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CRYSTAL DESIGN APPROACHES FOR SELECTION OF COFORMERS

Pharmaceutical Science

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ABSTRACT

Enhancing the solubility and dissolution of drugs is being an important step in research. To select coformers for crystallization which can increase solubility is an important step to be considered. In this review the different approaches for the selection of coformers is explained. The pKa based model can be considered as pre-tool. The software used for Cambridge Structural Database are also explained with their domains. Other methods like cosmo-rs, molecular electrostatic potential surface, lattice energy comparison, Hirschfeld surface analysis, Hansen's solubility parameter, thermodynamics and Gibb's free energy for design of cocrystals are also discussed. The review concludes with a list of commercially available cocrystals, drug and coformer used.

KEYWORDS

Crystal Design, Coformers, Cambridge Structural Design, Cosmo-Rs, Gibb's free energy.

Study of coformers with its drug compatibility has to be done before selection of coformers and is the important step to be solved. There is no proper regular and systemic approach for the selection of coformer. Many theoretical or expected and experience-based approaches have been mentioned for the selection of coformers. The list of coformers are generally selected from the substances that are identified as Generally Recognized As Safe (GRAS) by USFDA(Chandel et al., 2011).

Different approaches for the selection of coformers is done by the following techniques:

1. pKa BASED MODEL:
The difference in the pKa values of the drug and coformer are calculated. Generally, if the difference exists greater than 2 or 3 then salts are formed. If the ΔpKa value is less than 0 then cocrystals may be formed. There maybe chance of either salt or cocrystal formation when the difference lies between 0-3 (Yuan et al., 2010).
$\Delta pKa = [pKa\,(base) - pKa\,(acid)]$[57]

It can help as the prescreening tool and is the simplest tool that is available for cocrystal screening (3). Cruz-cabeza has done a set of 6465 crystalline complexes using Cambridge structures design and applied it in pKa screening. He found a linear relationship between the ionization and value of ΔpKa. Zone I have ΔpKa < -1 are non-ionic and zone III having ΔpKa >4 are ionic and zone II having ΔpKa -1to 4 may be either. For every increase in 1 ΔpKa value the proton transfer increases by 17%.

2. Cambridge Structural Database (csd): CSD is used to have a knowledge of hydrogen bonding possibility. 'Atoms' and 'Powder Cell' are two softwares used to visualize structure after information from CSD (Savjani, 2015). CSD is a continuously growing database of exact 3-dimensional structures of organic and metal organic compounds known by x-ray and neutron diffraction studies. It was started in the year of 1965 by Cambridge Crystallographic data centre, department of chemistry, Cambridge University (Battle et al., 2010). It provides all the information on bibliography, crystallographic data like structure lattice, crystal systems, symmetry, space groups, crystal packing, conformational analysis; molecular geometry, dimensions and stereochemistry. The relationship between structure and properties is also discussed[65]. CSD can be used to know the following details of a coformer

i) Crystal packing feature
ii) H-bond motif and their occurrence
iii) H-bond donor, acceptor and relation between them for prediction of cocrystal formation
iv) To assess the risk of polymorphism by H-bond propensities
v) Interaction of drug and coformer maps

Different domains of CSD used for crystal formation application are:

A. Hydrogen Bond Motif Searches: The inter molecular and intra molecular H-bonds frequency of occurrence between special functional groups can be known from the database(Wood et al., 2014). This is based on sython design principle; which assess the competition between homo and heterosynthons for a given API and coformer (Desiraju, 1995). Depending on the understanding of geometrics and orientations of present intermolecular interactions coformers are selected for co-crystallization with API.

B. Hydrogen Bonding Propensity: it explains the affinity of hydrogen bond formation between highly strongest hydrogen bond donor and highly strongest H-bond acceptor. The next bond is formed between the stronger H-bond acceptor and stronger H-bond donor (Etter, 1990, 1991a). It happens as the following steps (Delori et al., 2013; Galek et al., 2009).

1. Functional group definition and detection of dataset – the functional groups present in the drug are identified which are used for further detection.
2. Data sampling with model fitting – 2D structures of donor and acceptor are gathered and fitted in the model using a logistic regression procedure.
3. Model validation – the selected model is validated by using different statistical methods like Area Under Curve.
4. Target assessment – the H-bond propensities are selected for the target molecule I the range of 0-1.

This method takes into consideration the chemical environment of donor and acceptor atoms, their competition, aromaticity along with steric density (Chisholm et al., 2006; Wood & Galek, 2010).
c. Molecular complementary (Fabian's approach) – it is developed by Fabian (Fábián, 2009). He observed that cocrystal forming molecule have a similar molecular shape and polarity. Polarity factors are described by dipole moment, fraction of nitrogen and oxygen (FNO). Shape factors are described by short axis length (s), short/long axis ratio (s/l), medium/long axis ratio(m/l). this also maybe the reason why similar sized molecules tend to co-crystallize more (Duggirala et al., 2016; Fábián & Friščić, 2011). This method is particularly used when there are no hydrogen bond forming molecules in the target (Karki et al., 2010). And so, this tool is an excellent method for screening of coformers before co-crystallization experiment so as to select a good cocrystal.

3. Conductor Like Screening Model For Real Solvents(cosmo-rs):
This method was developed by Andreas Klamt. It has a theory of unique combination of the liquid phase thermodynamics and quantum chemical information which is applied for having an accurately predicted thermodynamic equilibrium properties of solvents (Klamt, 2011, 2018). This method is applied in prediction of solubility, solvate screening, hydrate screening, solvent screening, pKa prediction, coformer ranking, partition coefficient calculations etc, This is applied in cocrystal screeningas it assumes that miscibility of the components of cocrystals in melt phase after super cooling are similar to the solid state cocrystals; not taking into consideration the long range of packing order (Abramov et al., 2012; Loschen & Klamt, 2015). It eliminates the formation of hydrates and solvates (Abramov, 2015). The excess of the enthalpy H_{ex} of a final mixture of API and coformer to that of the individual pure cocrystal states represent the tendency towards cocrystal formation (Loschen & Klamt, 2016; Sathisaran & Dalvi, 2018).

$H_{ex} = H_{AB} - x_m H_{pureA} - x_n H_{pureB}$

Where,
H_{ex} - is excess enthalpy
H_{AB} – enthalpy of stiociometric mixture of compound A and B
x_m – molefraction of compound A
x_n – molefraction of compound B
H_{pureA} – enthalpy of pure form of compound A
H_{pureB} – enthalpy of pure form of compound B

4. Molecular Electrostatic Potential Surface (meps):
It is similar to the COSMO-RS method except that the intermolecular interactions are considered theoretically and experimentally in gaseous phase rather than in the liquid phase as in COSMO-RS. It takes into consideration, Gibbs free energy which is practically easy than enthalpy calculations (Hunter, 2004). The maxima and minima of the electrostatic potentials obtained are converted into hydrogen bond donor(α) and hydrogen bond acceptor(β) and the formation of cocrystal is estimated by their difference in interaction site energy pairs in cocrystal form and two pure individual forms (Hunter, 2004; Musumeci et al., 2011). The pairing is as explained by Etter, strongest hydrogen bond donor pairs with strongest hydrogen bond acceptor (Etter, 1990, 1991b). The process of MEPS goes as:

i. Optimization of geometrical shapes of API and coformers using DFT ab initio calculations.
ii. Finding maxima and minima on MEPS
iii. Determination of hydrogen bond donor (α) and Hydrogen bond acceptor(β)
iv. The difference between energies of interaction sites ΔE and pure forms (E_1 and E_2) and energy of cocrystal E_{co} are calculated.

5. Lattice Energy Comparision:
It is a virtual screening method which considers thermodynamic principles into consideration for the prediction of potential coformers. It explains that stable cocrystals are formed if the lattice energy of the cocrystal formed is higher than the pure components.

Karamertzanis et al explained lattice energy calculation in three steps

i) Obtaining large number of confirmations and their stability by CrystalPredictor (Issa et al., 2009; Karamertzanis & Price, 2006). Estimating inter and intramolecular energies and interpolating them over the precomputed ab initio calculations. It decreases the lattice energy by changing the variables that affect it.
ii) The data quality is improved by re-minimizing the energy by using CrystalPredictor.
iii) DMF flex algorithm is used to calculate intermolecular energy, molecular charge and thus the accuracy of calculating the lattice energies are improved (Karamertzanis & Price, 2006).

$E_{lattice} = U_{inter} + \Delta E_{intra}$
Where,
$E_{lattice}$ - lattice energy
U_{inter} – inter molecular lattice energy
ΔE_{intra} – conformational intramolecular energy penality

And,
$E_{lattice} = E_{lat(cocrystal)} - (E_{lat(coformer)} + E_{lat(partner)}$

If the difference is higher there is a greater possibility of cocrystal formation. It is applied in solid and liquid phases of salts, solvates and other systems. There is no requirement of assumptions about hydrogen bonds. Also, the issues regarding the different conformations are also avoided using the penalty energy reduction during the calculations (Issa et al., 2009; Kazantsev et al., 2010). Thus, it is better used than in other models.

PIXEL is the software used through this approach, developed by Gavezzotti (Gavezzotti, 2002, 2003); it uses the types of cohesive energies like coulombic, polarization, dispersion and repulsive forces. It is applied in cocrystal engineering(Surov et al., 2017a, 2017b).

6. Hirshfled Surface Analysis:
The partitioning of electron density within the crystal into molecular fragments defining the space that the molecule occupies in the crystal lattice is the main reason for Hirschfeld surface analysis (Spackman & Byrom, 1997). It is explained by electron distribution as the shape defining criteria and a function of weight w(r) to explain electron density at a given point 'r' for a specific molecule in the crystal lattice (Dunitz & Gavezzotti, 2009; Spackman & Jayatilaka, 2009).

$W(r) = \rho_{promolecule(r)} / \rho_{procrystal(r)}$
$= \sum A \epsilon molecule\ \rho_A(r) / \sum A \epsilon crystal\ \rho_A(r)$
$\sim \rho_{molecule(r)} / \rho_{crystal(r)}$

$\rho_A(r)$ is spherical average of atomic electron density on nucleus A promolecule and procrystals are sums of atoms of molecules and crystal if $w(r) > 0.5$ then a crystal has Hirschfeld surface (Dunitz & Gavezzotti, 2009; Spackman & Jayatilaka, 2009).

7. Hansens Solubility Parameter (hsp):
It was introduced by Hildebrand and Scott that miscible compounds exhibit similar solubility parameters (Hildebrand & Scott, 1964). According to Hansen, solubility parameters are divided into partial solubility parameters like polar (δ_p), hydrogen bonding(δ_h) and dispersion(δ_d).

Total solubility parameter, δ_t is determined by
$\delta_t = (\delta_p^2 + \delta_h^2 + \delta_d^2)^{0.5}$

According to Mohammed et al, if $\Delta\delta < 7\ MPa^{0.5}$ coformer and API are miscible and cocrystals are formed (Musumeci et al., 2011). This method is worth in other fields also along with pharmaceuticals (Hansen, 1967; Krauskopf, 1999).

8. Thermodynamics And Gibbs Free Energy For Design Of Cocrystals:
Taylor and day confirmed that cocrystals are more stable thermodynamically than their individual counter parts (Taylor & Day, 2018). It is explained by Gibbs free energy. Only enthalpy values of individual components and cocrystals were considered for knowing the efficiency of cocrystals formation(Roca-Paixão et al., 2019). Later, it was observed that Gibbs free energy in cocrystal thermodynamics alone can be ruled out without complete information of entropy of coformers and with full overview of thermodynamics of cocrystals formation(Perlovich, 2015).

In order to reduce the time and cost of finding newer coformers from GRAS and EAFUS list, screening methodologies are used to reduce the number of experimental trials and find potential coformers.

List Of Coformers Commercially Available:

Commercial name	Drug	Coformer
Suglat	Ipragliflozin	L-Prolin
1. Entresto®	Valsartan	Sacubitril
2. Steglatro®	Ertugliflozin	Z-Pyroglutamic acid
3. Depakote®	Valproic acid	Valproate sodium
4. Lexapro®	Escitalopram	Oxalate
5. Beta chlor®	Chloral hydrate	Betaine

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