A Factor Analysis for Complex Systems Containing Nimesulide

G. CESCHEL,[1] P. MAFFEI,[1] M.C. DRAGANI,[2] M.M. GENTILE,[2] C. DI PALMA,[2] M.L. MORELLI,[1] A. FINI[3]

[1]Department of Pharmaceutical Sciences, Via San Donato 19/2, University of Bologna, 40127, Italy

[2]Dompè S.p.A., Via Campo di Pile, 67100 L'Aquila, Italy

[3]Chemical Science Institute, Via San Donato 15, 40127 Bologna, University of Bologna, Italy

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ABSTRACT: Binary systems containing Nimesulide and PEG 4000 were prepared by the melting method in the concentration range 3–25% w/w of the drug. The systems are homogeneous in the molten state, while, after cooling, two phases were formed of different density. They were manually separated and separately studied. Upper phases are richer in PEG 4000, while the lower ones contain the drug at levels even higher than those of the starting mixtures. The two phases were examined by DSC and UV techniques; high dissolution rates were observed with upper phases, while lower phases did not display improvement with respect to a physical mixture or micronized drug. With the aim to avoid phase separation, a third component was added to the binary system containing 5% w/w drug, during the melting. The ternary systems were prepared containing sodium dodecyl sulfate, triethanolamine, polysorbate 80, poloxamer, and cetomacrogol: a homogeneous phase was obtained only in two cases (with the addition of sodium dodecyl sulfate and triethanolamine), but only in the presence of triethanolamine dissolution rate was improved. Finally, a factor analysis was performed for complex systems containing a combination of the four additives, each one at two concentrations (1.25 and 2.5% w/w), to evaluate the optimum system in terms of both kinetic and composition parameters. Results suggest that additives affect mainly the physical aspect of the formulation rather than the kinetic behavior, which appears little improved only in a few cases. J Pharm Sci 94: 639–650, 2005

Keywords: nimesulide; factor analysis; complex systems

INTRODUCTION

The dissolution in gastrointestinal fluids of poorly soluble drugs is a crucial point that must be taken into account in preformulation and formulation studies of oral dosage forms. In fact, solubility and dissolution rate of drugs affect absorption and bioavailability.[1] In most cases, the gastrointestinal absorption of drugs is due to passive diffusion described by the Fick equation, so that the higher the gastrointestinal fluid concentration, the better are the absorption and bioavailability.

The drug dissolution in aqueous media is described by the Noyes-Withney equation:

$$dC/dt = SD/h(C_S - C) \quad (1)$$

where dC/dt is the dissolution rate, S is the specific surface of the drug particles, D is the diffusion coefficient, C_S is the drug solubility, and h is the stagnant diffusion layer thickness. This equation shows the possibility to improve the dissolution rate by increasing C_S.

The improvement of both solubility and dissolution rate by inserting a drug into a solid dispersion

Correspondence to: G. Ceschel (Telephone: 39 051 2095620/619; E-mail: ceschel@biofarm.unibo.it)

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has been widely discussed and reported in a number of articles.[2–11]

Parameters such as composition, molecular weight, crystallization, amorphization, melting point, solubility, surface activity, and dissolution ability have been widely considered as important factors for the release and availability of the drug, as well as a number of disadvantages arising by the use of a solid dispersion or its mode of preparation by the comelting method.

The list of the drugs examined in the form of solid dispersions together with PEGs of different types is very long,[12–17] but none containing Nimesulide (NIM), a modern NSAID, which presents problems of solubility and dissolution rate. Moreover, very few articles can be found in the literature concerning the increasing of NIM solubility.[18–20]

In this work NIM was chosen as a drug model, because it is important to improve its dissolution behavior and its solubility, being this drug 1.95 μg/mL soluble, at acid pH, and 59.31 μg/mL at pH 7.4.[21]

The study of the system Nimesulide/PEG 4000 (NIM/PEG) was carried out along three different guidelines. In the first part of the study only binary systems were prepared as physical mixtures and as solid dispersions by comelting method, and examined their morphological aspect, crystallinity and release characteristics, concerning drug dissolution. Because on cooling the systems displayed an evident phase separation, in a second step ternary systems were considered, adding to previous systems either surfactants, or a basic substance with the aim to avoid this phenomenon.[22–24]

The surfactants should operate reducing the interfacial tension, and making easier the dispersion of NIM inside the matrix. Moreover, they might increase the drug affinity for aqueous media, improving the dissolution. The polymers should increase the matrix viscosity, avoiding the possible NIM precipitation during the cooling stage and producing a more homogeneous drug distribution. The basic compound should form a salt with the NIM sulfonamide group and improve the solubility into the hydrophilic matrix.

Finally, as a third step, by means of a factor analysis, we evaluated, through dissolution tests, the possible synergic action of all these auxiliary agents, present together and forming complex systems at two different concentration levels. A factor analysis performed on the dissolution parameters obtained for 16 different complex systems should find the optimum combination useful for practical applications.

EXPERIMENTAL

Materials

Nimesulide (NIM) was purchased by FLAMMA (Bergamo, Italy). Polyethylene Glycol 4000 (PEG 4000) was generously supplied by EIGENMANN VERONELLI (Milano, Italy). Poloxamer Lutrol L-127 (POL) was generously supplied by BASF ITALIA (Comun Nuovo, Bergamo, Italy). Polyethylene Glycol Cetyl Ether Cetomacrogol 1000 (CET) and Polysorbate-80 were generously supplied by Respharma (Milano, Italy). Sodium dodecyl sulfate (SDS) was purchased by I.C.M. (Milano, Italy). Triethanolamine (TEA) was purchased by BASF ITALIA (Comun Nuovo, Bergamo, Italy). All other materials and solvents used were of analytical reagent grade as received.

Preparation of Physical Mixtures and Solid Dispersions

Comelted Binary Systems

Physical mixtures were first prepared according to the following weight compositions: NIM content was in the range of 3–25% w/w with PEG 4000. The systems were indicated as BIN-3, BIN-5, BIN-10, BIN-15 BIN-20, and BIN-25, respectively. The binary mixtures thus obtained were melted in a thermostated container to obtain the solid dispersions: at temperature of about 60°C, PEG melts and NIM gets soluble in the melted mass, originating a yellow and transparent system in each case. The systems were then left to cool inside a graduated tube at room temperature. On cooling at room temperature, two phases were visible at macroscopic level, and they were accurately manually separated and separately studied as two different systems, called as upper (U) and lower (L) phases. In some cases the separation could not be carried out precisely, due to the absence of a clear differentiation of the phases and especially when the two phase ratio was far from 50:50.

Ternary Systems

Two percent w/w of the following substances was added to the binary system containing NIM 5% w/w (BIN-5): sodium dodecyl sulfate (SDS), polysorbate 80 (PSO), poloxamer (POL), and cetomacrogol 1000 (CET). Two further systems were prepared containing one 1% w/w SDS + 1% w/w CET and the other one adding triethanolamine

(TEA) 2.5% w/w, to obtain a stoichiometric salt with the acidic group present in NIM molecule (5% w/w); accordingly the concentration of PEG was reduced to 92.5% w/w. Throughout the article, the ternary systems were indicated as TER-SDS, TER-PSO, TER-POL, TER-CET, TER-CET/SDS, and TER-TEA, respectively. Each third component was added during the melting of the system NIM/PEG, and the ternary systems thus obtained were left to cool at room temperature.

The phases of all the mixtures were separately grounded before analysis.

Complex Systems

The content of each additive was considered at a low (1.25% w/w) and high (2.5% w/w) level, indicated respectively with (−) and (+) symbols. Sixteen systems were prepared, suitably combining the number of the additives (4) and their content levels (2): each of them contained constant concentration of the drug (10% w/w) and varying the PEG concentration. The additives were added to the molten phases, containing NIM and PEG.

Morphologic Analysis

Some macroscopic characteristics of solid dispersions, such as the system homogeneity (each phase showed a different color) and the relative volume of different phases, were examined. The same samples were investigated by optical microscopy (ZEISS model 2064395—magnification: 50×).

Drug Content Analysis

A UV/VIS spectrophotometer Perkin Elmer (mod. Lambda), was used to detect the content of the drug into the systems and the drug dissolved in the *in vitro* test. The materials obtained by the comelting were dissolved in methanol and the absorbance read versus a blank containing the same amount of PEG dissolved in methanol. Measurements were carried out at 300 nm.

The NIM content in each sample was evaluated by means of a previously prepared calibration curve. When two phases were present in the final systems, the composition was determined for both upper and lower phases. When only one phase was present, the composition of upper and lower portions was anyway determined to verify the homogeneity of the system.

Differential Scanning Calorimetry

Thermal analysis was carried out by a Perkin-Elmer instrument (model DSC7), under dry nitrogen purging gas flux. The instrument head thermoregulation was guaranteed by connection to a cooling system. Samples with weight within the range of 1–5 mg were sealed in 50-μL aluminum pans with holes (Perkin-Elmer). Heating and cooling rates of 5°C/min in the temperature range of 25–160°C were used.

In Vitro Dissolution Test

A paddle dissolutor, type AT7, according to USP23/NF, was used. Dissolution fluid was 500 mL of a pH 7.4 phosphate buffer. Temperature was thermostated at 25°C and the buffer was stirred at 50 rpm. The mass of samples added to the dissolution medium was calculated to contain about 24 mg of NIM. A continuous flow system was used and the blank corrected absorbance at 300 nm was recorded sequentially in a 5-min cycle. A 20 mL/min. flow was guaranteed by a peristaltic pump (Watson-Marlow model RB). The fluid was filtered (0.45 μm cellulose acetate screen filter) prior to enter the working cell. The considered parameters were: the initial dissolution rate, taken as the slope of the profile within the first 15 min; the NIM percent released after 1 h of dissolution and the time necessary to obtain 50% of dissolution of the drug (t_{50}).

Factor Analysis

A 2^4 full factorial design was used to optimize the composition of solid dispersion systems, designed in terms of lowest (−) and highest (+) levels of the independent variables of the system. The two levels were chosen according to the solubility of each additive in PEG 4000 and then transferred to PEG 4000 at the highest values found. As an example, the complex system (− − −) contained 1.25% w/w of each additive, together with 10% w/w NIM and 85% w/w PEG; the complex system (+++) contained 2.50% w/w of each additive, together with 10% w/w NIM and 80% w/w PEG.

The concentrations of the different excipients (X_1 for SDS, X_2 for CET, X_3 for TEA, and X_4 for POL), added to 10% NIM/PEG solid dispersions were chosen as independent variables of the system. The different excipients were used at two levels: 1.25% w/w (−) or 2.50% w/w (+). The dependent variables (Y) in this case were three

kinetic parameters, measured during the dissolution tests: initial dissolution rate (as Y_1), the time necessary to obtain 50% of dissolution (as Y_2) and the % released after 1 h (as Y_3). For each dependent variable, the polynomial equations that completely describe the system were also calculated. The general expression for these equations is as follows:

$$Y = a_0 + a_1X_1 + a_2X_2 + a_3X_3 + a_4X_4$$

Mathematical elaboration of experimental data was carried out by the computer program NEMROD.[25]

RESULTS AND DISCUSSION

Binary Systems

DSC analysis is widely used to investigate the structure of solid dispersions and to evidence possible drug/matrix interactions, through the shape of the peaks, the melting temperatures, and the specific melting heats offered by the thermograms.[7,12]

Figure 1 shows the thermograms carried out separately with drug and excipient. NIM shows a quite narrow melting peak and a melting point at $T = 146^{\circ}C$ (Fig. 1A, a). The cooled phase lacks crystallinity, because a second scanning, after 30 min, does not reveal any endothermic peak (Fig. 1A, b). Crystallinity was recovered after 24 h, by the presence of a melting signal with the same temperature peak and heat of fusion as the first scanning (Fig. 1A, c). The melting point for PEG is at $T = 58^{\circ}C$, with a wide and asymmetric peak shape due to its chemical composition, which is a mixture of macromolecules having molecular mass around 4000.

The heating curves for NIM/PEG physical mixtures at NIM concentrations in the range of 5–60% w/w show the melting peak of the matrix and of the drug. The first ones are not significantly shifted to higher temperatures (m.p. around $T = 60^{\circ}C$), compared to PEG alone, but display the same peak shape. Peaks, whose height increases with NIM concentration in the mixture, are present for NIM at 146°C. This behavior can be explained as due to a partial dissolution of drug into the molten matrix during the heating run. Thermograms of upper and lower phases for all BIN systems show only the PEG melting peak. Thermal cycles were also performed: to a previous heating step, a cooling step followed at the same cooling rate (5°C/min.): no exothermic signal due to liquid/solid transition for NIM was detected, for the mixtures and also for NIM alone; while PEG crystallization yielded an evident exothermic peak, both alone or in the physical mixtures of different compositions.

Thermal analysis did not show any notable difference regarding thermal events of NIM, PEG, and their physical or comelted mixtures, even though some NIM influence on thermal crystallization of PEG can be appreciated. The main reason is that the situation inside the system is altered as far as scanning proceeds.

From the examination of thermograms it can be suggested: (a) NIM dissolves into melted PEG, even during the scanning, reaching saturation at the scanning temperatures, when its concentration overcomes 20% w/w; (b) previous comelting leaves NIM in a molecularly dispersed or amorphous form that DSC cannot appreciate; (c) the presence of PEG prevents or slows down possible recrystallization of NIM; (d) the presence of NIM affects the recrystallization of PEG and at high drug concentration (>40% w/w) the crystallization of PEG is prevented (at least in short times); (e) the recover of a crystalline structure appears delayed, even when NIM is pure: the melting peak reappears after 24 h, while PEG recovers its crystallinity soon after solidification and its melting peak is always visible; (f) in the presence of NIM, the PEG melting peak is no more regular and symmetric, and decreases as NIM concentration increases. These observations are equally valid for both phases recovered after cofusion for all the compositions.

The main characteristic aspect of the NIM/PEG systems obtained by comelting is a phase separation, observed after a slow cooling at room temperature. Probably this aspect is due to an initial mutual solubility in the molten state, from which two saturated solid phases originated at the two opposite sites of a phase diagram of the system. Because the study of the phase diagram was not the main aim of this research, we leave out this aspect to give a detailed insight into this step of the research. Moreover, because these observations concerning systems are probably far from an equilibrium state, further considerations could appear incautious, in view of the fact that these systems, more properly, should be considered as supersaturated and thus metastable systems and destined to change with time.

During the comelting step, heating was prolonged until a complete miscibility was observed in the melted state; phase separation started during

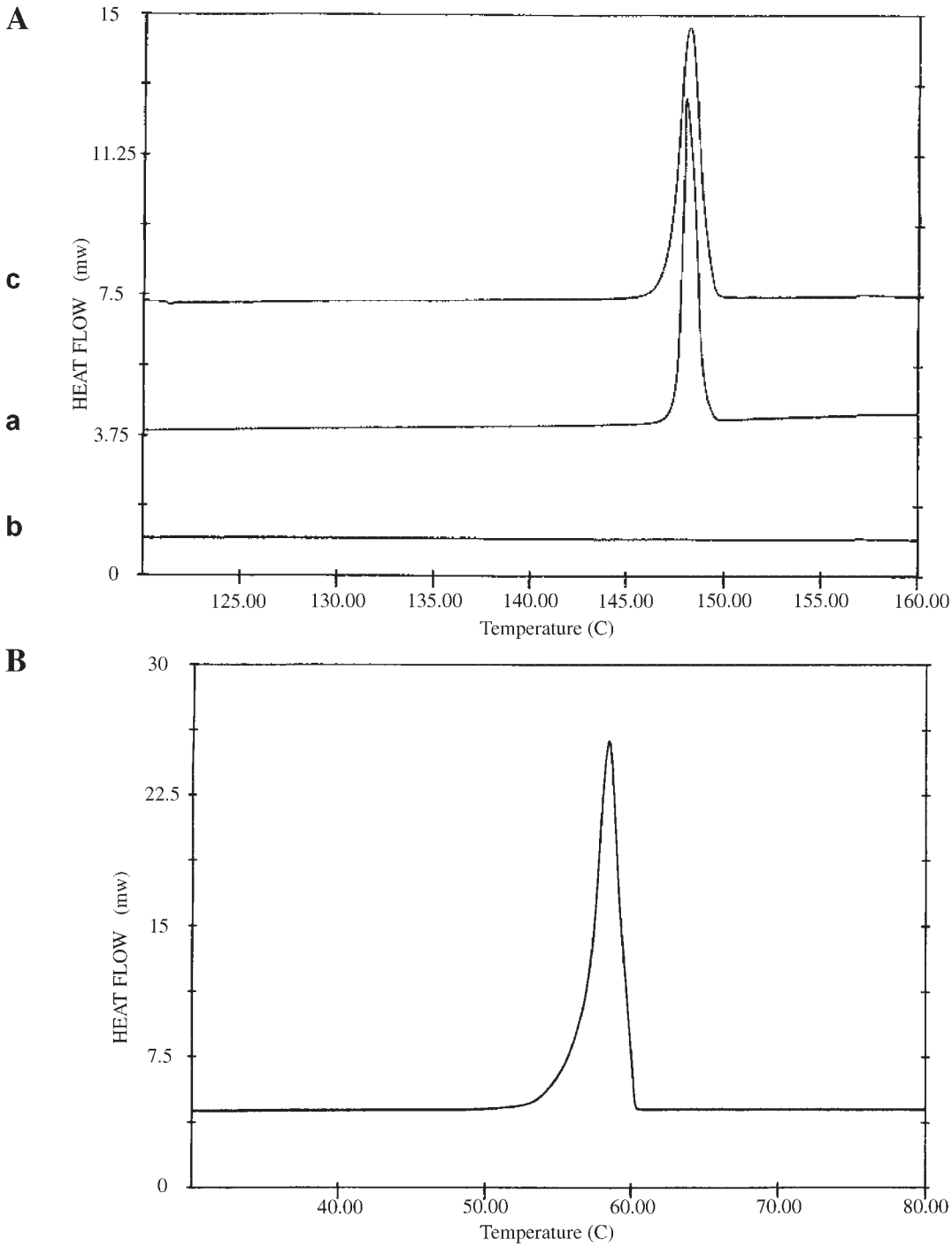

Figure 1. Thermograms of pure components. (A) Nimesulide: (a) first melting; (b) second melting, after a cooling run; (c) third melting, after 24 h at room temperature from the first melting. (B) PEG 4000.

the cooling step, when the two phases were still liquid, and was evident after solidification. Table 1 reports the NIM content in upper and lower phases: the different concentration values confirm the nonhomogeneity of the systems: the lower phase is richer in drug, and the levels are even higher than those of the starting mixtures.

It can be hypothesized that lower phases contain PEG dissolved into NIM, while the upper phase is constituted by NIM dissolved into PEG.

Table 1. NIM Content (% W/W) in the Lower (L) and Upper (U) Portion of the Different Bin Systems

System	Phase	NIM Content % w/w	V_U/V_L Ratio
BIN-3	U	1.42 SD 0.12	90:10
	L	16.41 SD 0.11	
BIN-5	U	1.81 SD 0.01	80:20
	L	23.24 SD 0.98	
BIN-10	U	2.67 SD 0.12	75:25
	L	24.44 SD 0.26	
BIN-15	U	2.94 SD 0.10	75:25
	L	36.41 SD 0.29	
BIN-20	U	7.49 SD 0.08	
	L	39.76 SD 0.87	
BIN-25	U	8.85 SD 0.78	70:30
	L	45.73 SD 1.34	

Considering the systems up to NIM 15% w/w, it can be appreciated a fair constancy of NIM concentration into upper phases: $2.2 \pm 0.6\%$ w/w; this value can be considered approximately the apparent solubility of NIM into PEG. As a consequence higher values, observed for the systems BIN-20 and BIN-25, can be considered as due to a supersaturation, not yet evolved to equilibrium at the time of the examination.

This will be confirmed (see below) by the dissolution profiles of upper phases that practically overlap, independently of the starting concentration.

Table 1 also shows the volume ratio of the two phases: this is different for different systems, and changes according to NIM concentration. The volume ratio between lower and upper phases ranges from 10:90 for 3% w/w drug concentration to 30:70 for higher concentrations (20 and 25% w/w). It was not possible to accurately measure the relative volume because the boundary between the two phases was not clearly definite, and it was difficult to carry out the division of the final mass and to evaluate the phase ratio.

Figure 2 represents the dissolution profiles of upper and lower phases of BIN systems, in comparison with micronized NIM and a physical mixture of 5% w/w NIM and PEG; while Table 2 shows the dissolution parameters.

The highest dissolution rate and concentrations, after 1 h of dissolution, were achieved with the samples of the lowest concentrations, nominally containing 3–15% w/w NIM: these values are higher than those found for NIM alone or in physical mixture with PEG ($p < 0.05$). Higher concentration leads to a supersaturation of the upper phase; moreover, the decreased amount of PEG inside the system decreases also the hydrophilicity of the whole system, thus decreasing the dissolution rate.

These parameters are fairly constant for BIN-3, -5, -10, and -15 systems upper phases; a mean value of $5.58 \pm 0.33\%$/min represents the maximum improvement concerning the initial dissolution rate that can be obtained combining NIM and PEG in a comelted system. At 20 and 25% w/w nominal NIM concentration and for all lower phases, initial dissolution rate and % released after 1 h of dissolution of these samples recall the values expressed by a 5% w/w physical mixture. Lower phases, which are formed (according to the previous hypothesis) by PEG dissolved into solid NIM do not offer a real improvement of the dissolution rate (mean initial dissolution rate: $1.59 \pm 0.39\%$/min), rather a decreasing trend of the parameter, with respect to the corresponding upper phases.

Below 75% w/w PEG content inside the system, the behavior of all these systems is leveled: the presence of PEG appears rather important both to improve wettability and solubilization: kinetic parameters are in most cases (except the highest concentration considered) higher than those of micronized NIM or when in physical mixture with PEG.

The results lead to two considerations: (a) when NIM does not exceed 2.94% w/w (concentration found for BIN-15 upper phase), the solid systems can reach a satisfactory equilibrium during the cooling; (b) drug particles, not dissolved in PEG, remain or crystallize in a dispersed form and are able to dissolve, likewise micronized NIM or NIM/PEG physical mixture. In both cases the drug is dispersed into a large amount of PEG, that is, the hydrophilicity of the system is high and levels the differences originated by concentration or physical state of the drug. Differences with respect to the pure drug are, however, well evident, and suggest the need of somewhat change of the drug to improve the dissolution behavior.

Ternary Systems

To avoid phase separation, a third component was added to the BIN-5 system during the melting. As a first approach, the solubility of the additives in PEG 300 was tested at room temperature, because it recalls the conditions of the molten PEG 4000. The additives were chosen among surfactants, to improve the dispersion of the two components and favor mutual solubilization; or

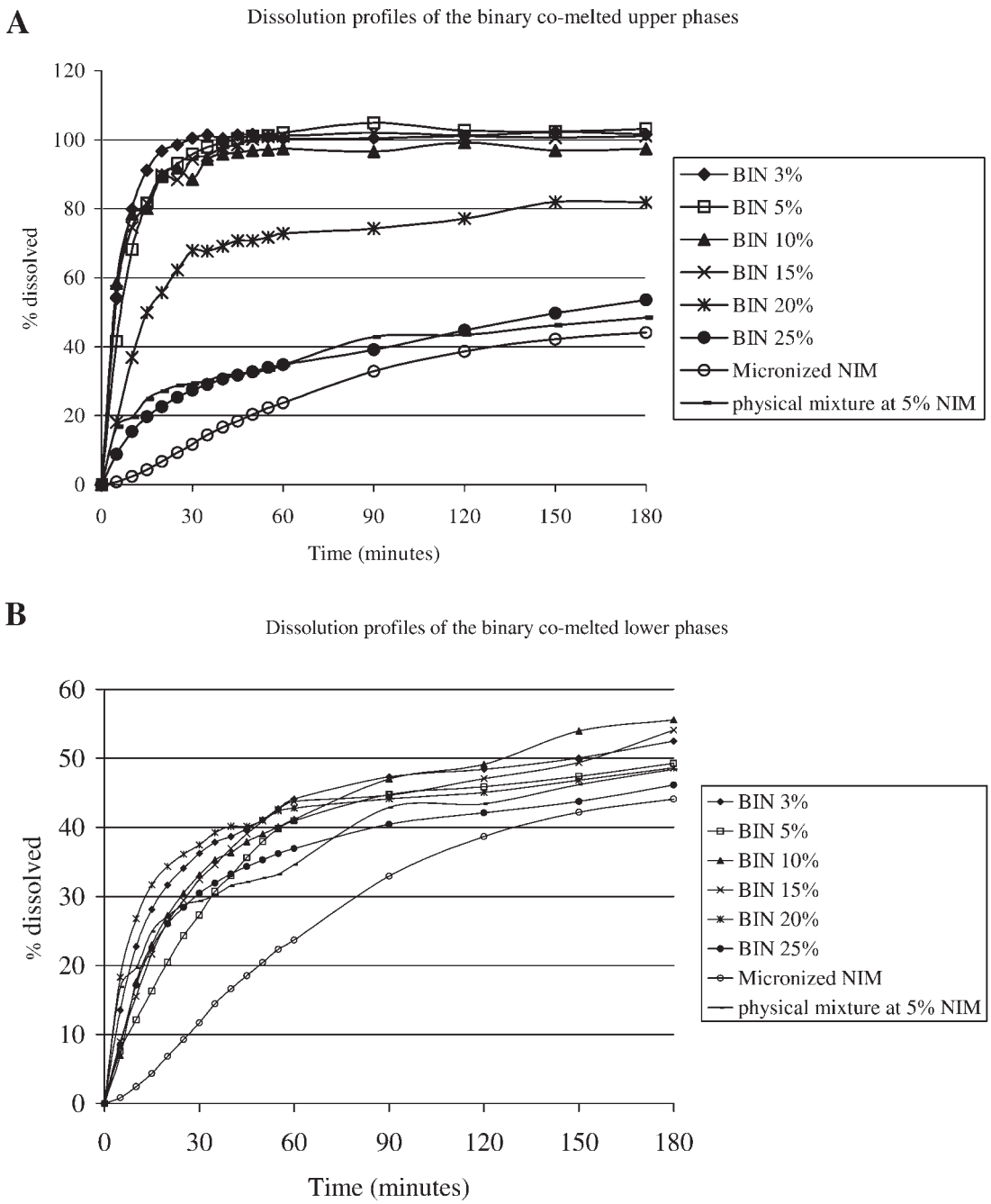

Figure 2. Dissolution profiles of the upper (A) and lower (B) phases for BIN systems, together with a physcial mixture (5% NIM) and pure micronized NIM.

hydrophilic polymers, to increase the viscosity of the whole mass during cooling and hinder the separation; or a hydrophilic and soluble hydroxyamine, to form a salt with the NIM sulphonamide group, increasing the solubility of the drug inside the hydrophilic mass of PEG. The comelted systems contained 5% w/w NIM and 2% w/w of each additive, with the exception of TEA, whose concentration was 2.5% w/w, which is stoichiometric for the formation of a salt with NIM.

Table 3 reports the results concerning the homogeneity of TER systems, the V_U/V_L ratio and NIM content in both phases. The system containing SDS is formed by only one phase, where PEG crystal texture is clearly visible at microscope, when compared with a sample of pure PEG.

Table 2. Initial Dissolution Rate, % Nim Released after 1 Hour of Dissolution and Time Necessary to Obtain 50% of Dissolution (T_{50}) of Nim in Bin Systems

System	Phase	Initial Dissolution Rate (%w/w/min)	t_{50} (min)	% Released (After 1h)
BIN-3	U	6.07 SD 0.06	≈5	100.19 SD 9.23
	L	1.88 SD 0.01	≈150	44.08 SD 5.29
BIN-5	U	5.45 SD 0.05	≈6	102.09 SD 8.11
	L	1.09 SD 0.02	≈180	40.96 SD 2.53
BIN-10	U	5.34 SD 0.09	≈4	97.40 SD 4.89
	L	1.53 SD 0.01	≈120	41.14 SD 2.33
BIN-15	U	5.44 SD 0.06	≈5	101.15 SD 7.22
	L	1.44 SD 0.02	≈150	43.74 SD 3.69
BIN-20	U	2.33 SD 0.01	≈15	72.77 SD 6.68
	L	2.11 SD 0.03	≈180	31.24 SD 2.99
BIN-25	U	1.31 SD 0.02	≈150	34.88 SD 2.68
	L	1.50 SD 0.02	≈180	36.93 SD 2.58
Physical mixture (5% NIM)		1.66 SD 0.01	≈180	34.57 SD 3.01
Micronized NIM		0.29 SD 0.01	≈180	23.69 SD 1.22

Systems containing PSO and POL showed again two phases, as the corresponding BIN system, but with a different volume ratio (90:10 U/L). CET practically hindered the phase separation, because lower phase had a very reduced volume. Systems containing TEA and SDS/CET presented a unique phase.

Table 3 confirms a homogeneous distribution of NIM between upper and lower portions (when only one phase is present), within the experimental error; and different concentrations were found only when the systems appeared inhomogeneous at optical observation.

Figure 3 shows the dissolution profiles of upper portions of TER systems: a notable improvement of most ternary formulations examined can be observed with respect to the simple BIN-5 system, taken as reference, or physical mixture or pure NIM. Table 4 shows the dissolution parameters: it emerges that the presence of TEA in TER system guarantees both an initial high dissolution rate and release extent after 1 h of dissolution, together with the formation of a unique phase; while SDS, through forming at the same way only one phase, does not offer dissolution improvement. CET and POL improve the initial dissolution rate, but not the amount of drug released after 1 h of dissolution.

As a consequence, the extemporary formation of a salt, in the presence of TEA, appears a simple method to promote a real improvement, on passing from binary to ternary systems providing a homo-

Table 3. NIM Content (% W/W) in the Lower (L) and Upper (U) Portion of the Different Ternary Systems and Number of the Phases Found after Cooling

System	Number of Phases	Phase	NIM Content % w/w	V_U/V_L Ratio
TER-SDS	1	U	5.55 SD 0.02	—
		L	4.94 SD 0.04	
TER-PSO	2	U	3.63 SD 0.08	90:10
		L	11.91 SD 0.01	
TER-POL	2	U	3.95 SD 0.08	90:10
		L	32.72 SD 0.09	
TER-CET	2	U	2.12 SD 0.01	97:3
		L	14.01 SD 0.02	
TER-CET/SDS	1	U	5.75 SD 0.02	—
		L	4.51 SD 0.02	
TER-TEA	1	U	5.56 SD 0.01	—
		L	4.78 SD 0.02	

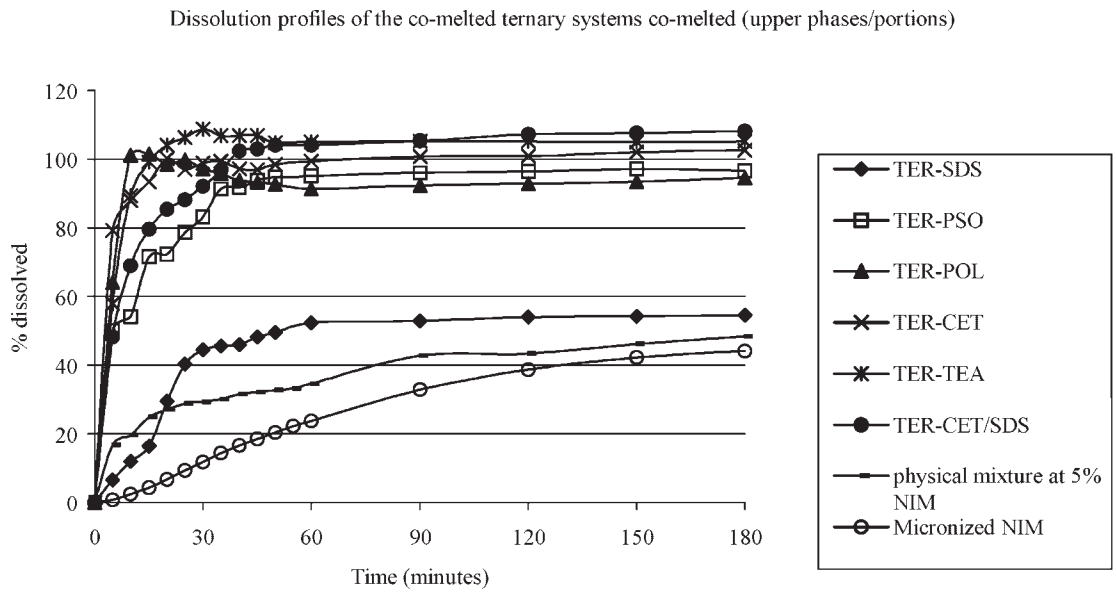

Figure 3. Dissolution profiles of the upper phases of the TER systems together with a physical mixture of 5% of NIM in PEG 4000 and micronized NIM.

geneous distribution of the drug inside the solid dispersion, without altering the kinetic parameters.

Complex Systems

Because the contemporary presence of SDS and CET improved the dissolution behavior, this fact suggested to better examine, by means of a factorial analysis, a series of complex systems, containing together POL, CET, SDS, and TEA, at a concentration ranging from 1.25 to 2.50% w/w, and in addition a 10% w/w NIM concentration.

All these systems appeared homogeneous both in the molten and in the solid phase, suggesting a homogeneous distribution of NIM inside the mass; this solid mass was colored yellow, showing the characteristic crystalline hexagonal texture of PEG. The apparent homogeneity of samples was confirmed by spectrophotometrical analysis at 300 nm of two amounts (one for both upper and lower portions, as it was previously reported in the presence of two phases) of each solid dispersion dissolved in methanol.

Table 5 shows the dissolution parameters for the complex systems studied: it emerged that the values are almost leveled for each parameters. As an example, Figure 4 shows the comparison between some of these and previous systems. Two complex systems, containing all the components at the lowest ($- - - -$) and at the highest ($++++$) concentration of the four additives, display a comparable dissolution behavior with respect to the upper phase of the binary system of the same composition (BIN-10), but a very different profile with respect to a physical mixture of the same composition.

Table 4. Initial Dissolution Rate, % w/w Nim Released after 1 Hour of Dissolution and Time Necessary to Obtain 50% of Dissolution (T_{50}) of NIM in the U Portions of TER Systems

Systems	Initial Dissolution Rate (%w/w/min)	t_{50} (min)	% w/w Released (After 1 h)
TER-SDS	1.10 SD 0.01	≈50	52.27 SD 4.89
TER-PSO	4.77 SD 0.03	≈5	95.16 SD 10.10
TER-POL	6.76 SD 0.04	≈2	91.35 SD 9.55
TER-CET	6.23 SD 0.05	≈1.5	99.35 SD 8.89
TER-CET/SDS	6.61 SD 0.08	≈5	104.02 SD 9.85
TER-TEA	5.31 SD 0.06	≈7	101.28 SD 10.02

Table 5. Initial Dissolution Rate, % NIM Released after 1 Hour of Dissolution and Time Necessary to Obtain 50% of Dissolution (T_{50}) of NIM in the U Portions of the Complex Systems

Systems	Initial Dissolution Rate (% w/w/min)	t_{50} (min)	% Released (After 1 h)
(− − − −)	5.13 SD 0.08	5.58	101.79 SD 10.02
(+ − − −)	5.02 SD 0.09	5.40	98.21 SD 9.55
(− + − −)	4.30 SD 1.02	8.10	103.59 SD 9.88
(− − + −)	4.85 SD 0.81	7.30	101.15 SD 8.36
(− − − +)	5.15 SD 0.06	5.10	101.79 SD 10.88
(+ + − −)	4.37 SD 0.05	6.16	99.23 SD 9.32
(+ − + −)	4.13 SD 0.03	7.50	100.00 SD 10.33
(+ − − +)	4.75 SD 0.09	4.40	99.54 SD 8.07
(− + − +)	4.03 SD 0.03	7.20	102.82 SD 4.23
(− − + +)	2.80 SD 0.01	7.60	102.31 SD 9.77
(− + + −)	3.58 SD 0.02	9.30	101.79 SD 6.32
(− + + +)	4.32 SD 0.03	7.10	99.18 SD 8.74
(+ − + +)	4.60 SD 0.02	7.10	101.28 SD 9.36
(+ + − +)	3.63 SD 0.01	9.00	100.51 SD 11.12
(+ + + −)	3.68 SD 0.02	8.10	98.72 SD 8.79
(+ + + +)	3.15 SD 0.03	10.00	99.92 SD 9.65

To better understand the influences imported by the mutual differences in composition a factor analysis was performed.

Factor Analysis

The experimental design based on a factor analysis is a statistical approach for setting up experiments in such a manner that the required information is obtained as efficiently and precisely as possible. This strategy provides a relationship, usually in the form of mathematical model, between factors acting on the system and the response or properties of the system (the system being a process or a formulation). The information thus obtained is then used to achieve the aim of project with a minimum number of experiments.

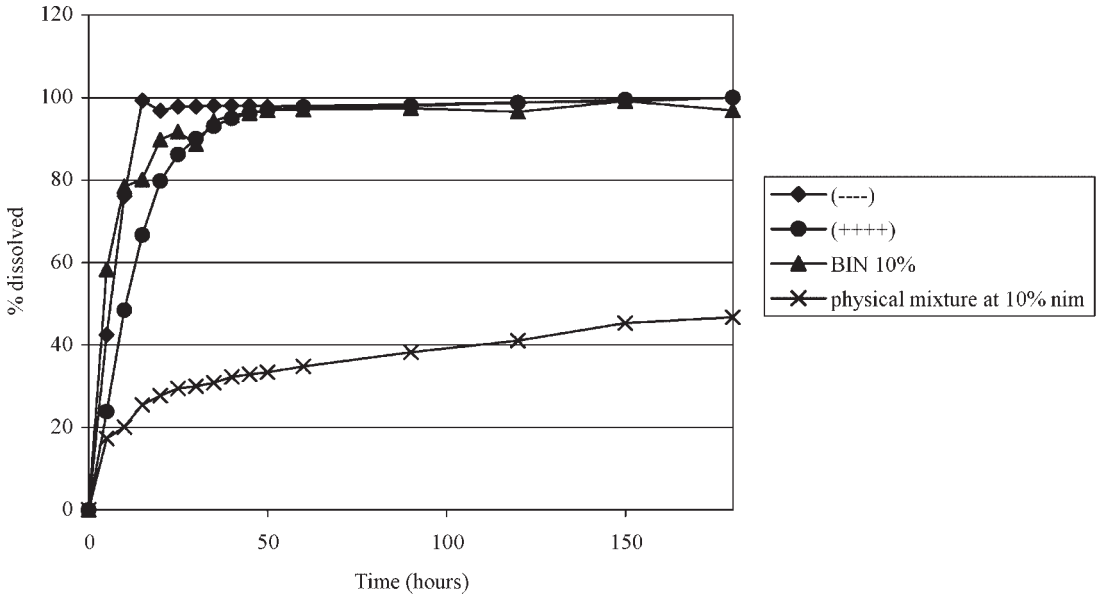

Figure 4. Dissolution profiles of two complex systems having all the additives at the low (− − −) and high (+++) levels, of the upper phase of the BIN-10 system and of the physical mixture at 10% w/w of NIM concentration.

Table 6. Sensitivity Values of Independent Variables on Four Dependent Variables

		Coefficient	F. Inflation	Escart Type	t. exp.	Signif. %
	Y_1: %/min					
Coefficient	a_0	4.218	1.00	0.133	31.82	<0.01
	a_1	−0.107	1.00	0.133	−0.81	44.2
	a_2	−0.123	1.00	0.133	−0.93	37.6
	a_3	−0.036	1.00	0.133	−0.27	78.8
	a_4	−0.494	1.00	0.133	−3.73	0.336
	Y_2: t_{50}					
Coefficient	a_0	7.184	1.00	0.303	23.75	<0.01
	a_1	−0.064	1.00	0.303	−0.21	83.1
	a_2	0.541	1.00	0.303	1.79	9.8
	a_3	−0.014	1.00	0.303	−0.05	96.3
	a_4	0.991	1.00	0.303	3.28	0.726
	Y_3: % released					
Coefficient	a_0	100.739	1.00	0.344	293.00	<0.01
	a_1	−0.733	1.00	0.344	−2.13	5.4
	a_2	−0.253	1.00	0.344	−0.74	48.3
	a_3	−0.616	1.00	0.344	−1.79	9.8
	a_4	0.077	1.00	0.344	0.22	82.1

The concentrations of different excipients (X_1 for SDS, X_2 for CET, X_3 for TEA, and X_4 for POL), added to 10% NIM/PEG during comelting, were chosen as independent variables of the system: the concentration levels considered were 1.25% w/w or 2.50% w/w. The dependent variables were three kinetic parameters, measured during the dissolution tests, namely: initial dissolution rate (as Y_1), the time necessary to obtain 50% of dissolution (as Y_2), and % released after 1 h (as Y_3). Table 6 reports the dependence of the three variables as a function of the four additives. The contemporaneous action of independent on dependent variables were found not significant. In fact, polynominal coefficient values suggest a limited influence of each additives on the kinetic parameters. In the case of the initial dissolution rate, the presence of additives inside the original formulation decreases the parameter: in each case, with the exception of TEA, their importance is very low. The same can be found for t_{50}: in this case, only CET and TEA appears to improve the parameter; while for percentage released the original formulation works so well that changes involve only a decrease of the parameter.

As a conclusion, it does not appear from these results the necessity to formulate complex systems, because some simpler TER systems demonstrated to be able to avoid phase separation observed for BIN systems and provide satisfactory kinetic parameters for the release of the drug.

CONCLUDING REMARKS

All the experimental results suggest the importance of physical as well chemical modification of the scarcely soluble NIM to improve its solubility and dissolution behavior.

1. Binary systems NIM/PEG 4000, formulated as solid dispersions of different compositions, produce, after cooling of the molten mixture, two solid phases, containing different concentration of the drug.
2. The phase richer in PEG behaves better to dissolution, improving the initial dissolution rate and the drug solubilized after 1 h, with respect to the pure NIM.
3. Ternary systems were prepared to avoid phase separation and obtain a homogeneous distribution of NIM inside the cooled mass.
4. Among the examined additives, only SDS, SDS coupled with CET, and TEA fulfill the requirements.
5. Complex systems containing together POL, CET, SDS, and TEA do not exert a synergic effect on dissolution behavior, resulting from

a factor analysis of the composition of the systems associated to kinetic parameters.

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