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Original Article

Predictive Application of Hansen Solubility Parameters in the Design of Methocarbamol-Ascorbic Acid Cocrystals for Solubility and Dissolution Enhancement

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ABSTRACT

Background: Methocarbamol, a centrally acting skeletal muscle relaxant, exhibits poor aqueous solubility, limiting its bioavailability. Cocrystallization offers a promising approach to enhance solubility and dissolution without altering pharmacological activity. This study aimed to design Methocarbamol-Ascorbic acid Cocrystals (MAC) using Hansen Solubility Parameters (HSPs) to predict miscibility and confirm improved physicochemical performance. **Materials and Methods:** HSPs were calculated using the Van Krevelen-Hoftyzer group contribution method to predict drug-coformer compatibility. Cocrystals were prepared by the solvent evaporation method in a 1:1 molar ratio. Characterization was performed using Fourier-Transform Infrared Spectroscopy (FTIR), Powder X-ray Diffraction (PXRD), and Differential Scanning Calorimetry (DSC). Solubility and dissolution studies were carried out in aqueous, 0.1 N HCl, and phosphate buffer (pH 6.8) media. **Results and Discussion:** Theoretical analysis indicated a Δδ value of 10.96 $MPa^{0.5}$, suggesting moderate miscibility with good hydrogen bonding potential between methocarbamol and ascorbic acid. FTIR confirmed hydrogen bonding interactions. PXRD revealed new crystalline peaks and DSC displayed altered endothermic transitions, confirming cocrystal formation. The MAC cocrystal exhibited enhanced solubility (2.07 mg/mL in 0.1 N HCl) and faster dissolution (99.3% release in 30 min) compared to pure methocarbamol (1.14 mg/mL, 87.2% release). The improvement may be attributed to hydrogen bonding and reduced lattice energy, which improved wettability and dissolution rate. **Conclusion:** Cocrystallization of methocarbamol with ascorbic acid successfully enhanced solubility and dissolution behaviour. Theoretical predictions aligned with experimental outcomes, validating HSPs as an effective tool for coformer selection and demonstrating cocrystallization as a viable strategy to improve biopharmaceutical performance of poorly soluble drugs.

Keywords: Methocarbamol, Ascorbic Acid, Cocrystal, Solubility, Dissolution Studies.

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INTRODUCTION

Solid dosage forms such as tablets and capsules are preferred for their convenience and patient compliance; however, poor aqueous solubility often limits the bioavailability of many drugs (Chadha *et al.*, 2012; Agustina and Setyaningsih, 2023). Several methods to improve their physicochemical characteristics have been investigated to get around this. A promising method that enhances the mechanical, stability, and solubility of Active Pharmaceutical Ingredients (APIs) without changing their chemical or pharmacological characteristics is cocrystallization (Duggirala *et al.*, 2016; Aitipamula *et al.*, 2012; Kumar and Nanda, 2018; Thakkar *et al.*, 2010; Kumar *et al.*, 2012; Schultheiss and Newman, 2009). Crystalline complexes made up of an API and a cocrystal former (coformer) in a particular stoichiometric ratio and bound together by non-covalent interactions are known as pharmaceutical cocrystals (Stoler and Warner, 2015). In 2018, the FDA defined pharmaceutical cocrystals as crystalline substances consisting of two or more distinct molecules—one being the API - combined in a specific stoichiometric ratio within a single crystal lattice and held together through non-ionic and noncovalent interactions. A coformer, in this context, refers to a molecule that forms non-ionic interactions with the API within the crystal lattice, is not considered a solvent (including water), and is generally non-volatile (Santosh, 2017).

The Hansen Solubility Parameter (HSP) model forecasts solubility and miscibility by breaking down cohesive energy into its dispersion (δd), polar (δp), and hydrogen bonding (δh)

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components, providing a quantitative approach for predicting cocrystal formation. The overall solubility parameter can be computed as $\delta^2 = \delta d^2 + \delta p^2 + \delta h^2$ (Novaes *et al.*, 2023). HSPs can be estimated using group contribution techniques such as the Hoftyzer-van Krevelen method or contemporary computational methods, including machine learning and Conductor-like Screening Model for Real Solvents (COSMO-RS) models, which enhance prediction accuracy for intricate compounds. These parameters are instrumental in understanding intermolecular interactions and in predicting physicochemical properties. The Hoftyzer-van Krevelen method is based on the principle that the overall solubility behavior of a molecule can be predicted by summing the contributions of its individual structural groups. The difference in total solubility parameters (Δδ) provides a quantitative measure of the miscibility between two components (Sanchez-Lengeling *et al.*, 2018; Li *et al.*, 2024).

Methocarbamol was authorized in 1957 to treat muscular spasms and is used as a temporary treatment for acute musculoskeletal conditions that cause excruciating muscle spasms (Schlegelmilch *et al.*, 2009). It has also been used off-label to treat several unpleasant ailments, such as fibromyalgia, inflammatory arthritis, and low back pain (Sibrack *et al.*, 2022; Beebe *et al.*,2005; Richards *et al.*, 2012). Methocarbamol (chemically carbamic acid ester), reduces motor activity and inhibits polysynaptic reflex transmission mainly at the spinal level, without directly affecting muscle contractility (Truitt *et al.*, 1958; Roszkowski, 1960). Methocarbamol can also function as an anticholinergic inhibitor of the midbrain reticular activating system, which lowers muscle tone and depresses polysynaptic reflexes (Doherty and Shields, 1958). According to the biopharmaceutical categorization system, methocarbamol is categorized as a class-II medicine (low permeability and water solubility). These findings prompted attempts to use a cocrystal method to increase methocarbamol's solubility. The selection of the coformer was done based on HSPs. Following their synthesis utilizing ascorbic acid as coformer, the cocrystals were described and assessed.

MATERIALS AND METHODS

Methocarbamol was provided as a gift sample from Hetero Pharma Pvt. Ltd., India, and Ascorbic acid was sourced from Finar Chemicals Pvt. Ltd., India, Chloroform was obtained from Merck Life Science Pvt. Ltd., India, Disodium hydrogen phosphate dihydrate was purchased from HiMedia Laboratories Pvt. Ltd., India, and Potassium dihydrogen phosphate was obtained from Merck Life Science Pvt. Ltd., India.

Prediction of HSPs

The HSPs for methocarbamol and a few selected coformers (caffeine, glycine, myristic acid, ascorbic acid and succinic acid) were determined using the group contribution method, Van Krevelen-Hoftyzer approach. This method is based on the principle that the overall solubility behavior (δ) of a molecule can be predicted by summing the contributions of its individual structural groups. The difference in total solubility parameters (Δδ) provides a quantitative measure of the miscibility between two components. When Δδ values are small (typically ≤5 MPa½), the components are likely to be miscible, whereas larger values suggest reduced compatibility. Moderate Δδ values (5-10 $MP^{0.5}$) favor partial miscibility and facilitate the formation of stable cocrystals through specific intermolecular interactions. Thus, Δδ serves as a critical predictor for assessing the feasibility of cocrystal formation between a drug and its coformer (Mohammad *et al.*, 2011).

Calculation of HSP Components

The HSPs for methocarbamol and the coformers were calculated using the group contribution method following the combined models of Fedors and Van Krevelen-Hoftyzer.

$$(\delta_d) = \frac{\sum F_{di}}{\sum V_i}$$

$$(\delta_p) = \frac{\sqrt{(\sum F_{pi}^2)}}{\sum V_i}$$

$$(\delta_h) = \frac{\sqrt{(\sum E_{hi})}}{\sum V_i}$$

$$\Delta\delta = [(\delta_{d2}-\delta_{d1})^2+(\delta_{p2}-\delta_{p1})^2+(\delta_{h2}-\delta_{h1})^2]^{0.5}$$

Volume-Dependent Solubility Parameter (δv) (Bagley *et al.*, 1971): The δv parameter was calculated using.

$$\delta_v = (\delta^2_d+\delta^2_p)^{0.5}$$

Miscibility Assessment using Ra(v): The Ra(v) factor, representing the "distance" between two compounds in Hansen solubility parameter space, was calculated as:

$$R_{a(v)} = [4(\delta_{v2}-\delta_{v1})^2+(\delta_{h2}-\delta_{h1})^2]^{0.5}$$

Methocarbamol cocrystal preparation

In a glass vial, 50 mg of methocarbamol and 50 mg of ascorbic acid were dissolved in 10 mL of chloroform in a 1:1 stoichiometric molar ratio until both the drug and conformer were completely dissolved (1 hr) with gentle stirring. Whatman filter paper was used to remove any remaining particles from the solution after the solute had been clearly dissolved in the solvent. After that, the resultant solution was left to evaporate at room temperature gradually. The resultant cocrystal was gathered, ground into a powder with a mortar and pestle to reduce the particle size, and then used for characterization.

Fourier-Transform Infrared Spectroscopy (FTIR)

Using the FTIR spectrophotometer (Bruker Alpha), FT-IR spectra were obtained using the potassium bromide disc method. The wavelength range used for the scans was 500-4000cm^{-1}.

Measurements using Powder X-ray Diffraction (PXRD)

The PAN analytical Benchtop X-ray diffractometer was used to investigate the PXRD patterns of methocarbamol and cocrystals. The following were the established measuring conditions: Copper metal target, 40 kV, 40 mA, and a kα filter. The 2θ range of 5-40°C was used for the analysis. To prevent particle orientation during processing, methocarbamol and the cocrystals were placed on the sample holder and flattened.

Thermal property measurements

A Mettler-Toledo DSC apparatus was used to perform the samples' Differential Scanning Calorimetry (DSC) examination, utilizing an empty standard aluminum pan as a reference unit. The device was indium-calibrated for temperature and heat flow accuracy before use. In sealed non-hermetic aluminum pans, 10 mg of powdered methocarbamol and cocrystals were heated to a temperature range of 50-250°C at a heating rate of 10°C/min. The tests were conducted at a flow rate of 50 mL/min in a dry nitrogen gas atmosphere.

Solubility

Solubility studies were performed for both methocarbamol, and the Methocarbamol-Ascorbic Acid (MAC) cocrystals. Each sample was introduced into 10 mL of dissolution media, including ethanol, dimethyl formamide, and phosphate buffer (6.8), each in separate glass vials. The mixtures were maintained at room temperature (25±2°C) for approximately 24 hr to ensure equilibrium. Once equilibrium was achieved, an aliquot of the samples was filtered through Whatman filter paper, and the drug concentration was measured spectrophotometrically at 220 nm.

Dissolution test

Dissolution tests were performed using a Labindia DS 8000 apparatus. The tests were conducted in 900 mL of Phosphate buffer (pH 6.8) maintained at 37 ± 0.5°C and stirred at 50 rpm. A 10 mg dose of the MAC cocrystal was added to the dissolution medium, and samples were withdrawn at predetermined time intervals of 5, 10, 15, 20, 25, and 30 min over a total duration of 45 min. To maintain sink conditions, the dissolution medium volume was replenished to 900 mL with fresh buffer after each sampling. The collected samples were immediately filtered, appropriately diluted, and analyzed using UV-visible spectrophotometry at 222 nm.

RESULTS

Prediction of HSPs

For methocarbamol, the obtained values for the dispersion (δd_i), polar (δp_i), and hydrogen bonding (δh_i) components were 19.13, 5.75, and 14.93 $MP_a^{0.5}$, and the total solubility parameter (δ) was 24.93 $MP_a^{0.5}$ (Table 1). The HSP values for ascorbic acid were determined as δd_i = 20.10, δp_i = 19.45, and δh_i = 22.49 $MP_a^{0.5}$, with a total δ of 35.89 $MP_a^{0.5}$. The difference in total solubility parameters (Δδ = 10.96 $MP_a^{0.5}$) indicates a moderate miscibility between methocarbamol and ascorbic acid. The difference in total solubility parameters (Δδ) between the methocarbamol and ascorbic acid was 15.67, suggesting limited miscibility based solely on overall cohesive energy. The volume-dependent solubility parameter (δv) was calculated as 13.73. The Ra(v) factor, representing the "distance" between the two compounds in solubility parameter space, was found to be 158.3.

Following the same methodology, Δδ, δv and Ra(v) were calculated for the selected coformers (Table 1 and also see supplementary material for calculations). While a higher Ra(v) generally indicates reduced miscibility, the substantial hydrogen-bonding capacity of ascorbic acid and methocarbamol likely facilitates cocrystal formation, demonstrating that specific intermolecular interactions can overcome inherent differences in dispersion and polar forces.

Preparation of cocrystals

In the present work, cocrystals for methocarbamol were prepared using ascorbic acid as a conformer. The cocrystals were prepared using the solvent evaporation method. The melting point of methocarbamol (95.3°C) and ascorbic acid (189-190°C) differed significantly from that of the cocrystal, which exhibited a new melting range of 167-169°C. This shift toward an intermediate melting temperature supports the successful formation of a cocrystal.

Fourier-Transform Infrared Spectroscopy (FTIR)

A reliable and widely used spectroscopic technique for analyzing the interaction between the API and coformer is infrared spectroscopy, which is especially useful for detecting the creation of hydrogen bonds in cocrystals (Qiao *et al.*, 2011). When compared to the FTIR spectra of methocarbamol (Figure 1), the MAC cocrystals showed a shift in absorption peaks (Figure 2). The absorption peaks of MAC cocrystal showed shifting of O-H stretching from 3588.96 to 3600.90 cm^{-1}, N-H stretching from 3446.78 to 3452.94 cm^{-1}, C-H stretching from 2824.00 to 2858.59 cm^{-1}, C=O stretching from 1671.48 to 1720.42 cm^{-1}, C=C stretching from 1598.60 to 1599.50 cm^{-1}. The shifting of the absorption peaks of FTIR spectra of MAC cocrystal indicates the appearance of intermolecular hydrogen bond interactions between functional groups of methocarbamol and ascorbic acid.

Measurements using Powder X-ray Diffraction (PXRD)

A non-destructive technique for detecting changes in a molecule's crystal lattice is PXRD. Every molecule has a distinct XRD pattern, and any changes to a molecule's crystal lattice have an impact on the relative intensity and 2θ position of peaks. PXRD studies are useful for detecting a new crystalline phase because the XRD pattern produced by the new crystalline phase is different from that of its parent molecule (Padrela *et al.*, 2012; Bolla *et al.*, 2017; Chernyshev, 2023). The PXRD pattern of MAC cocrystal diffractogram (Figure 3) showed difference with the PXRD pattern of the starting materials (Figure 4). The PXRD pattern of cocrystal has new crystalline peaks at 2θ values of 10.29, 10.41, 11.70, 12.58, 13.40, 14.10, 15.63, 16.03, 17.03, 17.21, 17.47, 19.88, 19.72, 20.93, 22.46, 23.56, 24.71, 24.85, 25.13, 21.13, 27.94, 29.96, 24.66, 31.61, 35.46, 37.43, 45.11. It indicated that, MAC cocrystal has a different crystal lattice arrangement with the crystal lattice of methocarbamol. The change in crystal lattice arrangement of molecules indicates the formation of cocrystal.

Table 1: Theoretical prediction of cocrystal formation by the Hoftyzer-Van Krevelen method.

Sample	δ value	Δδ	Δδ ≤ 5MPa$^{0.5}$	δv	Ra (v)
Methocarbamol	24.93	-	-	-	-
Ascorbic acid	35.89	-	-	-	-
Caffeine	29.3	-		-	-
Glycine	24.60	-	-	-	-
Myristic acid	19.31	-	-	-	-
Succinic acid	28.87	-	-	-	-
Methocarbamol: ascorbic acid	15.67	10.96	Yes	13.73	158.3
Methocarbamol: caffeine	17.62	4.37	Yes	17.42	55.76
Methocarbamol: glycine	3.203	0.35	Yes	2.55	241.6
Methocarbamol: myristic acid	9.357	5.62	Yes	4.06	91.64
Methocarbamol: succinic acid	5.85	3.94	Yes	5.70	219.75

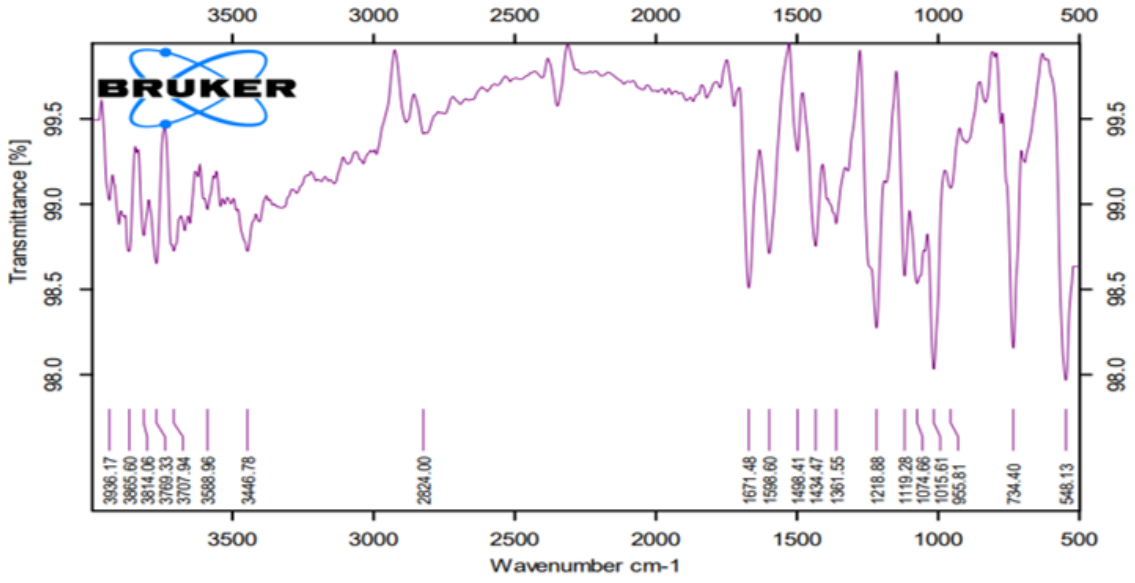

Figure 1: FTIR spectra of methocarbamol.

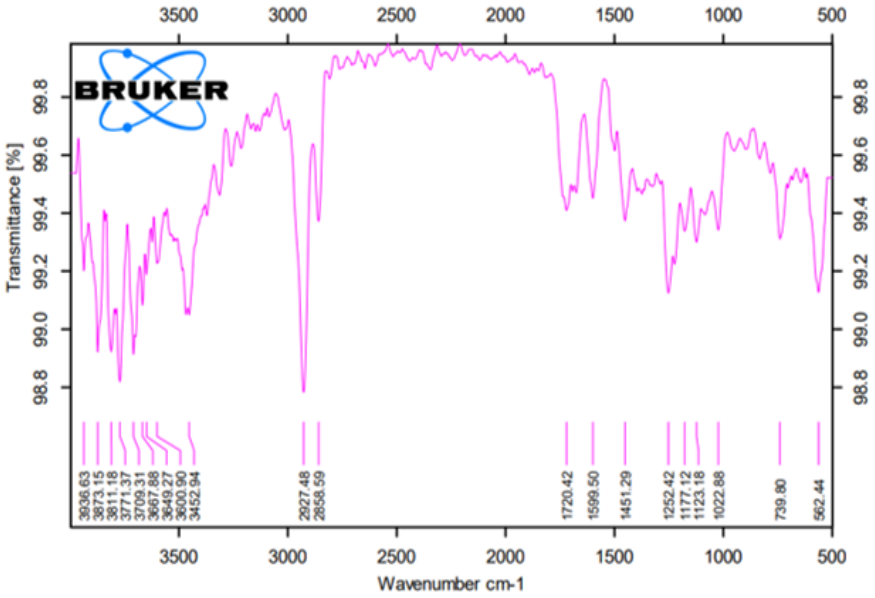

Figure 2: FTIR Spectra of MAC cocrystal.

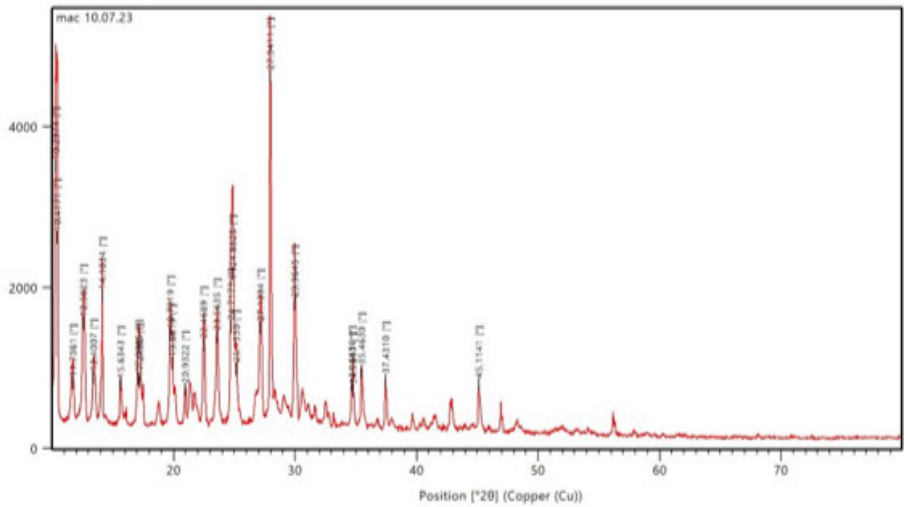

Figure 3: PXRD of MAC by solvent evaporation method.

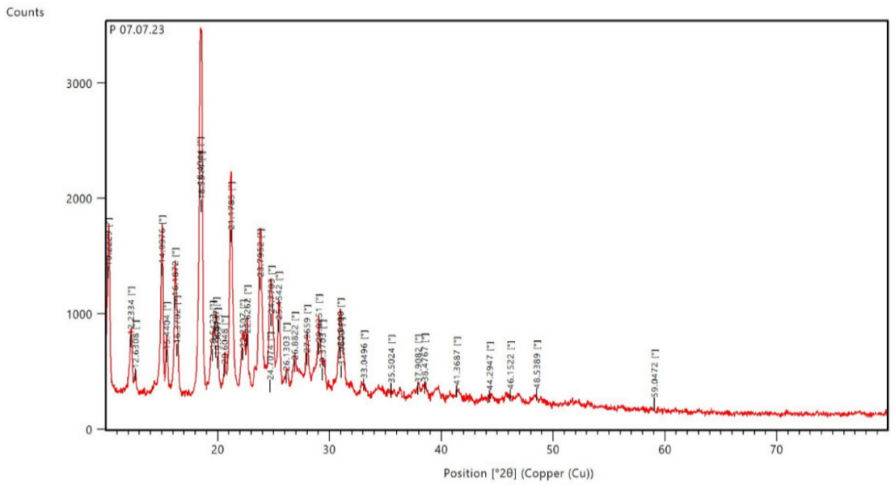

Figure 4: PXRD of methocarbamol.

Solubility

The studies on saturated solubility of methocarbamol, MAC cocrystals were conducted in various dissolution mediums, including an aqueous medium, 0.1N HCl, and phosphate buffer at pH 6.8. Methocarbamol exhibited low solubility across all tested dissolution mediums (Aqueous medium = 0.025 mg/mL, 0.1N HCl = 1.141 mg/mL, and phosphate buffer at pH 6.8 = 0.242 mg/mL). In contrast, the MAC cocrystal demonstrated enhanced solubility in the phosphate buffer at pH 6.8, measuring 0.844 mg/mL, in 0.1N HCl at 2.073 mg/mL, and in aqueous media at 0.091 mg/mL. These results indicate that the synthesized cocrystals possess greater solubility compared to pure methocarbamol.

Thermal property measurements

To investigate the molecular state of methocarbamol within the cocrystal, DSC was used. A clear endothermic peak at 98.06°C, which is the melting temperature of the crystalline drug, was visible in the DSC thermograms for methocarbamol and the MAC cocrystal (Figure 5). On the other hand, endothermic peaks linked to MAC were visible in the produced cocrystal at 97.18°C, 165.57°C, and 184.01°C (Figure 6). When compared to methocarbamol, the created cocrystal's peaks show noticeable changes, which suggests that the cocrystal formed successfully.

Dissolution test

The dissolution profile of methocarbamol and MAC cocrystals in a phosphate buffer solution at pH 6.8 is illustrated in the Figure 7. The initial percentage of drug release (after 5 min) for methocarbamol and MAC cocrystal is 3.6% and 6.2%, respectively, while the final percentage of drug release (after 30 min) for methocarbamol and MAC cocrystal is 87.2% and 99.3%, respectively. These results indicate that the MAC cocrystal exhibited improved dissolution characteristics compared to the methocarbamol drug. The MAC cocrystal demonstrated superior dissolution behavior in comparison to methocarbamol.

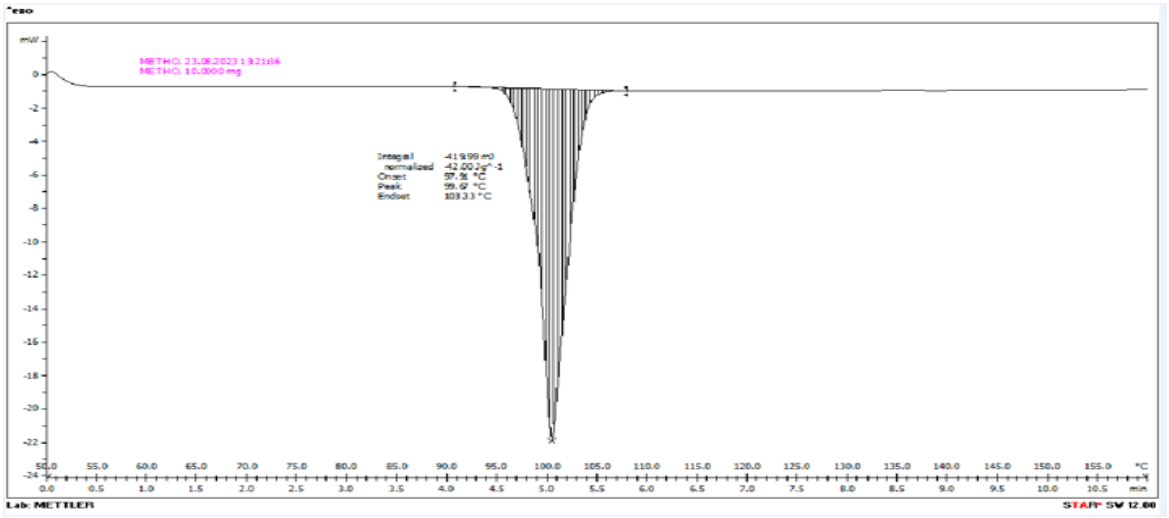

Figure 5: DSC thermogram of methocarbamol.

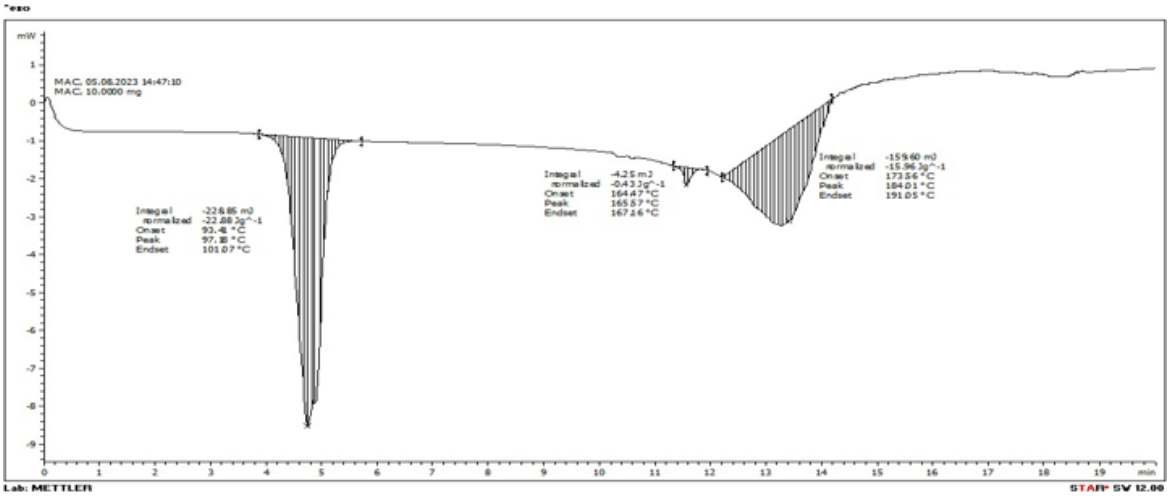

Figure 6: DSC thermogram of MAC cocrystal.

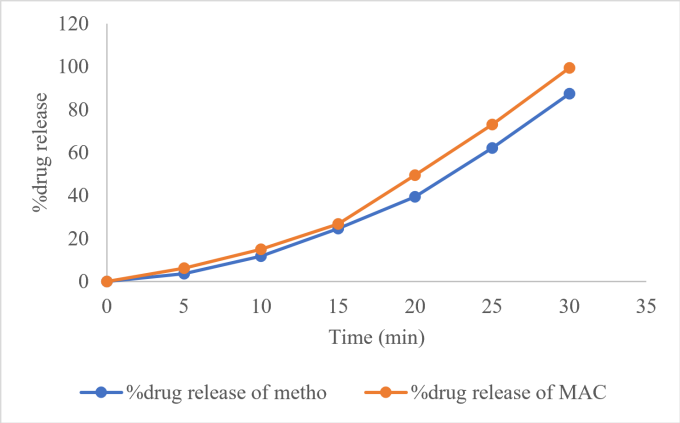

Figure 7: Dissolution profiles of methocarbamol, MAC cocrystal.

DISCUSSION

The study demonstrated that cocrystallization of methocarbamol with ascorbic acid effectively enhanced the solubility and dissolution of the poorly soluble drug. Theoretical prediction using HSPs confirmed moderate miscibility between methocarbamol and ascorbic acid, with a $\Delta\delta$ value of 10.96 $MPa^{0.5}$, supporting the feasibility of cocrystal formation. FTIR analysis revealed characteristic shifts in -OH, $-NH_2$, and C=O stretching vibrations, confirming hydrogen bonding between the drug and coformer without chemical modification of the parent structures. PXRD patterns of the Methocarbamol-Ascorbic acid Cocrystal (MAC) showed new peaks and altered intensities compared with pure methocarbamol, indicating formation of a distinct crystalline lattice. DSC thermograms exhibited multiple endothermic transitions at 97.18°C, 165.57°C, and 184.01°C, confirming the presence of a new crystalline phase and ruling out physical mixing.

Solubility studies demonstrated nearly two-fold enhancement in 0.1 N HCl (2.07 mg/mL for MAC vs. 1.14 mg/mL for methocarbamol), and improved dissolution behavior with 99.3% release in 30 min compared to 87.2% for the pure drug. The improved solubility and faster dissolution are attributed to the disruption of the parent lattice and formation of strong intermolecular hydrogen bonds that facilitate better wettability and reduced lattice energy. Overall, both theoretical and experimental data confirmed the successful formation of methocarbamol-ascorbic acid cocrystals. The findings validate HSP-based prediction as an efficient tool for coformer selection and emphasize cocrystallization as a viable approach to enhance the biopharmaceutical performance of BCS Class II drugs.

CONCLUSION

Pharmaceutical cocrystals of methocarbamol were successfully synthesized with ascorbic acid, yielding satisfactory results. The preparation of the methocarbamol cocrystals was conducted using the solvent evaporation technique, followed by characterization through FTIR, PXRD, and DSC, which validated the formation of new solid crystalline phases. FTIR analysis indicated molecular interactions between methocarbamol and the coformer. PXRD analysis of the newly synthesized cocrystals showed new endothermic diffraction peaks in comparison to methocarbamol. DSC analysis indicated that the melting points of the MAC cocrystals differed from those of the initial components. The synthesized cocrystals exhibited enhanced solubility (2.07 mg/mL) compared to methocarbamol (1.14 mg/mL) in 0.1N HCl, along with improved dissolution behavior. The predicted HSPs indicated that the theoretical parameters were in good agreement with the experimental results. Therefore, the findings confirm that cocrystallization enhances the physicochemical properties of the drug methocarbamol.

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ABBREVIATIONS

HSP: Hansen Solubility Parameter, **MAC:** Methocarbamol-ascorbic acid, **FTIR:** Fourier-Transform Infrared Spectroscopy, **PXRD:** Powder X-ray Diffraction, **DSC:** Differential scanning calorimetry.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

Agustina, R. E. N. I., & Setyaningsih, D. (2023). Solid dispersion as a potential approach to improve dissolution and bioavailability of curcumin from Turmeric (*Curcuma longa* L.). *International Journal of Applied Pharmaceutics*, 37–47. https://doi.org/10.22159/ijap.2023v15i5.48295

Aitipamula, S., Banerjee, R., Bansal, A. K., Biradha, K., Cheney, M. L., Choudhury, A. R., Desiraju, G. R., Dikundwar, A. G., Dubey, R., Duggirala, N., Ghogale, P. P., Ghosh, S., Goswami, P. K., Goud, N. R., Jetti, R. R. K. R., Karpinski, P., Kaushik, P., Kumar, D., Kumar, V., (2012). Polymorphs, salts, and cocrystals: What's in a name? *Crystal Growth and Design*, *12*(5), 2147–2152. https://doi.org/10.1021/cg3002948

Bagley, E. B., Nelson, T. P., & Scigliano, J. M. (1971). Three-dimensional solubility parameters and their relationship to internal pressure measurements in polar and hydrogen bonding solvents. *Journal of Paint Technology*, *43*, 35–42.

Beebe, F. A., Barkin, R. L., & Barkin, S. (2005). A clinical and pharmacologic review of Skeletal Muscle Relaxants for musculoskeletal conditions. *American Journal of Therapeutics*, *12*(2), 151–171. https://doi.org/10.1097/01.mjt.0000134786.50087.d8

Bolla, G., Chernyshev, V., & Nangia, A. (2017). Acemetacin cocrystal structures by powder X-ray diffraction. *IUCrJ*, *4*(3), 206–214. https://doi.org/10.1107/S2052252517002305

Chadha, R., Saini, A., Arora, P., & Bhandari, S. (2012). Pharmaceutical cocrystals: A novel approach for oral bioavailability enhancement of drugs. *Critical Reviews in Therapeutic Drug Carrier Systems*, *29*(3), 183–218. https://doi.org/10.1615/CritRevTherDrugCarrierSyst.v29.i3.10

Chernyshev, V. V. (2023). Structural characterization of pharmaceutical cocrystals with the use of laboratory X-ray powder diffraction patterns. *Crystals*, *13*(4), 640. https://doi.org/10.3390/cryst13040640

Duggirala, N. K., Perry, M. L., Almarsson, Ö., & Zaworotko, M. J. (2016). Pharmaceutical cocrystals: Along the path to improved medicines. *Chemical Communications*

(Cambridge, England), *52*(4), 640–655. https://doi.org/10.1039/c5cc08216a, https://pubmed.ncbi.nlm.nih.gov/26565650/

Guide for industry. Regulatory classification of pharmaceutical co-crystals. (2018). United States Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER).

Kumar Bandaru, R., Rout, S. R., Kenguva, G., Gorain, B., Alhakamy, N. A., Kesharwani, P., & Dandela, R. (2021). Recent advances in pharmaceutical cocrystals: From bench to market. *Frontiers in Pharmacology*, *12*, Article 780582. https://doi.org/10.3389/fphar.2021.780582

Kumar, S., & Nanda, A. (2018). Approaches to design of pharmaceutical cocrystals: A review. *Molecular Crystals and Liquid Crystals*, *667*(1), 54–77. https://doi.org/10.1080/15421406.2019.1577462

Li, C., Li, Z., Liu, X., Xu, J., & Zhang, C. (2024). Machine learning approach to predict Hansen solubility parameters of cocrystal coformers via integrating group contribution and COSMO-RS. *Journal of Molecular Liquids*, *408*, Article 125319. https://doi.org/10.1016/j.molliq.2024.125319

Mohammad, M. A., Alhalaweh, A., & Velaga, S. P. (2011). Hansen solubility parameter as a tool to predict cocrystal formation. *International Journal of Pharmaceutics*, *407*(1–2), 63–71. https://doi.org/10.1016/j.ijpharm.2011.01.030

Novaes, F. J. M., De Faria, D. C., Ferraz, F. Z., & De Aquino Neto, F. R. (2023). Hansen solubility parameters applied to the extraction of phytochemicals. *Plants*, *12*(16), Article 3008. https://doi.org/10.3390/plants12163008

O'Doherty, D. S., & Shields, C. D. (1958). Methocarbamol; new agent in treatment of neurological and neuromuscular diseases. *Journal of the American Medical Association*, *167*(2), 160–163. https://doi.org/10.1001/jama.1958.02990190014003

Padrela, L., De Azevedo, E. G., & Velaga, S. P. (2012). Powder X-ray diffraction method for the quantification of cocrystals in the crystallization mixture. *Drug Development and Industrial Pharmacy*, *38*(8), 923–929. https://doi.org/10.3109/03639045.2011.633263

Qiao, N., Li, M., Schlindwein, W., Malek, N., Davies, A., & Trappitt, G. (2011). Pharmaceutical cocrystals: An overview. *International Journal of Pharmaceutics*, *419*(1–2), 1–11. https://doi.org/10.1016/j.ijpharm.2011.07.037

Regulatory classification of pharmaceutical co-crystals: Guidance for industry. (2018). Center for Drug Evaluation and Research, United States Department of Health and Human Services, FDA. https://www.fda.gov/media/81824/download

Richards, B. L., Whittle, S. L., Van Der Heijde, D. M., & Buchbinder, R. (2012). The efficacy and safety of muscle relaxants in inflammatory arthritis: A Cochrane systematic review. *Journal of Rheumatology*, *39*, 34–39.

Roszkowski, A. P. (1960). A pharmacological comparison of therapeutically useful centrally acting Skeletal Muscle Relaxants. *The Journal of Pharmacology and Experimental Therapeutics*, *129*, 75–81. https://doi.org/10.1016/S0022-3565(25)25789-5

Sánchez-Lengeling, B., Roch, L. M., Perea, J. D., Langner, S., Brabec, C. J., & Aspuru-Guzik, A. (2019). A bayesian approach to predict solubility parameters. *Advanced Theory and Simulations*, *2*(1), Article 1800069. https://doi.org/10.1002/adts.201800069

Schlegelmilch, R., Eydeler, A. U., Barkworth, M., & Radeke, A. (2009). Bioequivalence study with two different oral formulations of methocarbamol in healthy subjects. A mono-centre, comparative, randomized, open-label, single-dose, 2-way crossover study. *Arzneimittel-Forschung*, *59*(5), 238–242. https://doi.org/10.1055/s-0031-1296391

Schultheiss, N., & Newman, A. (2009). Pharmaceutical cocrystals and their physicochemical properties. *Crystal Growth and Design*, *9*(6), 2950–2967. https://doi.org/10.1021/cg900129f, https://pubmed.ncbi.nlm.nih.gov/19503732/

Sibrack, J., Patel, P., & Hammer, R. (2022). Methocarbamol. In *StatPearls* [Internet]. StatPearls Publishing

Stoler, E., & Warner, J. C. (2015, August 14). Non-covalent derivatives: cocrystals and eutectics. *Molecules*, *20*(8), 14833–14848. https://doi.org/10.3390/molecules200814833, https://pubmed.ncbi.nlm.nih.gov/26287141/

Thakkar, H., Patel, B., & Thakkar, S. (2010). A review on techniques for oral bioavailability enhancement of drugs. *International Journal of Pharmaceutical Sciences Review and Research*, *4*(3), 203–223.

Truitt, E.J., & Little, J. M. (1958). A pharmacological comparison of methocarbamol (AHR-85), the monocarbamate of 3-Ortho methoxyphenoxy-1,2-propandiol with chemically related interneuronal depressant drugs. *Journal of Pharmacology and Experimental Therapeutics*, *122*, 239–246.

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