RESEARCH ARTICLE

Three-dimensional Hansen Solubility Parameters as Predictors of Miscibility in Cocrystal Formation

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Abstract

The objective of this study was to investigate whether the miscibility of a drug and coformer, as predicted by Hansen solubility parameters (HSPs), can indicate cocrystal formulation. It was also our aim to evaluate various HSPs-based approaches in miscibility predication. It is concerned with some new aspects of solvent properties, and these properties can help predict solvent behavior during the manufacturing processes and will be useful in predicting behavior in many other fields of endeavor. The work on the solubility parameter, in particular, deals with fundamental attractions among materials and should have broad application. To say that hydrogen bonding had no significant effect on solvent retention without defining hydrogen bonding was not satisfactory. To better define hydrogen bonding and polar bonding, a study based on the solubility parameter was initiated. This eventually led to the concept of a three-dimensional (3D) solubility parameter (E). The 3D solubility parameter is has been assumed that ΔE is given by the simple sum of the energies arising from dispersion forces, ΔE_d, polar forces, ΔE_p, and hydrogen bonding forces, ΔE_h. Group contribution method for the estimation of Hansen solubility parameters of pure organic compounds is presented by characteristic groups ensure the prediction of HSP for a broad series of organic compounds, including those having complex multiring, heterocyclic, and aromatic structures. The predictions are exclusively based on the molecular structure of compounds, and no experimental data are needed. Solubility parameters for solutes are obtained by group contribution method. Using Fedor's substituent constants, Hoy's molar attraction constants and Van Kreevalen constants were calculated and are currently used methods. The resultant Δ values of active pharmaceutical ingredient and coformers are compared, and their solid-state miscibility is expressed. Possibility of cocrystal formulation by Krevlens is $\Delta\delta < 5$MP and Greenhalgh $\Delta\delta < 7$MP can be predicted.

Key words: Cocrystal formation (Fedor's substituent constants, Hoy's molar attraction constants, and Van Kreevalen constants), Hansen solubility parameters, group contribution methods

INTRODUCTION

The poor solubility and dissolution rate of active pharmaceutical ingredient (API) are one of the main challenges in pharmaceutical development and are becoming more common among new drug candidates over the past due to the use of high throughput and combinatorial screening tools during the drug discovery and selection phase. The improvement of solubility and dissolution profiles of these lipophilic drug molecules without altering the molecular structure is a particular change for the successful development of pharmaceutical product.[1] According to the biopharmaceutical classification system (BCS), the compounds mostly belong to Class II which are poorly soluble and highly permeable according to the pH of gastrointestinal fluid and tend to present dissolution-limited absorption. Despite their high

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permeability, these drugs often have low oral bioavailability because of their slow and limited release of drug in gastrointestinal fluid. Therefore, one of the major challenges of the pharmaceutical industry is to apply strategies that improve the dissolution and/or apparent solubility of poorly soluble drugs to develop such problematic compounds into orally bioavailable and therapeutic effective drug.[2]

In the pharmaceutical industry, many life-saving drug compounds have to be discarded during the commercial production due to their low solubility, and solubility improvement of poorly water-soluble compound is one of the main challenges for the successful development of new drug.[2,3] Many approaches have been adopted for improving the aqueous solubility of drug such as micronization, salt formation, emulsification, solubilization using cosolvent, and use of coformer drug vehicles for delivery of poorly soluble drugs. Although these techniques have been shown to be effective at enhancing oral bioavailability, success of this approach is dependent on the specific physicochemical nature of the molecules being studied. Over the past decade, there has been growing interest in the design of pharmaceutical cocrystal, which emerges as a potential approach to enhance the solubility of drug.[4] Cocrystallization as a method of obtaining new forms of APIs with improved physicochemical properties (e.g., solubility, stability, and melting point) has gained much attention in the recent year and is a promising alternative to so for employed preparation of salt, hydrates, solvates, and other forms. Cocrystal design for a specific APIs is based on evaluating possible heteromolecular synthons, which are reliable hydrogen-bonding motifs sustaining crystal structures.[5]

Oral ingestion route is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, cost-effectiveness least sterility constraints, and flexibility in the design of dosage form. Crystal engineering offers a number of routes to improved solubility and dissolution rate, which can be adopted through an in-depth knowledge of crystallization, processes, and the molecular properties of API. Frequently, however, the API crystallizes into one or more crystal forms that possess undesirable physical properties, and hence, there is a need for the development of crystalline form of APIs with desired physicochemical properties. Various options are available including single components and multiple components modifications of an API, including polymorphs, salts, solvates, and hydrates. In addition to these established crystalline API modification, pharmaceutical cocrystal or crystalline molecular complexes involving an API have recently attracted interest as an alternative approach.[6]

As example fenofibrate (FNO) (isopropyl ester of 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl propanoic acid) is a widely used hypolipidemic drug. Its pharmacological activity consists in reducing triglyceride and cholesterol concentration in plasma. Solubility and permeability are the fundamental parameters controlling the rate and extent of drug absorption. According to the biopharmaceutical classification system (BCS), FNO is a Class II having low solubility and high permeability. Bioavailability of FNO solely depends on dissolution rate in the gastrointestinal tract. This drug is used mostly in lipid regulation as it decreases low-density lipoprotein (LDL) and very-LDL levels and increases high-density lipoprotein level.[2]

By relying on robust intermolecular interactions with demonstrated solid-state reproducibility, synthon-based cocrystal design has become increasingly important to the synthesis of new cocrystal materials. In the future, automated searches for formulation probabilities pertaining to the molecular structure of an API of interest will be an important step toward rational pharmaceutical cocrystal design.[4-6] The present investigation deals with formulation and pharmaceutical characterization of molecular complexes of FNO and coformer cocrystal.

SOLUBILITY

Solubility is major important physicochemical property of drug that is pertinent in pharmaceutical field because it helps in determining the extent of absorption and oral bioavailability. Solubility is defined as maximum amount of solute that will dissolve the most stable crystalline form in given volume of solvent at equilibrium condition of temperature and pressure. More correctly, solubility is defined as buffered, unbuffered, and intrinsic solubility.[7]

Buffered solubility is the solubility at given pH, and intrinsic solubility is solubility of neutral form of ionized drug. Unbuffered solubility is usually measured in water and is the saturated solubility of compound at final pH of solution. Solubility is the typical physical property referring to the ability of a given substance, the solute, to dissolve in a solvent.

Solvent

The component which forms major part of a solution and is capable to dissolve another substance to form a uniformly disperse mixture at the molecular level.

Solute

The solubility of solute is the maximum quantity of solute that can dissolve instance, the solute, to dissolve in a solvent, or quantity of solution at specified temperature.

Application of solubility

- Solubility is a fundamental importance in a large number of scientific disciplines and practical

applications, ranging from raw material processing to finished goods.

- Solubility is also said to be one of the "characteristic properties of a substance," which means that solubility is commonly used to describe the substance, to indicate a substance's polarity, to help to distinguish it from other substances as well as a to guide applications of substance [Table 1].[8]

Importance of solubility

- The most convenient and commonly employed route of drug delivery is oral ingestion due to its ease of administration, high patient compliance, cost effectiveness, least sterility constraints, and flexibility in the design of dosage form.
- The major challenge with the design of oral dosage forms lies with their poor bioavailability.
- The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, presystemic metabolism, and susceptibility to efflux mechanisms.
- The main cause for low bioavailability is attributed to poor solubility and low permeability.
- Solubility is an important aspect for other dosage forms such as parenterals as well. It is also important to achieve the desired pharmacological response.
- The drugs which are poorly soluble in water often require high doses to reach therapeutic plasma concentrations after oral administration.
- For any drug to be absorbed, it must be present in the form of an aqueous solution at the site of absorption. Water is mostly the solvent of choice for liquid pharmaceutical formulations. Most of the drugs are either weakly acidic or weakly basic having poor aqueous solubility.
- Among the new chemical entities being developed (NCE's), 40% are practically insoluble in water. The drugs which are administered orally it is a known fact that solubility is the most important one rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response.
- To improve the drug solubility and thereby increasing its oral bioavailability remains one of the most challenging aspects of drug development process, especially for oral- drug delivery system.
- The poor solubility and low dissolution rate of poorly water-soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability.

For BCS Class II drugs, especially, the bioavailability may be enhanced by increasing the solubility and certain aspects such as properties of drug under consideration, nature of excipients to be selected, and nature of intended dosage form [Figure 1].[9] The rate-limiting step for the BCS Class II drugs is drug release from the dosage form and solubility in the gastric fluid and not the absorption, so increasing the solubility in turn increases the bioavailability for BCS Class II drugs. The BCS has divided all the drugs into four classes.[8,9]

- Class I - High soluble and high permeable
- Class II - Low soluble and high permeable
- Class III - High soluble and low permeable
- Class IV - Low soluble and low permeable

Techniques for solubility enhancement

Solubility improvement techniques can be categorized into physical modification, chemical modifications of the drug substance, and other techniques.

Physical modifications

Particle size reduction includes micronization and nanosuspension, modification of the crystal habit includes polymorphs, amorphous form, and cocrystallization, drug dispersion in carriers includes eutectic mixtures, solid dispersions, solid solutions, and cryogenic techniques.

Chemical modification

Change of pH, use of buffer, derivatization, complexation, and salt formation.

Miscellaneous methods

Supercritical fluid process, use of adjuvant such as surfactant, solubilizers, cosolvency, hydrotrophy, and novel excipients.[9,10]

Table 1: Solubility criteria as per the USP and BP

Descriptive term	Part of solvent required per part of solute
Very soluble	<1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10000
Practically insoluble	10,000 and over

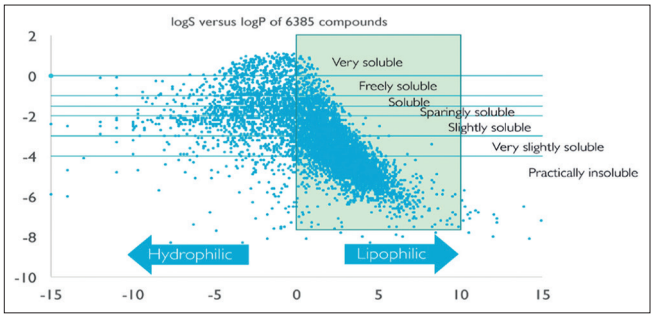


Figure 1: Flowchart of new chemical entities' in pipeline which is >80% are insoluble in nature

SOLUBILIZATION

The process of solubilization involves the breaking of interionic or intermolecular bonds in the solvate the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and solute molecular ion [Figure 2].[11]

The process of solubilization containing the following steps:

- The separation of the molecule of the solvent to provide space in the solvent for solute. The breaking of intermolecular ionic bonds in the solute.
- The interaction between the solvent and the solute molecule or ion [Figure 3].

HANSEN SOLUBILITY PARAMETER

The concept of a solubility parameter (δ) was introduced by Hildebrand and Scott, who proposed that materials with similar δ values would be miscible (Hildebrand and Scott, 1964). The Hansen solubility parameter (HSP) model in 1967, which was developed later, is based on the concept of dividing the total cohesive energy into individual components, i.e. dispersion, polar, and hydrogen bonding. HSPs have been widely used to predict liquid-liquid miscibility, miscibility of polymer blends, surface wettability, and the adsorption of pigments to surfaces (Hansen, 2007). In pharmaceutical sciences, HSPs have been used to predict the miscibility of a drug with excipients/carriers in solid dispersions. Further, it has been suggested that HSPs could predict the compatibility of pharmaceutical materials, and their use is recommended as a tool in the pre-formulation and formulation development of tablets. This study investigated whether the miscibility of a drug and its coformer components, as predicted by theoretical miscibility tools, could be used to predict the formation of cocrystal. FNO was selected as the model API. The HSPs of the coformers and FNO were calculated using group contribution methods. The miscibility of FNO with a coformer was predicted using three established miscibility tools. Based on the prediction of miscibility, laboratory screening for cocrystals was conducted using thermal methods and liquid-assisted grinding. The preliminarily characterization of cocrystal was performed using high-performance liquid chromatography, thermal methods, and powder X-ray diffraction.[12]

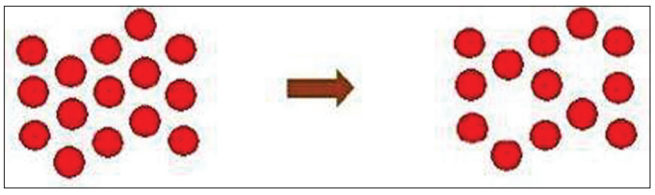


Figure 2: The representation of holes opens in the solvent

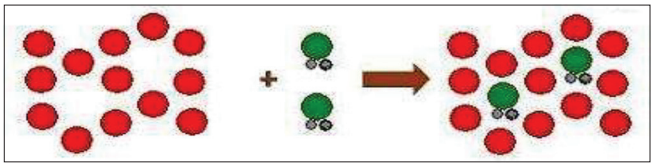


Figure 3: The representation of free solid molecule is integrated into the hole in the solvent

The concept of cohesive energy by means of numbers is been used, and the most common way is the solubility parameter δ concept. δ is the square root of cohesion energy density (CED) of a material, as it was developed by Hildebrand *et al*. based on regular solution theory.[13-15] They said that the heat of mixing two materials together is given as follows:

$$\Delta H = V_T \left(\sqrt{E_{v1} / V_{m1}} - \sqrt{\Delta E_{v2} / V_{m2}} \right)^2 \emptyset 1 . \emptyset 2 \quad (1)$$

ΔH is the heat of mixing, V_T is the total volume, ΔE_v is the energy of vaporization, V_m is the molar volume, δ is the volume fraction, and 1 and 2 stands for the solute and solvent. Hildebrand *et al*. named the energy of vaporization per unit volume as the cohesion energy density (CED).

$$\delta=(CED)^{0.5}=(\Delta E/V)^{0.5} \quad (2)$$

Where, V is the molar volume.

Hansen assumed that total cohesion energy is the sum of dispersion E_D, polar E_P, and hydrogen bond energy E_H

$$E_T=E_D+E_P+E_H \quad (3)$$

And by dividing both sides of the equation by molar volume V, we will have the total Hansen solubility parameter or Hansen solubility parameters δT:

$$\delta^2_T = \delta^2_D + \delta^2_P + \delta^2_H$$

Where:

δ = Total solubility parameter
δ = Dispersion interactive (London) force
δ = Permanent dipoles in interacting molecules, called dipole-dipole interactive forces
δ = Hydrogen bonding force.

If δ_T of both solute and solvent is alike, this will allow predicting solubility according to equation.[1] The common used units for δ in literatures are (J/m^3) 0.5, MPa 0.5, or (cal/cm^3) 0.5, where 1 (cal/cm^3) 0.5 is equivalent to 2.0421 MPa 0.5 or (J/m^3) 0.5.[2] δ calculation methods were varied between practical and theoretical ones according to either direct/indirect measuring of intrinsic properties of material as evaporation temperature, viscosity, and solubility in predetermined solvents.

GROUP CONTRIBUTION METHODS

These methods have been used to estimate the solubility parameter. Van Kreevlen's, Fedor's, and Hoy's method have reviewed these techniques and given tables of group values [Tables 2-6]. The molar volume of solvents and polymers can also be estimated by group contribution techniques. The group contribution values of van Kreevlen's and Hoftyzer are based on cohesive energy data of polymers/coformer. The group contribution techniques are based on the assumption that the contributions of different functional groups to the thermodynamic property are additive.[15]

The group contribution method is used for theoretical calculation which helps for the selection of coformer which is compatible with drug. The Hansen solubility parameter predicts whether drug and coformer are compatible and form the molecular complex with drug and coformer. The group contribution reduces practical work by predicting whether the molecular complex is formed or not. The Fedor's method, Hoy's method, and Van Kreevlen's method calculation are based on the attachment of atom or molecules from the structure. These methods are used for theoretical calculation of solubility. The theoretical prediction or possibility of cocrystal formulation by krevelens and Greenhalgh methods mainly confers, based on delta(Δ) value ≤ 5MP and ≤ 7 MP respectively.[16]

Methods for estimating solubility parameter/group contribution method

The partial solubility parameters describe the ability of molecule to interact with another one of the some or different types through intermolecular forces. The molecular force and molar volume are composed by the sum of the contribution of all structural fragments which are present in the molecules.[17-19] Fedor's supposed group contribution to the molar volume of molecules and van Krevelen/Hoftyzer group contribution to the molecular forces by combining both methods and partial solubility parameters can be calculated as follows:

$$\delta_d = \frac{\sum_i \mathrm{Fd}_i}{\sum_i V_i} \quad (4)$$

$$\delta_P = \frac{\sqrt{\sum_i F2p_i}}{\sum_i V_i} \quad (5)$$

$$\delta_h = \frac{\sqrt{\sum_i Fh_i}}{\sum_i V_i} \quad (6)$$

Where,
i = Structural group within the molecules
F_d = Group contributions to dispersion forces
F_p = Group contributions to polar forces
F_h = Group contribution to hydrogen bond energy
V_i = Group contribution to molar volume.

CAMBRIDGE STRUCTURAL DATABASE (CSD)[20-24]

The CSD is a repository for small molecule crystal structures. Scientists use single-crystal X-ray crystallography to determine the crystal structure of a compound. Once the structure is solved, information about the structure is saved, but in CSD, scientists can search and retrieve structures from the database. Scientists can use the CSD to compare existing data with that obtained from crystals grown in their laboratories. The information can also be used to visualize the structure in a variety of software such as atoms and powder cell. This is particularly important for analytical reasons because it facilitates the identification of phases present in a crystalline powder mixture without the need for growing crystals.

Many of the small molecules are organic compounds that can potentially act as medical drugs, and CSD is used for

Table 2: Atomic and group contributions to the heat of vaporization

Atom or group	Δh_i, Cal/mol	Atom or group	Δh_i, Cal/mol
CH_3	1780	COOH	8970
$=CH_2$	1780	$COOCH_3$	5600
CH_2	990	$COOC_2H_5$	6230
=CH	990	NH_2	3530
CH	–380	Cl	3400
O	1630	F*	2060
OH	7250	Br*	4300
	4270	I*	5040
CHO	4700	NO_2*	7200
		SH*	4250

Table 3: Atomic and group contributions to the normal and true lyoparachor

Atom or group	Δli, (cal/g)$^{4/5}$ cm^3/mole	$\Delta\lambda$i, (cal/g)$^{3/4}$ cm^3/mole
C	−1193.6	−804.5
H	844.8	593.4
N	−112.7	−48.3
O (ether)	178.3	146.5
O (ketone)	2092.1	1505.4
O (Ketone)*	2206.0	1573.0
O (carboxylate)	903.6	649.1
O (anhydride)*	1330.5	956.0
O (carbonate)*	660.0	477.0
CN (aliphatic)*	2504.0	1810.0
CN (aromatic)*	2133.0	1553.0
Cl	873.9	643.1
Br	217.2	189.5
I	−17.2	40.5
Branch in carbon chain	−132.7	−94.7
Benzene in ring bonds	5788.6	4002.4
Cyclohexene ring bonds	1166.1	793.7
Cyclohexene ring bonds*	2860.0	19.67.0
O (carbonate)*	550	420
F**	530	380
Sn**	−1440	−960
NO_2 (nito)**	1680	1230
Double bond**	1470	1010
Double bond*	1670	1174
Triple bond**	3580	2510
Tripe bond*	3344	2334
Pyridine ring bonds**	5900	4130
Furan ring bonds**	4260	2950

*As per reference 17, ** Provisional values

structural comparisons among these related molecules that can suggest new leads for drug design.

The information stored in the CSD for each entry can be considered in three classes.

- First, there is the text-based (and sometimes numeric) information, containing the bibliography (i.e., full literature reference, where appropriate), chemical names and formulae, some experimental information about the crystal structure determination procedure, and any other information that may be available (e.g., compound's use and color and shape of crystals).
- Second, there is chemical connectivity information in the form of a two-dimensional structural diagram, which is the basis of much of the sophisticated search mechanisms for the CSD system.
- Third, there is the crystallographic information, consisting of unit cell dimensions and space group, and atomic coordinates. In this third category, where the true value of the database lies.

The rational design of cocrystals is usually based on supramolecular synthons. However, this has some limitations which are usually handled by cocrystal screening, a trial-and-error procedure. For practical applications, development costs will depend on the number of screening experiments needed before a suitable cocrystal former is found. Hence, it is important to find such factors by the statistical analysis of data on cocrystals from the CSD.[25]

COCRYSTALLIZATION

"Cocrystals are homogeneous solid phases containing two or more neutral molecular components in a crystal lattice with defined stoichiometry, which are solids at room temperature

Table 4: Molar attraction constants at 25°C

Atom or group	Δf_i, cal$^{1/2}$ cm$^{3/2}$	Atom or group	Δf_i, cal$^{1/2}$ cm$^{3/2}$
CH_3	214	H (variable)	80–100
CH_2	133	O (ether)	70
CH (single bonded)	28	CO (ketone)	275
C (single bonded)	–93	CO_2 (ether)	310
CH_2=(double bonded)	190	CN	410
-CH=(double bond)	111	Cl (mean)	260
C=(double bonded)	19	Cl (single)	270
CH≡C	285	Cl (twinned as in CCl_2)	260
-CT≡C-	222	Cl (triple as in CCl_3)	250
Phenyl	735	Br (single)	340
Phenylene (o, m, p)	658	I (single)	42
Naphthyl	1146	CF_2	150
Ring, 5-membered	105-115	CF_3	274
Ring, 6-membered	95-105	S (sulfides)	225
Conjugation	20-30	SH (thiols)	315
		NO_3 (nitrate)	440
		NO_2 (aliphatic nitro)*	440
		PO_4 (organic phosphate)	500

*As per reference 17, ** Provisional values

Table 5: Atomic and group contributions to the energy of vaporization and molar volume at 25°C

Atom or group	Δe_i, Cal/mole	$\Delta \mu_z$, Cal/mole/no. C-atoms	Δv_i, cm^3/mole
CH	970	0	–0.5
CH_2	1230	0	16.5
CH_3	990	0	34.0
OH	7830	–0.08	8.7
NH_2	2570	–0.09	19.0
Cl	2790	–0.06	24.0
CHO	4340	–0.17	26.0
COOH	7830	+0.22	27.0
CH_3CO	-	-	42.5
$CH=CH_2$	2000	0	44.0
CH_3COO	5550	–0.10	50.5
$CH(CH_3)_2$	2950	0	6705
Phenyl	7450	–0.22	75.0
Cyclohexyl	7040	–0.22	95.0

and are held together by weak interactions, mainly hydrogen bonding." Cocrystals can be constructed through several types of interaction, including hydrogen bonding, p stacking, and Van der Waals forces. Solvates and hydrates of the API are not considered to be cocrystals by this definition. However, cocrystals may include one or more solvent/water molecules in the crystal lattice. Cocrystals often rely on hydrogen-bonded assemblies between neutral molecules of API and other component. For non-ionizable compounds, cocrystals enhance pharmaceutical properties by modification of chemical stability, moisture uptake, mechanical behavior, solubility, dissolution rate, and bioavailability.[26,27]

A pharmaceutical cocrystal can be designed by crystal engineering with the intention to improve the solid-state properties of an API without affecting its intrinsic structure. Cocrystals can be considered as molecular complexes which differ from solid solutions or mixed

Table 6: Atomic and group contributions to the energy of vaporization and the molar volume at 25°C

Atom or group	Δe_i, Cal/mole	Δv_i, cm³/mole
CH_3	1125	33.5
CH_2	1180	16.1
CH	820	−1.0
C	350	−19.2
$H_2C=$	1030	28.5
-CH=	1030	13.5
C=	1030	−5.5
HC≡	920	27.4
-C≡	1690	6.5
Phenyl*	7630	71.4
Phenylene (o, m, p)*	7630	52.4
Phenyl (trisubstituted)*	7630	33.4
Phenyl (tetrasubstituted)*	7630	14.4
Phenyl (pentasubstituted)	7630	−4.6
Phenyl (hexasubstituted)	7630	−23.6
Ring closure 5 or more atoms	250	16
Ring closure 3 or 4 atoms	750	18
Conjugation in ring for each double bond	400	−2.2
Halogen attached to carbon atom with double bond	−20% of Δe_i of halogen	4.0
Co_3 (carbonate)	4200	22.0
COOH	6600	28.5
CO_2	4300	18.0
CO	4150	10.8
CHO (aldehyde)	5100	22.3
CO_2CO_2 (oxalate)	6400	37.3
C_2O_3 (anhydride)	7300	30.0
HCOO (formate)	4300	32.5
$CONH_2$	10000	17.5
CONH	8000	9.5
CON	7050	−7.7
HCON	6600	11.3
HCONH	10500	27.0
COCl	5000	38.0
NH_2	3000	19.2
NH	2000	4.5
N	1000	−9.0
-N=	2800	5.0
CN	6100	24.0
NO_2 (aliphatic)	7000	24.0
NO_2 (aromatic)	3670	32.0
NO_3	5000	33.5
NO_2 (nitrite)	2800	33.5
SCN	4800	37.0
NCO	6800	35.0

(*Contd...*)

Table 6: (*Continued*)

Atom or group	Δe_i, Cal/mole	Δv_i, cm³/mole
NF_2	1830	33.1
NF	1210	24.5
O	800	3.8
OH	7120	10.0
OH (disubstituted or adjacent C atoms)	5220	13.0
PO_4	5000	28.0
PO_3	3400	22.7
SH	3450	28.0
S	3380	12
S_2	5700	23.0
SO_3	4500	27.6
SO_4	6800	31.6
F	1000	18.0
F (disubstituted)	850	20.0
F (trisubstituted)	550	22.0
CF_2 (for perfluoro compounds)	1020	23.0
CF_3 (for perfluoro compounds)	1020	57.3

*As per reference 17, ** Provisional values

crystals. Cocrystals are divided into cocrystal anhydrates and cocrystal hydrates. Salts can be differentiated from cocrystals in that the former mainly improve solubility and stability of a compound, while the later is an alternative to salt when salts do not have solid properties due to the absence of ionizable salts in API. Structural properties of a cocrystal are based on structure of cocrystal former. Examples of cocrystal former include ascorbic acid, gallic acid, nicotinamide, citric acid, glutamic acid, histidine, urea, saccharine, glycine, succinic acid, sucrose, and alpha-ketoglutaric acid.[28]

Role of crystal engineering in pharmaceutical science

Crystal engineering strategies have been used in understanding and predicting hydrogen-bonding interactions in API. Pharmaceuticals are generally comprised of an API, a formulation containing inactive ingredient as a carrier system, and a package for market performance and appeal.[29] A crystalline form of the API is strongly preferred because of their relative ease of isolation and the physicochemical stability that the crystalline solid state affords. The vast majority of APIs occurs as solids; these include salts, polymorphs, cocrystals, and hydrates/solvates, as shown in Figure 4. The use of crystalline materials can result in problems such as poor solubility properties or the existence of more than one crystalline from of an API. However, crystal engineering affords a paradigm for rapid development of a pharmaceutical cocrystal.[30]

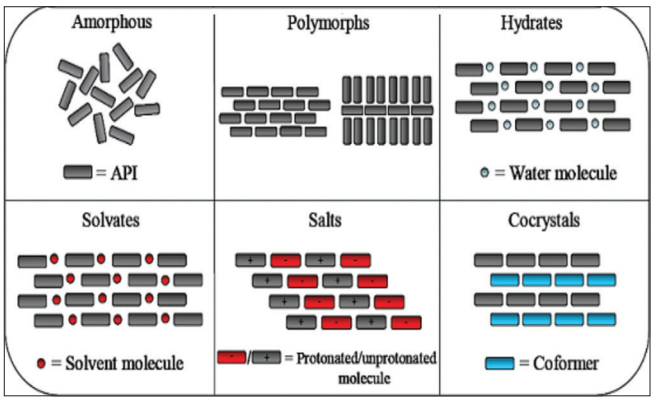


Figure 4: Comparison of cocrystal and other solid forms

Cocrystal versus salts, solvates, solid dispersions, and hydrates

Salt formation is generally directed at a single acidic and basic functional group, and cocrystal can simultaneously address multiple functional groups in a single reaction, including acidic, basic, and non-ionizable molecules. In the formation of salts, transfer of hydrogen atom occurs and it does not occur in the formation of cocrystals.[31]

If one component is liquid at room temperature, then the crystals are designated as solvates, and if both components are present in solid form, then crystals are designated as cocrystals. In solvates, one component is present in a liquid form, so they are less stable as compared to cocrystal. When solvent present in solvates is water, then it is termed as hydrates [Figure 5].

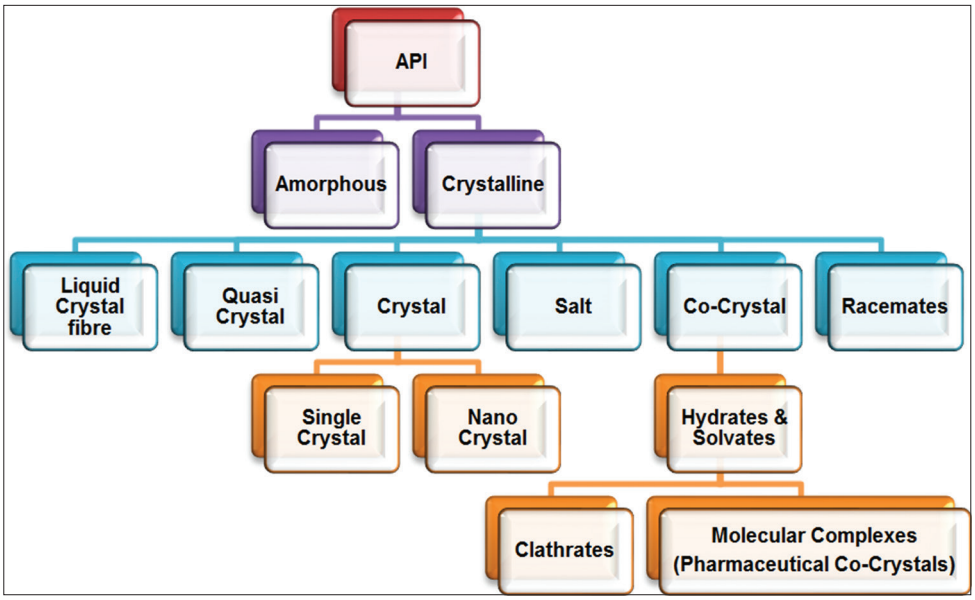


Figure 5: Various states of powders present in solid form

Problems encountered during the development of API

During the development and formulation of any API, several stringent performance parameter (e.g., solubility, dissolution rate, and stability) needs to be carefully considered [Figure 6]. It is thus not surprising that poor biopharmaceutical properties are the main reason that <1% of active compounds eventually make it into marketplace.[32-34]

Improvement in physicochemical properties by pharmaceutical cocrystal formation

It has been well established that issues ranging from poor solubility and inadequate dissolution properties to lack of crystallinity and attendant instability has been faced by the pharmaceutical industry. Recent studies have shown that an opportunity exists to use cocrystallization to replace the solid forms of API that is being used, by taking advantage of supramolecular synthons.[35]

Improvement in melting point behavior through cocrystallization

The thermal stability (i.e., melting point) is a fundamental physical property. There have been several literature reports where cocrystallization was used as a tool in improvement of melting point behavior of an API. These results showed that the API melting point can typically be fine-tuned according to which coformer is chosen; therefore, if a higher melting cocrystal is desired, then a higher melting coformer should be selected and *vice versa*.[36]

Modulating solubility through cocrystallization

The aqueous solubility of a drug substance is one of the fundamental properties evaluated early in discovery. Majority

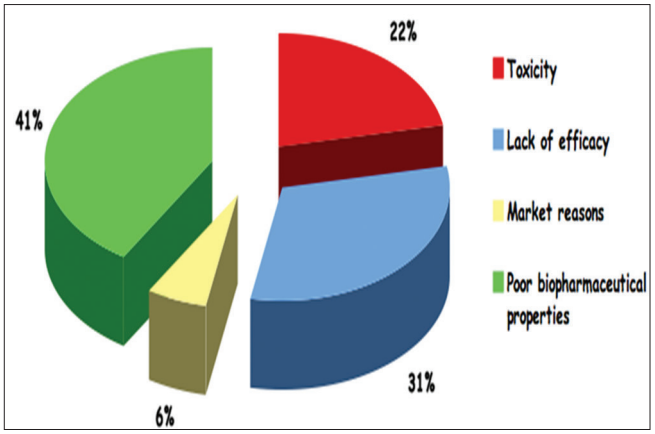


Figure 6: Success rate of new chemical entities development

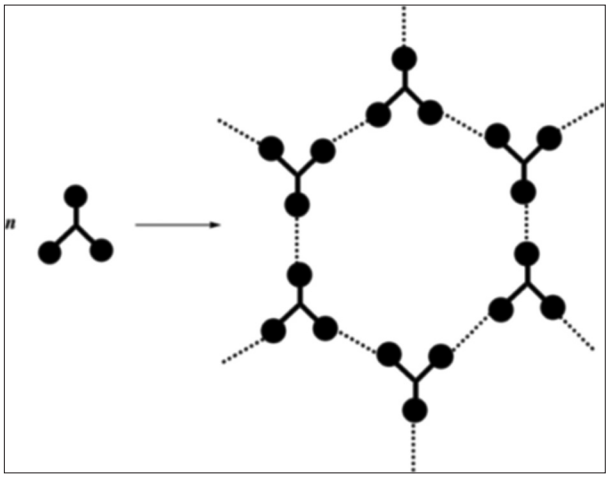
of APIs fall into BCS classification II, i.e., low solubility and high permeability; furthermore, aqueous solubility is a major indicator of the solubility in the intestinal fluids.[36] To generally describe solubility, the pharmacopoeia (USP) uses seven different solubility expressions as shown in Table 1.

Pharmaceutical cocrystals have been demonstrated to profoundly modify the solubility of the parent API, and at least 90 APIs have been studied in the context of cocrystallization. Often APIs that are targeted for pharmaceutical cocrystallization display undesirable solubility and possess multiple hydrogen bonding sites.[36]

In fact, Bak *et al.* highlighted the ability of a series of pharmaceutical cocrystals for improving the solubility of the parent API. It was found that oral administration of the cocrystal showed a maximum plasma concentration 8 times greater compared to the oral administration of the pure API. Similarly, Childs *et al.* highlighted a cocrystal that exhibited approximately 4-fold increase in plasma concentration over the pure API after a single oral dose.[37]

Hydrogen bond in cocrystal

- The success of cocrystal design by utilizing hydrogen-bonded supramolecular synthons clearly shows the importance of hydrogen bond in forming cocrystals.
- After metal coordination bonds and ionic interactions (e.g. dipole-dipole), the strongest interactions in crystal engineering are hydrogen bonds.
- Due to the strength, directionality, and ubiquitous presence of hydrogen bonds in organic molecules, it is also termed as the "key-interaction" in crystal engineering.
- For most pharmaceutical cocrystal structures, hydrogen bonds take an important role in directing intermolecular recognition between an API and a coformer molecule.
- A graph-set notation system introduced by was used widely to describe and label hydrogen-bond motifs.
- In the graph-set system, four principal motifs are used which are as follows: Chains (C), dimers (D), rings (R), and intramolecular hydrogen bonds (S), as descriptors of hydrogen-bonded molecular solids.



In addition, the following guidelines were proposed to facilitate the design of hydrogen-bonded solids: (1) All good proton donors and acceptors are used in hydrogen bonding; (2) if six-membered ring intramolecular hydrogen bonds can form, they will usually do so in preference to forming intermolecular hydrogen bonds; (3) the best proton donors and acceptors remaining after intramolecular hydrogen-bond formation form intermolecular hydrogen bonds to one another. With self-complementary hydrogen bond donor and acceptor, the formation of carboxylic acid homosynthon through C=O•H–O hydrogen bond is very common. Another widely studied homosynthon is amide homodimer, forming a cocrystal through C=O•H–N hydrogen bond. Counting donors and acceptors are insufficient to describe their complementarity. The formation of synthons is governed by the strength of hydrogen bonds between cocrystal formers rather than by the number of available groups.[18,38]

Mechanism of solubility enhancement

Solubility is determined by strength, crystal lattice, and salvation of cocrystal components. Solubility can be increased by lowering lattice energy or increasing solvent affinity. This is maintained by cocrystal formation. On the other hand, salvation plays a decisive role as hydrophobic drugs exhibit limitations due to solvent-solute interactions which reduce the observed solubility below that determine by lattice energy. Salvation lowers the observed solubility by as much as an order of magnitude in organic solvents and by as much as three orders of magnitude in water.[39] Melting point often stands a parameter to judge aqueous solubility of cocrystal indicate that solubility is frequently limited by salvation and not by lattice energy. In organic solvents, the melting point and cocrystal solubility are inversely proportional to magnitude of solvent-solute interaction which is proportional to magnitude of lattice strength. Consequently, melting point will be a poor indicator of aqueous solubility of cocrystals. Cocrystal solubility also been correlated with conformer solubility, as conformers generate or modify the physicochemical properties of API's and this is because of a decrease in salvation barrier for a cocrystal to an extent proportional to that of the pure components.[40] Examples of some pharmaceutical cocrystals with improved solubility of API are summarized in Table 7.

Cocrystal synthesis

Cocrystals contain two or more components which are held together by supramolecular synthons. To obtain cocrystal,

Table 7: Examples of some API with improved solubility through cocrystallization

Drug	Coformer	Method of preparation	Solubility	
			Drug	Cocrystal
Indomethacin	Saccharin	Supercritical fluid	2.5–4 μg/ml	3.7 mg/ml
Norfloxacin	Isonicotinamide	Solvent evaporation	0.21 mg/ml	0.59 mg/ml
Itraconazole	Succinic acid	Grinding	5 μg/ml	18 μg/ml
-	Maleic acid	-	-	17 μg/ml
Tadalafil	Salicylic acid	Neat cogrinding	0.41 mg/ml	1.4 mg/ml
Meloxicam	Aspirin	-	0.005 mg/ml	0.22 mg/ml
Miconazole	Succinic acid	Solvent evaporation	200 μg/ml	600 μg/ml

functional groups capable of forming supramolecular hetero- or homo-synthons should be present in the API and coformer. In supramolecular synthons approach, steps involved in developing cocrystals are as follows: (1) Choosing the target molecule (API), (2) finding the complementary functional groups which is capable of forming a hydrogen bond (coformer selection), and (3) methods of preparation.[41]

One of the main challenges in pharmaceutical cocrystal development is the selection of coformers that are compatible with a particular API. A general approach to coformer selection is by "tactless" cocrystal screening, whereby a predetermined library of pharmaceutically acceptable/approved compounds is used to attempt cocrystallization. The lead cocrystal candidate with superior physicochemical and pharmacological properties can then be developed into a dosage form.[28]

In another word, we can say that typical crystal form selection process comprises two stages of development after a target API molecule has been selected: (1) Discover as many pharmaceutical crystal forms as possible and (2) then examine the physicochemical properties of the newly discovered crystal forms. At the stage of crystal form discovery, two primary approaches are used. The more straightforward approach is largely based on trial-and-error. The alternative approach for crystal form discovery is the supramolecular architecture which recognizes supramolecular synthons as a design tool and can be more selective, time-efficient, and cost-effective. The supramolecular synthon approach uses crystal engineering to carefully analyze the relevant supramolecular arrangements that an API might exhibit by utilizing the CSD[42] and effectively prioritizes all possible guest molecules for crystal form screening of drugs, and another parameter is hydrogen bonding [Figure 7]. The supramolecular synthon approach is a statistical analysis that utilizes the CSD to effectively prioritize coformers for crystal form screening if an appropriate supramolecular heterosynthon can be identified. Examples of supramolecular heterosynthon.[43]

Another parameter is Hansen solubility parameters study which was used to investigate whether the miscibility of a drug and coformer is matching with the theoretical data. Hence, supramolecular synthon approach, CSD, hydrogen bonding, and Hansen solubility parameters these are most important parameter for selection of coformer in the cocrystal formation. In this review, all the parameters are explain and correlate with each other and cocrystal formation.[44,45]

Supramolecular synthon approach

A pharmaceutical cocrystal can be designed by crystal engineering with the intention to improve the solid-state properties of an API without affecting its intrinsic structure. Crystal engineering affords a paradigm for rapid development of pharmaceutical cocrystals. It can be defined as an application of the concepts of supramolecular chemistry to the solid state with particular emphasis on the idea that crystalline solids are actual manifestations of self-assembly. Crystal engineering relies on the basic principles of supramolecular chemistry, chemistry beyond the molecule, in developing novel entities by manipulating the non-covalent intermolecular interactions. Crystal engineering is also based on understanding the basic behind formation of synthons using non-covalent interaction. The term synthon was coined by Corey in the context of organic chemistry and defined as "structural units within supermolecules which can be formed and/or assembled by known or conceivable intermolecular interactions" [Figure 8]. A supramolecular synthon is a pattern that is composed of molecular and supramolecular elements. When crystal patterns repeat regularly, the pattern of interactions can be called a supramolecular synthon.[46]

Supramolecular synthons are further categorized into

Supramolecular homosynthon: Composed of identical self-complementary functionalities

Supramolecular heterosynthon: Composed of different but complementary functionalities.

Example of the supramolecular synthon which is commonly used is given as follows [Figure 9]:

1. Homosynthon formed between carboxylic acid dimer
2. Heterosynthon formed between carboxylic acid group and pyridine group
3. Homosynthon formed between amide dimer
4. Heterosynthon formed between carboxylic acid group and amide group
5. Heterosynthon formed between alcohol and ether group.

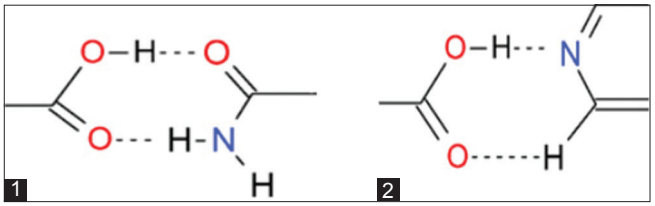


Figure 7: Supramolecular heterosynthons (1) carboxylic acid/amide (2) carboxylic acid/aromatic nitrogen

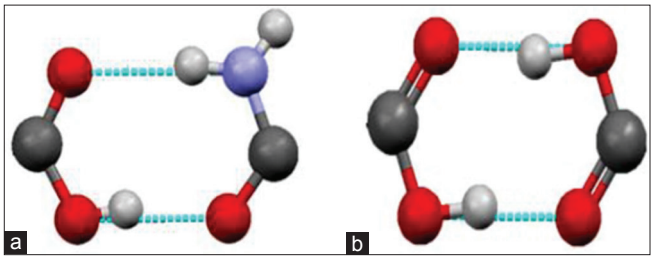


Figure 8: Types of supramolecular synthons. (a) Supramolecular homosynthon (in this case between two carboxylic acid groups). (b) Supramolecular heterosynthon (In this case between carboxylic acid and amide group)

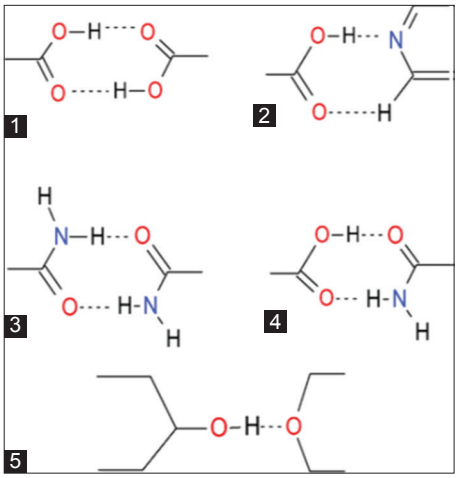


Figure 9: Most common supramolecular synthons in crystal engineering

DESIGN OF COCRYSTALS

The crystal engineering experiment typically involves the CSD survey followed by the experimental work. Cocrystals designed on the principal of the supramolecular synthesis; it provides a powerful approach for proactive discovery of novel pharmaceutical solid phases. Cocrystals consist of multiple components in given stoichiometric ratio, where different molecular species interact by hydrogen bonding and non-hydrogen bonding. The use of hydrogen bonding rules, synthons, and graph sets may assist in the design and analysis of cocrystal systems. In general, though prediction of whether cocrystallization will occur is not yet possible and must, at present, be answered empirically. Cocrystal formation may be rationalized by consideration of the hydrogen bond donors and acceptors of the materials that are to be cocrystallized and how they might interact. All good proton donors and acceptors are used in hydrogen bonding, six-membered ring intermolecular hydrogen bonds form in preference to intermolecular hydrogen bonds, and the best proton donor and acceptor remaining after intermolecular hydrogen-bond formation will form intermolecular hydrogen bonds to one another (but not all acceptors will necessarily interact with donors). A detailed understanding of the supramolecular chemistry of the functional groups present in a given molecule is the prerequisite for designing the cocrystals because it facilitates the selection of the suitable cocrystal former.[47] Supramolecular synthons that can occur in common functional group to design new cocrystals and certain functional groups such as carboxylic acids, amides, and alcohols are particularly amenable to formation of supramolecular heterosynthon. The strong hydrogen bond includes (N-H---O), (O-H---O), (-N-H---N), and (O-H---N). The weak hydrogen bonds involves the –C-H---O and C-H---O=C.[17,18]

Methods of preparation of cocrystals

Cocrystal formation described in the literature indicates the notoriously difficult situation, these systems present with regard to preparation, and it has been known to take 6 months to prepare a single cocrystal of suitable quality for single X-ray diffraction analysis. This is partly because such a heteromeric system will only form if the non-covalent forces between two (or more) molecules are stronger than between the molecules in the corresponding homomeric crystals. Cocrystals can be prepared by solvent and solid-based methods. The solvent-based methods involve slurry conversion solvent evaporation, cooling crystallization, and precipitation. The solid-based methods involve net grinding, solvent-assisted grinding, and sonication (applied to either to wet or dry solid mixtures)80-85°.[48]

Neat grinding method

The accurately weighed quantity of drug and coformer in 1:1 molar ratio was grounded in mortar and pestle for 30 min, and the powder obtained was collected and stored in desiccator till further use.[49]

Solvent drop grinding

In the solvent drop grinding method, drug and coformer were weighted in 1:1 molar ratio and ground together with addition of 3–4 drops of ethanol. The mixture was ground for 30 min at room temperature.[4,7-45]

Slow evaporation method

The accurate weight of drug and coformer in 1:1 molar ratios was separately dissolved in ethanol. After stirring, it was mixed with each other store for 48 hrs at room temperature. The crystal obtained was collected and stored in tight container and stored in desiccators for further use.[46]

Antisolvent addition method

FNO (drug) and coformer were weight in 1:1 molar ratios were dissolved in 20 ml ethanol using moderate stirring. The solution was then filtered through a Whatman filter paper to remove any undissolved material. Distilled water was then added drop-wise to the above solution with constant stirring to induce cocrystal precipitation. The cocrystals were allowed to dry overnight in desiccators.[44]

Solution cocrystallization method

FNO (drug) and coformer in 1:1 molar ratio were dissolved in 20 ml ethanol with sonication, the saturation solution was kept overnight to evaporate solvent, and the crystal obtained after evaporation of ethanol was allowed to dry in the air.[45]

Slurry method

FNO (drug) and coformer were carefully weighted in 1:1 molar ratio, respectively. Both powders were mixed

homogeneously in mortar, and 15 ml of water was added to mixture to form slurry sample solution. The formed cocrystal was dried at temperature of 40°C for 48 h. The solid crystal was collected and stored in desiccators.[46]

PHYSICOCHEMICAL PROPERTIES OF COCRYSTALS

Melting point

Melting point is the temperature at which the solid phase is at equilibrium with the liquid phase. Melting point was found to be an important physical property where many physicochemical properties such as processability, solubility, and stability of drug depend on it. The melting point of FNO and its coformers (succinic acid, saccharin, and sucrose) was found to be 78–84°C by open capillary method. The differential scanning calorimetry observations showed the melting endotherm at 83.98°C.[49]

Hygroscopicity

Stability of a solid drug in the presence of atmospheric moisture can be explained clearly by hygroscopicity. Cocrystals generally exhibit less hygroscopicity than a crystal.[49]

Mechanical properties

To design a dosage form, mechanical properties of API play a prominent role. Mechanical properties of API help in formulation and processing of drug products. The crystalline structural properties influence these mechanical properties.[49]

Solubility

Cocrystal solubility is dependent on solution composition and pH. Cocrystal solubility can be calculated using the following equation.

$$[R]_T = \frac{K_{sp}}{[A]_T}\left(\frac{1+K_a}{[H^+]}\right)$$

$[R]_T$ = Total drug concentration at equilibrium,
K_{sp} = Solubility product of cocrystal,
K_a = acid ionization constant,
$[A]_T$ = Total coformer concentration,
$[H^+]$= Hydrogen ion concentration.

Cocrystal solubility is predicted to increase with pH and decreases as the coformer concentration solution increases.[45]

Bioavailability

Bioavailability is a measurement of the extent to which a drug reaches the systemic circulation. This is the main physicochemical property for a pharmaceutical cocrystal.[45]

Saturation solubility studies

Saturation solubility studies were carried out using ethanol as a solvent. Each excessive quantity (100 mg) of FNO and equivalent prepared cocrystals were taken in screw-capped test tubes with fixed volume (10 ml) of ethanol. The resultant suspension was treated at 37° with 100 rpm in incubator shaker. After 24 h, samples were withdrawn and filtered through 0.2 µ filter. The filtrate was suitably diluted with ethanol and analyzed at 290 nm in a UV/Vis spectrophotometer.[40]

Drug content

The prepared cocrystals were weighed, and process yield was calculated. From the prepared cocrystals, powder equivalent to 100 mg FNO was weighed and dissolved in 100 ml ethanol. The solution was filtered through a Whatman filter paper, and volume was adjusted to 100 ml. After sufficient dilution with ethanol, samples were analyzed spectrophotometrically at 290 nm, and FNO content was calculated.[40,41]

$$\%\ \text{Drug content} = \frac{\text{Actual amount of drug in co crystal}}{\text{Therotical amount of drug in co crystal}} \times 100$$

Stability studies

Stability studies for the samples were carried out as per the ICH guidelines. The samples (each 100 mg, $n = 3$) were kept for stability studies at 40 ± 2° and 75 ± 5% RH for 6 months in an environmental test chamber. The samples were kept in glass vials sealed with rubber plugs. After 6 months, the samples were withdrawn and analyzed for appearance, drug content, dissolution, Fourier transform infrared, and X-ray diffraction study.[42]

Advantages of cocrystals[45,46]

- Cocrystals having advantages such as stable crystalline form (as compared to amorphous solids).
- No need to make or break covalent bonds.
- Theoretical capability of all types of API molecules (weakly ionizable/non-ionizable) to form cocrystals.
- The existence of numerous potential counter-molecules (food additives, preservatives, pharmaceutical excipients, and other APIs).
- The only solid form that is designable through crystal engineering.

- Can be produced using solid-state synthesis green technologies high yield, no solvent, or by-products.
- Cocrystal formulation may offer for the pharmaceutical industry, opportunity of intellectual property protection, and the possibility of extending the life cycles of old APIs.
- Cocrystals are less prone to suffer polymorphic transformation, thus avoiding undesirable downstream processing surprises.
- Cocrystal do not involve structural modification of the parent molecules; therefore, in the case of designing cocrystals of marketed drugs, their development programs (including clinical trials) would be significantly shorter and less risky than those of NCEs.

Applications of cocrystals[45-50]

- Cocrystal engineering is relevant to production of energetic materials, pharmaceuticals, and other compounds. Of these, the most widely studied and used application is in drug development and more specifically, the formation, design, and implementation of active pharmaceutical ingredients, or API's.
- Changing the structure and composition of the API can greatly influence the bioavailability of a drug.
- The engineering of cocrystals takes advantage of the specific properties of each component to make the most favorable conditions for solubility that could ultimately enhance the bioavailability of the drug.
- The principal idea is to develop superior physicochemical properties of the API while holding the properties of the drug molecule itself constant.

CONCLUSION

The present investigation shows that the miscibility of drug and coformers as predicated by Hansen solubility parameter (HSP) can indicate cocrystal formulation. HSP for FNO drug over twenty coformers was calculated according to the group contribution method. The selection of coformer was based on hydrogen bond present in structure which clearly shows the importance of hydrogen bonding in forming cocrystals. Using Fedor's substitution constants, Hoy's molar attraction constants and Van Kreevalen's constant were calculated and currently used method. The resultant δ values of drug and coformers are compared, and their solid-state miscibility is expressed. Possibility of cocrystal formulation by krevlens is $\Delta\delta < 5$MP and Greenhalgh $\Delta\delta < 7$MP. There was a significant improvement in solubility and dissolution rate of drug in all cocrystal formulation due to alternation of surface properties of drug. The results revealed that the new solid-state form of FNO with coformer shows higher dissolution rate and are stable. By considering overall results, the cocrystal should be useful approach to improve poor solubility and dissolution rate.

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