

Step-by-step guide to using the Glass Solution Companion app

The Glass Solution Companion app is a small software application made with the intention to assist the calculations for performing the drug-in-polymer solubility predictions associated with the *Melting point depression* method, *Recrystallization* method and the *Melting and mixing* method. The software, source code and Excel template (both empty and filled-in example) is available at:

<http://www.mn.uio.no/glass-solution-companion>

For more information on using the methods please refer to publications from Larsen et al. (2024, submitted – not yet available) and Meiland et al. (2022).

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References

Meiland, P., Larsen, B. S., Knopp, M. M., Tho, I., & Rades, T. (2022). A new method to determine drug-polymer solubility through enthalpy of melting and mixing. *International Journal of Pharmaceutics*, 629, 122391.

Larsen, B.S., Meiland, P., Tzdaka, E., Tho, I., & Rades, T. (2024), A unifying approach to drug-in-polymer solubility prediction: Streamlining experimental workflow and analysis, *European Journal of Pharmaceutics and Biopharmaceutics*, 203, 114478.

1 Installing the app

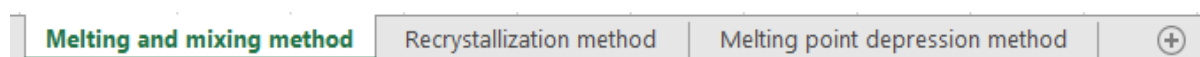
The app can be installed using the Exe-file downloaded from the link on the website. If it has not been done before, installing with the Exe-file will also prompt the user to install Matlab Runtime. This is a necessary for the application to run. Alternatively, the user can run the source code directly Matlab is already installed on the computer. The app was originally coded in version R2022b, though it should be possible to also use other versions of Matlab.



2 Filling-in the Excel template

The Excel template called needs to be filled-in with experimental data consisting of both physical chemical information on the drug-polymer combination as well as DSC data. This template can be downloaded from the website.

In general, green fields in the template need to be filled-in with data, while grey fields need to be left empty for calculations. It is not necessary to fill-out all the marked green fields for data points. If any green fields for data points are left empty, they will not be considered for the analysis. It is also possible to add more data points than the number of green fields. Simply continue filling-in data points below the marked green fields. These will still be included in the analysis. All calculations will be filled-in by the software in the grey fields, while outliers defined by the user during operation of the software will be marked as such under “outlier” next to the corresponding data points. Since the software will overwrite any information in the grey fields during operation, it is recommended to save a copy of the used template after a completed session of analysis with the software if the user wish to save the calculations.



Information for each prediction method can be filled-in by clicking on their corresponding sheets in the bottom of Excel window. Not all sheets need to be filled-in to run the program. The corresponding excluded methods can then be skipped while operating the software for analysis.

2.1 Physical chemical parameters

On the left side of each method sheet is a list of drug-polymer specific information that needs to be filled-in. These are *molecular weight* of the drug and polymer, *True density* of the drug and polymer (commonly measured by helium pycnometry – for exploration this can be put as 1 g/mL as a placeholder leading to an associated error in extrapolation), *Melting enthalpy* and *Melting point* measured on the pure drug. Specifically for the *Melting and mixing* method, the starting drug fraction of the supersaturated ASD or physical mixture used for equilibrium samples also needs to be indicated (here it is assumed that the same starting drug fraction was used for all samples – if different starting drug fractions were used, χ and equilibrium drug fraction can be calculated for each sample by filling-in and analysing multiple templates).

	A	B	C
1	Physical chemical parameters		
2			
3	Molecular weight		
4	Drug	357.8	Da
5	Polymer	13000	Da
6			
7	True density		
8	Drug	1.32	g/mL
9	Polymer	1.36	g/mL
10			
11	Melting enthalpy		
12	Pure drug	109.68	J/g
13			
14	Melting point		
15	Pure drug	159.77	°C
16			
17	Starting drug load		
18	Xdrug2	0.9022	
19			
20	Solubility at 25 °C		
21	Calculated		
22	Upper		
23	Lower		

2.2 Melting and mixing method

Results from melting physical mixtures of drug and polymer can be put into the green fields under “Results from melting physical mixtures”, including *drug fraction* of each sample as well as *melting point* and *enthalpy of fusion* from the DSC measurement. Here it is recommended to report the melting point as either the peak maximum of the endotherm in the thermogram or as the weighted average over the endotherm weighted from the difference in heat flow from the baseline. During analysis, the Flory-Huggins interaction parameter (χ /chi) will be calculated for each sample and reported on the right. It is the average of these χ -values that is used to generate the *enthalpy of melting and mixing* curve. Also, user-decided outliers, if any, will be marked on the right by the software application during operation.

E	F	G	H	I	J	K	L	M
Results from melting physical mixtures								
Drug fraction (xdrug)		Melting point		Enthalpy of fusion		Calculated chi		Outlier
0.9025		158.44 °C		89.41 J/g				
0.9025		158.41 °C		89.15 J/g				
0.9025		158.40 °C		87.99 J/g				
0.8049		156.56 °C		78.60 J/g				
0.8049		156.57 °C		76.51 J/g				
0.8049		156.24 °C		76.51 J/g				
0.7033		152.98 °C		62.80 J/g				
0.7033		152.02 °C		62.39 J/g				
0.7033		151.17 °C		62.26 J/g				
0.6049		149.90 °C		50.26 J/g				
0.6049		149.47 °C		50.38 J/g				
0.6049		150.17 °C		50.88 J/g				
0.5048		147.65 °C		37.06 J/g				
0.5048		147.10 °C		38.42 J/g				
0.5048		147.46 °C		38.63 J/g				
0.4048		143.97 °C		29.08 J/g				
0.4048		143.98 °C		29.33 J/g				
0.4048		138.56 °C		27.87 J/g				
0.3043		129.40 °C		22.55 J/g				
0.3043		137.46 °C		21.22 J/g				
0.3043		128.34 °C		20.57 J/g				
0.2032		128.32 °C		12.94 J/g				
0.2032		122.42 °C		12.66 J/g				
0.2032		127.73 °C		12.78 J/g				
0.1018		116.16 °C		2.56 J/g				
0.1018		118.09 °C		2.28 J/g				
0.1018		118.76 °C		4.50 J/g				

Results from melting equilibrated ASDs can be put into the green fields under “Results from melting glass solutions”, including *annealing temperature* of each sample as well as *melting point* and *enthalpy of fusion* from the DSC measurement. Here it is recommended to report the melting point as either the peak maximum of the endotherm in the thermogram or as the weighted average over the endotherm weighted from the difference in heat flow from the baseline. During analysis, the equilibrium drug fraction as well as the χ will be calculated for each sample and reported on the right. It is the average of these χ -values that is used to generate the *Flory-Huggins extrapolation* curve, while the calculated equilibrium drug fractions are used as data points on the graphs. Alternatively, the calculated equilibrium drug fractions can be used for extrapolation with other solubility models.

O	P	Q	R	S	T	U	V	W	X	Y	Z
Results from melting equilibrium glass solutions											
Annealing temp		Melting midpoint		Delta enthalpy		Calculated Xdrug		Calculated chi		Outlier	
150 °C		157.20 °C		0.8023 J/g							
150 °C		157.07 °C		0.8429 J/g							
150 °C		157.09 °C		0.8692 J/g							
145 °C		157.92 °C		18.3810 J/g							
145 °C		158.12 °C		17.2000 J/g							
145 °C		157.98 °C		17.1490 J/g							
140 °C		158.37 °C		44.4390 J/g							
140 °C		158.27 °C		43.9710 J/g							
140 °C		158.21 °C		44.2490 J/g							
135 °C		158.70 °C		54.4040 J/g							
135 °C		158.71 °C		55.2270 J/g							
135 °C		158.58 °C		54.9950 J/g							
130 °C		158.33 °C		62.3830 J/g							
130 °C		158.43 °C		60.3510 J/g							
130 °C		158.29 °C		61.2210 J/g							
125 °C		158.30 °C		64.4120 J/g							
125 °C		158.09 °C		64.0990 J/g							
125 °C		158.28 °C		63.9330 J/g							
120 °C		158.11 °C		68.7250 J/g							
120 °C		158.12 °C		68.0620 J/g							
115 °C		157.89 °C		69.8560 J/g							
115 °C		157.99 °C		69.6760 J/g							
110 °C		158.00 °C		72.2500 J/g							
110 °C		157.86 °C		71.3790 J/g							
100 °C		157.66 °C		60.9770 J/g							
°C		°C		J/g							
°C		°C		J/g							

2.3 Recrystallization method

Recorded *glass transitions* from samples of known *drug fractions* can be put into green fields under “Results from glass transition of glass solutions”. In addition, the recorded glass transition of the pure drug and pure polymer can be put into the green fields under “Gordon-Taylor equation” and “Kwei equation”. When using the software, fittings to linear, Gordon-Taylor and Kwei will be done simultaneously, and the user can then select their preferred model to be used as a standard curve for calculating the equilibrium drug fractions in this method. The equation for the model used for this purpose will be marked next to the equation in the Excel template.

Glass transitions recorded on equilibrated ASDs together with the *annealing temperature* (equilibrium temperature) can be put into the greens fields under “Results from glass transition of equilibrium glass solutions”. This data is then used to calculate the equilibrium drug fraction.

E	F	G	H	I	J
Results from glass transition of glass solutions					
Drug fraction (xdrug)	Tg				
0.9025	46.65 °C		Linear equation		
0.9025	47.34 °C		A		°C
0.9025	47.14 °C		B		°C
0.8525	49.53 °C				
0.8525	48.89 °C		Gordon-Taylor equation		
0.8525	49.08 °C		k		
0.8049	50.24 °C		Tg drug	45.15	°C
0.8049	50.4 °C		Tg polymer	125.50	°C
0.8049	50.84 °C				
0.7536	51.45 °C		Kwei equation		
0.7536	51.66 °C		k		
0.7536	50.84 °C		q		°C
0.7033	53.14 °C		Tg drug	45.15	°C
0.7033	53.89 °C		Tg polymer	125.50	°C
0.7033	53.3 °C				
0.6049	56.56 °C				
0.6049	56.79 °C				
0.6049	56.13 °C				
0.5048	57.81 °C				
0.5048	58.18 °C				
0.5048	58.24 °C				
0.4048	60.61 °C				
0.4048	65.04 °C				
0.4048	61.22 °C				
0.3043	67.34 °C				
0.3043	71.8 °C				
0.3043	69.21 °C				
0.2032	93.89 °C				
0.2032	95.49 °C				
0.2032	94.89 °C				
0.1018	95.47 °C				
0.1018	91.61 °C				
0.1018	93.98 °C				

Similar to the previous method, calculated drug fractions as well as the χ -values will be calculated for each sample and reported on the right during operation of the software.

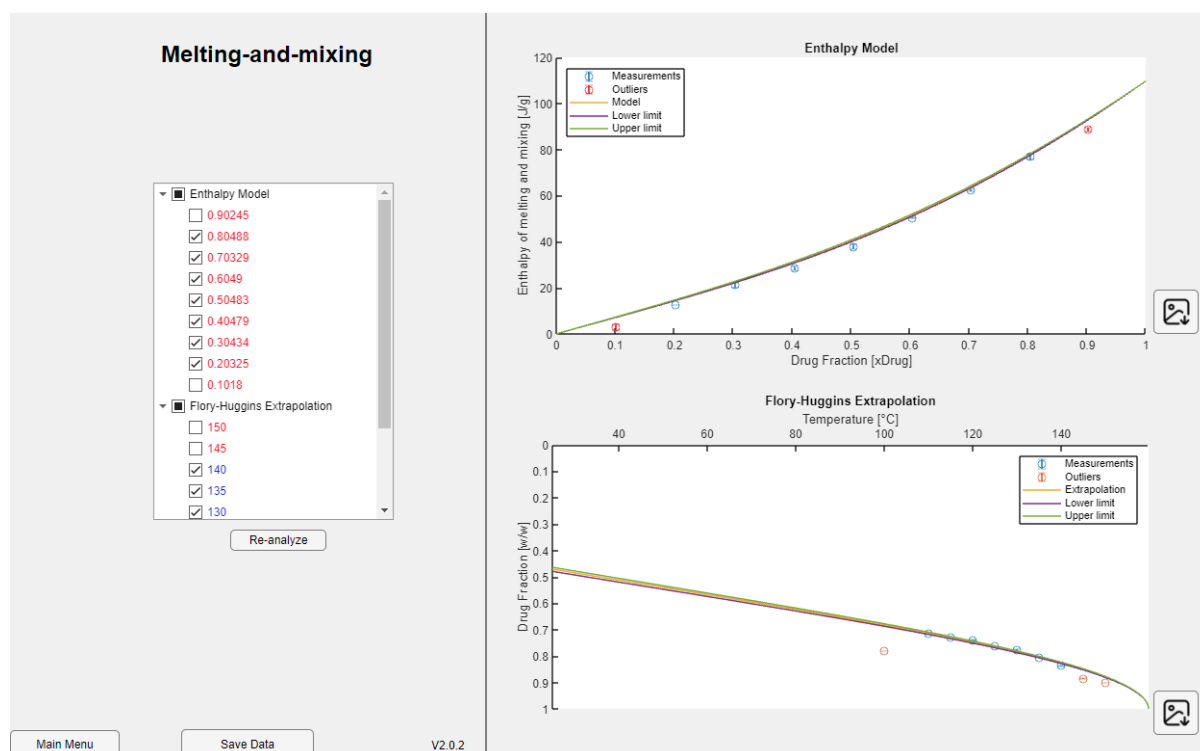
2.4 Melting point depression method

Melting point (Mp) results from melting physical mixtures of known *drug fractions* can be put into the green fields under “Results from melting physical mixtures”. It is recommended to report both the onset, midpoint (peak maximum) and offset of the melting endotherm, since all of these can be collected simultaneously from a single DSC experiment. The Flory-Huggins extrapolation can easily be prepared for the three methods simultaneously and the preferred interpretation of dissolution temperature can then be decided while operating the software. Which interpretation is selected, as well as the calculated χ -values for each sample will be reported on the right.

[illegible]

3 Operating the software application

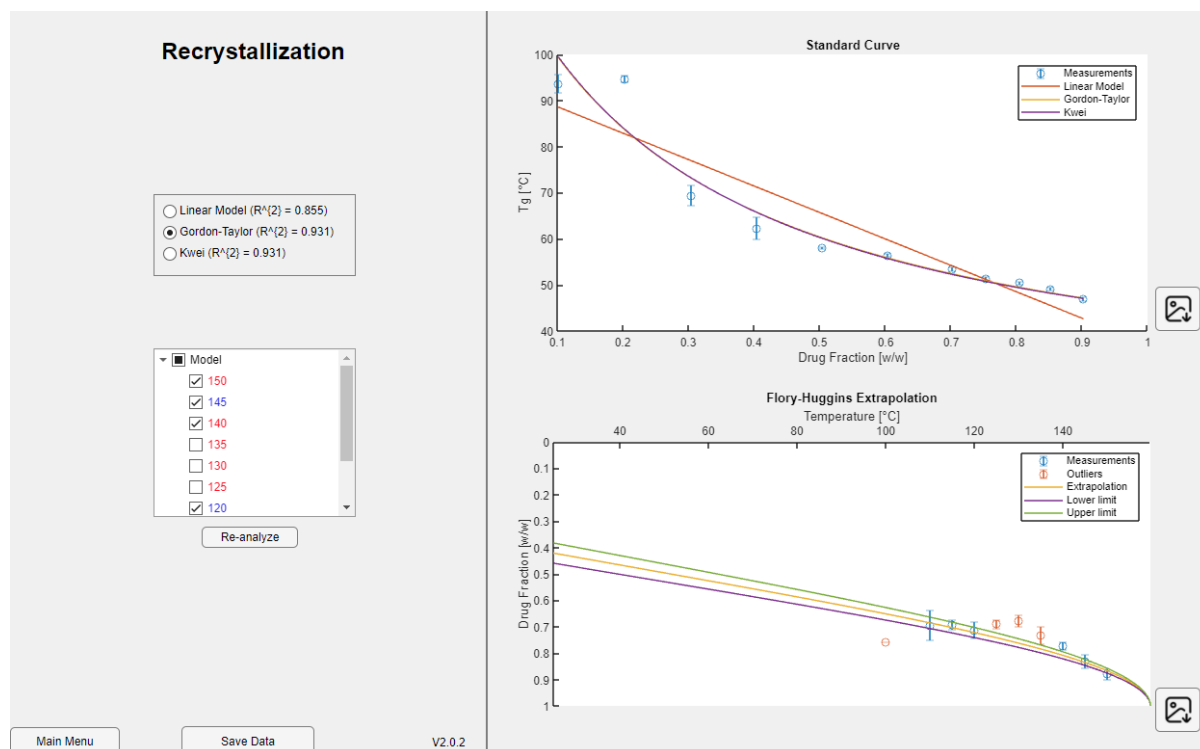
The software application can either be used by installing the exe-file or by running the app from the Matlab project folder if Matlab is installed. After opening the app, the filled-in template can be uploaded by pressing “Upload”. Please make sure that the filled-in template is not opened while uploading the file or performing the analysis. To proceed with analysis, select one of the three methods. If any data is missing from the spreadsheet, a pop-up warning will appear asking for the specific data needed.



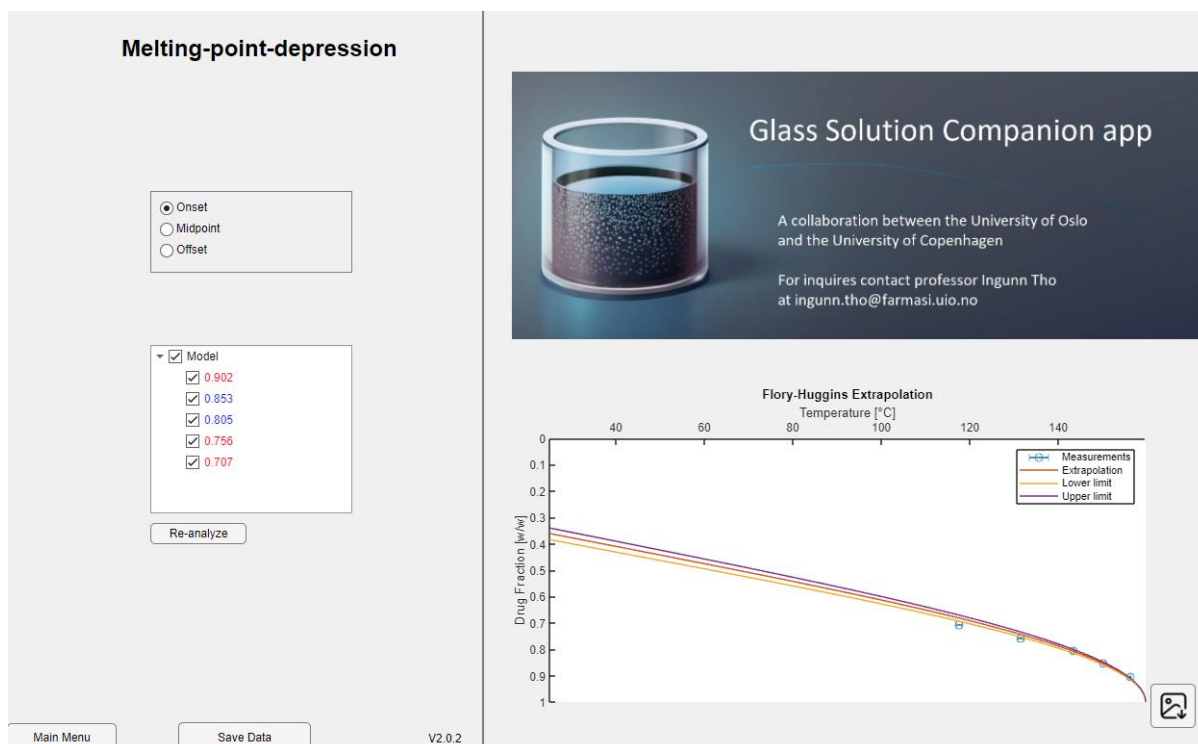
During analysis, the application will give suggestions for potential outliers by colouring individual data points in red on the left side. The user can evaluate the individual data points on the graphs displayed on the right side. If there is a wish to explore changes in the graphs when omitting certain data points, these data points can be deselected from the menu on the left. New graphs can then be generated on included data points by pressing “Re-analyze”.

The analysis results can be saved by pressing “Save data”. This will save all calculations performed together with any marked outliers in the uploaded excel spreadsheet. It should be noted, that doing this will overwrite any previous calculations performed in the uploaded in spreadsheet. If the user wishes to save previous calculations, it is recommended to save a back-up version of their spreadsheet. The excel spreadsheet needs to be closed for the data to be saved correctly. By opening the uploaded spreadsheet, the user will gain access to all calculations performed, including the calculated soluble drug fractions (x_{drug}) and χ -values, as well as the calculated solubility with 95 % confidence interval at 25 °C. This data can be used for alternative extrapolation models or to compare the results between methods.

The software will generate graphs for each method as they are analysed. These can be saved individually by pressing the button at the bottom-right side of the graph. For the *Melting and mixing* method, the graphs showing the enthalpy of melting and mixing vs. the drug fraction as well as the Flory-Huggins extrapolation on the resultant equilibrium drug fractions are generated. For the *Recrystallization* method, both the glass transition vs. drug fraction and the Flory-Huggins extrapolation are generated. While for the *Melting point depression method* only the Flory-Huggins extrapolation is generated. To perform analysis for a different methods, the user can navigate back to the starting menu by pressing the *Main menu* button in the lower left corner.



For both the *Recrystallization* method and the *Melting point depression* method, some options must be considered. In the *Recrystallization* method, the user must decide on whether to model the glass transition – drug fraction relationship by fitting to a *linear* model, the *Gordon-Taylor* equation, or the *Kwei* equation. The R^2 value for each of the fitting models are depicted in the menu on the left side, where the fitting model can also be chosen. Which fitting model was selected will be saved in the uploaded template when proceeding to the *Melting point depression* method. In the *Melting point depression* method, the user must decide on which interpretation of the *melting point* to use, including *onset*, *midpoint* and *offset*. This option determines which data set of *melting points* the application uses for the analysis. If all data sets are filled out, this will allow for quick evaluation of the difference and comparison to the other methods. If any full data sets are missing, the option to analysis those will be made unavailable. The software cannot analyse partial data-sets, therefore for any *onset*, *midpoint* or *offset* with included data points, a temperature needs to be filled out for each listed drug fraction in the spreadsheet.



Thank you for using this application. We would like to encourage you to share your results and experiences. The filled-in templates can be used to share your data, either attached to published papers as supplementary material or in data repositories. Sharing your measurements together with the calculations in this transparent manner would be useful for conducting comparisons between the methods.

For any questions or feedback, please reach out to Professor Ingunn Tho at ingunn.tho@farmasi.uio.no.