An Improved Automated Setup for Solubility Determination of Drugs

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Introduction

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.

Abstract

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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 photodetector. 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, solubility of tris(hydroxymethyl)aminomethane (TRIS) in water + methanol, water + 1-propanol, methanol + 1-propanol, water + methanol + 1-propanol and the solubility of trisodium citrate in water + methanol mixtures at various temperatures were measured using the developed setup. The previous setup have a number of shortcomings and could not been used for most of drugs. As an example, most of drug powders could adsorb solvent vapors at the end of injection syringe and form 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 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.

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:

\[
IPD = 100 \left( \frac{C_{\text{Measured}} - C_{\text{Reported}}}{C_{\text{Reported}}} \right)
\]

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.²

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 overcame 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 literature¹⁰,¹¹ 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 Repta¹³ and the worst agreement was observed for the same data reported by Pitah et al.²¹

### 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%, 10% 23 and 28% 24, 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.25–27

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 setup was developed and validated. Replacing the 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.

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Automated Solubility Determination

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