A solid-state NMR method for characterization of pharmaceutical eutectics

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Supplementary information

Materials and methods

Rivaroxaban was a generous gift from Alkem Pharma, India. Caffeic acid and coumaric acid were purchased from Hi Media, Mumbai.

Preparation of samples

Eutectics were prepared by liquid-assisted grinding method in which rivaroxaban and coformers were ground in 1:2 ratio using mortar and pestle. A mixture of ethanol and acetone (1:1 v/v) was added as a catalyst. The mortar and pestle provided the energy required for intermolecular hydrogen bonding interaction between rivaroxaban and coformers. The formation of eutectics was confirmed by DSC.

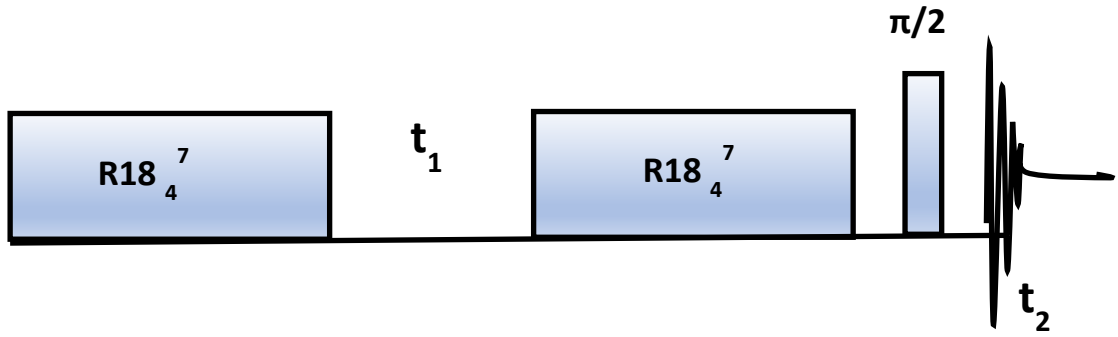
DSC was conducted on a Mettler Toledo DSC822e instrument by measuring the enthalpy change between 25 °C and 300 °C. The melting points obtained from the DSC curve of rivaroxaban, caffeic acid, and coumaric acid were 231.5 °, 225 °C, and 223 °C respectively. The melting point of rivaroxaban caffeic acid and rivaroxaban coumaric acid were 186°C and 176°C which confirmed the eutectic formation of rivaroxaban with coformers.[1]

Physical mixtures were prepared by physically mixing rivaroxaban and coformers in 1:2 ratio using a spatula.

Solid-State NMR

All the solid-state NMR experiments were performed on a Bruker AV 700 MHz spectrometer using 1.3 mm probe with a spinning frequency of 60 KHz. The 90° excitation pulse for proton was 1.8 µs. For DQSQ experiments, $R18^4_7$ symmetry-based pulse sequence is used for the excitation of DQ coherences with RF field 2.25 times spinning frequency.[2] 12 transients were collected for each of the 256 t_1 increments. The excitation and reconversion time was 66.67 µs. The recycle delay of rivaroxaban, caffeic acid, and coumaric acid were 80 s, 80 s, 30 s

respectively. The delay of eutectics and physical mixtures were 100 s. The pulse program of DQSQ experiment is given below.



Deconvolutions of the ^{1}H MAS spectra were carried out using the DMFIT program. [3] Uncertainties in the area of each signal were estimated from the Monte–Carlo error analysis included in the DMFIT program.

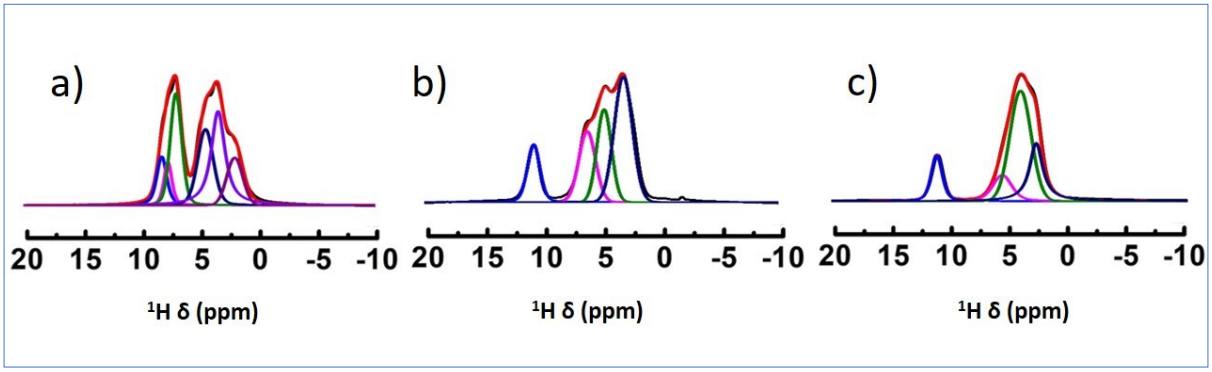


Fig. S1 Deconvoluted ^{1}H MAS spectra of a) rivaroxaban b) caffeic acid and c) coumaric acid

Table S1 Results of the deconvolution of the spectra of rivaroxaban and coformers

Rivaroxaban				Caffeic acid				Coumaric acid			
δ [a] (ppm)	Area (%)	Error [b] (%)	No of protons	δ [a] (ppm)	Area (%)	Error [b] (%)	No of protons	δ [a] (ppm)	Area (%)	Error [b] (%)	No of protons
8.2	9.5	0.04	2	12.3	14.2	0.17	1	12.6	12.7	0.06	1
7.6	6.6	0.04	1	8.5	21.0	0.33	2	8.0	12.5	1.8	1
6.9	22.0	0.38	4	7.3	24.0	0.36	2	6.7	50.0	0.23	4
4.4	20.4	0.32	4	5.9	40.6	0.16	3	5.6	24.5	0.18	2
3.4	29.4	0.32	5								
1.9	11.9	0.04	2								
Total protons			18	Total protons			8	Total protons			8

[a] isotropic chemical Shift. [b] Uncertainties in area of each signal were estimated by Monte-Carlo error analysis using DMFIT software.

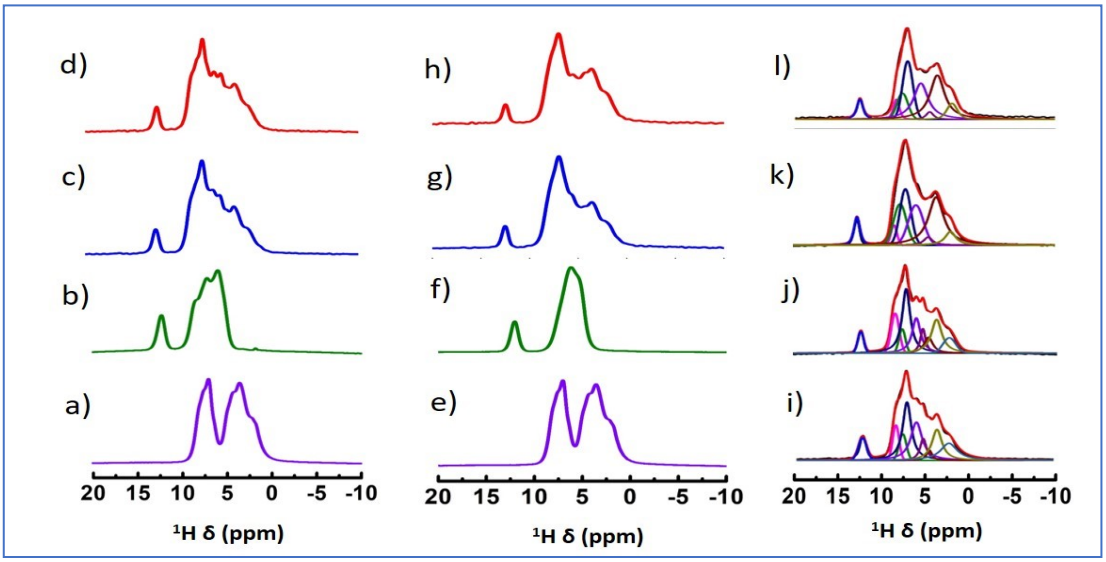


Fig. S2 ^{1}H MAS spectra of a) rivaroxaban, b) caffeic acid, c) rivaroxaban caffeic acid eutectic, d) rivaroxaban caffeic acid physical mixcture, e) rivaroxaban, f) coumaric acid, g) rivaroxaban coumaric acid eutectic and h) rivaroxaban coumaric acid physical mixcture. Deconvoluted ^{1}H MAS spectra of i) rivaroxaban caffeic acid eutectic, j) rivaroxaban caffeic acid physical mixture, k) rivaroxaban coumaric acid eutectic and l) rivaroxaban coumaric acid physical mixture recorded on 700 MHz spectrometer at 60 KHz spinning frequency.

Table S2 Results of the deconvolution of the spectra of eutectics

rivaroxaban caffeic acid eutectic				rivaroxaban coumaric acid eutectic			
δ [a](ppm)	Area (%)	Error [b] (%)	No of protons	δ [a](ppm)	Area (%)	Error [b] (%)	No of protons
12.3	6.0	0.14	2	12.6	6.1	0.15	2
8.4	8.6	0.99	3	8.3	3.4	0.15	1
7.6	7.3	1.68	3	7.6	14.9	2.04	5
7.1	20.9	0.14	7	6.9	17.6	1.12	6
6	14.1	1.21	5	5.8	17.0	0.15	6
5.2	9.8	1.76	3	4.4	3.0	3.7	1
4.5	2.9	2.81	1	3.5	31.6	0.15	11
3.6	15.5	0.14	5	1.8	6.1	0.15	2
2.2	14.3	0.14	5				

[a] isotropic chemical Shift. [b] Uncertainties in area of each signal were estimated by Monte-Carlo error analysis using DMFIT software.

Table S3 Results of the deconvolution of the spectra of physical mixtures

rivaroxaban caffeic acid physical mixture				rivaroxaban coumaric acid physical mixture			
δ [a](ppm)	Area (%)	Error [b] (%)	No of protons	δ [a](ppm)	Area (%)	Error [b] (%)	No of protons
12.3	4.4	0.11	2	12.6	5.1	0.13	2
8.3	10.7	0.11	4	8.3	4.5	0.13	2
7.5	5.2	0.11	2	7.6	8.9	4.48	3
7.1	26.5	0.11	9	6.9	18.5	1.08	6
5.9	15.0	0.73	5	5.4	24.2	2.05	8
5.2	6.3	0.11	2	4.4	2.5	2.28	1
4.5	6.9	1.61	2	3.5	29.6	0.13	10
3.6	17.9	0.11	6	1.8	6.4	0.13	2
2.2	6.6	0.11	2				

[a] isotropic chemical Shift. [b] Uncertainties in area of each signal were estimated by Monte-Carlo error analysis using DMFIT software.

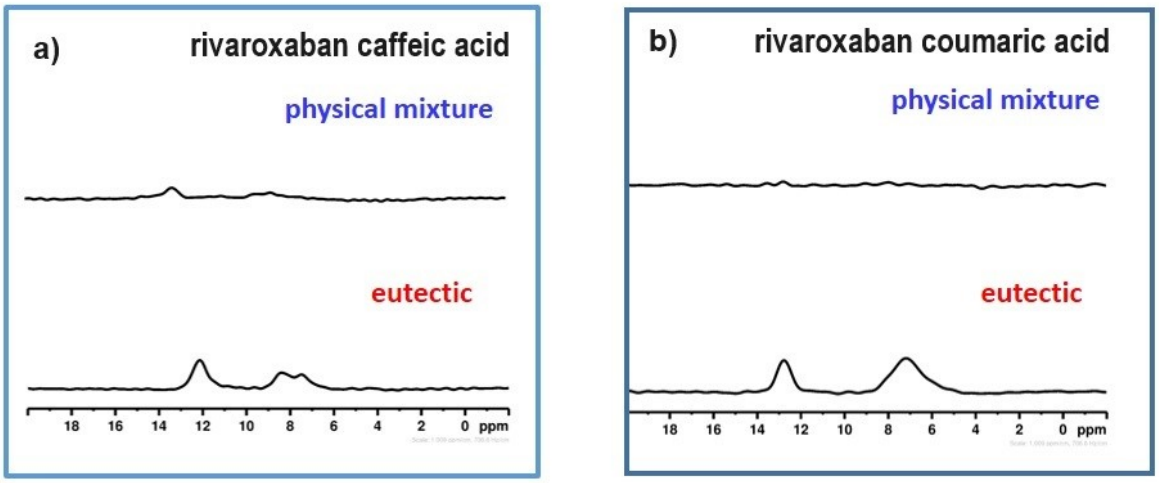


Fig. S3 a) slice extracted from the DQSQ spectra of rivaroxaban caffeic acid eutectic and physical mixture at 20.56 ppm and b) slice extracted from the DQSQ spectra of rivaroxaban coumaric acid eutectic and physical mixture at 20.71 ppm. The strong peaks are only evident in eutectic and not the physical mixtures.

References

(1) Shaligram, P. S.; George, C. P.; Sharma, H.; Mahadik, K. R.; Patil, S.; Vanka, K.; Arulmozhi, S.; Gonnade, R. G. *CrystEngComm,* 2023,**25**,3253-3263.
(2) Nishiyama, Y.; Agarwal, V.; Zhang, R. *Solid State Nucl. Magn. Reson,* 2021, **114**, 101734.
(3) Massiot, D.; Fayon, F.; Capron, M.; King, I.; Le Calvé, S.; Alonso, B.; Durand, J. O.; Bujoli, B.; Gan, Z.; Hoatson, G.. *Magn. Reson. Chem,* 2002, **40**, 70–76.