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Characterization of nifedipine microparticles prepared by Hot Air Coating technique

L. Giovannelli [a], S. Bellomi [a], F. Pattarino [a,*], B. Albertini [b]

[a] *DiSCAFF, Università degli Studi del Piemonte Orientale, Via Bovio, 6-28100 Novara, Italy*
[b] *Dipartimento di Scienze Farmaceutiche, Università di Bologna, Italy*

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Abstract

In the present work, the Hot Air Coating (HAC) technique was used to prepare microparticulate systems containing nifedipine. Binary mixtures constituting of nifedipine and cetearyl alcohol (CA) in different proportions (30:70, 50:50, 70:30) were studied: they were homogenized by mixing or milling before spray treatment and successively subjected to a coating procedure with the HAC apparatus fed with air at 120 °C under a pressure of 4.5 atm. Morphology, entrapment efficiency, drug stability, thermal behaviour and the drug dissolution profile of HAC-treated and non-treated materials were examined and compared. The HAC products show the possession of physical and physico-chemical properties and dissolution behaviour different from those of the initial physical mixtures. The operative conditions employed in the spray process allow the obtaining of microparticles containing relevant percentages of the drug (at least up to 50%). Moreover, the experimental results give evidence that the milling pre-treatment of mixtures, unlike mixing, has significant effects on the properties of the lipid-coated microparticles.

Keywords: Microparticles; Microencapsulation process; Spray coating method; Hot Air Coating technique; Nifedipine

1. Introduction

Much research effort (Atilla Hincal and Suheyla Kas, 2000) has been spent studying microparticles as drug delivery systems because of the undoubted advantages that they offer: among them, protection from deteriorative reactions or adverse environmental conditions; improvement bioavailability of the bioactive molecules and taste masking of non-palatable drugs.

Microparticulate materials are manufactured by several methods, which include coacervation, interfacial polycondensation, fluid bed coating, solvent evaporation, spray drying and spray congealing. Spray techniques are appealing to the pharmaceutical field for preparation of microparticulate-sustained drug delivery systems. Many papers concerning spray techniques have been published in recent years and some of them have examined in detail the effects of the manufacturing

* Corresponding author. Tel.: +39 321 375 863; fax: +39 321 375 821.
E-mail address: pattarino@pharm.unipmn.it (F. Pattarino).

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conditions on the properties of microparticles (Eldem et al., 1991; Giunchedi and Conte, 1995; Yajima et al., 1999).

Recently, a valid alternative method to spray congealing, the Hot Air Coating process (HAC), has been proposed for the encapsulation of pharmaceuticals (Rodriguez et al., 2004). With this new technology, in appropriate operative conditions, a mixture of solid substances is heated and immediately cooled to form microparticles. Whereas spray congealing may cause damage to the drug; during HAC process, the therapeutic agent is subjected to relatively high temperature just for few seconds, reducing the risk of thermal damage.

In the present work, a formulation for the controlled release of nifedipine has been studied. Nifedipine is an oral calcium-channel blocking agent, widely used in the treatment of angina pectoris and hypertension. It is a poorly water-soluble molecule that exhibits limited bioavailability after oral administration due to extensive first-pass hepatic metabolism. Nifedipine has a short biological half-life (3–4 h) and its antihypertensive effect lasts only a few hours (Murad, 1990). Conventional nifedipine formulations are known to lead to significant fluctuations in plasma drug concentrations (Foster et al., 1983), limiting the safe use of this drug in hypertensive emergency. In addition, nifedipine is susceptible to chemical degradation as a consequence of light exposure (Testa et al., 1979) and its handling usually requires appropriate precautions to prevent photo-oxidative reactions.

The aim of this work was to prepare microparticles of nifedipine coating with a low-melting lipid (cetearyl alcohol, CA) using the HAC technique; to characterize these systems in terms of drug loading and release, morphology, size and physical state of particles; and to evaluate the influence on the properties of microparticles of two different homogenizing procedures, applied to the nifedipine/CA mixtures before the HAC process.

2. Materials and methods

2.1. Materials

Cetearyl alcohol (CA) is a mixture of aliphatic alcohol, whose principal components are stearyl alcohol ($C_{18}H_{38}O$) and cetyl alcohol ($C_{16}H_{34}O$); this excipient conforming to EP 4 and nifedipine conforming to USP 23 were obtained from ACEF Spa (Fiorenzuola d'Arda-Piacenza, Italy). All other chemicals and solvents used were of analytical reagent grade and were supplied by Sigma (St. Louis, Missouri).

2.2. Methods

2.2.1. HPLC analysis of nifedipine

Nifedipine was analysed by high-performance liquid chromatography (Pietta et al., 1981). The HPLC apparatus, a Shimadzu system, consists of a LC-10 AD pump, an injection valve Reodyne 7225 fitted with a 50 μl sample loop, a SPD-10 A detector, a CTO-10AS oven and a data station equipped with the Class-VP5 software (Shimadzu, Germany). Separation was performed on a Spherisorb® S3 ODS2 Waters column (4.6 mm × 100 mm, 3 μm) (Milford, MA, USA) at constant temperature (25.0 °C). The mobile phase was represented by a phosphate buffer solution (0.01 M, adjusted to pH 6.10) and methanol (45:55, v/v); flow rate 0.5 ml/min. The drug detection was performed recording the absorbance at 237 and 254 nm.

2.2.2. Preparation of physical mixtures

Nifedipine was used as received (particle diameter <75 μm). Before use, the excipient (CA) was milled by blade milling (A 11 basic IKA, Staufen, Germany) and sieved using a set of ASTM sieves ranging from 200 (75 μm) to 25 (710 μm) mesh.

Nifedipine was added to CA in appropriate amounts to obtain samples of different compositions: 30:70, 50:50, 70:30 (w/w) nifedipine/cetearyl alcohol mixture.

Before HAC, the nifedipine/CA mixtures were subjected to one of two homogenizing treatments. In the first, the mixture was subjected to two cycles (1 minute each) of milling (19500 rpm). In an alternative procedure, the mixture was mixed by a rotating mixer (Mz/500 MATIC, Zuma s.r.l., Milano, Italy) at 36 rpm for 15 min. Each studied mixture was randomly sampled and analysed for nifedipine content by HPLC.

2.2.3. Preparation of microparticles by Hot Air Coating

The solid mixture was aspirated into the instrument by a Venturi-effect due to the special design of the apparatus (Rodriguez et al., 2004).

The powder mixture aspirated into the apparatus meets a flow of hot air injected into the instrument at a temperature of 120 °C and at a constant pressure (4.5 atm). In these conditions, CA melts and surrounds nifedipine particles forming a thin continuous solid coat.

HAC materials were collected and stored in appropriate recipients in the dark until analysis.

2.2.4. Microscopy characterization

The morphology of the materials was evaluated by optical microscopy (Nikon eclipse TE 300) equipped with an image analysis software (Imaging Workbench 4.0 AXON). Single components and mixtures, before and after treatment with the spray apparatus, were analysed at different magnifications.

2.2.5. Entrapment efficiency and dissolution studies

Drug entrapment efficiency was evaluated on randomly collected samples of each HAC batch: 10 mg of each sample were dissolved in 10 ml of methyl alcohol, diluted with the mobile phase (1:100) and the amount of nifedipine was determined by HPLC. Each experiment was performed in triplicate and the obtained values were compared with nifedipine content in NT mixtures.

The drug dissolution rate from the different nifedipine/CA systems, subjected or non-subjected to HAC treatment, was assessed at 37.0 ± 0.1 °C using the Flow-Through method (Apparatus 4 USP 25, CY1-50 Sotax). Amounts of each sample equivalent to 10 mg of nifedipine were placed in an aluminium pan and introduced into the cell of the apparatus; a phosphate buffer solution (pH 6.50; 0.10 M) was employed as dissolution medium (900 ml). After starting, aliquots of the medium were removed at prefixed times, filtered by a 0.45 μm membrane filter unit (Millex® HV, US Millipore) and analysed for the nifedipine content. The plot of dissolved nifedipine versus time was constructed and from the first part of the curve, the apparent dissolution rate constant, K_{diss}, was calculated. Each experiment was carried out in triplicate.

2.2.6. Thermal analysis

DSC analysis was performed on a Perkin Elmer Pyris 1 DSC equipped with an Intracooler II (Perkin Elmer). The instrument was calibrated using indium and zinc.

Weighed samples (5–6 mg) of each material were heated in sealed aluminium pans from 15 to 180 °C at two different scanning rates (10 and 200 °C/min) under nitrogen purge (20 ml/min). Mixtures pre-treated by blade milling or by rotating mixer and the corresponding HAC-treated systems were analysed.

2.2.7. Stability study

The effect of light on the chemical stability of nifedipine was evaluated by exposing mixtures and HAC materials to 365 nm monochromatic light (Hayase et al., 1997); the degradation of nifedipine powder was also investigated.

Hundred milligrams of each material were layered in an aluminium pan ($\phi = 40$ mm) and kept in the light for 24 h. At scheduled times, the pan was withdrawn and 10 mg of the content were dissolved in 10 ml of methyl alcohol; after dilution (1:100) with the mobile phase, the solution was analysed by HPLC for nifedipine concentration.

Degradation data, fitted to a first-order kinetics model, allowed calculation of the rate constant of the photochemical reaction, K_{degr}, for each of the considered systems.

3. Results and discussion

Preliminary tests (data not shown) suggested cetearyl alcohol with dimensions in the range 212–500 μm as the best choice for the system preparation.

Three binary mixtures of nifedipine and CA were subjected, before Hot Air Coating, to a procedure aimed to feed the spray apparatus with homogeneous mixtures. Two different operations were adopted: mixing carried out with a rotating-body mixer; and milling performed by a small blade milling apparatus. The homogeneity of the mixtures was assessed before spray process (Table 2).

The HAC process applied to both mixed and milled mixtures can lead to microparticle formation: at the operating temperature (120 °C), CA melts, surrounds nifedipine particles and, on cooling, forms a continuous, solid coating around the drug crystals. Indeed, HAC products (T products) possess physical and physico-chemical properties and dissolution behaviours different from those shown by the corresponding physical mixtures (NT products), as

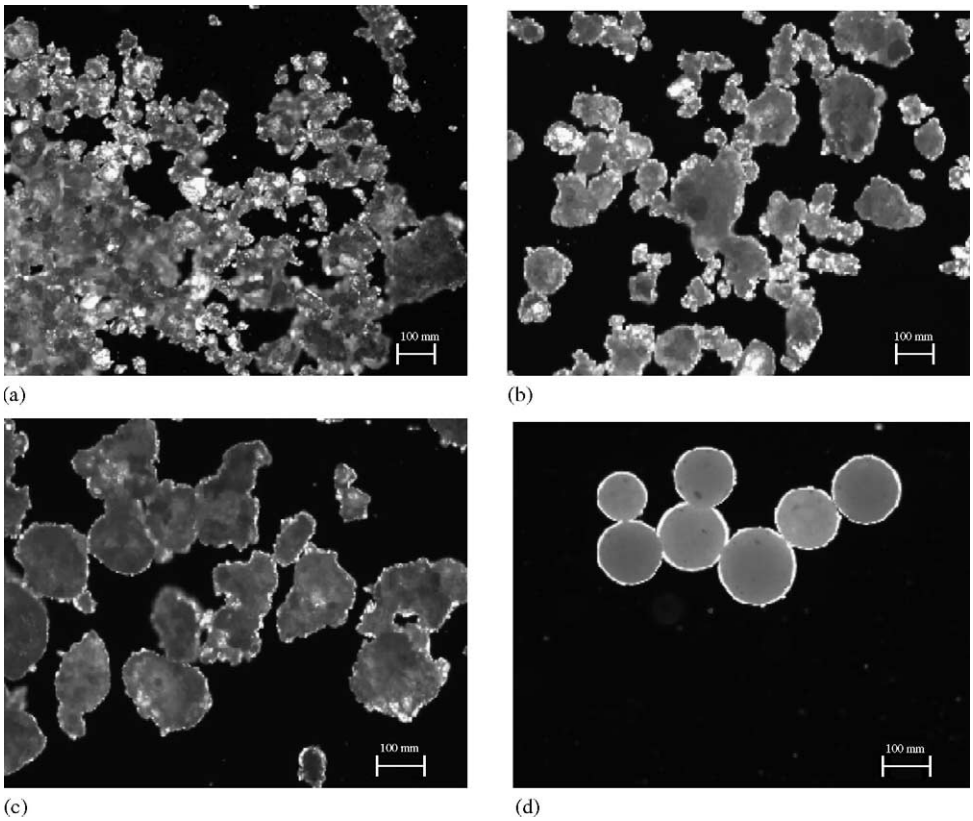

Fig. 1. Micrographs of samples containing 30% drug (magnification 4×). Non-treated mixtures subjected to mixing (a) or milling (b); HAC microparticles from mixtures subjected to mixing (c) or milling (d).

demonstrated by the results of the characterization study.

3.1. Microscopy characterization

Microscopic inspection of mixtures homogenized by mixing does not show the presence of aggregates; a non-homogeneous distribution of drug and CA can be observed, mainly for systems with the highest nifedipine content. Microparticles obtained by HAC show the presence of large agglomerates, particularly when a high percentage of excipient is present. On the other hand, HAC products of high-nifedipine content are constituted primarily of microparticles with drug adherent to their surface.

Mixtures homogenized by milling show a morphology similar to that of HAC systems prepared from mixed materials: nifedipine crystals are present at the surface of the excipient particles, even if in a lesser extent; the surface seems smoother, particle size seems unchanged after the milling operation (as experimentally verified by sieve analysis) and the amount of free drug is decreased.

The different morphologies of these two kinds of systems (mixed and milled mixtures) can be explained keeping in mind that the blade chopper movement increases the material temperature; as a consequence, during pre-treatment the excipient could melt and partially coat nifedipine particles, while the shear forces involved prevent the agglomerate formation.

Treatment of milled mixtures by HAC produces microparticles, whose dimensional and structural characteristics are better than those of the corresponding materials obtained from mixed system. In Fig. 1, the micrographs of 30%-nifedipine NT and T systems are shown; it can be noted that the HAC particles have a rounded form, their surface appears smoother than before treatment, they look more uni-

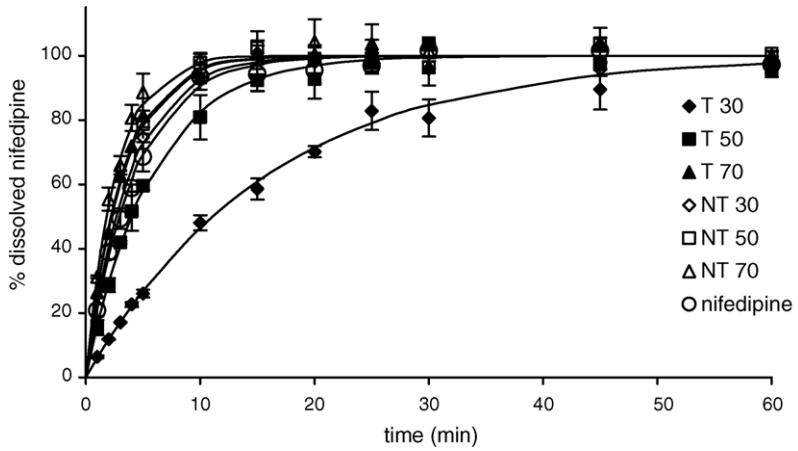

Fig. 2. Dissolution profiles of non-treated (NT) systems subjected to mixing and the corresponding HAC-treated products (T). The values are means of three experiments; error bars represent the 95% confidence limits.

form in size and crystals of free nifedipine are almost absent.

3.2. Dissolution study

The dissolution profiles give important evidence of the differences existing between HAC and non-HAC systems and indicate a significant influence of the pre-treatment procedure. The dissolution curves of mixtures and microparticles and their apparent dissolution rate constants are reported in Figs. 2 and 3 and in Table 1.

The dissolution rate profiles of mixed nifedipine–CA mixtures and of microparticles prepared from them are shown in Fig. 2. The calculated apparent dissolution rate, K_{diss} (Table 1), shows evidence of some differences between the two materials; while K_{diss} of 30%-drug mixture can be considered to be the same as the 100% nifedipine, this parameter increases for mixtures consisting of

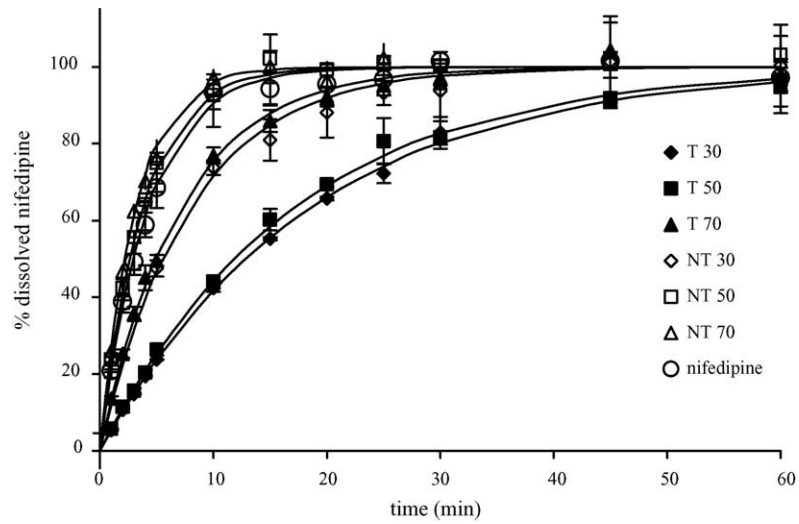

Fig. 3. Dissolution profiles of non-treated (NT) systems subjected to milling and the corresponding HAC-treated products (T). The values are means of three experiments; error bars represent the 95% confidence limits.

Table 1
Dissolution rates of non-treated (NT) and treated (T) systems subjected to milling or mixing

Nifedipine:CA	Apparent dissolution rate ($mg\,l^{-1}\,h^{-1}$) ± S.E.			
	Mixed system		Milled system	
	NT	T	NT	T
30:70	15.58 ± 0.12	3.75 ± 0.07	7.55 ± 0.04	3.24 ± 0.15
50:50	18.89 ± 0.13	10.42 ± 0.09	15.82 ± 0.14	3.51 ± 0.07
70:30	22.73 ± 0.20	18.35 ± 0.11	18.99 ± 0.13	8.45 ± 0.10
100:0	15.20 ± 0.19			

increased percentages of nifedipine, probably because of a promoting effect of the excipient. The nifedipine dissolution profile of 70%-drug HAC samples is comparable to those of the control, suggesting that the rapid transit into the HAC apparatus does not allow formation of microparticles. On the other hand, mixtures with a drug ≤50% content seem to form coated particles, K_{diss}, of 30%-nifedipine system being lower than that of the 50%-nifedipine. For the latter, it could be hypothesized that there was an incomplete coating of the drug particles, as a consequence of non-optimal operating conditions, i.e., kind of pre-treatment, fast flow rate into the spray apparatus or insufficient amount of CA.

The dissolution study on milled samples gives some enlightening informations (Fig. 3 and Table 1). For NT mixtures, K_{diss} values are lower than that of the corresponding mixed ones; moreover, while rate constants of 50%- and 70%-drug milled mixtures are similar to that of 100%-nifedipine system, the dissolution rate of the 30%-nifedipine mixture is halved ($7.55\,mg\,h^{-1}$) indicating the formation of a partial coating around the drug during the mixture pre-treatment. HAC samples show lowered dissolution rates; K_{diss} values of 30%- and 50%-drug systems are similar to that of 30%-nifedipine HAC microparticles prepared from the mixed samples, suggesting the complete coating of the drug. The dissolution profile of the 70%-nifedipine milled system superimposes the curve of the 30%-drug NT mixture, leading to the conclusion of an incomplete CA coating formation.

As has been claimed previously and experimentally verified, the blade chopping action raising the material temperature can lead to the partial coating of nifedipine particles before the spray process, thus, decreasing the percentage of drug available for an immediate dissolution. This phenomenon, while significant for 30%- and 50%-nifedipine mixtures, poorly affects the dissolution behaviour of that with the highest drug content (70%).

3.3. Entrapment efficiency

NT mixtures and microparticles have been subjected to drug content determination in order to evaluate the HAC technique efficiency; in Table 2, the percentages of nifedipine in each system and the calculated coefficients of variation (C.V.) as the homogeneity parameter are reported.

The percentages of drug present in mixtures pre-treated with the rotating mixer are always higher than those of corresponding HAC materials; C.V. values of HAC products are higher than those of corresponding NT mixture.

The milling pre-treatment gives the opposite result: after HAC treatment, C.V. are lower than before (high homogeneity) and their drug content is almost similar

Table 2
Homogeneity and percentages of nifedipine in non-treated mixtures (NT) and microparticles (T)

Nifedipine:CA system	Nifedipine actual C.V. (%)			
	Mixed system		Milled system	
	NT	T	NT	T
30:70	29.01	25.56	28.80	28.54
	4.00	*10.90*	*10.90*	*4.20*
50:50	47.40	44.49	48.85	49.02
	2.70	*5.00*	*3.00*	*0.34*
70:30	73.59	58.48	68.26	60.61
	4.44	*14.80*	*7.10*	*4.20*

All mixtures were subjected to milling or mixing before HAC process. The values are means of three experiments. In italics: the calculated coefficients of variation.

to that of the corresponding initial mixture, with the exception of 70%-nifedipine HAC product.

The variability of nifedipine recovery in non-treated and treated materials can be ascribed to the different conditions adopted in homogenizing the binary systems before microencapsulation process. As pointed out before, during the milling operation an appreciable temperature increase of both apparatus and material was observed. The rise of temperature can allow the adhesion among nifedipine and CA particles and the partial coating of the drug crystals. The mixing operation does not give similar effect: in the encapsulation step, drug and excipient particles, while contiguous, flow through the apparatus at different rates and significant segregation phenomena consistent with the faster pneumatic transport of nifedipine particles (size <75 μm) occur. The segregation is more evident for mixtures constituted of high nifedipine percentages, irrespective of the homogenizing operation (Table 2).

3.4. DSC study

Ford and Mann (2002) demonstrated that high-speed DSC, which can give a snapshot of a material without phase changes induced by the slow temperature scanning, is able to show the existence or the formation of polymorphic forms of a substance, even in the presence of other components. In our work, analysis of nifedipine alone by high-speed DSC (at a scanning rate of 200 °C/min) demonstrated that the drug is in Form I and that the fast transit of CA–nifedipine mixtures through the spray apparatus does not determine any polymorphic modifications of the drug (Fig. 4).

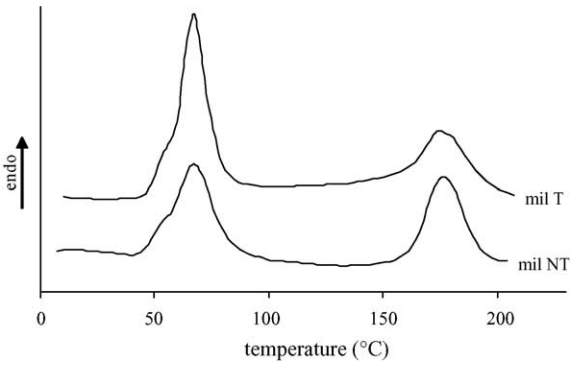

Fig. 4. High-speed DSC thermograms of non-treated milled (mil NT) mixture and the corresponding HAC microparticles (mil T) constituted of 70% nifedipine and 30% CA (scanning rate = 200 °C/min).

According to Vippagunta et al. (2002), DSC analysis is unsuitable to give information about the solid state of a drug when it is soluble in the excipients—as in our case, for nifedipine in cetearyl alcohol. Therefore, in order to evaluate the effects of the spray treatment on the structure of our binary mixtures, attention was focused on thermal data related to the excipient.

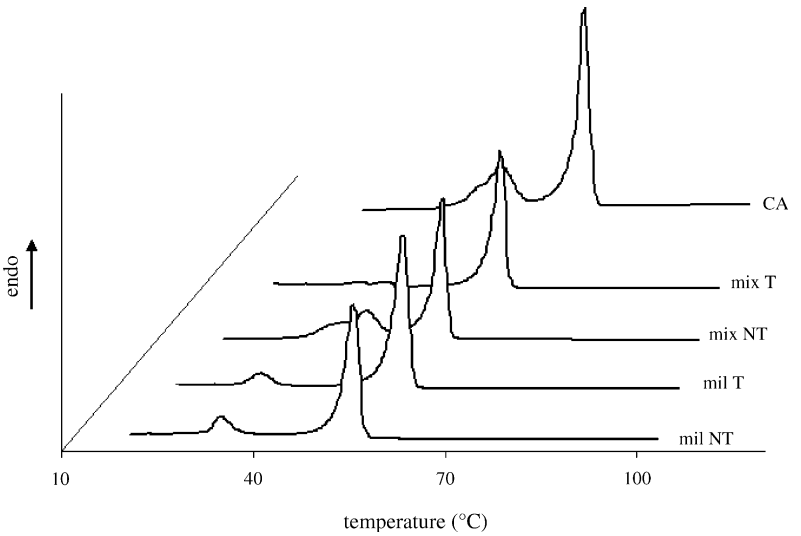

Fig. 5. DSC thermograms of non-treated mixed (mix NT) and milled (mil NT) mixtures and the corresponding HAC microparticles (mix T and mil T), 30% nifedipine and 70% CA (scanning rate = 10 °C/min).

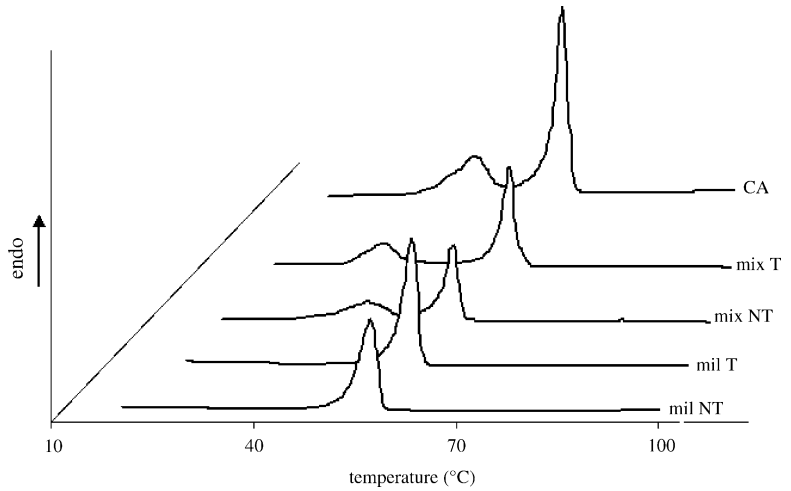

Fig. 6. DSC thermograms of non-treated mixed (mix NT) and milled (mil NT) mixtures and the corresponding HAC microparticles (mix T and mil T), 50% nifedipine and 50% CA (scanning rate = 10 °C/min).

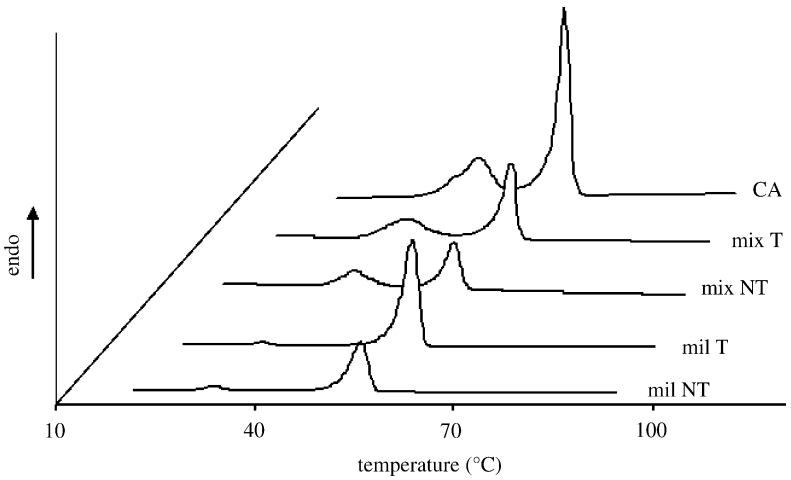

Fig. 7. DSC thermograms of non-treated mixed (mix NT) and milled (mil NT) mixtures and the corresponding HAC microparticles (mix T and mil T), 70% nifedipine and 30% CA (scanning rate = 10 °C/min).

Table 3
Enthalpic data of non-treated mixtures and HAC microparticles (scanning rate = 10 °C/min)

Nifedipine:CA	ΔH (J/g) (T = 52.9 °C)				$\Delta H_T/\Delta H_{NT}$	
	Mix NT	Mix T	Mil NT	Mil T	Mix	Mil
0:100	127.6	–	–	–	–	–
30:70	87.6	91.0	99.4	118.2	1.04	1.19
50:50	63.7	71.6	87.1	104.9	1.12	1.20
70:30	38.4	58.5	48.0	93.5	1.52	1.95

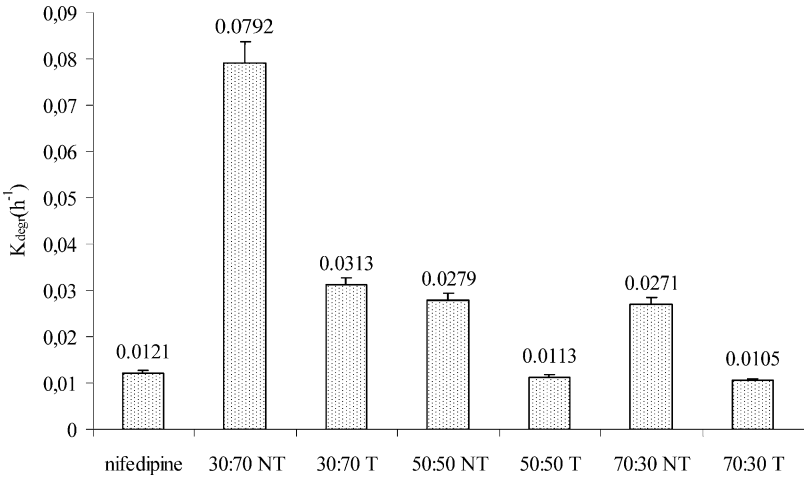

Fig. 8. Degradation rate constants of NT and T milled systems. Each value is mean of three experiments. Bars indicate S.E.

Calorimetric runs performed at 10 °C/min (Figs. 5–7) show for cetearyl alcohol two endothermic peaks: the peak at 41.7 °C can be attributed to the melting of laurylic and miristic alcohols (present as a minor fraction in the excipient), while that at 52.9 °C corresponds to cetyl- and stearyl-alcohols. For both NT and T systems, a similar profile has been observed. In Table 3, the normalized enthalpy of this peak and $\Delta H_T/\Delta H_{NT}$ ratio for all the considered systems are reported. Enthalpies of the three physical mixtures prepared both, by mixing or milling pre-treatment diminish with decreasing CA content. Enthalpy values of mixed mixtures are proportionally related to the percentages of CA, suggesting the absence of interactions between components, while for milled mixtures ΔH values are higher than expected. The peak at 52.9 °C can be associated with a monotectic species originating from the dissolution of nifedipine in CA (Corrigan et al., 2003) due to the increase of temperature during the homogenizing operation.

Also for HAC treated systems, the peak at 52.9 °C shows increased ΔH values leading to the hypothesis that an aliquot of the drug dissolves in the melted excipient during HAC treatment at 120 °C. The $\Delta H_T/\Delta H_{NT}$ ratio for milled mixtures is higher than for mixing ones, confirming that this kind of homogensing process significantly affects the structure of a sprayed product; milling pre-treatment seems to promote the dissolution and coating of drug during HAC process.

3.5. Drug stability

Nifedipine is a photosensitive compound and its photo-oxidation kinetics has been studied by several authors in different conditions (Testa et al., 1979; Duhm et al., 1972; Schlossmann, 1972; Jakobsen et al., 1979; Higuchi and Shiobara, 1978).

To evaluate the protective effect of microencapsulation, the stability of nifedipine was examined exposing the milled mixtures and the corresponding microparticles to a light source of 365 nm. The degradation study produced profiles compatible with first-order kinetics; the calculated oxidation rate constants of milled systems are reported in Fig. 8. The K_{degr} values of the microencapsulate systems constituting 50 and 70% of nifedipine are not significantly different from that of 100%-nifedipine solid system, indicating the absence of a protective effect of coating against degradation. Furthermore, 30%-nifedipine microparticles show a rate constant value higher than that of the other HAC materials and 100%-nifedipine, suggesting a promoting effect of the excipient on the drug photo-oxidation. The enhancing activity of CA seems to be confirmed by the results obtained for non-treated systems; their rate of degradation is higher than that of nifedipine alone and while 50 and 70% drug mixtures show similar K_{degr} values, the rate constant of the 30%-nifedipine mixture is about three times higher. It has also to be noted that the degradation kinetics parameter of the coated systems is always 2.5 times lower than that of the respec-

tive non-treated mixture, irrespective of the drug/CA ratio of the sample. HAC treatment does not modify the stability profile of the bioactive compound, but the potential promoting effect of cetearyl alcohol on the photo-oxidative reaction cannot be neglected, so that CA could not be considered an optimal excipient for nifedipine.

The results of the present work demonstrate that appropriate proportions of nifedipine and CA, when treated by Hot Air Coating, lead to the formation of microparticles. A uniform distribution and a high entrapment efficiency of the drug (almost 50%) is accomplished; the integrity of nifedipine is preserved during treatment and the coating of cetearyl alcohol significantly modifies the drug dissolution rate, although the coating excipient does not seem to improve the photochemical stability of the active molecule.

The homogenizing treatment of the starting materials has a significant influence on the properties of the final product; the milling of nifedipine–CA mixture before HAC leads to a more complete coating of the drug crystals.

In conclusion, the obtained results allow us to hypothesize that following HAC, nifedipine particles are coated by a solid film constituted of cetearyl alcohol and drug. Moreover, we confirm that Hot Air Coating is able to coat solid materials of pharmaceutical interest; therefore, it can be proposed as valid, alternative method of microencapsulation.

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References

Atilla Hincal, A., Suheyla Kas, H., 2000. Micro- and nanoparticulate release systems. In: Wise, D.L. (Ed.), Handbook of Pharmaceutical Controlled Release Technology, Part III. Dekker, New York, pp. 271–429.

Corrigan, D.O., Healy, A.M., Corrigan, O.I., 2003. The effect of spray drying solutions of bendroflumethiazide/polyethylene glycol on the physicochemical properties of the resultant materials. Int. J. Pharm. 262, 125–137.

Duhm, B., Maul, W., Medenwald, H., Patzschke, K., Wegner, L.A., 1972. Pharmacokinetics and biotransformation of radioactively labeled 4-(2′-nitrophenyl)-2,6-dimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine in animals. Arzneimittelforschung 22, 42–53.

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. Pharmacol. Res. 8, 47–54.

Ford, J.L., Mann, T.E., 2002. High Speed differential scanning calorimetry of polymorphic transitions of nifedipine, Science Proceedings of British Pharmaceutical Conference, Manchester, 23–25 September.

Foster, T.S., Hamann, S.R., Richards, V.R., Bryant, P.J., Graves, D.A., McAllister, R.G., 1983. Nifedipine kinetics and bioavailability after single intravenous and oral doses in normal subjects. J. Clin. Pharmacol. 23, 161–170.

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

Hayase, N., Itagaki, Y., Akutsu, S., Inagaki, S., Abiko, Y., 1997. Effects of photodegradation of nifedipine on dog erythrocyte membranes. J. Pharm. Soc. Jpn. 117, 202–210.

Higuchi, S., Shiobara, Y., 1978. Quantitative determination of nifedipine in human plasma by selected ion monitoring. Biomed. Mass Spectrom. 5, 220–223.

Jakobsen, P., Pedersen, O., Lederballe, Mikkelsen, E., 1979. Gas chromatographic determination of nifedipine and one of its metabolites using electron capture detection. J. Chromatogr. 162, 81–87.

Murad, F., 1990. Drugs used for the treatment of angina: organic nitrates, calcium-channel blockers, and β-adrenergic antagonists. In: Goodman Gilman, A., Rall, T.W., Nies, A.S., Taylor, P. (Eds.), The Pharmacological Basis of Therapeutics. Pergamon Press, New York, pp. 764–783.

Pietta, P., Rava, A., Biondi, P., 1981. High-performance liquid chromatography of nifedipine, its metabolities and photochemical degradation products. J. Chromatogr. 210, 516–521.

Rodriguez, L., Albertini, B., Passerini, N., Cavallari, C., Giovannelli, L., 2004. Hot Air Coating technique as a novel method to produce microparticles. Drug Dev. Ind. Pharm. 30, 913–923.

Schlossmann, K., 1972. Fluorometric determination of dimethyl-4-(2′-nitrophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate and its main metabolite. Arzneimittelforschung 22, 60–62.

Testa, R., Dolfini, E., Reschiotto, C., Secchi, C., Biondi, P.A., 1979. GLC determination of nifedipine, a light sensitive drug, in plasma. Farmaco, Ed. Pratica 34, 463–473.

Vippagunta, S.R., Maul, K.A., Tallavajhala, S., Grant, D.J.W., 2002. Solid-state characterization of nifedipine solid dispersion. Int. J. Pharm. 236, 111–123.

Yajima, T., Umeki, N., Itai, S., 1999. Optimum spray congealing conditions for masking the bitter taste of clarithromycin in wax matrix. Chem. Pharm. Bull. 47, 220–225.