Supplementary Information (SI) for CrystEngComm.

Mechanochemical synthesis of drug–drug eutectics of the anthelmintic drug, praziquantel, with NSAIDs

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Supporting Information

Materials & Methods

All the reagents and solvents used for the material synthesis were purchased from commercial sources (Aldrich, Hyderabad, and TCL, Tokyo) and used as received.

Mechanochemical Screening: Different compositions of praziquantel (mole fraction of PZQ from 0.1 to 0.9), along with four anti-inflammatory drugs such as ibuprofen, aspirin, paracetamol, and indomethacin, were thoroughly ground using a mortar and pestle for 30 minutes. These screening experiments were performed in duplicate and repeated at least 5 times to ensure reproducibility. The compositions identified through this preliminary screening were subsequently subjected to scale-up studies using ball milling. The consistency in the eutectic formation and their stability were validated by melting-point determination and hot-stage microscopy (HSM) analysis.

(*The 30-minute duration was selected based on a series of trial experiments conducted at 15, 30, and 45 minutes. The 15-minute experiments did not produce reproducible results or a clear melting event characteristic of the eutectics. In contrast, both the 30- and 45-minute experiments yielded consistent, comparable results, allowing reliable determination of the eutectic compositions and their unique melting points*.)

Hot-stage microscopy: The thermal events were measured using an optical transmission microscope (Leica DM 2500 P) equipped with a Mettler Toledo hot stage and a wide zoom camera. All compositions of the drug-drug mixture were analysed, and melting points were recorded using an optical and hot-stage microscope within a temperature range of 30-300 ℃ and a heating/cooling rate of 2 ℃/min. The samples were placed on a microscope slide and placed in the hot stage, where the melting was observed.

Differential Scanning Calorimetry (DSC): The eutectic points were determined using DSC thermograms obtained using a Mettler Toledo DSC and analysed using STARe software. We used aluminium crucibles containing roughly 5-7 mg of sample in a dynamic nitrogen environment (40 mL/min) and a heating rate of 10 ℃/ min in the temperature range of 30-160 ℃.

X-ray powder diffraction (PXRD): The diffraction patterns were collected at room temperature on a Philip's X'Pert pro using Cu K_α radiation (λ=1.54060A Å) in the 2θ range of 10-35 ° (step size 0.0330°; time/step:18.8700s 40mA, 45Kv)

Fourier-transform infrared spectroscopy (FT-IR): The spectra of solid phases were collected on a Bruker Alfa-E Unit. Twenty-five scans were collected for each sample at a resolution of 4 cm^{-1} over a wavenumber region of 4000 to 400 cm^{-1}.

Scanning Electron Microscope (SEM): Micrographs were obtained using a Hitachi Tabletop JEOL 500SL scanning electron microscope operated in the range of 5-30kV. The samples were prepared by powder tapped in a carbon double-sided adhesive tape fixed on the sample holder.

Dissolution: The apparent solubility was measured to assess the impact of eutectic formation on drug solubility enhancement. The solubility of the drug-drug combination was evaluated in 10mL of Milli-Q water using a pelletized sample on a bench-top shaker. Pellets were prepared by separately weighing 300mg praziquantel and all four eutectics, along with 2.5% sodium starch glycolate and compressed them under a hydraulic press at a total pressure of 100 $kg/cm^{2.}$ Bench top shaker was used for continuous agitation of samples under controlled speed and temperature conditions. To ensure uniform mixing, the shaker was operated at 100 rpm with orbital shaking. The samples were placed in conical flasks, secured properly to prevent spillage and shaken for 1 hour. After 30 minutes and 60 minutes, 2 mL of the solution was collected using a syringe filter with a 0.2 µm pore size. The filtered samples were analysed using HPLC to determine the percentage availability of the drug.

Stability of the eutectic combinations: In accordance with ICH recommendations for intermediate-stability testing, samples were stored at 30 °C ± 2 °C and 65% RH ± 5% RH for 6 months. In our study, the eutectic mixtures were kept in a sealed desiccator containing a saturated NaCl solution, a commonly used and reliable method for maintaining a relative humidity of approximately 75% at controlled temperatures. The desiccator was maintained at 30 °C.

High-performance liquid chromatography (HPLC): The analysis was conducted using a Shimadzu HPLC system (Shimadzu, Japan) consisting of binary mobile phase delivery pumps (LC-20, Shimadzu, Japan) equipped with a photodiode array (PDA) detector (SPD-20AC HT, Shimadzu, Japan). The chromatographic separation was performed using a C18 analytical column (4.6 × 250 mm, 5µm). The experiment was conducted using a binary mobile phase consisting of acetonitrile and water (60:40, V/V) at a column temperature of 30°C. the run time was set to 15 minutes with a flow rate of 1ml/min. a sample volume of 10µL was injected, and absorbance measurements were taken at a fixed wavelength of 210 nm. The retention time of PZQ was approximately 6.13 minutes with a stabilised pressure of 79 Kgf/cm^2. The stock solution of praziquantel was prepared by dissolving 100mg of praziquantel in an acetonitrile-water mixture (60:40) to obtain a 100 ml solution. The standard solution was prepared by

diluting aliquots of the stock solution to achieve concentrations ranging from 100 ppm to 500 ppm. The calibration curve was constructed by plotting the peak areas obtained at a wavelength of 210 nm against the injected concentration. The solution collected during dissolution was used as the sample solution for HPLC analysis.

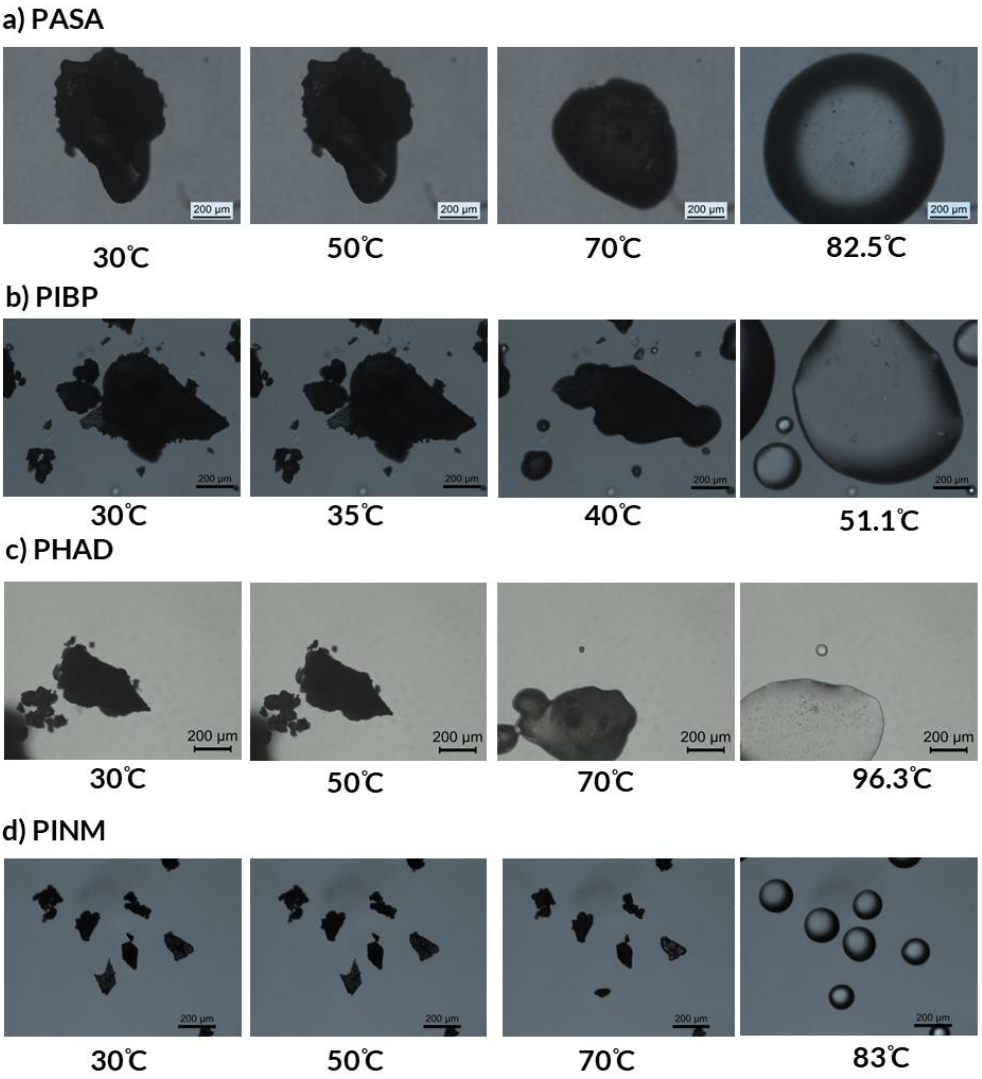


Fig. S1 Hot stage microscope images of the a) PASA; b) PIBP; c) PHAD, and d) PINM

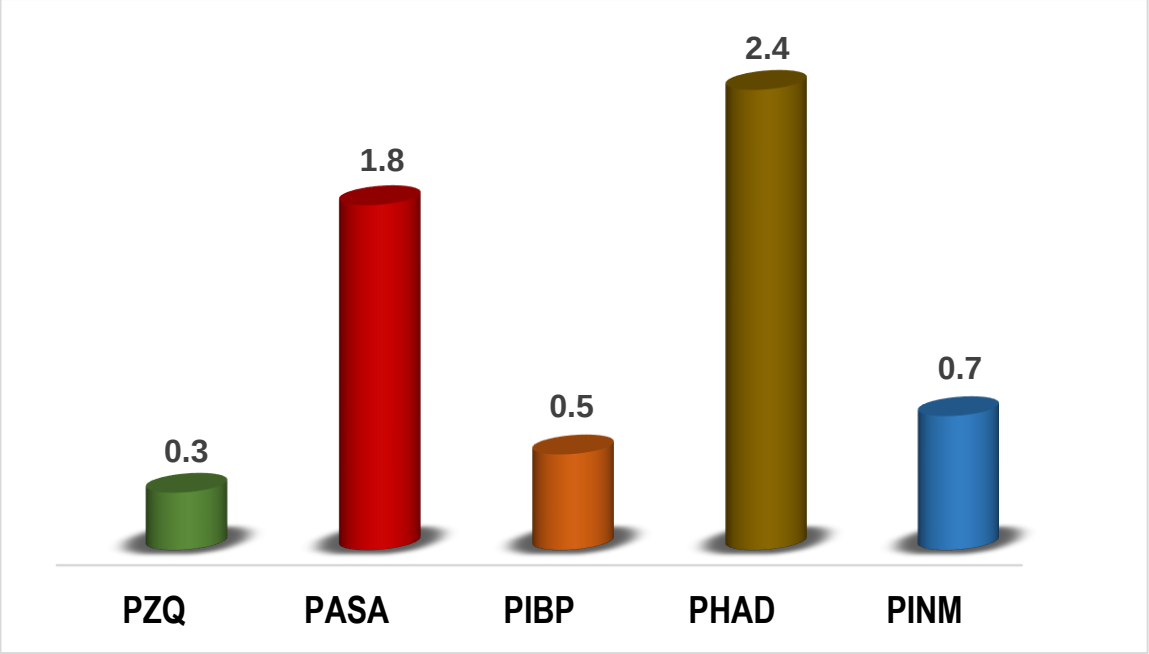


Fig. S2 Thermodynamic (equilibrium) solubility of PZQ and the eutectic mixtures determined after 24 hours. Solubility is provided in mg/mL.

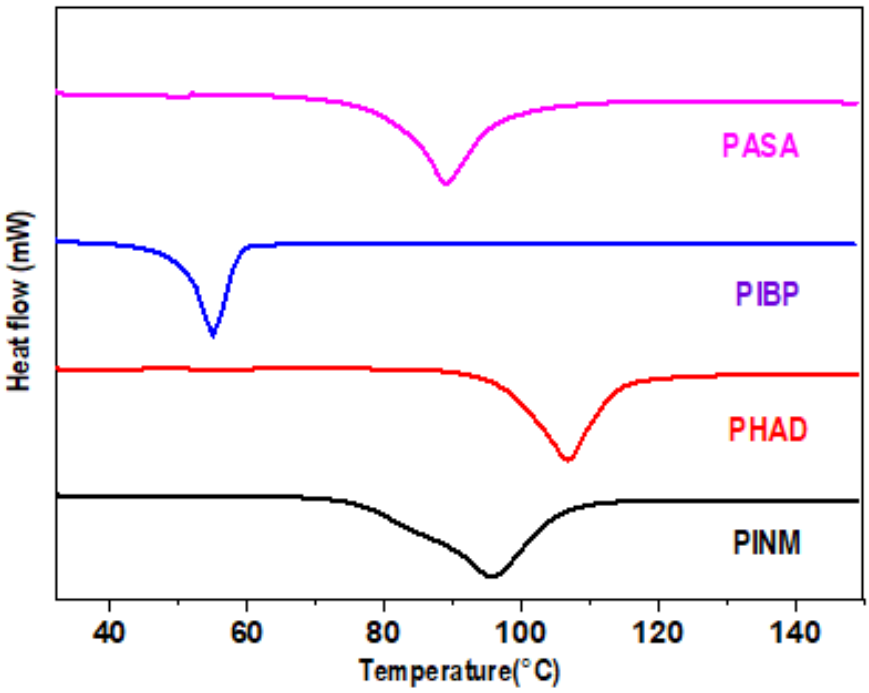
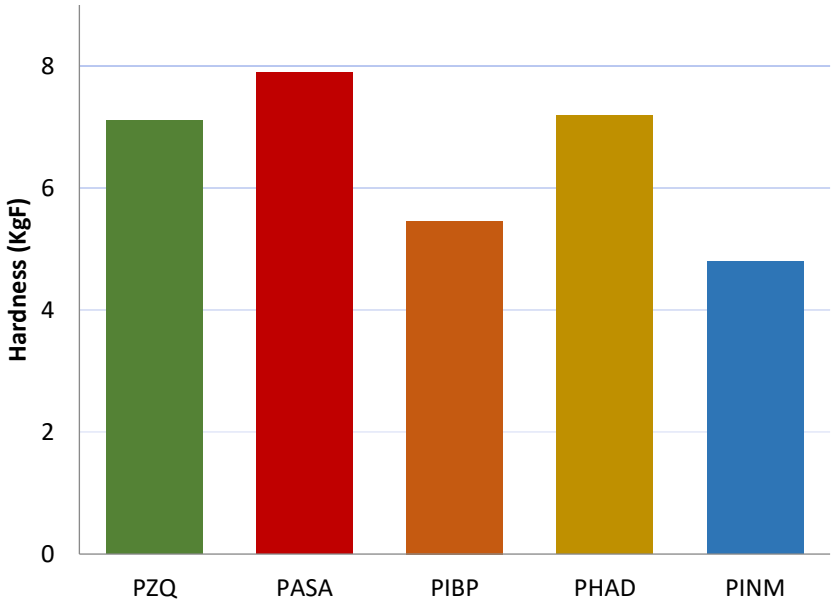


Fig. S3 The DSC thermogram of the material left after the dissolution studies, highlighting the stability of the eutectics.

Table S1 The IR peaks of the eutectic components and the mixtures. The retention of the individual peaks indicates the formation of the eutectics. The peaks are mentioned in wavenumber (cm^{-1}).

Compounds	Characteristic IR Peaks	Eutectics	
Prazequental	• 2932 C–H stretching • 2855 C–H stretching • 1648/1627 C=O stretching • 1457/1421 C–$C_{(aromatic)}$ stretching		
Aspirin	• 3300 O–H $_{(COOH)}$ stretching • 1684 C=$O_{(COOH)}$ stretching • 1752 C=$O_{(Ester)}$ stretching • 1605 C–$C_{(aromatic)}$ stretching	2933 2855 1753 1691 1648 1626 1456 1421	PASA
Paracetamol	• 3327 O–H $_{(COOH)}$ stretching • 3100-3400 N–H stretching (broad) • 1651 C=O stretching • 1609/1564 C–$C_{(aromatic)}$ stretching	3330 2933 2856 1650 1626 1609 1564	PHAD
Ibuprofen	• 3300 O–H stretching (broad) • 3000 C–$H_{(aromatic)}$ stretching • 2874 C–$H_{(alkyl)}$ stretching • 1712 C=O stretching • 1507 C–$C_{(aromatic)}$ stretching	2930 2863 1713 1650 1628 1508 1451 1421	PIBP
Indomethacin	• 3022 C–$H_{(aromatic)}$ stretching • 2950 C–$H_{(alkyl)}$ stretching • 1716 C=$O_{(COOH)}$ stretching • 1690 C=$O_{(amide)}$ stretching • 1589 C–$C_{(aromatic)}$ stretching	2930 2854 1715 1649 1626 1567 1447 1419	PINM



Fig, S4. Hardness of the tablet prepared at 75 kg/cm^2 of pressure.

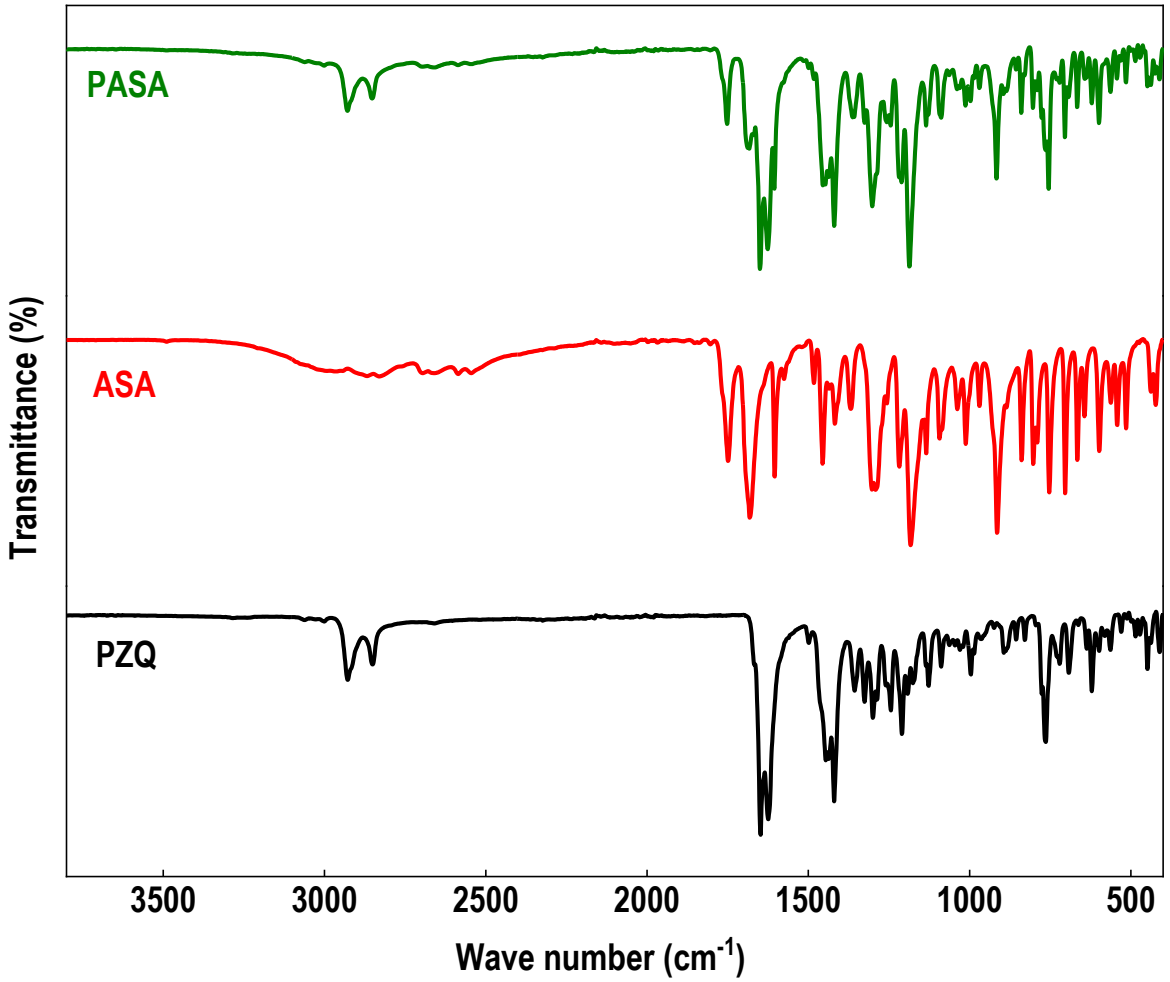


Fig. S5 IR spectrum of the eutectic mixture and its components for PASA

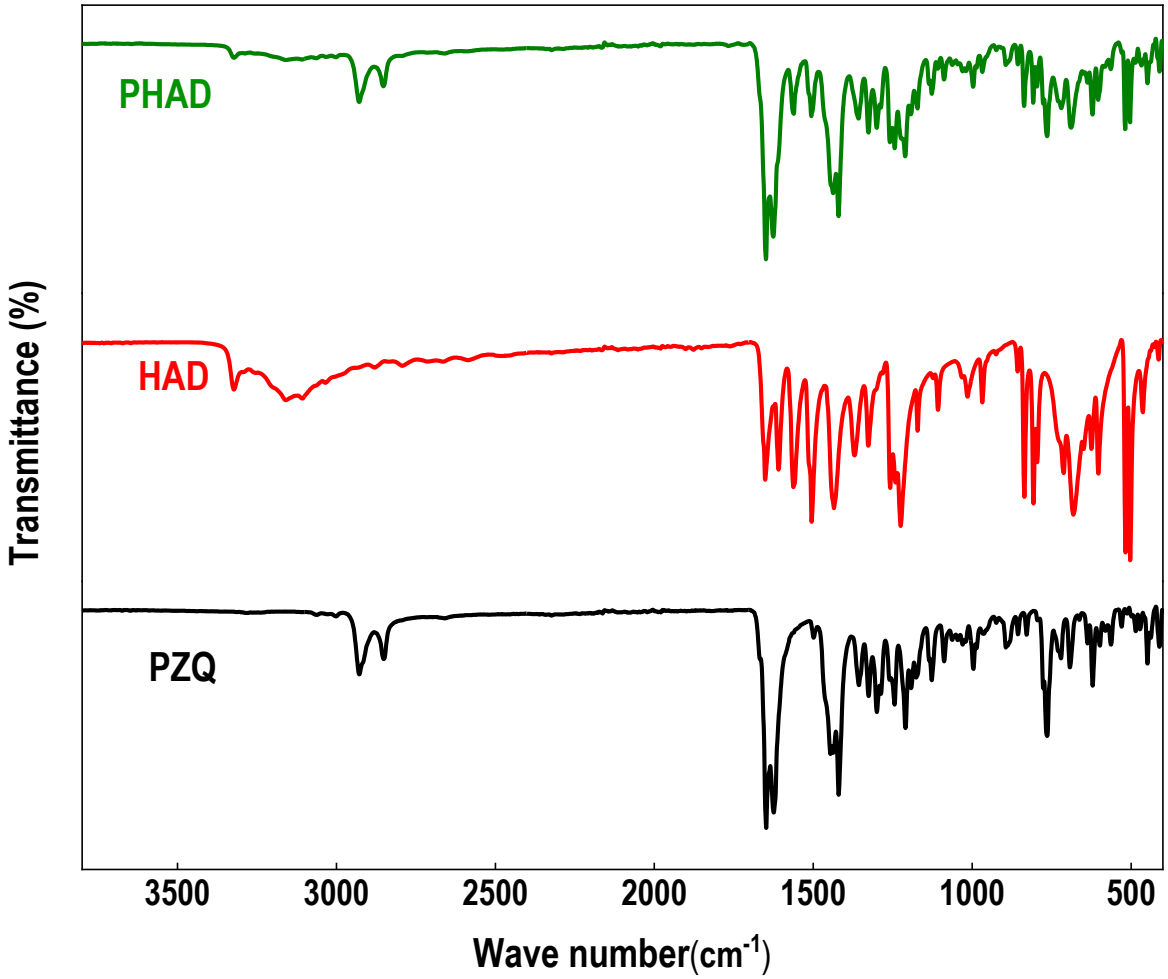


Fig. S6 IR spectrum of the eutectic mixture and its components for PHAD

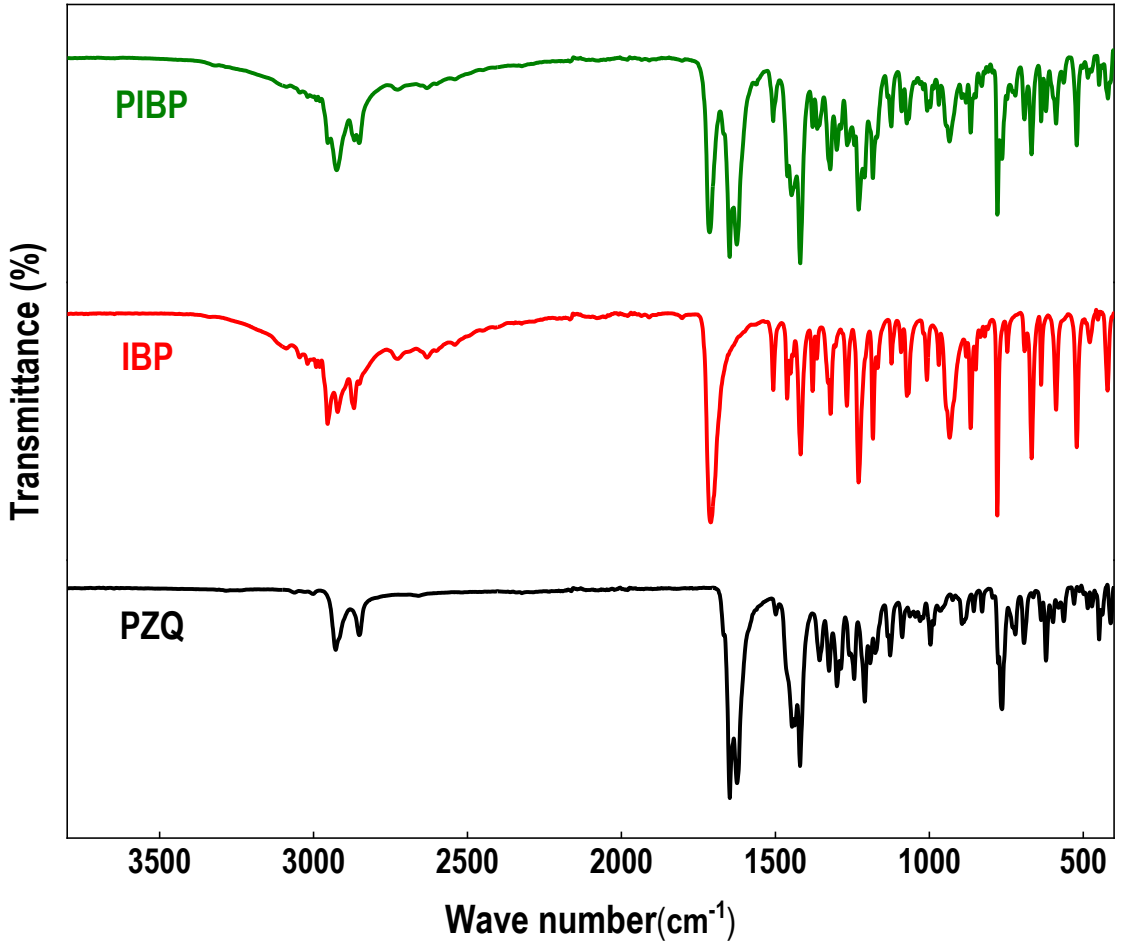


Fig. S7 IR spectrum of the eutectic mixture and its components for PIBP

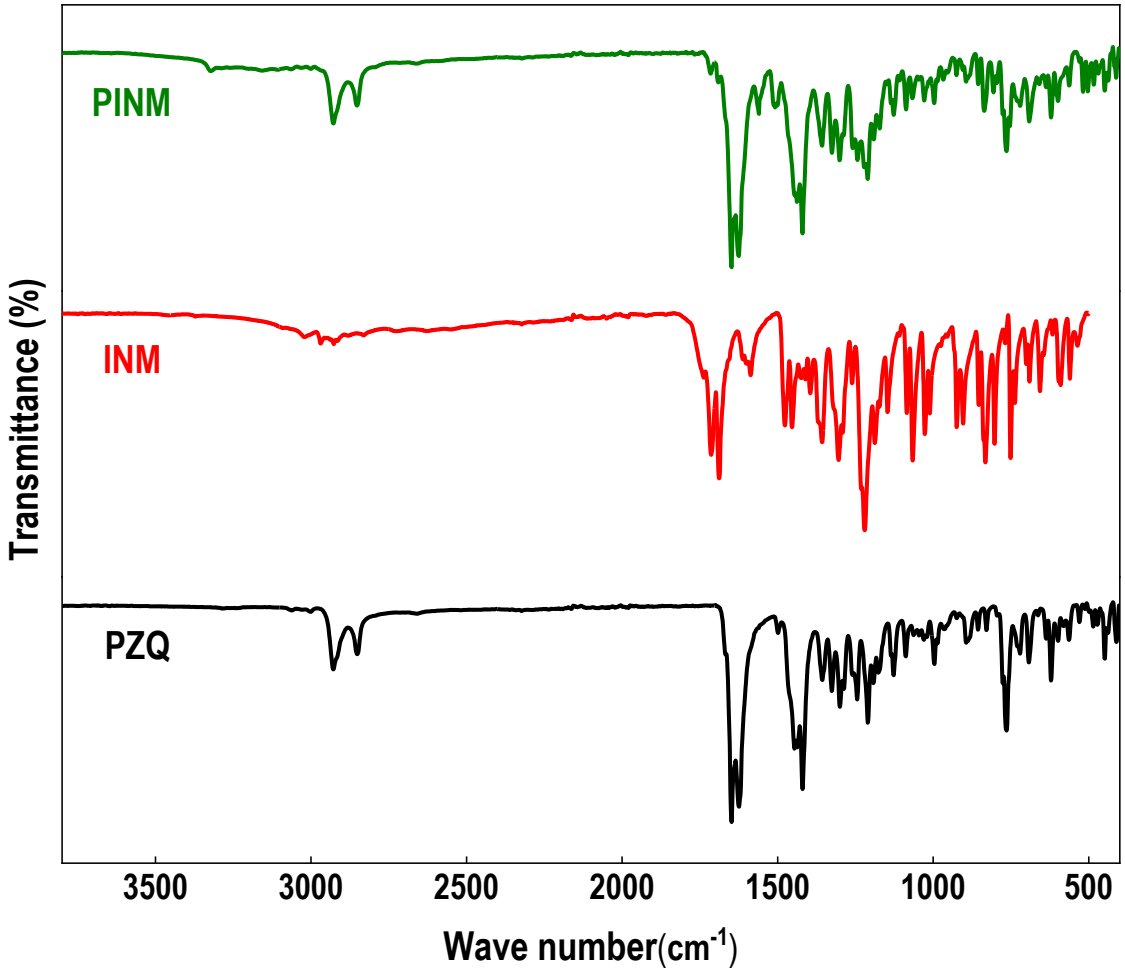


Fig. S8 IR spectrum of the eutectic mixture and its components for PINM

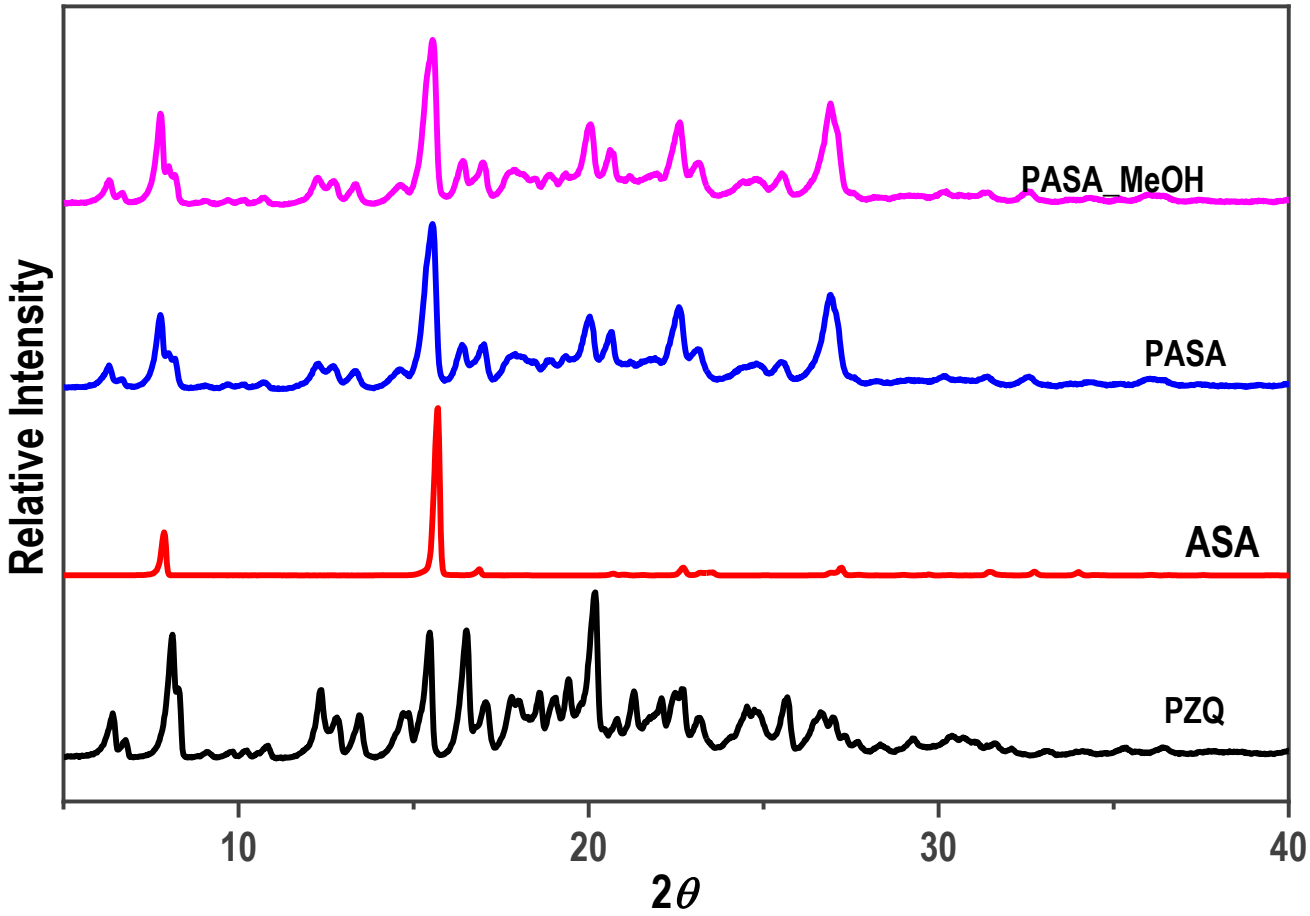


Fig. S9 PXRD patterns of eutectic mixture PASA, prepared by neat grinding and in the presence of methanol, along with the pure components.

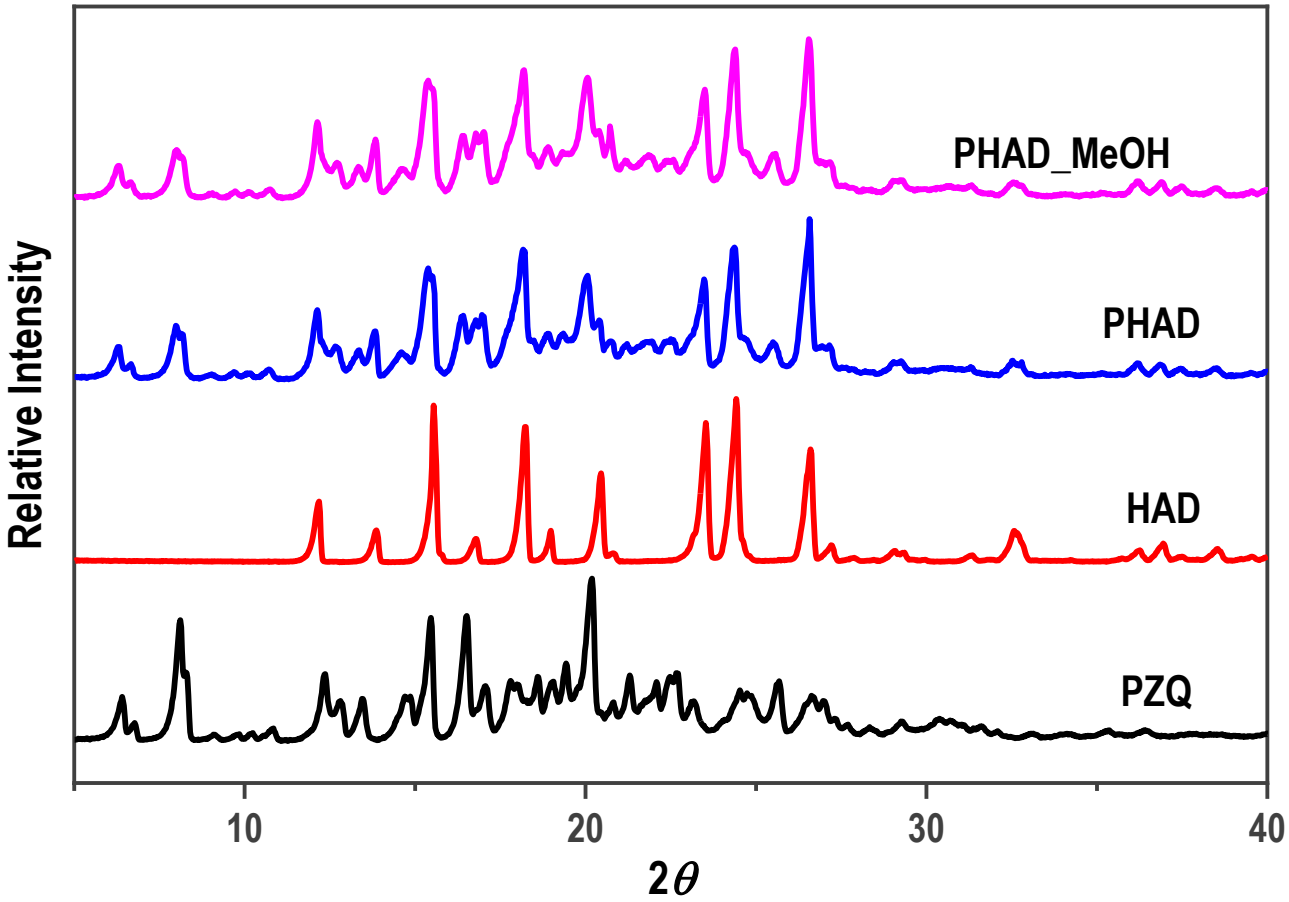


Fig. S10 PXRD patterns of eutectic mixture PHAD, prepared by neat grinding and in the presence of methanol, along with the pure components.

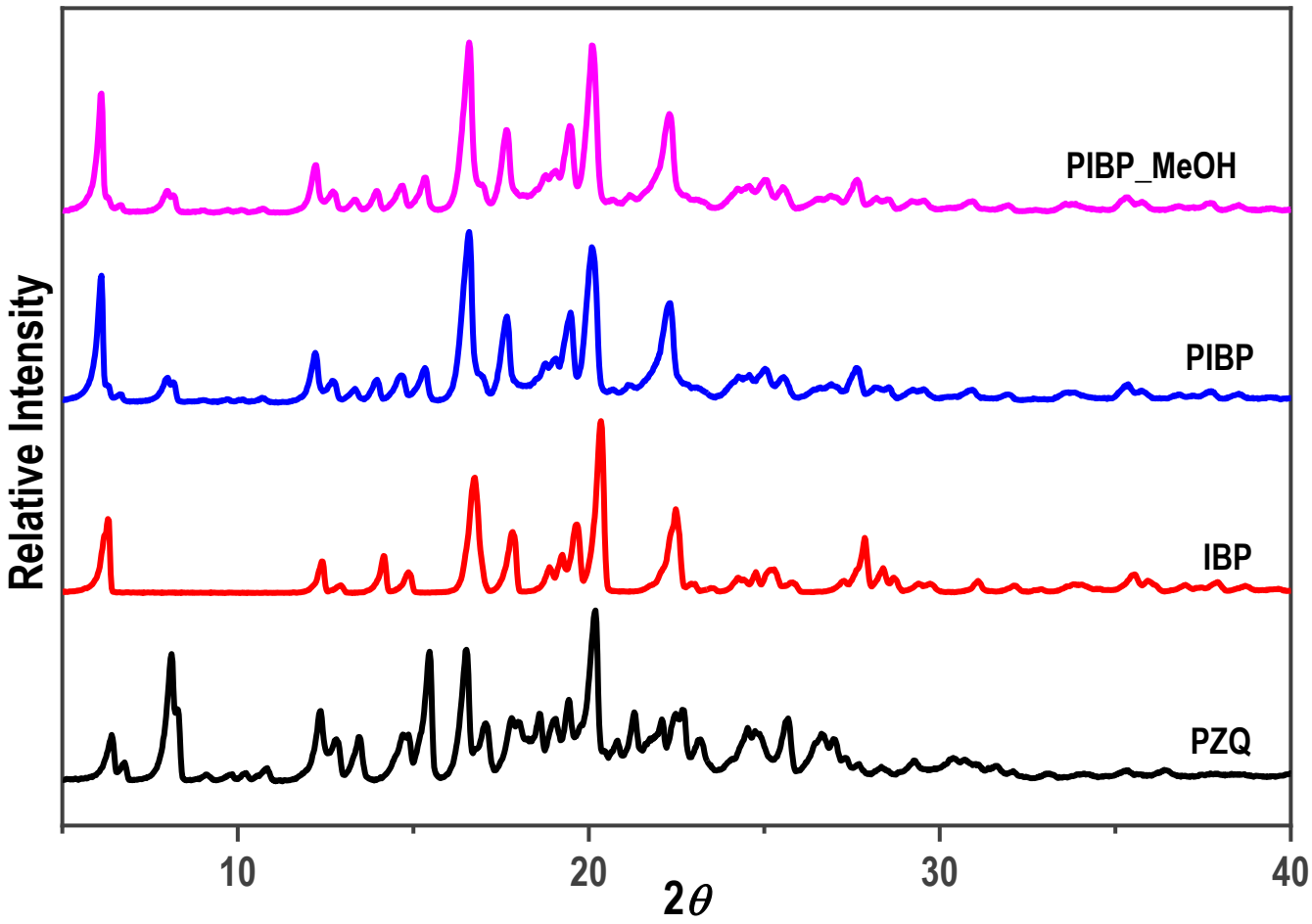


Fig. S11 PXRD patterns of eutectic mixture PIBP, prepared by neat grinding and in the presence of methanol, along with the pure components.

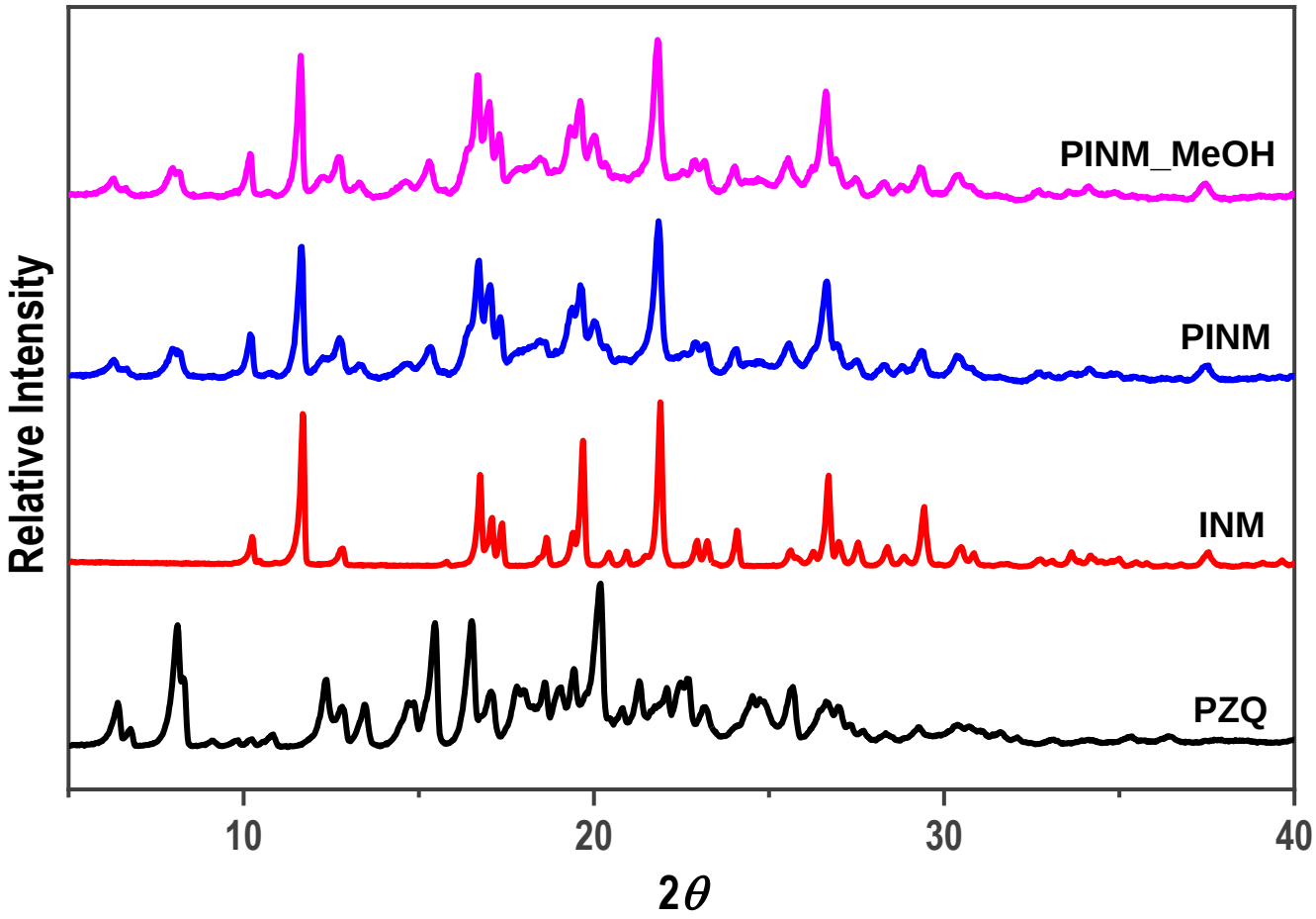


Fig. S12 PXRD patterns of eutectic mixture PINM, prepared by neat grinding and in the presence of methanol, along with the pure components.