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Research paper

Effect of poloxamers on nifedipine microparticles prepared by Hot Air Coating technique

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Abstract

The Hot Air Coating (HAC) technique was used to prepare microparticles consisting of 30% nifedipine coated with different lipid mixtures. Cetearyl alcohol or cetearyl alcohol and 5% or 15% of a poloxamer (Pluronic F68 or Pluronic F127) were used as excipients. HAC products were analyzed in terms of morphology, flowability, thermal properties and nifedipine release behaviour, in order to elucidate the role played by the Pluronics on the physico-chemical and pharmaceutical characteristics of microparticles. HAC particles were spherical and their surface appeared scale-worked; thermal studies demonstrated the existence of relevant interactions among the system components and the dissolution experiments led to the hypothesis that the drug is released primarily by diffusion through the lipid coating: the poloxamer and its concentration have a significant influence on the pharmaceutical properties of the dosage form, as shown by the *a* parameter of Weibull model.

Keywords: Nifedipine; Hot Air Coating; Microparticles; Poloxamers; Drug release rate; Weibull model

1. Introduction

Nifedipine is an oral calcium-blocking agent used in the treatment of angina pectoris and hypertension; although it is absorbed almost completely, it displays low bioavailability because of its short biological half-life with significant fluctuations in plasma concentrations [1] and its extensive first-pass metabolism [2].

Numerous attempts have been made to improve its therapeutic efficacy and patient compliance; osmotic controlled release tablets and pellets, granules and solid dispersions have been proposed and in such systems different carriers (urea, lactose, PEG, PVP, phospholipids, polycaprolacton, acrylic polymers and PEO/PPO/PEO copolymers) were employed [3,4]. The PEO/PPO/PEO triblock copolymers are commercially available non-ionic macromolecular surface active agents which have attracted considerable interest in the biotechnological and pharmaceutical fields for their unique surfactant, thermogelling and bioadesive properties, low toxicity and minimal immune response [5].

PEO/PPO/PEO copolymers have been used to prepare matrix erosion-controlled pellets of nifedipine that release the drug following zero-order kinetics [6].

Recently [7,8] we investigated the use of the Hot Air Coating technique for the preparation of a microencapsulated dosage form. In this spray process, a solid mixture of the drug and the excipients is aspirated into the HAC apparatus by a Venturi-effect. The powder mixture meets a flow of hot air injected into the instrument at a controlled temperature (over the melting point of the lipid excipient) and at a known and constant pressure; under these conditions, the excipient melts and surrounds the drug particles, forming a thin continuous solid coat. With this technique, employing a cetearyl alcohol–nifedipine mixture, spherical microparticles able to slowly release the drug were produced [8].

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The present study was undertaken to develop and characterize the microparticles prepared by Hot Air Coating and constituted of nifedipine coated with PEO/PPO/PEO copolymer-cetearyl alcohol mixtures, to evaluate the physico-chemical and pharmaceutical properties of such microparticulate systems and to study the effect of the polymeric surfactant utilized as co-excipient on the morphology and release performances of the HAC-prepared dosage forms.

2. Materials and methods

2.1. Materials

Cetearyl alcohol (C) and nifedipine (N), conforming to EP 5 and USP 28 respectively, were purchased from ACEF Spa (Piacenza, Italy). Pluronic F68 and Pluronic F127 were supplied by Sigma (St. Louis, MO, USA). All other chemicals and reagents were of analytical grade.

2.2. Preparation of microparticles

Cetearyl alcohol and Pluronic F68 or Pluronic F127 were milled and sieved separately and the 212–355 μm fractions were used: appropriate amounts of fatty alcohol and poloxamer (F68 or F127) were manually mixed to give the selected coating mixture for the drug. The composition of the studied systems is reported in Table 1.

Microparticles consisting of nifedipine and cetearyl alcohol or cetearyl alcohol–poloxamer mixture were obtained by Hot Air Coating: after milling homogenization (2 cycles 30″ each at 19,500 rpm), the drug-excipient mixtures were treated in the HAC apparatus, fed with air at 80 °C under a pressure of 250 kPa.

2.3. Morphology and flowability of systems

The shape and surface characteristics of the microparticles were observed by scanning electron microscopy (SEM) using an ISI 100 A microscope (International Scientific Instruments). The material to be tested was coated with gold and photographed.

The flowability of drug-excipient mixtures and microparticles was assessed as previously reported by Nazzal et al. [9]. Briefly, the angle of spatula was measured using a protractor and a steel spatula with a 9×45 mm blade. The spatula was inserted to the bottom of the heap that was carefully built by dropping the material through a funnel at a height of 8 cm from the horizontal surface. Then the angle of the heap formed on the spatula, withdrawn vertically, was measured as the angle of spatula.

Table 1
Composition of the systems

System	Composition (%)			
	N	C	Pluronic F68	Pluronic F127
N	100	–	–	–
NC	30	70	–	–
NCF68-5	30	65	5	–
NCF68-15	30	55	15	–
NCF127-5	30	65	–	5
NCF127-15	30	55	–	15

2.4. Thermal analyses

Samples of single components, mixtures and HAC-processed materials were examined by high-speed DSC, using a Pyris 1 DSC equipped with a cooling system (Perkin-Elmer, USA) at a heating rate of 200 °C min^{-1} in a stream of N_2 gas (20 ml min^{-1}); 5–10 mg of the samples was placed in sealed pans and analyzed between 20 and 220 °C. The instrument was calibrated with indium.

The thermal properties of the studied systems were also examined by thermogravimetric analysis. The TGA measurements were carried out on a Pyris 1 TGA (Perkin-Elmer, USA) calibrated on Curie point references (alumel, nickel and perkalloy); 10–15 mg of the samples was subjected to a scanning rate of 20 °C min^{-1} under 20 ml min^{-1} nitrogen purge and heated in open platinum pan up to 550 °C.

2.5. In vitro dissolution studies

The amount of drug in the microparticles was determined as previously reported [8].

Nifedipine alone and microparticles of nifedipine were submitted to the dissolution assay with the USP Apparatus I (basket method): 12 mg of pure drug or an amount of microparticles equivalent to 12 mg of nifedipine was used for the test. Double distilled water (900 ml maintained at 37 °C) was used as the dissolution medium with a stirring rate of 100 rpm. The dissolution equipment was maintained in the dark. At pre-determined time intervals, 5 ml samples of the medium were withdrawn and immediately replaced by the same volume of fresh dissolution medium. The samples were filtered through a 0.45 μm membrane filter and analyzed spectrophotometrically at 237 nm for drug content (Lambda 35 – Perkin-Elmer, USA).

Each test was carried out in triplicate and the dissolution data were analyzed using the Weibull function [10]:

$$\frac{M_t}{M_\infty} = 1 - e^{-at^b} \quad (1)$$

Regression and statistical analyses were performed using Excel for Windows XP.

3. Results

3.1. Morphology and flowability of systems

The mixtures submitted to the spray treatment were constituted of particles of prismatic form and of differing size (Fig. 1(a)), the biggest ones being particles of excipients

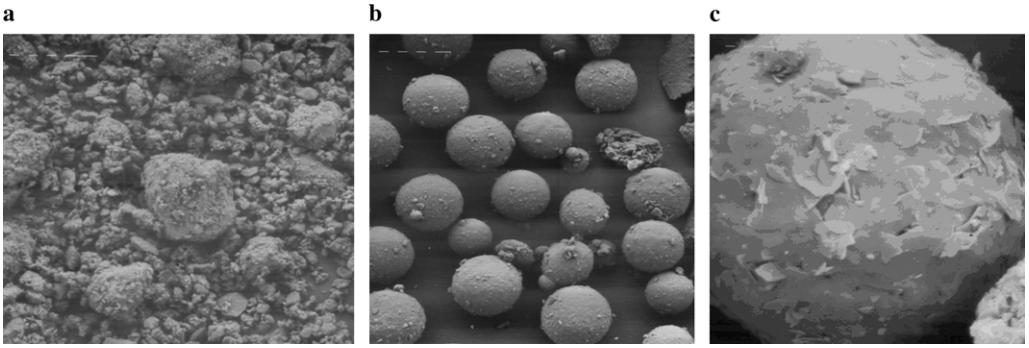

Fig. 1. SEM-micrographs of (a) nifedipine-cetearyl alcohol–Pluronic F68 mixture [30:55:15] (90×) and the corresponding HAC microparticles (b: 42×), (c: 420×).

(212–355 μm) and the smallest nifedipine (75 μm). In Figs. 1(b) and (c) the micrographs of microparticles containing 15% Pluronic F68 (fraction 212–355 μm) are shown; the surface of the microparticles under high magnification (Fig. 1(c)) does not appear smooth, but constituted of overlapped scales, sometimes with small particles adherent to the surface.

The angles of spatula of nifedipine–cetearyl alcohol and nifedipine–cetearyl alcohol–Pluronic mixtures and of microparticles obtained from them, are reported in Table 2. The flowability of systems passed through the HAC apparatus was always higher (lower angles of spatula) than that of the non-treated mixtures.

3.2. Thermal analysis

The high-speed DSC analysis was carried out on all the studied systems: as an example, in Fig. 2 the calorimetric profiles of the pure components, the binary system (NC) and the system containing 5% Pluronic F127 (NCF127-5) before and after HAC treatment are reported. The endothermic peak in the lowest range of temperatures (50–110 °C) corresponds to the melting of the excipients (melting temperature 49–56 °C; Pluronics 52–58 °C) and that at the highest temperatures (170–220 °C) to the drug (172–174 °C). In the case of drug–excipient mixtures and microparticles, significant shifts of the onset temperature for both peaks can be observed and for microparticles the enthalpies of the drug are slightly lower than those of the corresponding starting mixtures.

The thermal behaviour of the pure components, drug–excipient mixtures and microparticles analyzed by thermogravimetry is depicted in Figs. 3–5 where the first derivative (DTG) curves for non-treated mixtures, microparticles and pure components are reported. Cetearyl alcohol, nifedipine and poloxamers show separate steps of degradation/evaporation: the signal in the range 175–275 °C corresponds

Table 2
Flowability of non-treated mixtures and microparticles obtained by HAC

System	Angle of spatula (°)	
	Mixtures	HAC microparticles
NC	44.4	32.2
NCF68-5	44.4	35.9
NCF68-15	43.4	31.8
NCF127-5	44.8	39.7
NCF127-15	43.7	34.7

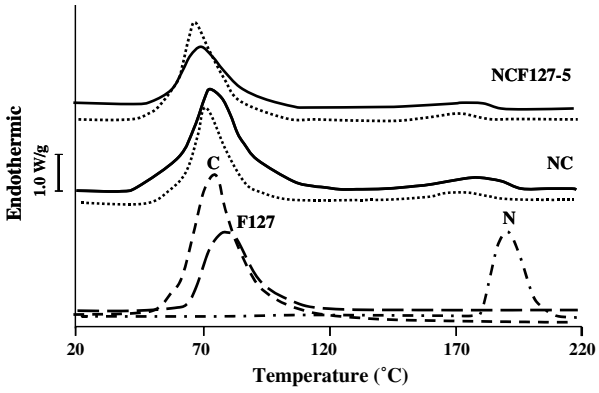

Fig. 2. DSC runs of pure components (N = nifedipine; C = cetearyl alcohol; F127 = Pluronic F127), binary (NC) and ternary (NCF127-5) mixtures (···) and microparticles obtained from them (—).

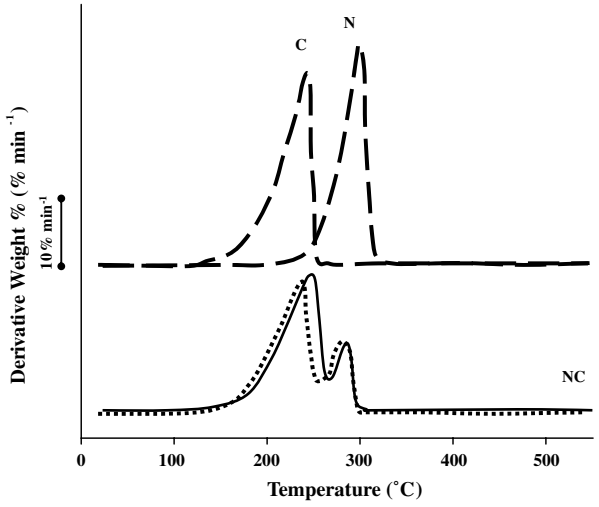

Fig. 3. DTG plots for binary systems. Pure components (– –), microparticles (—), mixture before HAC treatment (···).

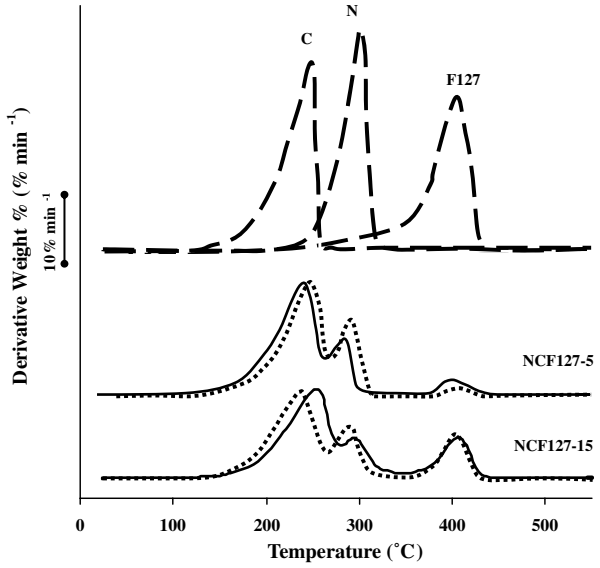

Fig. 4. DTG plots for systems containing 5 and 15% Pluronic F127. Pure components (– –), microparticles (—), mixture before HAC treatment (···).

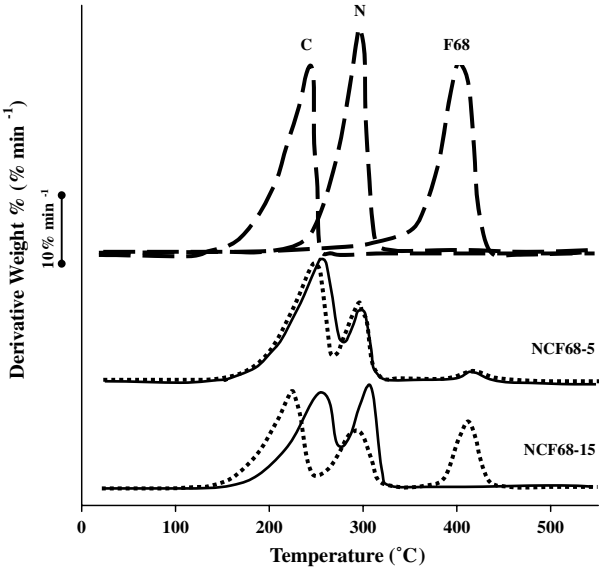

Fig. 5. DTG plots for systems containing 5 and 15% Pluronic F68. Pure components (– –), microparticles (—), mixture before HAC treatment (···).

to the fatty alcohol (C), the one from 275 to 320 °C to the drug (N) and the third above 350 °C to the poloxamer (Pluronic F68 or F127).

The weight loss for the cetearyl alcohol–nifedipine mixture occurs in two stages (Fig. 3) and for mixtures containing the polymeric surfactant three steps of decomposition are present (Figs. 4 and 5). Each step corresponds to the evaporation (C) or degradation (N and poloxamers) of a pure component.

In the DGT profile of NC microparticles a significant shift of the onset of degradation is observed for the drug, while for the excipient no remarkable changes can be noted. The presence of the poloxamer in the NCF68 and NCF127 microparticles leads to evident modifications in the onset temperatures, mainly for cetearyl alcohol and nifedipine.

3.3. Release studies

In Figs. 6 and 7, the release profile of nifedipine from microparticles prepared with Pluronic F127 or F68 is compared to that of microparticles without Pluronics and to the dissolution curve of the drug alone. In the dissolution profile of pure nifedipine, after a short lag time, a fast increase of the nifedipine concentration in solution up to the maximum can be observed. The release curves of the drug from the microparticles show an exponential-like shape without a lag time. The release profile of nifedipine from NCF127-5 system superimposes that from NC system, while the amount of drug released from NCF127-15, NCF68-5 and NCF68-15 microparticles is always higher than that from nifedipine–cetearyl alcohol HAC products.

Release and dissolution data were fitted to the Weibull function and Table 3 summarizes the results of the regres-

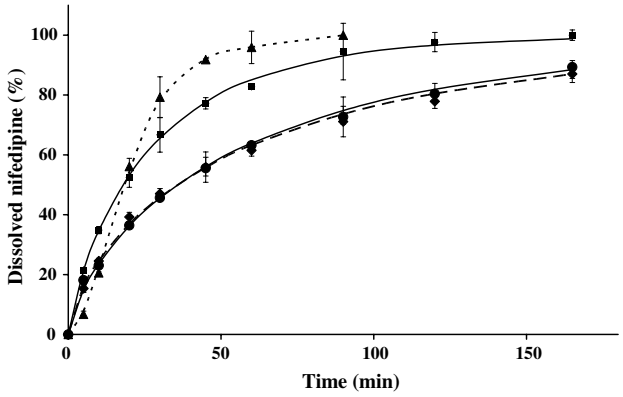

Fig. 6. Dissolution profiles of nifedipine (▲) and nifedipine microparticles: NC (♦); NCF127-5 (●); NCF127-15 (■). The values are means of three experiments; error bars represent the 95% confidence limits.

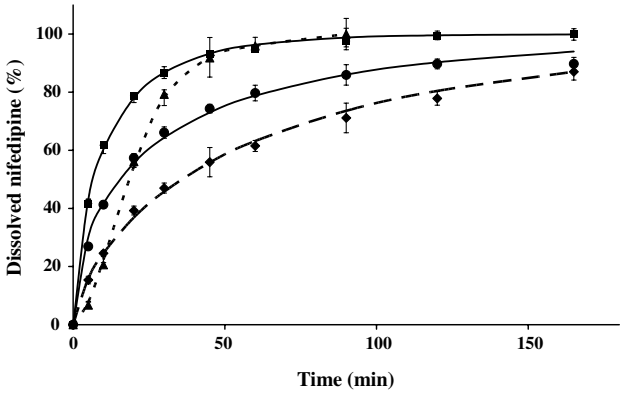

Fig. 7. Dissolution profiles of nifedipine (▲) and nifedipine microparticles: NC (♦); NCF68-5 (●); NCF68-15 (■). The values are means of three experiments; error bars represent the 95% confidence limits.

Table 3
Estimates of the Weibull parameters for nifedipine and nifedipine microparticles and related statistics

System	Parameter			
	a	*b*	R^2	F^a
N	0.0059	1.6299	0.9897	382.9
NC	0.0553	0.7069	0.9958	1406.6
NCF68-5	0.1411	0.5844	0.9939	976.4
NCF68-15	0.1698	0.7370	0.9907	636.8
NCF127-5	0.0500	0.7349	0.9942	1021.6
NCF127-15	0.0653	0.8072	0.9965	1717.0

[a] $p < 0.00005$.

sion analysis: scale (*a*) and shape (*b*) parameters of Weibull equation are reported together with R^2 and *F* statistics. The value of the kinetic parameter *b* for the pure nifedipine reflects the sigmoid shape of its dissolution curve, while for microparticles *b* values are consistent with the exponential trend of the release profiles. Moreover, for microparticles, the *a* values for systems containing Pluronic F127 are lower than those with Pluronic F68 and are always higher than that obtained for drug-cetearyl alcohol microparticles. The *a* parameter value raises for increasing percentages of the copolymer excipient.

4. Discussion

In the HAC technique, a mixture of powders of low melting temperature substances and a drug is processed in a stream of hot air that allows the melting of the excipient and the coating of the bioactive compound particles [7,8]. In the present work, the same temperature and pressure of the transport fluid (80 °C and 250 kPa, respectively) are used to process both binary (cetearyl alcohol and nifedipine) and ternary (cetearyl alcohol, nifedipine and poloxamer) mixtures. The selected operating conditions lead to products significantly different from the starting mixtures. As shown in Table 2, the spray treatment increases the flowability of both binary and ternary mixtures and the type and amount of the copolymer have a significant effect on this property: the angles of spatula of NCF68 microparticles are lower than those of NCF127 systems and, for increasing percentages of both copolymers, higher flowabilities (lower angles of spatula) are observed. This finding suggests that the spray process leads to the formation of rounded particles. In fact, visual and microscopic inspection (Fig. 1) reveals that HAC products are spherical particles whose surface appears scale-worked. The fast movement of the mixture through the apparatus and the limited time of exposition of the material to high temperature can justify the surface morphology of microparticles.

The results of thermal studies indicate that the poloxamer has a profound influence on the physico-chemical and pharmaceutical properties of microparticles. The high temperature scanning rate adopted in the DSC runs can evidence the presence of polymorphs, but the depression of melting enthalpy of the drug observed in our case cannot be associated with its polymorphic transition: changes in the onset temperature are observed for both excipient(s) and drug and they can be ascribed, according to Horvat [11], to the interactions among the system components during the DSC run. So, the HAC process does not determine any polymorphic transformation of the stable polymorph – Form I – used as the starting material. Pluronics do not modify the crystallinity of the drug, the DSC profiles of systems containing these components being similar to those of Pluronic-free ones.

Thermogravimetric analysis gives some interesting information about the interactions among the components of the studied systems. The DTG patterns of non-HAC and HAC systems constituted of nifedipine and cetearyl alcohol (Fig. 3) are very similar and largely superimposed, while, for the microparticles containing Pluronics, the curves are different compared to the corresponding mixtures (Figs. 4 and 5). Microparticles containing the copolymer show significant shifts of the decomposition onset of cetearyl alcohol and drug, more remarkable in the presence of 15% poloxamer and in particular when Pluronic F68 is employed. Moreover, it should be noted that in the profile of NCF68-15 microparticles the DTG signal of Pluronic F68 disappears and that of nifedipine increases notably: for NCF127-15 microparticles the derivative peak of the copolymer is still present and that of the drug is less evident than in the DTG profile of the mixture before HAC treatment. Although the interactions among the formulation components during the thermal run cannot be neglected, the observed changes in DTG profiles are to be ascribed to the interactions established during the spray treatment and in particular to the partial solution of nifedipine and poloxamer in cetearyl alcohol. Moreover, a partial solution of the drug in the polymeric surfactant melted during HAC process is possible: this hypothesis is supported by the results obtained by Ho et al. [4] on nifedipine–Pluronic F68 systems. Thus the TG results demonstrate the presence of a stronger interaction of the drug with Pluronic F68 than with Pluronic F127.

The presence of the poloxamer in the microparticles has a profound effect on the release of the drug. The nifedipine release profiles from Pluronic-containing microparticles are considerably different from the dissolution of the pure drug and the curve of NC microparticles (Figs. 6 and 7). The release of the drug is not modified when Pluronic F127 is used at 5%, while it is faster with 15% of this poloxamer. On the other hand, 5% Pluronic F68 is sufficient to enhance the nifedipine release and the effect is more evident increasing its percentage in the formulation. The higher hydrophilicity of Pluronic F68 respect to F127 poloxamer can explain the differences in the drug release observed for the microparticles containing these polymeric surfactants.

The results of the regression analysis carried out applying the Weibull equation to the data from the dissolution assays indicate that the release of nifedipine from HAC microparticles is satisfactorily described by this model (Table 3). The *b* parameter values for microparticles are

lower than that of nifedipine alone. Papadopoulou et al. [10] and Kosmidis et al. [12] demonstrated that values of $b > 1$ are indicative of a complex release mechanism, while for $0.69 < b < 1$ the diffusion (0.69–0.75) or the diffusion with the contribution of another mechanism (0.75–1) has to be considered. Therefore, in our case, the b parameter for pure nifedipine indicates the existence of a predominant mechanism related to the erosion of drug particles; the low b value for HAC treated materials is comparable to that of systems from which the drug is primarily released by diffusion. Although the surface morphology of microparticles seems to indicate an incomplete, discontinuous coating of the drug, the results of the release assays and those from the thermal studies suggest that HAC microparticles are microencapsulated systems that deliver nifedipine primarily by diffusive transport through the excipient coating.

The a parameter of the Weibull model can be regarded as the kinetic parameter of the release process. The calculated values of this parameter (Table 3) confirm that the release rate of nifedipine from NCF68 microparticles is significantly higher than from systems containing Pluronic F127. An amount corresponding to 15% of the co-excipient rises the a value for both NCF68 and NCF127 microparticles.

The obtained results substantiate that during the spray treatment significant interactions were established between the drug and the excipients; the high release rate observed for NCF68 systems can be justified by the more hydrophilic coating of microparticles prepared with Pluronic F68.

5. Conclusions

The HAC process allows the production of microparticles of nifedipine coated with cetearyl alcohol or Pluronic–cetearyl alcohol mixtures. The microparticles are spherical and their surface appears to be constituted of overlapped scales. The HAC products release the drug primarily by diffusion through the lipid coating. The differences in the release profiles can be ascribed to phenomena that occur during the spray process (nifedipine solution in the melted excipient and drug coating). The release of nifedipine from HAC microparticulate systems can be modulated by the appropriate choice of the type and proportion of the poloxamer used as co-excipient.

Acknowledgement

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