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Hansen Solubility Parameters in Pharmaceutical Cocrystal Screening: From Group Contribution Methods to Machine Learning-Assisted Prediction

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ABSTRACT
This review summarizes the theoretical basis of HSPs and discusses the major group contribution methods used for HSP estimation, including the Fedors, Hoy, and Van Krevelen approaches. The application of HSPs in pharmaceutical cocrystal screening, acceptance criteria for cocrystal prediction, and representative case studies involving poorly soluble drugs are critically examined. The advantages and limitations of HSP-based prediction methods are also discussed, highlighting the need for experimental validation of predicted cocrystal systems. Furthermore, recent advances involving machine learning, artificial intelligence, molecular descriptors, and COSMO-RS-assisted screening strategies are reviewed as emerging approaches to improve prediction accuracy and coformer selection. The integration of traditional group contribution methods with modern computational technologies is expected to accelerate pharmaceutical cocrystal discovery and reduce experimental workload. Overall, HSP-based screening remains a valuable and practical tool for early-stage cocrystal development and continues to evolve through advances in data-driven and computational methodologies.

INTRODUCTION

The development of pharmaceutical cocrystals has become an important strategy for improving the solubility, dissolution, stability, and bioavailability of poorly water-soluble drugs [1–4]. A critical challenge in cocrystal engineering is the identification of a suitable coformer capable of interacting with an active pharmaceutical ingredient (API) to form a stable crystalline phase [5,6]. Because experimental screening of hundreds of potential coformers is labour-intensive and expensive, predictive tools have gained increasing attention [7,8]. Among these, Hansen Solubility Parameters (HSPs) are widely used as a preliminary screening method because they provide a simple estimation of molecular compatibility using only structural information [9–12].

Evolution of HSP-Based Cocrystal Prediction

The application of HSPs to pharmaceutical cocrystals was first systematically explored by Mohammad, Alhalaweh, and Velaga in 2011.Their work demonstrated that the difference between the solubility parameters of an API and a coformer could be used to estimate the probability of cocrystal formation [13]. The study proposed that compounds with similar cohesive energy densities exhibit greater molecular affinity and therefore a higher tendency to form cocrystals [13,14].

Subsequent investigations expanded the use of HSPs as a rapid screening tool and integrated them with other approaches such as supramolecular synthons, hydrogen-bond analysis, pKa prediction, and crystal structure databases [15–19]. Researchers recognized that HSPs alone cannot fully explain cocrystal formation, but they remain valuable for reducing the number of coformers subjected to experimental evaluation [10,16,20].

Theoretical Basis of Hansen Solubility Parameters

HSPs predict drug-coformer miscibility, which can suggest cocrystal formation and aid in cocrystal screening. Solubility properties can be utilised to forecast the compatibility of cocrystal components, which can aid in the selection of potential coformers before thorough cocrystal screening.

These methods were used to calculate the solubility parameter. Different functional groups' contributions to thermodynamic properties is additive, according to group contribution methodologies.[21.]For theoretical calculations, the group contribution approach is used, which aids in the selection of a drug-coformer compatibility. The Hansen solubility parameter indicates whether an API and its coformer will form a molecular complex. By forecasting whether the chemical complex will form or not, the group contribution lowers practical work. The calculations for Fedors, the Hoy's, and the Krevelen approach involves the binding of atoms or molecules to a structure.

HSP theory assumes that intermolecular interactions arise from three major contributions:

- Dispersion forces (δd)
- Polar interactions (δp)
- Hydrogen-bonding interactions (δh)

The total Hansen Solubility Parameter is calculated as:

$\delta t = \sqrt{(\delta d^2 + \delta p^2 + \delta h^2)}$

When the HSP values of an API and a coformer are similar, the molecular compatibility is expected to be greater, thereby increasing the likelihood of cocrystal formation. This principle has become the foundation for many cocrystal screening studies

Calculating the solubility parameter-By Group Contribution Method

A molecule's intermolecular force interaction is described by its partial solubility characteristics. All structural pieces in molecules contribute to molecular force and molar volume. We can estimate Fedor's claimed group contribution to molecule molar volume and van Krevelen/Hoftyzer group contribution to molecular forces using the [22-24]partial solubility parameters. [25]

It is usual practice to compute the HSP using the group contribution method since it just needs the compound structure[26,27] HSP calculation's most common group contribution methods are Fedors, Hoy, and van Krevelen.[28] An example for solubility parameter calculation is shown below.

Calculation of HSPs and molar volume for Indometacin by using group contribution method.[29]

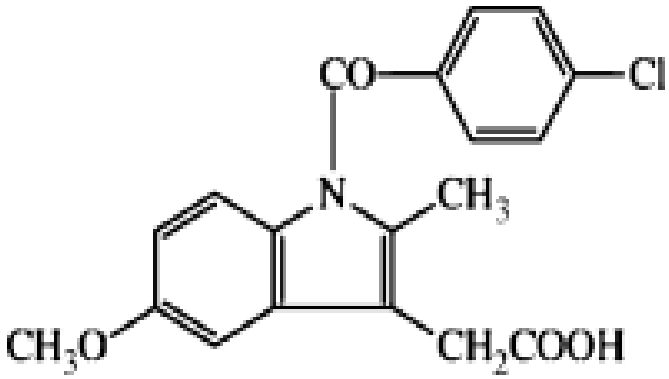

Fig-1 Structure of Indometacin

Table 1. Fedors substituent method[30]

Structural group)	No.of Groups	Constant energy mixing for each fragment (cal/mol	Total ΔΔU (cal/mol)	Constant molar volume foreach fragment (cm3 /mol)	Total ΔV (cm3 /mol)
-CH^3	2	1125	2250	33.5	67
–CH^2–	1	1180	1180	16.1	16.1
=CH–	3	1030	3090	13.5	40.5
>C=	5	1690	8450	6.5	32.5
–Cl	1	2760	2760	24	24
–O–	1	800	800	3.8	3.8
–CO–	1	4150	4150	10.8	10.8
–COOH	1	6600	6600	28.5	28.5
–N<	1	1000	1000	-9.0	-9.0
Conjugated bond	7	400	2800	-2.2	-15.4
Ring closure 5ormore atoms	2	250	500	16.0	32
			∑ΔΔU=33580		ΔV=230.8

ΔΔU is constant for energy mixing and ΔV is constant for molar volume

Based on Fedors substituent constant;

$$\delta = \sqrt{\Sigma\Delta\Delta U}$$

$$= \sqrt{\frac{\Sigma\Delta V}{33580}}$$

$$= \sqrt{\frac{230.8}{145.49}}$$

$$\delta = 12.06H \text{ or } 24.12 \text{ mpa}^{0.5}$$

Table 2. Hoys method

Structural group	No of group	Molar attraction	Total molar attraction	ΔV	Total ΔV
-CH3	2	148.3	296.6	21.548	43.096
–CH2–	1	131.50	131.50	15.553	15.553
=CH–	3	117.12	351.36	13.417	40.251
>C=	5	98.12	490.6	7.42	37.1
–Cl	1	205.06	205.06	24	24
–O–	1	114.98	114.98	6.462	6.462
–CO–	1	262.96	262.96	17.265	17.265
–COOH	1	326.58	326.58	27	27
–N<	1	61.08	61.08	12.569	12.569
Conjugated bond	7	23.26	162.82	--	--
Ring closure 5 or more atoms	2	-23.44	46.88	--	--
phenylene (ortho, meta, para)	o-1	9.69	9.69	--	--
	m-2	6.6	13.2	--	--
	p-1	40.33	40.33	--	--
Base value	1	135.1	135.1	--	--
			2648.74		223.296

$$\delta = \frac{\sum \text{molar attraction}}{V}$$

$$= \frac{2648.74}{223.296}$$

δ =11.86 H or 23.72 mpa$^{0.5}$

Table 3. Partial solubility or van krevelen method[31]

Group Frequency	No of groups	Fd(J $^{1/2}$ cm$^{3/2}$ mol^{-1})	Fp^2(J$^{1/2}$cm$^{3/2}$ mol^{-1})	Fh (J/mol)	Vm (cm^3/mol)
–CH2–	1	270	0	0	16.1
–CH3	2	840	0	0	67
>C=	5	350	0	0	-27.5
=CH–	3	600	0	0	40.5
–Cl	1	450	302,500	400	24
–CO–	1	290	592,900	2000	10.8
–COOH	1	530	176,400	10000	28.5
–N<	1	20	640,000	500	-9
-O-	1	100	160000	3000	3.8
Phenylene (o, m,p)	1	1270	12100	0	52.4
Ring closure 5 or more atoms	2	380	0	0	32
∑		5100	1,883,900	20400	238.6

Where, Fd = Group contributions to dispersion forces
Fp = Group contributions to polar forces
Fh = Group contribution to hydrogen bond energy
V = Group contribution to molar volume
$\delta d = \sum F\, d/V$ = 21.37mpa$^{0.5}$
$\delta p = (\sum Fp2 / V)^{0.5}$ = 5.75mpa$^{0.5}$
$\delta h = (\sum U\, h /V)^{0.5}$ = 9.24mpa$^{0.5}$

$$\delta^2 T = \sqrt{\delta d^2 + \delta p^2 + \delta h^2}$$ = 23.98 mpa$^{0.5}$

Table 4. Calculated HSP values of coformers by different methods

Name of Conformer	Fedor's	Hoys	van Krevelen
Drug-indometacin	24.12	23.72	23.98
Saccharin sodium	27.78	28.1	23.99
Urea	29.43	34.61	21.71

Acceptance Criteria for Cocrystal Prediction: The scientists, Krevelen and Greenhalgh, propose a theoretical prediction of the co-crystal The scientists Krevelen and Greenhalgh propose a theoretical prediction regarding the co-crystal formulation. According to Krevelen, co-crystals may form if the value deviation is less than 5 MPa1/2. If the difference is 7 MPa1/2, Greenhalgh suggests the possibility of co-crystal formation. Furthermore, Salem et al. recently introduced a cut-off value of 8.18 MPa1/2, which is relaxed from previous values, making it more trustworthy.formulation. According to Krevelen, co-crystals may form if the value deviation is less than 5MPa$^{1/2}$. If the difference is 7 MPa$^{1/2}$, Greenhalgh suggests the formation of co-crystals.[32,33] Furthermore, Salem et al. recently shared a cut-off value of 8.18 MPa1/2, which is relaxed from previous values, which is more trustworthy.[34,35]

Table 5. Based on HSP, possibility of cocrystal formation

Sl.no.	Coformer	Fedors	Hoy"s	van Krevlen	Inference
1	Aspirin	-1.58	-2.85	3.75	**Cocrystal may form**
2	Benzamide	-4.73	-1.78	0.42	**Cocrystal may form**
3	Saccharin sodium	-3.66	-4.38	-0.01	**Cocrystal may form**
4	Urea	-5.31	-10.89	2.27	----

According to scientist Greenhalgh, the cut-off value is (5 MPa$^{1/2}$ to 8.18 MPa$^{1/2}$), and indometacin can be matched with the three coformers listed above (aspirin, benzamide, and saccharin sodium) to form effective cocrystals.

Pharmaceutical Applications

HSP-based screening has been applied successfully in the development of cocrystals for a variety of poorly water-soluble drugs. Studies involving compounds such as indomethacin, carbamazepine, meloxicam, itraconazole, and lamotrigine have demonstrated the usefulness of HSP calculations in identifying promising coformers before conducting laboratory experiments [5,20]. By narrowing the range of potential coformers, this approach can reduce both the time and resources required for experimental screening, thereby improving the efficiency of cocrystal development programs[20]

Limitations of HSP-Based Prediction

Despite its practical value, the HSP approach has certain limitations. The method primarily evaluates the overall compatibility between molecules and does not provide information about crystal packing or intermolecular arrangements within the solid state [2]. In addition, HSP calculations cannot reliably predict the stoichiometric ratio of the resulting cocrystal or distinguish between different polymorphic forms [4,19]. Factors such as molecular conformation, hydrogen-bond competition, and crystallization kinetics may also influence cocrystal formation but are not adequately captured by HSP calculations alone . Therefore, HSP analysis should be regarded as an initial screening technique rather than a definitive predictive tool. Confirmation of cocrystal formation still requires experimental characterization using techniques such as powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), Fourier-transform infrared spectroscopy (FTIR), and single-crystal X-ray diffraction (SCXRD).

Recent Advances

Recent developments in computational pharmaceutical science have expanded the application of Hansen Solubility Parameters (HSPs) beyond conventional group contribution methods such as those proposed by Fedors, Hoy, and Van Krevelen [14,36]. While these traditional approaches remain widely employed for estimating HSP values, recent studies have explored machine-learning techniques to improve prediction accuracy and facilitate the rapid screening of potential coformers [22]

Machine-learning algorithms, including Random Forest, Support Vector Machine (SVM), Artificial Neural Networks (ANN), and Extreme Gradient Boosting (XGBoost), have been applied to predict Hansen solubility parameters directly from molecular descriptors and structural features .These models are trained using datasets containing experimentally determined HSP values and have demonstrated improved predictive performance for complex pharmaceutical compounds when compared with conventional group contribution methods [37,-39].

In addition to HSP prediction, machine-learning models have been utilized to identify potential cocrystal-forming pairs by integrating HSP differences with molecular descriptors, hydrogen-bonding characteristics, and physicochemical properties [40]. Such approaches enable rapid virtual screening of large numbers of API–coformer combinations before experimental evaluation, thereby reducing the time and resources required for cocrystal discovery .

Recent investigations have also combined HSP calculations with COSMO-RS simulations and artificial intelligence frameworks to enhance coformer selection and improve the prediction of cocrystal formation These hybrid computational approaches provide a more comprehensive assessment of molecular compatibility than HSP calculations alone and have shown superior predictive capability in several pharmaceutical systems . As pharmaceutical databases continue to expand, data-driven methodologies are expected to play an increasingly important role in the design and optimization of pharmaceutical cocrystals.[41,42]

Future Perspectives

The growing availability of computational resources and pharmaceutical databases is expected to expand the role of HSP-based prediction in cocrystal research. Future developments are likely to involve the integration of HSP calculations with artificial intelligence, COSMO-RS simulations, molecular electrostatic potential analysis, and crystal structure databases. Such multidisciplinary approaches have the potential to improve the accuracy of coformer selection while minimizing experimental effort. As a result, HSPs are expected to remain an important component of early-stage cocrystal screening, particularly when used alongside complementary computational and experimental techniques[39]

CONCLUSION

Hansen Solubility Parameters have evolved from a simple miscibility concept into one of the most widely used computational tools for pharmaceutical cocrystal screening. Their ability to rapidly assess drug–coformer compatibility makes them particularly valuable during early-stage formulation development. Although HSPs cannot independently predict successful cocrystal formation, they substantially reduce experimental effort and serve as an effective starting point for coformer selection. Recent advances in machine learning and computational chemistry are further enhancing the predictive capability of HSP-based methods, ensuring their continued relevance in modern crystal engineering.

CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

Not applicable

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AI TOOL DECLARATION

The authors declare that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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