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Hot Air Coating Technique as a Novel Method to Produce Microparticles

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ABSTRACT

In this work a new technology to produce microparticles, as well as the equipment suitable for its application, is described. This technique, called hot air coating (HAC), was developed to overcome the drawbacks of the conventional spray-congealing technique and consists of a special venturimeter, deliberately designed to prevent any hindrance along the axial path through which the powder is conveyed. In HAC technology, the raw material is a solid, generally small granules, which is aspirated through the ''Venturi effect'' and accelerated in a flux of hot air to soften and then to melt the excipient, especially on the particle surface. The microparticles then solidify during falling in air at room temperature. Model formulations, containing acetaminophen or theophylline as drugs and glycerilmonostearate, stearic acid, or carnauba wax as coating waxes, were tested. The choice of the optimal operating parameters was found to be a function of the formulation and of the particle size of the starting material. A pressure of 3 atm and a temperature of 20–60°C above the melting point of the excipient were found generally to be the optimal parameters for the coating process. The morphology, the in vitro dissolution profile, and the possible drug/excipient interactions of formulations containing different percentages (30%, 50%, and 70% w/w) of acetaminophen were evaluated. The results show that the morphology and dissolution profiles of the microparticles were quite different from those of the starting material; in particular the best coating was achieved by microparticles lower than 500 μm. Therefore, the HAC process could be a viable alternative to the conventional spray-congealing technique to produce microparticles with a high drug content.

Key Words: Hot air coating technique; Waxes; Microparticles; Spray-congealing.

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INTRODUCTION

One of the most frequently used strategies to obtain controlled-delivery systems is to prepare microparticles. The most popular technological procedures, also used in the industrial production of these systems, are organic phase separation (coacervation),[1,2] solvent evaporation methods,[3,4] fluid bed coating, and spray-drying.[5,6]

Despite certain advantages, such as small particle sizes and the possibility of using several kinds of excipients, these techniques present well-known problems related to the use of organic solvents[7] and/or water; therefore, their residuals in the microspheres have to be removed through time consuming drying steps. To date, several studies have been published concerning the preparation of controlled-release systems using solvent-free preparation methods.[8,9] Recently, a different approach for solvent-free preparation of polymeric microparticles was developed consisting of melting and grinding steps.[10] Another strategy developed a new hot-melt fluid bed coating method, which used low melting coating agents such as polyethyleneglycol[11] or beeswax.[12]

Obviously, the spray-congealing technique (also called spray-cooling), atomizing a solution or a dispersion of the drug into a molten excipient, overcomes the problem of residual solvents and the nebulized droplets solidifying in air at room temperature, without a subsequent drying step. In previous works,[13,14] we showed that the spray-congealing method by means of ultrasonic atomization easily yields spherical, controlled-release microparticles with good encapsulation efficiency. However, this technique could present some drawbacks, especially from the point of view of industrial manufacturing. In particular, they include thermal degradation of the drug (for heat-sensitive drugs) during its permanence in the molten mixture before spraying, difficulty in achieving a drug loading exceeding 25% w/w, due to the difficulty of atomizing so highly viscous system, the dimension of the collection room required to obtain a satisfactory yield, and mostly, the difficulty of operating it according to good manufacturing practices (GMPs).

With the aim of overcoming the drawbacks of the spray-congealing technique and of taking advantage of its numerous potential applications, an innovative technique, called hot air coating (HAC), proposed as an alternative to the above mentioned method, was developed.

In the first part of the work, specific equipment suitable for HAC is described in detail. Then the results of preliminary studies on formulations containing acetaminophen and theophylline as model drugs and stearic acid, glycerilmonostearate, and carnauba wax as excipients are reported. Finally, the results concerning the influence of the operating parameters and the effect of formulation variables on microparticle properties such as shape and surface morphology, particle size distribution, physico-chemical properties, drug loading, and in vitro dissolution behavior are presented.

MATERIALS AND METHODS

Materials

Micronized acetaminophen (AAP) (the average particle size stated by the supplier was 90% w/w less than 10 μm), stearic acid, glycerilmonostearate, and carnauba wax were purchased from Polichimica Srl. (Bologna, Italy), while theophylline (TH) (90% w/w less than 500 μm) was supplied by Fluka Chemie GmbH (Switzerland).

Preparation of the Samples

Microparticles were obtained by processing, with the equipment described in the following section, different kinds of raw materials (physical mixture, dry granules, extruded granules, and granules prepared by hot kneading). Unless indicated, the weight of the batch was 20 g.

The physical mixture of the drug and the excipient was mixed in a mortar for 10 minutes; then the mixture obtained was compacted using a single-punch tableting machine (Korsch, mod EKO, Berlin, Germany) at a compression pressure of 50 kN cm^2. The tablets were then ground using a dry granulator (Erweka AR401) and sieved to obtain dry granules.

The extruded granules were obtained using a laboratory-scale single-screw extruder, operating at a temperature ranging from 50°C to 80°C±5°C at a pressure up to 70 atm. The diameter of the extrudates was 1 mm; then they were ground using a dry granulator (Erweka AR401) and sieved. The physical mixture was also hot kneaded at its softening temperature, then cooled, ground, and sieved.

Development of the Hot Air Coating Apparatus

The HAC process was developed to overcome some restrictions of the conventional spray-congealing technique. What differentiates the two methods is that in the first technique, the raw material is solid, generally

small granules, which are aspirated and accelerated in a flux of hot air in order to soften and then to melt more or less completely the excipient, especially on the particle surface; then the microparticles solidify in air when they fall at room temperature. To properly manage the solid particles and carry out the coating process, the atomizer must take advantage of the Venturi effect to generate some degree of vacuum, by means of which the solid particles are aspired at the inlet and then introduced in a laminar flux of hot air in which the melting process occurs, minimizing their contact with the inner walls of the device. In practice, the atomizer works like a particular kind of venturimeter.

Nowadays, several types of pneumatic venturimeters are commercially available and are used, for example, to accelerate sand and other solid abrasives used to sandblast, to launch powdered enamels, or to produce vacuum or to aspire and to convey powders. In these devices, according to the conventional scheme of a laboratory vacuum pump, the operating fluid travels axially through the device while the solid material or the air are aspirated radially. This operating scheme, however, is not suitable for the HAC process because the angulated pathway would lead the powders to impact on the inner walls of the venturimeter, involving a high risk of their thermal degradation. To avoid this problem, a particular kind of venturimeter was developed in which the pathways of the operating air and of the solid material are exchanged, reserving the axial pathway, rectilinear and devoid of obstacles, to the solid material to be processed, homogeneously dispersed in a faint flux of air, at the same time sucked by the device.

Description of the Apparatus

Figure 1 reports the schematic diagram of the instrument developed for the HAC process.[15] It consists of a special venturimeter, deliberately designed to prevent any hindrance along the axial path through which the powder is conveyed.

This venturimeter is operated by a flux of electrically heated hot air (A), and a thermocouple (B) maintains the temperature at the preset value of ±1°C.

Due to the design and the inner shape of the venturimeter, a Venturi effect occurs at the vertex of the conical gap (C) through which the hot air is injected into the axial pipe, which then aspires the starting material (D), and provides the automatic feeding of the device. Further, the starting material, sucked through the Venturi effect, is delivered through a funnel (E), vibrating at the frequency of 25 Hz. The feeding rate tested is 12.5 g/min.

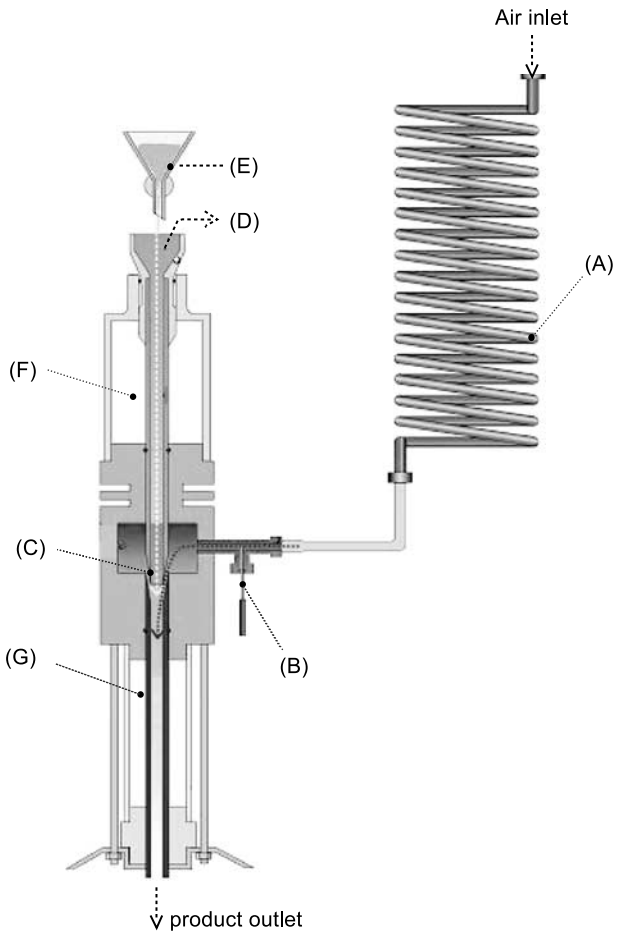

Figure 1. Schematic diagram of the HAC apparatus: (A) electrically heated hot air, (B) thermocouple, (C) conical gap (venturi effect), (D) raw material aspiration (feeding), (E) vibrating funnel, (F) upper thermostatic jacket, and (G) lower thermostatic jacket.

The raw material then flows downwards along an axial path driven by a nonturbulent flux of air, which minimizes the impacts on the inner metallic walls of the venturimeter. Therefore, the fusion of the superficial layer of the starting material occurs during the process, to form a continuous coating of low-melting excipient, whose thickness depends on the physical characteristics of the raw material (nature of the excipient, drug/excipient ratio, particle size, etc.) and on the preset working parameters (e.g., pressure, temperature, speed of the operating air, and feeding rate of the starting material). Moreover, the venturimeter is surrounded by two thermostatic jackets, an upper (F) and a lower one (G). The upper jacket is intended to prevent the conductive heating of the inlet through which the powder is fed, while the lower one

keeps the whole metallic structure below the conical inlet of the hot air at the melting point of the excipient.

Since microparticles solidify during falling at room temperature at the outlet, processing large batches would require cooling the collection chamber (for example, using liquid nitrogen).

Particle Size Analysis

The size distribution of the microparticles was evaluated by sieve analysis, using a vibrating shaker (Octagon Digital, Endecotts, London, UK) and six standard sieves (Scientific Instruments Srl., Milano, Italy) in the range of 75–750 μm.

Determination of Drug Content

The drug content of the microparticles was determined using a procedure previously reported[13] and conveniently modified according to the acetaminophen (AAP) and theophylline (TH) properties (solubility, wavelength). Briefly, 10 mg of microparticles were weighed and then added to 100 mL of pH 6.5 buffer for AAP and pH 7.4 buffer for TH. To melt the carrier, the sample was heated to 65°C or 75°C, depending on the melting point of the excipient, and then shaken for 24 h to extract the drug. Finally, the solution was filtered and the drug content was assayed spectrophotometrically (UV-Vis spectrophotometer Model UV2, Unicam, Cambridge, UK) at 243 nm for AAP and 271.8 nm for TH.

Scanning Electron Microscopy

The shape and surface characteristics of the microparticles were observed by scanning electron microscopy (SEM). The microspheres were sputter-coated with Au/Pd using a vacuum evaporator (Edwards) and examined using a scanning electron microscope (Philips 500- Eindhoven- NH).

In Vitro Dissolution Studies

In vitro dissolution tests were performed using the U.S. Pharmacopeia (USP) 24 paddle method (Pharmatest, Steinheim, Germany) rotating at 50 rpm. As dissolution medium, 900 mL of pH 6.5 buffer for AAP and 900 mL of pH 7.4 buffer for TH was used at a temperature of 37°C; each sample contained 40 mg of AAP and 10 mg of TH. The aqueous solution was filtered and continuously pumped (12.5 mL/min) to a flow cell in a spectrophotometer (UV2 Spectrometer, Unicam, Cambridge, UK). The amount of drug dissolved was analyzed at 243 nm for AAP and 271.8 nm for TH. The dissolution tests were performed at least in triplicate; the standard deviation did not exceed 5%.

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) measurements were performed using a Perkin-Elmer DSC 6 (Perkin Elmer, Beaconsfield, UK). The calibration of the instrument was performed with indium and lead for the temperature, and with indium for the measurement of the enthalpy. The samples, weighing 6–8 mg, were placed into the DSC under a nitrogen flux (20 mL/min) and heated from 30°C to 190°C at a scanning rate of 10°C/min. Each analysis was carried out in duplicate.

RESULTS AND DISCUSSION

Preliminary Tests

The first step of the work was the optimization of the operating parameters of the instrument. There-

Table 1. Influence of the raw material on the drug loading (%) of the microparticles (the theoretical drug content was 50% w/w in the formulations A, B, and C).

Microparticle size (μm)	Physical mixture			Dry granules			Extruded granules			Hot-kneaded granules		
	A	B	C	A	B	C	A	B	C	A	B	C
75–200	71.75	65.43	54.74	72.59	62.92	84.89	37.85	59.73	51.24	54.89	54.27	60.40
200–355	13.03	24.11	32.80	24.75	37.85	38.42	40.03	40.36	52.30	50.06	48.95	52.90
355–500	2.79	17.56	23.37	31.62	31.45	41.96	35.76	36.25	50.10	48.83	51.63	53.00
500–600	5.15	9.65	28.01	30.45	19.62	39.80	39.84	38.96	51.19	53.63	51.62	56.50
600–750	1.40	12.54	21.90	38.96	24.63	43.58	43.94	41.52	52.47	49.18	49.88	57.90
750–1000	2.01	7.81	–	45.68	14.85	38.35	42.43	37.29	49.11	51.05	50.26	54.50

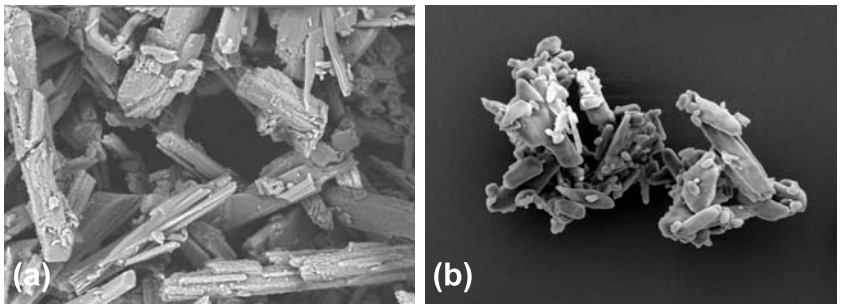

Figure 2. SEM pictures: (a) TH crystals (250×) and (b) micronized AAP (1000×).

fore, preliminary tests were performed to setup the apparatus and to examine the influence of the characteristics of the raw material (kind and particle size of the starting material) and of the process variables (air pressure and air temperature) on the properties of the microparticles.

The apparatus was tested using four different raw materials: physical mixture, dry granules, extruded granules, and hot-kneaded granules. To select the suitable raw material, the uniformity of the drug loading in each microparticle size of the coated sample was evaluated. Table 1 reports the effect of the raw material type on the drug loading of the microparticles for three model formulations: TH:glycerilmonostearate (A), TH:carnauba wax (B), and AAP:stearic acid (C). All the formulations had a 1:1 w/w drug to excipient ratio. The experimental data show that it is not possible to give general rules regarding the selection of the best raw material—for formulations A and B the uniformity of the drug loading in every fraction was provided by the hot-kneaded material, while for formulation C the best performance was obtained with the extrudate. These different behaviors could be due to the differences in size and shape of the drugs; AAP was in a micronized form (Fig. 2b) while the TH crystals had an acicular shape (Fig. 2a) and more than 90% (w/w) of its particles was less than 500 μm. Probably, during the hot-kneading process, TH undergoes stronger modification both in size and shape than during extrusion; this phenomenon could explain the enhancement of the drug loading uniformity. Moreover, Table 2 evidences that there were no significant differences in drug content between the untreated (hot-kneaded) and the coated samples of formulation A, indicating that the HAC process did not modify the drug uniformity.

The next step was to investigate the effect of using sieved or unsieved raw materials on the particle size of the microparticles. Figure 3 shows the particle size distribution of a 100-g batch of formulation C treated at 100°C and 3 atm (the yield was 90% w/w); the results pointed out a remarkable increase of particle size after the process. On the contrary, this behavior is less evident using a known particle size; for example, when processing the 75–200 μm fraction, only 9% w/w of the final product showed an increase in size (in the range of 200–355 μm). This fact is probably due to the adhesion of the smaller particles on the surface of the bigger ones. Therefore, the final particle dimension is a function of the size of the feeding material and is not determined by the HAC treatment, unless unsieved material is used to feed the apparatus.

Then, to select the optimal values of air pressure and air temperature, a screening of the three formulations was performed. Each raw material was processed at four values of pressure (1.5, 2, 3, and 4 atm) and at a wide temperature range (from 60°C to 120°C for formulations A and C and from 80°C to 160°C for formulation B). The data, in terms of drug loading, shape, and dissolution behavior (not shown), evidence that good results were obtained using an air pressure of 3 atm and an air temperature of 20–60°C above the melting point (mp) of the excipient. Thus, for stearic acid (mp=60°C) the optimal temperature range was

Table 2. Comparison of drug content of untreated and coated samples (formulation A).

Particle size (μm)	Hot-kneaded (% w/w)	Microparticles (% w/w)
75–200	50.40	54.89
200–355	49.38	50.06
355–500	53.47	48.83
500–600	52.24	53.63
600–750	50.70	49.18
750–1000	49.77	51.05

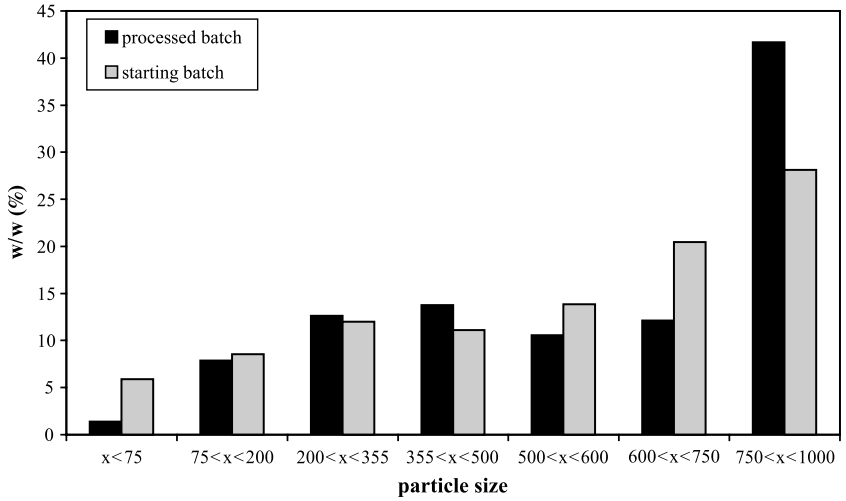

Figure 3. Comparison of particle size distributions of a 100-g batch containing AAP and stearic acid (1:1 ratio) before and after the process.

80–120°C, while for carnauba wax (mp=80°C) it was 100–150°C.

In addition to drug loading and final shape of microparticles, the effective coating of the microparticles was investigated by performing, dissolution tests. Figure 4 shows the dissolution profiles of formulation B microparticles (200<×<355 μm) compared to pure TH and hot-kneaded granules. Theophylline was completely dissolved after 2 minutes, while hot-kneaded granules (200<×<355 μm) released only 35% of TH after 30 minutes. However, microparticles exhibited a better controlled release than the granules and after 30 minutes 15% of TH was released, thereby pointing out a fairly good coating effect. These results provided evidence for the feasibility of this technique, thereby producing controlled-release microparticles

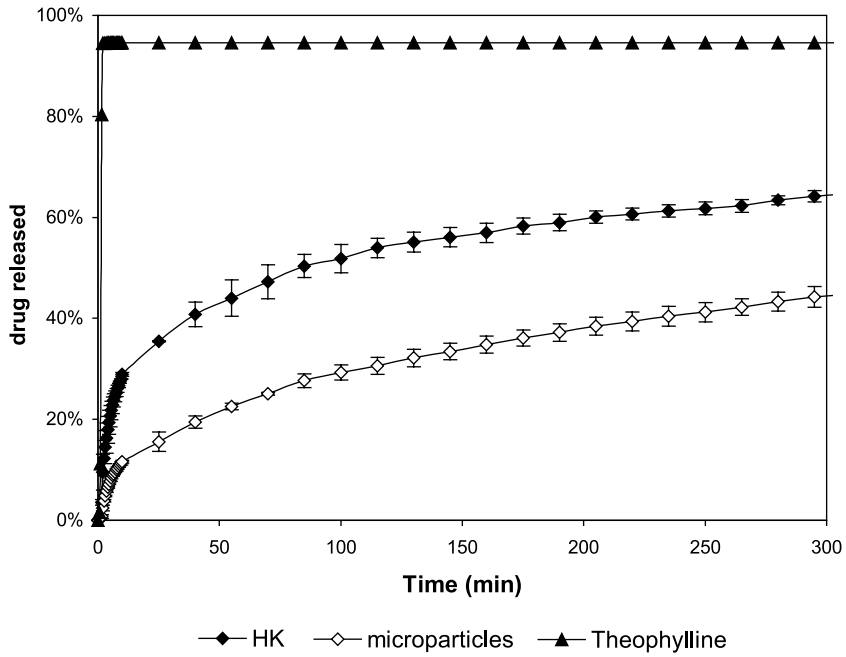

Figure 4. In vitro dissolution profiles of TH and carnauba wax samples (formulation B, 200<×<355 μm) in pH 7.4 buffer.

having 50% w/w of drug loading, which are difficult to obtain using the spray congealing method.

Furthermore, it was found that the air temperature was related to the particle size of the starting material; when increasing the particle size, it was necessary to increase the air temperature to obtain an effective coating. For example, for coating granules containing stearic acid (formulation C) of 75–200 μm diameter, an air temperature of 80°C was sufficient, while coating the 500–600 μm fraction required an air temperature of 110°C. It is important to emphasize that in any case the heating step required a very short time, minimizing the risk of thermal degradation.

Once it was demonstrated that it was possible to obtain controlled-release microparticles and that the release could be modified by simply selecting some variables (air temperature and pressure), the usefulness of this process to modify the release behavior of AAP as a function of both drug loading and particle size was investigated.

Evaluation of AAP and Stearic Acid Formulations

The following step of the investigation focused on formulations containing AAP and stearic acid (formulation C) at different w/w ratios (AAP/stearic acid 30:70 = formulation C1; AAP/stearic acid 50:50 = formulation C2; AAP/stearic acid 70:30 = formulation C3) to evaluate the morphology, the in vitro dissolution profiles, and the possible drug/excipient interactions.

As described in the previous part, the extrudates were selected as raw materials for formulation C, the drug content being quite uniform in all microparticle sizes.

Figure 5 shows the SEM pictures of the extruded granules and the final microparticles of formulations C1, C2, and C3. The SEM analysis points out the great differences in morphology between the extrudates (Fig. 4a and c) and the corresponding microparticles (Fig. 4b and d) for formulations C1 and C2; in fact, the

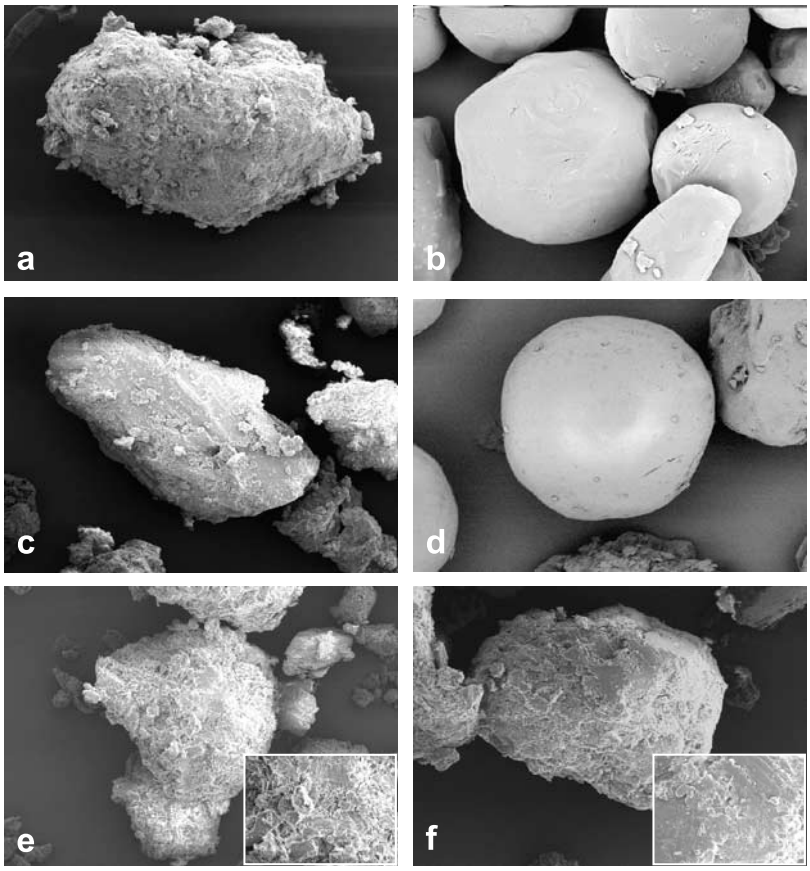

Figure 5. SEM pictures of: a) C1 extruded granules (400 ×), b) C1 coated microparticles (570 ×), c) C2 extruded granules (375 ×), d) C2 coated microparticles (320 ×), e) C3 extruded granules (350 ×) with a detail of the surface (1600 ×), and f) C3 coated microparticles (300 ×) with a detail of the surface (1600 ×).

microparticles had a more spherical shape and a more regular surface, suggesting a homogeneous coating of the treated samples.

In contrast, at higher drug content (C3), the differences between the extrudates (Fig. 4e) and the related treated microparticles (Fig. 4f) are less evident; only at high magnification (1600 ×) is it possible to individuate a slight smooth surface of the microparticles.

To evaluate the influence of drug loading and particle size of the final microparticles on the AAP release behavior, in vitro dissolution profiles of pure drug, extruded granules, and microparticles of C1, C2, and C3 were performed and compared.

Figure 6a shows the dissolution profiles of the C1 samples of different granule sizes; the time selected on the x axis was 30 minutes, to better illustrate the differences of the dissolution curves. These dissolution

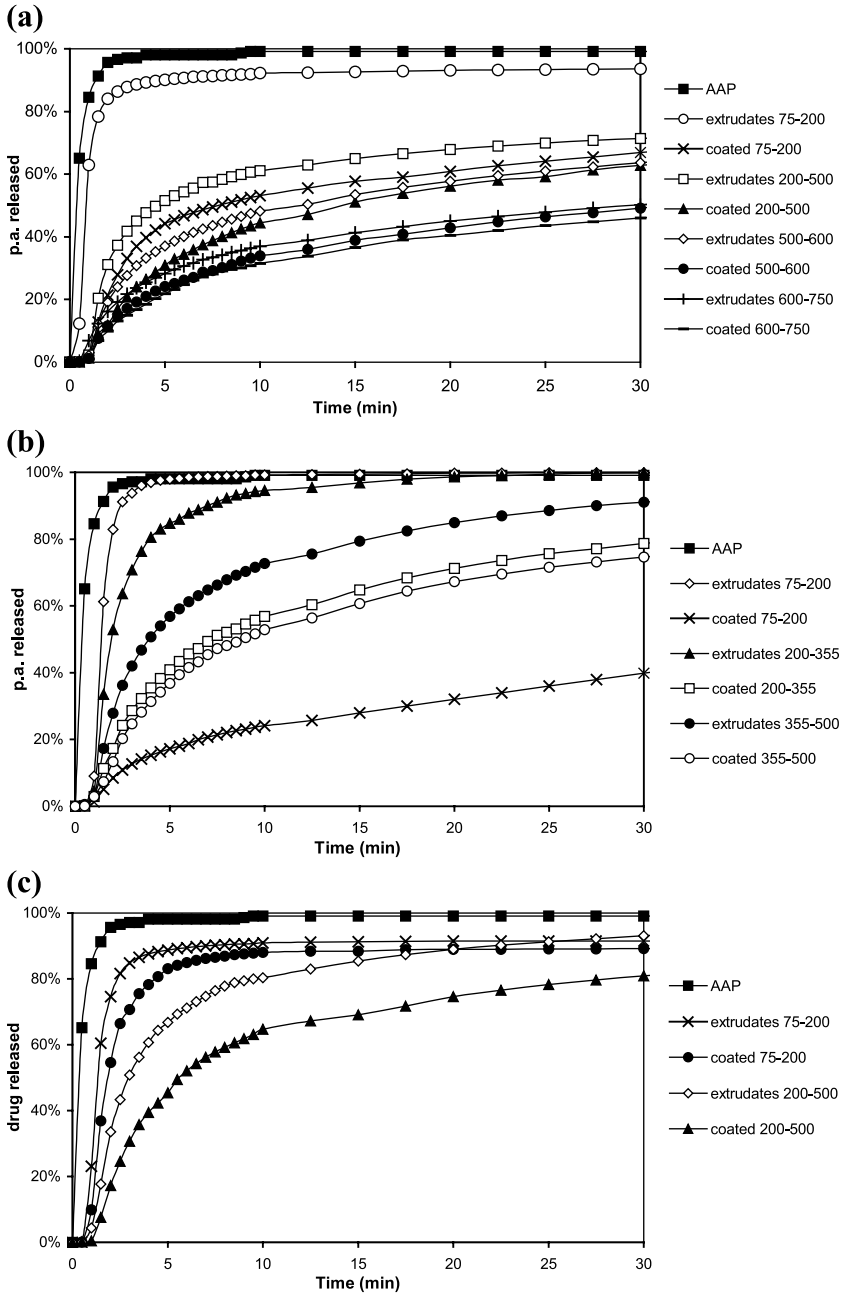

Figure 6. a) In vitro dissolution profiles of C1 samples in pH 6.5, b) in vitro dissolution profiles of C2 samples in pH 6.5, and c) in vitro dissolution profiles of C3 samples in pH 6.5.

profiles indicate that the drug released from the microparticles was considerably lower in comparison to pure AAP and the extrudates; in particular, 90% of pure drug (having a solubility of 20 mg/mL) was already dissolved in 2 minutes. The extrudates (75–200 μm) released 60% of drug in 2 min, while the related coated microparticles released only 20% of drug in the same amount of time. The difference in drug release was maintained also after 10 min; the extruded granules came to 90% and the microparticles reached almost 50% of the dissolved drug. This behavior confirmed that a homogeneous coating of the particles was obtained during the HAC process.

Figure 6a also shows that the differences in the drug release between untreated and coated microparticles decreased as the particle size of the starting material increased; in fact, in the $200 < \times < 500$ μm and $500 < \times < 600$ μm fractions a difference of about 20% in the drug dissolved between the initial granules and the microparticles was still present, while in the bigger fraction ($600 < \times < 750$ μm), the dissolution curves of the extrudates and of microparticles were almost superimposed, indicating that the process did not achieve a homogeneous and effective coating. Figure 6b reports the dissolution profiles of 75–200 μm, 200–355 μm, and 355–500 μm fractions of C2 samples. As for C1, microparticles of 75–200 μm showed a controlled release of AAP while in the bigger fractions the difference between the dissolution curves of the extruded samples and of the final microparticles was remarkably reduced, especially for the 355–500 μm fraction. The 70% w/w of AAP (C3) (Fig. 6c) showed the same behavior; only the 75–200 μm and 200–355 μm fractions evidenced an adequate controlled release.

Therefore, comparing the dissolution profiles of C1, C2, and C3 formulations, it is clear that the differences in the dissolution curves between untreated and coated samples tend to decrease as the sample sizes and the amount of the drug in the formulation increases (compare C1 with C3). Moreover, an effective coating is achieved up to 500 μm for all the microparticles, and samples larger than 500 μm are not suitable for the HAC process because of the poor coating of the final microparticles.

Afterwards, DSC studies were performed to evaluate possible interactions between the drug and the excipient in all the samples and to assess possible modifications of the solid state of the drug (i.e., transformation from the crystalline form into the amorphous one and/or into a different polymorphic form) during the HAC process. In fact, considering that the drug can exist in at least two polymorphic forms[16,17] and that the HAC technique involves the use of heat, even if for a short time, the process could lead to such drug solid state modifications. Figure 7 reports the DSC curves of acetaminophen (a), stearic acid (b), C1 extrudates (c), C1 microparticles (d), C2 extrudates (e), C2 microparticles (f), C3 extrudates (g), and C3 microparticles (h). The DSC curve of pure acetaminophen (curve a) shows a single endothermic peak at $171.09° \pm 0.74$°C, due to the melting of the drug, which corresponds to the monoclinic system, also called form I.[16,17] Monoclinic acetaminophen is the commercially used form, while form II (rhombic polymorph) is the metastable polymorph (melting point at 157°C) and more soluble than form I.[16] The third polymorph (form III) has not been isolated because of its unstability.[17]

The thermograms of the samples (c–h) clearly show a shift of the drug endothermic peak from 171°C to 165°–166°C in C1 and C2 samples (curves c–f) and to 155°C in C3 samples (curves g and h), suggesting the transformation of the drug from the original form I into the polymorphic form II,[18] both into the extruded

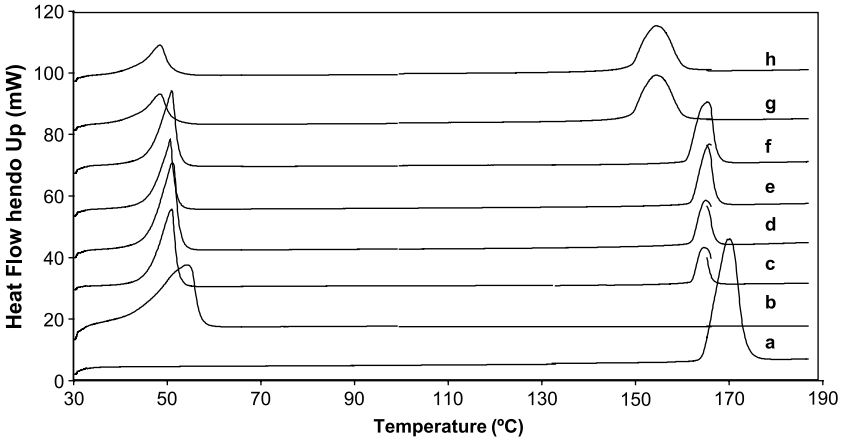

Figure 7. DSC thermograms of acetaminophen (a), stearic acid (b), C1 extrudates (c), C1 coated microparticles (d), C2 extrudates (e), C2 coated microparticles (f), C3 extrudates (g), and C3 coated microparticles (h).

(curves c, e, and g) and coated samples (curves d, f, and h).

To better investigate this behavior, the DSC analysis of the physical mixture (30% w/w of AAP) was then performed. The DSC curve (not shown) displayed a drug endothermic peak at 165.30°±0.8°C, suggesting that the modification of the drug solid state already happened in the mixing step (10 min in a mortar).

Therefore, it is important to emphasize that the shift of the drug melting point was not related to the HAC process.

CONCLUSIONS

These preliminary results suggest that the HAC technique could be a valid alternative to the spray-congealing technique to produce controlled-release microparticles, at least for the examined formulations. The selection of the kind of raw material and the choice of operating parameters depend on the properties of the formulation and on particle size. The coated microparticles showed quite different morphology and dissolution profiles with respect to the starting material; in particular, the most interesting dissolution profiles are achieved by the smaller particle sizes and samples having up to 50% of drug.

The most significant advantages of this novel technique are the use of solid samples as starting materials; the short time of exposure to high temperature (never exceeding 0.5 sec), minimizing the risk of thermal degradation; and the possibility of processing formulations with a high drug/excipient ratio, which have a too high viscosity to be processed by a conventional spray-congealing apparatus. However, the apparatus showed some drawbacks related to the low amount of material that can be processed (about 10 g/min) and to the difficulty of effectively coating granules of large particle size. As a consequence, further studies are in progress to optimize the method and possibly to scale up the apparatus.

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