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Self-emulsifying pellets prepared by wet granulation in high-shear mixer: influence of formulation variables and preliminary study on the in vitro absorption

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Abstract

A method of producing self-emulsifying pellets by wet granulation of powder mixture composed of microcrystalline cellulose, lactose and nimesulide as model drug with a mixture containing mono- and di-glycerides, polisorbate 80 and water, in a 10-l high shear mixer has been investigated.

The effects of the formulation variables on pellets characteristics were evaluated by mixtures experimental design and by a polynomial model, in order to describe the phenomenon, to verify eventual interactions among components of the mixture and to investigate the feasibility of scaling-up. After determination of size distribution, the pellets were characterised by scanning electron microscopy, dissolution and disintegration tests, and by in vitro absorption test

Such an approach, applied to the development of a self-emulsifying system for nimesulide as poorly water-soluble model drug, resulted in different formulations with improved drug solubility and permeability characteristics. The data demonstrate that pellets composed of oil to surfactant ratio of 1:4 (w/w) presented improvement in performance in permeation experiments.

Keywords: Pelletisation; High-shear mixer; Mixture experimental design; Self-emulsifying pellets; Intestinal permeability

1. Introduction

Self-emulsifying drug delivery systems are known to be useful for the improvement of oral bioavailability

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of poorly water soluble drugs (Constantinides, 1995; Humberstone and Charman, 1997). In particular, they are able to self-emulsify rapidly in the gastro-intestinal fluids, forming, under the gentle agitation given by gastro-intestinal motion, fine O/W emulsions. In such a system, the lipophilic drug is present in solution, in small droplets of oil. The large interfacial area generated by these small droplets, promotes drug diffusion into intestinal fluids (Pouton, 2000; O'Driscoll, 2002). Moreover, the emulsion droplets lead to a faster and more uniform distribution of the drug in the gastrointestinal tract, minimizing the irritation due to the contact between the drug and the gut wall (Charman et al., 1992; Shah et al., 1994; Khoo et al., 1998). In addition to the effects described above, the improved drug bioavailability could be partly ascribed to the effect of the monoglyceride components of such self-emulsifying systems, which are supposed to increase membrane permeability (Chicco et al., 1999)

Such systems are normally prepared as liquid dosage forms that can be administrated in soft gelatine capsules, which have some disadvantages especially in the manufacturing process (in-process controls), with consequent high production costs. An alternative method which is currently investigated by several authors, is the incorporation of liquid self-emulsifying ingredients (oil/surfactant/water mixture) into a powder in order to create a solid dosage form (tablets, capsules). Examples of such solid systems are pellets produced by extrusion/spheronisation, which can finally be incorporated into hard gelatine capsules (Newton et al., 2001) or the inclusion in microporous or cross-linked polymeric carriers (Chiellini et al., 2003).

The purpose of the present work was to investigate the feasibility to incorporate a mixture of mono- and di-glycerides, polysorbate 80 and water into a powder mixture of microcrystalline cellulose, lactose and nimesulide as water-insoluble model drug, in order to obtain self-emulsifying pellets using the 10-l Roto-J Zanchetta high shear mixer.

Formulations with different component ratios were investigated by mixture experimental design. The results were statistically analysed in order to evaluate the effects of formulation components on the granulometric characteristics of the pellets and to investigate the feasibility of scaling-up.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose (Microcel 101®, Faravelli, Milano, Italy); lactose monohydrate (Granulac 200®, Meggle, Wasserburg, Germany); mono- and di-glycerides (Cithrol GMO®, Croda, Singaphore); polysorbate 80 (Montanox 80 VG PHA®, Seppic, Castris, France) and nimesulide reagent-grade (Prodotti Gianni, Milano, Italy) were used as starting materials.

2.2. Experimental design and statistical analysis

Some experimental analyses were carried out with Roto-J, in order to value the feasibility of the wet granulation for the production of solid self-emulsifying systems. These analyses were used for the optimisation of process variables and for quality control of granulation characteristics. The resulting information allowed to extrapolating the quantitative limitations for each component of the mixture, obtaining an irregular experimental region, which represents only a restricted part of the study's area (Table 1 and Fig. 1a).

In order to explore the restricted region, an experimental strategy for mixture was followed; this strategy allowed to decrease the number of analysis and to achieve the optimisation of the system. The study's area can be represented in the mixture space by an ellipsoid with the following general Eq. (1):

$$\sum_{i=1}^{q}\left(\frac{x_i - x_{0i}}{h_i}\right)^2 \leq 1 \quad (1)$$

where x_{0i} represents the proportion of each mixture component for point x_0 (overall centroid of the

Table 1
Lower and upper limits of the formulation components

Components	Lower constraints (%)	Upper constraints (%)
Lactose (X_1)	16	24
Microcrystalline cellulose (X_2)	27	37
Water (X_3)	37.5	42.5
Polysorbate 80 (X_4)	2	8
Mono- and di-glycerides (X_5)	1	5

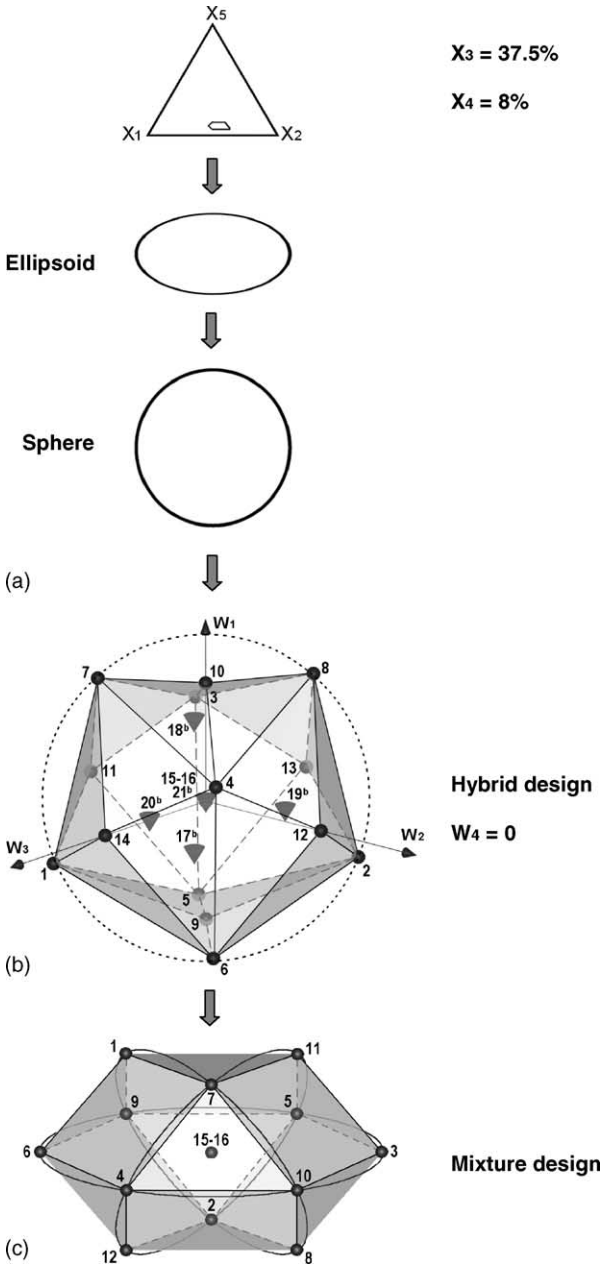

Fig. 1. The transformation steps of ellipsoidal region to the unit spherical region, along with the corresponding experimental design. To avoid overcrowding of the experimental points (c) only reports some experimental points.

polyhedron) and h_i corresponds to one half of the range of interest for component i. In our case, Eq. (1) becomes Eq. (2):

$$\left(\frac{x_1 - 0.2}{0.04}\right)^2 + \left(\frac{x_2 - 0.32}{0.05}\right)^2 + \left(\frac{x_3 - 0.40}{0.025}\right)^2 + \left(\frac{x_4 - 0.05}{0.03}\right)^2 + \left(\frac{x_5 - 0.03}{0.02}\right)^2 \leq 1 \quad (2)$$

To simplify the system, the ellipsoid was transformed to a spherical region, so that a classical design could be adopted (Fig. 1a). The transformation from the ellipsoid in a spherical region was conducted in two steps: firstly, the location of the origin of the new system to be at the centroid of the ellipsoid (point x_0) was defined and then the axes of the original components ($q = 5$) were rotated so as to define a new system (spherical) in terms of $q - 1$ (in our case, $q - 1 = 4$) mathematically independent orthogonal variables W_1, W_2, W_3, W_4. Inside this spherical region, to reduce the number of experimental run, a Hybrid design (Fig. 1b) was chosen (Campisi et al., 1998; Lewis et al., 1999). Finally the experimental trials were inversely converted in the original design for mixtures ($q = 5$).

In Table 2, the coordinates of the 16 experimental design points are shown, with other 5 experimental checkpoints, which are necessary for testing the model adequacy.

The results were analysed by unvaried analysis of variance (ANOVA) to allow identification of statistically significant correlations between the formulation factors and the experimental responses. Mixture design as well as plots and contours surface here presented were obtained using the NEMRODW program (Mathieu et al., 2003).

2.3. Preparation of the binder solution

The binder solution was prepared by mixing oils (mono- and di-glycerides), polysorbate 80 and nimesulide 1% in different proportions (see Table 2) oil (w/w calculated with respect to cellulose and lactose total weight). The oil-surfactant mixture was stirred for 15 min. Successively the self-emulsifying systems were prepared by adding distilled water to the oil-surfactant mixture under gentle stirring.

Table 2
Hybrid design point coordinates *Wi* with the corresponding mixture component proportions X_i in %

	W_1	W_2	W_3	W_4	X_1	X_2	X_3	X_4	X_5
Design point									
1	−0.354	−0.612	0.612	0.354	19.45	31.14	39.79	4.69	4.93
2	−0.354	0.612	−0.612	0.354	22.51	31.58	38.86	3.41	3.63
3	0.354	−0.612	−0.612	0.354	19.12	34.97	38.86	3.41	3.63
4	0.354	0.612	0.612	0.354	21.52	30.04	41.39	3.41	3.63
5	−0.75	−0.433	−0.433	0.250	18.14	33.43	41.39	3.41	3.63
6	−0.75	0.433	0.433	0.250	21.50	30.01	38.47	6.39	3.63
7	0.75	−0.433	0.433	0.250	18.12	33.39	38.47	6.39	3.63
8	0.75	0.433	−0.433	0.250	20.52	28.47	40.99	6.39	3.63
9	−0.707	0	0	−0.707	17.13	31.85	40.99	6.39	3.63
10	0.707	0	0	−0.707	22.88	29.92	40.12	5.18	1.90
11	0	−0.866	0	−0.5	17.74	35.06	40.12	5.18	1.90
12	0	0.866	0	−0.5	21.06	33.66	38.21	5.18	1.90
13	0	0	−0.866	−0.5	19.57	31.32	42.04	5.18	1.90
14	0	0	0.866	−0.5	21.08	33.69	40.42	2.91	1.90
15	0	0	0	1	19.55	31.29	39.82	7.44	1.90
16	0	0	0	0	20.00	32.00	40.00	5.00	3.00
Test points									
17[a]	−0.3953	−0.2282	−0.1614	−0.1250	21.66	31.43	39.55	4.59	2.76
18[a]	0.3953	−0.2282	−0.1614	−0.1250	19.19	33.90	39.55	4.59	2.76
19[a]	0	0.4564	−0.1614	−0.1250	19.80	31.69	41.15	4.59	2.76
20[a]	0	0	0.4841	−0.1250	19.62	31.40	39.85	6.37	2.76
21[a]	0	0	0	0.5	19.73	31.57	39.89	4.85	3.97

[a] Test points used for validity of the postulated model Eq. (3).

2.4. Equipment

The 10 l (laboratory scale) Zanchetta Roto-J granulator and the 50 l Zanchetta Roto P granulator, already described in a previous work (Vojnovic et al., 1993a,b), were used in the experiments.

2.5. Granulation manufacture

The granulation procedure was standardised on the basis of preliminary trials. Preparation in 10 l Roto-J granulator: 1.5 kg batches containing lactose and microcrystalline cellulose, according to the experimental plans (see Table 2), were mixed at an impeller speed of 100 rpm for 10 min. The total amount of nimesulide used in each experiment was 1% (w/w) of 1.5 kg, that is 15 g in each experiment. The mixture was granulated with self-emulsifying system, which was added by spraying at a flow rate of 60 ml/min, a pressure of 4.0 bar and atomised by a pneumatic nozzle with a diameter of 0.3 mm. During this step the impeller speed was kept at 100 rpm. In the subsequent massing stage the impeller speed was increased to 250 rpm for 10 min. The preparation in 50 l Roto P granulator was carried out using the following conditions: 7.5 kg batch was firstly mixed for 5 min at 150 rpm, then during the massing phase an impeller speed of 250 rpm and a massing time of 9 min were used. The binder solution was atomised at a flow rate of 270 ml/min, to keep the spraying time constant compared to the laboratory scale preparations. The wet pellets were dried in a hot-air oven at 40 °C until they reached constant weight.

2.6. Pellet characterisation

2.6.1. Size and size distribution of the pellets

A vibrating apparatus (Octagon 200, Endecotts, London, UK) and a set of sieves (2000, 1250, 800, 630, 500 and 400 μm) plus a receiver were used for size distribution determinations. Retained weight data were used to construct cumulative percent undersize distributions. Median diameter and spread were determined as the 50% value and the difference between 99% and 1% value, respectively.

2.6.2. Disintegration time

The disintegration time of pellets in size fraction mode value was studied in deionised water at 37 °C using a disintegration test apparatus (Model ZT3, Erweka). Six pellets from each formulation were evaluated. The end point was taken as the time for disintegration of the pellets.

2.6.3. Scanning electron microscopy

The pellets morphology was evaluated by scanning electron microscopy (SEM). Samples were sputter-coated with Au/Pd using a vacuum evaporator (Edwards, Milano, Italy) and examined using a scanning electron microscope (Model 500, Eindhoven, The Netherlands) at 10 kV accelerating voltage using the secondary electron technique.

2.6.4. In vitro dissolution studies

The USP 24 rotating basket apparatus (Model DT-1, Erweka, Heusenstamm, Germany) with a stirring rate of 100 rpm and a temperature of 37 °C was used. The composition of the dissolution medium was 0.2 M KH_2PO_4/0.2 M NaOH (pH 7.4) according to USP 25. Samples of pellets, containing a suitable amount (10 mg) of nimesulide for sink conditions ($C < Cs$) were placed in the basket, that was then deepen in 500 ml of dissolution medium. Five ml samples were withdrawn at regular time intervals, filtered and assayed spectrophotometrically at 396 nm. The aliquots withdrawn for analysis were immediately replaced with equal volume of fresh dissolution medium at the same temperature. The excipients did not interfere with the UV analysis. The results were averaged from at least triplicate dissolution experiments and the standard deviations were within 4% of mean value.

2.6.5. Size determination of the droplets

The size of the emulsion droplets after they have been sprayed from the 0.3 mm nozzle and those released from the pellets was determined in the same buffer used for dissolution test at 37 °C. The samples collected at various time intervals, were centrifuged and analysed using laser light scattering technique (Coulter N4 Plus, Coulter Corporation, Miami, Florida, USA), according to the method described in literature (Chiellini et al., 2003). The results were averaged from at least triplicate experiments and the standard deviations were within 3% of mean value.

2.6.6. In vitro absorption experiments

Intestinal permeation experiments were performed using a Krebs-Ringer modified buffer (pH 7.4; 37 °C), as donor and receiver phase, as it's able to maintain intestinal cells homeostasis (Schilling and Mira, 1990).

The experimental set-up consisted of a thermostatic (37 °C) donor environment (1000 ml pH 7.4 buffer) containing a circular holed holding plate carrying up to six intestine holders. Each holder is made up by a cylindrical glass vessel connected to an "U" glass capillary whose left portion was represented by intestine (Meriani et al., 2004). A symmetrical intestine holders disposition on the holding plate was needed in order to avoid preferential fluxes inside the donor environment. Intestine holders volume (four in our case), filled by pure buffer, represented the receiver environment ($V_r = 4 \times 12\,cm^3 = 48\,cm^3$). Both receiver and donor phases were continuously oxygenated (95% O_2, 5% CO_2), in order to keep the intestinal cells alive during the experiment. While oxygen bubbles also ensured receiver volume homogeneity, mixing conditions in the donor environment were guaranteed by an impeller (rotational speed 70 rpm).

Male Wistar rats (Centro Servizi di Ateneo, Settore Stabulario e Sperimentazione animale, Trieste University, Italy) weighing approximately 250 g were fasted for 12 h (water ad libitum), and then sacrificed by CO_2. Small intestine (duodenum, jejunum and ileum) was removed, separated from the mesentery, rinsed with the buffer using a 10 ml syringe, then cut in 4 different sections. Each section was everted on a teflon rod, and fixed on its location by means of surgical thread.

At the beginning of the permeation test, the holding plate (carrying four intestine portions) was immersed in the donor environment (pure buffer pH 7.4) and a proper amount of formulation was added immediately after. Whatever the formulation considered, the corresponding amount of nimesulide contained was equal to 1 mg. Nimesulide concentration in each receiver environment was determined by means of an optic fibre apparatus (ZEISS, Germany), connected to a spectrophotometer (ZEISS, Germany, wavelength 393.4 nm) (Meriani et al., 2004). As each experimental test was performed on three animals, drug concentration at each time was the mean of 12 experimental data.

For a correct evaluation of the experimental data, it was necessary to verify the good homeostasis of the intestinal cells during the experiments. This is associated

to phenol red (marker) permeability values ranging between 6×10^{-4} cm/min and 9×10^{-4} cm/min, as higher values indicate progressive cells dying (Schilling and Mira, 1990). According to the procedure described in literature (Meriani et al., 2004), we measured a phenol red permeability across the intestinal membrane equal to 7.8×10^{-4} cm/min, so we could affirm that the integrity of the system was ensured during the 60 min experiment. A blank permeation test (no nimesulide in the donor phase) was performed, in order to verify that the intestinal secretions did not interfere with the absorption process (Grassi and Cadelli, 2001). This study was approved by the Italian Ministry of Health (D. LVO 116/92) in accordance with the 'Principle of Laboratory Animal Care'.

3. Results and discussion

The 21 experimental runs (16 design points plus 5 check points) were carried out in a completely random order according to the experimental design (see Table 2); the observed responses are listed in Table 3.

The results showed that the process of wet granulation, using the 10 l Roto-J granulator, allowed to obtain pellets with relatively small size, a low dispersion, and high percentage in modal fraction, with fast disintegration time. The median diameter (Y_1) and the percentage in modal fraction (Y_2), that are the most significant parameters for evaluating the granulation process, were selected as experimental responses in order to analyse the effects of components at the same time, using a polynomial model Eq. (3):

$$Y = b_1X_1 + b_2X_2 + b_3X_3 + b_4X_4 + b_5X_5 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{14}X_1X_4 + b_{15}X_1X_5 + b_{23}X_2X_3 + b_{24}X_2X_4 + b_{25}X_2X_5 + b_{34}X_3X_4 + b_{35}X_3X_5 + b_{45}X_4X_5 \quad (3)$$

The estimates of model coefficients (Eq. (3)) for the two response variables (16 design points) have been determined by multiple regression analysis using the NEMRODW program (Mathieu et al., 2003) and the results are listed in Tables 4 and 5.

From the analysis of variance table, the R^2 were computed and their values were $R^2 = 0.999$ with an $R_A{}^2 = 0.996$ for Y_1, and $R^2 = 0.998$ with an $R_A{}^2 = 0.965$ for Y_2, respectively. On the basis of the preliminary

Table 3
Particle size analysis and values of disintegration time for each formulation

No. of experiment	Median diameter (μm)	Spread (μm)	Size fraction mode value (μm)	% in modal fraction	% Size fraction <400 μm	% Size fraction >2000 μm	Disintegration time ± S.D. (min)
1	688	261	630–800	90.0	2.8	0.5	5.03 ± 0.92
2	967	1043	800–1250	69.5	3.7	16.6	4.45 ± 2.79
3	918	314	800–1250	85.5	2.8	1.3	1.83 ± 0.43
4	742	812	800–1250	60.1	8.4	7.4	1.63 ± 1.02
5	842	797	800–1250	78.3	5.3	0.8	3.75 ± 2.29
6	893	886	800–1250	79.3	2.1	9.1	2.92 ± 1.58
7	649	237	630–800	93.3	1.4	0.2	2.52 ± 0.51
8	946	1208	800–1250	66.3	3.3	19.8	1.77 ± 1.02
9	816	842	800–1250	75.5	3.4	5.9	2.99 ± 1.21
10	869	1313	800–1250	60.7	4.5	17.6	2.01 ± 0.72
11	672	377	630–800	78.9	6.7	0.3	2.55 ± 1.07
12	646	488	630–800	71.2	8.5	0.2	2.52 ± 0.94
13	760	812	800–1250	59.7	7.6	9.9	0.9 ± 0.63
14	512	570	630–800	50.8	18.3	0.1	1.34 ± 0.72
15	835	1143	800–1250	65.4	4.9	12.3	1.77 ± 0.98
16	982	554	800–1250	86.3	1.1	5.7	2.01 ± 1.47
17	966	1305	800–1250	78.2	5.4	7.4	2.12 ± 1.55
18	892	553	800–1250	87.0	2.5	4.3	1.86 ± 0.90
19	900	1132	800–1250	80.4	2.1	6.1	2.06 ± 0.95
20	956	1033	1250–2000	80.0	1.8	20.4	4.81 ± 1.04
21	933	163	800–1250	92.2	0.9	4	2.86 ± 0.94

Table 4
Estimates and statistical significance of the model coefficients Eq. (3) for the two measured response variables

Coefficients	Y_1	Significance (%)	Y_2	Significance (%)
b1	−546.172	1.05*	−141.022	11.1
b2	−726.316	<0.01***	−18.555	73.2
b3	−6217.515	<0.01***	−445.955	7.2
b4	−3237.461	<0.01***	−447.356	1.18*
b5	−19108.889	<0.01***	−369.201	33.2
b12	1552.508	0.205***	212.507	27.1
b13	6020.482	<0.01***	823.547	5.3
b23	9882.817	<0.01***	737.218	5.7
b14	9672.891	<0.01***	1106.978	0.235**
b24	4272.366	<0.01***	914.656	0.390**
b34	21464.463	<0.01***	1218.514	2.00*
b15	30373.809	<0.01***	901.382	11.7
b25	31956.215	<0.01***	936.732	8.4
b35	32503.131	<0.01***	1097.035	14.1
b45	21610.997	<0.01***	1192.961	7.3

* $\alpha < 0.05$.
** $\alpha < 0.01$.
*** $\alpha < 0.001$.

trials, the error variance (s^2) was estimated inside the experimental dominium and it resulted being 121 for Y_1 and 25 for Y_2 with 14 degrees of freedom. This estimate of the error variance was employed to have a model independent measure of the pure error for testing the model adequacy. This way, the residual sum of squares (SS_E) can be partitioned in two components: one due to pure error (SS_{PE}) and another due to lack of fit (SS_{LOF}). A statistical test based on the F ratio can be used for testing the significance of the null hypothesis about zero lack of fit of the model.

For the two considered response variables the estimated residual variance was $MS_E = 19709$ and $MS_E = 160$ for Y_1 and Y_2, respectively. The experimental error variance was estimated as follows: $MS_{PE} = 121$ with 14 degrees of freedom (d.f.), $MS_{LOF} = 76.77$ with 1 d.f. for Y_1, and $MS_{PE} = 25$ with14 d.f., $MS_{LOF} = 5.26$ with 1 d.f. for Y_2. The value of the F statistic was $F = 0.63$ with a with significance level $p = 0.474$ for Y_1 and $F = 0.21$ with $p = 0.67$ for Y_2, respectively. Hence, the lack of fit of *F*-test is clearly non significant. Thus, it can be concluded that the fitted model Eq. (3) is can be adequate for prediction purposes, as showed from the results obtained by the five check points reported in Table 5.

Isoresponse surfaces were drawn from the obtained equations for the two response variables using NEMROD program (Mathieu et al., 2003). In order to obtain a two-dimensional representation of the isoresponse surface, X_4 and X_5 were chosen as constant variables and fixed at 5 and 3%, respectively (Fig. 2a and b).

The plot of the effects was always traced using the model Eq. (3), in order to analyse the effects of each component of the mixture about the two experimentally selected responses (Y_1 and Y_2).

In Fig. 3 the predicted values Y_1 and Y_2 were plotted for the blends defined on each of the five rays, using the reference blend as the overall centroid of the

Table 5
Predicted and experimental value in the check points

No. of experiment	Y_1 experiment	Y_1 prediction[a]	Y_2 experiment	Y_2 prediction[a]
17	966	966.6	78.2	77.1
18	892	892.4	87.0	87.5
19	900	905.1	80.4	75.8
20	956	957.0	80.0	81.8
21	933	934.4	92.2	91.1

[a] Values calculated by Eq. (3).

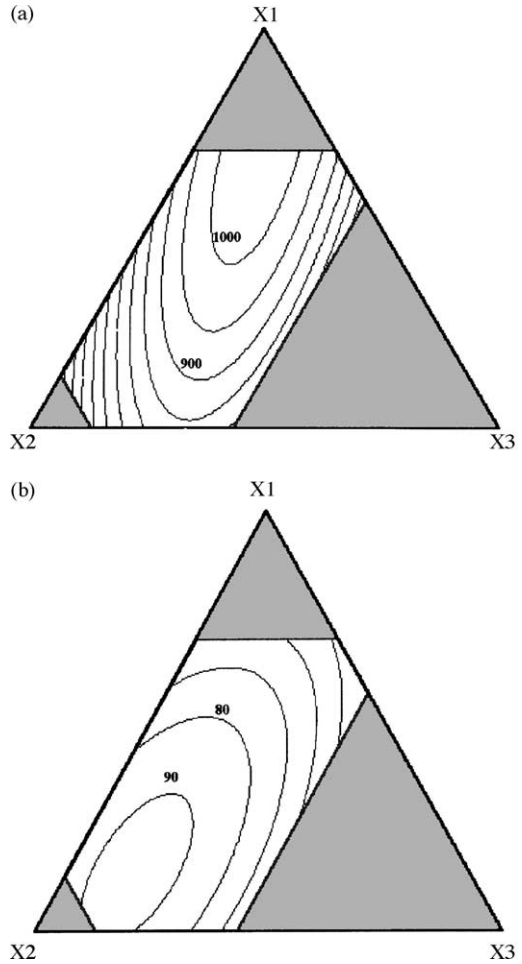

Fig. 2. Contour plot for Y_1 (a) and Y_2 (b) in the restrained region for the mixture component system when $X_4 = 5\%$, $X_5 = 3\%$, $\Delta Y_1 = 50\,\mu m$, $\Delta Y_2 = 10\%$. Percentage composition of the vertices (pseudocomponents): X_1 ($X_1 = 27.5$, $X_2 = 27$, $X_3 = 37.5$), X_2 ($X_1 = 16$, $X_2 = 38.5$, $X_3 = 37.5$), X_3 ($X_1 = 16$, $X_2 = 27$, $X_3 = 49$).

experimental region ($X_1 = 20\%$, $X_2 = 32\%$, $X_3 = 40\%$, $X_4 = 5\%$, $X_5 = 3\%$).

The response trace plots illustrates the effects of each component as one moves away from the reference blend. The parabolic nature of the curves indicates that the estimated value is quite sensitive to changes of the quantity of each component.

Particular results were obtained with lactose: the response Y_1 increased when more lactose was present in the formulation; this may be explained by the fact that the water dissolved the lactose contained in the formulation, increasing the agglomeration of the powder and giving a decrease of Y_2 with a concentration superior to 20%.

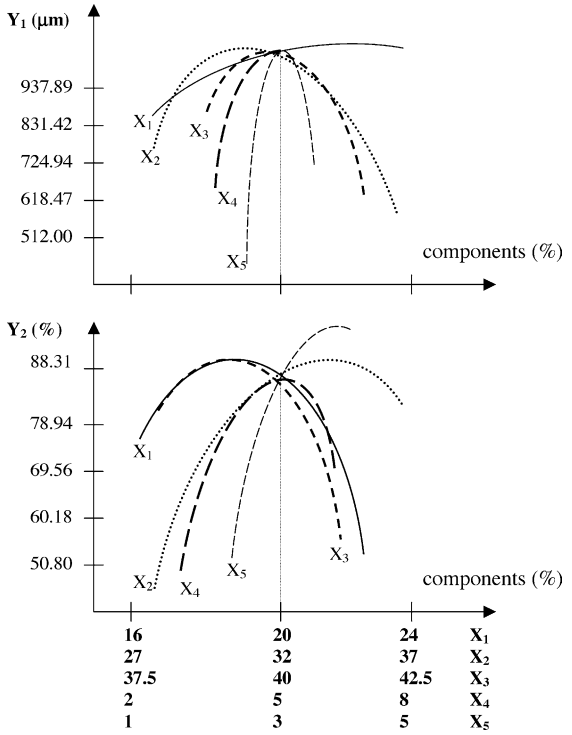

Fig. 3. Plot of the estimated responses for median diameter (Y_1) and % in modal fraction (Y_2) along the X_i, $i = 1, 2, 3, 4, 5$ rays using Eq. (3). The values along the abscissa represent the amount of each component along its ray passing through the reference blend ($X_1 = 20$, $X_2 = 32$, $X_3 = 40$, $X_4 = 5$, $X_5 = 3\%$).

On the contrary, when the quantity of microcrystalline cellulose and of mono- and di-glycerides increased in the formulation, Y_1 decreased, while Y_2 increased.

In order to verify the above-mentioned self-emulsifying behaviour of such systems, two formulations were chosen for testing the formation of oil droplets: formulations number 3 and 15, with an oil/surfactant w/w ratio of 1:1 and 1:4, respectively. The results are reported in Fig. 4. It can be observed that the droplets forming from composition 3 are more or less of the same size, either generating from the pellets or from the corresponding emulsion (average diameter of 370 nm). On the contrary, formulation 15 in the form of pellets is able to generate significantly smaller droplets (average diameter of 160 nm) with respect

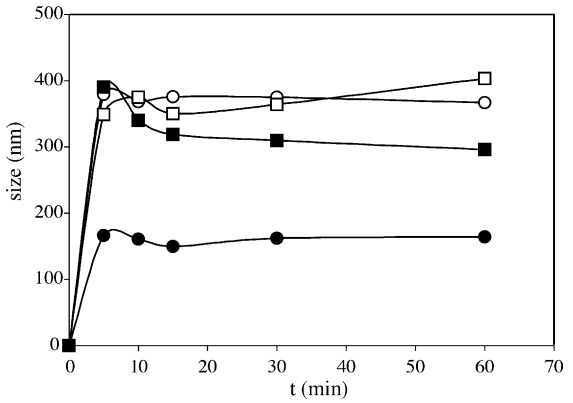

Fig. 4. Median droplet as function of the time the emulsion 15 (◯), emulsion 3 (□), pellets 15 (●), pellets 3 (■).

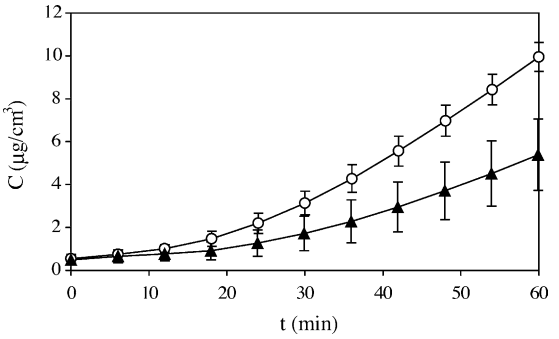

Fig. 6. Nimesulide absorption curves (concentration in the intestinal lumen *C* vs. time *t*) from the different release systems considered (formulation 3 (▲), formulation 15 (◯)).

to the corresponding emulsion (average diameter of 368 nm). Such phenomenon could explain the results obtained in the dissolution studies and in the permeation experiments. The dissolution profiles shown in Fig. 5 indicate a faster drug dissolution kinetics from formulation 15, than from formulation 3, which is in accordance with the smaller size of the droplets generated from composition 15: the smaller diameter, the larger is the total surface area available for drug diffusion towards the donor environment. These assumptions could also account for the better performances of formulation 15 in permeation experiments (Fig. 6): the faster drug dissolution kinetics led to a higher drug concentration gradient across the intestinal membrane.

However, the better permeation observed with formulation 15 could also be due to the higher surfactant content that could have made the intestinal wall more

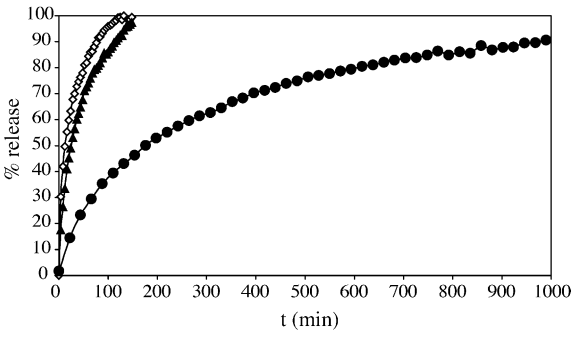

Fig. 5. Percentage released in the environment as function of time for formulation 3 (▲), 15 (◊) and pure nimesulide (●).

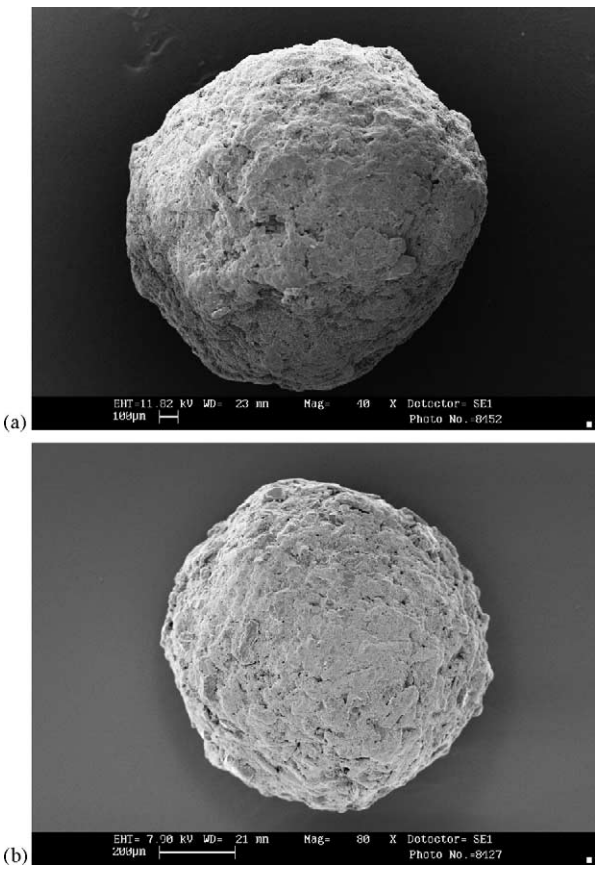

Fig. 7. SEM photographs of formulation 3 (a), formulation 15 (a).

Table 6
Observed response values in the scale-up check points (experiments 1 and 15, see Table 3)

Experiment	Equipment	Median diameter (μm)	Spread (μm)
1	Roto-J	688	261
1	Roto P 50	538	1065
15	Roto-J	835	1143
15	Roto P 50	724	1200

permeable (by membrane partial disruption). Moreover, the pellets showed a satisfactory regular spherical shape (Fig. 7).

The technological transfer of the production process is an obligatory passage in order to develop a pharmaceutical dosage form (such as pellets, in this case). The scale-up of the self-emulsifying pellet production was verified with the experiments number 1 and 15 as selected points of the experimental region, using the 50 l Roto-P. Firstly, the same strategy successfully used in previous works (Vojnovic et al., 1993a,b, 1996) was adopted: in order to maintain the same impeller peripheral rate (Vp) as in the Roto-J, an impeller speed of 154 rpm was used in the Roto-P. However, we noticed that using this velocity we obtained a granulated product but not a spheronised product. Thus, to overcome this problem, the impeller speed of 250 rpm successfully used in the Roto-J was employed also in the Roto P. The results obtained with the latter strategy, reported in Table 6, confirmed the possibility of scaling-up the selected experiments.

Some differences can be noticed between the products obtained from the two scales of apparatus. However, these differences can be attributed primarily to differences in the geometric internal structure of the two equipments and secondarily to a "loading effect" (pressure exerted by a load of 1 kg or 7.5 kg), that is responsible for an increased viscosity of the system during the granulation process, yielding to different growth mechanisms depending on the scale of equipment used.

4. Conclusions

This study showed that the experimental design approach can be useful for the optimisation of processes and products in the industrial pharmaceutical field. This approach applied to the study of solid pharmaceutical dosage forms, such as the self-emulsifying pellets produced by wet granulation, led to a mathematical model describing the effects of formulation components on the product characteristics. Therefore, by such mathematical equations, the response behaviour can be predicted over the whole experimental field.

Such an approach, applied to the development of a self-emulsifying system for nimesulide as poorly water-soluble model drug, allowed to find different formulations with improved drug solubility and permeability characteristics.

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