

Characterization of donepezil prepared by cogrinding with salicylic acid and *p*-aminobenzoic acid

Weenawan Somphon*, Sirimol Makatan

Department of Chemistry, Faculty of Liberal Arts and Science, Kasetsart University, Kamphaeng Saen Campus, Nakhon Pathom 73140 Thailand

*Corresponding author, e-mail: faaswnw@ku.ac.th

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ABSTRACT: Two systems for the formation of cocrystals of donepezil were investigated using donepezil hydrochloride and donepezil solvate with salicylic acid and *p*-aminobenzoic acid. The donepezil solvate was prepared through an acid-base reaction between a hydrochloride salt and a base in methanol. Donepezil HCl (DH) and the solvate with salicylic acid and *p*-aminobenzoic acid (PABA) at 1:1 molar ratios were prepared using the cogrinding method. Cocrystals were characterized using attenuated total reflection-FTIR spectroscopy (ATR-FTIR), nuclear magnetic resonance spectroscopy (^{13}C and ^1H NMR), Powder X-ray diffraction, and differential scanning calorimetry. These results indicate that the cogrinding process could induce cocrystal formation in donepezil systems through a simple process that allows for rapid screening of cocrystals of donepezil.

KEYWORDS: donepezil hydrochloride, donepezil solvate, pharmaceutical solids, screening, spectroscopy

INTRODUCTION

The efficiency of an oral drug is dependent on its physical and chemical properties. One of the challenges in the drug development processes is to improve the performance and physicochemical properties of oral delivery of solid state drugs^{1–3}. Drugs or other active pharmaceutical ingredients (APIs) typically exist in several solid forms such as polymorphs, hydrates, solvates, salts, cocrystals, and amorphous solids^{4,5}. Cocrystal formation is one technique used in the development of new oral solid state forms of APIs^{6,7}. Pharmaceutical cocrystals are a subclass of cocrystals that have been defined by the US Food and Drug Administration (FDA), as APIs (neutral or ionized) and excipients (or coformers) present at a stoichiometric ratio in a single crystal lattice. Mixtures of APIs and coformers can form cocrystals (neutral molecules), salts (proton transfer charged molecules), and cocrystal salts (charged and neutral molecules in a compound). Cocrystals of APIs have been optimized to have greatly improved physicochemical properties, such as solubility, stability, bioavailability, and hygroscopicity. Cocrystallization can generate new crystal structures and may produce forms that provide properties beneficial for an oral dosage drug^{8–11}. To date, most of the literature on cocrystals of APIs has focused on poorly soluble market drugs^{12–14}. Industrial processing has

primarily concentrated on producing neutral drugs that contain an amine, examples are fexofenadine and paroxetine. These drugs have typically been crystallized with HCl to increase their solubility in water^{15,16}. However, undesirable side effects in the stomach can occur with these preparations. We are interested in the development of a method to form cocrystals of an ionized API. Previous studies have shown that there are opportunities for improving the physical properties of solid forms of drugs such as fluoxetine HCl (Prozac)¹⁷, Ivabradine HCl¹⁸, and tramadol HCl¹⁹. Cocrystallization of drug salts has a number of advantages including providing improved stability, solubility, and dissolution rate.

Donepezil HCl (DH) is used to treat Alzheimer's disease (AD) and is a reversible acetylcholinesterase inhibitor²⁰. Donepezil has improved the cognitive function of patients with mild-to-moderate AD diseases. This drug is considered safe and patients have shown a high tolerance to extended treatment^{21,22}. However, the high absorption and high lipophilicity of DH may cause side effects in the gastrointestinal system²³. Furthermore, the DH crystal structure is unstable and can be transformed into several anhydrous and hydrates forms^{24–27}. These crystal transformations can result in polymorphs with different chemical and physical properties, compared to the original DH crystals, resulting in altered bioavailability. In addition, DH has an extremely

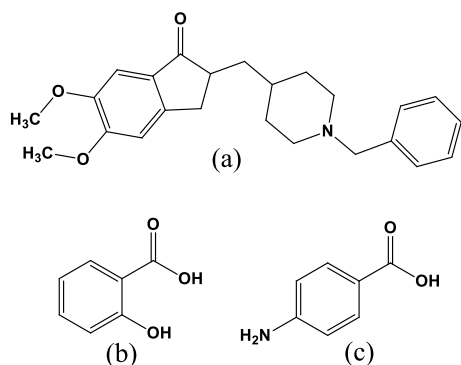


Fig. 1 Chemical structures of (a) donepezil, (b) salicylic acid, and (c) *p*-aminobenzoic acid.

bitter taste when taken orally; thus, improved physicochemical properties of DH may aid in patient compliance. Salt formation from donepezil with oxalic acid²⁸, with various carboxylic acids (e.g., maleic acid, fumaric acid, citric acid, salicylic acid, tartaric acid, and succinic acid)²⁹, salicylic acid and derivatives³⁰, and sulfonic acids³¹ have been reported. Patients claimed that the new donepezil salts, which were mixed with carboxylic acids (including salicylic acid), prevented the bitter taste of DH²⁹.

In this study, we were interested in donepezil-salicylate and donepezil hydrochloride-salicylic acid, which occur in several polymorphic forms and that exhibit strong fluorescence in a salt solvate, e.g., 3-, and 5-methylsalicylate methanolate³⁰. However, these salts or cocrystals have been created using traditional solution-based methods. The grinding method, a technique is routinely used in the pharmaceutical industry, is proposed as an alternative for forming donepezil cocrystals. We attempted to form cocrystals of donepezil HCl and the solvate using a cogrinding method as two coformers (salicylic acid and *p*-aminobenzoic acid). Both coformers are involved as primary compounds in the synthesis of pharmaceutical compounds^{32–34}. The approach taken aimed to understand the mechanisms involved in the process-induced cocrystal formation and to develop a solvent-free method.

MATERIALS AND METHODS

Chemicals and solvents

Donepezil hydrochloride (DH), salicylic acid (SA), and NaOH were purchased from Sigma-Aldrich, and *p*-aminobenzoic acid (PABA) from Acros Organics. All chemicals (> 98% purity) were used without any further purification. All solvents used were analytical grade. The chemical structures of donepezil and the two coformers are shown in Fig. 1.

Preparation of donepezil solvate

Donepezil solvate (DP-M) was prepared the same as previously described³⁵ with slight modification. To a solution of DH (0.02 mmol, 8.3 mg) in methanol (2 ml) 1.0 M NaOH (4.0 ml) was added. Colourless fine crystals were obtained and analysed using ATR-FTIR, PXRD, and DSC.

Preparation of donepezil

hydrochloride/donepezil solvate with coformers

Cogrinding in 1:1 M ratios of DH and DP-M with coformers (SA and PABA) was performed in all combinations. Preparations contained 0.02 mmol of DH (8.3 mg), DP-M (8.2 mg), and coformers: SA (0.02 mmol, 2.8 mg); PABA (0.02 mmol, 2.7 mg) which were ground for approximately 30 min using a mortar and pestle.

Attenuated total reflection-FTIR spectroscopy (ATR-FTIR)

IR spectra were collected on a Perkin-Elmer model Spectrum GX spectrometer, over the range of 4000–500 cm^{−1} with a UATR and a diamond/ZnSe crystal accessory.

Nuclear magnetic resonance (¹³C and ¹H NMR) spectroscopy

Experiments were performed on a Bruker Avance 300 (300 MHz) spectrometer in CD₃Cl at room temperature.

Powder X-ray diffraction (PXRD)

PXRD spectra were recorded on a Bruker AXS D8 Advance diffractometer, equipped with a CuK_α sealed tube X-ray source operating at 40 kV and 30 mA. The data were collected in the range 3–90° 2θ in steps of 0.02° with a scanspeed of 0.5 s/step.

Differential scanning calorimetry (DSC)

DSC was performed on an NETZSCH DSC 204 F1 Phoenix differential scanning calorimeter. Samples were placed in aluminium pans under nitro-

gen (flow rate 30 ml/min) with a heating rate of 5 °C/min in the range 25–380 °C.

RESULTS AND DISCUSSION

Characterization of donepezil solvate

FTIR absorbance spectra of the donepezil solvate (DP-M) was compared with DH (Fig. 2). The spectra of the DP-M does not exhibit bands $\nu(\text{N-H})$, NH^+ at 2460, 2420, 2406, and 2389 cm^{-1} in DH. The $\nu(\text{C=O})$ of DH at 1698 cm^{-1} was shifted to 1682 cm^{-1} . The $\nu(\text{C-N})$ of DH at 1312 cm^{-1} was shifted to 1306 cm^{-1} for DP-M. Furthermore, DP-M had a band of $\nu(\text{O-H})$ at 3364 cm^{-1} that belonged to the OH group from the methanol in the lattice (Fig. 2a). The DSC thermograms and PXRD patterns of DP-M are shown in Fig. 2bc. There were endothermic peaks at 87.5 and 94.8 °C, which corresponded to the evaporation of MeOH and melting point of donepezil. Diffraction peaks of DP-M were detected at $2\theta = 5.6, 11.3, 22.9, 23.4, 34.2^\circ$. This clearly confirmed the presence of a new solid form, which is closely resembled structures in literature^{30,36}.

Donepezil HCl and the donepezil solvate cocrinding systems

The ATR-FTIR spectra of the cocrinding products are shown in Fig. 3. The DH-SA product had peaks, $\nu(\text{C=O})$ at 1696 and 1654 cm^{-1} , compared with DH (1696 cm^{-1}) and SA (1660 cm^{-1}). The $\beta(\text{O-H})_c$ at 1464 cm^{-1} of SA was shifted to 1459 cm^{-1} with almost the complete disappearance in SA of $\nu(\text{C-O})_c$ at 1324 cm^{-1} and $\beta(\text{O-H})_h$ at 1382 cm^{-1} shifted to 1385 cm^{-1} . Furthermore, the peak intensity of DH $\nu(\text{C-N})$ at 1312 cm^{-1} decreased and shifted to a weak band at 1309 cm^{-1} (Fig. 3a). The changes and shifts in the peaks of $\nu(\text{C=O})$ and $\nu(\text{C-N})$ of DH in the formation of DH-PABA were similar to those seen with DH-SA formation (Fig. 3b). In DH-PABA, the $\nu(\text{C=O})$ at 1660 cm^{-1} was shifted to 1663 cm^{-1} , the peak intensity of $\beta(\text{O-H})$ at 1420 cm^{-1} decreased and the $\nu(\text{C-OH})$ band at 1285 cm^{-1} shifted to 1288 cm^{-1} (Fig. 3b). The $\nu(\text{C=O})$ observed in cocrystals were obtained above 1600 cm^{-1} and the sharp peak of $\nu_s(\text{COO}^-)$ around 1400 cm^{-1} was not found^{37,38}. These results imply that DH may associate with SA and PABA through hydrogen bond interactions of the amine hydrochloride salt, as seen in the spectra of N-H^+ present in DH and with the carboxylic acid of the coformers (2460–2389 cm^{-1}). Furthermore, the chloride ion appears to be acting

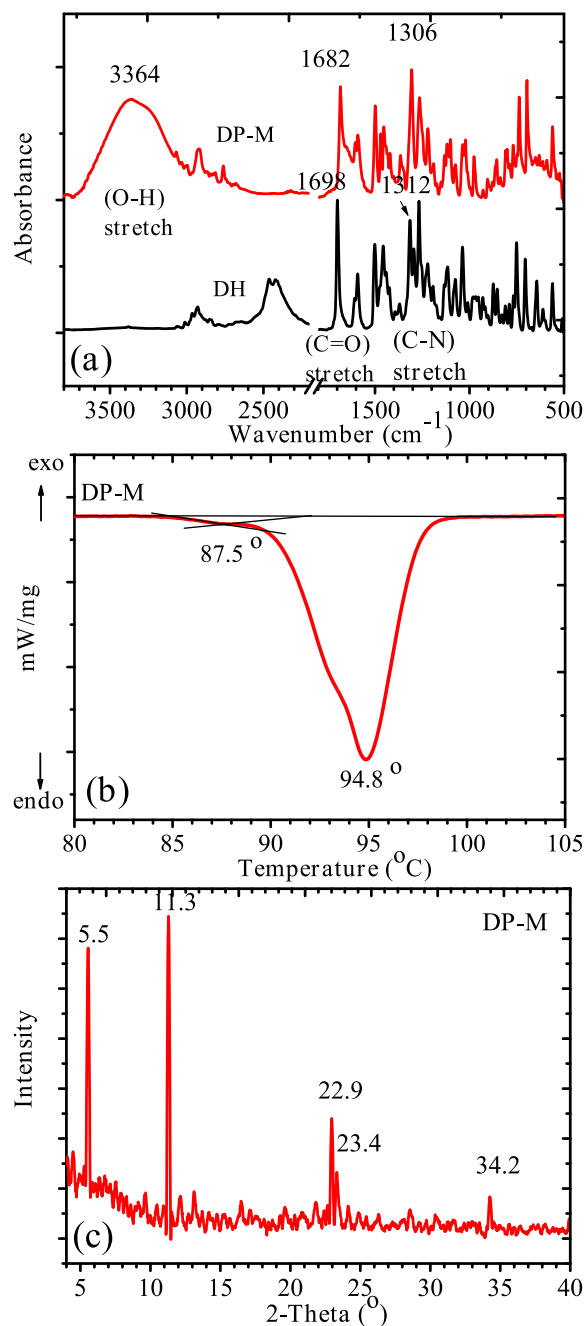


Fig. 2 (a) ATR-FTIR absorption spectra of donepezil hydrochloride (DH) and donepezil solvate (DP-M); (b, c) DSC thermograms and PXRD diffractograms of donepezil solvate.

as a hydrogen donor¹⁷. These compounds are a cocrystal salt, which contains a positive charge from the piperidyl moiety (N-H^+), a negative charge (Cl^-) and a neutral molecule from the coformers. The FTIR absorption spectra of neutral donepezil

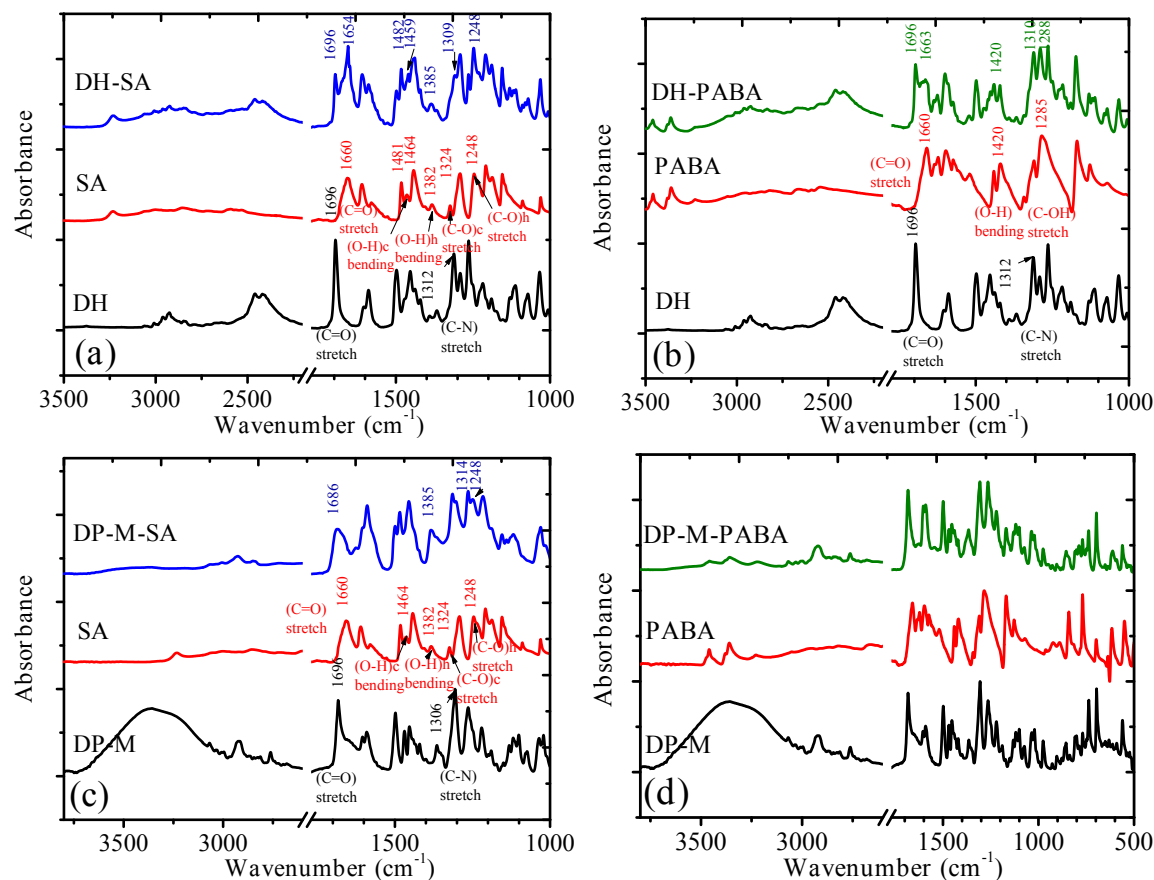


Fig. 3 ATR-FTIR absorption spectra of (a) DH, SA and DH-SA cogrinding products, (b) DH, PABA, and DH-PABA cogrinding products, (c) DP-M, SA and DP-M-SA cogrinding products, and (d) DP-M, PABA and DP-M-PABA cogrinding products.

solvate (DP-M) and with SA and PABA are shown in Fig. 3cd. The DP-M-SA product shows a shift of $\nu(\text{C}=\text{O})$ at 1660 to 1686 cm^{-1} in SA. The $\beta(\text{O}-\text{H})_{\text{c}}$ peak in SA-based compounds at 1464 cm^{-1} was absent, whereas the shifts of $\nu(\text{C}-\text{N})$ from 1306 to 1314 cm^{-1} are consistent with DH-SA. The hydroxyl group of SA, $\beta(\text{O}-\text{H})_{\text{h}}$ at 1382 cm^{-1} and $\nu(\text{C}-\text{O})_{\text{h}}$ at 1248 cm^{-1} , shifted to a medium peak at 1385 cm^{-1} and a weak peak of 1248 cm^{-1} , respectively. However, the changes of PABA in DP-M-PABA was only slightly shifted compares to the starting materials.

Fig. 4 shows the ^{13}C and ^1H NMR spectra of DH, SA, DH-SA, DH-PABA, and DP-M-PABA cogrinding products, respectively. ^{13}C and ^1H NMR chemical shifts of donepezil were referenced from earlier studies³⁹. The ^{13}C shifts of the piperidine ring- CH_2 (C16), the resonance shifted from 60.82 ppm (pure DH) to 60.93 ppm (DH-SA and DH-PABA), and the C15 (piperidine ring) shifted from 52.18 ppm (pure DH) to 52.39 ppm (DH-SA) and 52.30 ppm (DH-

PABA). ^1H NMR of DH-SA shows a change the signal of OH (OH2) of SA from 10.39 ppm (pure SA) to 10.71 ppm, and C16 (pure DH) signal shift from 4.14 to 4.18 ppm. The peaks that are shifted in DH-PABA and DP-M-PABA spectra were distinct. In the case of DH-PABA, the product causes a major interference with the signals, and we could not differentiate the OH from COOH signal (12 ppm, s, 1H) and NH_2 (5.9 ppm, d, 2H) of PABA⁴⁰. However, a small change of the spectral signal of C16 (4.43–4.48 ppm) and C20 (7.64–7.61 ppm) from DH was obtained. The signal of DP-M-PABA shifts signal of C2 (DH) from 3.24–3.33 ppm (m) to 3.07–3.11 ppm (d), C3 (DH) from 3.41–3.52 ppm to 3.18–3.27 ppm (m), C4 (DH) 7.11 to 7.16 ppm, C19 (DH) from 7.15–7.46 ppm to 7.28–7.37 ppm (t). The C20 (DH) was missing and obtained the signal of MeOH at 3.54 ppm. These signal shifts suggest that the grinding process-induced cocrystal formation.

PXRD thermograms of the components DH-

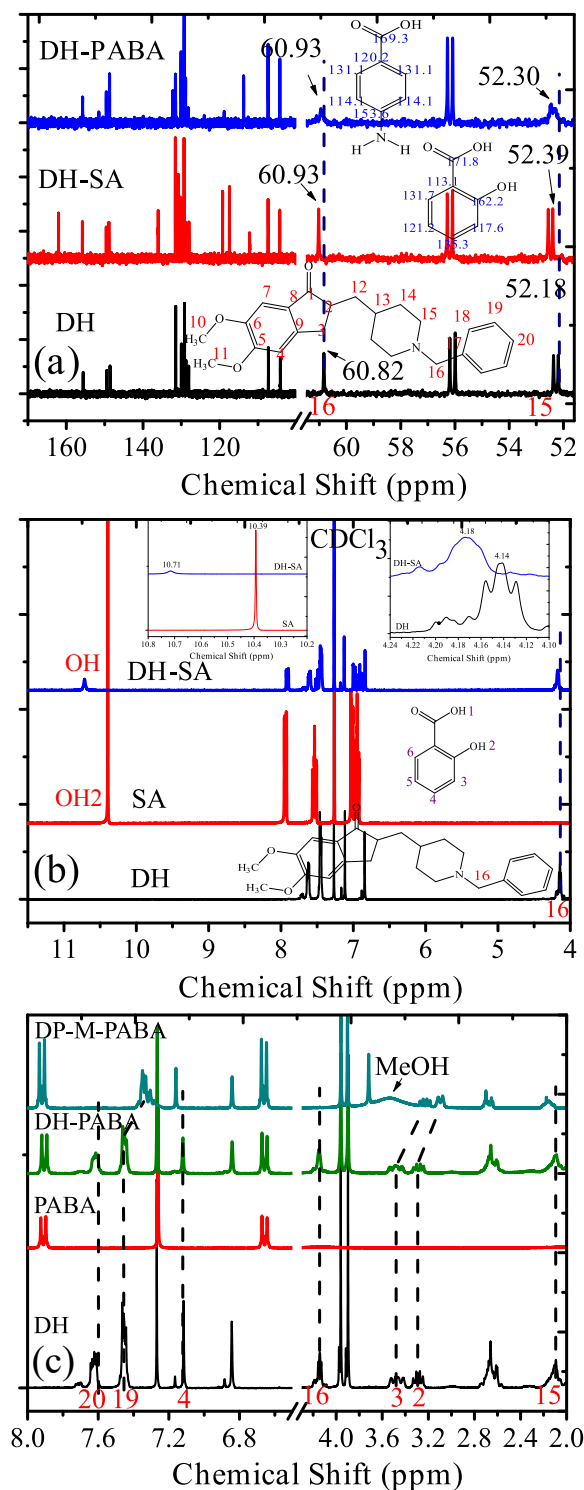


Fig. 4 (a) ^{13}C NMR spectra of DH, DH-SA, and DH-PABA; (b) ^1H NMR spectra of DH, SA, and DH-SA; (c) ^1H NMR spectra of DH, PABA, DH-PABA, and DP-M-PABA.

SA/DH-PABA and DP-M-SA/DP-M-PABA are shown in Fig. 5. The DH diffraction patterns and 2θ peaks from I in Ref. 24 were used as a reference. PXRD of DH-SA and DH-PABA show a combination of peaks from the starting materials and new peaks with several weak intensities due to unreacted components (Fig. 5a). Amorphous phases for the DP-M-SA and crystalline phases DP-M-PABA are shown in Fig. 5b. However, the diffraction patterns of all products were distinguishable from those of the starting materials. These results indicate the formation of a new crystal phase. DSC measurements of pure APIs (DH and DP-M), coformers (SA and PABA) and the physical mixtures from the cogrinding samples were obtained. Fig. 6ab show the DSC curves of the DH-SA and DH-PABA cocrystals. The melting points of DH, SA, and PABA are 230.5, 160.9, and 191.8 $^{\circ}\text{C}$, respectively. Endothermic peaks for DH-SA were observed at 100.4, 180.4, and 253.5 $^{\circ}\text{C}$, and DH-PABA were observed at 164.8 $^{\circ}\text{C}$. The DP-M-SA had endothermic peaks at 89.7 (weak), 157 (weak), and 246.8 $^{\circ}\text{C}$, respectively (Fig. 6c). DP-M-PABA exhibited endothermic peaks at 220 $^{\circ}\text{C}$ (Fig. 6d). The first and second endothermic temperatures of DH-SA and DP-M-SA represent the melting points of DH and SA in the different formations. The broad endothermic peaks at 253.5 and 246.8 $^{\circ}\text{C}$ may correspond to the fusion of the cogrinding powders and include the decomposition temperature of donepezil (DH 225–226 $^{\circ}\text{C}$)²⁵. The endothermic temperature at 164.8 $^{\circ}\text{C}$ of DH-PABA and at 220 $^{\circ}\text{C}$ of DP-M-PABA, correspond to the melting point of the cogrinding powders in the different formations. The cogrinding products of the APIs with the coformers resulted in new thermal events with little relationship to the melting peaks of the starting components to indicate the generation of the cocrystal forms.

CONCLUSIONS

Donepezil solvate was obtained through an acid-base reaction between a hydrochloride salt and a base in methanol. Two systems of donepezil hydrochloride and donepezil solvate (DP-M) with two coformers (salicylic acid and *p*-aminobenzoic acid (PABA) were prepared based on a cogrinding method. FTIR, ^{13}C and ^1H NMR, PXRD, and DSC analysis confirmed the process-induced cocrystal salt and cocrystal formations from a solvent-free method. Furthermore, this appears to be the first report of the formations of donepezil with *p*-aminobenzoic acid. These findings provide a great opportunity for cocrystal systems where donepezil cocrystals are used in the cogrinding method for

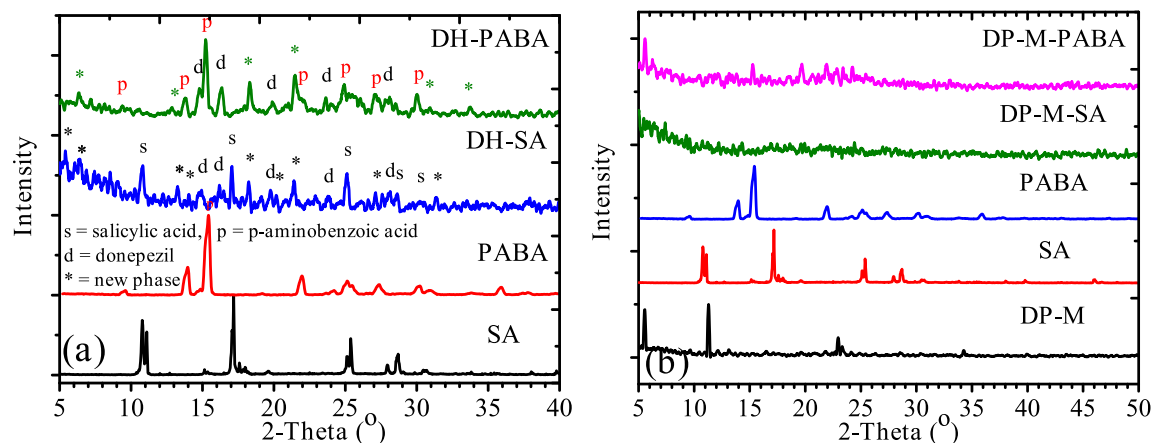


Fig. 5 PXRD patterns of (a) SA, PABA, DH-SA and DH-PABA and (b) DP-M, SA, PABA, DP-M-SA and DP-M-PABA.

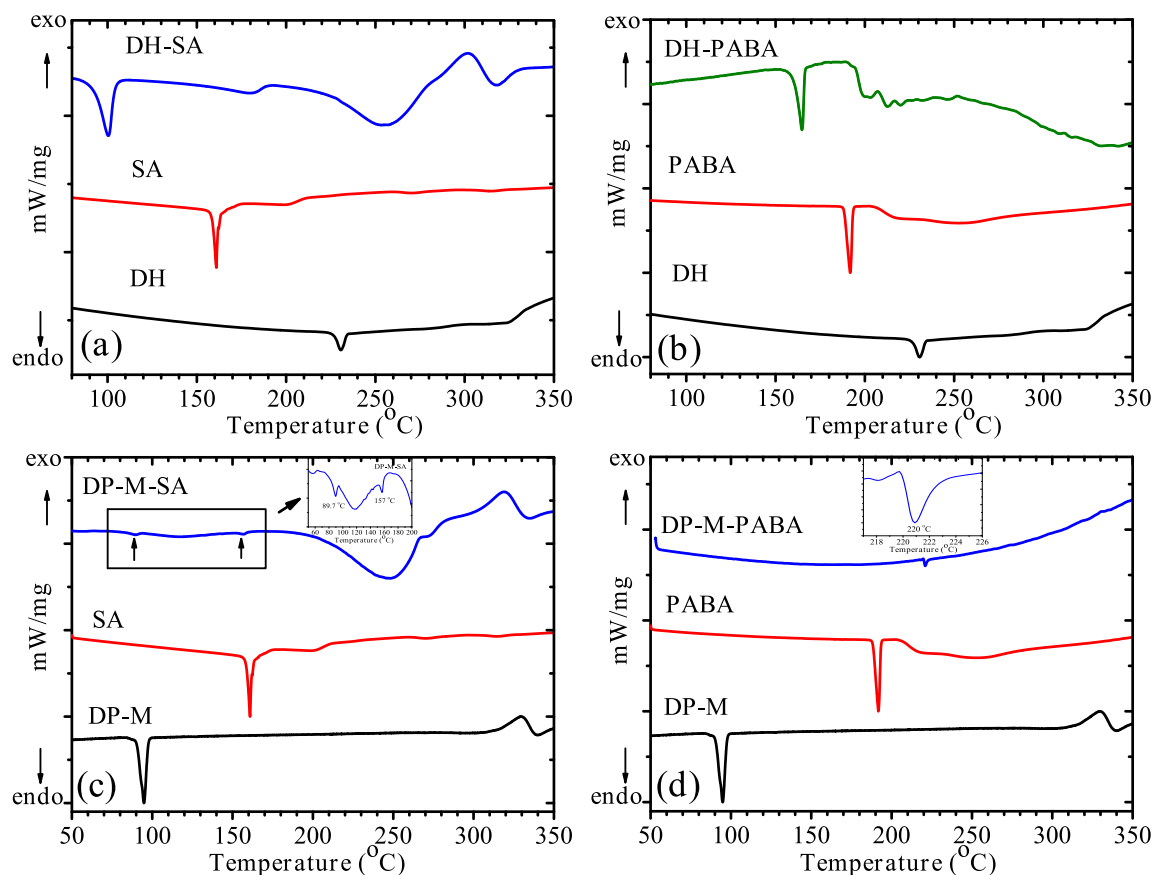


Fig. 6 DSC thermograms of (a) DH, SA and DH-SA, (b) DH, PABA and DH-PABA, (c) DP-M, SA and DP-M-SA, and (d) DP-M, PABA and DP-M-PABA.

preparation. This is an example of new green-chemistry, using a simple process that appears to be well suited for rapid screening of cocrystals of donepezil for industrial processes.

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