Exploring the polymorphism of sofosbuvir via mechanochemistry: effect of milling jar geometry and material

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Figure SI 1. Experimental patterns of form 1 (left), form A (middle) and form B(right).



Figure SI 2. Crystal structures of sofosbuvir form 1, A and B.



Figure SI 3. Visualization of the pores existing in form 1 (calculation of voids¹).

More details about the crystal structures can be found in our previous work related to sofosbuvir polymorphs.²

Evidence of presence of polar solvents in the glassy material of sofosbuvir obtained after milling



Figure SI 4. TGA of glassy material obtained after milling of sofosbuvir with MeOH.



Figure SI 5. TGA of glassy material obtained after milling of sofosbuvir with MeOH. Later it was proved that the water remained and formed a hydrate.

Kinetics of polymorphic transformation



Figure SI 6. Polymorphic transformations of sofosbuvir starting from form 1 in PP (right) with the addition of n butyl acetate. Milling experiments were performed $\eta=0.1 \mu l/mg$.



Figure SI 7. Polymorphic transformations of sofosbuvir starting from form 1 in SS (left) with in PP (right) with the addition of anisole. Milling experiments were performed η =0.1 µl/mg.



Figure SI 8. Polymorphic transformations of sofosbuvir starting from form 1 in PP jars with the addition of THF. Milling experiments were performed η =0.2 µl/mg.

DEM energy calculations

The geometry of each milling jar, which was used in DEM simulations, replicates the real jars used in experiments. The maximum displacement from the centre of the jar to either side was set to 1.5 cm and the milling jar was moved with a frequency of 25 Hz in horizontal direction.

By using the DEM approach, the position, velocity, acting forces, etc. were tracked for each individual milling ball. The total contact energy of the milling balls with the jar walls can be predicted by calculating the temporal development of the overall kinetic energy of the milling balls. The overall kinetic energy at any time step is defined as the sum of kinetic energies of both milling balls according to the following equation.

$$E_{sum} = \frac{1}{2}mv_1^2 + \frac{1}{2}mv_2^2$$

where *m* is the mass of each ball, v_1 and v_2 are their velocities. The mass of each ball is calculated from its diameter and density. Each simulation was run for up to 9 s in real time with a time step of 10⁻⁵ s. It was observed that the balls in each jar needed approximately 2 seconds to reach a steady state motion after which the maximal overall kinetic energy is relatively constant. For statistical averaging, the time interval from 4 to 9 s was used. A longer time interval (1000 s) was also tested, and the results are with the same statistical error, so the time of 9 s is sufficient to obtain representative values. Several initial positions of the milling balls were also tested, and no effect was observed.

In addition, we performed DEM simulations where we tested the effect of all properties of both jars (i.e., Young modulus) and no significant change of the overall kinetic energy was observed. Only small changes were found by changing the coefficient of restitution, which represents how much kinetic energy remains after a collision of two objects. As expected, the maximum overall kinetic energy slightly increases (30% in whole range) with increase of coefficient of restitution.



Figure SI 9. Effect of Young's modulus- no significant effect.



Figure SI 10. Effect of coefficient of restitution. Kinetic energy increases with increase of coefficient.

Particle number	N _p	2	[-]
Particle diameter	d _p	5	[mm]
Particle density	ρ _p	8000	[kg·m ⁻³]
Young's modulus (steel)	Y	$2 \cdot 10^{11}$	[Pa]
Young's modulus (PE)	Y	$2 \cdot 10^{9}$	[Pa]
Young's modulus (simulations)	Y	$2 \cdot 10^7 - 2 \cdot 10^{11}$	[Pa]
Poisson's ratio (steel)	v	0.29	[-]
Poisson's ratio (PE)	v	0.46	[-]
Coefficient of restitution	e	0.5	[-]
Sliding friction coefficient (steel/steel)	μ	0.7	[-]
Sliding friction coefficient (PE/steel)	μ	0.2	[-]
Time step	Δτ	$1 \cdot 10^{-7}$ - $1 \cdot 10^{-5}$	[s]

Table 2. Material properties of each jar, physical and mechanical data and operational conditions.

Calculation of probability for SS and PP jars

For the calculation of the probability of the ball to hit the powder if it is distributed on the surface of the jar, first we needed to calculate the surface of each jar. For the calculation of each jar surface, we used the real dimensions of the balls and the jars, and which are shown if **Figure SI 7**.

<u>SS jar:</u>

Surface of 2 spheres: $A_{SS \ sphere} = \alpha^* 2^* 4\pi r^2$, where r is the radius of the sphere and fraction of surface covered with a powder α

Surface of the SS jar: $A_{SS jar cup} = 4\pi r^2$, where r is the radius of the circle and h is the height of the cylinder

<u>PP jar:</u>

Surface of 2 spheres: $A_{SS \ sphere} = \alpha * 2 * 4\pi r^2$, where r is the radius of the sphere and fraction of surface covered with a powder α

Surface of the PP jar: $A_{PP jar cup} = \pi r^2 + 2 \pi r^2$

Considering the dimension of individual jars the ratio of probabilities P_{PP}/P_{SS} [= (A_{sphere} / A_{jar} _{cup})_{PP} / (A_{sphere} / A_{jar} cup)_{SS}], will be about 2 times higher in PP jar compared to SS jar.

Surface temperature measurements with thermal camera

Table S3. Measured surface temperature of SS jars after 0, 10, 20, 30, 40 and 60 minutes of milling.

Time (min)	T _{Jar 1} (°C)	Т _{Jar 2} (°С)	T _{Average} (°C)
0	20.9	23	22.0±1.5
10	25	24	24.5±0.7
20	25.5	25.8	25.7±0.2
40	26.2	26.1	26.2±0.1
60	27.8	27.3	27.6±0.4

Table S4. Measured surface temperature of PP jars after 0, 10, 20, 30, 40 and 60 minutes of milling.

Time (min)	T _{Jar 1} (°C)	T _{Jar 2} (°C)	T _{Average} (°C)
0	23.4	24.5	24.0±0.8
10	31.8	29	30.4±2.0
20	32.9	31.3	32.1±1.1
40	34.3	33.2	33.8±0.8
60	35.9	36	36.0±0.1



Figure SI 8. Photos of measured surface temperatures of SS and PP jars after 0, 10, 20, 30, 40 and 60 minutes of milling.

<u>Crystallographic data, thermal characterization, and interaction energies for sofosbuvir</u> <u>hydrate</u>

Empirical formula	$C_{22}H_{31}F_1N_3O_{10}P_1$
Formula weight	547.48
Crystal system	Orthorhombic
Space group	P2 ₁ 2 ₁ 2 ₁
Т(К)	120
Radiation	Cu Kα
a (Å)	9.187550(8)
b (Å)	13.996380(9)
c (Å)	20.528931(11)
α (°)	90
β (°)	90
γ (°)	90
V (ų)	2639.865(3)
Z	8
Refins. collected	57181
Indep. refins.	4741
GOF	1.0189
R1, wR2 [I > 2σ(I)]	0.0287, 0.0743
R1, wR2 (all data)	0.0290, 0.0747
Δρmax, Δρmin (e Å–3)	0.21, -0.27
CCDC number	2110412

Table SI 2. Crystallographic data and details of refinements of sofosbuvir hydrate.



Figure SI 11.a) Experimental and calculated XRD pattern of sofosbuvir hydrate, b) The unit cell of the hydrate which consists of 8 molecules, c) Visualization of hydrogen bonds formed by the water molecule with the sofosbuvir molecules.

The thermal stability of the hydrate was evaluated by DSC and TGA. Thermal analysis suggests that the hydrate is stable up to a temperature of 80 °C. As we can see from the crystal structure and the calculation of the interaction energies between water and the molecules of sofosbuvir , water plays a decisive role in the hydrate formation. Specifically, it forms three hydrogen bonds with sofosbuvir molecules, and the strength of the total interactions between water and the three different molecules of sofosbuvir were calculated to be -83.8, -56.7 and -40.8 kJ/mol each, indicating a strong connection. Therefore, the removal of the water molecules leads to full amorphization of the hydrate.



Figure SI 12. DSC thermograph of sofosbuvir hydrate.

Figure SI 13. TGA thermograph of sofosbuvir hydrate.



Figure SI 14. Calculated interaction energies between a molecule of water and the molecules of Sofosbuvir within radius 3.8 Å.

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