# Combined pre-formulation approach for the selection of naproxen-polymer-solvent candidates for the preparation of amorphous solid dispersion

**Katarina Gurkina**[1], **Zoltán Márk Horváth**[1], **Ruslans Kačanovs**[2], **Valentyn Mohylyuk**[1]

[1]Leading Research Group, Faculty of Pharmacy, Rīga Stradiņš University, Riga, Latvia; valentyn.mohylyuk@rsu.lv

[2] Faculty of Medicine and Life Sciences, University of Latvia, Riga, Latvia

PBP WORLD MEETING

15th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology (PBP); Prague, Czech Republic, 2026.03.23-26.

## Introduction

- Naproxen is generally classified as a Biopharmaceutics Classification System (BCS) Class II compound, characterized by low aqueous solubility in low pH media and high permeability.
- To enhance the oral bioavailability of such poorly soluble drugs, **amorphous solid dispersions** (**ASDs**) have been widely used, where the active substance is molecularly dispersed within a polymeric matrix.
- One of the key manufacturing techniques for production of **ASDs** usually involve a **drug–polymer–solvent system**, the selection of which must satisfy specific physicochemical and process-related criteria to ensure efficient manufacturing, safety, stability, and performance of the resulting dosage form.
- **The aim of this study** was to narrow down the list of possible **drug–polymer–solvent systems** for the formulation of naproxen **ASDs**, using a specific workflow (**Fig.1**).

## Materials

- **Naproxen** (Biosynth, Slovakia)
- **PVP K25** (Povidone)
- **Kollidon VA 64** (copovidone)
- **Soluplus** (BASF SE, Germany)
- **Eudragit E PO** (poly (butyl methacrylateco-(2-dimethylaminoethyl) methacrylate-co-methyl methacrylate 1:2:1; Evonik AG, Germany)
- **Apinovex LV** (polyacrylic acid; Lubrizol Advanced Materials, Inc., USA)
- **PVAl SRP 80, 4-88,** and **3-82** (polyvinyl alcohol; Merck AG, Germany)
- **Acetonitrile, chloroform, THF, ethyl acetate** and **xylene** were of Pharmacopeia grade and used as received

## Methods

- **Screening based on solubility parameters (SP):** solvent screening for naproxen and the selected polymers was conducted using the **Hansen Solubility Parameters in Practice (HSPiP) software** [1]**,** which applies the solubility parameter (SP) approach to assess the likelihood of **drug–solvent**, **polymer–solvent**, and **drug–polymer** compatibility. Yamamoto–Molecular Breaking (Y-MB) and the Hoftyzer– Van Krevelen (H–VK) methods were used for this purpose. The solubility distance (Ra) was calculated from the dispersion (δD), polarity (δP), and hydrogen bonding (δH) parameters of the drug or polymer (1) and solvent (2) [1]*:*
- $R_a^2 = 4(\delta D1 - \delta D2)^2 + (\delta P1 - \delta P2)^2 + (\delta H1 - \delta H2)^2$
- Smaller Ra values indicate a higher likelihood of dissolution; solvents with Ra ≤ 5 (VK) were selected for further assessment.
- **Solubility tests:** were performed for naproxen in the selected solvents, using a shake-flask method. Alongside, a parallel experimental visual assessments of the solubility of the polymers in the same solvents, as well as in water at gastric related media (0.1 N HCl) [2] were performed.
- **Precipitation test:** was performed in 0.1 N HCl [2] solution with pre-dissolved polymer (60, 40, and 20 wt. %). Specified amount of naproxen solution in acetonitrile (20 mg/mL), to achieve the proportion of 500 mg of naproxen per 1 L of dissolution medium (0.5 mg/mL), was added. UV absorption was determined directly within 10 mm pathlength quartz cuvettes (at room temperature) with UV-1900i spectrophotometer (Shimadzu, Japan). Spectra were recorded at 5-minute intervals over a 2-hour period (n = 3).

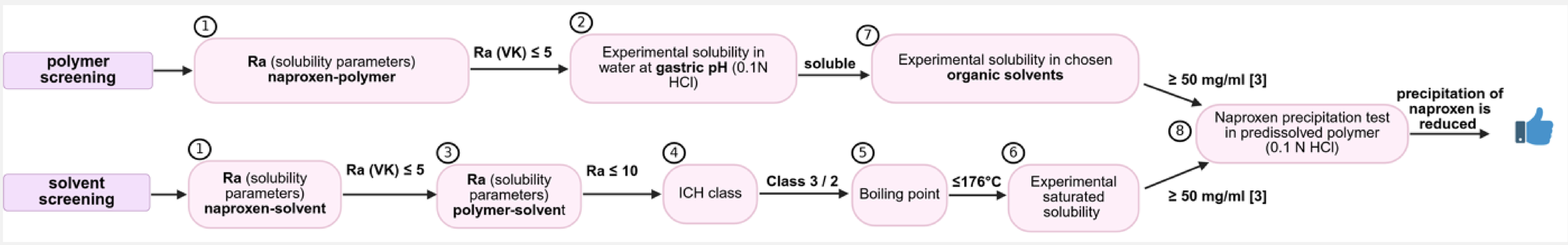


**Fig. 1. Workflow for solvent and polymer selection for naproxen formulation development**

| Solvent | ICH class | Boiling point (°C) | Ra (VK) | Ra (Y-MB) | Experimental solubility (naproxen) (mg/ml) |
|---|---|---|---|---|---|
| ***Chloroform*** | *2* | **1 (61–62)** | **1 (1.7)** | *2 (5.29)* | 3 (48.46) |
| ***THF*** | *2* | *2 (65–66)* | *2 (3.75)* | **1 (5.06)** | **1 (376.51)** |
| ***Ethyl acetate*** | **3** | 3 (76–78) | 4 (4.62) | 3 (7.11) | *2 (49.89)* |
| ***Xylene*** | *2* | 4 (144–145) | 3 (4.33) | 4 (8.4) | 4 (3.87) |

**Table 1. Ranking of solvents by ICH, boiling point, HSP values, and saturated solubility**

| SMILES sections | Naproxen | | Chloroform | THF | Ethyl acetate |
|---|---|---|---|---|---|
| | Ra (Y-MB) | Ra (VK) | Ra values | | |
| **XCCOX** | 7.99 | 4.75 | 3.12 | 6.27 | 6.51 |
| **XCC(OC(=O)C)X** | 6.0 | 4.02 | 2.62 | 6.05 | 7.10 |
| **XCC(N1CCCCCC1(=O))X** | 6.92 | 5.57 | 4.02 | 6.61 | 7.67 |
| ***Experimental solubility*** | | | >50 mg/ml | >50 mg/ml | >50 mg/ml |

**Table 2. Solubility parameters for Soluplus**

## Results

- Solvents for naproxen with **Ra ≤ 5** (VK) were obtained and ranked according to ICH class, boiling point; naproxen solubility in these solvents was evaluated and compared with solubility parameters obtained with HSPiP software (**Table 1**).
- Based on the **Ra values,** THF, chloroform, ethyl acetate, and xylene were identified as the most suitable organic solvent candidates for naproxen (**Table 1**).
- According to the ICH classification, ethyl acetate is the least toxic among these solvents, whereas chloroform and THF exhibit the lowest boiling points. Experimental saturated solubility testing confirmed that **THF** provides the highest solubility for naproxen, dissolving up to **376.5 mg/mL**, while xylene showed the poorest solubility, with a maximum of **3.9 mg/mL** (**Table 1**).
- The SP-based approach for polymer-drug-solvent screening has limitations, as it does not fully account for specific molecular interactions, including hydrogen bonding, therefore theoretical predictions often deviate from experimental solubility outcomes. Regarding polymers, the SP of individual structural subunits were used to estimate suitable solvents, however, the approach does not account for the relative contributions of each subunit, as well as their proportions and spatial distribution in the polymer chain, which explains the deviation of theoretical solubility predictions from experimentally observed results.
- Visual solubility assessment showed that all investigated polymers were soluble in water at gastric pH (0.1 N HCl) [2]. Used **PVA grades** at a concentration of **50 mg/mL** were **insoluble** in all tested organic solvents, whereas **Soluplus** and Kollidon VA 64 were **soluble in all solvents except xylene** at the same concentration, while PVP K25 exhibited solubility only in chloroform. (**Table 2**)
- To identify polymers that enhance drug solubility and reduce precipitation un under gastric conditions, precipitation tests were carried out for naproxen with polymers **PVP K25, Kollidon VA 64, Eudragit E PO, Apinovex LV,** and **PVAls** (**SRP; 4-88; 3-82**) at a **60 %** polymer load (considering naproxen-polymer solid dispersion) and **Soluplus** at **60** and **20 %** polymer load. The best precipitation inhibition results were obtained with Soluplus. Soluplus at 20% load outperformed other tested polymers at 60% load (**Fig. 2**). Among other polymers at 60% load, PVAl polymers showed only modest precipitation inhibition, while PVP K25, Kollidon VA 64, Apinovex LV, and Eudragit E PO unexpectedly accelerated naproxen's precipitation.

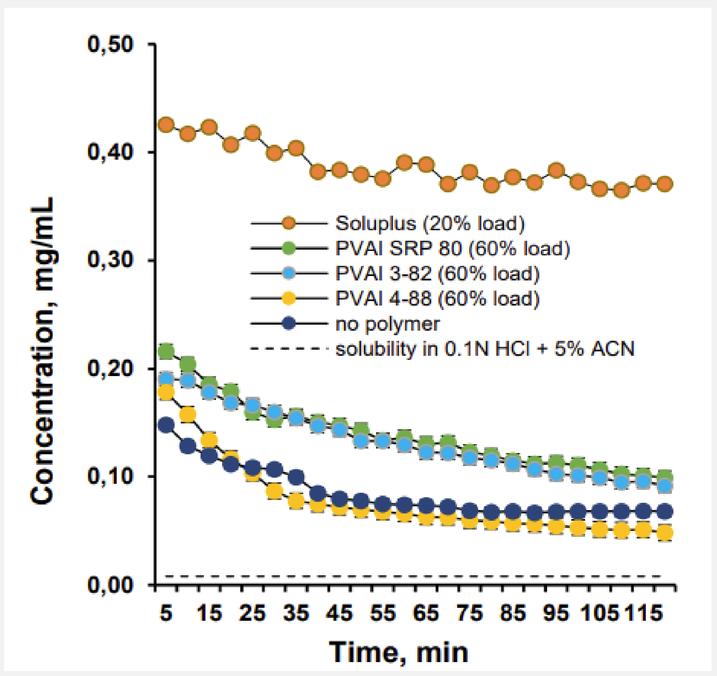


**Fig. 2. Precipitation test: effect of polymer on naproxen precipitation (polymer concentration of 0.75 mg/ml; drug:polymer 40:60; Soluplus: 0.125 mg/ml; 80:20 drug:polymer)**

## Conclusion

A list of solvent-drug-polymer systems for naproxen was successfully narrowed down, with the one among the promising polymer–solvent-drug combination for naproxen ASD manufacturing being **Soluplus in combination with ethyl acetate**, **chloroform, tetrahydrofuran,** or **acetonitrile**. The used workflow turned out to be effective for this purpose, with HSPiP software being a useful tool, while having its own limitations, and Ra values from the Y-MB method aligning more closely with experimental solubility than those from the H–VK method, indicating higher predictive reliability.

**Ref. 1:** Hansen, C.M., Hansen Solubility Parameters A User's Handbook. 2nd ed. ed. 2007: CRC Press.
**Ref. 2:** European Directorate for the Quality of Medicines & HealthCare (EDQM). (2025). 5.17.1. Recommendations on dissolution testing. In European Pharmacopoeia (12th ed.). Council of Europe; https://pheur.edqm.eu
**Ref. 3:** Vasconcelos T, Marques S, das Neves J, Sarmento B. Amorphous solid dispersions: Rational selection of a manufacturing process. Adv Drug Deliv Rev. 2016 May 1;100:85-101. doi: 10.1016/j.addr.2016.01.012. Epub 2016 Jan 27. PMID: 26826438.

Finansē Eiropas Savienība NextGenerationEU
2027 Nacionālais attīstības plāns

**Funding:** FLP project No. Izp-2024/1-0037 "Elucidation of the mechanism of amorphization and dissolution of bad glass former as a function of drug-polymer interaction and preparation method" is financed by the Latvian state budget.

Gurkina K, Horváth ZM, Kačanovs R, Mohylyuk V. Poster: Combined pre-formulation approach for the selection of naproxen-polymer-solvent candidates for the preparation of amorphous solid dispersion. 15th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical