**Supplementary information**

**Binary and Ternary Approach of Solubility of Rivaroxaban for Preparation of Developed Nano Drug Using Supercritical Fluid**

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**Table (S1):** Calculation of pressure fluctuation during the sampling.

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| --- |
| At (T=308K, P=12 MPa) and (Tc=304.12 K, Pc= 7.370 MPa)By the top chart for CO2, and two parameters Tr and Pr, the Z-factor is calculated Tr= 1.0127 and Pr= 1.628 => Z =0.31P1 Vcell = Z n1 R T112 MPa\*300 cm3 = 0.31 \* n1\* 8.314\* 308K => n1= 4.535Sampling loop: Ploop Vloop = Z nloop R Tloop12 MPa \* 0.6 cm3= 0.31 \* nloop\* 8.314\* 308 K=> nloop = 0.0091n1 – n2 = nloop n1-nloop = 4.535 – 0.0091= 4.5259 (n2)P2 V2 = Z n2 R T2 => P2 \* 300 cm3 = 0.31 \* 4.5259 \* 8.314 \* 308 k => P2= 11.9758 MPa (0.024) less than 0.1 MPa |

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| --- |
| At (T=338K, P=30 MPa) and (Tc=304.12 K, Pc= 7.370 MPa)Tr= 1.111 and Pr= 4.0705 => Z =0.65P1 Vcell= Z n1 R T130 MPa\* 300 cm3 =0.65\* n1\* 8.314\* 338K => n1= 4.927Sampling loop: Ploop Vloop = Z nloop R Tloop30 MPa \* 0.6 cm3 = 0.65\* nloop\* 8.314\* 338 K => nloop = 0.0098n1 – n2 = nloop n1-nloop = 4.927-0.0098 = 4.917 (n2)P2 V2 = Z n2 R T2 => P2 \* 300 cm3 = 0.65\* 4.917 \* 8.314 \* 338 K => P2= 29.94 MPa (0.06) less than 0.1 MPa |

The pressure fluctuation during the sampling is very low (less than 0.1 MPa), and before the experiments the below calculation has been done for highest and lowest temperature and pressure.

In the section pressure values were reported with an accuracy of ±0.1 MPa.

**Table (S2):** The amount of ethanol (Co-solvent), density of the mixture and mass of CO2 in mixture.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| T (K) | P (MPa) | Mass CO2 (gr) | Mole CO2 | Mole Ethanol | Mass Ethanol (gr) | ml Ethanol | Density mixture kg/m3 |
| 308 | 12 | 230.526 | 5.238 | 0.162 | 7.463 | 0.009 | 769.049 |
| 308 | 15 | 244.818 | 5.563 | 0.172 | 7.926 | 0.010 | 815.183 |
| 308 | 18 | 254.661 | 5.786 | 0.179 | 8.244 | 0.010 | 846.855 |
| 308 | 21 | 262.320 | 5.960 | 0.184 | 8.492 | 0.011 | 871.442 |
| 308 | 24 | 268.662 | 6.105 | 0.189 | 8.698 | 0.011 | 891.764 |
| 308 | 27 | 274.107 | 6.228 | 0.193 | 8.874 | 0.011 | 909.184 |
| 308 | 30 | 278.904 | 6.337 | 0.196 | 9.029 | 0.011 | 924.511 |
| 318 | 12 | 197.919 | 4.497 | 0.139 | 6.407 | 0.008 | 663.137 |
| 318 | 15 | 222.951 | 5.066 | 0.157 | 7.218 | 0.009 | 744.526 |
| 318 | 18 | 237.054 | 5.386 | 0.167 | 7.674 | 0.010 | 790.143 |
| 318 | 21 | 247.110 | 5.615 | 0.174 | 8.000 | 0.010 | 822.566 |
| 318 | 24 | 255.030 | 5.795 | 0.179 | 8.256 | 0.010 | 848.041 |
| 318 | 27 | 261.612 | 5.944 | 0.184 | 8.469 | 0.011 | 869.171 |
| 318 | 30 | 267.276 | 6.073 | 0.188 | 8.653 | 0.011 | 887.326 |
| 328 | 12 | 152.055 | 3.455 | 0.107 | 4.923 | 0.006 | 512.598 |
| 328 | 15 | 196.482 | 4.464 | 0.138 | 6.361 | 0.008 | 658.448 |
| 328 | 18 | 217.239 | 4.936 | 0.153 | 7.033 | 0.009 | 726.002 |
| 328 | 21 | 230.622 | 5.240 | 0.162 | 7.466 | 0.009 | 769.360 |
| 328 | 24 | 240.576 | 5.466 | 0.169 | 7.788 | 0.010 | 801.508 |
| 328 | 27 | 248.553 | 5.648 | 0.175 | 8.047 | 0.010 | 827.211 |
| 328 | 30 | 255.249 | 5.800 | 0.179 | 8.263 | 0.010 | 848.744 |
| 338 | 12 | 115.251 | 2.619 | 0.081 | 3.731 | 0.005 | 390.452 |
| 338 | 15 | 166.569 | 3.785 | 0.117 | 5.393 | 0.007 | 560.437 |
| 338 | 18 | 195.354 | 4.439 | 0.137 | 6.324 | 0.008 | 654.767 |
| 338 | 21 | 212.907 | 4.838 | 0.150 | 6.893 | 0.009 | 711.934 |
| 338 | 24 | 225.351 | 5.120 | 0.158 | 7.296 | 0.009 | 752.301 |
| 338 | 27 | 234.987 | 5.339 | 0.165 | 7.607 | 0.010 | 783.468 |
| 338 | 30 | 242.874 | 5.519 | 0.171 | 7.863 | 0.010 | 808.918 |

**Table (S3):** Calculation method of the amount of ethanol (Co-solvent), density of the mixture and mass of CO2 in mixture.

Calculating density of mixture in Specific temperature and pressure

After determined nsolute by this equation $y\_{2}^{'}=\frac{n\_{Solute}}{n\_{Solute}+n\_{Co2}+n\_{Eth}}  $is specified.

After that we must calculate solute by this equation. $n\_{solute}=\frac{C\_{s}V\_{s}}{M\_{s}}$

Cs: the solute concentration in the collection vial. (It is obtained from calibration curve)

Vs: volume of the collection vial

* Ms: mass of drug

According to added 3% mol of ethanol, so CO2 is 97%. Therefore, we can calculate nCO2 and neth in loop.

Calculating mole of mixture in loop by$ n\_{mix}=\frac{m\_{mix}}{M\_{mix}}$

Calculating mixture molar mass in loop by $M\_{mix}=0.03\*M\_{Eth}+0.97\*M\_{CO\_{2}}$

Calculating mixture mass in loop by $ρ\_{mix}=\frac{m\_{mix}}{V}$

V= 300 $μl$ vloum cell

Calculating mixture density in loop by bottom equations

$$ρ\_{mix}=\frac{ρ\_{CO\_{2}}ρ\_{Eth}}{x\_{Eth}ρ\_{CO\_{2}}+x\_{CO\_{2}}ρ\_{Eth}}$$