerated particles. Sucralfate gel before drying possessed median volume diameter of 8.4 microns, and 90% of the particle population was smaller than 31.2 microns.

Table 2. Volume Diameter (µm) of Sucralfate Water Suspensions before Drying and Prepared with Dried Products

	Before drying		Spray dried		Microwave dried	
	d_v50	d_v90	d_v50	d_v90	d_v50	d_v90
Sucralfate Powder	10.3	43.8	-	-	-	-
Sucralfate Gel	8.4	31.2	6.4	16.6	6.9	30.8
Sucralfate Gel:Mannitol, 1:1	6.7	20.2	6.1	16.5	5.5	22.6

Neither of the drying procedures increased the size of the rehydrated sucralfate gel particles. The microwave-dried sucralfate gel dispersion showed size distribution similar to spray dried, despite the granular form. Visual inspection of the microwave-dried lumps immersed in water revealed that the material was porous (evident air bubbling) and, on contact with water, underwent rapid spontaneous disintegration and dispersion. This characteristic of microwave-dried gel can be considered advantageous for solid dosage form performance. The mean particle size of the sucralfate gel suspensions containing mannitol was slightly shifted toward smaller values (see **Table 2**), indicating that the presence of mannitol facilitated particle dispersion.

Rheology of Suspensions

The colloidal behavior of sucralfate gel is supported not only by the small particle size, but also by its peculiar rheology. In the development of dried sucralfate gel, it was considered essential for the dried product, after dispersion in water, to show the same rheological behavior of sucralfate gel suspension before drying. Then, the rheology of sucralfate gel suspension 20% wt/vol before drying was compared to the rheology of suspensions prepared with dried products. It was already shown that sucralfate gel suspensions present a yield stress point and a shear-thinning behavior that assure the rigidity of the system and the necessary fluidity on shaking. Both properties are well-known requirements for an efficient pharmaceutical use of suspension [12].

Figure 2 shows an example of a typical rheogram of sucralfate gel suspension before drying, compared to microwave-dried and spray-dried sucralfate gel suspensions. Sucralfate gel suspension before drying is characterized by a high-yield stress value, indicating flow resistance at low stresses like those involved in particle sedimentation, and low viscosity at high stresses. This supports the physical stability of the suspension: thick at rest, fluid after shaking. The thixotropy area and the presence of a characteristic spur, previously shown in rheograms of sucralfate gel [13], was less evident here because of the short time of sample equilibration in the rheometer body. The typical rheological parameters measured on the sucralfate gel suspensions prepared (ie, static yield value and limiting viscosity) are reported in **Table 3.**

Sucralfate gel suspension before drying exhibited an important static yield value (ie, the y-axis intercept extrapolated from the up-flow curve), which was indicative of strong interactions developed between particles at rest. Despite the high yield value, the viscosity under shear (ie, the limiting viscosity) was very low, indicating the fluidity of the suspension after the yield value. Therefore, the suspension coagulated on standing, making the static yield stress the important parameter for its stability because the limiting viscosity was too low to hinder the sedimentation of particles.

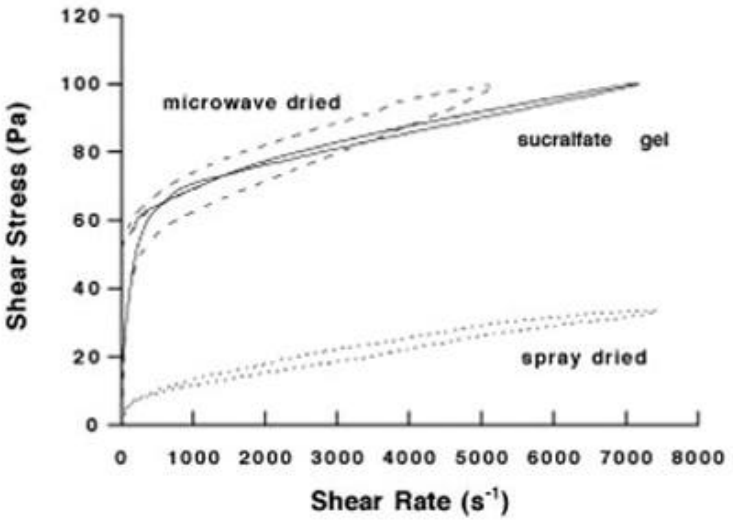

Figure 2. Rheogram of suspensions prepared with sucralfate gel, spray-dried sucralfate gel, and microwave-dried sucralfate gel.

Table 3. Rheological Parameters of Sucralfate Gel Suspensions before and after Drying (mean ± SD; n = 3)

		Limiting viscosity (mPa*s)	Static yield value(Pa)
Sucralfate Gel Suspensions	Before drying	4.1 ± 0.1	71.2 ± 0.7
	spray dried*	3.1 ± 0.1	13.0 ± 0.1
	microwave dried*	5.7 ± 0.4	61.1 ± 16.3
Sucralfate Gel: Mannitol 1:1 suspensions	before drying	60.5 ± 9.5	152.3 ± 1.8
	spray dried*	13.0 ± 0.4	103.3 ± 1.8
	microwave dried*	11.3 ± 2.5	59.1 ± 1.3

* Mean values obtained from different batches of dried sucralfate gel.

The suspension prepared with spray-dried sucralfate gel showed a strong reduction of yield value. The suspension appeared more fluid at rest also on visual inspection and the limiting viscosity was slightly reduced. An important settling of particles, not present before drying, was observed with this suspension. The suspension prepared with the microwave-dried product, however, did not lose the original rheological characteristics of sucralfate gel. In fact, this

suspension showed a slight increase of limiting viscosity, but not significantly different yield value.

In conclusion, the drying procedure of sucralfate gel suspension determined a strong reduction of its typical plastic behavior when the spray-drying technique was used. Employing the microwave-drying technique, the dried sucralfate gel suspended in water maintained the original rheology of sucralfate gel.

Because the spray-drying technique modified the intrinsic ability of sucralfate gel to form a stable suspension in water, mannitol was added as a gel protector for drying. The addition of mannitol in a ratio of 1:1 created a substantial change in the rheological parameters of sucralfate gel suspension before drying (**Table 3**). This change was attributed to mannitol-undissolved particles, since the polyalcohol was present in a high amount. The dilution with water performed on suspension before drying eliminated this effect on rheology parameters. In fact, the dried products dispersed in water showed rheological parameters lower than the corresponding suspension before drying. Comparing the 2 drying procedures, it appears that both dried powder suspensions showed a similar limiting viscosity, but different yield values, which was higher for spray-dried sucralfate gel.

Bioadhesion to Pig Gastric Mucosa

As previously indicated, the higher therapeutic activity of sucralfate gel was attributed to its rheological properties, which determined a strong bioadhesiveness toward gastric mucosa. For this reason, experiments for measuring the bioadhesion to pig gastric mucosa using suspensions of sucralfate gel before and after drying, in the presence or absence of mannitol, were conducted. As a reference, a suspension of sucralfate amorphous powder was tested (**Figure 3**).

Figure 3a shows the percentage of mucosa covered by sucralfate and its persistence during washing. Four different suspensions were tested: sucralfate gel, spray-dried sucralfate gel, microwave-dried sucralfate gel, and sucralfate amorphous powder suspension.

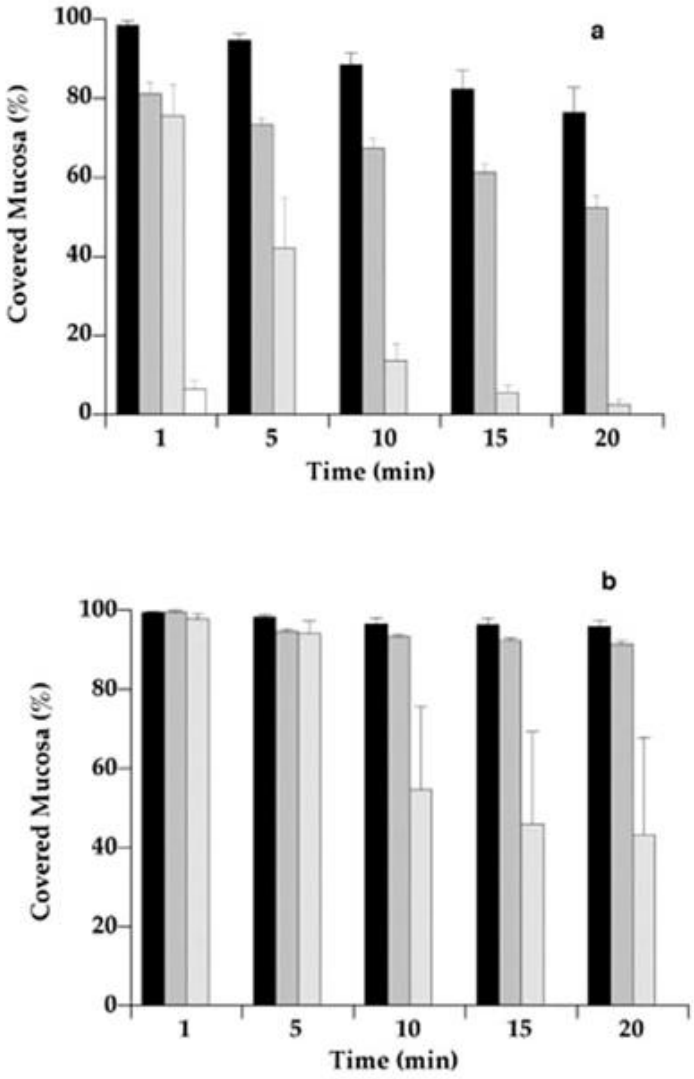

Figure 3. Percentage of pig gastric mucosa covered with sucralfate suspension vs washing time (mean value, SEM). Panel a: sucralfate suspensions: before drying (■), microwave dried (■), spray dried (■), sucralfate powder (□); Panel b: sucralfate gel:mannitol 1:1 suspensions: before drying (■), microwave dried (■), spray dried (■).

Sucralfate gel suspension proved to be very adhesive to pig gastric mucosa. In fact, more than 80% of the mucosa was still covered by the preparation after 20 minutes of washing. The bioadhesion of sucralfate amorphous powder was weak, however; the product was completely rinsed away after only 2 minutes. The behavior of the dried sucralfate gels was significantly different. After 20 minutes, more than 50% of the mucosa was still covered by the microwave-dried sucralfate gel, but only 2% was covered by the spray-dried sucralfate gel. The bioadhesion of the microwave-dried product was lower than the value

obtained with sucralfate gel before drying, but it remained very high. **Figure 4** shows the samples of pig gastric mucosa coated with sucralfate gel and sucralfate amorphous powder preparations taken 10 minutes after the beginning of rinsing. The bioadhesiveness of the gel, in particular before drying (**Figure 4a**) and after microwave drying (Figure 4b), was clearly supported by the figure. The very low bioadhesion of the spray-dried (**Figure 4c**) and amorphous powder (**Figure 4d**) suspensions is also shown.

The presence of mannitol, as a gel protector for the drying procedure, proved to be beneficial for the bioadhesion of the dried sucralfate gel (**Figure 3b**). In fact, the bioadhesion of dried gels improved when mannitol was added. In particular, the behavior of microwave-dried gel was not significantly different from sucralfate gel before drying. The spray-dried sucralfate gel with mannitol possessed a lower bioadhesion than the microwave-dried gel, but its bioadhesion improved compared to the spray-dried gel without mannitol.

Acid Neutralization Equivalent

The USP 24 monograph of sucralfate reports a test for measuring the acid neutralization equivalent of the product. This test checks the reactivity of sucralfate with hydrochloric acid; it is significant for the prepared dried products because it is related to their reactivity. The limit of the USP is that 1 g of sucralfate must neutralize at least 12 mEq of acid in 1 hour.

The effect of drying procedures on this parameter was verified for all the preparations. The value exhibited by sucralfate gel before drying was 21.2 ± 0.1 mEq/g. This value was reduced to 17.7 ± 0.1 mEq/g for the spray-dried sucralfate gel and to 18.2 ± 0.2 for the microwave-dried gel. The neutralization equivalent was not changed by the addition of mannitol before drying and remained not significantly different from the value of sucralfate gel dried in the absence of mannitol. However, the value of acid neutralization capacity of all gel forms was significantly higher than the one shown by the amorphous powder, which was 15.1 ± 0.3 mEq/g.

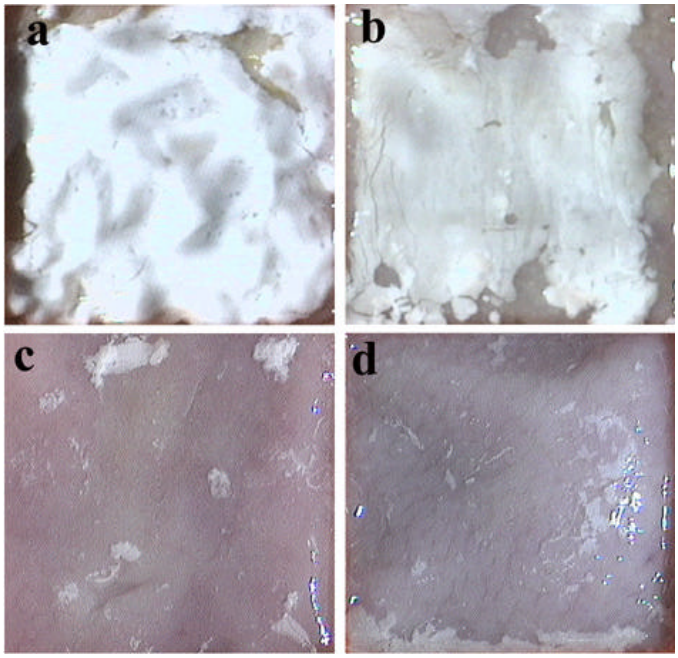

Figure 4. Pig gastric mucosa covered by sucralfate suspensions after 10 minutes of washing: (a) sucralfate gel suspension, (b) microwave-dried sucralfate gel suspension, (c) spray-dried sucralfate gel suspension, (d) sucralfate amorphous powder. Surface area shown corresponds to 6.76 cm

CONCLUSIONS

The results obtained in this study allow us to conclude that microwave drying of sucralfate gel gives rise to a powder retaining the typical gel characteristics. The use of mannitol as a gel protector agent during the microwave drying further improves the capability of the dried powder to restore the gel form of sucralfate.

With the spray-drying technique typical sucralfate gel properties disappear, in particular bioadhesion. In this case the maintenance of satisfactory bioadhesion can be obtained only by using mannitol as a gel protector.

The micromeritics of microwave-dried sucralfate gel facilitates the preparation of solid dosage forms. In fact, the dried product possesses a granular morphology suitable for direct compression because it is a free-flowing and strongly coherent granular powder. In contrast, the powder obtained by spray drying is dustier and requires a granulation process to be transformed into a solid suitable for tabletting.

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