



## An Improved Automated Setup for Solubility Determination of Drugs

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### ABSTRACT

**Background:** Solubility of a drug/drug candidate is an essential information in the pharmaceutical area. Classical solubility determination method used in the laboratories are expensive and time-consuming. Attempts were made to provide an automated solubility determination setup based on a laser monitoring technique.

**Methods:** In a previously developed setup, drug powder was added to a given quantity of the solvent which made some troubles in practical applications. The present work reports another setup which adds solvent to a given mass of the drug. The validity of the measured solubilities is checked by comparing the measured solubilities of acetaminophen at two temperatures in water and ethanol mixtures with the corresponding data from the literature.

**Results:** The results reveal that the improved setup could overcome the limitations of the previously developed setup and could be used for drug solubility determination.

**Conclusion:** The improved setup overcomes the troubles made in the previous setup and could be used in generating large amount of solubility data to be used in the pharmaceutical industry.

### Introduction

Solubility of a drug/drug like compound is essential information in drug discovery since poor soluble compounds have limitations to proceed in drug discovery processes. In development stage, aqueous solubility investigations are important issues for oral or parenteral drug liquid formulations.<sup>1,2</sup>

The shake-flask method is the most common solubility determination procedure in which an excess amount of drug is added to a given volume (or mass) of the solubility medium.<sup>3</sup> An additional amount of drug should be added to make a saturated solution in equilibrium state. After equilibration, the excess solid should be removed from the saturated solution using either filtration or centrifugation and the quantification of drug concentration is measured usually by a UV spectrophotometric analysis. In high throughput screening studies, the shake-flask method is not recommended and automated setups are preferred.

The next method for determination of drug's solubility is the synthetic method which is based on disappearance of the solid solute from the suspension monitored by a laser beam. The disappearance of solutes could be achieved either by changing the temperature or by adding a known amount of the solvent.<sup>3</sup>

An automated setup has been reported in an earlier work<sup>4</sup> in which glass tubes (syringes) with different diameters and constant length were used to dispense the drug powder into the dissolution vessel. The filled tube with drug powder was weighed using an electronic balance before filling and after addition of the required mass of drug for saturation of the solution, and the mass difference determines the mass of drug added to saturate the solution. As the particles of the drug are added, the intensity of the laser beam changed gradually and increased again when the drug is completely dissolved. Then, another mass of the drug is

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dispensed to the vessel, and the procedure is repeated until the laser beam could not return to the maximum value, which means the last added powder could not be dissolved. This was checked several times, and then the system was stopped, and the total amount of the added drug powder was recorded and used to calculate the solubility value. The recorded signals for neat solvents by the laser system were considered as the maximum intensity of the signals detected by the photoconverter. The performance of the setup was validated using the measured solubility of acetaminophen in water at various temperatures ranging from 20 to 40 °C and in ethanol and propylene glycol at 25 °C and their comparisons with the measured data using methods other than laser monitoring technique, in which the IPDs (individual percentage deviations) varies from -13.8% to 20.6% with the overall IPD of 11.6% which is less than 25%. Very good agreements between measured and reported data points confirmed the validity of the setup for solubility measurements. In addition to the mentioned validation data points, the aqueous solubility of acetaminophen in the presence of different concentrations of SDS,<sup>4</sup> solubility of tris(hydroxymethyl)aminomethane (TRIS) in water + methanol,<sup>5</sup> water + 1-propanol,<sup>6</sup> methanol + 1-propanol,<sup>7</sup> water + methanol + 1-propanol<sup>8</sup> and the solubility of trisodium citrate in water + methanol<sup>9</sup> mixtures at various temperatures were measured using the developed setup. The previous setup<sup>4</sup> have a number of shortcomings and could not be used for most of drugs. As an example, most of drug powders could adsorb solvent vapors at the end of injection syringe and forms paste which make troubles with addition of small amounts of drug powder. Powder packing in the syringe is another trouble with most of the pharmaceutical compounds.

This work is aimed to present an improved version of the previously reported setup<sup>4</sup> for the determination of drug solubility on the basis of laser monitoring technique. The setup was validated using the measured solubility of acetaminophen at various temperatures, the corresponding data points collected from the literature and also the data generated using the previous setup. Acetaminophen was used as a model drug, since its solubility is widely investigated, is a chemically stable compound, is easily available and its solubility was measured using a previous version of our developed setup.

### Materials and Methods

As described in Introduction, the previous setup adds drug's powder to the solution and the process was followed up until the saturation of the solution and appearance of non-dissolved drug particles in the solution. A number of troubles including

formation of drug paste at the injection end of the syringe due to the adsorption of solvent vapor on drug powder and also packing the powder within the syringe. To overcome these troubles, it is possible to replace the addition of drug powder into the solution until saturation of the solution with addition of the solvent to complete dissolving of the particle's from the drug suspension. The process of solubility determination in the improved setup could be completed by disappearance of the suspension and formation of the saturated solution of the drug. Figure 1 shows a photograph of the improved setup. The experimental solubility of acetaminophen was determined using the improved setup for its validation, and the obtained data were compared with the corresponding data available from the literature.<sup>10-21</sup>

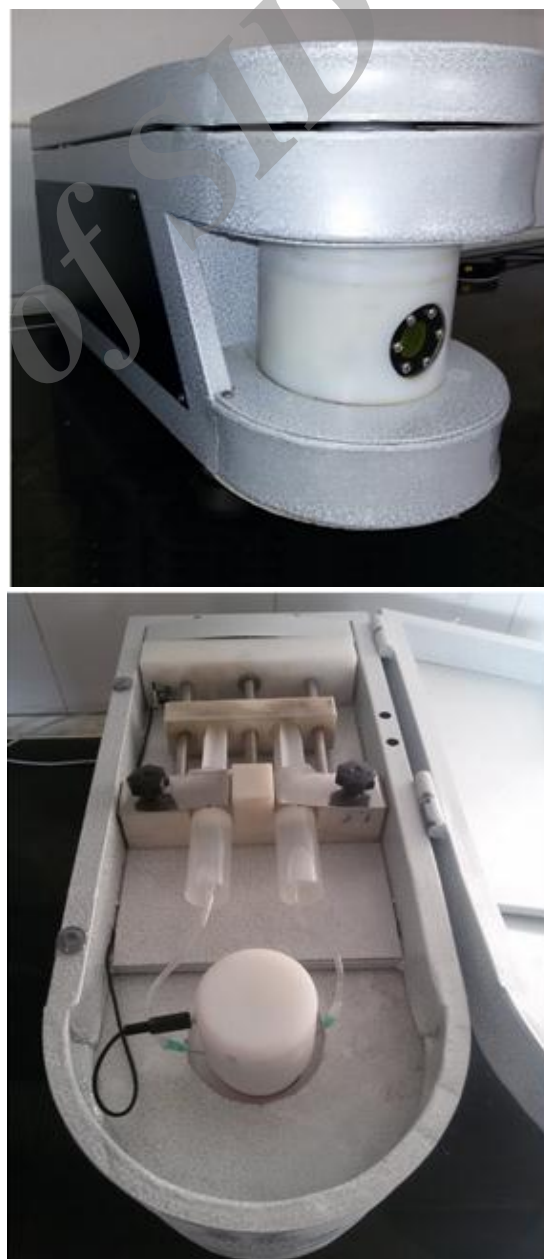


Figure 1. A photograph of the setup.

## Materials

Acetaminophen powder (purity of 99.0%) was purchased from Daana Pharmaceutical Company (Tabriz, Iran). Double distilled water was used for the preparation of the solutions. Ethanol (0.999 mass fraction purity) was supplied by Scharlau Chemie (Barcelona, Spain).

## Validation of the instrument

Measured acetaminophen solubilities in aqueous and ethanolic solutions at two temperatures were compared with the corresponding values obtained from the literature. The differences were computed using the individual percentage deviation (IPD) defined as:

$$IPD = 100 \left( \frac{C_T^{\text{Measured}} - C_T^{\text{Reported}}}{C_T^{\text{Reported}}} \right) \quad \text{Eq.(1)}$$

which is a similar value to the relative standard deviation (RSD) values used to check the repeatability of the experimental measurements in the solubility studies.<sup>2</sup>

## Results and Discussion

The measured solubility data of acetaminophen in water and ethanol and three binary solvent mixtures

of ethanol + water, the RSD for repeated experiments, the measured solubility using a previous setup and the IPD values for two solubility values are listed in Table 1. All RSD values are less than 5% revealing the acceptable precision of the improved setup for determination of the solubility. The obtained IPD values varied from -4.6% to 6.5 % with the overall of 2.8%. Concerning the RSD value of 2.2% and the wider variations of the solubility data of acetaminophen measured by the classical shake-flask method, one could consider that there are excellent agreements between data measured by the improved and previous setups. As described in Introduction, there are some practical limitations for the previous setup which overcome in the improved setup.

To compare the validity of the measured solubility data using the improved setup, the data was also compared with the corresponding data collected from the literature<sup>10-21</sup> and listed in Table 2 along with the calculated IPD values. The best agreement was observed for the solubility of acetaminophen in water at 25 °C reported by Chow and Repta<sup>15</sup> and the worst agreement was observed for the same data reported by Pitah et al.<sup>21</sup>

**Table 1.** Measured molar solubility of acetaminophen (with the relative standard deviations) in the solvent systems (mass ratio for mixed solvents) at 20 and 25 °C using the improved setup and the corresponding data measured using a previous setup.

Solvent system	Temperature (°C)	Improved setup	RSD	Previous setup	IPD
Water	25	0.0966	0.8	0.1000	-3.4
Water	20	0.0835	3.7	0.0837	-0.2
Water:Ethanol (8:2)	25	0.2983	2.2	0.3127	-4.6
Water:Ethanol (8:2)	20	0.2310	3.9	0.2170	6.5
Water:Ethanol (5:5)	25	1.0605	3.6	1.0920	-2.9
Water:Ethanol (5:5)	20	0.9633	1.7	0.9680	-0.5
Water:Ethanol (3:7)	25	1.4049	1.5	1.3890	1.1
Water:Ethanol (3:7)	20	1.3192	1.3	1.2910	2.2
Ethanol	25	0.9081	0.4	0.8860	2.5
Ethanol	20	0.8630	2.5	0.8260	4.5
		Overall	2.2	Overall	2.8

**Table 2.** Measured molar solubility of acetaminophen at 20 and 25 °C using the improved setup and the corresponding data taken the literature measured using classical shake-flask method.

Solvent	Temperature (°C)	Measured	Literature data	Reference	IPD
Ethanol	25	0.9081	1.0605	11	-14.4
Ethanol	25	0.9081	0.8860	12	2.5
Ethanol	20	0.8630	0.8260	12	4.5
Water	25	0.0966	0.0989	11	-2.3
Water	25	0.0966	0.0994	13	-2.8
Water	25	0.0966	0.09851	14	-1.9
Water	25	0.0966	0.0950	15	1.7
Water	25	0.0966	0.09133	16	5.8
Water	25	0.0966	0.09923	17	-2.7
Water	25	0.0966	0.09326	18	3.6
Water	25	0.0966	0.1323	19	-27.0
Water	25	0.0966	0.100	20	-3.4
Water	25	0.0966	0.07277	21	32.7
			Overall		8.1

The overall IPD reported in Table 2 was 8.1%. Concerning the RSD values for repeated experiments from the same laboratory, as examples up to 9.2%,<sup>22</sup> 10%<sup>23</sup> and 28%<sup>24</sup>, 8.1 % could be considered as an acceptable value. Employing such an automated setup, it is possible to measure required experimental solubility data of pharmaceuticals which usually collected by time consuming shake-flask method.<sup>25-27</sup>

The main advantages of the improved setup are; 1) a wider temperature range, 2) suitable for the solubility measurement of a highly low soluble drugs to very soluble drugs, 3) very similar measured solubilities to those determined using the common shake-flask method, 4) no need for chromophor groups on the drug molecule, 5) more repeatable results when compared with a previously reported setup, and 6) affecting parameters, such as stirrer rate, required time for equilibration, etc., could be adjusted by the user.

### Conclusion

An improved automated solubility determination setup was developed and validated. Replacing the addition of drug powder to the solvent with a new system, i.e. addition of solvent to a dissolution bottle containing a given mass of drug, overcomes the troubles made in a previous setup. The improved setup could be used for faster solubility measurements to speed up the drug discovery and development processes in the pharmaceutical industry.

### Conflict of interests

The authors claim that there is no conflict of interest.

### References

1. Faller B, Ertl P. Computational approaches to determine drug solubility. *Adv Drug Deliv Rev.* 2007;59(7):533-45. doi:10.1016/j.addr.2007.05.005
2. Jouyban A. *Handbook of Solubility Data for Pharmaceuticals*. Boca Raton: CRC Press; 2010.
3. Jouyban A, Fakhree MAA. Experimental and computational methods pertaining to drug solubility. Acree Jr WE, editor. *New York: Toxicity and Drug Testing*, New York: Intech Publisher; 2012.
4. Jouyban-Gharamaleki V, Jouyban-Gharamaleki K, Shayanfar A, Khoubnasabjafari M, Jouyban A. An automated system for determination of drug solubility based on laser monitoring technique. *J Lab Autom.* 2015;20(1):3-9. doi:10.1177/2211068214554801
5. Jouyban-Gharamaleki V, Jouyban-Gharamaleki K, Soleymani J, Acree Jr WE, Jouyban A. Solubility determination of tris(hydroxymethyl)aminomethane in water + methanol mixtures at various temperatures using a laser monitoring technique. *J Chem Eng Data.* 2014;59(7):2305-9. doi:10.1021/je500368p
6. Jouyban-Gharamaleki V, Jouyban-Gharamaleki K, Soleymani J, Acree Jr WE, Jouyban A. Solubility determination of tris(hydroxymethyl)aminomethane in water + 1-propanol mixtures at various temperatures. *J Chem Eng Data.* 2014;59(11):3723-7. doi:10.1021/je500620m
7. Jouyban-Gharamaleki V, Jouyban-Gharamaleki K, Soleymani J, Kenndler E, Acree Jr WE, Jouyban A. Solubility of tris(hydroxymethyl)aminomethane in methanol + 1-propanol mixtures at various temperatures. *J Chem Eng Data.* 2014;59(12):4227-30. doi:10.1021/je5009685
8. Jouyban-Gharamaleki V, Jouyban-Gharamaleki K, Soleymani J, Acree Jr WE, Kenndler E, Jouyban A. Solubility of tris(hydroxymethyl)aminomethane in water + methanol + 1-propanol mixtures at various temperatures using a laser monitoring technique. *J Chem Eng Data.* 2015;60(8):2515-20. doi:10.1021/acs.jced.5b00396
9. Soleymani J, Jouyban-Gharamaleki V, Jouyban-Gharamaleki K, Acree Jr WE, Kenndler E, Jouyban A. Solubility of trisodium citrate in water + methanol mixtures at various temperatures. *J Mol Liq.* 2016;221:166-70. doi:10.1016/j.molliq.2016.05.077
10. Jiménez JA, Martínez F. Thermodynamic magnitudes of mixing and solvation of acetaminophen in ethanol + water cosolvent mixtures. *Rev Acad Colomb Cienc.* 2006;30(114):87-99.
11. Soltanpour Sh, Jouyban A. Solubility of acetaminophen and ibuprofen in binary and ternary mixtures of polyethylene glycol 600, ethanol and water. *Chem Pharm Bull.* 2010;58(2):219-24. doi:10.1248/cpb.58.219
12. Jiménez JA, Martínez F. Temperature dependence of the solubility of acetaminophen in propylene glycol + ethanol mixtures. *J Solution Chem.* 2006;35(3):335-52. doi:10.1007/s10953-005-9007-8
13. Jouyban A, Chan HK, Chew NYK, Khoubnasabjafari M, Acree Jr WE. Solubility prediction of paracetamol in binary and ternary solvent mixtures using Jouyban-Acree model. *Chem Pharm Bull.* 2006;54(4):428-31. doi:10.1248/cpb.54.428
14. Manzo RH, Ahumada AA. Effects of solvent medium on solubility. V. Enthalpic and entropic contributions to the free energy changes of disubstituted benzene derivatives in ethanol:water and ethanol:cyclohexane



- mixtures. *J Pharm Sci.* 1990;79(12):1109-15. doi:10.1002/jps.2600791214
15. Chow YP, Repta AJ. Complexation of acetaminophen with methyl xanthenes. *J Pharm Sci.* 1972;61(9):1454-8. doi:10.1002/jps.2600610922
16. Dearden JC, Patel NC. Dissolution kinetics of some alkyl derivatives of acetaminophen. *Drug Dev Ind Pharm.* 1978;4(6):529-35. doi:10.3109/03639047809081824
17. Paruta AN, Irani SA. Dielectric solubility profiles in dioxane–water mixtures for several antipyretic drugs. Effect of substituents. *J Pharm Sci.* 1965;54:1334-8. doi:10.1002/jps.2600540922
18. Walters V. The dissolution of paracetamol tablets and in vitro transfer of paracetamol with and without sorbitol. *J Pharm Pharmacol.* 1968;20:228-31. doi:10.1111/j.2042-7158.1968.tb09887.x
19. Bauguess CT, Sadlik F, Fincher JH, Hartman CW. Hydrolysis of fatty acid esters of acetaminophen in buffered pancreatic lipase systems I. *J Pharm Sci.* 1975;64(1):117-20. doi:10.1002/jps.2600640125
20. Kouach IM, Pitman IH, Higuchi T. Amino acid esters of phenolic drugs as potentially useful prodrugs. *J Pharm Sci.* 1975;64(6):1070-1. doi:10.1002/jps.2600640652
21. Pitah J, Milecki J, Fales H, Uekama K. Hydroxypropyl- $\beta$ -cyclodextrin: preparation and characterization; effects on solubility of drugs. *Int J Pharm.* 1986;29(1):73-82. doi:10.1016/0378-5173(86)90201-2
22. Khosravi D, Connors KA. Solvent effect on chemical processes. I: Solubility of aromatic and heterocyclic compounds in binary aqueous-organic solvents. *J Pharm Sci.* 1992;81(4):371-9. doi:10.1002/jps.2600810418
23. Kulkarni AR, Soppimath KS, Dave AM, Mehta MH, Aminabhavi TM. Solubility study of hazardous pesticide (chlorpyrifos) by gas chromatography. *J Hazard Mater.* 2000;80(1-3):9-13. doi:10.1016/S0304-3894(00)00276-4
24. Roy D, Ducher F, Laumain A, Legendere JY. Determination of the aqueous Solubility of drugs using a convenient 96-well plate-based assay. *Drug Dev Ind Pharm.* 2001;27(1):107-9. doi:10.1081/DDC-100000135
25. Mahboot A, Jouyban A. Solubility of sodium phenytoin in propylene glycol + water mixtures in the presence of  $\beta$ -cyclodextrin. *Pharm Sci.* 2015;21(3):152-6. doi:10.15171/PS.2015.30
26. Zakeri-Milani P, Ebrahimi S, Valizadeh H. Investigation of digoxin solubility in different cosolvent systems. *Pharm Sci.* 2012;18(2):87-92.
27. Eghrary SH, Zarghami R, Jouyban A. Solubility of losartan in several mono-solvents at different temperatures. *Latin Am J Pharm.* 2012;31(4):632-6