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DOI: 10.1002/slct.201700433

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Optimization of Omeprazole Synthesis: Physico-Chemical Steering Towards Greener Processes

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This work presents an optimization of the synthetic procedure for production of Omeprazole, a highly important pharmaceutical. The physico-chemical measurements of the protonation and solution processes regarding the Omeprazole precursors aided the conception of the optimization strategy based primarily on the modifications of the reaction media. To this end, the protonation (K^H) and solvation properties (solubilities, solution enthalpies, and entropies) of the starting materials and the intermediate were determined in different methanol/water mixtures and pure methanol, allowing the selection of the solvent optimal for the Omeprazole synthesis. In addition, it was proven that the energetically demanding refluxing procedure, which is conventionally used in the first step of the Omeprazol synthesis, was unnecessary. Similar holds for the time-consuming trituration employed in the step involving precipitation of the final product. It was shown that trituration period can be significantly reduced without affecting the purity of the product. Taking into account the above-mentioned findings, the improved procedure (compared to the standard one) for Omeprazol preparation was proposed. It was based on a greener process demanding less organic solvent, exhibiting enhanced energy- and time-efficiency, which could be implemented in the large scale production. The concept devised in this work could easily be extended to other systems ameliorating the synthetic procedures of valuable drugs, rendering higher profit and lowering ecological risks.

Introduction

Although the industrial process of production of any active pharmaceutical ingredient (API) are constantly being revised with the tendency to be improved in terms of product quality and cost-efficiency, they are often not optimized to full extent, even in the case of massively produced drugs. If continuous improvement of the API preparation process is not undertaken, the consequences are greater pollution and higher consumption of materials and utilities needed for production, which eventually makes the product more expensive and introduces higher impact of the process on the environment. Many approaches such as Effective mass yield, Atom economy, or Environmental (E) factor have been developed to strategically analyze the processes in order to assess waste production.[1,2] However, there are only a few concepts which are being used to reduce the waste. Classical optimization of synthesis is usually a trial and error kind of work, which often follows previously established sequences of experiments, and may not necessarily lead to the optimal solution for the specific demands of the case. It is not uncommon that some decisive variations are dismissed or completely ignored solely because a predetermined pattern is followed. On the other hand, by obtaining physico-chemical data regarding the reactions involved in the production process of an API, one can address optimization in a more systematic manner. It should be pointed out that a positive side of this approach is often the fact that it can be used to fine-tune the existing processes, without changing them to the extent that requires new administrative approvals to employ the newly developed procedures for API production. In this work we present such an approach used to optimize the synthesis of Omeprazole.

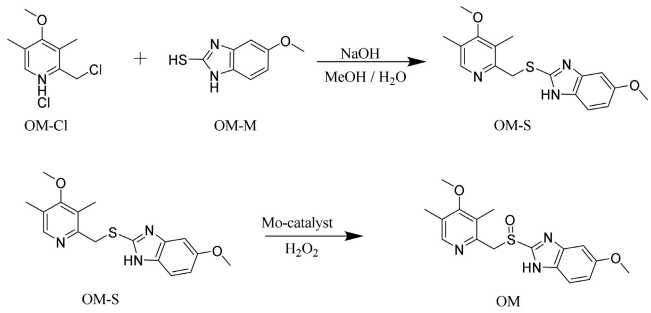
Omeprazole (5-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl)methylsulfinyl]-1*H*-benzimidazole, OM) is an active ingredient in many medications which are used in treatment of peptic ulcer, gastroesophageal reflux disease, and similar conditions caused by uncontrolled secretion of gastric acid.[3,4] It is a proton pump inhibitor, which irreversibly inhibits H^+/K^+-ATPase system at the secretory surface of gastric parietal cells. It is worth mentioning that it is indexed on the WHO list of essential medications. Synthesis of racemic form of this drug is commonly performed as a one-pot process involving condensation of pyridine ring with benzimidazole moiety *via* thioether formation, followed by oxidation of sulfur to sulfoxide (Scheme 1).

The aim of this work was to get an insight into the thermodynamic parameters that govern the reactivity of Omeprazole precursors and to use these data with the goal of

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/slct.201700433

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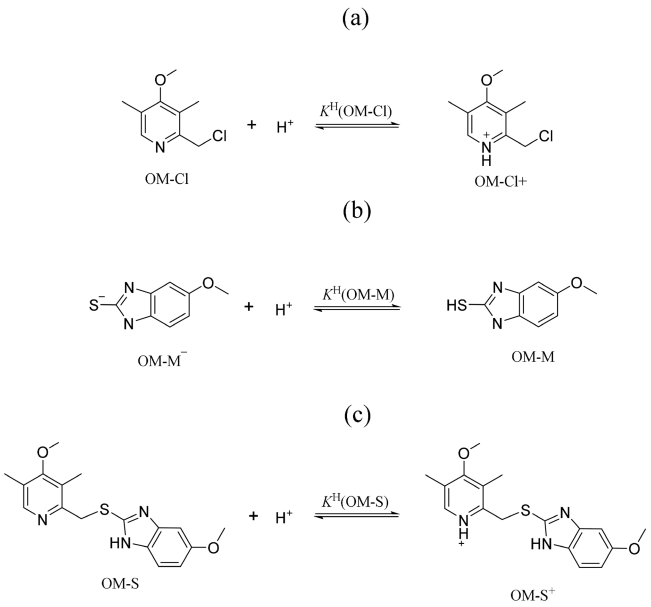
Scheme 1. Synthetic procedure of Omeprazole production; condensation of OM–Cl and OM–M followed by oxidation to Omeprazole.

achieving greener and more efficient synthesis, which could be implemented in the large-scale production.[5,6]

Results and discussion

One of the methods in production of racemic form of Omeprazole is one-pot reaction which has two stages. The first stage is condensation of 2-chlorometyl-4-metoxy-3,5-dimetyl-pyridine hydrochloride (OM–Cl) and 5-metoxy-1H-benzimidazole-2-thiole (OM–M) with the formation of thioether bond in methanol/water mixed solvent with NaOH added as deprotonating agent, since the condensation occurs between deprotonated forms of both compounds. Second stage is the oxidation of thioether to Omeprazole using peroxide (Scheme 1).[7,8]

It is well known that the protonation equilibrium constants depend on the properties of the solvent in which the protonation reactions take place, e.g. dielectric constant of the solvent, its proton donating/accepting affinities, and dipole moment of the solvent molecules. Bearing this in mind, in this work it was postulated that the use of a solvent in which the precursors would be more easily deprotonated, the condensation reaction would be more favorable, thus increasing the yield of the condensation reaction and also decreasing the time needed for the reaction completion. Another aspect which was taken into account concerned the solvation of the reactants (OM–Cl and OM–M) and the intermediate (OM–S), primarily to ensure that their solubility is high enough for the use in the one-pot industrial process. In order to prove the introduced concepts and consequently to determine the optimal conditions/procedure for the first step in the synthesis of Omeprazole, a systematic study of the protonation and solvation of the corresponding reactants and product, as well as the dependence of the related equilibria on the solvent composition was carried out.



Scheme 2. Protonation reactions of OM–Cl (a), OM–M (b), and OM–S (c).

The protonation properties of the precursor molecules in the first step of the Omeprazole synthesis, OM–Cl and OM–M, Scheme 2(a) and (b), respectively, as well as of the reaction product OM–S, Scheme 2(c), were studied by spectrophotometric-potentiometric titrations at 25 °C and $I_c = 0.05$ mol dm^{-3} ($TBAClO_4$) in water/methanol mixed solvents of different V(MeOH)/V(H_2O) ratios and in pure methanol.

Significant dependence of the UV spectra on the pH of the solution was observed in all cases (Figures 1(a), 3(a), 5(a) and Figures S1(a), S4(a), S7(a), S10(a), S13(a), S16(a), S19(a), S22(a), and S25(a); see ESI), which was ascribed to the change in the distribution of the (de)protonated species in the solution (the data gathered for the solvent of V(MeOH)/V(H_2O) = 5.73 ratio are shown in the main text as representative examples, whereas results obtained for other solvents are given in ESI). In all cases a good agreement between the experimental and calculated results was obtained (Figures 1(b), 3(b), 5(b) and Figures S1(b), S4(b), S7(b), S10(b), S13(b), S16(b), S19(b), S22(b), and S25(b); see ESI) rendering reliable protonation equilibrium constants (Table 1) and the characteristic spectra of the species present in the solution (Figures 2, 4, 6 and S2, S5, S8, S11, S14, S17, S20, S23, and S26, see ESI). Isosbestic points could be detected in the family of spectra recorded during titrations of OM–M and OM–S, indicating that two species existed in equilibrium, which was in agreement with the proposed reaction model, *i.e.* dissociation of the protonated pyridine and thiol group, respectively, whereas the protonation of

Table 1. Protonation constants of the investigated compounds at 25 °C and $I_c = 0.05$ mol dm^{-3} ($TBAClO_4$) in different mixed solvents and pure methanol determined by spectrophotometric-potentiometric titrations.[a]

V(MeOH)/V(H_2O) (x(MeOH))	1 (0.31)	5.73 (0.72)	12.6 (0.85)	pure MeOH (1)
log K^H(OM–Cl)	3.89(2)	3.66(2)	3.75(6)	5.01(2)
log K^H(OM–M)	10.67(4)	11.46(1)	11.72(4)	13.52(5)
log K^H(OM–S)	4.70(4)	4.15(4)	4.65(4)	5.22(1)

[a] uncertainties of the last digits are given as standard error of the mean ($N = 2$ or 3)

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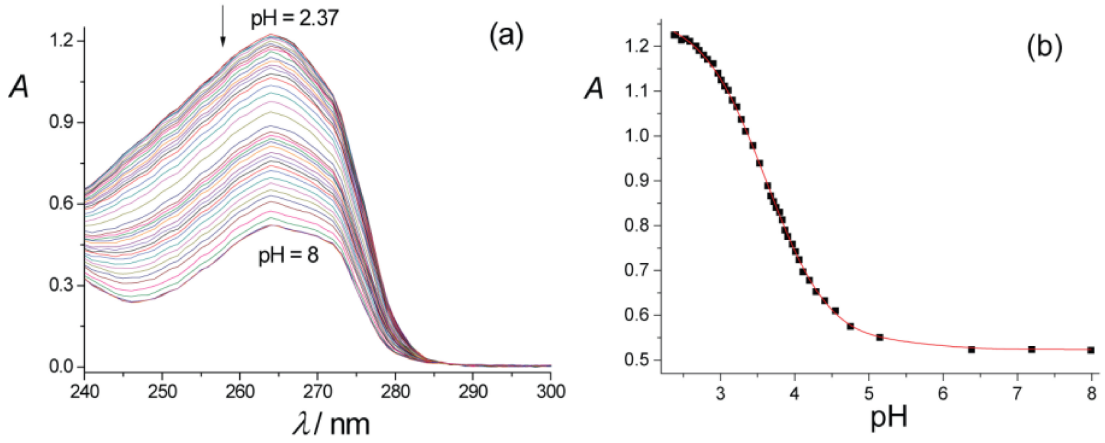


Figure 1. a) Spectrophotometric-potentiometric titration of OM–Cl ($c = 1.92 \times 10^{-4}$ mol dm^{-3}, $c(HClO_4) = 4.48 \times 10^{-3}$ mol dm^{-3}) with NaOH ($c = 7.07 \times 10^{-2}$ mol dm^{-3}) in MeOH/H_2O mixed solvent at 25 °C; V(MeOH)/V(H_2O) = 5.73, I_c = 0.05 mol dm^{-3} ($TBAClO_4$), l = 1 cm. b) Dependence of absorbance at 264 nm on pH. ■ experimental, — calculated.

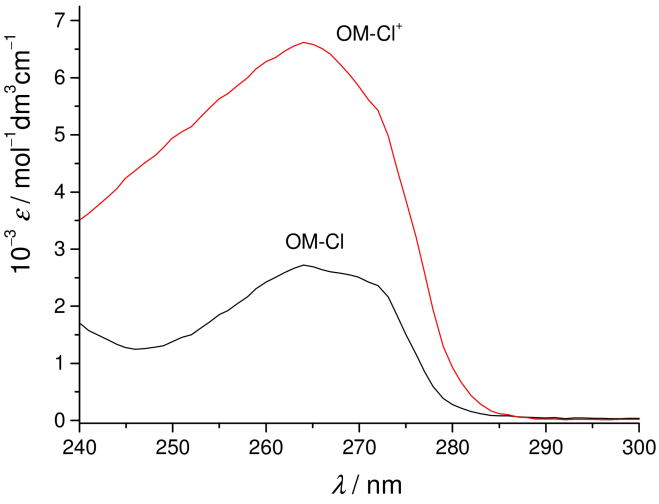


Figure 2. Characteristic spectra of OM–Cl protonation species in MeOH/H_2O mixed solvent; V(MeOH)/V(H_2O) = 5.73.

imidazole nitrogen did not occur in the pH-range studied. That agrees with the results of the studies of 2-mercaptobenzimidazole in water, where it was determined that the log K^H value for the imidazole group was 2.6.[9] The corresponding equilibrium was not studied, since it can be expected that it had little or no effect on the condensation reaction which was in the focus of this work. In the case of OM–Cl no isosbestic points were observed, due to the fact that upon protonation only a hyperchromic shift took place and the molar absorption coefficients of the protonation forms did not coincide at any wavelength (Figures 2, S2, S11, S20; see ESI). The distribution diagrams for all systems studied are given in Figures S3, S6, S9, S13, S15, S18, S21, S24, S27-30 (see ESI).

By inspecting the obtained K^H values given in Table 1, it can be seen that the protonation of OM–M is more favorable as the mole fraction of methanol increases, whereas in the cases of OM–Cl and OM–S there is a minimum in the value of the protonation constant at V(MeOH)/V(H_2O) = 5.73. Further on, for all three studied compounds the constants determined for protonation in pure methanol are much greater than those in

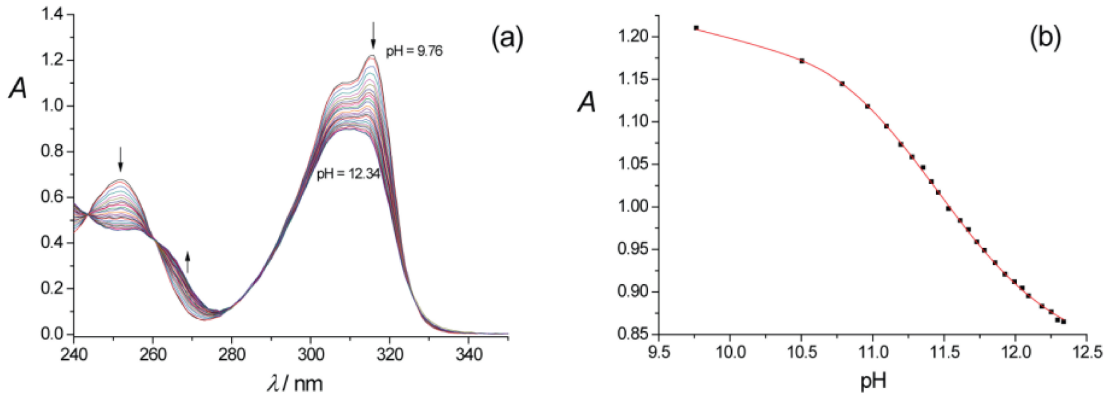


Figure 3. a) Spectrophotometric-potentiometric titration of OM–M ($c = 4.2 \times 10^{-5}$ mol dm^{-3}) with NaOH ($c = 7.08 \times 10^{-2}$ mol dm^{-3}) in MeOH/H_2O mixed solvent at 25 °C; V(MeOH)/V(H_2O) = 5.73, I_c = 0.05 mol dm^{-3} ($TBAClO_4$), l = 1 cm. b) Dependence of absorbance at 315 nm on pH. ■ experimental, — calculated.

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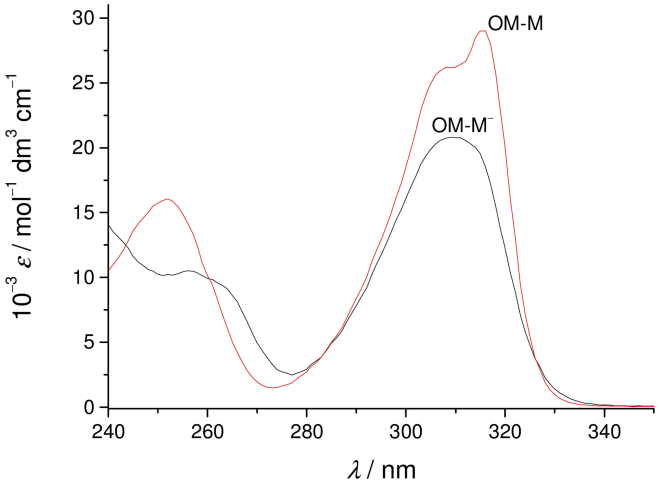


Figure 4. Characteristic spectra of OM–M protonation species in MeOH/H_2O mixed solvent; V(MeOH)/V(H_2O) = 5.73.

mixed solvents. These findings are in agreement with earlier studies of similar systems, i.e. protonation of neutral (e.g. amines) and negatively charged bases like carboxylates and thiolates in alcohol/water mixed solvents.[10–13] The obtained results can be explained by taking into account the solvation of the reactants and products in the mixed solvents, which can be quantitatively evaluated based on standard Gibbs energy of ion transfer from water to mixed solvent ($\Delta_t G^\circ$) of different composition.[14,15] In the case of protonation of anionic species (like OM-M$^-$) both reactants are charged species, whereas the product is neutral. Solvation of hydrogen ion is slightly more favorable in methanol/water mixed solvent at moderate V(MeOH)/V(H_2O) ratios in comparison to pure water.[14] However, standard Gibbs energy of H^+ transfer from mixed solvent to water reaches a minimum at x(MeOH) ≈ 0.75 (x stands for molar fraction) and solvation of hydrogen ion becomes significantly less favorable in solvents rich in methanol. Such behavior can be ascribed to preferential solvation effects.[16] On

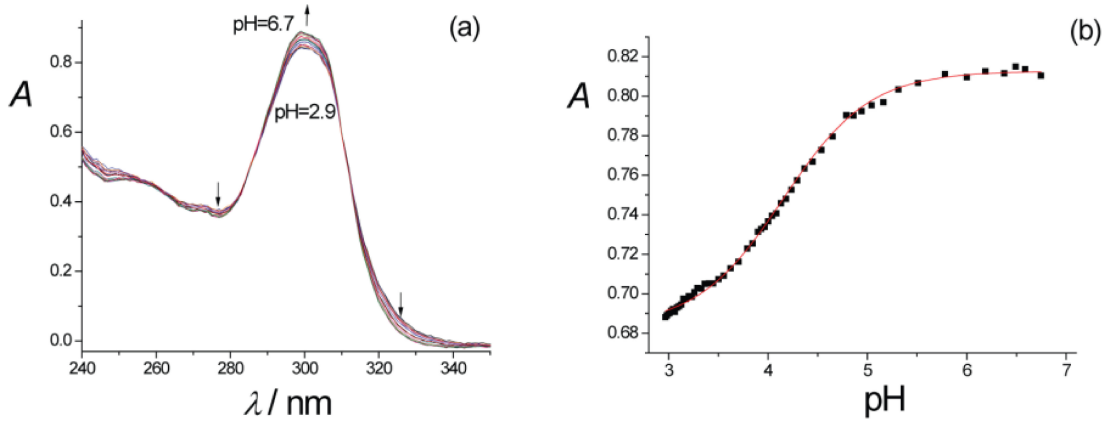


Figure 5. a) Spectrophotometric-potentiometric titration of OM–S (c = 4.98 × 10^{-5} mol dm^{-3}, c($HClO_4$) = 1.00 × 10^{-3} mol dm^{-3}) with NaOH (c = 4.52 × 10^{-2} mol dm^{-3}) in MeOH/H_2O mixed solvent at 25 °C; V(MeOH)/V(H_2O) = 5.73, I_c = 0.05 mol dm^{-3} ($TBAClO_4$), l = 1 cm. b) Dependence of absorbance at 300 nm on pH. ■ experimental, — calculated.

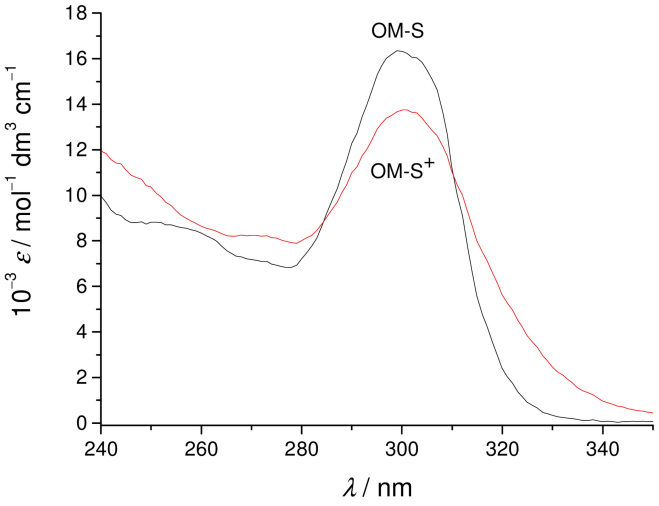


Figure 6. Characteristic spectra of OM–S protonation species in MeOH/H_2O mixed solvent; V(MeOH)/V(H_2O) = 5.73.

the other hand, the solvation Gibbs energies of the anions in most cases decrease as methanol content in the mixed solvent is raised, with almost linear dependence of $\Delta_t G^\circ$ on methanol molar fraction,[14] whereas the opposite is expected for neutral organic compounds.[17] The described solvation properties account for the fact that the protonation of OM-M$^-$ is more favorable as the V(MeOH)/V(H_2O) is increased. On the other hand, in the case of protonation of neutral species (like OM–Cl and OM–S), there is no difference in the number of charged species upon protonation. Therefore, in the water-rich solvent (x(MeOH) < 0.60) the changes in solvation Gibbs energies of the positively charged species (H^+ and OM-M$^+$ or OM-S$^+$) are mostly canceled out, while the neutral, deprotonated species are better solvated in less polar solvent, i.e. the one richer in organic component. This leads to a decrease in K^H values as mole fraction of methanol increases from 0.31 to 0.72. However, as already stated, with further increase in methanol content, solvation of H^+ ion becomes significantly less favorable,

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causing the increase in protonation equilibrium constant of OM–Cl and OM–S in such solvents (x(MeOH) = 0.85 and 1).

Although the results regarding the protonation properties suggest that higher water content should favor the condensation reaction, the aspect of reactant and product solubility should also be taken into consideration. For that reason, the solubility of OM–Cl, OM–M, and OM–S in the studied mixed solvents at different temperatures were determined spectrophotometrically (Tables 2-4). It was found that OM–Cl is more soluble in the solvent containing more water, since it is a hydrochloride salt and exists primarily in ionic form. On the other hand, both OM–M and OM–S exhibited better solubility in solvents richer in the organic component, which is also in agreement with their structural properties. The most pronounced change in the solubility was observed in the case of OM–S which was extremely soluble in methanol-rich solvents, whereas its solubility dropped drastically at V(MeOH)/V(H_2O) = 1 (Table 4). This is an important finding, as it indicates that the increase of water to methanol ratio could lead to precipitation of OM–S from the solution. That would, most likely, make the one-pot strategy for the synthesis of Omeprazole less efficient.

In all cases the solubility increased with the rise in temperature suggesting that the dissolution processes were endothermic. This was confirmed by calorimetric measurements providing the solution enthalpies (Table 6). In the case of OM–M the reaction enthalpy and entropy of solution could also be determined from temperature dependence of the corresponding equilibrium constant, i.e. solubility (van't Hoff plots, Figure 7). The obtained reaction enthalpy was in good agreement with the value determined calorimetrically. Analogous procedure could not be carried out for OM–Cl and OM–S due to the fact that the concentrations of their saturated solutions were too high.

Table 2. Temperature dependence of OM–Cl solubility in different methanol/water mixed solvents and pure methanol.[a]

		s(OM-Cl) / mol dm^{-3}			
V(MeOH)/V(H_2O)		1	5.73	12.6	pure MeOH
θ / °C	15	2.56(7)	2.20(8)	2.40(2)	1.25(4)
	25	3.06(7)	2.50(3)	2.44(4)	1.87(2)
	35	3.57(2)	2.75(0)	2.70(9)	1.99(8)
	45	3.69(6)	3.05(2)	2.91(1)	2.28(8)

[a] uncertainties of the last digits are given as standard error of the mean (N = 3)

Table 3. Temperature dependence of OM–M solubility in different methanol/water mixed solvents and pure methanol.[a]

		10^2 s(OM-M) / mol dm^{-3}			
V(MeOH)/V(H_2O)		1	5.73	12.6	pure MeOH
θ / °C	15	0.54(3)	1.78(8)	4.53(1)	5.69(2)
	25	0.79(5)	4.67(5)	5.74(1)	6.40(9)
	35	1.19(1)	6.67(7)	8.01(4)	9.09(1)
	45	1.53(3)	9.32(1)	9.89(6)	10.65(5)

[a] uncertainties of the last digits are given as standard error of the mean (N = 3)

Table 4. Temperature dependence of OM–S solubility in different methanol/water mixed solvents and pure methanol.[a]

		s(OM-S) / mol dm^{-3}			
V(MeOH)/V(H_2O)		1	5.73	12.6	pure MeOH
θ / °C	15	0.0026	0.231	0.265	0.293
	25	0.0063	0.365	0.569	0.781
	35	0.0092	0.946	1.311	1.518
	45	0.0135	1.833	1.922	2.126

[a] uncertainties of the last digits are given as standard error of the mean (N = 3)

Table 5. Solution thermodynamic parameters of studied compounds in different methanol/water mixed solvents and pure methanol.[a]

	OM-Cl	OM-M	OM-S
V(MeOH)/V(H_2O)		1	
$\Delta_{sol}H$ / kJ mol^{-1}		27(1)[c]	
$\Delta_{sol}S^{\circ}$ / J mol^{-1} K^{-1}		50.1(5)[c]	
V(MeOH)/V(H_2O)		5.73	
$\Delta_{sol}H$ / kJ mol^{-1}	21.38(7)[b]	27.63(6)[b]	
		28.0(5)[c]	
$\Delta_{sol}S^{\circ}$ / J mol^{-1} K^{-1}		71(1)[c]	
V(MeOH)/V(H_2O)		12.6	
$\Delta_{sol}H$ / kJ mol^{-1}	21.4(3)[b]	24.1(5)[b]	33.2(6)[b]
	–	20(1)[c]	–
$\Delta_{sol}S^{\circ}$ / J mol^{-1} K^{-1}	–	45(4)[c]	–
V(MeOH)/V(H_2O)		pure MeOH	
$\Delta_{sol}H$ / kJ mol^{-1}		17(2)[c]	
$\Delta_{sol}S^{\circ}$ / J mol^{-1} K^{-1}		35(5)[c]	

[a] uncertainties of the last digits are given as standard deviations
[b] values determined by calorimetric measurements
[c] values determined from van't Hoff plots

Table 6. Comparison of the existing and herein proposed methods for synthesis of Omeprazole.

	Time per batch / h	Reflux time / h	Methanol used per batch / L	Average yield / %
Existing method	8	1	1267	82
Proposed method	5	0	1164	83

Synthesis

Previously developed synthetic routes for Omeprazole-based proton pump inhibitors differ with regards to stereochemical composition of the products.[18,19] Methods used in production of Esomeprazole and other enantiomerically pure medications based on Omeprazole utilize different oxidation process

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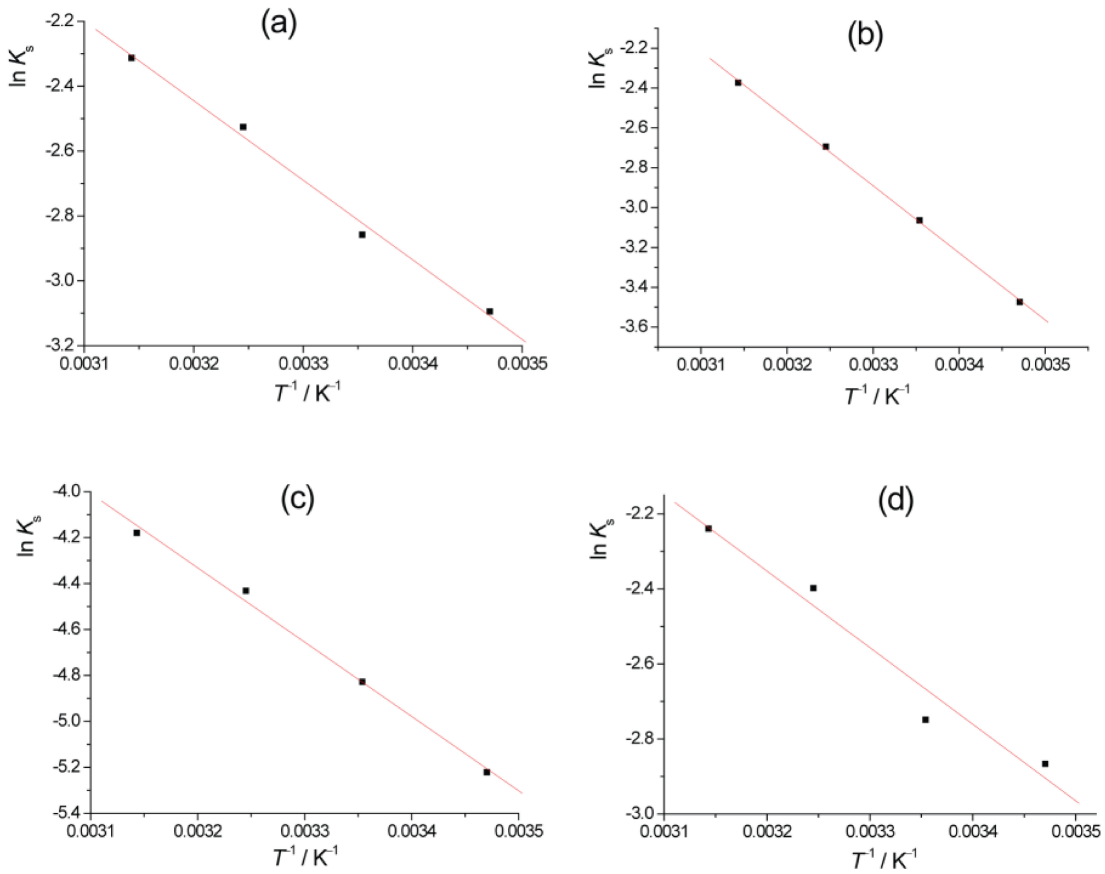


Figure 7. Van't Hoff plots for dissolution of OM–M in methanol/water mixed solvent. *V*(MeOH)/*V*(H_2O) = 12.6 (a), *V*(MeOH)/*V*(H_2O) = 5.73 (b), *V*(MeOH)/*V*(H_2O) = 1 (c), and pure methanol (d).

compared to the methods employed in production of racemic form.[i] Although the step in which thioether bond is formed could in principle be the same in both cases, different procedures are used due to different requirements of further steps of the synthesis, i.e. solvent used in the oxidation step and the need for isolation of the intermediate. The synthetic procedure discussed in this work results in the racemic form of Omeprazole. The oxidation is performed in the second stage of the one-pot process following formation of thioether bond (first stage) without isolation of the intermediate. Hydrogen peroxide is used as an oxidizing agent and the reaction is carried out at controlled pH value in order to achieve maximum catalytic effect of heptamolibdate catalyst. After the first stage, which is performed in methanol/water mixture, aqueous solution of catalyst is added, followed by peroxide drip with occasional pH correction.

Based on the above described results regarding the physico-chemical properties (K^H values and solubilities) of the reactants, the synthetic procedure was adjusted first by changing the methanol/water ratio in the solvent used, i.e. by increasing the water content (see Experimental). The extensive improvement accomplished by this slight modification was apparent on several accounts (Table 6). Firstly, it was found that by changing the water to methanol ratio the reaction rate was increased and thioether bond was formed in minutes on the large scale. Significant reduction of the production time was the most obvious benefit of the alteration in the procedure, but several other advantages were also realized. Namely, it was found that in the herein proposed optimal solvent mixture (*V*(MeOH)/*V*(H_2O) = 5.73), the addition of 2-(chloromethyl)-4-methoxy-3,5-dimethylpyridine hydrochloride caused substantial rise in temperature. Since the corresponding reaction is very fast, there is no risk of accumulation of unreacted compounds which could lead to runaway reaction. Moreover, the rise in temperature can be easily controlled by the rate of OM–Cl addition. Therefore, the heat produced in this way can also be used in order to accomplish complete conversion, i.e. synthesis of Omeprazole making the use of reflux (which has been used in the standard procedure) obsolete. The energy consumption during a large scale production can in that way be drastically lowered. It should also be noted that the consumption of the organic solvent (methanol) in the proposed procedure is decreased making the production both more cost-effective and ecologically friendlier.

The upper limit of *V*(MeOH)/*V*(H_2O) ratio in the solvent used is determined by the solubility of thioether intermediate, which is much less soluble in solvent of high water content. Namely, this compound must remain in the reaction mixture (as

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opposed to its separation as a new phase) in order to perform the one-pot process, and for that reason the mixed solvent of the $V(MeOH)/V(H_2O) = 5.73$ ratio was chosen as optimal.

After optimization of reaction parameters, focus was directed towards steps involving precipitation of the final product. After peroxide drip, sodium thiosulfate is added in order to decompose the residual peroxide. This also changes the pH of the solution, causing the precipitation of the product. After the precipitation relatively long trituration period has been employed in the standard procedure. This was also shown to be redundant, since reducing this period resulted in product of the same purity and profile as the one obtained by employing longer trituration periods (see Supporting Information). Furthermore, E-factor of the herein proposed procedure remained practically the same as in the case of conventional method ($\approx$ 11.2). In the last step raw material is recrystallized in order to remove trace impurities, namely unreacted thioether and sulfone which is formed by further oxidation of sulfoxide.

Conclusion

In this work the synthetic procedure for industrial production of an active pharmaceutical ingredient, namely Omeprazole, was optimized. The results of physico-chemical measurements served as a prerequisite to achieve this goal. The protonation equilibrium constants and solution properties (solubilities, solution enthalpies and entropies) of the starting materials in the synthesis of Omeprazole, as well as those of the intermediate, were determined in methanol/water mixed solvents of different methanol/water ratios. It was found that both protonation and solvation properties of the studied compounds significantly depend on the solvent composition. This was discussed by taking into account the charge and structural properties of different protonation species. Indications that preferential solvation plays an important role in defining the properties of the studied systems were recognized. The fact that dissociation of the precursor, OM–M is more favorable as the water content increases can be highlighted as one of the key findings in the context of synthetic procedure for production of Omeprazole. Since the ionized form of OM–M is the reactive species in the condensation reaction, the obtained results inspired the use of a different solvent mixture (compared to the conventional procedure) in the course of Omeprazole synthesis, i.e. the increase of water content. This was proven to be a decisive modification for optimization of the procedure rendering a faster and more cost-effective production of the drug. The reduced use of organic solvent additionally makes the proposed synthetic procedure greener and more ecologically friendly.

Supporting Information Summary

The results of all preformed potentiometric-spectrophotometric titrations are provided in the Supporting Information, together with the results of HPLC analyses and detailed NMR spectroscopic data of the samples of Omeprazole obtained by both conventional and modified procedure.

Acknowledgements

This work was funded by European Regional Development Fund and Croatian Ministry of Science Education and Sports, project Met4Pharm (RC.2.2.08-0024).

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Omeprazole · synthesis design · optimization · solvent effects · protonation

[1] J. Swarbrick, Encyclopedia of Pharmaceutical Science and Technology, CRC Press, Boca Raton., 2013.
[2] B. Radaram, M. Levine, *Tetrahedron Lett.* **2014**, *55*(35), 4905–4908.
[3] P. Lindberg, A. Brändström, B. Wallmark, H. Mattsson, L. Rikner, K.-L. Hoffmann, *Med. Res. Rev.* **1990**, *10*, 1–54.
[4] F. Andrasi, P. Berzsenyi, L. Farkas, J. Korosi, T. Hamori, P. Botka, I. Ling, T. Lang, *Pharmazie* **2004**, *59*, 365–366.
[5] S.-Y. Chou, S.-F. Chen, *Heterocycles* **1997**, *45*, 77–85.
[6] K. Kubo, K. Oda, T. Kaneko, H. Satoh, A. Nohara, *Chem. Pharm. Bull.* **1990**, *38*, 2853–2858.
[7] J.-E. Baeckvall, *Modern Oxidation Methods*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, **2010.**
[8] C. Yang, Q. Jin, H. Zhang, J. Liao, J. Zhu, B. Yu, J. Deng, *Green Chem.* **2009**, *11*, 1401–1405.
[9] W. O. Foye, J.-R. Lo, *J. Pharm. Sci.* **1972**, *61*, 1209–1212.
[10] a) B. G. Cox, *Acids and Bases: Solvent Effects on Acid-Base Strength*, Oxford University Press: Oxford, U.K., **2013**; b) B. G. Cox, *Org. Proc. Res. Dev.* **2015** *19*, 1800–1808.
[11] a) C. L. De Ligny, *Recl. Trav. Chim. Pays-Bas Belg.* **1960**, *79*, 731–736; b) M. Paabo, R. G. Bates, R. A. Robinson, *J. Phys. Chem.* **1966**, *70*, 247–251.
[12] F. Rived, I. Canals, E. Bosch, M. Rosés, *Anal. Chim. Acta* **2001**, *439*, 315–333.
[13] S. Sanli, Y. Altun, G. Alsancak, *J. Sol.Chem.* **2012**, *41*, 1352–1363.
[14] C. H. Rochester, *J. Chem. Soc. Dalton. Trans.* **1972**, 5–8.
[15] Y. Marcus, *Ion Properties*, CRC Press, Boca Raton, **1997.**
[16] a) Y. Marcus, *Phys. Chem. Chem. Phys.* **1999**, *1*, 2975–2983; b) Y. Marcus, *Monatsh. Chem.* **2001**, *132*, 1387–1411; c) F. Naderi, A. Farajtabar, F. Gharib, *J. Mol. Liq.* **2014** *190*, 126–132.
[17] M. K. Chantooni, I. M. Kolthoff, *J. Phys. Chem.* **1974**, *78*, 839–846.
[18] A. Satyam, PCT Int. Appl. 2014 WO 2014111957 A1 20140724.
[19] D. S. Bhalerao, G. C. M. Kondaiah, N. Dwivedi, R. K. Mylavarappu, L. A. Reddy, A. Roy, G. Nagaraju, P. P. Reddy, A. Bhattacharya, R. Bandichhor, *Synth. Commun.* **2010**, *40*, 2983–2987.
[20] P. B. Correia, C. C. Romao, L. B. Correia, M. F. Pereira, A. C. Fernandes, J. E. Borges, R. Tavares, M. D. C. Costa, F. Teixeira, PCT Int. Appl. 2003 WO 2003097606 A1 20031127.

Submitted: February 28, 2017
Revised: May 28, 2017
Accepted: June 1, 2017

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