Catalytic hydrogenation in the process of 2-((1-benzylpiperidin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydroinden-1-one hydrochloride synthesis I. Catalyst screening and finding the optimal reaction conditions

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Catalytic hydrogenation of 2-((1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)methylene)-5,6-dimethoxy-2,3-dihydroinden-1-one hydrochloride (**1**) to 2-((1-benzylpiperidin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydroinden-1-one hydrochloride (**2**) was investigated in the batch-slurry reactor. The 5% Pt/C catalyst was chosen to search the optimal reaction conditions because of its higher catalytic activity compared to other catalysts used in the work. To investigate the catalyst activity, selectivity and stability, the effect of agitation speed, catalyst loading, solvent, temperature, hydrogen pressure and catalyst reuse were studied.

The initial rate of hydrogenation increases with the increase of catalyst loading, with the temperature and solvent polarity, if alcohols were used as solvents. The hydrogenation rate decreases with higher hydrogen pressure and that was explained by competitive adsorption of both reactants.

The results also indicate that 5% Pt/C is a promising catalyst for **1** hydrogenation because at relatively mild reaction conditions selectivity towards main product was high (98%) and catalyst maintains its activity during successive runs.

Keywords: catalytic hydrogenation, catalyst screening, catalyst selectivity, optimal reaction conditions.

INTRODUCTION

2-((1-benzylpiperidin-4-yl)methyl)-5,6-dimethoxy-2,3--dihydroinden-1-one hydrochloride (**2**) is API (active pharmaceutical ingredient) available on the market under the name ARICEPT®. It is used for treatment of all kinds of senile dementia, in particular it is useful for the prevention and treatment of Alzheimer Disease by virtue of its acetylcholinesterase inhibitory action[1].

There are many processes described mainly in patent literature[2–11] for producing 2 and its pharmaceutically acceptable salts. It can be produced by catalytic hydrogenation of 2-((1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)methylene)-5,6-dimethoxy-2,3-dihydroinden-1-one hydrochloride (1) as presented in Scheme 1.

Because the starting compound has got more than one functionality susceptible to hydrogenation, a complete chemo-selectivity is unlikely. There is a certain number of impurities that can be generated as the side products of the reaction.

Since catalytic hydrogenation is the last production step for the preparation of **2**, there is a need for improving a hydrogenation step that minimizes or eliminates the impurities. For this particular reaction, a wide variety of catalysts (Pd, Pd(OH)$_2$, Pd/C, Pd/Al$_2$O$_3$, Pt, Pt/C, Pt(OH)$_2$, Rh and Ru) have been investigated. Each catalyst appears to have at least some of advantages and, notably, significant disadvantages.

The reaction conditions for hydrogenation of **1** can also significantly influence the yield of **2** and impurity profile.

The yield of **2** can be low due to an incomplete conversion of **1**. Alternatively, if **1** is completely consumed, the yield of **2** can be low due to the competing side reactions where a number of by-products are generated, such as 5,6-dimethoxy-2-(piperidin-4-ylmethyl)-2,3-dihydroinden-1-one hydrochloride,1-benzyl-4-((5,6-dimethoxy-2,3-dihydro-1H-inden-2-yl)methyl)piperidine hydrochloride, 2-((1-benzylpiperidin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydro-1H-inden-1-ol hydrochloride and others.

Therefore, the aim of the work is the search for the catalyst which will meet the requirements for high reaction selectivity and at the same time high activity, good stability and possibility of catalyst reuse. The influence of various process parameters i.e. temperature, pressure, agitation speed, concentration of **1**, solvents and mass of catalysts on the catalyst characteristics (activity, selectivity and stability) will be examined and the optimal conditions of the reaction will be defined in order to obtain the product in high purity and yield.

EXPERIMENTAL SECTION

Materials

Compound **1** was produced by patent application WO/2007/015052 A1. The structure of compound **1** was confirmed by: Mass spectrum m/e 376 (M+, H$^+$); and NMR analysis; H^1 NMR (CF$_3$COOD, 600MHz), δ 3.30 (m, 1H), 3.55 (m, 1H), 3.70 (m, 1H), 4.20–4.36 (m, 2H), 4.30 (s,2H), 4.33 (s, 3H), 4.39 (s, 3H), 4.49 (m, 1H),
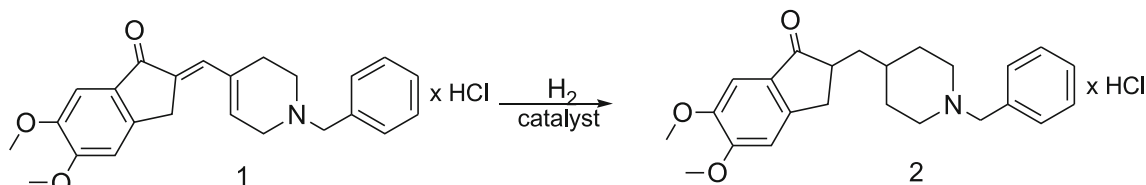
Scheme 1. Catalytic hydrogenation of 1 to 2

4.81 (m, 1H), 6.69 (s, 1H), 7.46 (s, 1H), 7.76 (s, 1H), 7.78- 7.87 (m, 5H), 7.90 (s, 1H).

The catalysts were supplied from Evonik Degussa, Germany (5% Pd/C, 10% Pd/C, 20% Pd/C, 5% Pd(OH)$_2$/C, 5% Pd+3,5%Pb/CaCO$_3$, 5%Pd/CaCO$_3$, 5%Pd/Al$_2$O$_3$, 3% Pt/C, 5% Pt/C, 10% Pt/C, Pt0$_2$/C, 1% Pt/C + 4% Pd/C, 5% Ru/Al$_2$O$_3$, 5%Ru/C, 5%Rh/C), Sigma – Aldrich Chemicals, UK (5% Pd/C, 10% Pd/C, 20% Pd/C, 5% Pd+3,5%Pb/CaCO$_3$, 5%Pd/CaCO$_3$, 5%Pd/Al$_2$O$_3$, 3% Pt/C, 10% Pd/C, 1% Pt/C + 4% Pd/C), Fluka, UK (Pt0$_2$/C), BASF, Italy (5% Pd(OH)$_2$/C, 5% Pt/C) and Johnson Matthey, UK (5% Ru/Al$_2$O$_3$, 5%Ru/C, 5%Rh/C). All catalysts were used as received.

Experimental Setup

The hydrogenation experiments for catalyst screening were carried out in a multiple reactor system (MRS), Figure 1, consisted of six 75 cm^3 capacity stainless steel autoclaves (Parr Instrument Company, U.S.A). All six vessels were stirred with a single magnetic stirrer bar and are capable of the operations up to 1200 min^{-1}. Each vessel was individually temperature controlled and has an individual gas inlet valve. The schematic of the multiple reactor system set-up is shown in Figure 1.

After a certain number of catalysts with good properties were chosen, detailed screening of chosen catalysts and the influence of process parameters (catalyst mass, pressure, temperature, solvent, stirring and concentration) on catalyst activity, selectivity and stability was investigated in 300 cm^3 stainless steel autoclave (Parr Instrument Company, U.S.A.). The reactor was fitted with a four-blade stirrer capable of operations up to 700 min^{-1}. The temperature of the liquid in the reactor was maintained at the desired value with the help of PID controller, which provided an alternate heating and cooling arrangement. The reactor was also equipped with an internal thermocouple and digital pressure transducer for temperature and pressure monitoring.

The relevant safety features such as a rupture disk and a high temperature – pressure cut off were also installed as part of the MRS and 300 cm^3 reactor setup. The schematic of the 300 cm^3 reactor set-up is shown in Figure 2.

Experimental Procedure

In a typical hydrogenation experiment, predetermined quantities of **1**, catalyst and solvent were charged into autoclave. The reactor was closed, and the contents were flushed three times with hydrogen. The reactor was then heated up to a desired temperature and pressurized with hydrogen to a desired level and the reaction mixture was stirred with desired agitation speed. A pressure was maintained constant throughout the reaction course by supplying hydrogen from a reservoir vessel through a constant pressure-regulator valve. The moment when desired pressure was achieved was assumed to be the start (time = 0) of the reaction. During the experiment the hydrogen pressure in the reactor was maintained constant. The samples of reaction mixture were taken periodically from reactor, diluted with methanol and were analyzed using high pressure liquid chromatography. In the reaction mixture concentration of **2**, **1**, two intermediates and two impurities were monitored.

Analytical Methods

The analysis of all the samples was carried out using the Agilent Technologies high pressure liquid chromatography (model 1200) with the DAD detector. The analytical conditions were the following:

Column & Packing: Phenomenex Gemini C18, 250 x 4,6mm (5 μm); Eluent A: Buffer NH$_4$OAc 10 mM, pH=6 diluted with acetonitrile in rate 2.7:1; Eluent B: Buffer NH$_4$OAc 10 mM, pH=4 diluted with acetonitrile
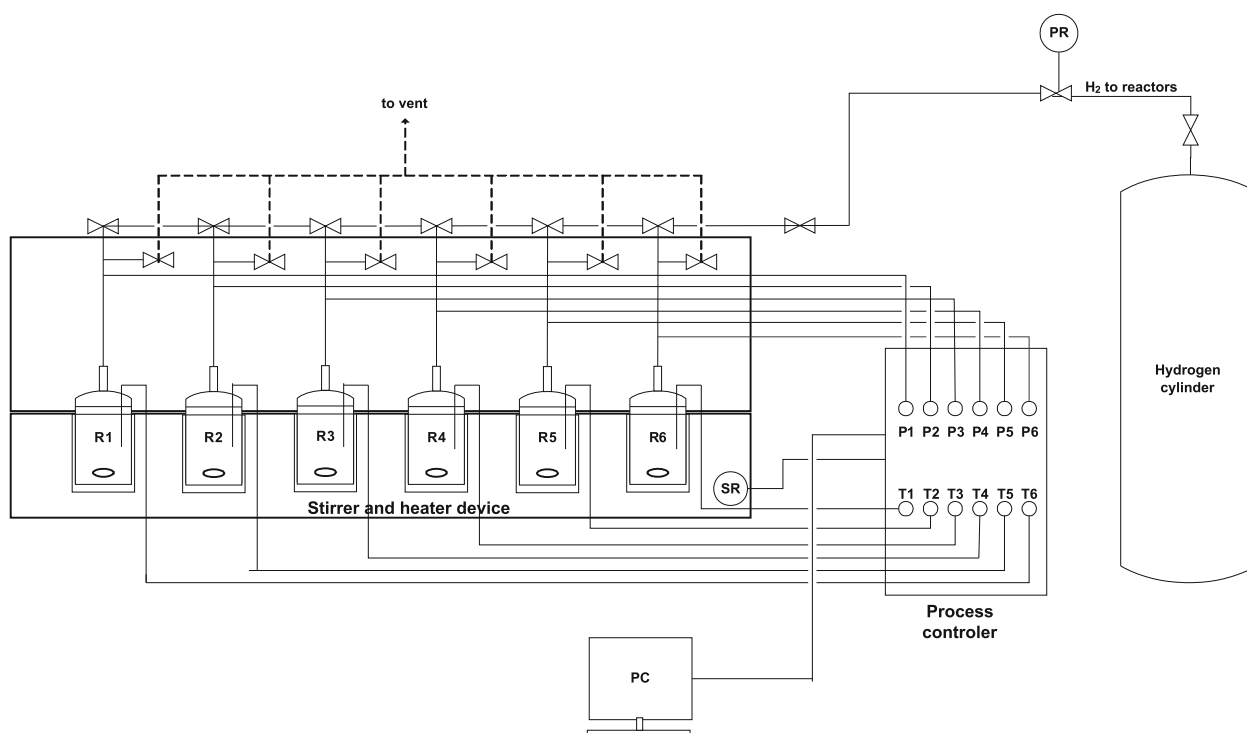
Figure 1. A schematic diagram of an experimental set-up for hydrogenation in a multiple reactor system (R1-R6, 75 ml reactors, PR, pressure regulator, SR, stirrer speed regulator, P1-P6, reactors pressures input , T1-T6, reactors temperature input)
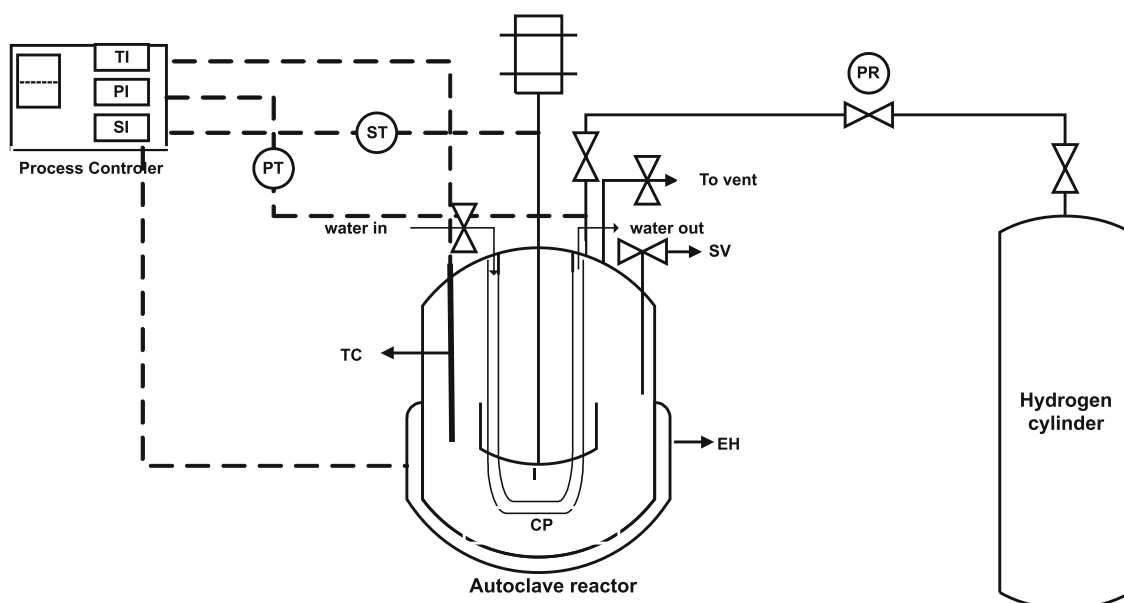
Figure 2. A schematic diagram of an experimental set-up for hydrogenation in 300 cm^3 autoclave reactor (TC, thermocouple, EH, electric heater, SV, sample valve, CP, cooling pipe, PR, pressure regulator, PT, pressure transducer, ST, stirring transducer, TI, temperature indicator, PI, pressure indicator, SI, stirring speed indicator)

in rate 0.54:1 Gradient: 0. min – 100% A, 20. min – 0% A Equilibration time: 20 min; Injection volume: 20 μL; Flow rate: 2.0 cm min^{-1}; Wavelength: 277 nm; Column temperature: 308 K; Autosampler temperature: 293 K.

The NMR analysis were recorded at Center for Nuclear Magnetic Resonance Spectroscopy, Rudjer Boskovic Institute, Zagreb, Croatia on Bruker Avance DRX 600 NMR spectrometer operating at 600.1 and 150.9 MHz. CF$_3$COOD was used as a solvent.

Results and Discussion

Catalyst screening

The influence of the catalyst type on the hydrogenation of **1** has been carried out over a commercially available catalyst under the same reaction conditions (c_1 =0.14 moldm^{-3}, V_{MeOH} = 0.175 dm^3, T= 308 K, p_{H2} = 0.2 MPa, m_{cat} =1.71 gdm^{-3}, N = 600 min^{-1}) in MRS. On all the catalysts tested under the used experimental conditions, the reaction was found to proceed through a complex consecutive/parallel reaction network. The reaction pathway, as presented in scheme 2, involves the formation of **2** (with the selectivity nearly 94%), two intermediates (**3**, **4**) and two impurities (A, B) as a result of further hydrogenation of product **2**.

Typical concentration-time plots showing the course of hydrogenation of **1** over the investigated supported noble metals are presented in Figure 3 and 4.

The catalyst activity and selectivity were two main criteria for the catalyst selection for **2** production. The moment when the concentration of Intermediate 4 in the reaction mixture was below 0.15 % (1.7 x 10^{-4} mol
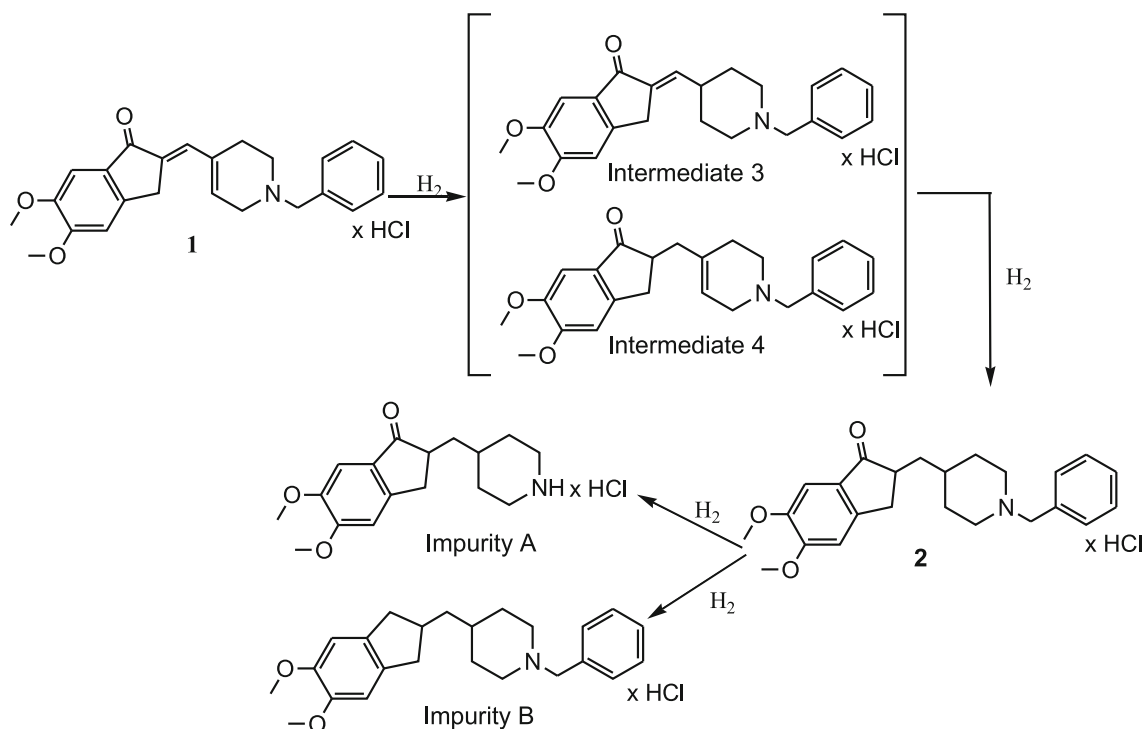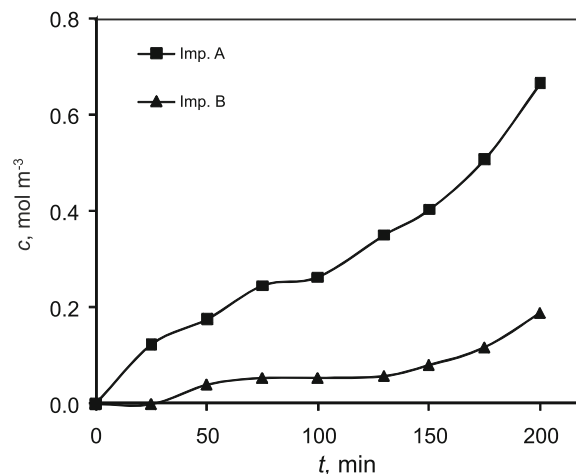

Scheme 2. Reaction pathway
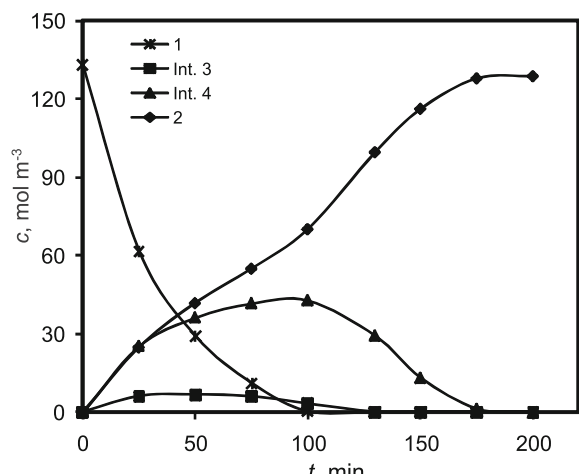
Figure 3. Typical concentration-time profile for hydrogenation of 1 (c_1 =0.14 mol dm^{-3}, V_{MeOH}= 0.175 dm^3, T= 308 K, p_{H2} = 0.2MPa, m_{cat} =1.71 g dm^{-3}, N = 600 min^{-1})

Figure 4. Concentration-time profile for two impurities in process of 1 hydrogenation (c_1 = 0.14 mol dm^{-3}, V_{MeOH} = 0.175 dm^3, T =308 K, p_{H2} = 0.2 MPa, m_{cat} =1.71 g dm^{-3}, N = 600 min^{-1})

dm^{-3}) was considered to be the end of the reaction and was used to compare the activity of different catalysts. The critical content of Intermediate 4 in the reaction mixture was defined as the content which can be eliminated in crystallization and recrystallization processes to get **2** with high purity.

The selectivity of various catalysts for hydrogenation of **1** was expressed as the content of **2**, and the content of impurities A and B in the reaction mixture at the moment when the reaction was finished, i.e. when the concentration of Intermediate 4 is below 1.7 x 10^{-4} mol dm^{-3}. The impurity denoted as Impurity B is most difficult to eliminate by the crystallization and recrystallization processes. At the end of the reaction it should not be present in the reaction mixture in the content above 0.20% (2.8 x 10^{-4} mol dm^{-3}). Also, the content of Impurity A should be below 0.6% (1.05 x 10^{-3} mol dm^{-3}). The hydrogenation patterns when the reaction was performed using different catalysts are presented in Table 1.

As can be seen in Table 1 the formation of undesired impurity A was observed when hydrogenation was carried out over Pd and Rh catalyst, regardless of different catalyst support and the concentration of catalytic active sites. The highest activity (shorter reaction time) and selectivity (highest purity of the reaction mixture) was observed with 5% Pt/C and this catalyst was used for further experimentation.

The influence of various process parameters on the catalyst activity and selectivity was investigated and optimized. Hydrogenation of **1** to **2** was carried out in 300 cm^3 Parr autoclave. The operative conditions of experimental runs are presented in Table 2.

Effect of agitation speed

To study whether gas-liquid mass transfer is controlling the reaction rate, the most important parameter is the agitation speed. Therefore **1** hydrogenation was performed with different intensities of stirring in the range of 100–700 min^{-1}.

Table 1. Catalytic properties of metal supported catalysts in the hydrogenation of 1 (c_1 =0.14 mol dm^{-3}, V_{MeOH} = 0.175 dm^3, T= 308 K, p_{H2} = 0.2 MPa, m_{cat} =1.71 g dm^{-3}, N = 600 min^{-1})

Catalyst type	Reaction time, h	HPLC results (area %)			
		Compound 2	Intermediate 4	Impurity A	Impurity B
5 % Pd/C	6	75.0	4.00	78.0	/
10 % Pd/C	6	60.0	0.55	36.2	/
5 % Pd(OH)$_2$/C	1	27.5	0.20	70.2	/
5% Pd/CaCO$_3$	8	64.6	1.58	13.3	/
5 % Pd/Al$_2$O$_3$	6	61.4	2.60	31.3	/
20 % Pd/C	6	42.6	0.18	55.2	/
5 % Pd + 3,5 Pb/CaCO$_3$	6	1.10	2.05	0.05	/
3 % Pt/C	12.5	86.0	0.56	4.5	1.67
5 % Pt/C	3.5	93.8	0	0.38	0.14
10 % Pt/C	4	80.8	0.01	1.71	1.08
PtO$_2$/C	2	89.0	/	2.46	1.50
1% Pt/C + 4% Pd/C	6	62.8	1.30	33.5	/
5 % Ru/C	24	3.0	2.30	0.15	/
5 % Ru/Al$_2$O$_3$	22	4.5	2.40	0.084	/
5 % Rh/C	4	73.0	4.70	11.2	/

Table 2. Operative conditions of experimental runs

Parameter	Range
Catalyst loading	0.57 – 2.86 g dm^{-3}
Solvents	EtOH, MeOH, acetone, water
Concentration of 1	0.07 – 0.24 mol dm^{-3}
Temperature	298 – 318 K
Hydrogen pressure	0.2 – 2 MPa
Agitation speed	100 – 700 min^{-1}

As shown in Fig.5 A, the intensity of agitation has no significant effect on the yield of **2**, but the time to achieve the yield decreases with the agitation rate. The data also demonstrated that the lowest content of impurity A and impurity B was attained when the agitation speed was about 400 min^{-1}. For that reason 400 min^{-1} was chosen as the optimal agitation speed, although the results presented in Fig. 5B show that only at the agitation speed above 600 min^{-1} the initial reaction rate remains constant which means that the reaction is performed in the kinetic regime.

Effect of catalyst loading

The influence of catalyst loading on the hydrogenation of **1** was studied over the previously optimized 5% Pt/C within a wide range (0.57; 1.14; 1.71; 2.28 and 2.86 g dm^{-3}). The influence of the amount of catalyst on the hydrogenation patterns is presented in Fig. 6. With

increasing the amount of the catalyst charged into the reaction system the initial reaction rate and monotonous decreasing in reaction time increases, but conversion of **1** to **2** remains unchanged. Although, the reaction time with higher catalyst loading was shorter, the concentration of both critical impurities increased significantly.

Considering all the above mentioned, the most suitable amount of the catalyst was 1.71 g dm^{-3} when all the parameters reached their optimal values at this amount.

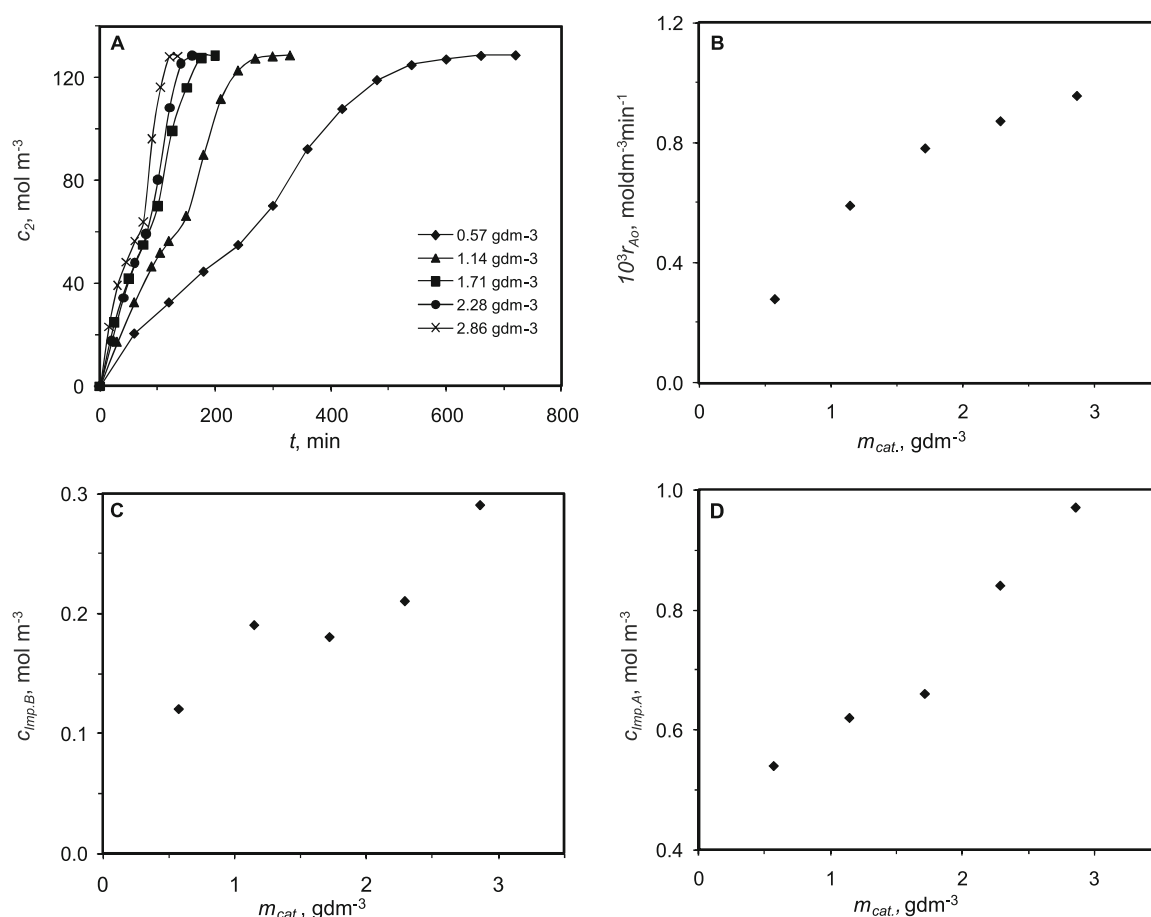*Effect of solvent*

Solvents are known to have a significant effect on the rate of catalytic hydrogenations. The effect of the solvent is attributed to various factors, which include the solubility of hydrogen, thermodynamic interaction of the solvent with reactants and products, competitive adsorption of solvent, etc[12]. A wrong selection of the solvent leads to a complete loss of selectivity and/or activity, thus destroying the possible utilization of a potentially efficient process in practice.

The solvents screened in this work represent the most conventional and easily available ones: water, methanol, ethanol and acetone. The data obtained with the most active catalyst 5%Pt/C are presented below. Typical concentration profiles of the product and impurities A and B and the influence of solvent on initial reaction rate are shown in Fig. 7.
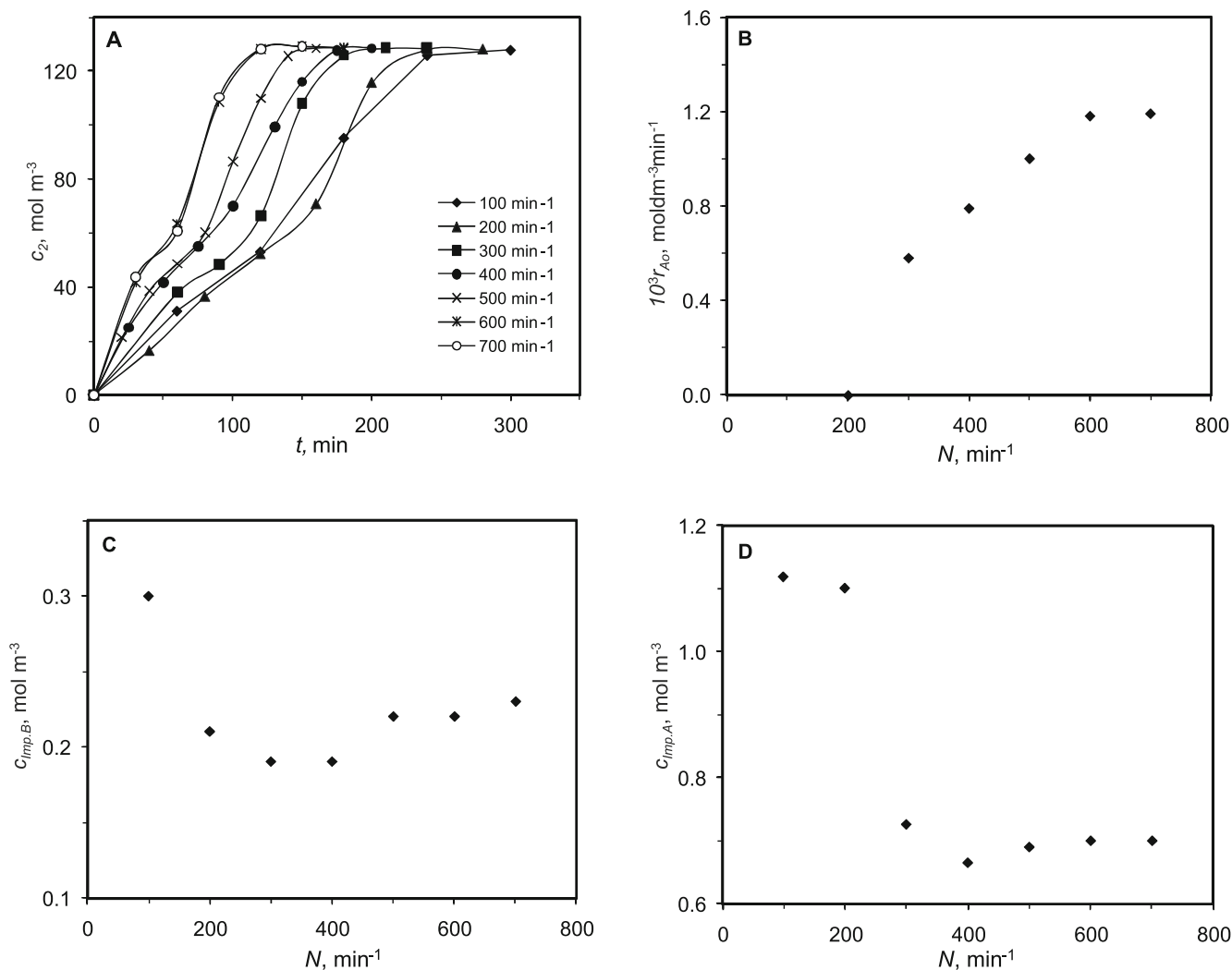
Figure 5. Effect of agitation speed on: A-concentration of 2; B-initial reaction rate; C-concentration of impurity B; D-concentration of impurity A. (c_1 =0.14 mol dm^{-3}, V_{MeOH} = 0.175 dm^3, T= 308 K, p_{H2} = 0.2 MPa, m_{cat} =1.71 g dm^{-3})

Figure 6. Effect of catalyst loading on: A-concentration of 2; B-initial reaction rate; C-concentration of impurity B; D-concentration of impurity A (c_1 =0.14 mol dm^{-3}, V_{MeOH} = 0.175 dm^3, T= 308 K, p_{H2} = 0.2 MPa, m_{cat} =1.71 g dm^{-3}, N = 400 min^{-1})
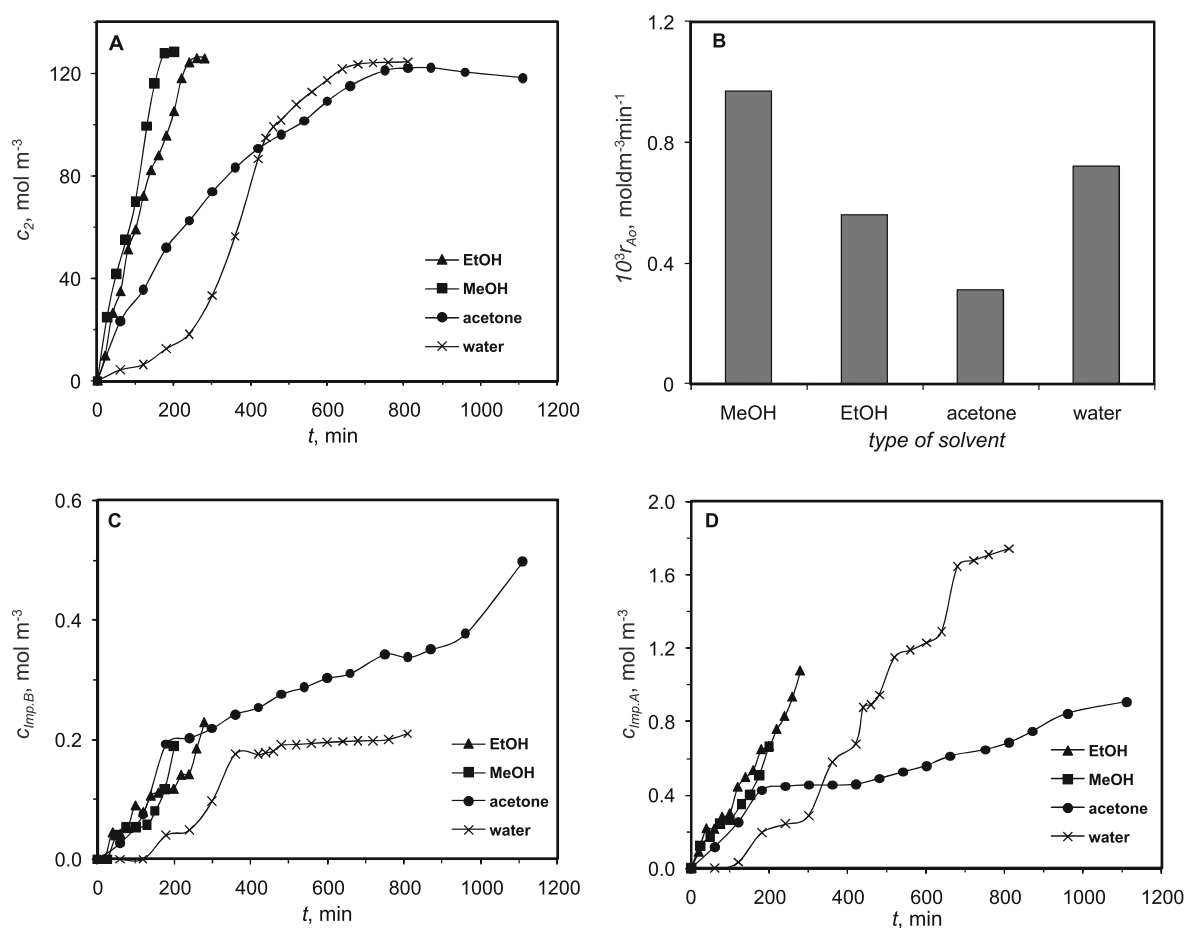
Figure 7. Effect of solvents on: A- concentration of 2; B-initial reaction rate; C-concentration of impurity B; D-concentration of impurity A. (c_1 =0.14 mol dm^{-3}, $V_{solvent}$ = 0.175 dm^3, T= 308 K, p_{H2} = 0.2 MPa, m_{cat} =1.71 g dm^{-3}, N = 400 min^{-1})

It has been stated that hydrogenation of less polar substrates in more polar solvents is preferred (and vice versa)[13–16]. The solvents used in this study exhibit a 4-fold variation in dielectric constants[*], whereas their dipole moments[**] vary from 1.69 (ethanol) to 2.88 Debye (acetone)[17]. As can be seen in Fig. 7 the catalyst activity and selectivity for **1** hydrogenation in a different solvent showed a correlation with either the solvent dielectric constant or its dipole moment only when alcohols were used as the solution. The lowest content of impurity A and impurity B and shortest reaction time was achieved with methanol as the solvent. Although the water has the grater dielectric constant, i.e. the greater polarity, 98% conversion was obtained after 13 h. This can be attributed to the low solubility of **1** in water.

The catalyst activity and selectivity in dipolar aprotic solvent (acetone) was low compared to the catalyst activity and selectivity in alcohols. Characteristic of acetone and other dipol aprotic solvents is the formation of electron-pair donor/electron-pair acceptor complexes associated with an electron transfer from a donor to an acceptor molecule[12]. Therefore, it could be proposed that acetone is adsorbed on metal surface and the solvent-catalyst interaction played a role in the catalytic performance.

[*] dielectric constants: ε(ethanol) = 24.3; ε(methanol) = 33; ε(acetone) = 20.7; ε(water) = 80

[**] dipole moments: μ(ethanol) = 1.69; μ(methanol) = 1.70; μ(acetone) = 2.88; μ(water) = 1.85
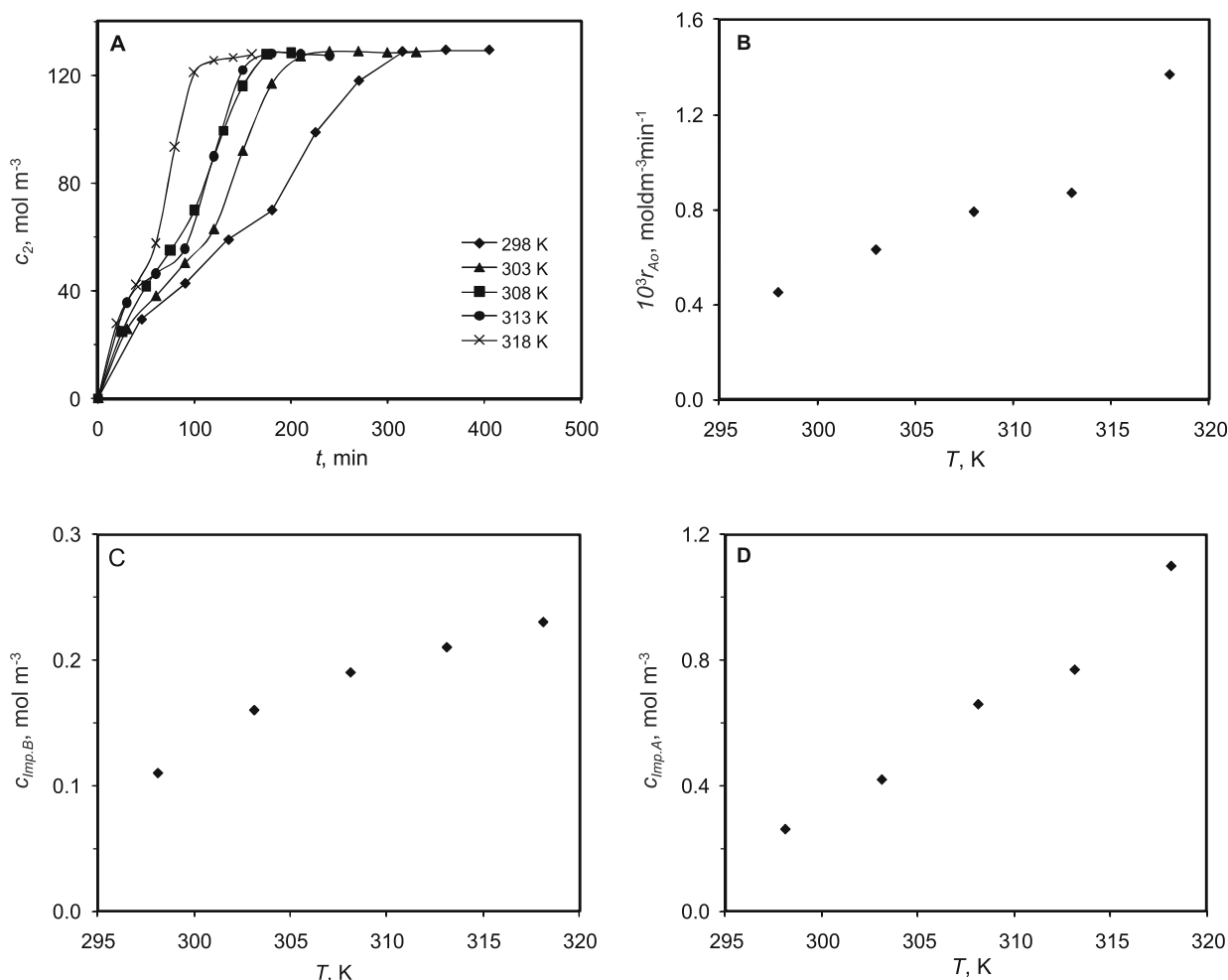
Effect of reaction temperature

Moreover, other reaction conditions, such as temperature and hydrogen pressure also exert certain influences on the synthesis of **2**. So, attention had been paid to their optimization. To study the effect of temperature on the product distribution and the initial reaction rate, hydrogenation was carried out in the temperature range of 298 to 318 K. The data presented in Fig. 8A and 8B clearly show that the time to reach 98% conversion of **1** slightly decreases and the initial reaction rate increases as the reaction temperature is increased.

But, at the same time the increase of the reaction temperature causes an increasing of impurity A and B (Fig. 8C and 8D). Thus, according to the results depicted in Fig. 8, 308 K was chosen to be the optimal reaction temperature for hydrogenation of **1** to **2** because the concentration of impurities B and A are still under the critical content and the duration of the reaction is reasonable (around 3–3,5h).

Effect of hydrogen pressure

The effect of hydrogen pressure on the hydrogenation of **1** was investigated and Fig. 9A shows the yield of the product versus the time when the hydrogen pressure is varied. At higher hydrogen pressure, the reaction was substantially slowed but the selectivity to the desired product **2** is always high and increases with hydrogen pressure from 95 to 98%. From Fig. 9B which illustrates the initial rate of hydrogenation as a function of hydrogen

Figure 8. Effect of temperature on: A-concentration of 2; B-initial reaction rate; C-concentration of impurity B; D-concentration of impurity A. (c_1 =0.14 mol dm⁻³, V_{MeOH} = 0.175 dm³, p_{H2} = 0.2 MPa, m_{cat} =1.71 g dm⁻³, N = 400 min⁻¹)
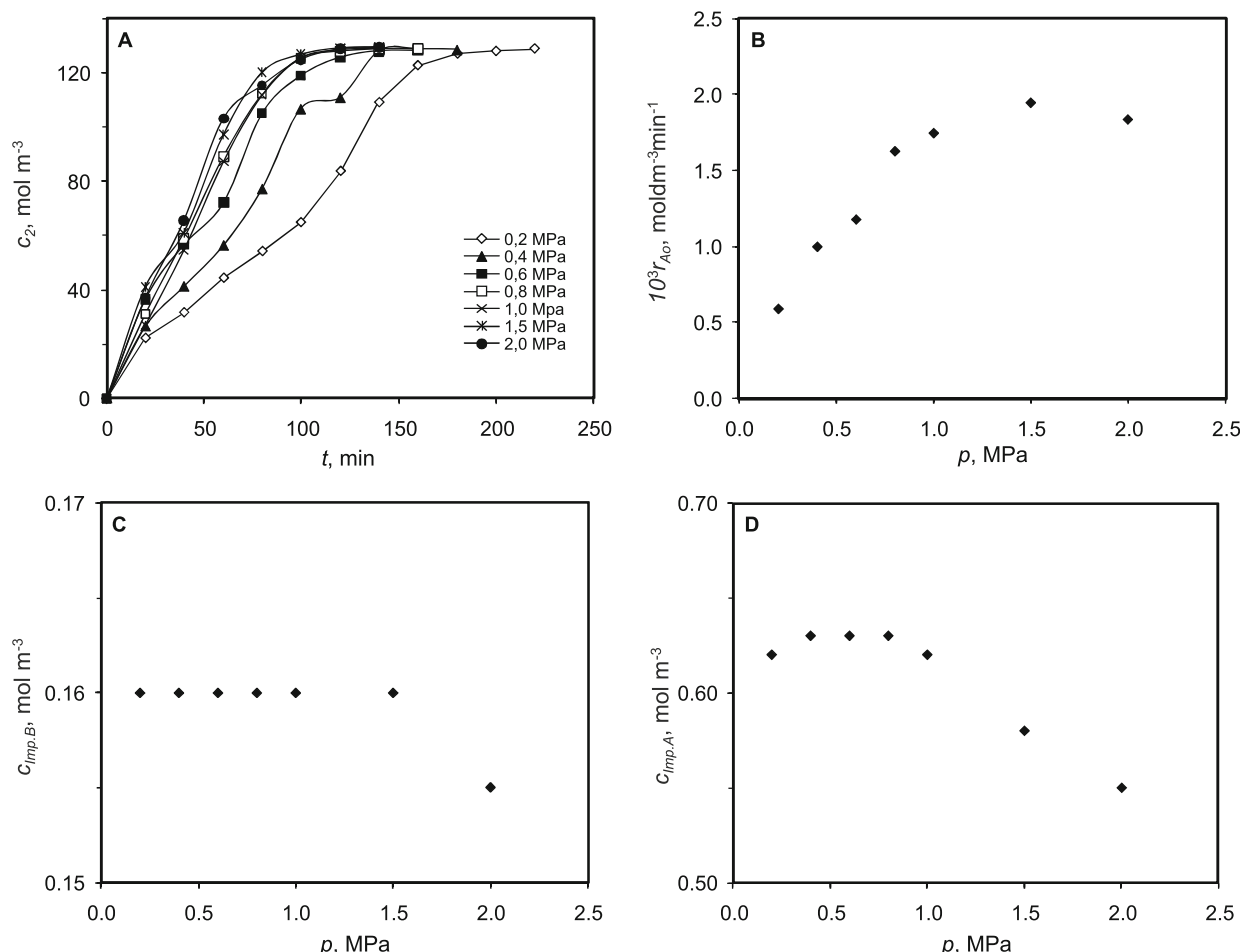
Figure 9. Effect of hydrogen pressure on: A-concentration of 2; B-initial reaction rate; C-concentration of impurity B; D-concentration of impurity A. (c_1 =0.14 mol dm^{-3}, V_{MeOH} = 0.175 dm^3, m_{cat} =1.71 g dm^{-3}, T= 308 K, m_{cat} =1.71 g dm^{-3}; N = 400 min^{-1})

pressure in the interval 0.2–2 MPa, it is visible that lower hydrogen pressure is preferred and after 1.5 MPa the rate of the formation of **2** slowly decreases. The decrease in the reaction rate at higher hydrogen pressure can be explained by a competitive adsorption of both reactants. Namely, at high hydrogen pressure less catalytic sites are available for **1** adsorption, which results in a lower reaction rate. The change in the reaction mechanisms was also proposed by other authors[18–19] who studied the influence of hydrogen pressure on the reaction rate.

From Fig. 9C and D it can be concluded that hydrogen pressure does not have a significant influence on the concentration of impurity A and B. Their concentration in the reaction mixture is also far under the critical value.

Catalyst stability

A valuable property of heterogeneous catalysts, in addition to their activity and selectivity, is a possibility to reuse them, looking forward to their practical application. Therefore, further research was focused on the stability and activity of the recovered 5%Pt/C catalyst performed in hydrogenation of **1** at the optimal process parameters which gave a product in the highest yield and satisfactory purity.

After the first run, the catalyst was separated by filtration, washed with the solvent and used again, completing seven cycles of hydrogenation. The results are presented in Fig. 10.

As shown in Fig. 10A, in the first cycle the 5% Pt/C catalyst reached a yield of **2** of 92% at 2 h of reaction. In

the further cycles the yield of the main product was the same but the time to reach this yield was longer (6 h in seventh cycle). The decrease of the initial reaction rate (Fig 10B) indicates that there may be a catalyst poisoning due to the adsorption of the reaction products on the catalytic active sites. However, despite the deactivation, the catalyst reaches a high level of **2** yield, even after seven hydrogenation cycles and the concentration of both impurities is under the critical content.
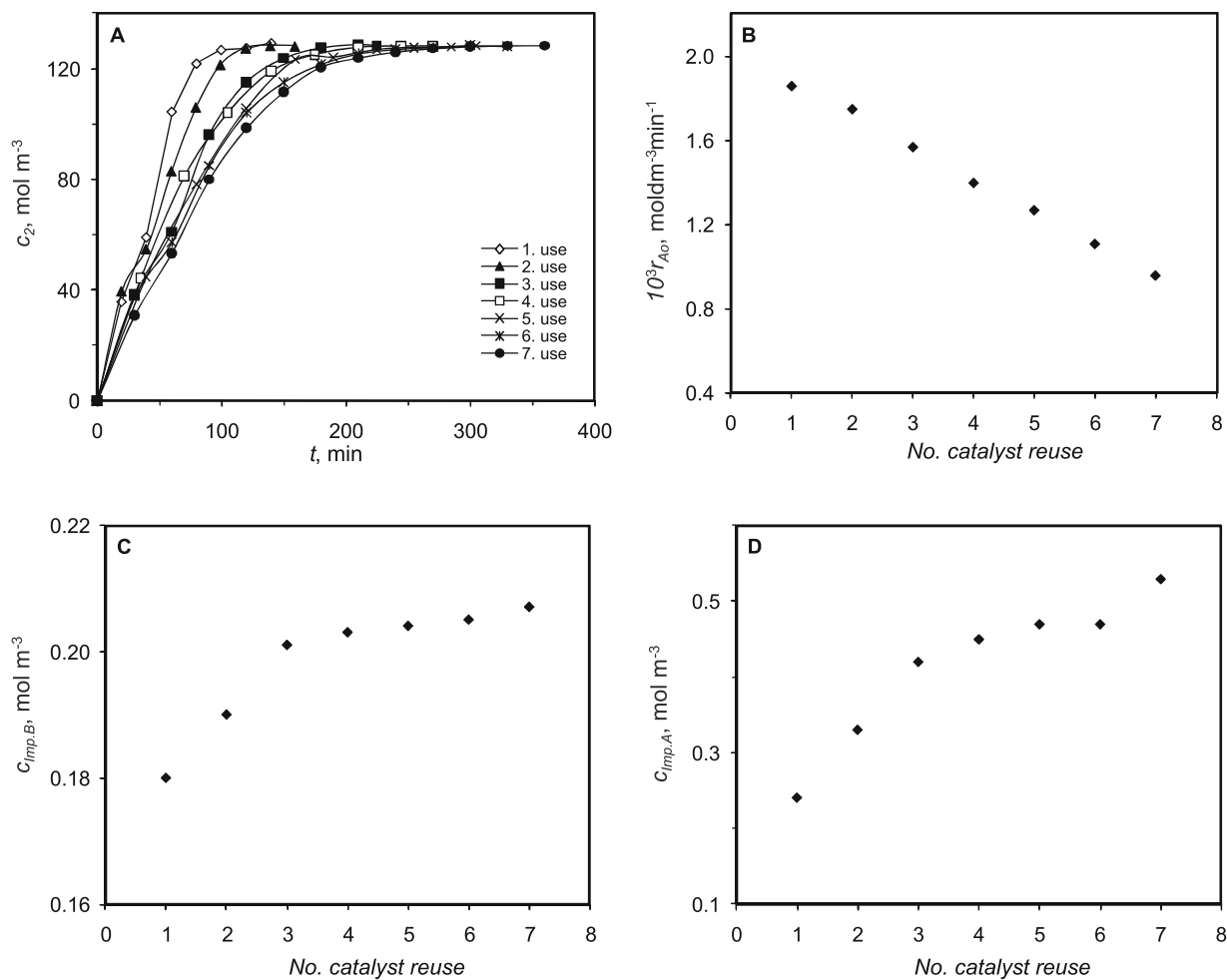
CONCLUSIONS

In this paper the hydrogenation of 2-((1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)methylene)-5,6-dimethoxy-2,3-dihydroinden-1-one hydrochloride to 2-((1-benzylpiperidin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydroinden-1-one hydrochloride was investigated in the laboratory-scale batch-slurry reactor. 5% Pt/C was identified as a suitable catalyst among several heterogeneous noble metal catalysts due to its greatest catalyst activity selectivity and stability.

Catalytic behavior of 5% Pt/C catalyst in the liquid phase hydrogenation of 2-((1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)methylene)-5,6-dimethoxy-2,3-dihydroinden-1-one hydrochloride was strongly influenced by the used solvent.

The initial rate of hydrogenation was found to increase with increasing of catalyst loading, with temperature and solvent polarity, if alcohols were used as solvent.

The hydrogenation rate decreases at higher hydrogen

Figure 10. The influence of the catalyst reuse on: A-concentration of 2; B-initial reaction rate; C-concentration of impurity B; D-concentration of impurity A. (c_1 =0.14 mol dm^{-3}, V_{MeOH} = 0.175 dm^3, p_{H2} = 0.2 MPa, T=308 K, m_{cat} =1.71 g dm^{-3}, N = 400 min^{-1})

pressure what was explained by competitive adsorption of both reactants.

The study of the stability of the catalyst used in the hydrogenation of 2-((1-benzyl-1,2,3,6-tetrahydropyridin--4-yl)methylene)-5,6-dimethoxy-2,3-dihydroinden-1-one hydrochloride in methanol showed that, although there is some deactivation, the catalyst approved a high conversion after seven reaction cycles.

The results indicate that the 5% Pt/C is a promising catalyst for 2-((1-benzyl-1,2,3,6-tetrahydropyridin-4-yl) methylene)-5,6-dimethoxy-2,3-dihydroinden-1-one hydrochloride hydrogenation because at relatively mild reaction conditions, selectivity towards main product was high (92%) and catalyst maintains its activity during successive runs what is important for its practical application.

NOTATION

c_1 concentration of 2-((1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)methylene)-5,6-dimethoxy-2,3-dihydroinden-1-one hydrochloride, mol m^{-3}

V_{MeOH} volume of methanol, dm^{-3}

T temperature, K

p_{H2} hydrogenation pressure, MPa

p pressure, MPa

m_{cat} mass of catalyst per unit volume, g dm^{-3}

N agitation speed, min^{-1}

t time, min

c_2 concentration of 2-((1-benzylpiperidin-4-yl) methyl)-5,6-dimethoxy-2,3-dihydroinden-1-one hydrochloride, mol m^{-3}

$c_{Imp.B}$ concentration of Impurity B, mol m^{-3}

$c_{Imp.A}$ concentration of Impurity A, mol m^{-3}

r_{Ao} initial reaction rate, mol dm^{-3} min^{-1}

Greek letters

ε dielectric constant

μ dipole moment

LITERATURE CITED

1. The American Society of Health- System Pharmacists, AHFS® *Consumer Medication Information*. ©Copyright, 2010. http://www.ncbi.nlm.nih.gov/pubmedhealth/?term=donepezil.

2. Gutman, A.L., Shokolnik, E., Tishin, B., Nisnevich, G. & Zaltzman, I. (2002). U.S. Patent No. 6,492,522. Washington, D.C.: U.S. Patent and Trademark Office.

3. Lerman, O., Kaspi, J., Arad, O., Alnabari, M. & Sery. Y. (2004). U.S. Patent No. 6,844,440. Washington, D.C.: U.S. Patent and Trademark Office.

4. Reddy, M.S., Eswaraiah, S., Thippannachar, M.V., Chandrashekar, E.R.R., Kumar, P.A.,Kumar, K.N. (2001). U.S. Patent No. 7,148,354. Washington, D.C.: U.S. Patent and Trademark Office.

5. Iimura, Y. (2001), U.S. Patent No. 6,252,081. Washington, D.C.: U.S. Patent and Trademark Office.

6. Yatendra, K., Mohan, P., Asok, N. & Nitin, M. WO Patent No. 2004082685(A1). World Intellectual property organization.

7. Sugimoto, H., Ogura, H., Arai,Y., Limura, Y., Yamanishi, Y. (2002). Research and development of donepezil hydro-

chloride, a new type of acetylcholinesterase inhibitor, *Jap. J. Pharmacology.* 89, 7–20.

8. Niphade, N., Mali, A., Jagtap, K., Ojha, R.C., Vankawala, P.J. & Mathad, V.T. (2008). *Org. Process Res. Dev.* 12 (4), 731–735. DOI/10.1021/op800066m.

9. Attanti, S. & Yadla, V. WO Patent No. /2008/010235. World Intellectual property organization.

10. Ashvin, K., Aggarwal, C., Vankatesran, S. & Lalit, W. US Patent No. 20100113793, Washington, D.C.: U.S. Patent and Trademark Office.

11. Thippannachar, M.V., Chintaman, N.N., Jayndal, V.P. & Chaturlal, M.A. Indian Patent Application no. 1073/MUM/2008.

12. Reichardt, C. (1990)*. Solvents and Solvent Effects in Organic Chemistry*; VCH: Weinheim,

13. Rajadhyaksha, R.A. & Karwa, S.L. (1986). Solvents effects in catalytic hydrogenation. *Chem.Eng.Sci.* 41, 1765. DOI: 10.1016/0009-2509(86)87055-5.

14. McClellan, A.L. (1963). *Tables of Experimental Dipole Moments, Vol. I*; Freeman and Co., San Francisco, DOI: 10.1002/ange.19650770627.

15. Singh, U.K. & Vanice, M.A. (2001). Kinetics of liquid-phase hydrogenation reaction over supported metal catalysts. *Appl. Catal. A: Gen.* 213, 1–24. DOI: 10.1016/S0926-860X(00)00885-1.

16. Cerveny, L. & Ruzicka, V.; *Catal. Rev.-Sci.Eng.* 1982, *24*, 503–566.

17. Bakker, J.J.W., Van der Neut, A.G., Kreutzer, M.T., Moulijin, J.A. & Kapteijn, F. (2010). Catalyst performance changes induced by palladium phase transformation in the hydrogenation of benzonitrile. *J. Catal.* 274, 176–191. DOI: 10.1016/j.cat.2010.06.013.

18. Bernas, H., Taskinen, A., Wärnå, J. & Murzin, Y. (2009). Hydrogenolysis of hydroxymatairesinol on a Pd/C catalyst. *J. Mol. Catal. A: Chem.* 306, 33–39, DOI: 10.1016/j. molcata.2009.02.015.

19. Meitzner, G., Mykyta, W.E.J. & Sinfelt, J.H. (1996). Methylamine hydrogenolysis on a rhodium catalyst-kinetics at high hydrogen partial pressures. *Catal. Lett.* 37, No.3–4,137–141. DOI: 10.1007/BF00807744.