J. Pharm. Res. 2024;23(1):1–6

Print ISSN: 0973-7200
Online ISSN: 2454-8405

Journal of Pharmaceutical Research

Review Article

Pharmaceutical Co-crystals: A Review on its Physico-chemical Properties and Role in the Management of Cancer

Manoleena Sarkar[1], Rajnandan Borah[1], Rajat Das[1,*], Pallab Ghosh[1], Chandrika Sharma[1], Jyochhana Priya Mohanty[1]

[1] *Department of Pharmacognosy, Himalayan Pharmacy Institute, Majhitar, E. Sikkim, 737136*

ARTICLE INFO

Article history:
Received 18.12.2023
Accepted 27.02.2024
Published 30.01.2024

* *Corresponding author.*
Rajat Das
rajatdas1992@yahoo.com

https://doi.org/
10.18579/jopcr/v23.1.74

ABSTRACT

Academic and industry researchers are becoming more interested in pharmaceutical cocrystals as they emerge as a new class of solid pharmaceuticals with enhanced physico-chemical features. Pharmaceutical co-crystal formation is a simple method for significantly altering a therapeutic substance's solid-state characteristics namely its solubility and consequently bioavailability. A drug's physico-chemical properties can be adjusted by a cocrystal between an active pharmaceutical ingredient (API) and co-former without altering the drug's molecular structure. Numerous types of co-crystals, nano co-crystals and co-crystal-loaded nanocarriers have shown significant promise in the fight against cancer through enhanced pharmacokinetic capabilities, decreased toxicities and improved physico-chemical properties. In this review the physico-chemical properties of co-crystals along with its impact in management of cancer have been demonstrated.

Keywords: Co-Crystals; Physicochemical; Co-Former; Bioavailability; Nanocarriers

INTRODUCTION

Less than 1% of active pharmaceutical compounds eventually make it onto the market due to inadequate biopharmaceutical qualities, not toxicity or lack of efficacy according to the pharmaceutical industry[1]. A novel product's development is hampered by an active pharmaceutical ingredient's poor water solubility and limited oral bioavailability[2]. Co-crystals is a class of crystalline materials which are composed of two or more components, have gained attention in sustainable and green research for their potential to enhance drug delivery. A novel strategy to upgrade the physicochemical properties of API is co-crystal formation[3]. Different definitions of Co-crystals from different journals are listed in Table 1.

Co-crystals combine the API with guest compounds that are approved by pharmaceuticals into a crystal lattice[7]. Pharmaceutical cocrystals are crystals made up of two or more discrete neutral molecules bonded together by non-covalent bond interactions such as (hydrogen bonding or vander Waals) where at least one of the components is an active ingredient (API) and the others are ingredients that are acceptable for use in pharmaceuticals. Several functional groups are particularly amendable to the formation of supramolecular synthons of co-crystals such as carboxylic acid, amides and alcohols. The US FDA originally published a draft of guidelines in 2011 that described "dissociable API excipient molecular complexes wherein both API and excipients are present in the same crystalattice". A coformer is a component that is generally nonvolatile and interacts non-ionically with the API in the crystal structure such as (ascorbic acid, gallic acid, glutamic acid, citric acid) which is depicted in Figure 1[8]. A pharmaceutical co-crystal's primary objective is to modify an API's hygroscopicity, physical and chemical stability and solubility. Pharmaceutical co-crystallization is a dependable technique for changing a drug's technical and physical characteristics without changing its pharmacological behavior such as its compressibility, stability, hygroscopicity and rate of dissolution.

Cancer ranks as the second foremost reason of death in various corners of the world[9]. This review emphasizes on co-crystals which are new therapeutic options for treating different types of cancer by changing the properties of

Table 1: Definitions of Co-crystals

Sl no	Definition	Ref
01.	A stoichiometric multi-component system connected by non-covalent interactions in which two different components are solid in the ambient environment is known as a Co-crystal.	[2]
02.	A pharmaceutical co-crystal is a single crystalline solid that incorporates two neutral molecules, one being an API and the other a co-crystal former	[4]
03.	Pharmaceutical cocrystals are crystalline molecular complexes containing therapeutic molecules.	[5]
04.	Cocrystals are solids that are neutral crystalline single-phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts.	[6]
05.	A co-crystal is a multicomponent crystal in which all components are usually solid at room temperature in a stoichiometric ratio and it involves non-covalent interactions such as hydrogen bonds, Vander-waals bonds, ionic bonds in a crystal lattice.	[7]

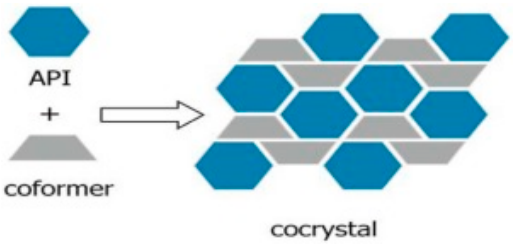

Fig. 1: Formation of co-crystals

authorized anticancer medications. At a dosage of 10^{-7} M the cocrystal demonstrates a distinct lethal effect on lung cancer cells (A549), although it demonstrates growth inhibitory effects on normal cells. On breast cancer cells it also exhibits anticancer action.

Advantages of Pharmaceutical co-crystals:

1. More stable compared to amorphous form.
2. Cocrystal solubility is proportional to ligand solubility.
3. Pharmaceutical cocrystals can enhance the properties of drugs such as Melting point, Tabletability, Solubility, Stability, Bioavailability, Permeability.
4. This method may be used for purification.

Crystal Engineering of Pharmaceutical Co crystals

The study of topochemical reactions in the solid state gave rise to the field of crystal engineering in the 1970s. A broad chemical definition of crystal engineering was published in 1989 followed by hetero-synthons and their potential applications for the design of pharmaceutical cocrystals in 2004[2]. By using crystal engineering a pharmaceutical cocrystal can be created with the goal of enhancing an API's solid-state characteristics without changing its fundamental structure[1]. Researchers frequently draw attention to themes related to functional group compatibility (synthons), such as phenol/N-heterocycle, acid/amide, and acid/N-heterocycle as well as cocrystal growth techniques including melting, sonication, solid-state grinding and evaporation. The first step should be to evaluate the API considering factors like the amount and configuration of donors and acceptors of hydrogen bonds, the pKa (potassium forming ability) and the conformational flexibility.

Characterization of co-crystals

Cocrystal characterization is a vital constituent part within cocrystal research. Particle X-ray diffraction (PXRD), infrared (IR), Raman spectroscopy, differential scanning calorimetry (DSC), scanning electron microscopy (SEM) and terahertz spectroscopy are frequently used methods to characterize the properties of cocrystals. Clarifying the structure of cocrystals' objective crystal shape and any potential deviations (such as polymorphs or hydrates) should be part of their physical characterization[10]. Major techniques used for the characterization are listed in Table 2.

Physico-chemical properties of Co-crystals

To ascertain if a cocrystal may be developed into a marketable dosage form, its Physico-chemical characteristics must be examined. The properties are mentioned below-

- **Melting point:** The temperature at which the solid and liquid phases stay in equilibrium is known as the melting point. The value of melting point is determined by dividing the change in fusion enthalpy by the change in fusion entropy[12]. A high melting point indicates the new materials' thermodynamic stability; hence, choosing a coformer with a higher melting point can improve an API's thermal stability[13]. The most frequently used techniques to determine the melting point and thermal analysis are differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA).
- **Solubility:** An important factor in determining pharmaceutical qualities of co-crystal is its solubility[13]. Cocrystal superior solubility over drug is due to increasing the free drug concentration, which is

Table 2: Different techniques used for characterization of Co-crystals

Sl no.	Technique used	Mechanism
01.	X-ray diffraction (XRD) studies	This analytical tool is employed for phase identification of unit cells associated with the co-crystal[10]. Samples were initially scanned between 5° and 40° 2θ[11]. Single crystal XRD is mainly employed for structural recognition by using software such as 'DIFFRAC.SUITE TOPAS'. Powder XRD is utilized in identification by detecting alterations in the crystal structure because of distinct co-crystals are linked to distinctive peaks.
02.	Differential Scanning Calorimetry (DSC)	DSC was performed by using Thermal Advantage DSC which was calibrated using indium & sapphire[11]. The pure and co-crystal components are heated at a regulated pace, and the resulting thermogram is carefully examined to determine whether co-crystal formation is possible. In contrast to the pure thermogram of drug and coformer, the thermogram of co-crystals displays an exothermic peak that is followed by an endothermic peak[9].
03.	Hot Stage Microscopy	It is a combination of microscopy & thermal analysis. A solid form's physicochemical properties are examined in relation to temperature and time. Under a microscope, the changes that happened while heating the co-crystal sample for evaluating the modifications, such as crystalline transformation, melting range, and melting point[10].
04.	Field emission scanning electron microscopy (FESEM)	FESEM is used to study the surface morphology of co-crystals[10]. In this method heat is not used, cold energy is utilized. The electrons are released from the conductor's surface using a high electric field. As a cathode, a tungsten filament with a thin, sharp needle is used. A scanning electron microscope is linked to the field emission source in order to take co-crystal micrographs.
05.	Vibrational Spectroscopy	Vibrational spectroscopy can be used to identify the structural behaviour of co-crystals since the energy absorbed or dispersed by the chemical bonds in the co-crystals will differ from that of the pure components.
06.	Nuclear Magnetic Resonance (NMR)	This method is widely used for characterization of pharmaceutical co-crystals due to their ability to provide structural information of co-crystals. This method is also used to distinguish co-crystals and salts since it can detect the degree of proton transfer.

available for absorption. There are various techniques to increase the solubility of medications, including solid dispersion, salt creation, amongst which co-crystallization has been used by several researchers. Due to the modified underlying crystal structure, a cocrystal will be less soluble than the original material. The majority of research provide data on powder dissolving across several time intervals.

- **Stability:** A criterion that is extensively researched while developing a novel chemical entity is stability. Various stability types must be considered on the basis of the molecule's structure and properties. Several stability tests are performed like chemical stability, thermal stability and photostability study. Various stability testing are being performed which are listed in Table 3.

- **Bioavailability:** Bioavailability is the extent to which a substance or drug becomes fully obtainable to its intended biological target. Low oral bioavailability of APIs is a significant obstacle when creating novel formulations[4]. The quantity of medication in the blood is assessed following oral delivery of the original form and subsequently the cocrystal.
- **Permeability:** Drug permeability is primarily obtained by the n-octanol/water partition coefficient, which can be calculated using log P and (C log P) for unmodified drug forms. Drug accessibility through the cellular membrane is a vital factor in drug absorption and distribution[15].

Impact of Pharmaceutical Co-crystals in the treatment of cancer

Statistics on co-crystals in the treatment of cancer

Cancer is regarded as one of the prevailing and major reasons for increased death worldwide and creating a huge global public health concern[16]. The statistics of different types of cancers is given in Figure 2. Because of their deadly toxicities, poor pharmacokinetic performance, and poor physicochemical characteristics, the applications of several anticancer treatments have been restricted. Numerous types of co-crystals have shown significant promise to fight against cancer through enhanced pharmacokinetic capabilities, decreased toxicities, and improved physicochemical properties. Additionally, these systems have shown passive targeting through the enhanced permeation and retention (EPR) effect[17]. There are different types of cancers out of which a few occurring kinds are colorectal cancer, endometrial cancer, lung cancer, kidney cancer, bladder cancer, leukaemia, pancreatic cancer, breast cancer, uterine cancer, liver cancer etc[18].

Table 3: Various stability testing for co-crystals

Sl no.	Tests performed	Major findings
01	Relative humidity stress	In this test the influence of water on the formulation is established by automated water sorption/desorption studies[4]. At the conclusion of the moisture balancing experiment, X-ray powder diffraction (XRPD) data obtained on the solid yield information on the final form[10].
02	Thermal stress	Based on accelerated stability conditions, high temperature stress is another frequent condition used to assess chemical and physical stability[10]. Under thermal stress induced by DSC (Differential Scanning calorimtetry) the amount of cocrystal formation increased with increasing co- grinding time[14].
03	Chemical stability	Co-crystals having advantages like stable crystalline form; no need to make or break covalent bonds. It is frequently examined at an early stage of a novel compound's development to reduce the possibility of potential chemical deterioration[10]. For initial investigations on solid materials, accelerated stability conditions like 40°C/75%RH and 60°C/75%RH are frequently utilized.
04	Solution stability	It is the capacity of the cocrystal components to remain in solution and not rapidly crystallize[4]. Both the dissolution buffers and the cocrystal thermodynamic stability have an impact on the cocrystal solution stability as the dissolving process will change the interactions between the drug, coformer, and solvent as well as the drug supersaturation level. A variety of vehicles are used in this regard- simulated gastric fluid (SGF), simulated intestinal fluid (SIF), formulation vehicles and buffered solutions[10].
05.	Photostability	Photostability research is conducted to examine how light affects medications that are sensitive to light. Cocrystals can have improved photostability compared to conventional crystal forms.

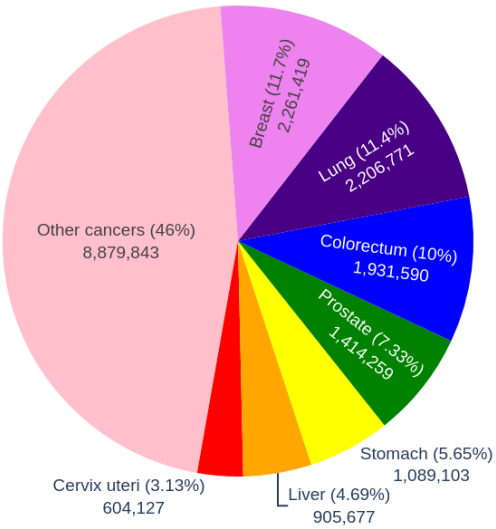

Fig. 2: Statistics of cancer worldwide

Literatures on Cancer Therapy

There are a few literatures which depict the effect of pharmaceutical co-crystals in Cancer treatment which are listed in Table 4.

DISCUSSION

In recent years, the pharmaceutical business and crystal engineering have made the design of medicinal cocrystals their primary focus. It was observed from various literatures that these co-crystals have a high impact on management of Cancer. Most of the co-crystals are widely used in the treatment of kidney cancer, bladder cancer, leukaemia, pancreatic cancer, prostate cancer, breast cancer, uterine cancer, skin cancer, liver cancer etc.

CONCLUSION

The research on co-crystal is a sustainable approach as it does not require any tedious reactions, which eliminate the use of large amount of solvents[15]. The pattern of supramolecular synthesis has evolved to the point that crystal engineering is now similar with that[28]. Co-crystals consists of API and a stoichiometric amount of a pharmaceutically acceptable co-crystal former[29]. Academic and industry researchers are becoming more interested in co-crystals because they emerge as a new class of pharmaceuticals with enhanced features. The assay mark of the pharmaceutical cocrystals is its ability to extensively tune a drug's physico-chemical without altering its molecular[3]. Cancer cases worldwide is constantly rising and the clinical uses of licensed chemotherapeutics seem to be restricted because to their qualities and poor pharmacokinetic performance[9]. Further researches should be conducted to observe the effect of pharmaceutical co-crystals in enhancement of other physico-chemical properties except those mentioned in this manuscript and also to develop some co-crystals of molecules/drugs except

Table 4: Different literatures on Cancer therapy

Sl no.	Project title	Major finding	Ref. no.
01.	A pharmaceutical cocrystal with potential anticancer activity	Quinoxaline acts as a basic skeleton of several potential anticancer drugs. It is co-crystallized with another organic molecule3-thiosemicarbano-butan-2-one oxime (TSBO, a virus replication inhibitor) and examined the anticancer activity of the cocrystal. The cocrystal exhibits a potential and specific cytotoxic effect on malignant cells.	19
02.	Autophagy-Inducing Inhalable Co-crystal Formulation of Niclosamide-Nicotinamide for Lung Cancer Therapy	An anthelminthic medication called niclosamide (NIC) has shown promise in treating drug-resistant cancers of different kinds. Rapid, continuous spray drying was used to create and assess niclosamide-nicotinamide (NIC-NCT) medicinal co-crystals. In this research when NIC-NCT co-crystals were tested on A549 human lung adenomas cells, they demonstrated better cytotoxic action than when the medication was used alone. In cancer cells, NIC-NCT co-crystals increased autophagic flow, indicating autophagy-mediated cell killing mechanistically.	20
03.	5-Fluorouracil Co-crystals and Their Potential Anti-cancer Activities Calculated by Molecular Docking Studies	A series of co-crystals containing 5-fluorouracil as the active pharmaceutical ingredient were prepared via mechanochemical grinding and a normal solution method. The new co-crystals were subjected to docking experiments utilizing the CDOCKER procedure in Discovery Studio Version 2.5 to explore their potential anti-cancer actions against human thymidylate synthase, a target protein for colorectal cancer.	21
04.	Novel pharmaceutical Novel pharmaceutical co-crystals of gefitinib: synthesis, dissolution, cytotoxicity, and theoretical studies	Gefitinib (GEF) is an ATP-competitive inhibitor. Using appropriate coformers such as cinnamic acid, sorbic acid, and resorcinol, three co-crystals of GEF were produced by combining a solvent-assisted grinding technique with a slow solvent evaporation process. It was observed that the co crystals of GEF used in the treatment of advanced non-small cell lung cancer	22
05.	Slow release of drug-drug release of Oxaliplatin with flavonoids: delaying hydrolysis and reducing toxicity	Oxaliplatin (OXA) is a third-generation, platinum based anti cancer agent. In this study, cocrystal formers baicalein (BAI) and naringenin (NAR) were used to create two unique drug–drug cocrystals of OXA. It was observed that OXABAI could have a greater impact on cancer cell inhibition compared to OXA.	23
06.	Synthesis of co-crystals of anti-cancer nandrolone as a potential leads towards treatment of cancer	The goal of the work being described is to create anti-cancer co-crystals of the synthetic anabolic-androgenic steroidal medication nandrolone, which is sold commercially. Co-crystallization is done using green grinding and reflux methods to obtain nandrolone (Nan): salicylic acid (Sal) and nandrolone (Nan): 3-amino-1,2,4- triazole (Tris) co-crystals followed by evaluation of their anti-cancer activity against HeLa cancer cell line Co-crystal-I (Nan:Sal) found to be a potent anticancer agent with anti-cancer activity comparable to standard drug.	24
07	Synthesis and characterization of l-amino acid doped 2aminopyridine co-crystals for anti cancer activity.	The standard slow evaporation approach was utilized to synthesize co-crystals of bis-2-aminopyridinium aspartate, 2-aminopyridinium-leucinate, bis-2aminopyridinuim glutamate and 2 amino pyridinium-tyrosinate. These co-crystals were identified by their UV and FTIR spectra. In comparison to other synthesized chemicals, bis-2-aminopyridinium aspartate kills the cancer cells compared to other synthesized compounds.	25
08	The supramolecular self-assembly of 5-fluorouracil and caffeic acid through cocrystallization strategy opens up a new way for the development of synergistic antitumor pharmaceutical cocrystal	In order to obtain additional understanding regarding the creation of new pharmaceutical cocrystals that exhibit synergistic antitumor activity between an active ingredient and the previous cocrystal, FL-CF-2H2O, a new cocrystal of FL containing caffeic acid (CF), has been effectively utilized and thoroughly examined. The study not only presented a novel crystalline form of FL with possible applications but it also presented a concept for the creation of pharmacological cocrystals with synergistic anticancer properties.	26
09	Temozolomide cocrystals exhibit drug sensitivity in glioblastoma cells	Temozolomide-Succinic acid and Temozolomide-Oxalic acid cocrystals (TMZ-SA and TMZ-OA) are equally sensitive to the reference medication Temozolomide when it comes to preventing the development and multiplication of human glioblastoma malignant cell lines U373, U87, and LN18. The hyrolytic stability, excellent solubility, and cytotoxic action of these pharmaceutical cocrystals are combined with other desired properties for preclinical research.	27

those already stated in the management of Cancer.

REFERENCES

1. Ning Q, Mingzhong L, Walkiria S, Nazneen M, Gary AD, T. Pharmaceutical cocrystals: An overview. *International journal of pharmaceutics*. 2011;419(1-2). Available from: https://doi.org/10.1016/j.ijpharm.2011.07.037.
2. Chandur VK, Sobhanan A, and ARS. Pharmaceutical co-crystals: an overview . 2020. Available from: https://doi.org/10.20959/wjpps202011-17537.
3. Bolla G, Sarma B, Nangia AK. Crystal Engineering of Pharmaceutical Cocrystals in the Discovery and Development of Improved Drugs. *Chemical Reviews*. 2022;122(13):11514–11603. Available from: https://doi.org/10.1021/acs.chemrev.1c00987.
4. Kumar AR, Saloni J, Kumar D, Lal S, Sharma S. An Overview on Pharmaceutical Co-Crystals. *Asian Journal of Pharmaceutical Research and Development*. 2019;7(2):39–46. Available from: https://doi.org/10.22270/ajprd.v7i2.483.
5. Jones W, Motherwell WDS, Trask AV. Pharmaceutical Cocrystals: An Emerging Approach to Physical Property Enhancement. *MRS Bulletin*. 2006;31(11):875–879. Available from: https://doi.org/10.1557/mrs2006.206.
6. Jafari MK, Padrela L, Walker GM, Croker DM. Creating cocrystals: A review of pharmaceutical cocrystal preparation routes and applications. 2018. Available from: https://doi.org/10.1021/acs.cgd.8b00933.
7. Varma NL, Hemalatha M, Sai M, Lakshmi B, Kavitha K, Hima K, et al. A comprehensive review on co-crystals. *Indo American Journal of Pharmaceutical Sciences*;2021(06):242–250.
8. Guo M, Sun X, Chen J, Cai T. Pharmaceutical cocrystals: A review of preparations, physicochemical properties and applications. *Acta Pharmaceutica Sinica B*. 2021;11(8):2537–2564. Available from: https://doi.org/10.1016/j.apsb.2021.03.030.
9. Kumbhar P, Kolekar K, Khot C, Dabhole S, Salawi A, Sabei FY, et al. Co-crystal nanoarchitectonics as an emerging strategy in attenuating cancer: Fundamentals and applications. *Journal of Controlled Release*. 2023;353:1150–1170. Available from: https://doi.org/10.1016/j.jconrel.2022.12.042.
10. Thayyil AR, Juturu T, Nayak S, Kamath S. Pharmaceutical Co-Crystallization: Regulatory Aspects, Design, Characterization, and Applications. 2020. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7191238/.
11. Padrela L, De Azevedo EG, Velaga SP. Powder X-ray diffraction method for the quantification of cocrystals in the crystallization mixture. *Drug Development and Industrial Pharmacy*. 2012;38(8):923–929. Available from: https://doi.org/10.3109/03639045.2011.633263.
12. Nate S, N A. Pharmaceutical cocrystals and their physicochemical properties. 2009. Available from: https://doi.org/10.1021/cg900129f.
13. Thenge R, Adhao V, Mehetre G, Chopade N, Chinchole P, Popat R, et al. Modification of Physicochemical Properties of Active Pharmaceutical Ingredient by Pharmaceutical Co-Crystals. *Drug Formulation Design*. 2023. Available from: https://doi.org/10.5772/intechopen.110129.
14. Lin HLL, Zhang GCC, Huang YTT, Lin SYL. An Investigation of Indomethacin–Nicotinamide Cocrystal Formation Induced by Thermal Stress in the Solid or Liquid State. *Journal of Pharmaceutical Sciences*. 2014;103(8):2386–2395. Available from: https://doi.org/10.1002/jps.24056.
15. Chettri A, Subba A, Singh GP, Bag PP. Pharmaceutical co-crystals: A green way to enhance drug stability and solubility for improved therapeutic efficacy. *Journal of Pharmacy and Pharmacology*. 2024;76(1):1–12. Available from: https://doi.org/10.1093/jpp/rgad097.
16. Novais MVM, Gomes ER, Miranda MC, Silva JO, Gomes DA, Braga FC, et al. Liposomes co-encapsulating doxorubicin and glucoevatromonoside derivative induce synergic cytotoxic response against breast cancer cell lines. *Biomedicine & Pharmacotherapy*. 2021;136:111123–111123. Available from: https://doi.org/10.1016/j.biopha.2020.111123.
17. Cooper GM, Hausman RE. The Development and Causes of Cancer. In: The Cell: A Molecular Approach. Sinauer Associates Inc. 2000.
18. Kara DD, Rathnanand M. Cocrystals and Drug-Drug Cocrystals of Anticancer Drugs: A Perception towards Screening Techniques, Preparation, and Enhancement of Drug Properties. . Available from: https://doi.org/10.3390/cryst12101337.
19. Saha R, Sengupta S, Dey SK, Steele IM, Bhattacharyya A, Biswas S, et al. A pharmaceutical cocrystal with potential anticancer activity. *RSC Adv*. 2014;4(90):49070–49078. Available from: https://pubs.rsc.org/en/content/articlelanding/2014/ra/c4ra03207a.
20. Ray E, Vaghasiya K, Sharma A, Shukla R, Khan R, Kumar A, et al. Autophagy-Inducing Inhalable Co-crystal Formulation of Niclosamide-Nicotinamide for Lung Cancer Therapy. *AAPS PharmSciTech*. 2020;21(7). Available from: https://doi.org/10.1208/s12249-020-01803-z.
21. Nadzri NI, Sabri NH, Vannajan S Lee, Halim SNA. 5-Fluorouracil Co-crystals and Their Potential Anti-cancer Activities Calculated by Molecular Docking Studies. *Journal of Chemical Crystallography*. 2016;46(3):144–154. Available from: https://doi.org/10.1007/s10870-016-0638-y.
22. Shaik A, Bhagwat PU, Palanisamy P, Chhabria D, Dubey P, Kirubakaran S, et al. Novel pharmaceutical co-crystals of gefitinib: synthesis, dissolution, cytotoxicity, and theoretical studies. *CrystEngComm*. 2023;25(17):2570–2581. Available from: https://doi.org/10.1039/D3CE00056G.
23. He-Mei Y, Bi-Jian NW, Zhou BJ, Hong MH, Zhu B, Qi MH, et al. Slow-release drug-drug cocrystals of oxaliplatin with flavonoids: delaying hydrolysis and reducing toxicity. 2020;21:75–85.
24. Urooj I, Choudhary M, Sammer Y. Synthesis of co-crystals of anti-cancer nandrolone as a potential leads towards treatment of cancer. *Journal of Molecular Structure*. 2021. Available from: https://doi.org/10.1016/j.molstruc.2020.128981.
25. Sinthiya A, Koperuncholan M. Synthesis and characterization of l-amino acid doped 2-aminopyridine co-crystals for anti-cancer activity. *Life Science Informatics Publications-Research Journal of Life Sciences*. 2019;5(2):754–762. Available from: http://www.rjlbpcs.com/article-pdf-downloads/2019/26/585.pdf.
26. Yu YMM, Wang LYY, Bu FZZ, Wang LLY, Li YTT, Wang CY, et al. The supramolecular self-assembly of 5-fluorouracil and caffeic acid through cocrystallization strategy opens up a new way for the development of synergistic antitumor pharmaceutical cocrystal. *CrystEngComm*. 2020;22(45):7992–8006. Available from: https://doi.org/10.1039/D0CE01297A.
27. Kusuma, Kanakaraju K, Lavanya V, Nangia A. Temozolomide Cocrystals Exhibit Drug Sensitivity in Glioblastoma Cells. *Proceedings of the National Academy of Sciences, India Section A: Physical Sciences*. 2014;84(2):321–330. Available from: https://doi.org/10.1007/s40010-014-0142-8.
28. Peddy V, Jennifer A, Mc JAM, Bis MJ, Zaworotko. Pharmaceutical co-crystals. *Journal of pharmaceutical sciences Mar*. 2006;95(3):499–516. Available from: https://pubmed.ncbi.nlm.nih.gov/16444755/.
29. Sekhon BS. Pharmaceutical co-crystals-a review. *Ars Pharm*. 2009;50(3):99–117. Available from: https://www.researchgate.net/publication/228617725_Pharmaceutical_co-crystals-a_review.