Using DOE to Achieve Reliable Drug Administration: A Case Study

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Abstract:
Design of experiments (DOE), a statistical tool, and mathematical modeling techniques are established and proven methodologies for process and product improvements in the pharmaceutical industry. This contribution presents a case study where an unsatisfactory dissolution capacity for the drug Roquinimex was overcome by investigating the process parameters with the help of an experimental design. By elucidating the detailed effects of temperature, dosing time, and dilution, conformity in the particle size distribution of the active pharmaceutical ingredient (API) from batch to batch in full-scale manufacturing could be ensured. As a direct result the manufactured drug met its specified dissolution capacity, which was a prerequisite for obtaining the desired bioavailability of the pharmaceutical oral formulation. This work demonstrates how the use of DOE in chemical process development adds value by allowing efficient and reliable improvements of a given synthetic step.

Introduction

The reproducible productions of organic crystals in the correct form (habit, solvate, and polymorph) are often troublesome for chemists and chemical engineers.[1] In addition, lack of uniformity in particle size can give heartache to pharmacists and formulators.[2] Although production of new polymorphs and solvates can be a source of profit for companies through extension of the patent lifetime, the inability to routinely manufacture a consistent crystalline form or particle size can lead to costly project delays, either in chemical development or pharmaceutical formulation.

One major difficulty in crystallization is that a number of experimental variables affecting crystal growth and particle size distribution are usually not independent from each other, i.e. they are normally interacting with each other to various degrees. Thus, it is often not satisfactory to rely just on your chemical intuition when searching for good crystallization conditions. A far better approach is to use a statistical experimental design, or design of experiments (DOE), when detailed insight of a crystallization process is necessary.[3] Within this context a case study of the manufacturing of a Pharmacia pharmaceutical product, namely, Roquinimex (1,2-dihydro-*N*,1-dimethyl-4-hydroxy-2-oxo-3-quinoline car-

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(1) (a) Brittain, H. G. *Polymorphism in Pharmaceutical Solids*; Marcel Dekker: New York, 1999. (b) Anderson N. G. *Practical Process Research & Development*; Academic Press: New York, 2000.
(2) Sandell, E. *Industrial Aspects of Pharmaceutics*; Swedish Pharmaceutical Press: Stockholm, 1993.
(3) Carlson, R. *Design and Optimization in Organic Synthesis*; Elsevier: Amsterdam, 1992.

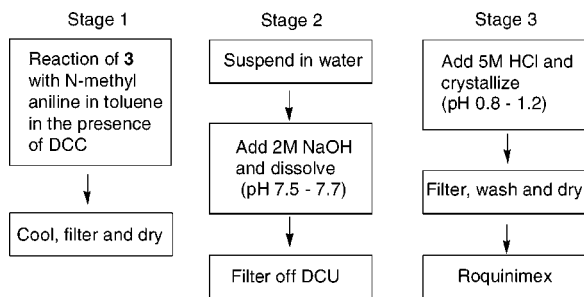***Table 1.*** **Yields and quality parameters for pilot- and full-scale batches**

entry	batch no.	yield[a] (%)	HN(Me)(Ph)[b] (ppm)	dissolution[c] (%)	crystal size[d] (μm)
1	P01	68	10	93.0	30
2	P02	71	60	86.4	30
3	P03	71	80	89.0	30
4	F04	52[e]	700	78.1	5
5	F05	72	600	77.1	3
6	F06	63	40	89.5	20
7	F07	76	50	94.5	25
8	F08	77	50	94.7	25
9	F09	59[f]	50	93.7	20

[a] Yield for the final step, i.e. the transformation of **3** to Roquinimex. [b] Byproduct measured by HPLC analysis. [c] In vitro dissolution of Roquinimex substance after 60 min in 0.005 M phosphate buffer (see ref 6). [d] Approximate length of the largest crystal as determined by SEM. [e] Some material losses occurred due to a partly damaged dust collector between vacuum pump and drying chamber. [f] The lower yield can be partly explained by the fact that the starting material **3** had a lower assay (ca. 90%) than normal (>98%).

Scheme 1. **Synthetic route**
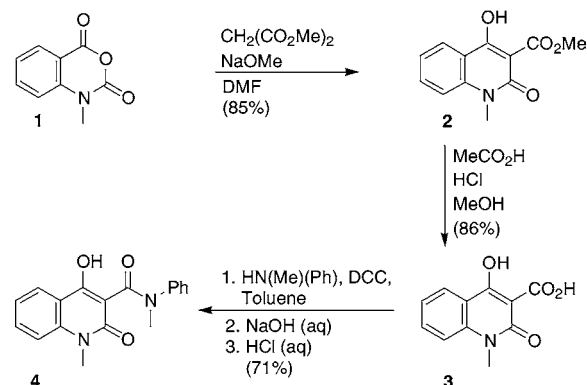
boxamide, **4**), will be presented. Roquinimex is a drug substance, which in humans has been found to have immunomodulating and antitumour activities.

Results and Discussion

Pilot-Scale Manufacturing. A manufacturing campaign of Roquinimex in the scale of 3 × 5 kg (batches P01−P03, entries 1−3, Table 1) was conducted with the intention of (i) testing and verifying the suitability of the process and (ii) supplying the active compound for formulation studies and tablet production for pivotal clinical trials. Roquinimex was manufactured according to a three-step synthetic route (Scheme 1). The synthesis started from *N*-methylisatoic anhydride (**1**), a commercially available material, which was initially transformed to the quinoline carboxylic acid methyl ester **2**. The hydrolysis of **2** in a mixture of glacial acetic acid and hydrochloric acid gave the quinoline carboxylic acid

Figure 1. Manufacturing of Roquinimex. Block diagram of the final process step.

Figure 2. In vitro dissolution data of Roquinimex tablets. The graph shows the batch specific mean value (%) of dissolved Roquinimex for the formulated tablets (content 2.5, 5, and 10 mg) after 60 min (see ref 5).

3 in a high yield. The last step, preparation of the carboxamide Roquinimex (**4**), was done via coupling of the carboxylic acid **3** with *N*-methyl aniline, resulting in a high-yielding product of high quality.

The final manufacturing step can be seen as an operation divided into three separate stages (Figure 1). The first stage is the amidation of **3** with *N*-methyl aniline using 1,3-dicyclohexylcarbodiimide (DCC) as a dehydrating coupling agent. The crude Roquinimex, consisting of a mixture of product and *N,N′*-dicyclohexyl urea (DCU), is then isolated and dried. In the second stage, the purification procedure, the crude Roquinimex is "titrated" in deionized water by addition of a 2 M sodium hydroxide solution. Roquinimex dissolves, and a plate filter removes the DCU. In the third stage, the crystallization procedure, addition of hydrochloric acid (5 M) at room temperature to the filtrated solution induces precipitation of the product. The substance is isolated by centrifugation and washed with deionized water before drying.

Full-Scale Manufacturing. As the project proceeded successfully, in terms of positive outcome of the clinical trials, it was decided that Roquinimex should be produced in full-scale batches and the process validated. The batches F04−F06 were manufactured in the scale of 3 × 60 kg analogous to previous pilot-batch protocols (entries 4−6, Table 1). The outcome of the campaign was foreseen in terms of yields, but the impurity profile of the substance was out of expectation. Two of the batches contained significantly higher levels of *N*-methyl aniline than previously observed (700 and 600 ppm for batch F04 and F05, respectively) although they were lower than the specified limit at that time (<1000 ppm).[4]

Tablet Formulation. The full-scale batches F04−F06 were submitted to pharmaceutical formulation. When the quality of the tablets was checked, it was realized that the uniformity in content and in in vitro dissolution of the manufactured tablets was unsatisfactory (Figure 2). As seen in Figure 2, the dissolution capacity for the tablets containing the batches F04 and F05 was significantly lower than for the tablets containing batch F06, i.e. approximately 15−20% less dissolved substance after 60 min. Instead, the obtained average dissolution data for these latter tablets was in good agreement with the dissolution previously observed for the tablets produced from the batches P01−P03 (Figure 2). The
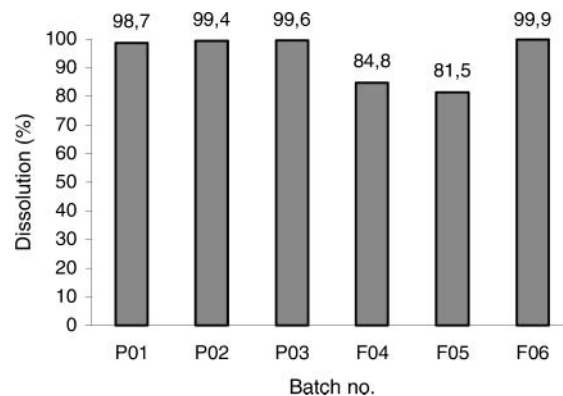
medium (0.1 M HCl) used in the tablet dissolution tests was chosen to simulate the pH of the gastric fluid to give as true a picture as possible of the bioavailability of the tablet in vivo.[5] For comparison, the dissolution capacities of the pure Roquinimex substance from both pilot- and full-scale batches were also investigated (Table 1).[6] As seen in Table 1, again the batches P01−P03 and full-scale batch F06 provided substances that were substantially easier to dissolve. However, due to poor wetting (floating aggregates) and due to a larger amount of substance to be weighed in, a test medium with higher solubility of Roquinimex including Brij 35 as a wetting agent had to be used.[6] Consequently, the dissolution data for the tablet versus substance could only be used for qualitative comparison. Still, it was suspected that the reason for the anomaly in dissolution capacity for the tablets was directly linked to an apparent lack of control when crystallizing the Roquinimex substance. Thus, the problem of not being able to reliably administer the drug orally to the patient would be an issue for the chemical process development efforts.

Solid-State Properties of Roquinimex. It is well-known that the physical properties of a drug substance may be important for the pharmaceutical formulations containing the substance.[2] For instance, particle size distribution and polymorphism may have an influence on the dissolution rate and the bioavailability of a solid oral formulation. As depicted in stage 3 (Figure 1, vide supra), the produced Roquinimex crystals were formed by precipitation from its sodium salt in aqueous solution by adding hydrochloric acid. Thus, the precipitation process took place at the interface between the salt solution and the added acid. Because of the low solubility of Roquinimex, 0.2 g/L of H_2O below pH 4 at 25 °C,[7] the formation and growth of particles were very fast. The presence of both amorphous structures and a large variety

(4) Later, it was realized that the FDA would not accept a limit higher than 100 ppm for the *N*-methyl aniline content. Consequently, future production would have to take this 10-fold decrease of *N*-methyl aniline into account.

(5) United States Pharmacopeia, paddle method. Rotation speed: 100 rpm. Volume: 500 mL. Medium: 0.1 M HCl. Sample: 2.5, 5, or 10 mg Roquinimex tablet. Temp: 37 °C.

(6) United States Pharmacopeia, paddle method. Rotation speed: 50 rpm. Volume: 900 mL. Medium: 0.005 M Phosphate buffer pH 6.8 with 0.01% Brij 35. Sample: ca. 100 mg Roquinimex. Temp: 37 °C.

(7) The solubility of Roquinimex (pK_a = 4.3) in water at 25 °C is strongly pH dependent. The solubility ranges from 0.2 mg/mL at pH below 4 to 120 mg/mL at pH 6.9. Hansen, B. *Roquinimex, the Solubility in Water at pH 3.8 to 6.9 and pK_a*; Pharmacia Document 21554F: Helsingborg, 1994.

in particle size distribution could thereby be suspected. To be able to avoid producing tablets with unacceptable properties, knowledge of the relationship between such properties of the drug substance and its pharmaceutical formulation was necessary. On this basis an investigation concerning crystal properties and particle size distribution of Roquinimex was launched. The solid-state properties of the substance, prepared in the batches P01–P03 and F04–F06, were examined with X-ray powder diffraction, DSC, TGA, and scanning electronic microscopy (SEM) methods.[8]

In the examination of all batches by SEM it was found that Roquinimex is a highly crystalline substance constituted by flaky crystals. No amorphous structures were detected. The Roquinimex molecule contains two fused rings bound to one single ring via an amide bridge. The absence of flexibility in the molecule, except for the amide bridge, means that the entire molecule, and not parts of it only, is moving when searching for the energetically optimal position for its absorption to an already existing particle. Clearly, this rigid nature of the Roquinimex molecule allows rapid formation of crystals, which prevents any formation of amorphous structures despite the fast precipitation process discussed earlier.

The X-ray powder diffraction analysis revealed no polymorphism for Roquinimex.[8] However, crystals formed by recrystallization from organic solvents, instead of precipitation from a water solution, showed other shapes than elongated flakes. Recrystallization from ethanol gave a large fraction of needles, while recrystallization from toluene resulted in well-shaped crystals that had approximately the same dimensions in all directions. These differences in appearances are just due to differences in preferential growth directions caused by the solvents.

As mentioned above, in all batches examined by SEM, only flaky crystals were observed. To various extents between batches these appeared as either free crystals or aggregates. Single crystals ranging from less than 1 up to 30 μm and aggregates ranging from 0.01 up to 1 mm were found. This heterogeneity in sizes and shapes was not surprising, considering the previously mentioned rapid formation of the crystals. Unfortunately, no reliable method based on sieving or laser diffraction could be developed to determine the particle size distribution.[9] The main reasons for this were adhesion between particles and measuring equipment and breaking of the brittle aggregates into smaller particles during the preparation and measurement of the sample, all resulting in erroneous results.

Although no method could directly indicate a desired particle size distribution, a distinct relation between crystal size and high dissolution capacity of Roquinimex could be detected. It seemed to be beneficial that the substance contained larger crystals (entries 1–6, Table 1). Solvent saturated with substance remaining in the crystal mass after filtration, and thus promoting aggregation of the crystals, might explain this observation. Upon drying the crystals, the
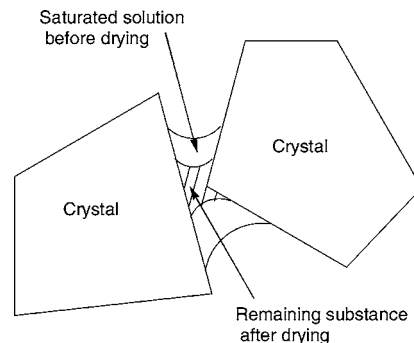

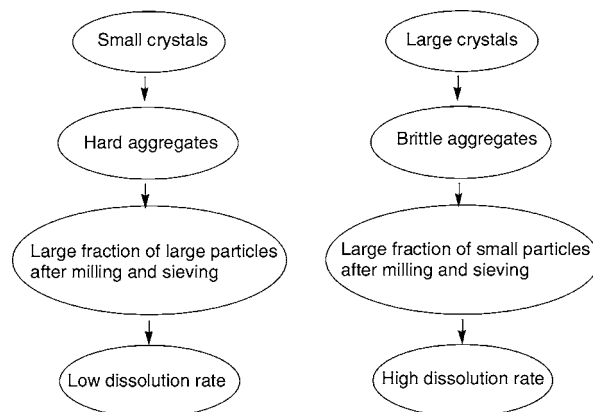**Figure 3.** Pictorial description of the aggregate formation of crystals.

Figure 4. The dependence between crystal size, aggregate, and bioavailability after pharmaceutical tablet formulation.

solvent evaporates, and dissolved substance precipitates at the contact point between the crystals, which become glued together as aggregates (Figure 3). The number of these contact points are directly linked to the size of the crystals, i.e. aggregates of equal size are hard (strong) when formed from small crystals and brittle (weak) when formed from large crystals. This has important implications for the pharmaceutical tablet formulation, as depicted in Figure 4, since brittle aggregates are of course easiest to break when milled and sieved.

After the investigation of the solid state properties it could be concluded that Roquinimex is a crystalline substance, which displays no polymorphism. A variety in crystal sizes between different batches could be detected suggesting a variety in particle size distributions. Thus, it was confirmed that the outcome of the final crystallization process of Roquinimex was crucial for obtaining good-quality end product, i.e. brittle aggregates and low content of N-methyl aniline. In other words, the final crystallization process of Roquinimex must be thoroughly defined and meticulously controlled to obtain a satisfactory pharmaceutical tablet formulation down the project line.

Design of Experiments. To be able to recapture control over the crystallization process, yielding the end product Roquinimex (see stage 3 in Figure 1), it was decided that a DOE study should be performed. The overall goal for this study was a crystallization process that could reliably deliver a drug fulfilling the quality parameters of substance dissolution capacity (dissolution > 90% after 60 min) and content level of N-methyl aniline (<100 ppm). In this case a two-

(8) Hansen, B.; Wadsten, T. *Roquinimex, Some Solid State Properties and Possible Polymorphism*; Pharmacia Document 21541F: Helsingborg, 1994.
(9) Hansen, B.; Ranklev, H. *Roquinimex, Particle Size Measurements*; Pharmacia Document 9520027: Helsingborg, 1995.

Table 2. Experimental variables and minimum and maximum levels used in the full factorial design

X_i	variables	(−)	0	(+)
X_1	temperature (°C)	20	25	30
X_2	dosing time of 5 M HCl (min)	15	22.5	30
X_3	concentration ($V_{water}/m_{Roquinimex}$ (mL/g))	6	8.5	11

Table 3. Full factorial design: experimental matrix and result[a]

	variables			response
exp	X_1	X_2	X_3	dissolution$_{60 min}$ (%)
1	-	-	-	66.7
2	+	-	-	87.6
3	-	+	-	83.4
4	+	+	-	93.4
5	-	-	+	63.0
6	+	-	+	93.7
7	-	+	+	70.3
8	+	+	+	88.6
9	0	-	0	88.8
10	0	-	0	86.5
11	0	-	0	89.7

[a] The exact values for the variables are listed in the Supporting Information.

level full factorial would be the most efficient way of understanding this crucial last step in the manufacturing and would enable us to learn more about all effects due to individual factors and their interactions (no confoundings present).[3] With the knowledge gained from the previous production, three experimental variables were expected to exert significant impact on the crystallization process. The selected variables were the temperature (X_1), dosing time of the hydrochloric acid (X_2), and final water dilution of compound (X_3) (Table 2). The levels of the different factors were chosen by again considering previous production. Just as important, other possible experimental variables, such as the strength of the hydrochloric acid, stirring rate in the reactor, and elapsed time between addition of hydrochloric acid and isolation of the product were kept constant. Thus, a full factorial design with three replicates gives us for $k = 3$ variables a design composed of $2^k + 3 = 11$ experiments. The experiments were performed in random order, and the outcome of each experiment was determined by measuring the substance dissolution rate over 60 min using the end value as the key response. As mentioned above, an important-quality parameter was also the level of *N*-methyl aniline.[4] However, this possible response was excluded, considering the previous insight that there is a good correlation between the property of high substance dissolution and low level of *N*-methyl aniline (Table 1). The experimental matrix, along with the chosen response, is depicted in Table 3.

The statistical analysis and the influencing effects of individual factors (b_i) as well as interactions (b_{ij}) of this full factorial design are shown in Table 4 (the effect of each variable X_i has been calculated using a polynomial function

Table 4. Factorial design: statistical analysis and influences of variables[a]

X_i	variables	effect dissolution$_{60min}$ (%)	std error[b]
X_1	temperature	10.3	0.7
X_2	dosing time of 5 M HCl	2.6	0.7
X_3	concn ($V_{water}/m_{Roquinimex}$)	−1.9	0.7
$X_1 \times X_2$		−3.2	0.7
$X_1 \times X_3$		2.3	0.7
$X_2 \times X_3$		−2.5	0.7
	mean value b_0	81.4	
	R^2	0.985	
	Q^2	0.924	
	RSD	2.11	

[a] Number of experiments = 11. [b] Estimated standard error of the regression coefficients (scaled and centered).

of the three experimental variables).[10] It can be seen that the effect from temperature is dominant over the other two factors, which in turn are approximately of the same magnitude as the interactive effects. However, all parameters are of importance, i.e. including them all in the multiple regression model leads to the highest correlation coefficients ($R^2 = 0.985$ and $Q^2 = 0.924$). Based on the data from Table 4, the response may be described, at 95% confidence level, as a polynomial equation with the listed variables. This gives the following model equation fitting the experimental data:

$$\text{dissolution}_{60min} (\%) = 81.4 + 10.3X_1 + 2.6X_2 - 1.9X_3 - 3.2X_1X_2 + 2.3X_1X_3 - 2.5X_2X_3$$

Modde calculated interpolation of the data gives a variation, within the experimental domain, in the response of between 63.6 and 95.1%.[11] The experiments verifying the mathematical model, using the variable settings that predict the highest and lowest response, are actually experiments 5 and 6 in the experimental matrix (Table 3). The respective experimental values of 63.0 and 93.7% are in good accordance with the model.

The observed effects of the separate variables are worth discussing. To achieve better crystallization, in terms of larger crystals, a high temperature is rudimentary (X_1, $b_1 = 10.3$). The other factors suggest a longer dosing time (X_2, $b_2 = 2.6$) and lower dilution (X_3, $b_3 = -1.9$) are beneficial. Additional information can be extracted from the interactive effects between the variables, which are of nearly equal magnitude. In Figure 5 the strong interaction between the temperature and the dosing time on the response is depicted graphically. For a given temperature the response increases with increasing dosing time, apart from a small curvature at the highest temperature, and for a given dosing time it increases with increasing temperature. This is as expected, since the response is dependent on the formed crystal size as discussed earlier. A longer dosing time would result in a slower rate of crystallization, which should benefit growth

(10) The Taylor expanded polynomial function up to second-degree terms: response = $b_0 + b_iX_i + b_{ij}X_iX_j$.
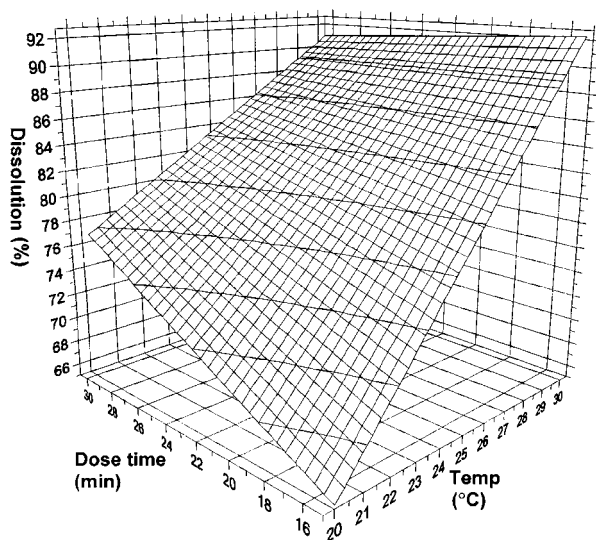(11) Modde 7.0, Umemetri AB, Umeå, Sweden.

Figure 5. Influence of the temperature (X_1) and the dosing time (X_2) on the dissolution capacity of Roquinimex (third variable $X_3 = 8.5$).
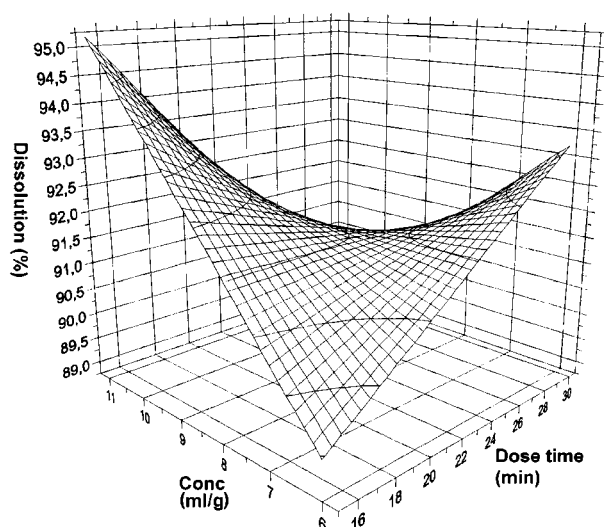

Figure 6. Influence of the dosing time (X_2) and the final concentration (X_3) on the dissolution capacity of Roquinimex (third variable $X_1 = 30$ °C).

of existing crystals to form larger crystals. This effect is amplified by a higher temperature, which can better redissolve newly formed small particles, again favoring growth of existing crystals. When considering concentration, the chemical intuition may suggest a higher dilution should also promote formation of large crystals due to lower chance of collision between small particles. However, by looking at Figure 6 we see something that resembles a surface with a saddle point. Thus, it is suggested that an optimized response can be found at either higher or lower dilution by expanding the experimental domain. This is a typical example of the benefits of DOE, namely woolly statements can be quantified.

An another interesting feature, which can be seen in Figure 6, is that the response surface actually represents something reminiscent of the robustness of the process. Given that the temperature is close to 30 °C, the dosing time and concentration are irrelevant within the specified levels with
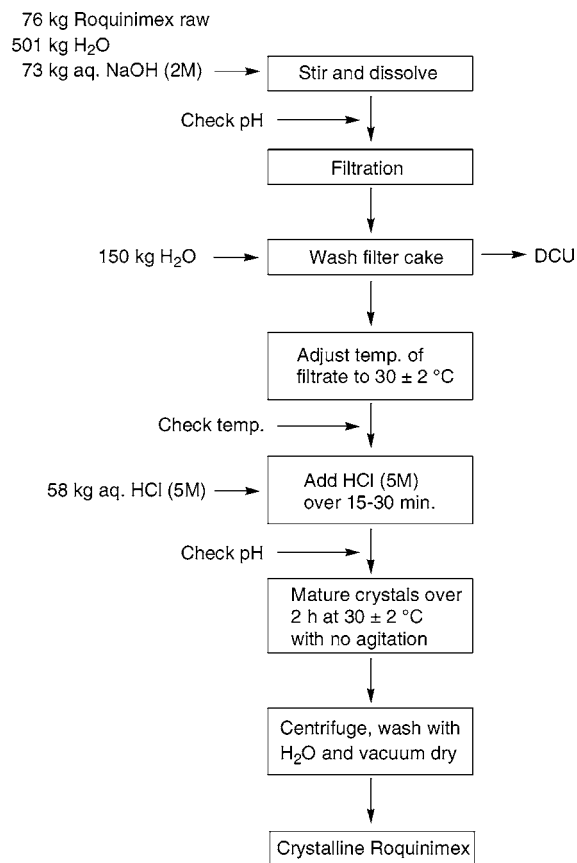

Figure 7. Block diagram of the master recipe for the purification and crystallization of Roquinimex.

respect to the desired substance dissolution capacity (>90%). The normal strategy when performing DOE, after initial screening followed by optimisation, is to conduct robustness testing. In this particular case Figure 6 suggests that neither further optimisation nor robustness testing is necessary to meet the goal of the DOE study.

Revised Full-Scale Manufacturing. The results and insights obtained from the DOE study led to a set of process parameters that were incorporated into a master recipe for producing 40 kg of Roquinimex. The block diagram of the purification and crystallization step of Roquinimex is displayed in Figure 7. The product obtained by applying this record, batches F07−F09 in Table 1 (entries 7−9), successfully met the predetermined quality parameters (see above) of substance dissolution capacity and remaining content level of *N*-methyl aniline. As a bonus, by shifting the process from precipitation towards crystallization, better yields were also obtained (Table 1).

In conclusion, this case study has shown that by applying DOE the intriguing aspects of particle size distribution and impurities in the Roquinimex substance could be controlled. Due to experimental design the crucial process parameters could be identified, which resulted in a scaleable and reliable process for manufacturing Roquinimex in a high quality. Thereby, this successful application of DOE gave the formulators and pharmacists the solution of the problem with deficient pharmaceutical tablet formulation.

Experimental Section

Synthetic Procedure for Designed Experiments. In a 500-mL three-necked round-bottomed flask connected to an external temperature-control unit and equipped with a mechanical stirrer, crude Roquinimex (30 g) was slurred in deionized water (150–300 mL). The pH was adjusted to 7.5–7.7 with 2 M NaOH and the reaction mixture filtered. The remaining DCU in the filter was rinsed with 30 mL of deionized water. The filtrate was transferred back to a 500-mL flask. The temperature was adjusted (20–30 °C) before adjusting the pH to 0.8–1.2 with 5 M HCl (dosing time [15–30] min). The suspension was stirred for additional 15 min before leaving it without stirring for 2 h at the defined temperature. The substance was isolated by filtration, washed with 2 × 200 mL of deionized water, and dried under vacuum at 35 °C. The quality of the substance, i.e., its dissolution capacity, was analysed using the dissolution method previously described.[6]

A Representative Synthesis of 1,2-Dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinecarboxylic Acid Methyl Ester (2). Dimethyl formamide (862 kg), 104 kg (787 mol) of dimethyl malonate, and 37.5 kg (694 mol) of sodium methoxide were charged into a reactor. The suspension was agitated for 90 min at 80–90 °C before 90 L of solvent was removed under reduced pressure. The temperature was adjusted to 83 °C before charging 77 kg (435 mol) of N-methylisatoic anhydride (**1**) in portions over 10 min. The temperature was adjusted to 96 °C before 125 L of solvent was removed under reduced pressure. The mixture was cooled to 40 °C, and 1309 kg of deionized water was charged. The suspension was cooled to 20 °C and agitated for 1.5 h. The pH was adjusted to 1.0 by charging 127.5 kg of concentrated hydrochloric acid. The suspension was cooled to 9 °C and agitated overnight. The substance was isolated by centrifugation and washed with 3 × 100 L of deionized water. Further drying under vacuum at 50 °C gave 84.2 kg of **2** (83% yield based on **1**) as a white crystalline solid. For analytical data see Supporting Information.

A Representative Synthesis of 1,2-Dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinecarboxylic Acid (3). Glacial acetic acid (532 kg) and 84.5 kg (361 mol) of **2** were charged and agitated in a reactor. Concentrated hydrochloric acid (199 kg) was charged before agitating for 2 h at 80–85 °C. The mixture was cooled to 63 °C, and 101 kg of MeOH was charged. Further cooling to 13 °C was followed by centrifugation of the suspension. The substance was washed with 2 × 70 kg of MeOH and dried under vacuum at 50 °C, which gave 75 kg of **3** (85% yield based on **2**) as a white crystalline solid. For analytical data see Supporting Information.

A Representative Synthesis of 1,2-Dihydro-N,1-dimethyl-4-hydroxy-2-oxo-N-phenyl-3-quinoline Carboxamide (Roquinimex, 4). Toluene (496 kg) and 75 kg (342 mol) of **3** were charged and agitated in a reactor. N-methyl aniline (38 kg (355 mol)) and 75 kg (364 mol) of 1,3-dicyclohexylcarbodiimide were charged. The suspension was stirred for 2 h at 80–85 °C before cooling it to 10 °C. The crude **4** was isolated by centrifugation and washed with 2 × 94 kg of toluene. Further drying under vacuum at 35 °C gave 152.5 kg of crude **4**, which was divided into two equal portions before further processing. Crude **4** (76 kg) was mixed with 501 kg of deionized water. The pH was adjusted to 7.5 by charging 73 kg of 2 M NaOH. The DCU was removed by filtering the suspension on a plate filter over to a new reactor. The DCU on the filter was washed with 150 kg of deionized water, which was also transferred to the new reactor. The temperature of the filtrate was adjusted to 29.6 °C before adding 58 kg of 5 M HCl over 25 min. The agitation was halted after 15 min, and the precipitate was allowed to mature for 2 h at 30 ± 2 °C. The substance was isolated by centrifugation and washed with 3 × 80 kg of deionized water. Further drying under vacuum at 35 °C gave 40 kg of Roquinimex (76% yield based on **3**) as a white crystalline solid. For analytical data see Supporting Information.

Warning! A product with minimum ignition energy (MIE) below 10 mJ is considered highly sensitive towards ignition. The use of nonconductors with high resistance should be restricted in handling such materials, and operations should be performed under nitrogen. Since the dry Roquinimex substance is only marginally outside this category (MIE-value of 11 mJ), such precautions should be seriously considered to prevent any dust explosion during handling.

Supporting Information Available

Release test results and ^{1}H NMR data of compounds **2**–**4**; raw data from the DOE experiments. This material is available free of charge via the Internet at http://pubs.acs.org.