

Mechanochemical Synthesis of Brexpiprazole Cocrystals to Improve Its Pharmaceutical Attributes

Mohsin R Arabiani^{a,c*}, Anurag Lodagekar^b, Balvant Yadav^b, Rahul B Chavan^a,

Nalini R Shastri^b, Parva Y Purohit^a, Pragna Shelat^d, Divyang Dave^{d*}

^a*Global IP, Amneal Pharmaceuticals Pvt. Ltd, Ahmedabad.*

^b*Solid State Pharmaceutical Research Group (SSPRG), Department of Pharmaceutics,
National Institute of Pharmaceutical Education and Research (NIPER), Hyderabad, India*

^c*Kadi Sarva Vishwavidyalaya, Gandhinagar, Gujarat, India*

^d*K. B. Institute of Pharmaceutical Education and Research, Kadi Sarva Vishwavidyalaya,
Gandhinagar, Gujarat, India*

*Corresponding authors. Divyang Dave and Mohsin R Arabiani

Tel. +91-79-67778376

Fax. +91-79-67778315

E-mail: mohsinr@amnealindia.com; mohsinalmighty@gmail.com; dave.kbiper@gmail.com

Address: Amneal Pharmaceuticals India, 901 – 911, Iscon Elegance, Nr. Hotel Crown Plaza,
S. G. Highway, Ahmedabad – 380015, Gujarat, India

Electronic supplementary information

Table S1 Summary of screening study

Samples	ΔpK_a	Cocrystal or salt formation	
		Predicted outcome	Experimental outcome
BREX: succinic acid	2.82	Salt-cocrystal hybrid	Yes
BREX: oxalic acid	7.2	Salt	No
BREX: malic acid	5.0	Salt	No
BREX: sebacic acid	3.7	Salt	No
BREX: tartaric acid	5.53	Salt	No
BREX: benzoic acid	4.22	Salt	No
BREX: caffeic acid	3.8	Salt	Eutectic
BREX: p-coumaric acid	4.42	Salt	No
BREX: cinnamic acid	3.98	Salt	No
BREX: ferulic acid	3.8	Salt	No
BREX: gallic acid	3.92	Salt	No
BREX: ascorbic acid	4.25	Salt	No
BREX: vanillic acid	3.91	Salt	No
BREX: catechol	-1.06	Cocrystal	Yes
BREX: resorcinol	-0.73	Cocrystal	No
BREX: phloroglucinol	-0.03	Cocrystal	No

Note: Yes- single melting in DSC with unique peaks in PXRD analysis of samples indicate cocrystal formation;
No- multiple melting peaks without unique peaks in PXRD

Table S2 Summary of thermal analysis by DSC

Samples	Onset (°C)	Peak (°C)	Enthalpy (J/g)
BREX	182.75	184.75	-74.94
CAT	103.73	106.06	-173.29
SU	187.11	190.12	-203.21
BREX: CAT	159.01	161.34	-58.9
BREX: SU	154.23	156.08	-97.82

Table S3 Dissolution parameters for plain BREX, physical mixture (PM) and cocrystals

Dissolution parameter	BREX	BREX: SU	BREX: CAT	PM1	PM2
$f_2^{\#}$	-	30.76	24.31	48.32	63.28
DE ₁₅	36.04	57.11	65.27	46.51	37.29
DE ₁₂₀	53.96	79.37	86.79	65.07	58.68

$\#$ with reference to plain BREX

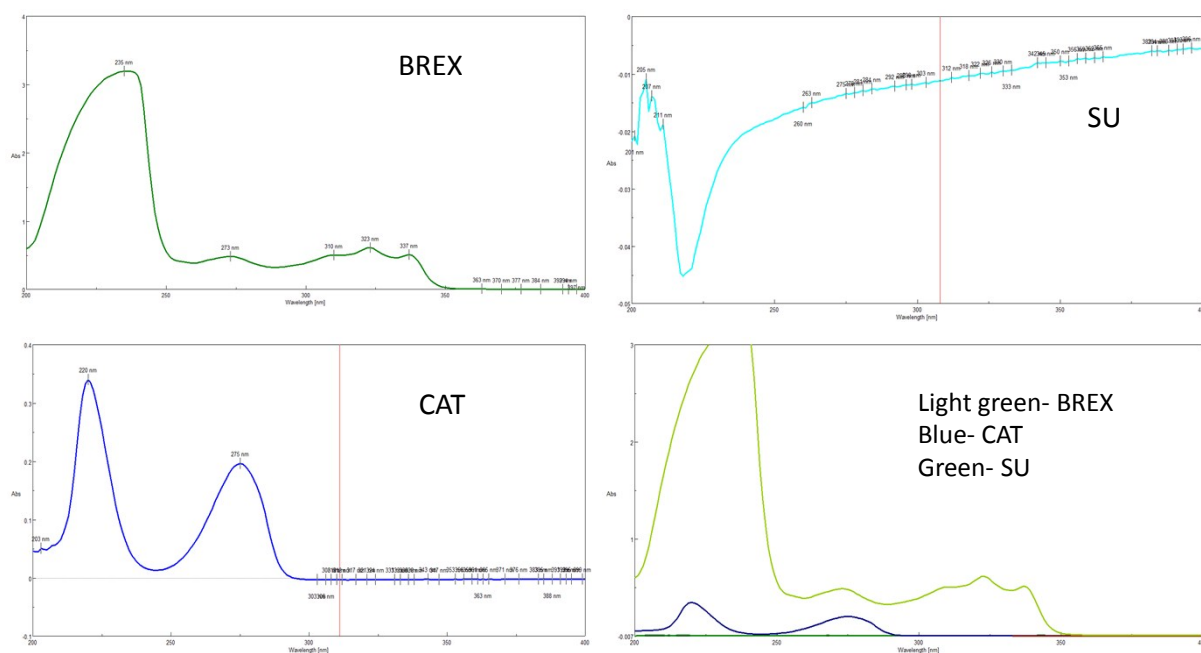


Figure S1 UV spectra of individual components and overlay. BREX- brexpiprazole; CAT- catechol and SU- succinic acid

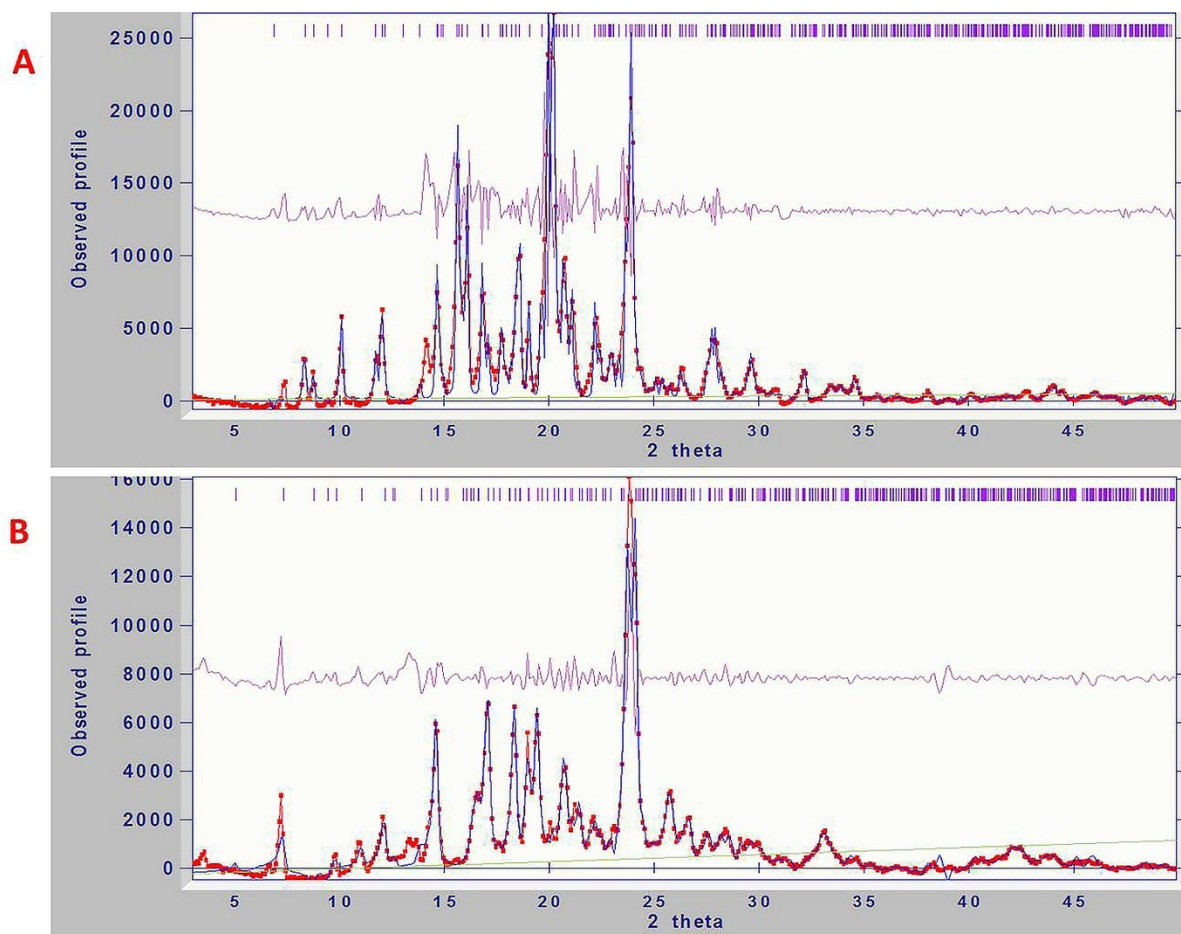


Figure S2 Pawley profile fitting for PXRD pattern of BREX: CAT cocrystal (A) and BREX: SU cocrystal (B)

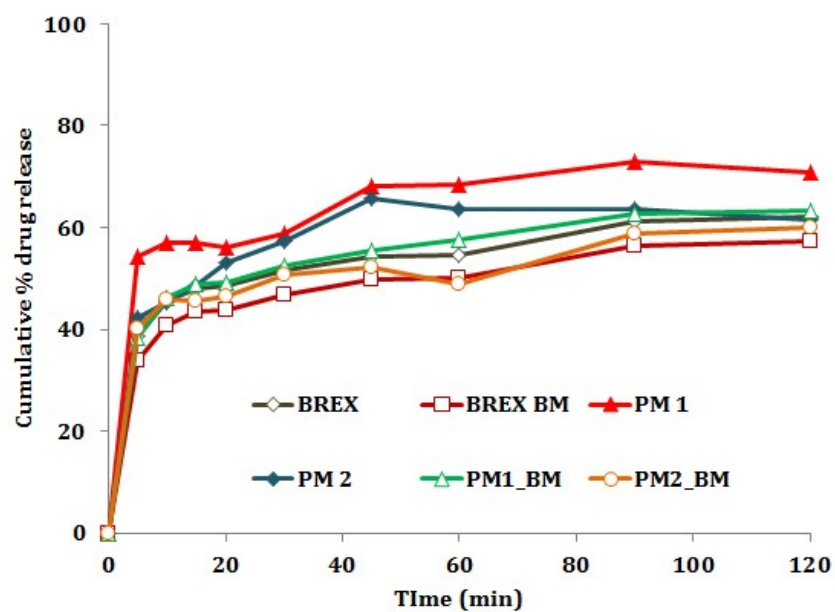


Figure S3 Dissolution profile comparison of plain un-milled drug (BREX) and its physical mixtures with coformers (PM1 and PM2) and the ball milled drug (BREX BM) and its physical mixtures (PM1_BM and PM2_BM)