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Synthesis and Structural Characterization of Some D-panthenol Cocrystals using Carboxylic acid as Coformers

Tunde Adewale

adewaletunde3@gmail.com

Federal University Otuoke

Olufunso O. Abosede

Federal University Otuoke

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Abstract

D-Panthenol (provitamin B5) is a pharmaceutically and cosmetically important active ingredient whose solid-state application is constrained by pronounced hygroscopicity and limited crystallinity. In this study, cocrystals of D-panthenol were designed and synthesized with three carboxylic acid coformers oxalic acid, isophthalic acid (2:1), and trimesic acid via slow solvent evaporation from methanol/ethanol solution, and the resulting solid forms were characterized by UV–Visible and Fourier Transform Infrared (FTIR) spectroscopy. UV–Visible spectroscopy revealed a consistent bathochromic (red) shift in the absorption maximum (λmax), rising from 210 nm in pure D-panthenol to 214 nm in the oxalic acid cocrystal (Dp–OX), 217 nm in the isophthalic acid cocrystal (Dp–ISO, 2:1), and 222 nm in the trimesic acid cocrystal (Dp–Trim). The magnitude of the shift scaled with coformer aromaticity and hydrogen-bonding capacity, and the aromatic coformers additionally introduced secondary absorption bands at 244, 273, and 302 nm (Dp–ISO) and 258, 283, and 320 nm (Dp–Trim), consistent with supplementary π→π* transitions. These electronic changes were corroborated by FTIR spectroscopy, which showed systematic shifts in the O–H stretch (3454–3464 cm^{-1}), C = O stretch (1737–1741 cm^{-1}), N–H/C = C bend (1637–1641 cm^{-1}), and C–O stretch (1111–1127 cm^{-1}) regions relative to pure D-panthenol. Because no new absorption bands emerged in any spectrum, the observed shifts are attributed to intermolecular hydrogen bonding rather than covalent modification, confirming that D-panthenol's molecular identity was preserved in all three cocrystals. Together, the UV–Visible and FTIR results provide convergent spectroscopic evidence that cocrystallization with carboxylic acid coformers systematically perturbs the electronic and vibrational environment of D-panthenol through non-covalent supramolecular interactions, supporting cocrystal engineering as a viable route to modified D-panthenol solid forms for pharmaceutical application.

1. Introduction

The performance of an active pharmaceutical ingredient (API) in a solid dosage form depends heavily on its solid-state properties, including crystal structure, polymorphism, hygroscopicity, thermal stability, and mechanical behaviour. Variations in these properties can produce substantial differences in dissolution rate, bioavailability, shelf life, and manufacturability even when the chemical composition of the API is unchanged (Brittain, 2009). Many APIs display suboptimal solid-state behaviour, including moisture sensitivity, poor flow, and instability under ambient storage conditions, and these limitations often necessitate costly formulation interventions and specialized packaging. Solid-state modification strategies capable of improving physicochemical performance without altering molecular identity have therefore become a central focus of modern pharmaceutical science (Hilfiker, 2006).

Traditional solid-form engineering approaches include polymorph selection, salt formation, and the preparation of solvates, hydrates, or amorphous dispersions. Each carries limitations: polymorphism risks undesirable phase transitions during storage, salt formation is restricted to ionizable compounds, solvates and hydrates are prone to solvent loss, and amorphous systems are thermodynamically unstable (Almarsson and Zaworotko, 2004). Pharmaceutical cocrystal engineering has emerged as a

versatile alternative for tailoring API physicochemical properties. Cocrystals are crystalline materials composed of an API and one or more neutral coformers assembled in a defined stoichiometric ratio through non-covalent interactions such as hydrogen bonding, π–π stacking, and van der Waals forces, allowing solid-state properties to be modified without altering the covalent structure or pharmacological activity of the API (Aitipamula et al., 2012). Regulatory authorities now recognize pharmaceutical cocrystals as distinct solid forms, reinforcing their scientific and industrial relevance (U.S. Food and Drug Administration, 2018).

D-Panthenol (provitamin B5), the alcoholic analogue of pantothenic acid, is widely used in pharmaceutical, dermatological, and cosmetic formulations for its humectant, moisturizing, anti-inflammatory, and wound-healing properties (Barel et al., 2014). Structurally, it contains multiple hydroxyl groups and an amide functionality that confer strong hydrogen-bonding capability. While beneficial for biological activity, these same features render D-panthenol highly hygroscopic, predisposing it to moisture uptake, agglomeration, and loss of crystalline integrity, which compromises stability and shelf life (Rowe et al., 2009). Conventional stabilization strategies such as encapsulation and polymer coating offer only limited improvement and add formulation complexity.

Carboxylic acids are attractive cocrystal coformers because of their strong hydrogen-bond donor/acceptor character, structural diversity, and regulatory acceptance; the carboxylic acid group readily forms robust supramolecular synthons with hydroxyl and amide groups, making it well suited to interaction with D-panthenol (Desiraju, 2003). Aliphatic and aromatic di- and tricarboxylic acids such as oxalic, isophthalic, and trimesic acid have been used successfully to cocrystallize other APIs, with documented improvements in stability and hygroscopicity. However, D-panthenol cocrystals with carboxylic acid coformers remain largely unexplored. This study therefore reports the synthesis of D-panthenol cocrystals with oxalic acid, isophthalic acid, and trimesic acid, and examines the resulting changes in electronic absorption (UV–Visible spectroscopy) and vibrational behaviour (FTIR spectroscopy) as spectroscopic evidence of cocrystal formation via intermolecular hydrogen bonding.

2. Experimental

2.1 Materials and Reagents

D-Panthenol (API), oxalic acid, isophthalic acid, and trimesic acid were of analytical grade and used as received, without further purification. Methanol and ethanol were used as crystallization solvents on account of their good solvating ability for both D-panthenol and the carboxylic acid coformers, their volatility, which facilitates controlled solvent evaporation, and their compatibility with pharmaceutical applications.

2.2 Preparation of D-Panthenol Cocrystals

Cocrystals of D-panthenol with each carboxylic acid coformer were prepared by slow solvent evaporation.

D-Panthenol–Oxalic Acid Cocrystal (Dp–OX)

D-Panthenol (0.103 g, 1 mmol) and oxalic acid (0.090 g, 2 mmol) were dissolved in 10 mL of ethanol and stirred at room temperature until a clear saturated solution formed. The solution was filtered into a clean vial, covered with perforated paper, and left undisturbed in a vibration-free environment at room temperature. Fine white round block crystals formed after 14 days and were collected and stored for analysis.

D-Panthenol–Isophthalic Acid Cocrystal (Dp–ISO, 2:1): D-Panthenol (0.206 g, 2 mmol) and isophthalic acid (0.13 g, 1 mmol) were dissolved in 10 mL of methanol and stirred at room temperature until a clear saturated solution formed. Following filtration and slow evaporation under the same conditions, fine white long crystals formed after 7 days and were collected and stored for analysis.

D-Panthenol–Trimesic Acid Cocrystal (Dp–Trim, 3:1): D-Panthenol (0.309 g, 3 mmol) and trimesic acid (0.15 g, 1 mmol) were dissolved in 10 mL of methanol and stirred at room temperature until a clear saturated solution formed. Following filtration and slow evaporation under the same conditions, needle-like white crystals formed after 3 weeks and were collected and stored for analysis.

2.3 Characterization

2.3.1 UV–Visible Spectroscopy. UV–Visible spectra were recorded on a JASCO V-730 spectrophotometer over the 200–400 nm range to examine changes in the electronic absorption behaviour of D-panthenol upon cocrystallization. Pure D-panthenol and each cocrystal were dissolved in a methanol–ethanol solvent system to yield clear solutions suitable for analysis, with the corresponding solvent used as blank. For each sample, the maximum absorption wavelength (λmax), peak intensity, and any additional absorption bands were recorded and compared across samples. Bathochromic shifts in λmax and the emergence of new absorption bands were taken as indicators of altered electronic environments arising from intermolecular interactions between D-panthenol and the coformers.

2.3.2 FTIR Spectroscopy. FTIR spectroscopy was used to probe molecular-level interactions between D-panthenol and the carboxylic acid coformers and to verify cocrystal formation by tracking changes in functional-group vibrations. Each dried sample (approximately 2–3 mg) was finely ground with spectroscopic-grade potassium bromide (KBr) and compacted into a transparent pellet using a hydraulic press. Spectra were collected on a PerkinElmer Spectrum 100 FTIR spectrometer over the 4000–400 cm^{-1} range, at a resolution of 4 cm^{-1}, averaged over 32 scans per sample, with a background spectrum recorded beforehand to correct for atmospheric interference. Spectral processing was carried out in Win-IR Pro (v. 3.0), and the characteristic O–H, C = O, C–O, and C–H absorption bands of pure D-panthenol were compared against those of the synthesized cocrystals to identify shifts indicative of intermolecular hydrogen bonding.

3. Results and Discussion

3.1 UV–Visible Spectral Analysis

The UV–Visible spectra of pure D-panthenol and its cocrystals with oxalic acid, isophthalic acid (2:1), and trimesic acid were recorded in a methanol/ethanol solvent system over the 200–400 nm range (Table 1). Pure D-panthenol displayed a single absorption band at approximately 210 nm, attributed to an n→π* electronic transition associated with its carbonyl group; the absence of absorption beyond 230 nm confirms the lack of extended conjugation, consistent with its simple aliphatic structure.

Upon cocrystallization, a clear bathochromic (red) shift was observed across all three systems, with the magnitude of the shift scaling with the structural complexity of the coformer. The Dp–OX cocrystal showed the smallest shift, with λmax moving to about 214 nm. Since oxalic acid is a simple, non-aromatic dicarboxylic acid, this modest shift is best explained by hydrogen-bonding interactions between its carboxyl groups and the hydroxyl/carbonyl groups of D-panthenol, which perturb the electron density around the chromophore without introducing new conjugated pathways. A more pronounced shift was observed for Dp–ISO (2:1), where the primary absorption band moved to approximately 217 nm and was accompanied by secondary bands at 244, 273, and 302 nm; because isophthalic acid contains an aromatic ring, its incorporation introduces π→π* transitions absent in the parent compound. The largest bathochromic shift was recorded for Dp–Trim, whose λmax moved to about 222 nm, with additional bands at 258, 283, and 320 nm. Trimesic acid's three carboxyl groups permit a more extensive hydrogen-bonding network than isophthalic acid, which, combined with its aromatic core, produced the most red-shifted and structurally complex spectrum among the systems studied.

The progressive bathochromic shift from pure D-panthenol (210 nm) through Dp–OX (214 nm) and Dp–ISO (217 nm) to Dp–Trim (222 nm) tracks the increasing aromaticity and hydrogen-bonding capacity of the coformers, indicating that cocrystallization systematically alters the electronic environment around D-panthenol's chromophore. This trend constitutes qualitative spectroscopic evidence of successful cocrystal formation via intermolecular interaction rather than simple physical mixing.

Table 1
UV–Visible Absorption Characteristics of D-Panthenol and Its Cocrystals

Sample	Appearance	Melting Point (°C)	λmax (nm)	Proposed Electronic Transition
D-Panthenol	White powder	68	210	n→π*
Dp–OX	Milky round block crystals	107	214	n→π* (H-bond influenced)
Dp–ISO (2:1)	Long crystals	165	217, 244, 273, 302	n→π* and π→π*
Dp–Trim	Needle-like white crystals	228	222, 258, 283, 320	n→π* and π→π*

3.2 FTIR Spectral Analysis

FTIR spectroscopy was employed to investigate the molecular interactions between D-panthenol and the carboxylic acid coformers and to confirm cocrystal formation through changes in characteristic vibrational frequencies. Spectra of pure D-panthenol, Dp-OX, Dp-ISO (2:1), and Dp-Trim were recorded over 4000–350 cm^{-1}, and the principal absorption bands are summarized in Table 2.

Pure D-panthenol displayed a broad O–H stretching band at 3460 cm^{-1}, attributed to extensive intermolecular hydrogen bonding in the solid phase, together with an aliphatic C–H stretch at 2930 cm^{-1}, a carbonyl (C = O) stretch at 1737 cm^{-1}, and bands at 1637, 1449, 1387, 1111, and 1033 cm^{-1} assigned to N–H bending, CH2 deformation, C–N stretching, and C–O stretching, respectively, consistent with the reported spectra of D-panthenol and structurally related alcohols and amides (Coates, 2000; Silverstein et al., 2015).

The Dp-OX cocrystal displayed a broad O–H stretch at 3464 cm^{-1}, alongside bands at 1639, 1462, and 1118 cm^{-1}. The subtle shifts relative to pure D-panthenol suggest alterations in the hydrogen-bonding environment, consistent with the establishment of intermolecular hydrogen bonds between the hydroxyl groups of D-panthenol and the carboxyl groups of oxalic acid; such spectral modification is a widely recognized indicator of pharmaceutical cocrystal formation, since hydrogen bonding perturbs the vibrational energies of the functional groups involved (Brittain, 2009; Schultheiss and Newman, 2009). The Dp-ISO (2:1) cocrystal displayed a broad O–H stretch at 3454 cm^{-1}, a slight shift to lower wavenumber relative to pure D-panthenol, with the 1641 cm^{-1} band remaining prominent and the C–O stretch shifting from 1111 cm^{-1} to 1127 cm^{-1}, suggesting modification of the chemical environment of the hydroxyl and carbonyl groups. Isophthalic acid's two carboxyl groups can act as both hydrogen-bond donor and acceptor, facilitating a stable supramolecular lattice (Desiraju, 1995; Shan and Zaworotko, 2008). The Dp-Trim cocrystal displayed a broad O–H stretch at 3460 cm^{-1}, an aliphatic C–H stretch at 2948 cm^{-1}, a carbonyl absorption at 1741 cm^{-1}, and additional bands at 1640, 1458, and 1114 cm^{-1}. Trimesic acid's three carboxylic acid groups enable multiple simultaneous hydrogen bonds, establishing an extensive hydrogen-bonding network that stabilizes the crystal structure, consistent with spectral changes documented for pharmaceutical cocrystals involving other multifunctional carboxylic acids (Aitipamula et al., 2012; Brittain, 2009).

Across all three cocrystals, the O–H stretching region (3454–3464 cm^{-1}), the carbonyl stretching region (1737–1741 cm^{-1}), and the C–O stretching region (1111–1127 cm^{-1}) shifted relative to pure D-panthenol. Because no new absorption bands emerged in any spectrum, these shifts are attributed to intermolecular hydrogen bonding between D-panthenol and the respective coformers rather than to covalent modification of the drug, indicating that the local chemical environment was altered while the covalent structure of D-panthenol was preserved.

Table 2
Major FTIR Absorption Bands of Pure D-Panthenol and Its Cocrystals

Sample	O–H Stretch (cm^{-1})	C–H Stretch (cm^{-1})	C = O Stretch (cm^{-1})	N–H/C = C Bend (cm^{-1})	CH Bending (cm^{-1})	C–O Stretch (cm^{-1})
D-Panthenol	3460	2930	1737	1637	1449, 1387	1111, 1033
Dp-OX	3464	–	–	1639	1462	1118
Dp-ISO (2:1)	3454	–	–	1641	–	1127
Dp-Trim	3460	2948	1741	1640	1458	1114

3.3 Correlation between UV–Visible and FTIR Findings

The UV–Visible and FTIR results provide complementary and mutually reinforcing evidence of cocrystal formation. The progressive bathochromic shift in λmax (210 → 214 → 217 → 222 nm) reflects a systematic perturbation of D-panthenol's electronic environment that scales with the aromaticity and hydrogen-bond-donating capacity of the coformer, from the non-aromatic oxalic acid to the tricarboxylic, aromatic trimesic acid. The parallel, coformer-dependent shifts observed in the O–H, C = O, and C–O stretching regions of the FTIR spectra indicate that this electronic perturbation originates from intermolecular hydrogen bonding between the hydroxyl/amide groups of D-panthenol and the carboxyl groups of the coformers. Critically, neither technique revealed new absorption features attributable to covalent bond formation, indicating that all three cocrystals arise from non-covalent supramolecular assembly that preserves the molecular identity of the parent API while modifying its solid-state electronic and vibrational environment.

Panel (A) shows the intramolecular O–H···O = C hydrogen bond within pure D-panthenol itself, linking the C2-hydroxyl group to the amide carbonyl oxygen. Panels (B)–(D) show the proposed intermolecular acid–amide synthon formed on cocrystallization with oxalic, isophthalic, and trimesic acid respectively: each coformer’s carboxyl O–H donates to the amide C = O of D-panthenol, while the amide N–H simultaneously donates to the coformer’s carbonyl oxygen, forming the two-point $R_{2,2}(8)$ ring characteristic of carboxylic acid–amide heterosynthons. This new intermolecular hydrogen bonding, superimposed on the retained intramolecular bond, is consistent with the shifts observed in the O–H, C = O, and C–O stretching regions of the FTIR spectra discussed above (Section 4.2). Grey dashed lines mark the remaining, unpaired carboxyl groups of oxalic, isophthalic, and (for trimesic acid) a third carboxyl group, which are proposed to extend the hydrogen-bonded motif into 1-D tapes (oxalic, isophthalic acid) or a more extensive 2-D/3-D network (trimesic acid), consistent with the greater hydrogen-bonding capacity noted for trimesic acid in Section 2.4.2. These proposed interactions are schematic and based on the established hydrogen-bonding tendencies of the functional groups involved; definitive bond geometry and distances would require single-crystal X-ray diffraction data.

4. Conclusion

D-Panthenol cocrystals with oxalic acid, isophthalic acid (2:1), and trimesic acid were successfully synthesized by slow solvent evaporation and characterized by UV–Visible and FTIR spectroscopy. UV–Visible analysis revealed a consistent bathochromic shift in λmax, increasing from 210 nm in pure D-panthenol to 214 nm (Dp–OX), 217 nm (Dp–ISO), and 222 nm (Dp–Trim), with the aromatic coformers additionally introducing secondary π→π* absorption bands; the magnitude of the shift scaled with the aromaticity and hydrogen-bonding capacity of each coformer. FTIR spectroscopy corroborated these findings, showing systematic shifts in the O–H, C = O, and C–O stretching regions across all three cocrystals relative to pure D-panthenol. The absence of new covalent absorption bands, combined with these coordinated shifts, confirms that cocrystal formation proceeded through intermolecular hydrogen bonding rather than chemical reaction, preserving the molecular identity of D-panthenol. Collectively, the convergent UV–Visible and FTIR evidence confirms that all three coformers produced new D-panthenol cocrystal phases with modified electronic and vibrational properties, supporting cocrystal engineering with carboxylic acid coformers as a viable, non-covalent strategy for modifying the solid-state behaviour of D-panthenol for pharmaceutical application. Further structural confirmation by single-crystal X-ray diffraction, together with moisture-uptake and thermal stability assessment, is recommended to complete the physicochemical profile of these cocrystals.

Declarations

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Data availability. All data generated or analysed during this study are included in this published article. Further information is available from the corresponding author on reasonable request.

References

1. Aitipamula S, Banerjee R, Bansal AK, Biradha K, Cheney ML, Choudhury AR, Desiraju GR, Dikundwar AG, Dubey R, Duggirala N, Ghogale PP, Ghosh S, Goswami PK, Goud NR, Jetti RRK, Karpinski PH, Kaushik P, Kumar D, Kumar V, … and, Zaworotko MJ. Polymorphs, salts, and cocrystals: What's in a name? Volume 12. Crystal Growth & Design; 2012. pp. 2147–52. 5.

2. Almarsson O, Zaworotko MJ. (2004). Crystal engineering of the composition of pharmaceutical phases: Do pharmaceutical cocrystals represent a new path to improved medicines? Chemical Communications, 2004(17), 1889–1896.
3. Barel AO, Paye M, Maibach HI. Handbook of Cosmetic Science and Technology. 4th ed. CRC; 2014.
4. Brittain HG. Polymorphism in Pharmaceutical Solids. 2nd ed. Informa Healthcare; 2009.
5. Coates J. Interpretation of infrared spectra, a practical approach. In: Meyers RA, editor. Encyclopedia of Analytical Chemistry. Wiley; 2000. pp. 10815–37.
6. Desiraju GR. Supramolecular synthons in crystal engineering: A new organic synthesis. Angew Chem Int Ed. 1995;34(21):2311–27.
7. Desiraju GR. Crystal Engineering: The Design of Organic Solids. Elsevier; 2003.
8. Hilfiker R, editor. Polymorphism in the Pharmaceutical Industry. Wiley-VCH; 2006.
9. Rowe RC, Sheskey PJ, Quinn ME. Handbook of Pharmaceutical Excipients. 6th ed. Pharmaceutical; 2009.
10. Schultheiss N, Newman A. Pharmaceutical cocrystals and their physicochemical properties. Cryst Growth Des. 2009;9(6):2950–67.
11. Shan N, Zaworotko MJ. The role of cocrystals in pharmaceutical science. Drug Discovery Today. 2008;13(9–10):440–6.
12. Silverstein RM, Webster FX, Kiemle DJ, Bryce DL. Spectrometric Identification of Organic Compounds. 8th ed. Wiley; 2015.
13. U.S. Food and Drug Administration. Regulatory Classification of Pharmaceutical Co-Crystals: Guidance for Industry. Center for Drug Evaluation and Research (CDER); 2018.

Figures

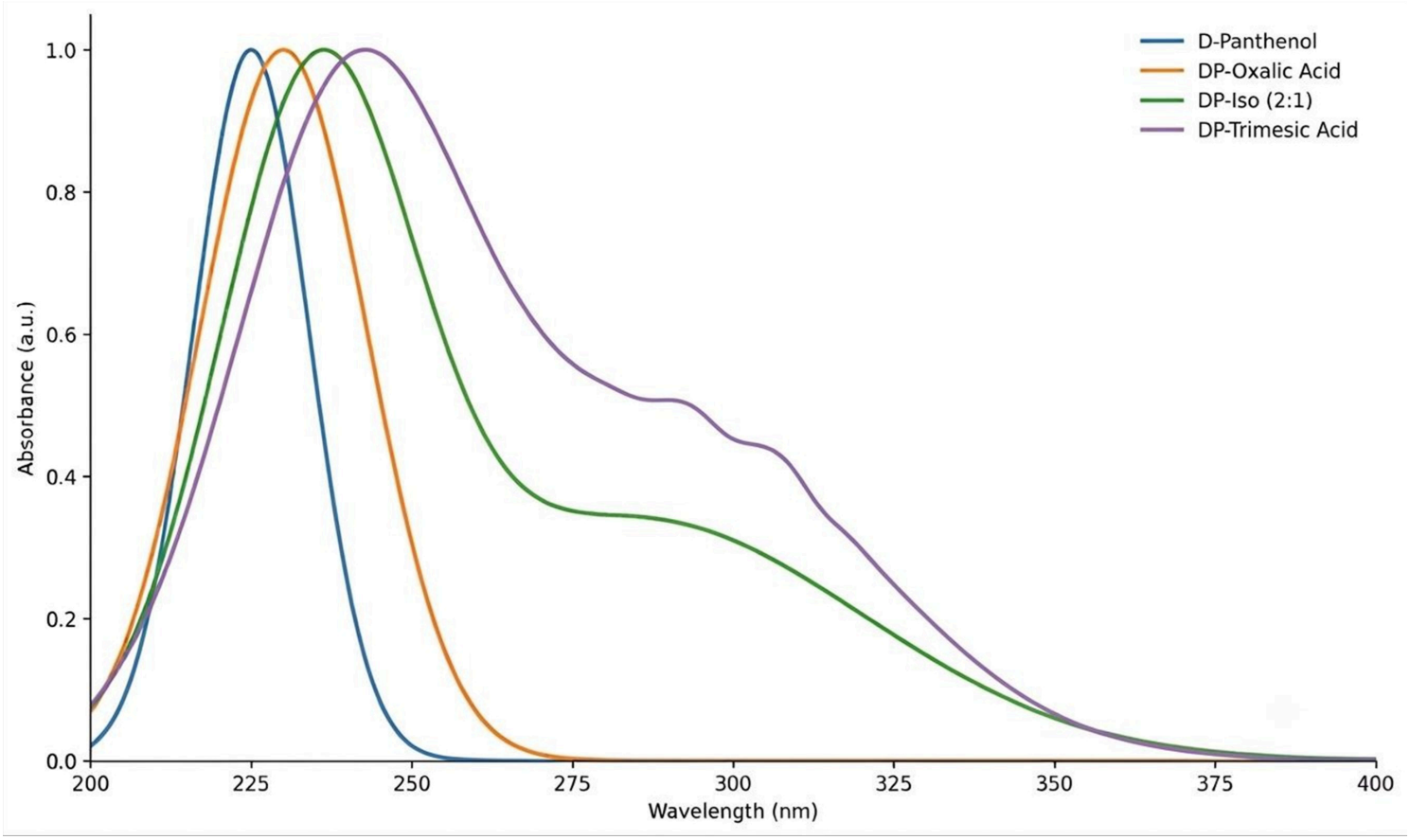

Figure 1

UV–Visible spectra of D-panthenol and its cocrystals with oxalic acid, isophthalic acid (2:1), and trimesic acid, recorded in methanol/ethanol over 200–400 nm (spectra normalized to peak absorbance).

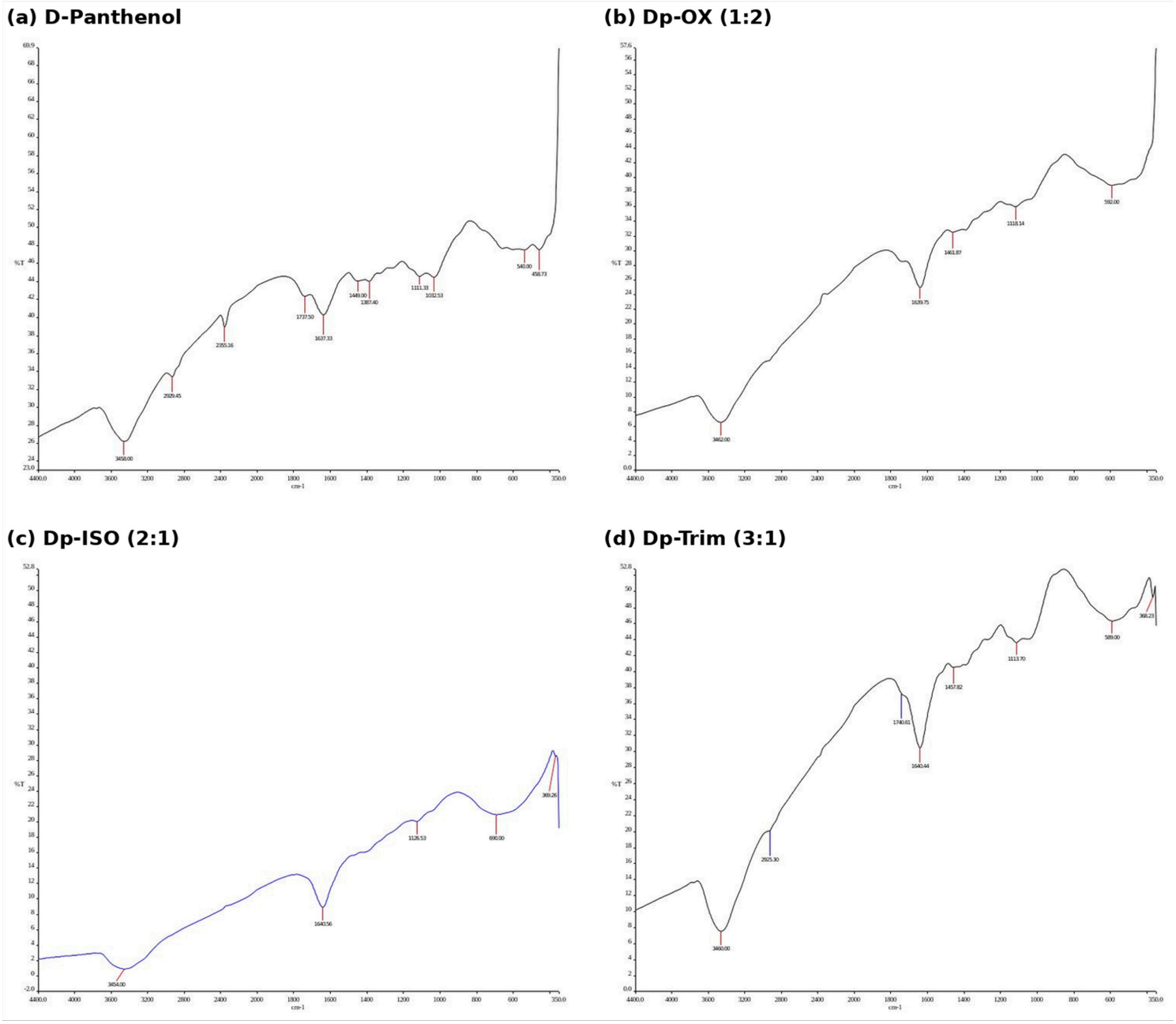

Figure 2

FTIR spectra (KBr pellet, 4000–350 cm⁻¹) of (a) pure D-panthenol, (b) Dp–OX, (c) Dp–ISO (2:1), and (d) Dp–Trim, with key absorption bands marked.

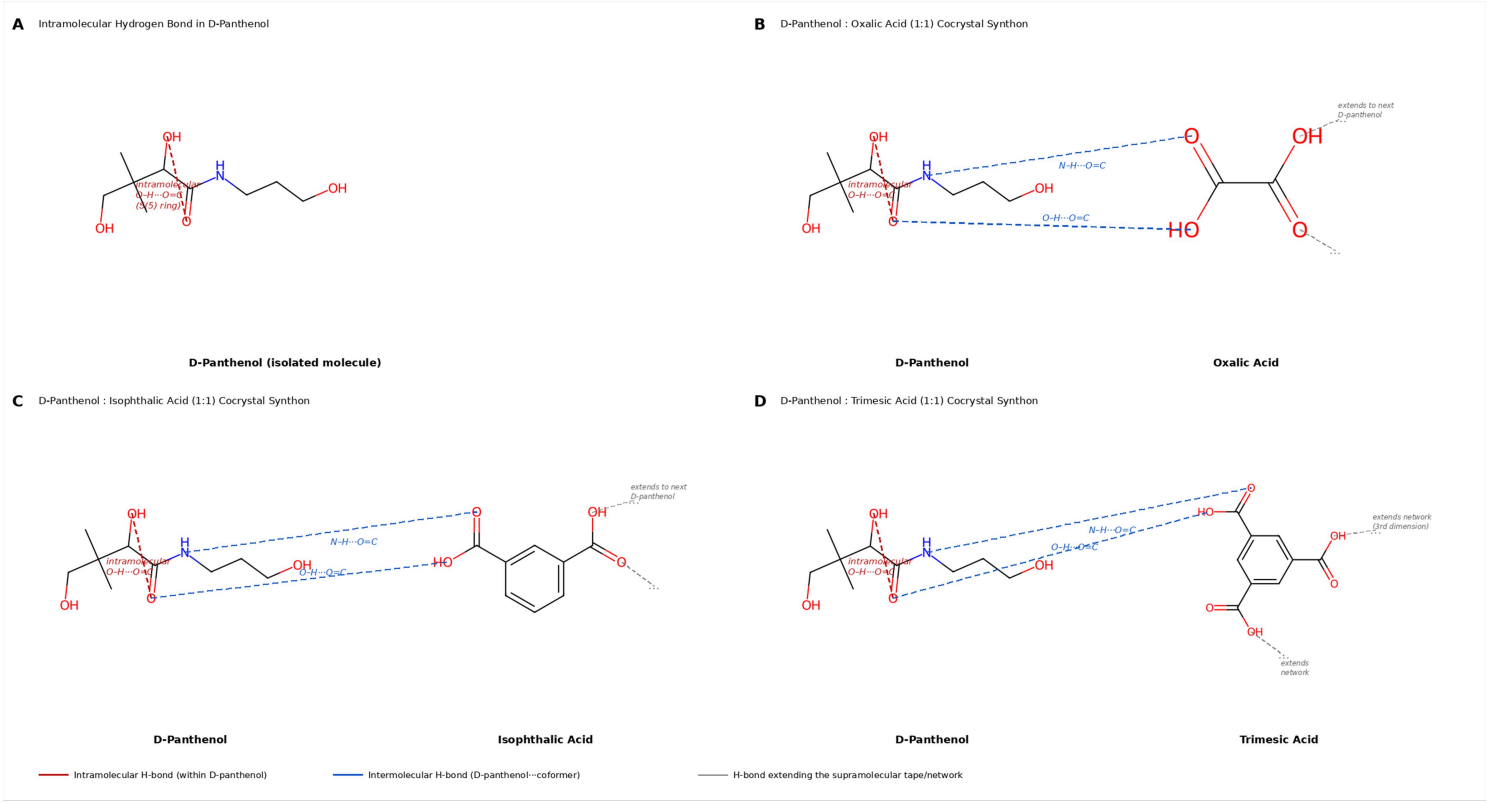

Figure 3

Fig 3.3. Proposed Intramolecular and Intermolecular Hydrogen-Bonding Interactions between D-Panthenol and Its Carboxylic Acid Coformers, Rationalising the FTIR Spectral Shifts

Panel (A) shows the intramolecular O–H···O=C hydrogen bond within pure D-panthenol itself, linking the C2-hydroxyl group to the amide carbonyl oxygen. Panels (B)–(D) show the proposed intermolecular acid–amide synthon formed on cocrystallization with oxalic, isophthalic, and trimesic acid respectively: each coformer's carboxyl O–H donates to the amide C=O of D-panthenol, while the amide N–H simultaneously donates to the coformer's carbonyl oxygen, forming the two-point $R_{2,2}(8)$ ring characteristic of carboxylic acid–amide heterosynthons. This new intermolecular hydrogen bonding, superimposed on the retained intramolecular bond, is consistent with the shifts observed in the O–H, C=O, and C–O stretching regions of the FTIR spectra discussed above (Section 4.2). Grey dashed lines mark the remaining, unpaired carboxyl groups of oxalic, isophthalic, and (for trimesic acid) a third carboxyl group, which are proposed to extend the hydrogen-bonded motif into 1-D tapes (oxalic, isophthalic acid) or a more extensive 2-D/3-D network (trimesic acid), consistent with the greater hydrogen-bonding capacity noted for trimesic acid in Section 2.4.2. These proposed interactions are schematic and based on the established hydrogen-bonding tendencies of the functional groups involved; definitive bond geometry and distances would require single-crystal X-ray diffraction data.