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Description and preliminary evaluation of a new ultrasonic atomizer for spray-congealing processes

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Abstract

A new atomizer that operates with ultrasonic energy is described. This apparatus is intended to obtain microparticulate drug delivery systems through spray-congealing or spray-drying technologies. In this work, some experimental results are reported on model systems submitted to spray-congealing. The formulations under examination contained theophylline and fenbufen as model drugs and stearic acid, carnauba wax, Cutina HR® and Compritol 888 ATO® as low melting excipients. Non-aggregate and spherical-shaped microparticles were obtained with all the materials tested; moreover, they had smooth surface and good flowability. The particle sizes depend on the amount of drug present and in each case the maximum size value of the distribution frequency was found to be 375 μ. In vitro release of the drug depends on its solubility and on the excipient lipophilicity. The results suggest that the ultrasound-assisted atomizer could be proposed as a possible alternative to traditional atomizers used for spray-congealing in the pharmaceutical field.

Keywords: Ultrasonic atomizer; Spray-congealing; Microparticles; Controlled-release

1. Introduction

Recently, microparticulate systems have received a great deal of attention due to advantages they offer with respect to single unit dosage forms (Akiyama et al., 1993; Varshoaz et al., 1997):

- good reproducibility of transport through the gastrointestinal tract (GIT);
- minimization of local damage to the GIT because of their wide distribution over a large area;
- lower risk of dose dumping.

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Among several methods widely described in the literature to obtain microparticles (coacervation, interfacial polymerization, solvent evaporation, extrusion-spheronization) spray-drying and spray-congealing techniques play an important role (Eldem et al., 1991; Giunchedi and Conte, 1995; Yajima et al., 1996). It is well known that the first stage for both processes is the atomization of a liquid, that is an aqueous or organic solution or suspension in spray-drying, or a molten lipid in spray-congealing.

Traditional atomizers (rotary, pressure or two-fluid atomizers) (Masters, 1985) use only a small amount of their operating energy (centrifugal, pressure or kinetic energy) to shatter the liquid, while most of this energy is transformed into kinetic energy of the particles. As a consequence, some problems can arise, such as a partial separation of the components in mixtures, or pores and presence of defects on the microparticles surface. Moreover, equipment dimension and cost increase when the speed of the atomized particles increases. These disadvantages can be reduced using an ultrasound (US) atomizer. In fact, when a liquid surrounds a solid vibrating element (sonotrode), the US energy is transmitted with high efficiency, causing atomization.

The surface energy of a liquid is a function of both its surface tension and its specific surface and increases when the liquid is atomized. With the ultrasonic atomizer the energy used is mainly transformed into surface energy with an efficiency ($\geq 85\%$; the remaining energy is mostly degraded to heat, only a small part of it being converted into kinetic energy. Most of the heat is produced in the US transducer and kept at a temperature not exceeding 50°C by means of an air cooler. Only a small part of the heat reaches the tip of the sonotrode and would be insufficient to keep its temperature at a proper value. Therefore, the continuous use of an additional inductive coil is required.

Ultrasonic atomizers used for inhalation therapy (Lashmar et al., 1994; Niven et al., 1995) or in non-pharmaceutical industrial branches are widely described in the literature (Morgan, 1993); from their characteristics, however, they seem not to be suitable for a pharmaceutical spray-congealing use.

Following our previous works on the ultrasound-assisted compaction (Rodriguez et al., 1996; Fini et al., 1997; Rodriguez et al., 1998; Sancin et al., 1999), we started to study the application of ultrasound energy to another field of pharmaceutical technology. In this paper, a US atomizer which is suitable for spray-drying and spray-congealing processes in pharmaceutical technology is described; the preliminary results obtained in the spray-congealing technique using theophylline and fenbufen as model drugs and a selected series of low melting excipients are reported.

2. Materials and methods

2.1. Materials

Cutina HR® (hardened castor oil, m.p. 80–88°C, Henkel Chimica, Bologna, Italy), stearic acid (according to pharmacopoeia FU-NF-BP, m.p. 69–70°C, Carlo Erba Reagenti, Italy), carnauba wax (m.p. 82–85°C, Produits Roche S. A., Neuilly S/Seine, France), Compritol 888 ATO® (glyceryl behenate, m.p. 69–74°C, Gattefossé Italia, Milano, Italy) were used as excipients.

Theophylline (TH) (Fluka Chemie A.G., Switzerland) and fenbufen (FB) (S.I.M.S., Firenze, Italy) were commercial samples and were used as model drugs. Fenbufen was micronized and particles formed aggregates preventing a size distribution analysis, while TH was milled and the fraction with a mean size of 112.5 μ was used. The other materials and reagents were of analytical grade.

2.2. Description of the US atomizer

Fig. 1 shows the scheme of the US atomizer developed for this study by Saitec s.r.l. (Bologna, Italy), the owner of the related patent. This model is a simplified one, intended for a lab-scale use; an improved, high-yield industrial version is also available.

The US-atomizer basically consists of three parts:

1. the US piezoelectric generator (piezoelectric ceramics);
2. an interchangeable booster allowing for the modification of the amplitude of the US wave;
3. a titanium vibrating surface (sonotrode) on which the atomization of the liquid occurs.

The correct operating of the atomizer is also provided by an inductive coil (D) controlled by a feed-back thermostatic device to heat and to keep the sonotrode at suitable temperature. An air cooler avoids the overheating of the US transducer and a thermostated and stirred reservoir of the liquid to be atomized, provides the feeding of the sonotrode at a constant rate (*E*).

The US atomizer operates at a constant frequency (in this apparatus 20 kHz) and at a maximum power output of 1.8 kW. The microparticles were collected in a cylindrical chamber (*F*) at room temperature.

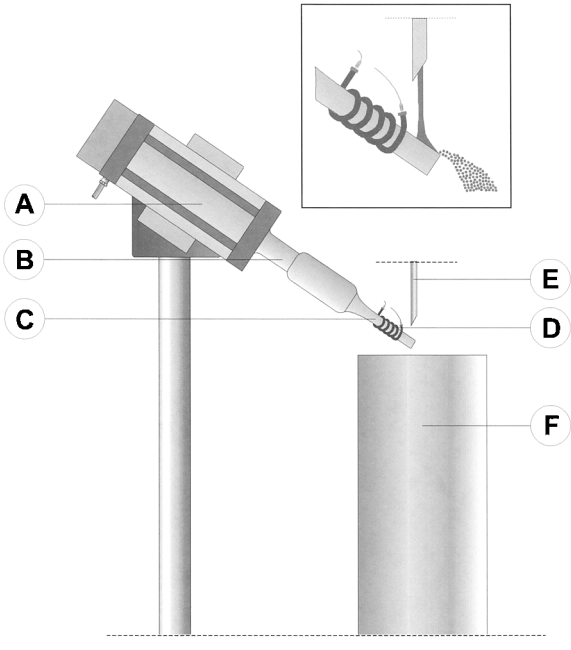

Fig. 1. Scheme of the ultrasonic atomizer (not in scale): (A) US generator; (B) booster; (C) sonotrode; (D) inductive coil; (E) supply funnel; (F) cylindrical chamber (collector).

2.3. Microparticles preparation

The lipidic excipient, at a temperature 10°C above its melting point, and the drug, when it was present, were stirred in the thermostated reservoir to avoid the sedimentation of the solid particles of the drug and the congealing of the excipient. During this step a partial dissolution of the drug into the molten wax occurs, as a function of their affinity. A reduction of the drug dimensions can also be detected, mainly in the case of needle shaped crystals like those of theophylline, due both to a mechanical and to a dissolution effect.

This fluid was poured (maximum feeding rate 500 ml/min) onto the oscillating surface (sonotrode), previously heated at the selected temperature. On the sonotrode, the liquid was shattered by ultrasound energy in small droplets which, freely falling, solidified by cooling at room temperature. The microparticles were then stored into a dessicator at room temperature.

To study the performance of the US atomizer, some excipients were preliminarily atomized. Then, two of these excipients (stearic acid and carnauba wax) were atomized after addition of 10 and 20% (w/w) of TH or FB as model drugs. These drugs differ from each other in water solubility at 25°C (TH 8.3 mg/ml) (Cohen, 1975) (FB 0.11 mg/ml) (Medicamenta, 1994) and in powder particle size (TH powder 99% smaller than 250 μm; while FB crystals were micronized).

2.4. Microparticles characterization

2.4.1. Particle size analysis

The size distribution of microparticles was evaluated using five standard sieves (Scientific Instrument s.r.l., Milan, Italy) of 75, 150, 250, 500 and 750 μm and the plots shown in Figs. 3 and 6(a–d), are the mean results of three different preparations for each formulation, using strictly similar experimental conditions.

2.4.2. Scanning electron and optical microscopy

The shape and the surface characteristics of the microparticles were evaluated by scanning electron microscopy (SEM) (Philips XL30) and by optical microscopy (Nikon SMZ-2T). The SEM

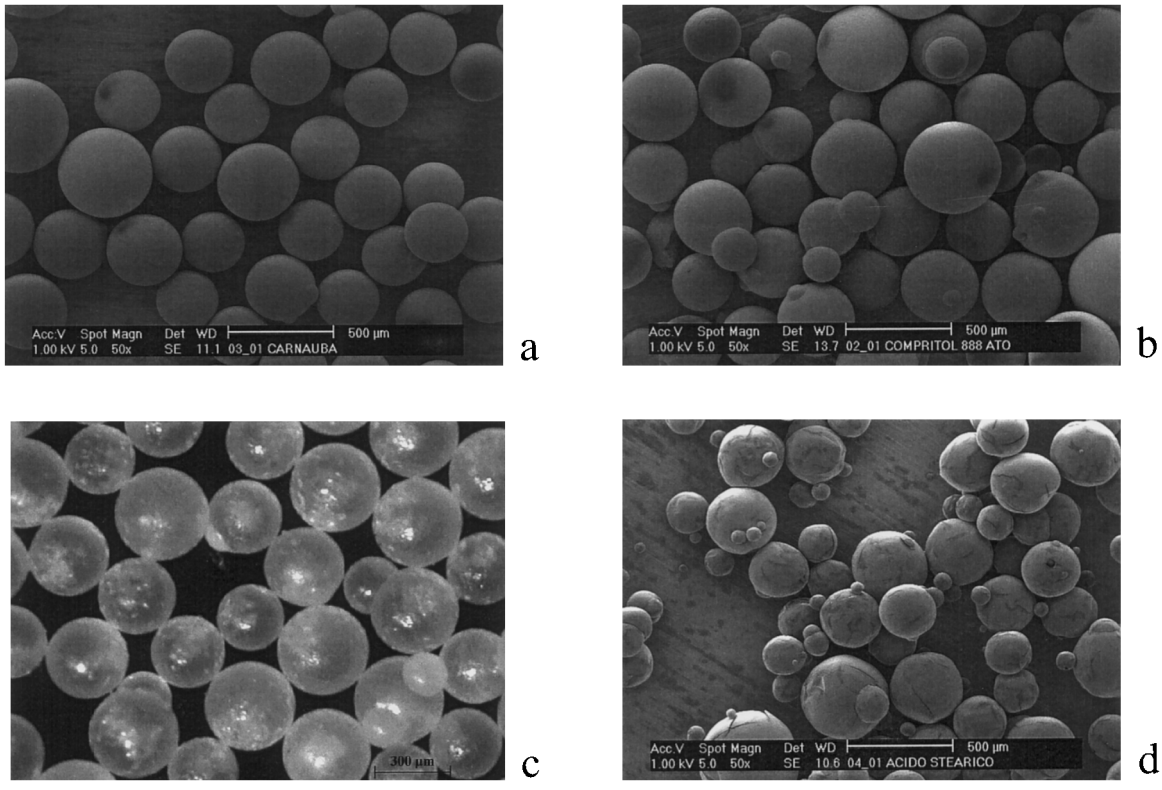

Fig. 2. SEM micrographs of (a) carnauba wax, (b) Compritol 888 ATO®, and (d) stearic acid and optical micrograph of (c) Cutina HR®. In all cases the microspheres contained no drug and were obtained by the US atomizer.

samples were preliminarily sputter-coated with gold. SEM micrographs are shown in Fig. 2(a, b, d), 4 and 5, while Fig. 2c is an optical micrograph.

2.4.3. Angle of repose

The angle of repose (φ) was measured using the apparatus suggested by FU IX. Each test was repeated five times.

2.4.4. Evaluation of drug loading (drug content)

Each sample of microparticles was washed on a filter with deionized water to eliminate any uncoated crystals, then dried and used for the evaluation of drug content and for drug release studies.

2.4.4.1. Microparticles containing TH. Deionized water (100 ml) were added to about 25 mg of microparticles; the sample was heated at temperature above the melting point of the excipient and shaken to extract the drug. After extraction, the sample was cooled to room temperature and filtered. The drug content was then determined spectrophotometrically (UV-Vis spectrometer mod. UV2, Unicam) at 271.8 nm.

2.4.4.2. Microparticles containing FB. Ethanol (100 ml) (this solvent was chosen due to the low solubility of fenbufen in water) were added to 15 mg of microparticles. The drug content was determined spectrophotometrically at 281 nm, as above described for TH.

The determination of TH and FB drug loading was performed on both unsieved and sieved microparticles to determine differences correlated to particle size.

2.4.5. Drug release studies

In vitro release tests were carried out using the USP 23 paddle apparatus rotating at 100 rpm. About 100 mg of microparticles were introduced into 1 l of pH 7.4 phosphate buffer at 37°C. The amount of drug release was spectrophotometrically determined at 271.8 nm for TH and at 285.4 nm for FB. All the release tests were performed 1 week after the preparation of the microspheres to avoid differences due to the ageing of material.

Fig. 7 shows the release profiles of TH and FB from microspheres with carnauba wax and stearic acid. The release was followed for 6 h and the profiles are the mean of six independent tests. The value obtained using the technique described in the previous section was considered as 100% release.

A portion of the same sample was used to perform both tests.

3. Results and discussion

3.1. Unloaded microparticles

To verify the possibility to obtain microparticles by means of the US atomizer, some lipidic excipients (stearic acid, carnauba wax, Cutina HR® and Compritol 888 ATO®) chosen among those most frequently used in the spray-congealing technology, were atomised in preliminary studies. Carnauba wax (Fig. 2a), Compritol 888 ATO ® (Fig. 2b) and Cutina HR® (Fig. 2c) microparticles were non-aggregated, spherical shaped and their surface was perfectly smooth, while on the surface of stearic acid microspheres (Fig. 2d) it was possible to see some imperfections.

Moreover Fig. 2c shows that the surface of Cutina HR® particles is smooth even when different sizes of particles are examined, in the case of stearic acid microspheres surface imperfections are evident on particles of different sizes (Fig. 2d); it can be further appreciated that very small particles adhere to the larger particle surface, deforming the shape of the final material.

The regular form of the microparticles was confirmed by their good flowability: Cutina HR®, carnauba wax and Compritol 888 ATO® microspheres had a repose angle (φ) lower than 20°, that means good flow properties, while stearic acid microparticles, had a higher repose angle ($>40°$), probably due also to their surface defects.

Fig. 3 shows the particle size distribution of the microspheres obtained with pure excipients: in all cases, this distribution can be described by a Gaussian curve, whose central point is close to 375 μm. These results suggest that the mean particle size of the microspheres in the absence of drug crystals depends on the operating parameters (frequency and amplitude of the US waves) rather than on physical properties (e.g. melting point or viscosity) of each excipient.

3.2. Drug loaded microparticles

Studies were then carried out using TH and FB as model drugs and carnauba wax and stearic acid as model excipients. These formulations were chosen to study how different properties of the two lipidic coatings and the different physico-chemical characteristics (water solubility and particle size) of the two drugs affected the production and the characteristics of the final microparticles.

Fig. 4 shows the SEM micrographs of FB in a micronized form (Fig. 4a, b). Both types of microparticles with 10 and 20% of drug loading (Fig. 4c, d) are non-aggregated and spherical shaped, like those previously obtained using pure

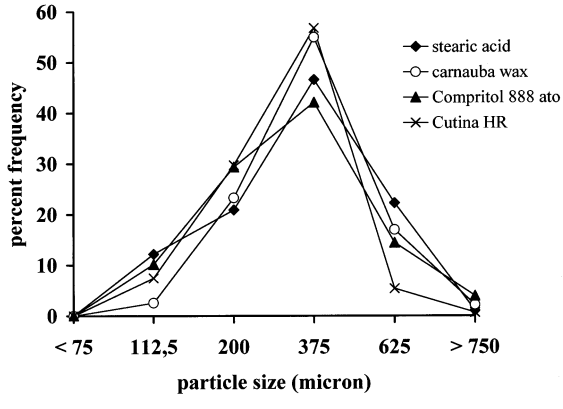

Fig. 3. Mean particle size distribution (three samples) of microspheres obtained by US atomizer.

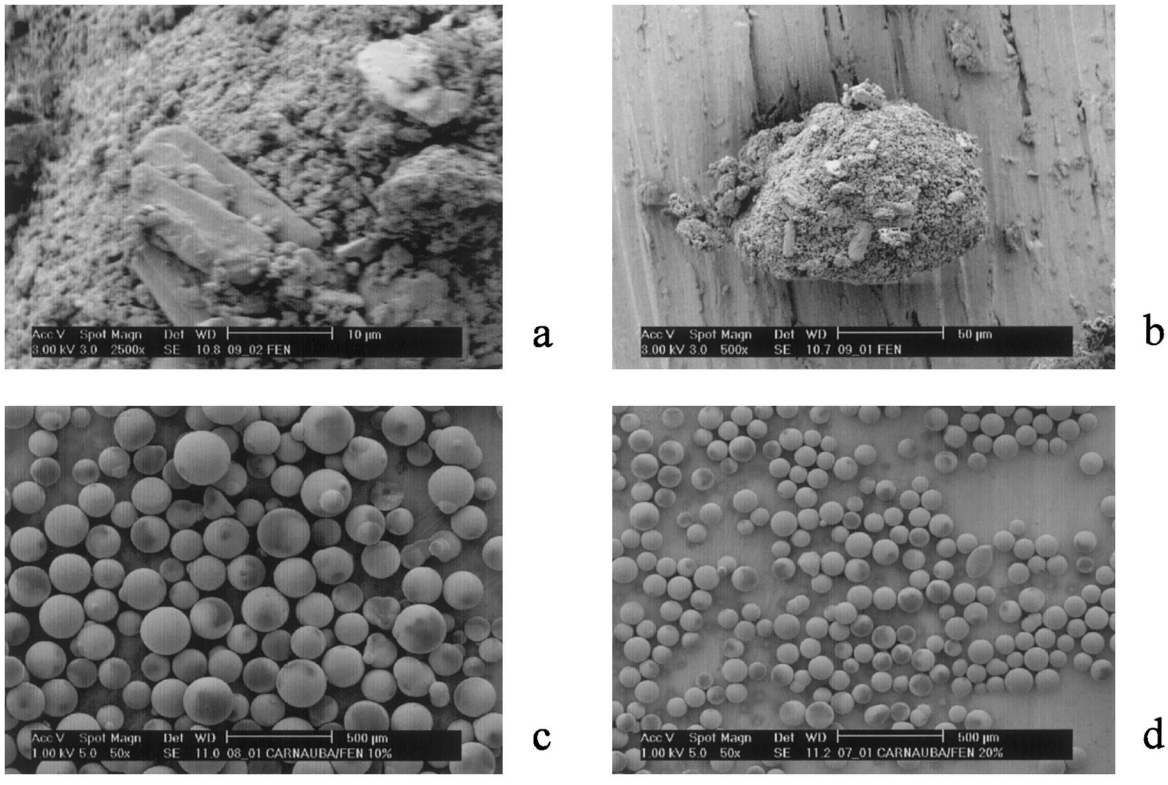

Fig. 4. SEM micrographs of: FB crystals at high (a) and low (b) magnification; 10% FB loaded carnauba wax microspheres at low (c) and high (e) magnification; 20% FB loaded carnauba wax microspheres at low (d) and high (f) magnification; detail of a FB 10% (g) and FB 20% (h) microsphere surface.

wax; the surface of the microspheres appears similar in 10% (Fig. 4e, g, at two different magnifications) and in 20% drug loaded microspheres (Fig. 4f, h, at two different magnifications).

Also the carnauba wax microparticles containing TH (Fig. 5b, c) are non-aggregated and spherical shaped, even if the crystals of this drug are needle-shaped (Fig. 5a, d, before milling and sieving). Their surface, however, sometimes exhibit some defects (Fig. 5e), probably due to the presence of TH crystals that remain partially uncoated.

Fig. 6 (a–d) display the size-distribution of microspheres containing drug particles. Regardless of the drug used, the microparticle size decreases as the drug percentage in the mixture increases. Particles are smaller than those of the pure excipients. This trend is clearly evident in carnauba wax microspheres, mainly when they contain FB (Fig. 6d): the most frequent particle fraction size of empty carnauba wax microspheres (375 μm) decreases to 200 and 112.5 μm (in the presence of 10 and of 20% of drug, respectively. A similar behaviour is present in stearic acid loaded microparticles, even though less evident. This effect was always found in all the examined systems: as the percentage of solid drug increases, the weight of the microspheres obtained per unit time decreases pointing out that the atomization process is slowed down and a higher energy (that means a longer sonication time) is required to atomize the same weight of microspheres. This extra amount of energy is spent fragmenting the material to a higher fineness.

In Tables 1 and 2 the content of drug (as drug loading percentage) experimentally found in each sieved fraction is reported as a function of the particle size. A number of informations can be extracted by these tables.

1. The drug percent in the starting mixture normally is higher than that in the final microparticles measured into the final material considered as a whole: this is due to the production of 'empty' microspheres, which do not contain the drug.
2. The smaller the microparticles are, the lower is the drug load found into them and vice versa. In the central fraction (375 μm) the starting and the final load tend to agree, while the drug amount into the largest microparticles widely exceeds the theoretical value.
3. Some of the smallest particles are formed only by the pure excipient (empty spheres); while some of the largest ones contain several drug crystals some of which remain partially uncoated.
4. This behaviour is similar for both TH and FB, despite the differences in shape and dimensions of the crystals.
5. The loss of drug is higher for the excipient carnauba wax and for the drug TH, moreover it is a direct function of the percentage of the drug. In the case of FB the influence of the initial drug load is less evident, whilst the recovery from stearic acid remains better.
6. The preceding results seem to point out that stearic acid performs intrinsically better in US atomization than carnauba wax. As far as the nature of the drug is concerned, the poor performing of TH can be mainly attributed to the shape and dimensions of its crystals, seeming reasonable that larger and less symmetrical crystals are worse incorporated into spherical shaped microparticles.

Fig. 7 shows the release profiles in pH 7.4 buffer of unsieved microspheres containing 10% of TH or FB: the release is affected by the nature of both the excipient and the drug. When the same drug is used, a significant increase of release

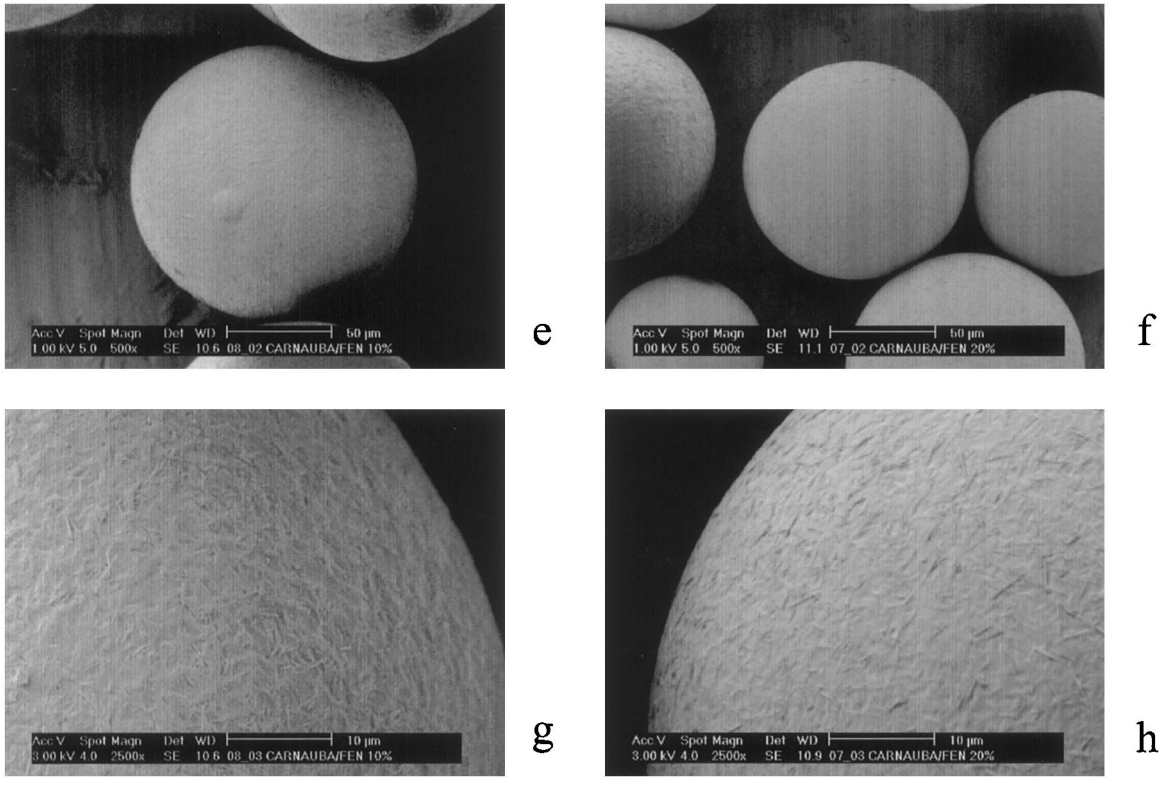

Fig. 4. (*Continued*)

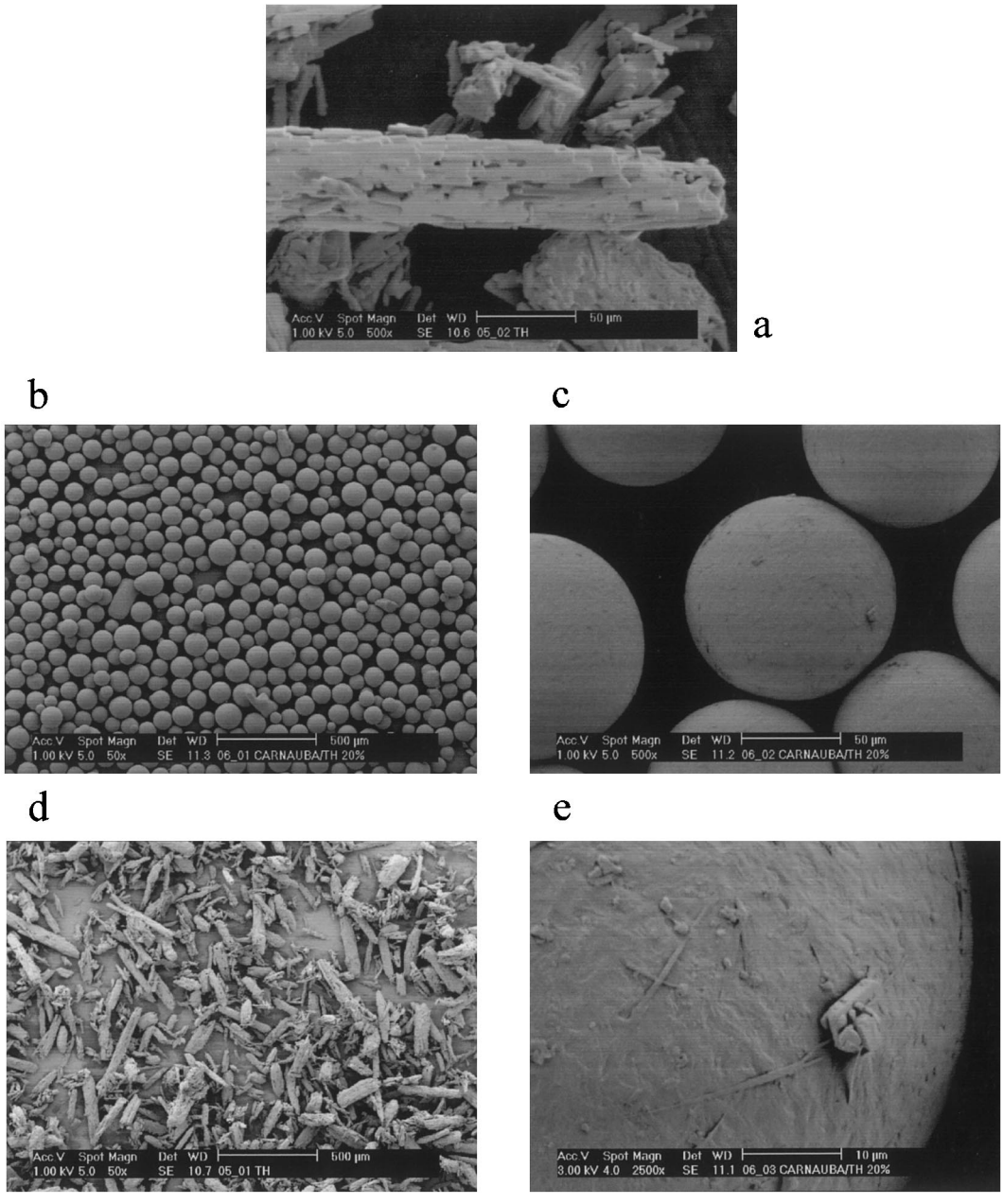

Fig. 5. SEM micrographs of: TH crystals at high magnification (a); 20% TH carnauba wax microspheres at low (b) and high (c) magnification; TH crystals at low magnification, unsieved raw material (d); detail of a microspheres surface (e).

can be detected when carnauba wax is replaced by stearic acid. In fact, the microparticles of stearic acid containing TH release about 80% of the drug in 60 min, while the carnauba wax microspheres release less than 30% drug after 6 h. This behaviour can be related to the different hydrophobicity of stearic acid and of carnauba wax, according with the results reported by Akiyama et

al. (1993) and to the well known erodibility of stearic acid. Moreover at the pH of the dissolution medium stearic acid ionizes and stearate anion decreases the surface tension of the medium and increases the wettability of the dissolving particles.

It can also be seen that in carnauba wax microspheres the drug release is significantly higher for TH than for FB, according to the different water solubility of the drugs.

Therefore, it can be concluded that, as for other traditional spray-congealing methods, a proper

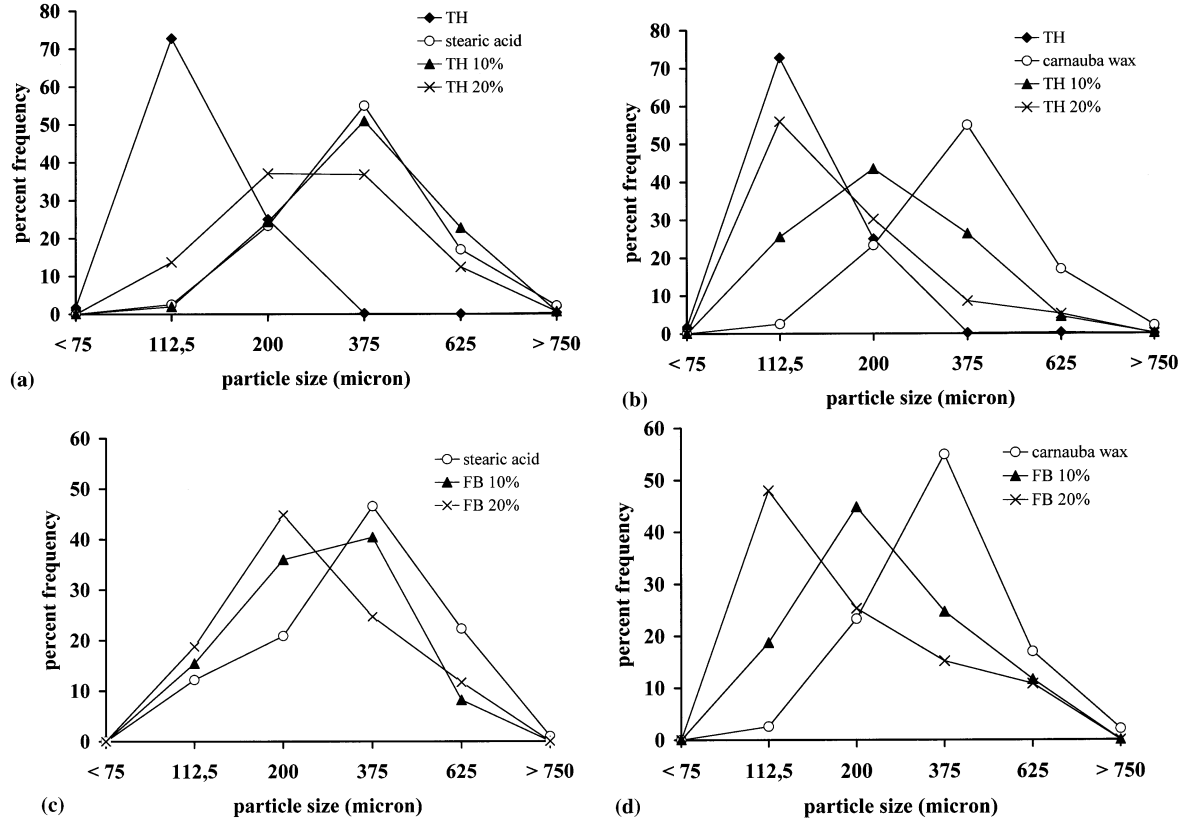

Fig. 6. Mean particle size distribution (three samples) of: (a) TH-stearic acid microspheres; (b) TH-carnauba wax microspheres; (c) FB-stearic acid microspheres; (d) FB-carnauba wax microspheres.

Table 1

Drug content (%)	Sieve fraction				
	112.5 μm	200 μm	375 μm	>500 μm	Unsieved
TH 10% stearic acid	7.02	9.75	11.57	18.08	8.57
TH 20% stearic acid	8.36	12.96	19.18	28.55	15.09
TH 10% carnauba wax	2.35	4.66	7.80	15.65	6.25
TH 20% carnauba wax	5.17	11.86	21.42	22.06	8.33

Table 2

Drug content (%)	Sieve fraction				
	112.5 μm	200 μm	375 μm	>500 μm	Unsieved
Fenbufen 10% stearic acid	6.91	8.08	8.90	13.51	7.70
Fenbufen 20% stearic acid	12.34	11.30	17.46	27.82	17.74
Fenbufen 10% carnauba wax	6.70	6.03	9.26	12.30	8.73
Fenbufen 20% carnauba wax	8.51	14.31	20.98	24.52	14.02

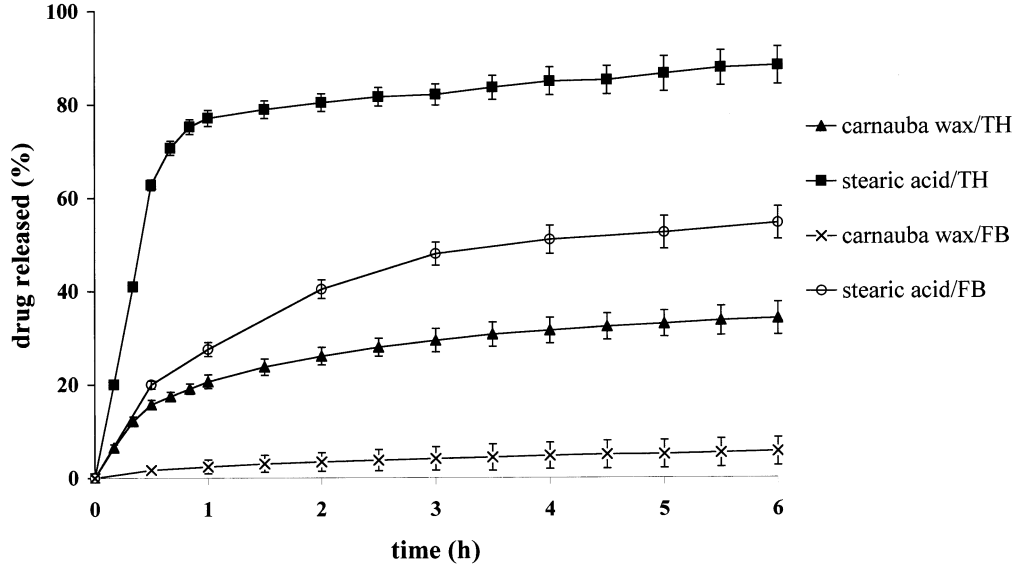

Fig. 7. Release profiles (mean values of six dissolution tests, 95% stat. confidence) in pH 7.4 buffer of unsieved microparticles containing 10% of FB and TH.

choice of the formulation can achieve the desired in vitro release profile.

4. Conclusions

The results described in this paper show that the US-atomizer can be considered a possible alternative to the traditional atomizers currently used in spray-congealing processes. Using this technique it is possible to obtain, simply and quickly, spherical shaped and smooth microparticles. Their dimension is contained within a narrow range and the release of an active agent can be modulated through a proper choice of the formulation (in terms of the excipient nature and the drug load).

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References

Akiyama, Y., Yoshioka, M., Horibe, H., Hirai, S., Kitamori, N., Toguchi, H., 1993. Novel oral controlled-release microspheres using polyglycerol esters of fatty acids. J. Controlled Rel. 26, 1–10.

Cohen, J.L., 1975. Theophylline. In: Florey, K. (Ed.), Analytical Profiles of Drugs Substances, vol. 4. Academic Press, New York, pp. 466–493.

Eldem, T., Speiser, P., Hincal, A., 1991. Optimization of spray-dried and -congealed lipid micropellets and characterization of their surface morphology by scanning electron microscopy. Pharm. Res. 8 (1), 47–54.

Fini, A., Fernandez-Hervaz, M.J., Holgado, M.A., Rodriguez, L., Cavallari, C., Passerini, N., Caputo, O., 1997. Fractal analysis of β-cyclodextrin-indomethacin particles compacted by ultrasounds. J. Pharm. Sci. 86 (11), 1303–1309.

Giunchedi, P., Conte, U., 1995. Spray-drying as a preparation method of microparticulate drug delivery systems: an overview S.T.P. Pharma Sci. 5 (4), 276–290.

Lashmar, U.T., Provasi, D., Poole, S.W., 1994. Evaluation of the delivery of suspensions from an ultrasonic nebulizer with and without the lung surfactant 'Exosurf'. Int. J. Pharm. 103, 119–123.

Masters, K., 1985. Spray Drying Handbook, 4th Edition. Pitman, Bath.

Medicamenta, 1994, Vol IV, 7th Ed, Cooperativa Farmaceutica Ed, Milano, pp. 692–694.

Morgan, A., 1993. Ultrasonic atomization. In: Advances in Sonochemistry. Vol. 3, JAI Press Ltd, London, pp. 145–164.

Niven, R.W., Ip, A.Y., Mittelman, S., Prestrelski, S.J., Arakawa, T., 1995. Some factors associated with the ultrasonic nebulization of proteins. Pharm. Res. 12 (1), 53–59.

Rodriguez, L., Cini, M., Cavallari, C., Passerini, N., Fini, A., Caputo, O., Bugamelli, F., 1996. Enhanced release in ultrasound-compacted solid dosage form. In: de Santé (Ed.), Minutes of Eur. Symp. Form. Poorly-available Drugs Oral Adm, Paris, pp. 409–412.

Rodriguez, L., Cini, M., Cavallari, C., Passerini, N., Saettone, M.F., Fini, A., Caputo, O., 1998. Evaluation of theophylline tablets compacted by means of a novel ultrasound-assisted apparatus. Int. J. Pharm. 170, 201–208.

Sancin, P., Caputo, O., Cavallari, C., Passerini, N., Rodriguez, L., Cini, M., Fini, A., 1999. Effects of ultrasound-assisted compaction on ketoprofen/Eudragit S100 mixtures. Eur. J. Pharm. Sci. 7 (3), 207–213.

Varshoaz, J., Kennedy, R.A., Gipps, E.M., 1997. Use of enteric polymers for production of microspheres by extrusion-spheronization. Pharm. Acta Helv. 72, 145–152.

Yajima, T., Nogata, A., Demachi, M., Umeki, N., Itai, S., Yunoki, N., Nemoto, M., 1996. Particle design for taste-masking using a spray-congealing technique. Chem. Pharm. Bull. 44 (1), 187–191.