Organic Process Research & Development **2005**, *9*, 344−347

Selectivity Control by Use of Near-IR for a Hydrogenation Process

Koen De Smet,* Jan van Dun, Bard Stokbroekx, Tom Spittaels, Christine Schroyen, Peter Van Broeck, Julien Lambrechts, Dirk Van Cleuvenbergen, Guy Smout, Jeroen Dubois, Andras Horvath, Jurgen Verbraeken, and Jef Cuypers

Chemical Development, Johnson & Johnson Pharmaceutical Research & Development and Janssen Pharmaceutica Geel, Turnhoutseweg 30, 2340 Beerse, Belgium

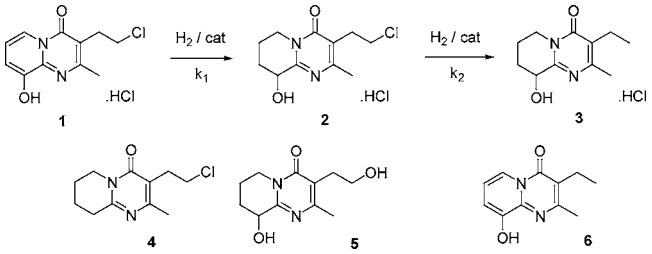
Abstract:

We applied process analytical technologies to solve the problem of selectivity in the hydrogenation of 3-(2-chloroethyl)-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one monohydrochloride (1) to (±)3-(2-chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-*a*]pyrimidin-4-one monohydrochloride (2). We showed that both mid-IR and near-IR (NIR) were suitable for in-line analysis of the hydrogenation. We chose to use NIR in the production environment due to easier implementation. We developed a NIR model by correlation of NIR results with HPLC results for a laboratory-scale hydrogenation reactor, and we used production batch data to adjust and confirm this model.

Introduction

The hydrogenation of 3-(2-chloroethyl)-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one monohydrochloride (**1**) to (±)3-(2-chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-*a*]pyrimidin-4-one monohydrochloride (**2**) is a key step in the synthesis of the antipsychotic agent Paliperidone.[1] This was performed with a carbon-supported palladium catalyst in MeOH at 50 °C and 0.15 bar hydrogen pressure. In addition to the desired product **2,** dehalogenated product **3** was also formed (Scheme 1). Structures **4** and **5** are other impurities formed under certain reaction conditions. Formation of **6** was never observed.

Scheme 1. **Hydrogenation of 3-(2-chloroethyl)-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one monohydrochloride (1) to (±)3-(2-chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one monohydrochloride (2)**



To meet specifications on impurities on the drug substance, we needed to have <0.5% residual **1** in the isolated product **2**, or less than 0.8 (w/w % rel) in the reaction mixture at the end of the hydrogenation. The content of **3** in isolated **2** was not critical to the quality of the drug substance (up to 15% could be removed in downstream processes) but represented a sensitive loss. To minimize losses of desired product **2** due to consecutive dehalogenation to **3**, while meeting the specifications on residual **1**, we tested the effect of several parameters (Table 1).

The best conditions from this screen gave in situ yields of 94.7% (Table 1, entry 1). During scale-up of this hydrogenation it was noticed that the reaction rates and times were not reproducible. Investigations to find the cause of the variability revealed that the catalyst deactivates. Although a pretreatment of **1** with charcoal was introduced, a very slow reaction was observed when the unreduced catalyst was too long in contact with the reaction mixture (Table 2, entry 1). This observation was also confirmed by experiment: if the catalyst is directly added to a reaction mixture under hydrogen atmosphere, the reaction is much faster (Table 2, entry 2).

The formation of side-product **3** was also monitored by HPLC as a function of time (Figure 1). It was observed that **3** was formed mainly at the end of the reaction. This means that, by using the best conditions, the k_1/k_2 ratio is sufficiently large to ensure good selectivity in case the reaction is stopped at the "right" time. Monitoring the H_2 consumption was obviously not able to provide a clear end-point determination. On the production site, because of the variability of the process and the long overall analysis time, off-line HPLC also proved to be too slow and impractical as a control method. It was clear that a fast analysis method was needed to monitor the evolution of the process in situ.

Discussion and Results

To improve process robustness we decided to use process analytical technologies (PAT) to define a clear endpoint of the reaction. If hydrogenation was stopped too early (too much starting material present) it was difficult to restart the hydrogenation due to catalyst deactivation. On the other hand, dechlorination could be suppressed by reducing the contact time of the product with hydrogen gas and catalyst.

1. Screening of the Analytical Tools To Determine the Endpoint. We evaluated two spectroscopic techniques (mid-IR[2] and near-IR[3]) on laboratory (lab) scale and for feasibility of implementation of the technique on the production floor.

* To whom correspondence should be addressed. E-mail: kdesmet@prdbe.jnj.com.

(1) Janssen, C. G. M.; Knaeps, A. G.; Kennis, L. E. J.; Vandenberk, J. EP 0368388, 1990.

(2) Rein, A. R.; Donahue, S. M.; Pavlosky, M. A. *Curr. Opin. Drug Discovery Dev.* **2000**, *3*, 734.

(3) Blanco, M.; Coello, J, Iturriaga, H, Maspoch, S., de la Pezuela, C. *Analyst* **1998**, *123*, 135−150.

Published on Web 02/25/2005
10.1021/op049782x CCC: $30.25

Table 1. **Parameter screening for the hydrogenation of 1**[a]

	conditions[a]			product ratio (LC w/w % rel)			
entry	catalyst	solvent	time (h)[b]	1	2	3	Σimp.
1	E101N/W 10%Pd	MeOH	5.05	0.2	94.7	3.1	1.85
2	E1506YA/W 10%Pd	MeOH	9.10	44	48.6	4.7	2.8
3	E196YA/W 10%Pd	MeOH	9.00	69.2	26.2	2.2	2.4
4	Rh 5%	MeOH	6.50	64.1	32.3	0.2	3.3
5	Pt 5%	MeOH	21.30	24.4	29.8	4.5	16.7[c]
6	E101N/W 10%Pd	H_2O	6.50	10.8	44.2	4.5	40.5[d]
7	E101N/W 10%Pd	10% HCl	5.40	86.5	10.7	0	2.8
8	E101N/W 10%Pd[e]	MeOH	5.45	8.1	81.4	5.3	5.2
9	E101N/W 10%Pd[f]	MeOH	8.40	0.35	77.6	19.8	1.7
10	E101N/W 10%Pd[g]	MeOH	12.15	33.1	61.6	2.5	2.8
11	E101N/W 10%Pd[h]	MeOH	24	0.07	91.3	7.6	1
12	E101N/W 10%Pd[i]	MeOH	30	9.2	82.4	7	0.8

[a] All reactions were conducted at lab scale using 60 g of catalyst/mol **1** in 1.8 L solvent/M **1** under 0.15 bar H_2 at 50 °C. [b] Reaction was stopped either when 4 mol/mol H_2 was absorbed or the reaction rate was too slow. [c] **4** was formed as main impurity. [d] **5** was formed as main impurity. [e] Reaction was performed under 5 bar H_2. [f] Reaction was performed at 40 °C. [g] Reaction was performed at 60 °C. [h] $ZnCl_2$ was added as additive. [i] 4-Chlorotoluene was added as additive.

Table 2. **Influence of catalyst addition mode on the hydrogenation time and product ratio**

		product ratio (LC w/w % rel)			
entry	time (h)	**1**	**2**	**3**	Σimp.
1	8:30	12.1	80.8	5.4	1.7
2	3:30	0.26	93.3	5.2	1.3

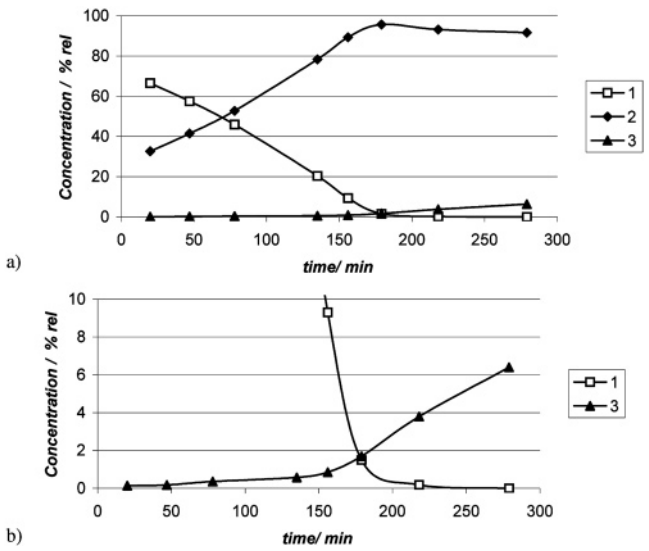


Figure 1. **(a) Evolution of concentrations of 1, 2, and 3 as a function of time in the hydrogenation reaction mixture. (b) Enlargement to visualize the concentrations of 3.**

We used a Buchi hydrogenation lab reactor to evaluate the suitability of the two IR techniques.

Mid-IR data were generated with a ReactIR apparatus. Disappearance of the signals from the aromatic region[4] (1650−1500 cm^{-1}) and the shift of the CO signal to lower wavenumbers (from 1720 to 1710 cm^{-1}) could be clearly visualized (Figure 2). Particles and/or gas-bubbles were not interrupting the IR signal when an ATR crystal was used.

(4) Colthup, N. B.; Daly, L. H.; Wiberley, S. E. *Introduction to infrared and Raman spectroscopy*; Academic Press: New York, 1990.

Near-IR (NIR) data were generated with a Buchi NIR analyzer.

The overtones of NIR spectra are somewhat broad, and bands are overlapped which makes it less ideal for fundamental interpretation. All chemical and physical information is present but has to be linked via multivariate analysis to a primary analytical technique (HPLC, GC, etc.). We analyzed some filtered samples (particles influence transmission) by transflection and correlated them to HPLC results. This study showed that NIR was also suitable for trending this hydrogenation reaction.

2. Defining Which Analyzer Will Be Used. The fact that existing process equipment (reactor, sampling systems, etc.) had to be used in combination with PAT made it necessary that requirements of production (such as workability, installation on existing equipment, safety, EX-zone (production area where explosion-proof equipment must be used), and maintenance) and analysis (robust analyzer, representative samples, maintenance of equipment, and result interpretation) also had to be considered during the method selection.

Finally, we chose NIR for two reasons. (i) The distance between the sampling unit and analyzer is much larger in NIR. Mid-IR can bridge a distance of 1.5 m, while NIR can bridge easily a distance of 100 m. As a consequence the NIR-analyzer can be placed in a non-EX-zone. (ii) The spectroscopic information obtained by mid-IR is very useful within chemical development but less important or even unimportant for the operator in chemical production. Indeed, the operator has to know the concentration of a certain component.

3. Lab-Scale Calibration. The sensitivity of NIR to the presence of particles and the temperature variations required a filter device between the reactor and a thermostatic NIR-flow-cell. On lab scale, we performed four reactions in a 5-L Buchi reactor under different conditions (Table 3).

For each reaction, five "end" samples were analyzed by NIR (four spectra were taken) and HPLC.

We linked the HPLC results to the spectra by multivariate analyses, more precisely partial least squares (PLS) in combination with data pretreatment (normalization by clo-

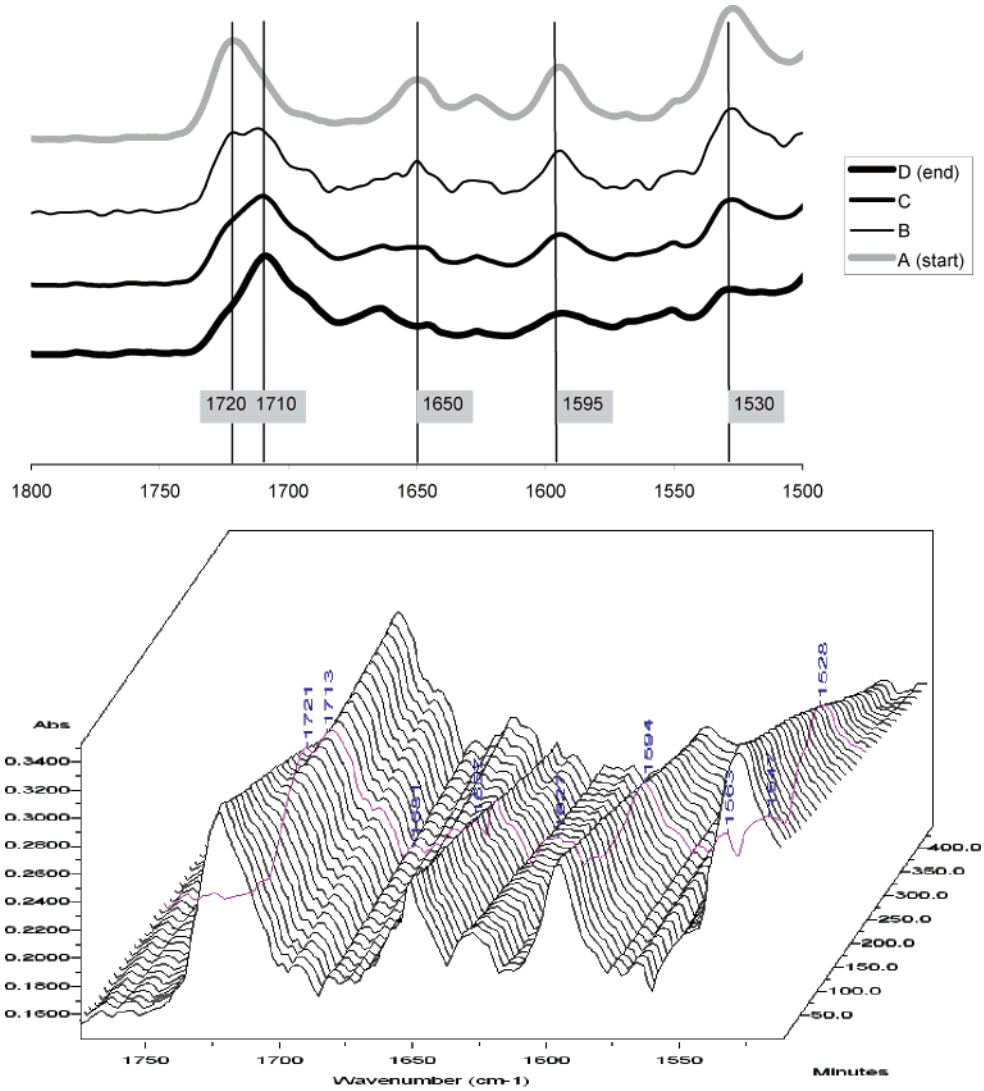


Figure 2. **Mid-IR spectra during the hydrogenation.**

Table 3. **Experimental parameters for the lab-scale model**

entry	temperature (°C	stirring speed (10^2 rpm)	pressure (bar)	catalyst load (g/mol)
1	50−52	8	0.150	60
2	50−52	7	0.150	90
3	50−52	14	5	60
4	55−57	7	5	60

sure, spectral range: 4392−4800, 5400−6600, 7800−9996 cm^{-1}). Sixty percent of the samples were used as calibration samples and the other 40% as validation samples.[5] Comparing the standard error of estimation (with that of calibration samples) and prediction (with that of validation samples) as a function of factors avoids an over-fitted model: 6−8 factors were found to be optimal (Figure 3).[6]

We found a good correlation between the HPLC results and the NIR results in the plot of HPLC concentration versus

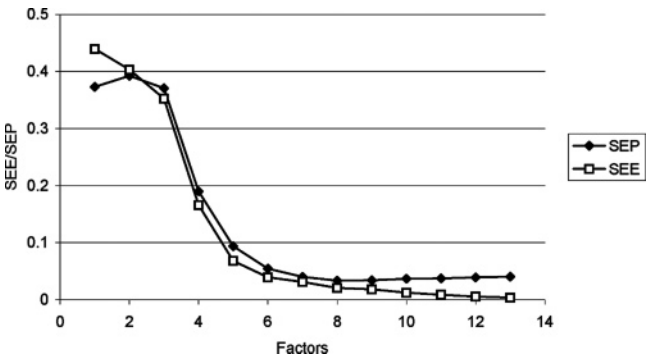


Figure 3. **Standard error of prediction and estimation for the developed model as a number of factors.**

the NIR-predicted concentration (Figure 4). Differences between the NIR results and the HPLC results can be attributed to errors of the primary method (HPLC), errors of the NIR model, and sampling errors. The standard error of estimation/prediction gave the error of the NIR/model (Figure 3), indicating that the endpoint detection of the reaction was not to be very precise but sufficient for our purpose.

4. Test on Production Scale. Scale-up of a process influences the process behavior and as a consequence also the

(5) Reactions were performed on lab scale where we took five samples which were analyzed four times by NIR to include small temperature differences in the NIR model.

(6) This rough NIR-lab model was not optimized in detail on lab scale. We found it useful to further optimize the NIR model in the production equipment.

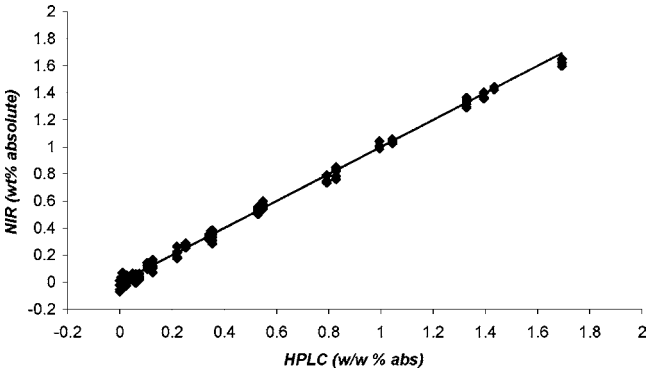


Figure 4. **Concentration correlation plot for the calibration set.**

Table 4. **Comparison of the predicted NIR results (based on lab-scale experiments) versus the HPLC results on samples of hydrogenation reaction mixtures from three production batches**

test batch	pressure (mbar)	time of sampling (h)	predicted NIR-results[a]	HPLC-results		
			1[b]	**1**[c]		**3**[c]
A	5×10^3	4	0.959 ± 0.04	1.05	12.9	7.1
		6	0.349 ± 0.03	0.06	0.5	15.3
B	150	5	0.110 ± 0.04	0.11	1.3	8.8
		7.5	-0.044 ± 0.03	0.03	0.25	12.2
C	150	5	0.377 ± 0.05	0.31	3.7	6.9
		7.5	0.124 ± 0.06	0.06	0.8	9.1

[a] Mean ± standard deviation. [b] % w/w, abs. [c] % w/w, rel.

NIR spectra and prediction results. To be able to build in the variability of the process (scale-up effects), we tested the lab-scale model for three batches of hydrogenation on production scale (A, B, and C in Table 4).[7] For each batch the first sample was taken during the process to check the evolution of the reaction. The second sample was taken at the end of the hydrogenation. The first samples (incomplete conversion) gave us a good indication about the hydrogenation time. In batch B for instance, we saw that the reaction was already completed, although a longer hydrogenation time was expected on the basis of hydrogen consumption (82% of the theoretical amount was consumed). In batch C, we decided to take the first sample at the same time as in B, and with this result we estimated the endpoint of the hydrogenation.

We used the spectra obtained on production scale in combination with HPLC results to refine the calibration and to obtain a robust model. This refined model gave a good real-time endpoint indication and clearly visualized the evolution of the hydrogenation. Batch losses due to process variability and product quality variations can thus be eliminated by the use of this PAT.

Conclusions

We demonstrated that two spectroscopic techniques (mid-IR and NIR) were suitable to define a clear endpoint of the hydrogenation and to minimize the side-product formation. Both techniques have the advantage that results can be obtained in real time (~1 min). Although mid-IR is more accepted in development, we decided to choose NIR for production scale, because it is easier to implement on existing production equipment in an EX-environment. A model developed on lab scale with four reactions (linking NIR results to HPLC data) already showed a good fit and was further refined by using data from the production batches. Using PAT for this hydrogenation did not eliminate process variability but secured a superior control of the manufacturing process in line with the FDA recommendations.[8]

Experimental Section

Instrumentation. Hydrogenations on lab scale were performed in a 5-L Buchi reactor, where a flange for the mid-IR probe or the NIR sample device replaced one of the sight glasses.

Mid-IR. In situ experiments were performed using a ReactIR 4000 spectrometer with a DiComp immersion probe (flushed with nitrogen). Air was used as background, and every 2 min a spectrum (resolution = 4 cm^{-1}, scans 128) was collected.

Near-IR. A NIR-analyzer of Buchi was equipped with a thermostatic flow cell delivered by Solvias. The NIR model was built by using HPLC as the primary analytical method.

General Procedure. A 5-L flask was charged with **1** (250 g, 0.91 mol), charcoal (50 g), and methanol (2184 mL). The mixture was heated to 50 °C, stirred for 1 h, and filtered, and the filter cake was washed with methanol (182 mL). This solution and the catalyst (Pd/C 10%, 54.6 g) were added to a 5-L stainless steel Buchi hydrogenation reactor, and the reaction was started at 50 °C and 150 mbar overpressure of hydrogen. The reaction was stopped when the NIR data showed 0.8% of residual **1** in the reaction mixture. After adding thiophene (3 g), the reaction mixture was filtered, and the filter was washed with methanol (364 mL). The methanol was evaporated from the reaction mixture (max 95 °C) to obtain a thick oil, to which water (910 mL) was added over 30 min at 85 °C. The mixture was cooled to 30 °C and treated with a solution of potassium acetate (178.3 g, 1.82 mol) in water (182 mL) dropwise over 1 h and then stirred at 5 °C for 3 h. The crystals were filtered, washed with water (2 × 254 mL), and dried in a vacuum at 40 °C to obtain the free base of **2** (152.5 g, 69% yield). HPLC (w/w %): **2** (99.4), **1** (0.06), **3** (1.2), **5** (0.15), sum of the rest of impurities 0.3%.

Hydrogenations on production were performed in a 3000-L reactor.

Received for review December 1, 2004.

OP049782X

(7) Each sample was analyzed by NIR (lab model) and HPLC. Differences between the NIR and HPLC results are due to different reaction conditions and the nonoptimized NIR-model.

(8) http://www.fda.gov/cder/OPS/PAT.htm#Additional.