Drug Development and Industrial Pharmacy, 22(5), 393-400 (1996)

Vitamin C Spray Drying: Study of the Thermal Constraint

T. F. Moura,[1] D. Gaudy,[2] M. Jacob,[2] A. Terol,[3]
B. Pauvert,[3] and A. Chauvet,[3]

[1]*Laboratorio de Tecnologia Farmacêutica, Universidade Federal da Paraiba Joao Pessoa, Paraiba, Brazil 58.053-010*
[2]*Laboratoire de Pharmacie Galénique, Pharmacotechnie et Biopharmacie, Université de Montpellier I, 34.060 Montpellier Cedex 01, France*
[3]*Laboratoire de Chimie Générale et Minérale, Université de Montpellier I, 34.060 Montpellier Cedex 01, France*

ABSTRACT

Temperature variation in the spray drying method has no effect on the ascorbic acid molecule. No chemical interaction between the colloidal silica and the ascorbic acid could be determined, but a physicochemical interaction "absorption" was determined. Colloidal silica improved the final yield of spray drying in proportion to its concentration. No polymorphic forms could be determined in the spray-dried ascorbic acid. Drug release from the ascorbic acid spray dried was found to be dependent on the Aerosil content: highest release rates were obtained with Aerosil.

INTRODUCTION

Spray drying is most commonly used in the chemical (plastics, pesticides, ceramics, fertilizers, pigments), food (powdered milk) and pharmaceutical industries (plant extracts, raw materials, excipients) (1-5). The aim of this technique is to obtain a dry product, more concentrated and easier to conserve or to work than extract solutions (6,7).

Plant extract solutions are thermolabile; therefore, this technique is less destructive than other concentration processes and drying by heat because the contact between the plant extract and the heat source is very brief (less than 1 sec) (5,8). It is reasonable to assume that an almost instantaneous drying of the product will avoid a maximum of hydrolysis, oxidation, and decomposition phenomena.

The decomposition of ascorbic acid during various process (fruit juice treatment, sterilization of injectable preparations) depends on two essential factors, pH and temperature (9). In our work, ascorbic acid (AA) was chosen because of its instability in aqueous solutions and to heat. Our objective was to ascertain the influence of temperature and the role of one adjuvant (Aerosil 200) of interest in spray drying (10) on AA stability during the drying process.

EXPERIMENTAL

Reagents and Equipment

Reagents were: ascorbic acid (Prolabo), dehydroascorbic acid (Aldrich), hydrochloric acid 37% RPE (Carlo Erba), colloidal silica (Aerosil 200, Degussa), anhydrous potassium bromide (Rhone-Poulenc), deuterated water (D_2O), and an aqueous solution of HCl at pH 3.

Equipment used: differential scanning calorimeter (Perkin-Elmer DSC, 4/TADS system); spectrophotometer 1 15 UV (Perking-Elmer) double beam; MSD BUCHI 190 spray dryer; infrared spectrometer (Perkin-Elmer 983G); proton nuclear magnetic resonance (BRUCKER) 250 MHz; x-ray diffraction spectrometer (SIGMA 80) equipped with a horizontal CGR goniometer with copper anticathode (Ka = 1.5404Å); pH meter APH AQUADATA 1000; dissolution apparatus ERWEKA DT6R; and polarized light optical microscope NIKON (Type 104) "Optiphot."

Method

The spray-dried materials were prepared at different concentrations of ascorbic acid (0, 2.5, 5.0, 7.5, and 10 g) and Aerosil 200 (10, 7.5, 5.0, 2.5, and 0 g) in 100 ml of the aqueous solution of HCl at pH 3, and at different inlet temperatures (140°, 150°, and 160°C).

Analysis of the spray dried materials consisted of evaluation of AA by ultraviolet (UV) spectrophotometry and determination of microscopic and physicochemical characteristics by differential scanning calorimetry (DSC), x-ray diffraction, H^+ NMR (nuclear magnetic resonance), and infrared (IR) spectrometry.

Samples, 100 mg, of each spray-dried material were transferred into a 100-ml volumetric flask and the volume completed with methanol (solution A). One milliliter of solution A was transferred into a 100-ml volumetric flask and the volume completed with the water solution of HCl at pH 3. Determination of the ascorbic acid concentration (n = 4) was carried out at the ascorbic acid specific wavelength (244 nm) at pH 3. Under these conditions, interference from dehydroascorbic acid is negligible. This acid in the same concentration of vitamin C does not contribute more than 3% to the optical density (Fig. 1).

The microscopic and physicochemical characteristics were determined as follows:

- Microscopic study of the spray-dried and the physical mixtures having vitamin C and Aerosil 200 at different concentrations was done on dry mounts under polarized light and photographed (ampl. × 500).
- Differential scanning calorimetry: assay samples of 2–3 mg and a starting temperature of 30°C were used. Measurements were made at 20°C min^{-1} under nitrogen stream using indium as a thermometric reference.
- X-ray study: the diagrams are realized at a speed of 15° θ h^{-1}; measurements were made between 2.3° θ and 20° θ (Philips generator, 40 kV, 20 mA).

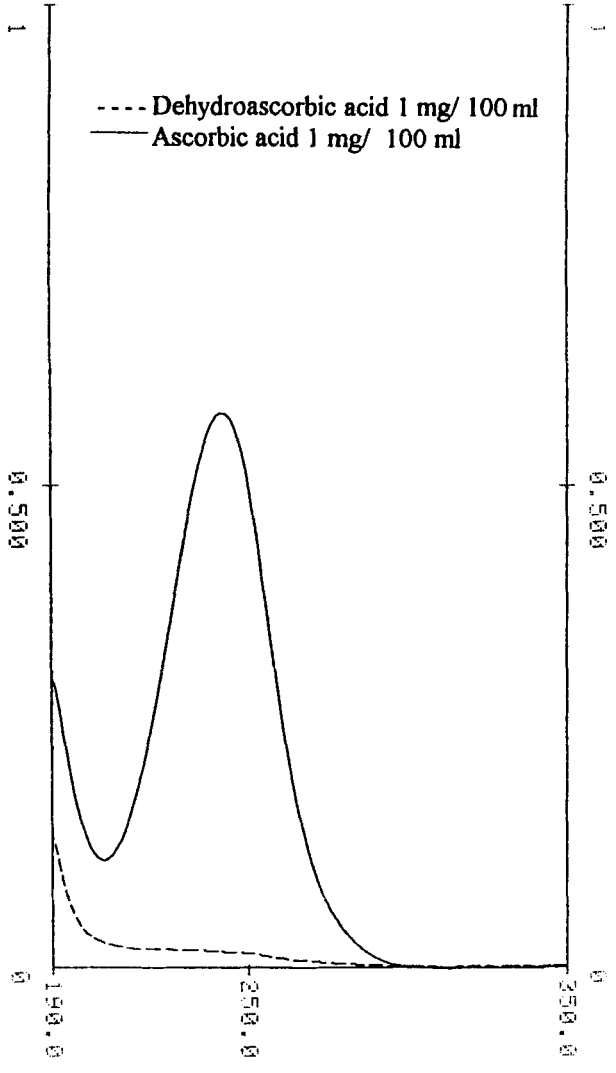

Figure 1. Dehydrascorbic acid influence on the ascorbic acid dosage determined by spectrophotometry

- H^+ NMR spectra were recorded in an aqueous deuterated solution (peak reference at 4.8 ppm).
- IR spectra were recorded at 3% concentration using a KBr disk.

Drug release: dissolution studies were carried out on the ascorbic acid spray dried at different concentrations (50, 75, and 100% w/w). The volume of the dissolution medium was 500 ml and stirring rate was 50 rpm. The method proposed by Gaudy et al. (11) was used at constant pH (= 3).

The influence of Aerosil concentration influence on the release of ascorbic acid from spray dried material was studied by analysis of variance and the Newman-Keuls test.

RESULTS AND DISCUSSION

Examination of Table 1 shows that irrespective of drying temperature, the best spray drying yields (near 90%) are obtained in the presence of 75% Aerosil. Quantitative analysis of the spray-dried material does not show any difference in ascorbic acid content, indicating that the temperature has no effect on this molecule, under the conditions used (Table 1).

From the studies using the polarized light microscope, it has found that:

- Vitamin C before and after spray drying or as physical mixture with Aerosil 200, is in the form of crystalline particles that diffract polarized light [Fig. 2(a)].
- Aerosil 200, before and after spray drying and in all physical mixtures, presents as an amorphous structure of silica particles.
- In all spray-dried materials having the adjuvant, only amorphous silica particles measuring between 20 and 100 μm were observed. The absence of vitamin C crystals suggests that the AA was absorbed by Aerosil during the spray-drying process [Fig. 2(b)].

These observations are in agreement with those obtained by electron microscopic analysis (12). Furthermore, UV spectra of all spray-dried samples are exactly the same as the AA standard. The absence of any displacement shows that there is no change in this molecule.

For the three different spray drying temperatures studied, the temperature increase has no influence on the quantity or yield of the spray-dried product. For this reason the structural study was effected only on those spray-dried groups prepared using an inlet temperature of 140°C.

The IR (Fig. 3) and H^+ NMR (Fig. 4) spectra from all spray dried samples were exactly the same as the standard vitamin C (13,14).

X-ray diffraction diagrams reveal that:

- Aerosil 200 before and after spray drying is completely amorphous and does not show diffraction.

Table 1

Spray Drying Conditions, Characteristics, and Yield of Samples

Spray-Dried Sample	θE (°C)	θS (°C)	ΔT (°C)	Aerosil (g/100 ml)	Ascorbic Acid (g/100 ml)	Flow Rate (ml/hr)	Mass Yield (g)	Percentage of Yield (%)	Ascorbic Acid (%)	Appearance[a]
10.0a	140	94	46	0	10	171.4	5.10	51.0	99.2	*
7.5a	140	95	45	2.5	7.5	166.7	7.16	71.6	99.1	**
5.0a	140	93	47	5.0	5.0	181.8	7.89	78.9	99.6	**
2.5a	140	94	46	7.5	2.5	171.4	8.80	88.0	99.4	**
10.0b	150	101	49	0	10	176.5	5.30	53.0	99.7	*
7.5b	150	103	47	2.5	7.5	162.2	7.45	74.5	99.3	**
5.0b	150	99	51	5.0	5.0	171.4	7.80	78.0	99.6	**
2.5b	150	101	49	7.5	2.5	181.8	9.00	90.0	99.5	**
10.0c	160	112	48	0	10	166.7	5.40	54.0	99.2	*
7.5c	160	109	51	2.5	7.5	176.5	7.31	73.1	99.4	**
5.0c	160	110	50	5.0	5.0	171.4	7.96	79.6	99.3	**
2.5c	160	113	47	7.5	2.5	176.5	8.90	89.0	99.5	**
0	160	110	50	10	0	175.8	6.30	63.0	0	**

[a].*Fine powder; **Very fine powder.

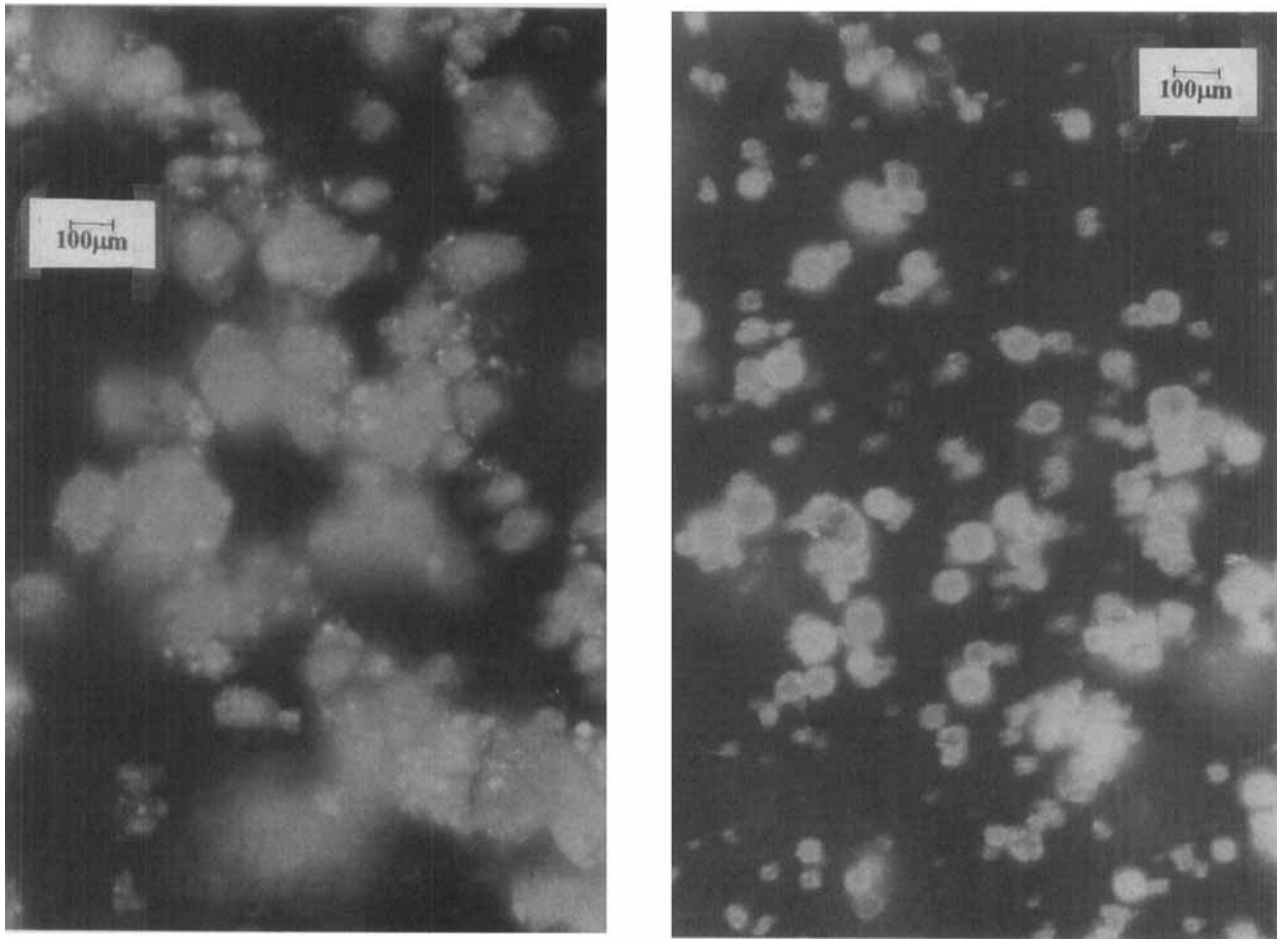

Figure 2. (a) Ascorbic acid (25%) and Aerosil 200 (75%) physical mixture; photography (×500). (b) Spray-dried sample 2.5a; photography (×500).

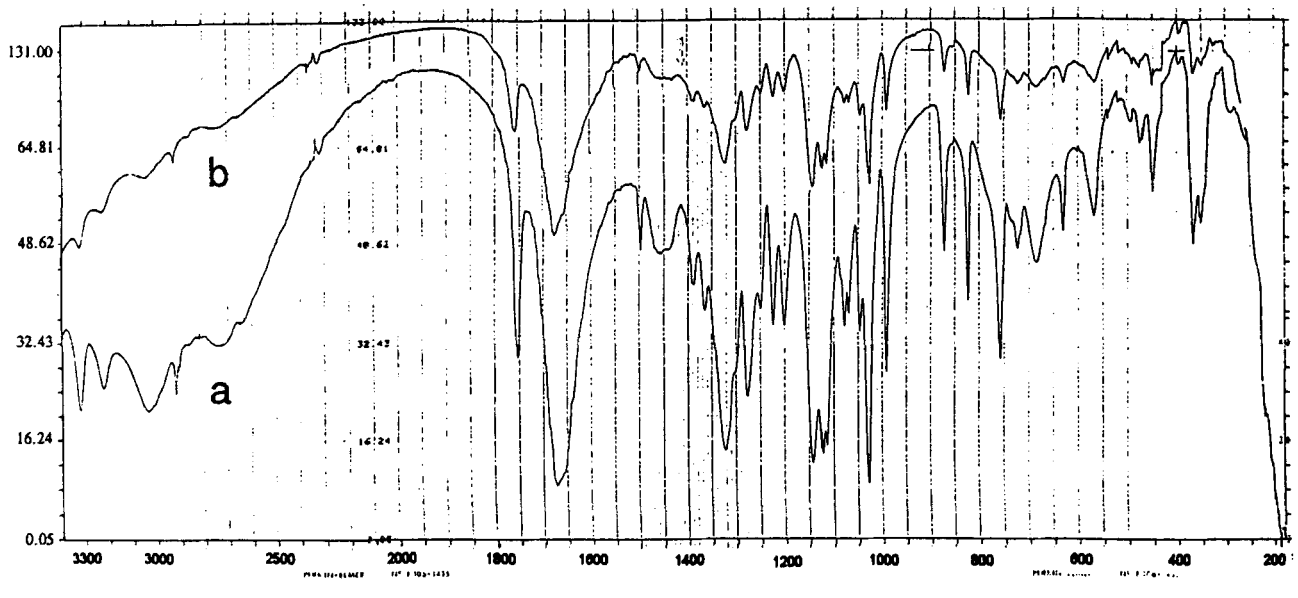

Figure 3. Infrared spectra: ascorbic acid raw material (a) and spray-dried sample 5.0a (b).

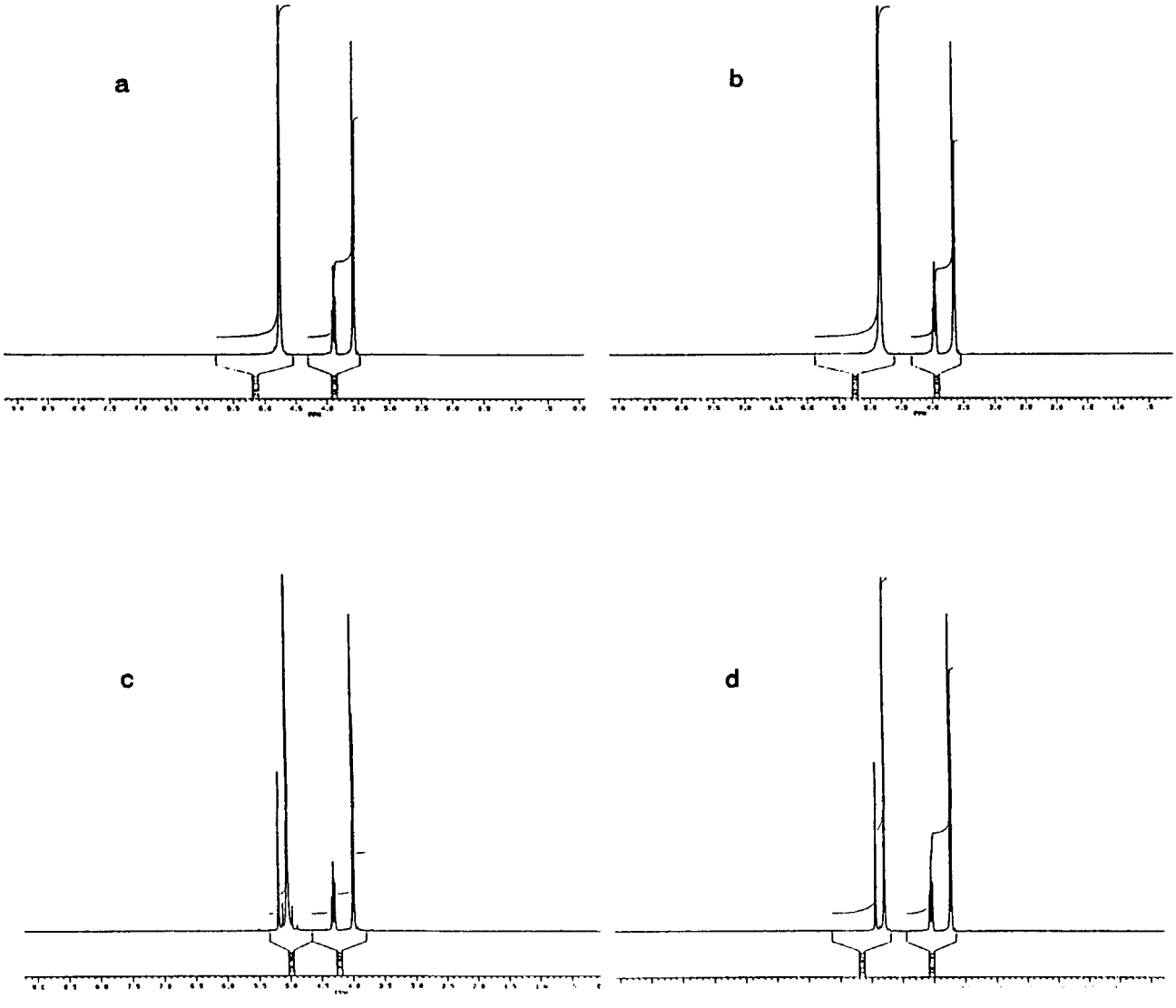

Figure 4. H^+ NMR spectra: ascorbic acid raw material (a), spray-dried samples 10.0a (b), 5.0a (c), and 7.5a (d).

- The diffraction profiles of all spray-dried products containing vitamin C are similar (Table 2), showing that there is no structural change in this molecule under the action of the thermic shocks generated by the spray-drying process (Fig. 5).

Moreover, analysis of Fig. 6 shows:

- There is no difference in the thermogram of the standard vitamin C before and after spray drying, with a melting point and an enthalpy in both cases of 191.8°C and 243.46 $J \cdot g^{-1}$, respectively.
- The thermogram of Aerosil 200 before spray drying does not show any peaks. After spray drying, however, there is a peak showing that water starts to leave at 40.7°C, the small energy (16.85 $J \cdot g^{-1}$) leads us to suppose that it corresponds to free water.

With regard to the spray-dried ascorbic acid, the thermogram (Fig. 7) shows a normal reduction of the melting endotherm. This reduction is proportional to the amount of Aerosil present.

Considering the results, it is clear that the spray-drying process does not impart any structural change to the ascorbic acid, it produces no polymorphism, and there is no chemical interaction between the acid and the Aer-

Table 2

Values of Diffraction Angles (θ), Reticular Distances (Å), and the Intensity Ratios (I/I_0) of the Different Spray-Dried Products Containing Vitamin C

(θ) (deg)	*d* (obs) (Å)	I/I_0
5.19	8.5149	16.2
7.00	6.3203	10.3
7.85	5.6682	7.0
7.98	5.5830	6.7
8.69	5.0980	25.9
9.90	4.4800	76.2
10.50	4.2267	10.8
11.70	3.7983	9.5
12.60	3.5309	42.2
13.35	3.3358	11.9
13.55	3.2875	10.0
14.00	3.1838	100.0
14.98	2.9799	72.9
16.60	2.6961	5.4
17.31	2.5887	16.7
17.71	2.5320	34.3
18.75	2.3962	14.3

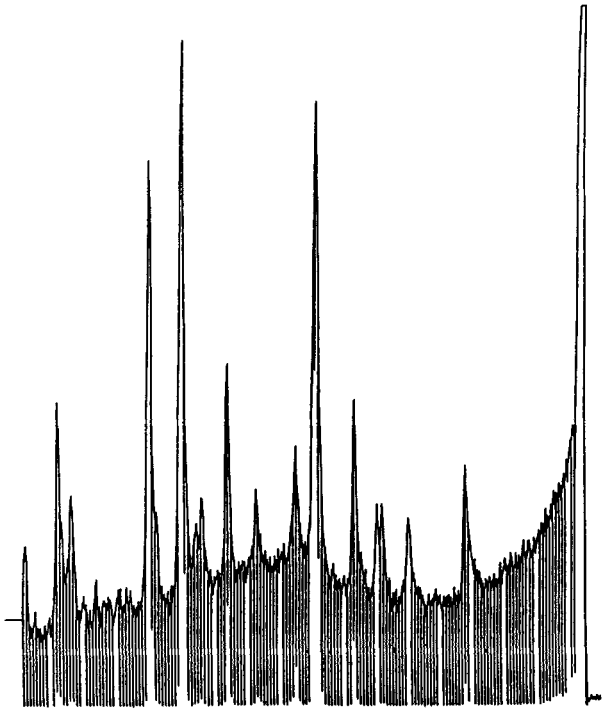

Figure 5. Spray-dried sample 5.0a; x-ray diagram.

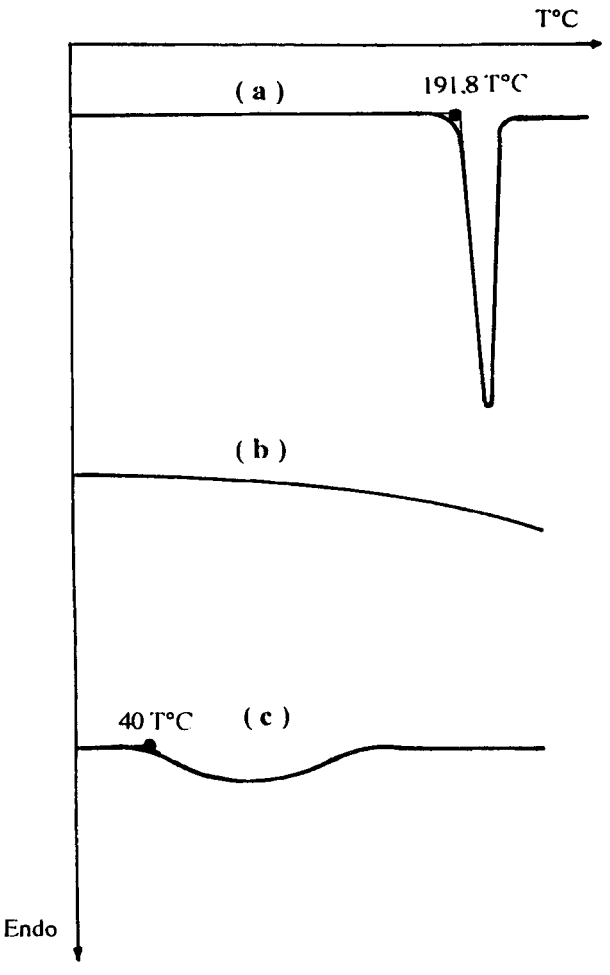

Figure 6. Thermogram of spray-dried sample 10.0a (a); and Aerosil 200 before (b) and after (c) spray drying.

osil. This may be explained by the small reactivity of the siloxan (Si—O—Si) and silanol (Si—OH) linkages.

The importance of colloidal silica lies in its technical role in increasing the final yield of spray drying (up to 90%) and absorbing the vitamin C crystals. This may be explained by an easiness of drying due to its capacity to absorb water (up to 30 times its weight), or by an increase in the droplet density helping recuperation of the spray-dried material.

Aerosil 200 in aqueous solution gives a colloidal suspension. When it is used as adjuvant in an ascorbic acid solution, most of this solution is absorbed by it. During the spray-drying process, the water is evaporated, leaving the vitamin C absorbed in the voids of the amorphous adjuvant. No inclusion complex or polymorphism was characterized.

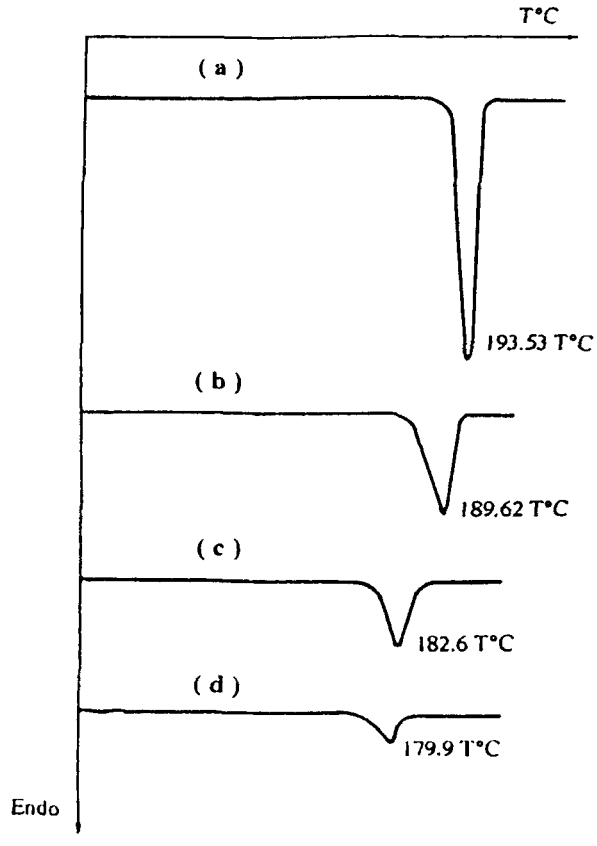

Figure 7. Thermogram of ascorbic acid raw material (a); and spray-dried samples 7.5a (b), 5.0a (c), and 2.5a (d).

Table 3

Statistical Analysis (ANOVA) of Spray-Dried Ascorbic Acid Release Efficiency

	Assay Number						Mean
	1	2	3	4	5	6	(± *SD*)
Spray-Dried Sample							
5.0a	73.90	74.80	76.60	76.70	76.90	75.80	75.77 ± 1.90
7.5a	75.00	76.60	76.30	72.70	72.80	74.60	74.67 ± 1.67
10.0a	73.30	74.10	73.60	72.90	70.00	73.30	72.87 ± 1.46

Analysis of Variance

Source of Variation	*SS*	*DF*	*E*	*F* Ratio	Prob.%	*SD*	CV
Total	57.30	17	3.37				
Factor	25.72	2	12.86	6.11	0.0114		
Residual	31.58	15	2.11			1.45	1.9%

Newman-Keuls Test, P = 5%; Factor 1: Vitamin C (%)

Means number: 2, 3
Least significant difference: 2.18

F1	Level	Means	Homogeneous Groups
1	50%	75.77	A
2	75%	74.67	A
3	100%	72.87	B

Concerning the lyoavailability: some differences were observed in the release of three different ascorbic acid samples spray-dried at pH 3 in 10 min. The comparative study of efficiency (Newman-Keuls test) shows two homogeneous groups (Table 3). Here drug release is much fastest with increased Aerosil content.

CONCLUSION

Considering all the assays, we can conclude that:

- Utilization of colloidal silica greatly improves the spray-drying ponderal yield (up to 90%).
- Colloidal silica absorbs the vitamin C during spray drying.
- The high temperatures and the thermic shocks occurring during the spray-drying process do not alter the inter- and intramolecular bonds, or the crystallinity, nor therefore, the structure of ascorbic acid.
- The spray-dried ascorbic acid release is much fastest with Aerosil contents.

REFERENCES

1. J. Da-Zoclanclounon, Réalisation de formes galéniques dérivées de *Newbouldia laevis* (SEEM), Thèse de Doctorat d'Université, Faculté de Pharmacie Montpellier I (1983).
2. M. Moisan, Mise au Point—les nébulisats, emploi en pharmacie, Plantes médicinales et Phytotérapie (T2)3, 221-231 (1968).
3. G. Sens, Olive—les extraits végétaux, historique et généralités, Phytotherapy, 1, 13-15 (1981).
4. S. Soediro, Comparaison entre divers extraits secs de Strychnos ligustrina Bl, Thèse Doctorat de 3ème cycle, Faculté de Pharmacie Montpellier I (1980).
5. K. Master, *Spray Drying*, 2nd ed., Georges Godwin, London, 1976.
6. J. Casadebaig, M. Jacob, G. Cassanas, D. Gaudy, G. Baylac, and A. Puech, Physicochemical and pharmacological properties of spray dried powders from *Fraxinus excelsior* leaf extracts, J. Ethnopharmacol., 26, 211-216 (1989).
7. D. Gaudy, A. Puech, and M. Jacob, Rôle de l'adjuvants dans l'optimisation de la production d'un extract sec végetal nébulisé: cas de l'extract de Noix vomique, Pharm. Acta Helv., (66)1, 5-10 (1991).
8. D. Gaudy, Contribution à l'optimisation des préparations galéniques à base de *Noix vomique*, Thèse de Doctorat d'Etat en Sciences Pharmaceutiques, Faculté de Pharmacie Montpellier I, 1984.
9. Z. Czuros and J. Petro, Investigations on catalysts. XIII. autoxidation of ascorbic acid as a function of pH values, Acta Chim. Acad. Sci. Hung., 7, 199-220 (1955).
10. M. Jacob et al., Elaboration d'extraits végétaux adsorbés. I. obtention d'un extrait de Belladone sur support "Aérosil," STP Pharma, 5(2), 79-95 (1976).
11. D. Gaudy et al., Automatisation de la mesure de lyodisponibilité des formes orales à libéracion ralentie: cas de la théophylline, STP Pharma, 5(11), 750-755 (1989).
12. T. Moura et al., Nébulisation de la vitamine C: etude de la contrainte thermique, 4ème Forum International sur la Recherche et le Medicament, Bordeaux 7-13 Octobre, 1993.
13. *Handbook of Proton-NMR Spectra and Data*, Vol. 2, Asahi Research Center Co., LTD, Tokyo, Academic Press, 1985.
14. *The Aldrich Library of Infrared Spectra*, 2nd ed., Aldrich Chemical Corp., 1975.