

## Effects of Raney-type Nickel Catalyst Production Scale Pretreatment

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Original scientific paper

Received: September 29, 2005

Accepted: March 15, 2006

The need for optimizing chemical production processes in pharmaceutical industry by taking economic issues into account has increased more than ever before. This work deals with the hydrogenation of TLP (*N*-3-fluor-acethyl-L-lisil-L-proline) over Raney-type Nickel catalysts for the production of an active pharmaceutical ingredient (API) and presents two specific findings at a production site, which influence the overall performance of the process. It is shown that the Raney-type Nickel catalyst pretreatment and the impurities present in the reactants have a large impact on the catalyst surface activity. Both considerably affect the number of cycles a batch of catalyst can be reused, which can obviously lead to increased cost efficiency.

*Key words:*

Raney-type Nickel catalyst, pretreatment, purity of reactant, impurities

### Introduction

Hydrogenations over Raney-type Nickel catalysts have been in widespread use for a several decades. Raney-type Nickel catalyst represents the best choice in most cases to achieve the high yields of desired product (enantiomers, racemates etc.). Nevertheless, a number of uncertainties still exist during the preparation of Raney-type Nickel catalysts, since its performance is heavily dependent on the quality of raw materials, employed solvents, and operating conditions (temperature, pressure) among other things.

The nature of solvent influences the activity and selectivity of hydrogenation over Raney-type Nickel catalysts. It was shown that the hydrogenation of acetophenone to 1-phenylethanol in a 2-propanol-/water/sodium hydroxide solvent mixture rises yield from 82,4 % to 99,5 %.<sup>1</sup> The activity of Raney-type Nickel catalysts will depend on the amount of residual aluminum present after leaching and whether the promoter is linked to nickel or to aluminum formation.<sup>2</sup> A number of papers can be found in the open literature dealing with the preparation or leaching of Raney-type Nickel catalysts in different ways. Zeifert et al.<sup>3</sup> prepared catalyst employing a two step procedure: the catalyst was first prepared by mechanical alloying followed by alkaline aluminum leaching, which led to a more stable structure. Furthermore, a study of a leaching method in the presence of bayerite with small amounts of sodium hydroxide revealed that 82 – 86 % of leaching level leads to largest active surface area for NiAl<sub>3</sub> alloys.<sup>4</sup> Devred et al. have studied the treatment of two nickel aluminium alloys with an aqueous sodium solution, which led to

a Raney-type Nickel type catalyst.<sup>5</sup> The activation process was very fast and after 10 s of leaching, most of the aluminium had been leached out as alumina. The longer leaching time was the better the observed catalytic performance – both in terms of activity and selectivity of catalysts – was reached. Osawa et al.<sup>6</sup> hydrogenated 2-alkanone over tartaric acid-NaBr modified Raney-type Nickel catalysts, which led to excellent optical yields. Kukula and Červený<sup>7</sup> also used tartaric acid modified catalyst for enantioselective hydrogenation of methylacetate to methyl-(3*R*)-hydroxybutyrate. It was found that decrease of aluminium content in catalyst increase optical yields. Imamura et al.<sup>8</sup> prepared a highly active Raney-type Nickel catalyst by leaching out the rare earth elements from LaNi and SmCo<sub>2</sub> in 1,2-diiodoethane or 1,2-dibromethane solutions, leaving a spongy, high surface area skeleton of nickel and cobalt. The selective hydrogenation of furfural over Raney-type Nickel, which had been modified prior to that by impregnating it with salts of heteropolyacids, has shown a higher catalytic activity and selectivity compared to the unmodified catalyst.<sup>9</sup> A novel concept for improving the activity of Raney-type Nickel by on-line ultrasonic irradiation clearly found out to inhibit the catalyst deactivation for the case of a three-phase hydrogenation of xylose to xylitol.<sup>10</sup> CO hydrogenation to methanol with Raney-type Nickel catalysts leads to 92,4 % conversion of CO and 99,8 % methanol selectivity by eliminating the water after leaching the catalyst.<sup>11</sup>

A present paper will show a method of Raney-type Nickel catalyst preparation for an industrial scale hydrogenation process for the production of an active pharmaceutical ingredient (API) and how this pretreatment influences on reactant conversion, process efficiency, and ultimately cost savings.

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## Experimental section

### Materials

The properties of a Raney-type Nickel catalyst, supplied by Degussa, Germany, are shown in Table 1. Catalyst is supplied in water solution. The reactant (intermediate) TLP (*N*-3-fluor-acethyl-L-lysyl-L-proline) was obtained from two sources and the properties of the Degussa, Germany, (Supplier 1) and Nichimen Chemical Corporation, Japan, (Supplier 2) reactants are shown in Table 2. The reactant OXO (etil-2-okso-4-phenylbutirate) was obtained from DMS Fine Chemicals, Netherlands (Supplier 3); the properties are shown in Table 3. We can see that impurities in OXO are negligible, on the contrary impurities in TLP play an important role. The impurities TFA Lysine and TFA-Lys-Pro DKP (Diketopiperazine) are the same nature from both TLP suppliers and in similar quantities, sulphate ash as impurity is defined only in TLP from supplier 1.

Table 1 – Properties of Raney-type Nickel catalyst.

Raney-type Nickel B113W	
Ni, $w_{\min}$ / %	93.0
Al, $w_{\max}$ / %	7.0
activity, $m_{H_2, \min} / m_{cat, \min}$	22
density, $\rho$ / kg l <sup>-1</sup>	1.3

Table 2 – Purity of TLP from different suppliers

	TLP	
	Supplier 1	Supplier 2
Pure TLP $x_{\min}$ / %	85	98
Impurities-total $x$ / %	15	2
TFA Lysine, TFA-Lys-Pro DKP	3	2
Sulphate ash	12	0

Table 3 – Purity of OXO

	OXO
	Supplier 3
Pure TLP $x_{\min}$ / %	99.0
Impurities – water $x_{\min}$ / %	0.2

### Analytical methods

To determine the quantity of non-converted TLP after hydrogenation phase, high performance liquid chromatography (HPLC) was performed using Agilent 1100 Series. The column was Hypersil

ODS 250 mm · 4,6 mm · 5  $\mu$ m at thermostat temperature 30 °C. Mobile phase was water : acetonitrile : (trifluoroacetic acid)  $\Psi_{H_2O/AcC/TFA} = 500:500:1$  at flow rate 1.0 ml min<sup>-1</sup>. The wavelength of detection was  $\lambda = 210$  nm. To determine the quantity of residual water, after pretreatment process of catalyst, standard Karl Fisher method in automatic mode was used.

### Procedure of pretreatment

The pretreatment of the catalyst was performed in a 500 l volume stainless steel reactor (ANSI 316L) at room temperature (around 293 K) and atmospheric pressure.

At first 100 kg of Raney-type Nickel catalyst water suspension was dosed into reactor and then an additional 200 l of demineralized water were added, while mixing of the whole solution at  $n = 280$  min<sup>-1</sup>. The solution was then left to deposit and the clear part was decanted out, while the thick slurry of Raney-type Nickel catalyst was left in the reactor. The washing and decanting procedure was repeated with an additional 300 l of demineralized water and followed by 5 times of 200 l of ethanol. After the last decantation step the sample is taken from bottom of reactor to measure part (%) of residual water still present in the catalyst. The catalyst pretreated, according to the above procedure, was used for each batch of the hydrogenation of TLP to produce the required API. After hydrogenation a separation phase of API product from catalyst was performed using candle filter (5  $\mu$ m). Separated catalyst was then regenerated each time according to the above described pretreatment procedure.

### Procedure of hydrogenation

The hydrogenation was performed in a 1200 l volume stainless steel reactor (ANSI 316L) at temperature 308 K and at 4 bars overpressure (hydrogen atmosphere) for 24 h. Stirring speed was 280 min<sup>-1</sup>. Catalysts mass fraction in reaction ethanol solution was 9.5 %. Intermediates TLP and OXO are dosed into reactor separately in mole ratio 1 : 2.8. Synthesis scheme of the hydrogenation is shown in Fig. 1.

## Results and Discussion

During the search of the suitable catalysts pretreatment procedure, the process performance was evaluated through:

- fraction of non-converted TLP in hydrogenation phase (limiting reactant)
- the number of multiple use of a single Raney-type Nickel catalyst batch

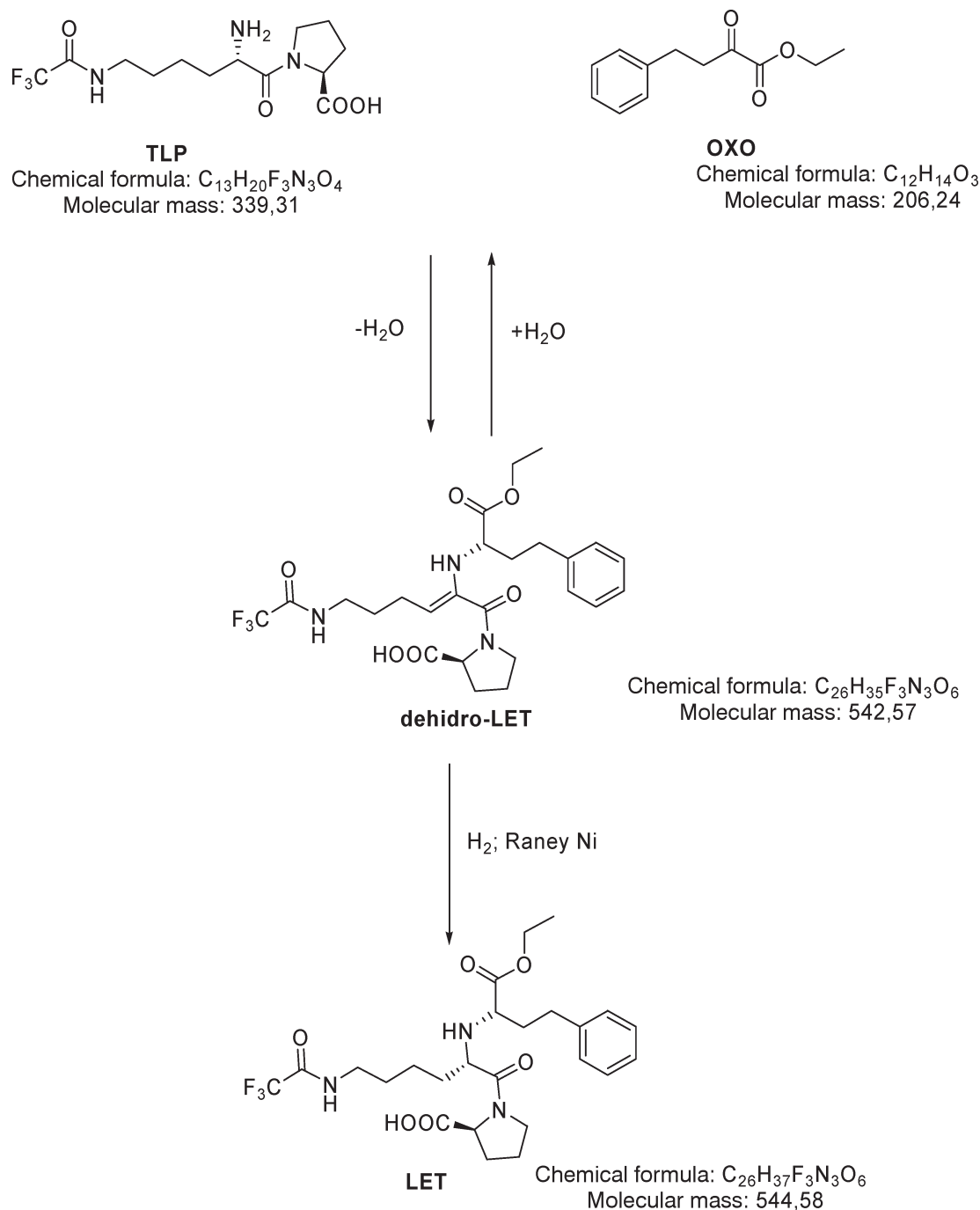


Fig. 1 – Synthesis scheme of hydrogenation (R. Agnič – Effects of Raney-type Nickel Catalyst production scale pretreatment)

During the process development at a small scale and subsequent scale up to industrial scale, a criterium was established that the Raney-type Nickel catalyst can have up to 3 % of residual water present (in order to achieve that one only needs to wash the catalyst with 3 batches of 200 l of ethanol). However, it is important to note that the maximal acceptable non-converted amount of TLP after the hydrogenation is 10 % and this should be taken into account, when determining the suitable catalysts pretreatment procedure.

After several production trials, it was noticed that 3 % of residual water in the catalyst is too high to start with, since it limits the extent of TLP conversion (reversible reaction as shown in Fig. 1), as well as substantially reduces the number of runs, in which a single catalyst batch can be reused. This is because the hydrogenation reaction of TLP to API reaches equilibrium at about 6 % of water in the solution (reversible reaction). Since the main reaction is slow at higher water fractions, side reactions gain in importance, thus the amount of oligomers being

formed increases. These oligomers deposit on the catalyst surface and start causing its deactivation over time. It was therefore decided to reduce the amount of residual water in the catalyst to 1 %. The catalysts pretreatment procedure described in the experimental section applies to this new criterium.

As shown in Fig. 2, the reduction of residual water in the catalyst for an additional 2 % (from 3 to 1 %) leads to higher process efficiency and prolonged life-cycle of catalyst itself. The number of hydrogenations in which a single catalysts batch can be reused has been increased substantially from 6 to 16. Again, the reason for this lies in the kinetics of hydrogenation. Since water is side product of the equilibrium limited hydrogenation reaction, a higher water fraction at the start will mean the reaction equilibrium is reached sooner, leading lower yields as well as to shorter life-cycle of catalyst. However, it is also important to note that during the catalyst pretreatment procedure the aluminium salts originally present in the catalyst are washed out and consequently additional active sites on surface of catalyst are released.

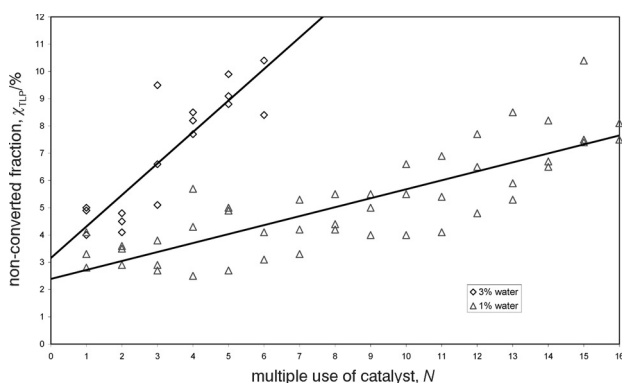


Fig. 2 – Effect of the starting amount of residual water in the catalyst on the reaction yields as a function of the number of catalyst reuse. The solid lines represent the trends. (R. Agnič – Effects of Raney-type Nickel Catalyst production scale pretreatment)

Therefore, the amount of water is an important factor that affects the process efficiency, however, it is not the only one. Fig. 3 demonstrates that the reaction yield, as a function of number of multiple use of a single catalysts batch, strongly depends on the amount of impurities initially present in the reactant TLP (as shown in Table 2). While using the low purity reactant from Supplier 1, the amount of non-converted TLP rises steadily during the number of repetition batches, irrespective of the fact that the starting amount of residual water in the catalyst was 1 %. On the other hand, the high purity reactant from Supplier 2 gave far better results with the reaction yield being more or less constant during the number of catalysts reuses. Obviously, the presence

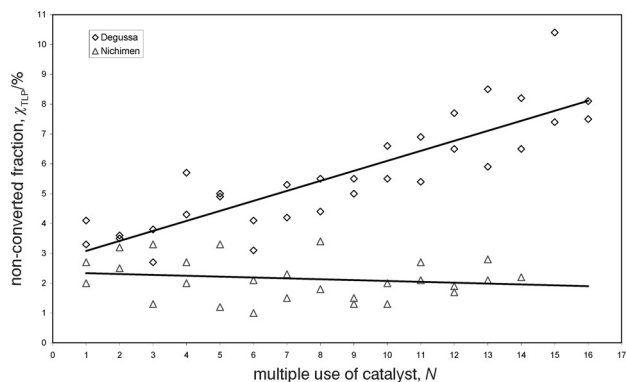


Fig. 3 – Effect of TLP purity as a function of catalyst multiple use. The starting amount of residual water in the catalyst was 1 % in both cases. The solid lines represent the trends. (R. Agnič – Effects of Raney-type Nickel Catalyst production scale pretreatment).

of a large quantity of impurities in the reactant compromises the activity of catalyst, however, the reason for this is still not entirely clear. It could be that the impurities participate at side reactions forming oligomers that deposit on the active catalysts sites (organic impurities) or simple deposit there by themselves (sulphate ash impurities). In any case, the message is clear; the use of a high-purity reactant is preferred, irrespective of the higher initial material costs.

Due to the shortage of high-purity TLP (from Supplier 2) it was not possible to determine the final number of multiple use of catalyst. A different experiment was, however, performed to determine the beneficial effect of using a high purity reactant. By using a single catalysts batch, the first couple of reaction batches were performed employing the low-purity TLP from Supplier 1, followed by a number of batches performed with high-purity TLP from Supplier 2. As can be seen from Fig. 4 the process

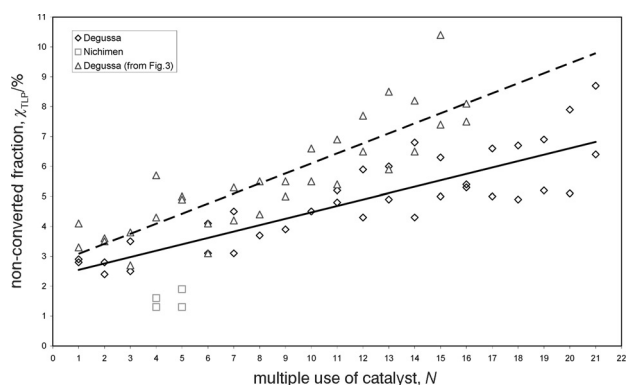


Fig. 4 – Process performance in terms of reaction yield while employing TLP of different purities for a single catalyst batch. The solid line represent the current process performance trend, whereas the dashed line represent the results obtained by employing a low-purity TLP as reactant only. (R. Agnič – Effects of Raney-type Nickel Catalyst production scale pretreatment).



performance using the latter was much better compared to the former and in line with the results obtained by only using the high-purity TLP from Fig. 3, even though one could argue that the catalyst was already deactivated to some extent by performing the first couple of batches with the low-purity TLP. Once we switched batches to using the low-purity TLP, the process performance started deteriorating with time, as expected. However, comparing the process performance from this point onward to that from Fig. 3, when the low-purity TLP was employed for all the runs, we see a slower decrease in reaction yield over time. The results seem to suggest that intermediate hydrogenations using high-purity TLP increase the final number of the Raney-type Nickel catalyst, which can be reused. It could well be that TLP with lower purity blocks catalysts active surface area with accumulation of impurities; while the intermediate use of TLP with higher purity causes a re-activation of surface sites, resulting in a considerable increase of the number of the catalyst, which can be reused. The mechanism of the re-activation could be explained with the impurities washing out from catalysts surface due to the concentration differences for impurities between catalyst surface and TLP reactant bulk.

## Conclusions

This paper describes efforts at a production site to decrease production costs in order to make the products price more competitive in an ever-increasing struggle for market share. It is shown that a simple and effective catalysts pretreatment method can substantially prolong the number of runs of a single batch catalyst, which can be reused. It is evident that water residual should be decreased to 1 % in catalyst suspension, which leads to achievement described in precedent sentence.

The importance of employing a high-purity reactant was also demonstrated. The increase in purity of TLP for 13 % or opposite decrease of impurities in TLP in the same range also means higher number of runs of a single batch catalyst.

In a yearly production of 200 hydrogenation batches, these two findings help to decrease the

production cost in the amount of more than 100000 €, irrespectively of the higher initial material costs of higher purity TLP. It is still not clear what the final number of multiple use of catalyst in hydrogenations with low impurity profile reactant will be; so this should be the case of further studies. Furthermore, a deeper insight into the mechanism of Raney-type Nickel catalyst deactivation would be very useful for further optimization of the whole production process.

## List of symbols

$c$	– concentration
$m$	– mass, g
$N$	– number of catalyst reuse
$n$	– stirring speed, $\text{min}^{-1}$
$w$	– mass fraction, 1
$\chi$	– mole fraction, 1
$\rho$	– density, $\text{kg l}^{-1}$
$\Psi$	– volume ratio, 1

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