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Research Article

COCRYSTALS: AN ALTERNATIVE APPROACH TO MODIFY PHYSICOCHEMICAL PROPERTIES OF DRUGS

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ABSTRACT

Co-crystallization is a new approach of enhancement of solubility, stability, bioavailability and other physicochemical properties. It offers a better optimization of physical and biopharmaceutical properties of drugs. Co-crystal formation involves intermolecular interaction such as Hydrogen bonding, Vander Waals forces and π-π stacking interactions. Robustness of potential intermolecular interaction and hydrogen bonding rules are the important aspects of co-crystallization experiment design. Characterization of co-crystal can be performed by power X-ray diffraction, single crystal X-ray diffraction, infrared spectroscopy, differential scanning calorimetry, scanning electron microscopy, solid state NMR, THz-TDS method. This review covers general consideration of selection of drug for co-crystallization, chemistry of co-crystallization including role of hydrogen bonding in co-crystallization, co-crystal effect on physicochemical properties and characterization of co-crystal using suitable method.

Keywords: Co-crystallization, physicochemical properties, hydrogen bonding.

INTRODUCTION

Poor dissolution rate, solubility, chemical stability andmoisture uptake influence therapeutic efficacy of manypharmaceuticals, and significantly lower the market valueof a drug[1].Among the biopharmaceuticalproperties, solubility remains a key issue withdrugs often discarded during commercialdue to their low solubility. Improvingsolubility of drugs is currently one of themain challenges for the pharmaceuticalindustry. Co-crystals offer a different pathway, where any API regardless of acidic, basic, or ionizable groups, could potentially be co crystallized[2]. Over 40 % of marketed drugs today have low solubility and in the R & D pipeline, 80 - 90 % of drug candidates could fail because of solubility issues[3].Therefore, in order to improve solubilityand dissolution rate, formulation scientists often used various basic approaches such as formation of salts, polymorphic and amorphous forms, solid dispersions, and inclusion complexes[4,5,6,7]. Co-crystallization alters the molecular interactions and composition of pharmaceutical materials, and is considered better alternative to optimize drug properties[2]. Multi-component crystals e.g. solvates,hydrates, co-crystals, salts play important role in thedesign of new solids particularly in the pharmaceutical area[1] [Fig:1]. Pharmaceuticalcocrystals provide an alternative way to modify the physicochemical properties of APIs; besides salt formation, and polymorphic and amorphous forms, that all have limitations in their utility[8].The definition of cocrystal has been a subject of intensedebate. In absence of a commonly accepted definition andto facilitate the organization of this review, the author definescocrystals as 'Crystals with structure constituted of multicomponents,generally in a stoichiometric ratio, among which oneor more components are neutral compounds[3].The cocrystal formation via crystal engineering approach requires a library of co-crystallizing agents or coformers[9]. A pharmaceutically acceptable, nontoxic coformer must be chosen to result in a pharmaceutically acceptable cocrystal.

Cocrystals can be made of non-ionizable drugs, which cannot undergo salt formation. In addition, for ionizable drugs, the number of suitable cocrystal formers can exceed the number of suitable salt formers[10].

Consideration for co-crystals[11] [Fig: 2]

(i) Drug molecules lacking easily ionisable functional groups (such as those containing carboxamide, phenol, weakly basic N-heterocyclic, etc.) can be intermolecular manipulated via co-crystals to tune their physicochemical properties.
(ii) Compound having particular sensitive groups to treatment of acid and base.
(iii) Availability of larger number of neutral GRAS compounds to make co-crystals as compared to counter ions to make pharmaceutical salts.
(iv) Overcoming problems in filterability through co-crystallizing a compound.

CHEMESTRY OF CO-CRYSTAL FORMATION

Co-crystal are formed to improve the solid-state properties of an API without affecting its intrinsic structure by co-crystal engineering. Crystal engineering is an application of theconcepts of supramolecular chemistry to the solid state with particular emphasis upon the idea that crystalline solids are actual manifestations of self-assembly[12,13]. Cocrystalsare constructed from intermolecular interactions such as van der waals contact forces, π-π stacking interactions, and hydrogen bonding. Crystal engineering involves modification of the crystal packing of a solid material by changing the intermolecular interactions that regulate the breaking and formation of non-covalent bonds, such as hydrogen bonding, van der waals force, π-stacking, electrostatic interactions, and halogen bonding[14].The term supramolecularsynthon is frequently used in the research field of cocrystals. It is defined as structural units within supramolecules which can be formed and/or assembled by known conceivable synthetic operations involving intermolecular interactions[15].Cocrystal formersthat contain carboxylic acids, amides, carbohydrates,alcohols, and amino acids are able to co-crystalize with APIs.

Role of hydrogen bonding in co-crystallisation

From a number of systematic studies of cocrystals it was recognized that, in general, all good hydrogen bond donors and acceptors would be used in hydrogen bonding. Furthermore, of particular importance to the design of cocrystals, it was noted that the best hydrogen bond donor tends to interact with the best hydrogen bond acceptor in a given crystal structure. This 'best-donor–best-acceptor' rule can be of great utility in the design of specific hydrogen bonding interactions[16]. Due to the large number of counter-molecules availablefor possible cocrystallization, a rational approach to cocrystaldesign is required to maximize experimental efficiency. Twoimportant aspects of cocrystallization experiment design includethe robustness of potential intermolecular interactions(i.e., assessing the likelihood of formation of specificinteractions, such as hydrogen bond motifs) and consideringgeneral hydrogen bonding rules. The evaluation of intermolecularinteraction robustness may be performed by analysing trendswithin the Cambridge Structural Database (CSD)[16,17].

Cocrystal of caffeine with oxalic acid, 2:1 drug:acid ratio, the anticipated O-H· · ·N bond is observed in each structure, with the equivalent nitrogen on each drug molecule hydrogen bonding to the carboxylic acid.This appears to be a result of the presence of the good N H proton donor on theophylline. Rather than forming the weak C H· · ·O bond, the oxalic acid carbonyl is directed toward a second theophylline molecule to form what appears to be a longN H· · ·Ointeraction (N· · ·O distance 3.204A°). Lacking a strong donor on the caffeine molecule this interaction was not possible[16].

Effect of co-crystallization on physicochemical properties

The need of co-crystallization is to improve the physicochemical property of the drug like solubility, melting point, stability, bioavailability etc. Each new cocrystal of any drug will exhibit a unique set ofproperties as expected by the structure--property relationship in materials science[18]. The changes in physical, chemical and mechanical properties of a drug introduced by cocrystallization are not always beneficial. Of course, whether or not a change is useful to drug delivery depends on various factors, such as intended route of administration, drug release profiles and manufacturing process. For example, high solubility is desired for fast release of a drug[3].

Solubilityand bioavailability

Cocrystallization may either enhance or reduce solubility or dissolution rate of a poorly soluble drug[19,20]. For example, the solubility of acyclovir l-tartaric acid is greater than amorphous and hydrate forms of acyclovir[21]. A unique example of the deteriorated solubility by cocrystallization is the melamine and cyanuric acid 1:1 cocrystal[3].

As solubility is complementary of dissolution, if cocrystal solubility is increased in comparison to API, intrinsic dissolution is also improved for cocrystals in comparison to pure drug and vice

versa.Co crystal of ionized drug co crystal solubility is mainly depending on solution pH. The prediction of this can be done by calculation based on degree of ionization and dissociation equillibria of cocrystals[22,23].

Melting point

The melting point is a fundamental physical property, and melting temperature shows the equilibrium between solid and liquid phase. We generally prefer the co-crystal having lower melting point than there API. The solid having lower melting point in comparison with other solid shows lowered susceptibility to degradation[24]. Differential scanning calorimetry (DSC) is the preferred technique for obtaining comprehensive melting point data, over a standard melting point apparatus or Kofler method, because additional thermal data such as the enthalpy of fusion can be determined. For example, the melting point and heat of fusion, both determined from DSC, are necessary when attempting to characterize a polymorphic pair of compounds as monotropic or enantiotropic[25].

Stability

Stabilityis an important parameter for the design of a dosage form. During co-crystallization there is alteration in molecular assemblies that changes the mechanical properties of solids. For this reason study of stability of polymorphic co-crystal is important. In the case of cocrystals and salts, solution stability may be a factor due to dissociation of the material resulting in precipitation of the less soluble parent compound or a less soluble form (such as a hydrate inaqueous media)[26]. The example of polymorphic cocrystals is Carbamazepine with saccharin and nicotinamide as coformer. These cocrystals are more stable than original API[27].

The other parameters such as tensile strength, elastic properties, breaking strength and tabletability, can be improve by using co-crystallization technique.

METHOD OF PREPARATION

Supercritical fluid atomization technique

Supercritical fluids use offers additional advantages compared to the classical co-crystalproduction methods. Co-crystallization with supercritical solvent (CSS) is a method where an API and a co-crystal former are mixed together by magnetic stirring after being pressurized by supercritical CO2 in a high-pressure vessel. The Supercritical Anti-Solvent (SAS) technique explores the anti-solvent effect of supercritical CO2 to precipitate particles (cocrystals) from solutions; the supercritical fluid enhanced atomization SEA technique explores essentially the CO2 atomization enhancement in a spray drying process. Theophyllinesaccharin co-crystal new form with a 1:2 stoichiometry was obtained by the supercritical fluid enhanced atomization process method that has not been previously reported by traditional screening methods[28].

Four co-crystals of Levetiracetam [Levetiracetam–d-tartaric acid 1:1 (LDTA), Levetiracetam–*R*/*S*-mandelic acid 1:1 (L(RS)MA), Levetiracetam–*S*-mandelic acid 1:1 (LSMA), and Levetiracetam–2,4-dihyroxybenzoic acid 1:1 (L2,4DHBA) were obtained by solvent drop and neat grinding[29].Piracetam is used to treat memory and balance problems by stimulating the central nervous system. Levetiracetam is an anticonvulsant medication used to treat epilepsy. These compounds share a pyrrolidone nucleus and an amide functional group. Levetiracetam has an additional ethyl group (Figure 3)[30].

Solvent evaporation technique

This technique is commonly used for the preparation of cocrystals. In this technique both drug substance and coformer are dissolved in a common solvent and allowed to slow evaporation of a solvent. The technique works on the principle of formation of hydrogen bond in favourable drug substance and a complementary coformer[31]. For example:- Cocrystal forming ability of anti-HIV drug Zidovudine and lamivudine is studied in this work. In this work Zidovudine-lamivudine cocrystals prepared by using solvent evaporation technique by taking equimolar ratio of both. Ethanol is used as a solvent. Zidovudine-lamivudine is taken in equimolar ratios to which 10mlof ethanol is used. The solvent is allowed to evaporate for 2 days. Single crystals wereobtained[32].

Grinding method

It has been witnessed a great progress incocrystal formation via grinding method overthe past few years. There are two differenttechniques for cocrystal formation via grinding.The first method is neat grinding, which is alsocalled dry grinding, consisting of mixing thestoichiometric cocrystal togetherand grinding them either manually, using amortar and pestle, or mechanically, using aball mill or a vibratory mill. This methodrequires one or both reactants exhibitingsignificant vapour pressures in the solid state[33].

Solvent drop technology

In solvent drop grinding technology the drug substance (API) and coformer are taken inequimolar ratios and these equimolar ratios are grind in a mortar and pestle to this addition offew amount of solvent. This solvent will act as a catalyst to favour co crystallization. This method is advantageous than solid state grinding in terms of yield, ability to control polymorphproduction, better product crystallinity, and a larger scope of cocrystal forme[31].For example-In this patent Intravenous formulation with water soluble cocrystals of Acetyl salicylic acid andthe anine.In this Acetyl salicylic acid-the aninecocrystals prepared by taking both in equimolarratios. Acetyl salicylic acid-the anine are taken in mortar and pestle in this few drops of methanolis added and grind until dried mass is formed. Further it is characterized[34].

Ultrasound assisted solution co crystallization

In ultrasound assisted solution co crystallization the API and cocrystal former are mixed togetherin appropriate solvent at a proper temperature. This solution was subjected to ultrasound pulsesin a sonoreactor after giving 6-12 pulses there is formation of turbid solution. To preventfragmentation cold water was supplied during sonication. Turbid solution was left for overnightfor drying of solvent. For example:-Ultrasound assisted cocrystals of Caffeine/maleic acid wereprepared. Slurry of Caffeine-maleic acid was prepared by taking equimolar ratios in methanol.This slurry was subjected to ultrasound pulses. Solid was filtered[35].

CHARACTERISATION OF CO-CRYSTALS

The characterization of co-crystal can usually be performed by powder X-ray diffraction (PXRD), single crystal X-ray diffraction (SXRD), Raman spectroscopy, Infraredspectroscopy (IR), differential scanning calorimetry (DSC), scanning electron microscopy(SEM), solid state nuclear magnetic resonance spectroscopy (SSNMR) and terahertz spectroscopy.

Powder X-Ray diffraction

PXRD is the most commonly used technique for the characterisation of co-crystals. This method include the diffraction pattern of X-rays from co-crystal and API and seen that the diffractogram of co-crystal is distinct from the API.

Single crystal X-ray Diffraction

SXRD technique is used to determine solid state structure of co-crystal at atomic level. Single-crystal X-ray diffraction may prove difficult on some cocrystals, especially those formed through grinding, as this method more often than not provides powders. However, these forms may be formed often through other methodologies in order to afford single crystals[25].

Raman Spectroscopy

Raman spectroscopy is a spectroscopic technique that is used as apowerful tool for distinguishing isostructural phase. Technique is used for the study of vibrational, rotational and other low frequency modes in a system.

Scanning Electron Microscope

SEM is a type of electron microscope that images a sample by scanning it with a highenergy beam of electrons in a raster scan pattern. The electrons interact with the atoms that make up the sample producing signals which provide information about the sample's surface topography. It is applied to determine the cocrystal micrograph and particle size in many examples[36,37].

Terahertz time-domain-spectroscopy (THz-TDS)

Terahertz spectroscopy is an alternative to powder X-ray diffraction in the characterisation of molecular crystals and used to distinguish between chiral and racemic hydrogen bonded co-crystals that are similar in molecular and supramolecular structure. The investigation of the cocrystal of theophylline with chiral and racemic forms of coformers using PXRD and Raman spectroscopy suggested that THz-TDS is comparable in sensitivity to diffraction methods and more sensitive than Raman to changes in cocrystal architectures[38].

Other physical methods of characterization may be employed. Thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) are two commonly used methods in order to determine melting points, phase transitions, and enthalpic factors which can be compared to each individual cocrystal former[39].

APPLICATIONS OF CO-CRYSTALS

Compared to other solid-state modification techniques employed by pharmaceutical industry, co-crystal formation appears to be an advantageous alternative for drug discovery (e.g. new molecule synthesis, nutraceutical co-crystals), drug delivery (solubility, bioavailability) and chiral resolution. Experts are of the opinion that pharmaceutical intellectual property landscape may benefit through co-crystallization[40].

THE MARKET AWAITS A COCRYSTAL DRUG PRODUCT

The market awaits a cocrystal drug product was the message from the IQPC Cocrystal meeting in Amsterdam on the 21st-22nd September. Although it appears that both Pharma and Biotech industries are actively engaging in cocrystal development, which should be considered as an extension of the solid form landscape, a marketed cocrystal form is yet to be realized.Legally, cocrystals are thought to be as patentable as per crystalline salt forms i.e. non-obvious, although some ambiguity still exists. Regulators may consider any submission of a cocrystal drug substance on a case by case basis. Process chemists are also getting to grips with the complexities of multi Kg production. There appears no doubt that cocrystals have utility and may offer additional novel routes to formulation and manufacture as well as increased patient benefits. The next few years may proof to be decisive as interest in cocrystals gains pace.

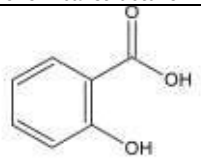
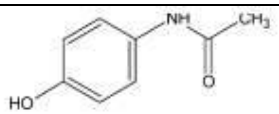
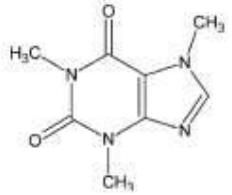
CONCLUSION

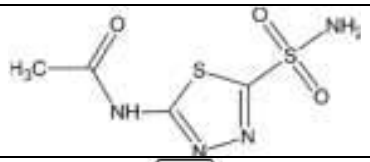
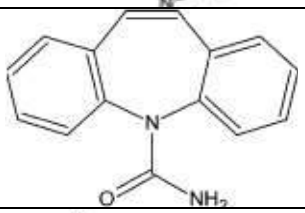
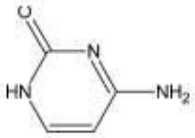
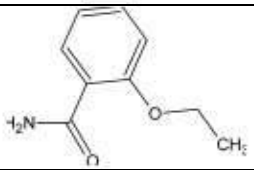
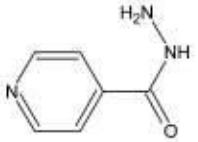
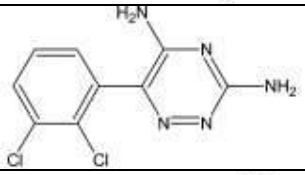
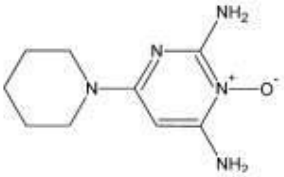
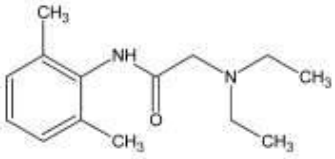
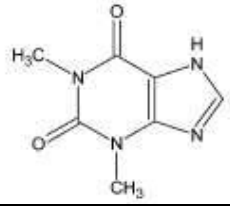
To achieve the desired therapeutic activity of drug, a research scientist go through several approaches that can enhance solubility, stability, bioavailability and other parameters. Co-crystallization is a new approach to pharmaceutical industry and co-crystal provide a new direction to deal with problems of poorly soluble drugs. Co-crystal have more potential than hydrates, solvates and amorphous forms to improve physicochemical properties. Co-crystal research will go through co-crystal polymorphism, salt co-crystal, glassy co-crystal and higher order co-crystal in future.

Table 1: List of some works performed on co-crystallization

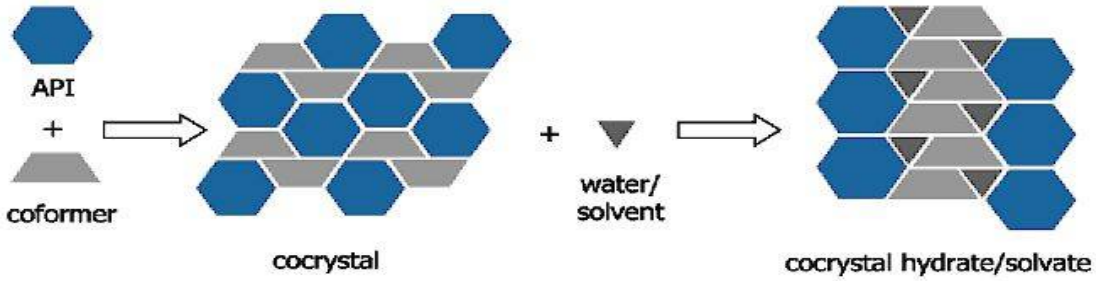
S. No.	Co-crystal	Method	Reference
1	Carbamazepine : itaconic acid	Solvent evaporation	Desai et al. 2014 [41]
2	Carbamazepine : Nicotinamide	Hot melt extrusion	Boksa et al. 2014 [42]
3	Danazol : Vanilin		Childs et al.
4	Lornaxicam : salicylic acid	Liquid assisted grinding	Patel et al. 2014 [43]
5	Paracetamol : Indomethacin, mefenamic acid	Solvent Evaporation, Grinding Method	Pathak et al.2013 [44]
6	Tenaxicam : Maleic acid, malonic acid, oxalic acid	Solvent Drop Grinding	Patel et al. 2012 [45]
7	Aceclofenac : Nicotinamide	Neat Grinding, solution crystallization	Sevukarajan et al. 2011 [46]
8	Acyclovir : L Tartaric acid, anhydrous citric acid	solution crystallization, Liquid assisted co-grinding	Masuda et al. 2011 [9]
9	Theophylline : Maleic acid, Malonic acid, Gluteric acid	Solution precipitation, solid state grinding	Trask et al. 2006 [16]
10	Indomethacin : saccharin	supercritical solvent technique	Velaga et al. 2008 [47]

Table 2: Other Drugs that can go under co-crystallization

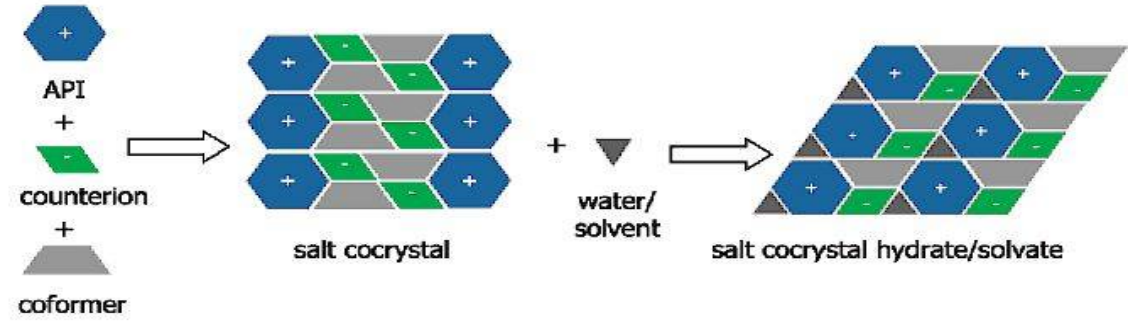
S. No.	Drug name	Chemical structure
1	Salicylic acid	
2	Acetaminophen	
3	Caffeine	

4	Acetazolamide	
5	Carbamazepine	
6	Cytosine	
7	Ethenzamide	
8	Isoniazid	
9	Lamotrigine	
10	Minoxidil	
11	Lidocaine	
12	Theophylline	

Example 1



Example 2



Example 3

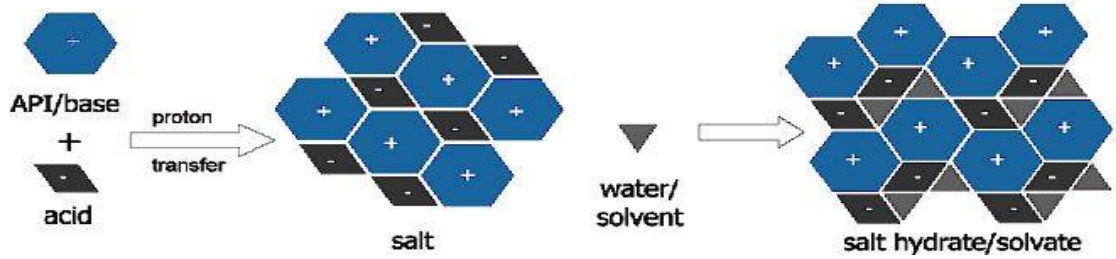


Fig. 1: Representation of a co-crystal, salt, co-crystal hydrate and salt co-crystal hydrate

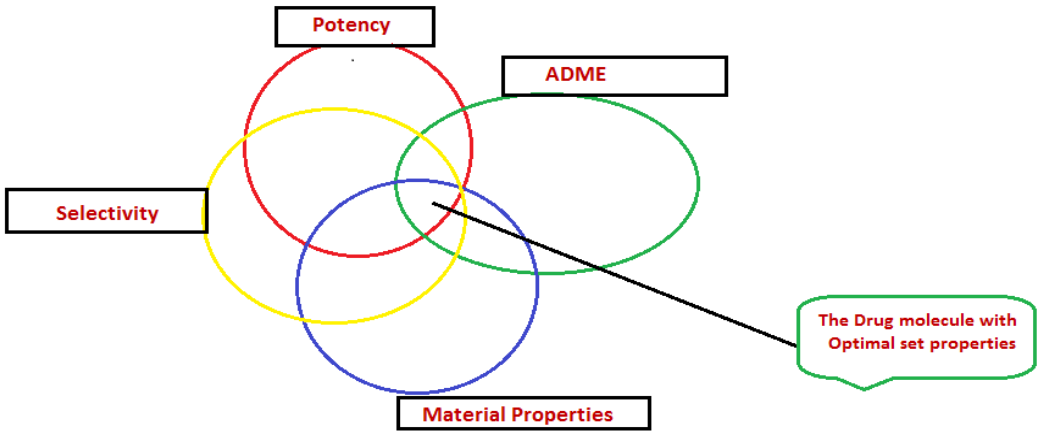


Fig. 2: A simplified schematic overview of the properties

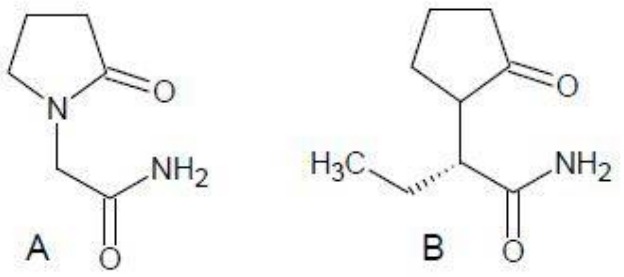


Fig. 3: The chemical structures of A. Piracetam and B. Levetiracetam

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