“Preparation and characterization of BCS class II drugs to enhance physicochemical attributes via co-crystallization approach”

A Thesis Submitted to

Nirma University

In Partial Fulfillment of the requirement for

The Degree of

Doctor of Philosophy

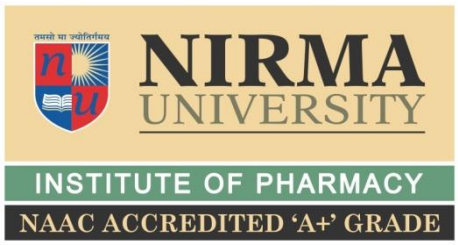
In Pharmacy

BY

Mr. Gunjan Vyas (15EXTPHDP114)

Guided by

Dr. Jigar Shah



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(August, 2023)

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I Mr. Gunjan Vyas, registered as Research Scholar, bearing Registration No.15EXTPHDP114 for Doctoral program under the Faculty of Pharmacy of Nirma University do hereby declare that I have completed the course work. pre-synopsis seminar and my research work as prescribed under R.Ph.D. 3.5.

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This is to certify that the thesis entitled **Preparation and Characterization of BCS Class II Drugs to Enhance Physicochemical Attributes via Co-crystallization Approach** has been prepared by me, under the supervision and guidance of **Dr. Jigar Shah**. The thesis is my own original work completed after careful research and investigation. The work of the thesis is of the standard expected of a candidate for Ph.D. Programme. The final hard bound copy of the thesis is submitted after incorporating all the suggestions / corrections suggested by the referees.

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Table of Content

Abstract

Co-crystallization is now known to be one of the established methods for the improvement of physiochemical properties of drugs in pharmaceutical research and development. With the application of crystal engineering, the conversion of drug moiety into co-crystal form is getting convenient. The Motive behind this work is to convert poor water-soluble drugs into co-crystal forms with the help of various co-crystallization techniques. Techniques that were applied are mainly solvent co-crystallization, co-crystallization by slurry formation, wet milling using Dyno mill, and liquid-assisted co-grinding. Ranolazine was used as a model compound to perform Drug:Coformer crystallization, and Telmisartan (TEL) and Hydrochlorothiazide (HCT) two drug substances was screened for Drug:Drug co-crystalization. Samples obtained from various methods were evaluated by various analytical techniques like microscopy, melting point analysis, X-ray Powder Diffraction (XRPD), and dissolution study.

Ranolazine (RAN) exhibits pH-dependent solubility, with high solubility in acidic pH and lower in basic pH. Cocrystal formation of Ranolazine (RAN) with Nicotinamide (NIC) has been synthesized and evaluated for different molar ratios (1:1, 1:2, 1:3 2:1 and 3:1). Various techniques like liquid-assisted grinding, slurry preparation and solvent evaporation were implemented to synthesize cocrystals. Conformational and characterization analysis has been performed using techniques like melting point analysis, powder X-ray diffraction and TGA. Saturation solubility of RAN alone along with cocrystals prepared in different molar ratios in buffers of different pH (1.2, 4.5 and 6.8) and water has been studied to establish enhancement in solubility. RAN cocrystals with NIC were shown to have enhanced solubility in basic pH. Utmost improvement in solubility has been observed for RAN:NIC molar ratio of 1:2.

Telmisartan (TEL) and Hydrochlorothiazide (HCT) fixed-dose combination is a known and effective combination for the treatment of hypertension. Both drugs are known for their low solubility and work has been done to get better solubility through crystallization of standalone moieties. The currently commercially available Fixed Dose Combination (FDC) of TEL and HCT, the usage of alkalizers in tablet formulation to uphold micro pH environment of the drug substance to augment solubility in the physiological environment, which makes the tablet formulation prone to gain moisture during storage. Drug-Drug cocrystal synthesis of TEL and HCT has been demonstrated by implementing the design of experiment (DoE). Molar ratios, different synthesis techniques and various solvents used for synthesis were evaluated in an orderly manner by applying the DoE concept. Prepared cocrystals were evaluated for melting point, differential scanning colorimeter, X-ray powder diffraction,

dynamic vapor sorption and saturation solubility. From the various techniques applied for characterization, it has been established that new crystal lattice of TEL:HCT cocrystal was formed. This new drug-drug cocrystal has been used in the manufacturing of tablet dosage form which demonstrates enhanced solubility, dissolution and no sensitivity towards moisture uptake compared to commercially accessible tablets.

Introduction

1. Introduction

1.1 Need of co-crystallization

One of the common issues experienced in drug research and development by discovery-based pharmaceutical businesses is the presence of therapeutic molecules with unacceptable physiochemical properties, such as slow intrinsic dissolution and poor water solubility and permeability. Moieties of this kind endow with a number of difficulties in the production of pharmaceutical drugs may result in slow dissolution rate in biological fluids, insufficient and inconsistent systemic exposure, and consequently subpar patient efficacy, especially when administered orally (Blagden et al.). More than 40% of the newly discovered compounds are found to be poorly soluble in water (Vishweshwar et al.). According to the Biopharmaceutical Classification System (BCS) these kinds of moieties fall in category II or Category IV (Figure 1) with low solubility.

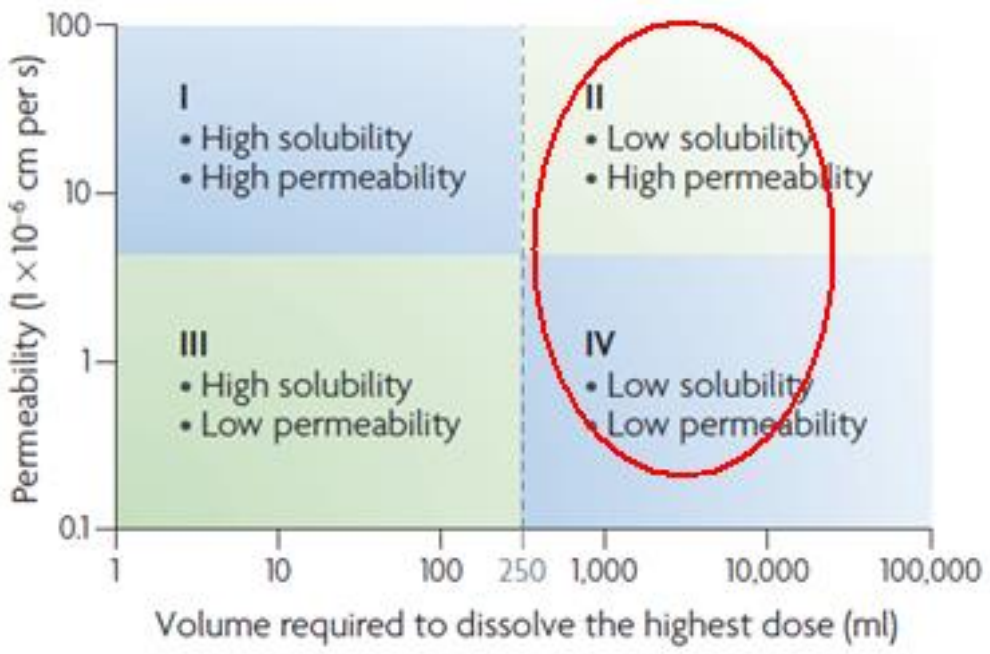


Figure 1.1. Biopharmaceutical Classification System (BSC) with highlighted class II and class IV (Vishweshwar et al.)

Active pharmaceutical ingredient (API) can exist in a variety of solid forms, including pure form, polymorphs, solvates, hydrates, salts, co-crystals, and amorphous solids (Figure 2). Each of these forms exhibits distinct physicochemical features that can significantly affect the physiochemical qualities as well as the bioavailability, manufactureability, purification, stability, and other performance factors of the drug (Yadav et al.).

It is estimated that more than half of the medications on the market are supplied as salts, making salt one of the most common solid-state procedures used to adjust the physical

properties of APIs to address the issue of inappropriate physiochemical qualities. (Schultheiss et al.).

The API must have a sufficient (basic or acidic) ionizable site in order for the salt production method to work. However, co-crystals, which are multicomponent assemblies held together by freely reversible, noncovalent interactions, provide an alternative route that might theoretically co-crystallize any API, regardless of whether it contains acidic, basic, or ionizable groups. (Schultheiss et al.).

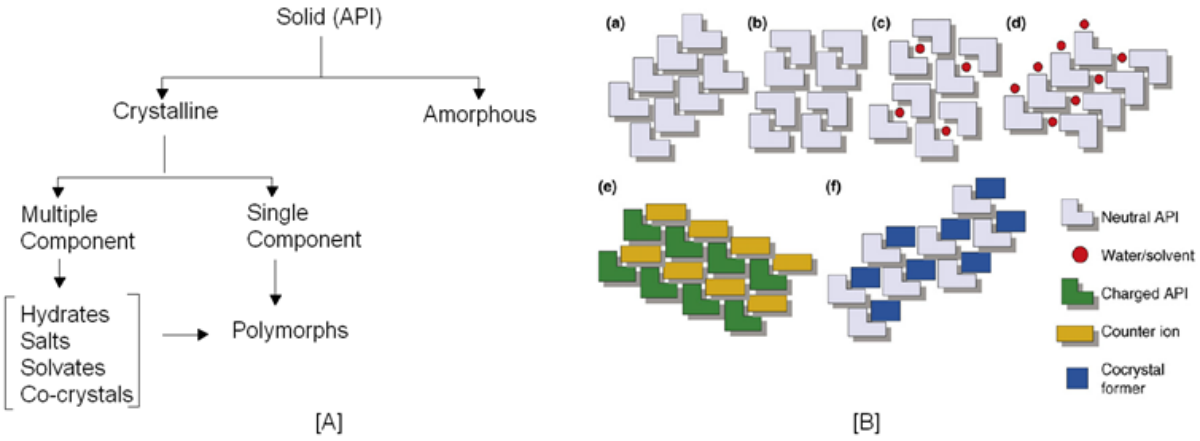


Figure 1.2[A] showing classification of various forms of solids (Sekhon). **Figure 1.2 [B**] pictorial presentations of some of the single-crystalline forms that an API might take: (a) API alone; (b) polymorph of API; (c) Clathrate form of API; (d) API in hydrate/solvate form; (e) Salt form; (f) Co-crystal. Hydrates, solvates, and polymorphs can also be produced by salts and co crystals (Shan et al.)

1.2 Pharmaceutical co-crystal engineering

Pepinsky in 1955 introduced the concept of crystal engineering, which was implemented by Schmidt in the context of organic solid-state photochemical reactions. Crystal engineering is in many ways synonymous with supramolecular synthesis (Vishweshwar et al.). The term supramolecular synthon was first put forward in 1995 by Desiraju to describe the association of two fragments to form a motif that links two molecules (William).

Crystal engineering is commonly considered to be the design and growth of crystalline molecular solids with the aim to improve the property of the material. Hydrogen bonding plays an important role in co-crystal engineering, as it is responsible for the majority of directed intermolecular interactions in molecular solids, which lead to the directed self-assembly of different components (Hickey et al.). For hydrogen bonding, Etter and co-

workers proposed some general rules which should be kept in mind for co-crystal formation (Etter):

(1) Hydrogen bonds use all reliable proton donors and acceptors.

(2) If intramolecular hydrogen bonding with six-membered rings are possible, they will typically form rather than intermolecular hydrogen bonds.

(3) Following the establishment of intramolecular hydrogen bonds, the best proton donors and acceptors that are still present create intermolecular hydrogen bonds with one another.

The crystal engineering experiments typically involve the Cambridge Structural Database (CSD) survey followed by experimental work (Yadav et al.). CSD is used to create supramolecular synthons, facilitating statistical analysis of packing motifs and providing empirical data on common functional groups and how they participate in molecular interaction (Vishweshwar et al.). The knowledge gained through analysis of the CSD, directed experiments and selecting appropriate starting components with appropriate molecular properties, which possess a high possibility to engage in specific intermolecular interactions, increases the probability to achieve the co-crystals (Hickey et al.). There are some common examples of supramolecular synthons having hydrogen bonding (Figure 1.3). N-H... O, O-H... O, N-H... N, and O-H.. N are examples of strong hydrogen bonds, whereas C-H... O-N and C-H...O=C are examples of weak hydrogen bonds (Naír Rodríguez et al.).

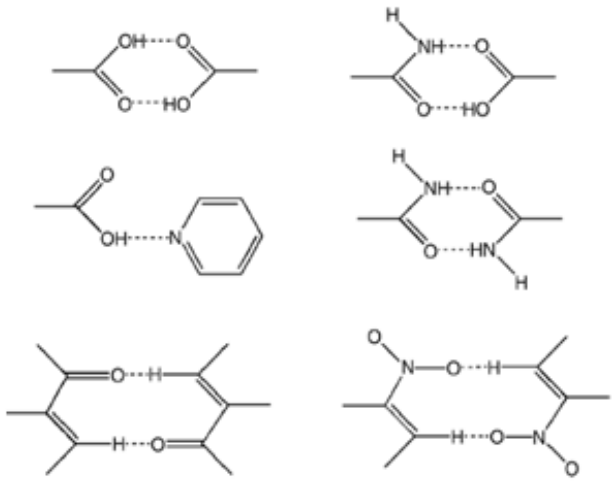


Figure 1.3 Supramolecular synthons the with possible hydrogen bonding between the API and the coformer functional groups (Naír Rodríguez et al.).

For proper design of co-crystals, a detailed understanding of the supramolecular chemistry of the functional groups present in a given molecule is a prerequisite, because it facilitates the selection of suitable co-crystal formers. In order to create new co-crystals, certain functional groups, such as carboxylic acids, amides, and alcohols, are particularly conducive to

supramolecular heterosynthon production (i.e., synthon formation between API and Coformer) (Yadav et al.).

1.3 Pharmaceutical co-crystals

Quinhydrone is an example of a well-known class of co-crystals; it was first reported at least in 1844 and 1893. However, co-crystals have only recently begun to appear in pharmaceuticals due to their unique ability to change physicochemical properties without affecting the structural integrity of the active pharmaceutical ingredient (API) and thus maintain biological activity (Mirz et al., Schultheiss et al.). "Crystalline materials composed of an API and one or more distinct co-crystal formers, which are solids at room temperature," is how pharmaceutical co-crystals are defined (Figure 1.4).

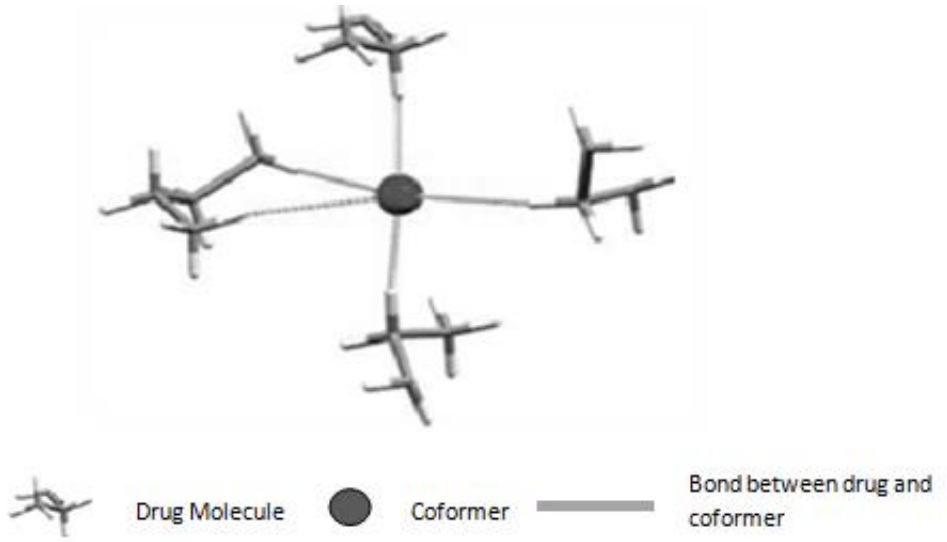


Figure 1.4 General concept of co-crystal structure in which several API molecules are attached with co-crystal former (Childs et al.)

Co-crystal formation is primarily influenced by interactions such as hydrogen bonding, π-stacking, and van der Waals forces. According to this definition, solvates and hydrates of the API do not meet the requirements for co-crystals, but co-crystals may contain one or more molecules of a solvent or water in the crystal lattice (Hickey et al.). Because they can theoretically be applied to all types of API molecules (weakly ionizable/non-ionizable), form stable crystalline form (compared to amorphous solids), do not require changes to covalent bonds, and are the only solid form that can be designed via patentable crystal engineering, co-crystals have an advantage over other solid forms. In addition, co-crystal formation benefits from numerous pharmaceutically acceptable counter-molecules (food additives, preservatives, pharmaceutical excipients, and other APIs) (Yadav et al.).

Table 1.1 List of various API with their co-crystal former, their method of preparation and property improved which are reported in various literatures (Naír Rodríguez et al.)

API	Co-crystal former	Preparation method	Enhanced property	Reference
Aspirin	4,4'-Dipyridil	Slurry		Walsh et al
Caffeine	Oxalic acid Glutaric ac id	Solvent-assisted grinding	Physical stability	Trask et al 2005
Carbamazepine	Nicotinamide Saccharin	Cooling crystallization	Physical stability, dissolution rate and oral bioavailability	Hickey et al 2007
Fluoxetine hydrochloride	Benzoic acid Succinic acid Fumaric acid	Solvent evaporation	Intrinsic dissolution rate	Childs et al.,2004
Flurbiprofen	4,4- Dipyridyl	Solvent evaporation		Oberoi et al 2005
Ibuprofen	4,4- Dipyridyl Nicotinamide	Solvent evaporation	Solubility	Walsh et al 2003; Oberoi et al 2005
lndomethacin	Saccharin	Solvent evaporation or solvent-assisted grinding	Physical stability and dissolution rate	Basavoj u et al 2008
ltraconazole	Malic acid Tartaric acid Succinic acid	Solvent evaporation	Improved dissolution rate	Remenar et al 2003
Norfloxacin	lsonicotinamide Succinic acid Malanie acid Maleic acid	Solvent evaporation	Solubility	Basavoj u et al 2006
Paracetamol	4,4- Dipyridyl	Solvent evaporation		Oswald et al 2004
Piroxicam	Saccaharin	Solvent evaporation		Childs et al 2007

There are many examples of co-crystals that are mentioned in the literature (Naír Rodríguez et al.) (Table 1.1) and with some of them being commercially available (Table 1.2), which proves co-crystallization to be an established methodology to improve physiochemical properties of the API (Shan et al.).

Table 1.2 Commercially available products having co-crystallized API with coformer used (Shan et al.)

S. No.	Commercially available products	Co-crystals (API : Coformer)
1	Tegretol®	Carbamazepine : Saccharin
2	Prozac®	fluoxetine HCl : Succinic acid
3	Viagra®	Sildenafil : Acetylsalicylic acid
4	Sporanox®	Itraconazol : 1,4-dicarboxylic acids

1.3.1 Drug:Coformer co-crystal

Ranolazine (RAN) is administered for the treatment of chronic angina and is categorized as a BCS Class II drug. Due to poor aqueous solubility, ranolazine exhibits variable pharmacokinetics, leading to poor oral bioavailability (~35 to 50%). RAN also has a short half-life of around 2 to 6 h, fast systemic clearance (>70%), and major hepatic first-pass metabolism via cytochrome P-450 3A (CYP3A) and CYP2D6 (Jerling, 2006). Formerly published works also report that plasma concentration achieved by RAN is therapeutically ineffective and also fluctuates when administered orally. To address this formulation challenge, a unique approach is required to improve the aqueous solubility, and dissolution rate, which can ultimately enhance RAN oral bioavailability (Wolff et al., 1998) (Reddy et al., 2010).

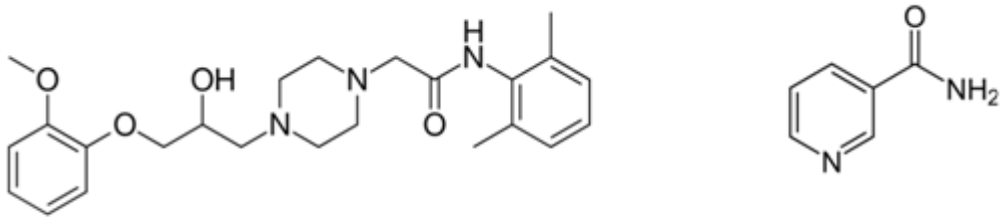
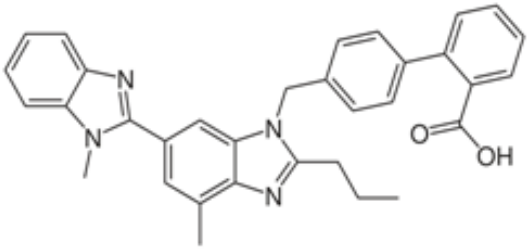


Figure 1.5 Molecular structure of Ranolazine (RAN) and Nicotinamide (NIC)

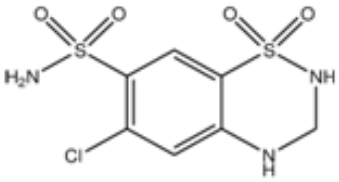
1.3.2 Drug:Drug co-crystal

In recent times, the usage of fixed-dose combination (FDC) to target multiple receptors for the treatment of chronic diseases like cardiovascular disease; diabetes, cancer, etc. is often adopted. The FDC helps to reduce multiple dosing to ensure improvement in patient compliance. However, challenges associated with physicochemical properties like solubility, etc. increase with the presence of multiple drugs in a single composition. In order to enhance

physicochemical properties, various techniques like salt formation, complexation and cocrystal formation are widely accepted and implemented in various drug developments (Friscic et al.). Out of all the techniques, cocrystal formation involving, drug-drug cocrystal preparation is one of the novel approaches that reduce the load of improvement of drug physicochemical properties of two drugs individually (Yadav et al.). Cocrystals are multicomponent molecular crystals made up of two or more chemically distinct molecules that are all in a stoichiometric ratio (Denniset al., Friscic et al., Dunitz). Drug substances with harmonizing functional groups that can contribute to the formation of supramolecular synthons are apt candidates to form cocrystals. The formation of supramolecular synthons can take place by common functional groups like carboxylic acid, amides and alcohols (Yadav et al.). The non-covalently bonded compounds are carboxylic acid – amide and alcohol – pyridine, carboxylic acid – aromatic nitrogen. The homosynthons which are carboxylic acid–carboxylic acid, amide–amide synthons formed cocrystal through intermolecular interactions (Aakeroy et al. 2005, Aakeroy et al. 2002, Aakeroy et al. 2009). Carboxylic acid is one of the most widely focused and studied functional groups in pharmaceutical cocrystals, which is having the propensity of forming supramolecular heterosynthones with aromatic nitrogen and chloride anions (Shan et al.). Figure 1.6 shows the molecular structure of drugs of attention, Telmisartan and Hydrochlorothiazide.



Telmisartan (TEL)



Hydrochlorothiazide (HCT)

Figure 1.6 Molecular structure of Telmisartan (TEL) and Hydrochlorothiazide (HCT)

The presence of the carboxylic acid group in TEL and aromatic nitrogen and chloride anion in HCT makes both moieties suitable to make supramolecular heterosynthone.

Telmisartan (TEL) and Hydrochlorothiazide (HCT) fixed-dose combination is a recognized and effective combination and is indicated for the treatment of hypertension. Both the moieties possess low solubility and for enhancement of solubility, individual cocrystals of both TEL and HCT are reported in the literature (Kundu et al., Shanmukha et. al.). TEL is insoluble in the physiological range of pH 3-7 and HCT possesses high solubility at alkaline

pH. In order to enhance the solubility of TEL and HCT, commercially available tablets (Mecardis HCT and Cresar H) use an inorganic alkalizer (Kundu et al.). Alkalizers like sodium hydroxide are known for moisture uptake tendency. The moisture sensitivity of these tablets is also mentioned on the leaflet of the product. Cocrystallization of TEL with HCT can enhance the solubility of both moieties and can be formulated into tablets without using any alkalizer.

The advanced technique reported in recent days elaborates on single-tablet regimens (STRs). The STR was safe and effective for the delivery of 3 combination APIs like bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) provide a significant impact on the people living with HIV. The STR was used as FDC as the first line of treatment after diagnosis of HIV and preferable over multiple tablet regimens (Stellbrink et al.). An FDC was evaluated clinically for the management of cardiovascular diseases. A phase 3 double-blind clinical trial was set up to understand the FDC containing bempedoic acid (180 mg) and exetimibe (10 mg) to lower the associated risk. The treatment was prolonged for 12 weeks in high-risk cardiovascular patients. The low-density lipoprotein level was analyzed to check the efficiency of FDC. The study suggests, combination therapy successfully lowered the low-density lipoprotein levels in comparison to placebo or other monotherapy selected during the study (Ballantyne et al.).

1.4 Design of Experiment

The Design of Experiments (DOE) is a mathematical approach to designing and performing experiments, as well as analyzing and interpreting the results. It is a branch of applied statistics that is used to perform scientific investigations of a system, process, or product in which input variables (Xs) are changed to see how they affect the measured response variables (Y) (Durakovic et al.). The design of the experiment is a versatile technique that may be applied to a variety of scenarios to identify significant input factors (input variables) and their relationships to the outcomes (response variable) (Durakovic et al.). DOE is also a type of regression analysis that may be used in a variety of scenarios. Common design types include comparison, variable screening, transfer function identification, system optimization, and resilient design. (Guo et al.). As the number of weakly soluble medications in the pipeline and market space has expanded, the manipulation of these pharmaceuticals' water solubility has become a crucial stage in preformulation research. The arrangement of molecules in a therapeutically active ingredient's three-dimensional crystal lattice determines its physicochemical characteristics, such as solubility, dissolution, bioavailability, stability, and so on (Kundu et al.). The nonpeptide angiotensin II antagonist telmisartan (TLM) is marketed

by the inventor under the trade names Micardis and Micardis plus and is widely used to treat arterial hypertension. Telmisartan is poorly soluble in water in the physiological pH range of 3 to 7 (Kundu et al.). Cocrystals are crystalline solids that are increasingly being used to develop APIs with enhanced physicochemical characteristics including solubility, stability, and bioavailability (Yamashita et al., Bhandaru et al.). Pharmaceutical cocrystals are categorised according to the coformer they were made with: API-coformer Cocrystals (coformer from the FDA-approved GRAS list) and drug-drug cocrystals (coformer is replaced with another API) are two different forms of cocrystals (Kundu et al.). Because of the potential to modify the physicochemical characteristics of many novel and current APIs, drug-drug cocrystals have sparked a lot of interest in crystal engineering (McNamara et al., Thipparaboina et al.). The drug-drug cocrystals may not only change the fundamental characteristics of the drugs, but they may also introduce new possibilities for the development of combined drug therapies with potential benefits such as synergistic and/or additive effects (Kundu et al., Cosgrove et al.), dose reduction, cost-effective treatment, and improved patient compliance (Kundu et al.).

The present investigation highlights the simplified methodology of cocrystal formation by eliminating additives. The concentration ratios between both the APIs were considered to support therapeutic concentration and respective co-former concentration. The cocrystallization mechanism promotes the solubilization capabilities of individual APIs which were supported by the In-vitro dissolution study. The innovative cocrystallization strategy increases the stability of the formulation and reduces moisture absorption in comparison to the marketed product. The mechanism of cocrystallization may be helpful in designing future FDC products helps to reduce the cost of manufacturing.

1.5 Co-crystal method of preparation

Co-crystal preparation methods can be broadly classified into two types, one being solvent-based, and the other being solid-based (Yadav et al.).

1.5.1. Solvent-based methods

1.5.1.1. Slurry conversion

Different organic solvents and water can be used to convert slurries. After adding the solvent to the mixture, the suspension should be agitated for a number of days at room temperature. The solid is then dried using a nitrogen flow after the solvent is decanted (Yadav et al.).

1.5.1.2. Solution co-crystallization

A primary condition for solution co-crystallization is that the API and co-former have similar solubility; otherwise, the less soluble component will precipitate as a single compound. It is also suggested to use polymorphic compounds, i.e., compounds that are present in more than one form to provide more structural flexibility and escape being locked into a single type of crystalline lattice or packing mode. A polymorphic component will increase the probability of the molecule adopting different packing arrangements in co-existence with another molecule. Besides the criteria of similar solubility and polymorphism, the capacity of the molecules to undergo intermolecular interactions is critical for co-crystallization. In practice, the drug and co-crystal former is added to a reaction vessel, where they are mixed with a solvent or mixture of solvents and heated to 70° for 1 h under reflux. The mixture is then allowed to cool under stirring to form co-crystals without seeding (Yadav et al.).

1.5.1.3. Anti-solvent addition/ Precipitation

This method mainly includes the use of buffers and organic solvents for the precipitation or recrystallization of the co-crystal former and active pharmaceutical ingredient (Yadav et al.).

1.5.2. Solid based methods

1.5.2.1. Neat (Dry) grinding

The first technique, known as neat (dry) grinding, is combining the cocrystal components together and then pulverising them either manually with a mortar and pestle or mechanically with a ball mill or a vibrating mill (Friscic et al.).

1.5.2.2. Solvent-Drop Grinding / Liquid-assisted grinding

This method is an alteration to the neat grinding process. It mainly includes the assistance of the grinding process by the addition of a minor quantity of solvent (Yadav et al.). The primary reason for introducing liquid assisted grinding was to speed up co-crystal formation in a solid state, but it was later discovered to be beneficial for the neat grinding process as well because it offers higher yields, higher product crystallinity, the ability to control polymorph formation, and a much wider range of reactants and products. (Friscic et al.).

1.6. Aim of the study

To enhance the physicochemical and pharmacokinetic properties of an active pharmaceutical ingredient falls under BCS II and IV using the co-crystallization technique.

1.6.1 **Research objective**

1. To identify suitable drug candidates in BCS II or IV that can be converted into cocrystal form.
2. To select and screen suitable coformer/drug and solvent that can support the synthesis of Drug:Coformer or Drug:Drug cocrystal.
3. Systematically design cocrystal synthesis experiments through DoE (Design of Experiment) methodology.
4. To synthesize the cocrystals using an optimized methodology.
5. To characterize the cocrystals using different analytical techniques.
6. To study stability study on finalized cocrystals
7. To perform a pharmacokinetic study
8. To manufacture the cocrystals into oral dosage form and compare it with the existing marketed formulation.

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Review Of Literature

2. Review of Literature

A thorough literature, patent and marketed product search pertaining to the topic was conducted in multiple phases.

Table 2.1: Compilation of literature reviewed along with key notes

S. No	Title of the research/article	Key notes
Co-crystallization		
1	Donald J. Abraham and David P. Rotella, "Burger's Medicinal Chemistry, Drug Discovery, and Development" Seventh Edition.	This is one of the fundamental information on cocrystal characteristics taken from a chapter of Burger's medicinal chemistry, drug discovery and development. It provides key aspects at the functional group level of a molecule that makes it eligible for co-crystallization. • A hierarchy of the possible supramolecular synthons, with a focus on supramolecular heterosynthons, for common functional groups likes carboxylic acids, amides, and alcohols. • In the context of pharmaceutical cocrystals, carboxylic acids are likely the most significant and extensively researched functional group, and they serve as an excellent example of how cocrystal design might be utilised. • Carboxylic acids have a propensity to combine with aromatic nitrogen atoms and chloride anions to produce supramolecular heterosynthons..
2	Ranjit Thakuriaa, et al., "Pharmaceutical cocrystals and	In this review, author made a thorough compilation of various successful

S. No	Title of the research/article	Key notes
	poorly soluble drugs", International Journal of Pharmaceutics, 2013 Aug 30;453(1):101-25	pharmaceutical cocrystals which demonstrated improvement in the physicochemical properties of poorly soluble drugs. The vital role of crystal engineering in the selection of apt coformer and the supramolecular synthons present in cocrystals are thoroughly captured. In addition to that, *In-vivo* studies performed on different cocrystals were also covered in the review.
3	Maryam Karimi-Jafari, et al., "Creating Cocrystals: A Review of Pharmaceutical Cocrystal Preparation Routes and Applications", Cryst. Growth Des. 2018, 18, 6370−6387	This is a review article that provides insight on cocrystalization techniques and their benefits. According to the authors, co-crystallization is one of the promising approaches to improve the physicochemical properties of drug substances. Also, Co-crystal synthesis provides a range of options, from routine laboratory scale to large-scale, to continuous production. This review provides examples of established and emerging co-crystal manufacturing routes. It also provides information on proven applications of co-crystals that continues to expand with interest and proven worth. It also supports co-crystals as it continues to demonstrate their worth and is likely to become more routine in drug development.
4	Nate Schultheiss and Ann Newman, "Pharmaceutical Cocrystals and Their Physicochemical Properties", Crystal Growth & Design, Vol. 9,	This is a review article comprises of correlation of various physiochemical properties of drug substance once converted in the form of cocrystal. Based on the

S. No	Title of the research/article	Key notes
	No. 6, 2009	comparison of various published work done, It concludes that 51% of cocrystals exhibits melting point between pure drug substance and coformer and 39% cocrystals exhibits a lower melting point. Additionally, for solubility its difficult to set any correlation because of complexity involved due to multiple components in the crystalline structure. Most of the cocrystals offer better stability due to resistant to hydrate formation, although generalization is difficult as it depends on different systems as well. Sparingly soluble compounds can be turned into soluble by the application of cocrystalization.
5	David J. Berry, et al., "Pharmaceutical cocrystals, salts and multicomponent systems; intermolecular interactions and property based design", Adv. Drug Deliv. Rev. (2017).	Co-crystals and salts offer a viable way to enhance the in vivo exposure of poorly soluble API molecules and a way to modify their physical behavior. Effective design of functional co-crystals and salt forms requires consideration of the following physicochemical parameters: intrinsic solubility of the API, the lipophilicity of both components (in terms of Log P), and ensuring phase stability.
6	Dalpiaz, A., et al., "Can pharmaceutical co-crystals provide an opportunity to modify the biological properties of drugs?", Drug Discov Today , 017 Aug;22(8):1134-1138.	It is a perspective/review published by the author based on current trends in cocrystal development. The author touched upon an interesting aspects of the biological properties of pharmaceutical co-crystals. Based on the molecules in the form of co-crystal can retain

S. No	Title of the research/article	Key notes
		some of the intermolecular interactions formed in the solid state in solution. Additionally, the author suggested that the interaction of supramolecular complex may interact with the protein, by a different molecular mechanism. As affinity of the drug substance on the receptor also depends on weak interactions present in the drug substance.
7	Takaaki Masudaa, et al., "Cocrystallization and amorphization induced by drug–excipient interaction improves the physical properties of acyclovir". International Journal of Pharmaceutics, 422 (2012) 160–169.	This work demonstrates the formation and characterization of the co-crystal of acyclovir with tartaric acid. Various characterization techniques like PXRD, Thermogravimetry/Differential Thermal Analysis, IR and HPLC. Synchrotron X-ray powder diffraction was used to determine the crystal structure of the co-crystal was determined. To assess the solubility enhancement of acyclovir co-crystals, the saturation solubility was measured in water, ethanol and phosphate buffer pH 6. With characterization techniques, hydrogen bond-linked interaction between acyclovir and tartaric was confirmed.
8	Yashika Bhalla, et al., "Daidzein cocrystals: An opportunity to improve its biopharmaceutical parameters", Heliyon 5 (2019) e02669.	In this article, the author demonstrated the formation of cocrystal of daidazein and the involvement of hydrogen bonding of daidzein with complementary functional groups of cytosine (C = O), theobromine (OH) and isonicotinamide (OH). These cocrystals demonstrated significant improvement in

S. No	Title of the research/article	Key notes
		physicochemical like solubility and other parameters. Additionally significant improvement in pharmacokinetic parameters like Cmax and AUC compared to the pure components was demonstrated through the *In-vivo* study.
Drug : Drug Cocrystals		
9	Kuan Lin Yeh and Tu Lee, "Intensified Crystallization Processes for 1:1 Drug-Drug Co-crystals of Sulfathiazole-Theophylline, and Sulfathiazole-Sulfanilamide", Cryst. Growth Des. 2018, 18, 3, 1339–1349.	In this research article, the author provided a technique to utilize pH-dependent solubility of sulfathiazole to prepare sulfathiazole-theophylline and sulfathiazole-sulfanilamide cocrystal. Also, the challenge of polymeric impurities in the synthesis was tackled by co-crystallization. The study resulted in 1:1 cocrystal of sulfathiazole–sulfanilamide and a 1:1 cocrystal of sulfathiazole–theophylline stable under stress temperature and humidity conditions for a month.
10	Ksenia V Drozd et al., Drug-drug cocrystals of antituberculous 4-aminosalicylic acid: Screening, crystal structures, thermochemical and solubility studies", Eur J Pharm Sci. 2017 Mar 1;99:228-239.	In this research work, the successful synthesis of cocrystal synthesis of 4-aminosalicylic acid with Caffeine and 4-aminosalicylic acid with Isonicotinamide. The solution techniques and solvent-drop grinding were the two techniques applied with methanol as a solvent. Methanol as solvent played a critical role in bridging the cocrystals. An increase in solubility by more than 2-fold was observed in dissolution studies.
11	Ranjit Thakuria and Bipul Sarma, "Drug-Drug and Drug-Nutraceutical	This publication is a review article illustrating the importance of Drug-drug and drug-

S. No	Title of the research/article	Key notes
	Cocrystal/Salt as Alternative Medicine for Combination Therapy: A Crystal Engineering Approach", Crystals 2018, 8, 101.	nutraceutical co-crystals and the benefits of these cocrystals. The author also emphasized care that has to be taken in the selection of the right drug candidate with the presence of complementary hydrogen-bonding synthons that play a key role in synthesis. The recent development and acceptability from health authorities and multiple benefits from the cocrystal synthesis made pharmaceutical companies invest more money.
12	Ksenia V. Drozd, et.al, "A Novel Drug-Drug Cocrystal of Carbamazepine with para-Aminosalicylic Acid: Screening, Crystal Structure and Comparative Study of Carbamazepine Cocrystals Formation Thermodynamics", CrystEngComm, Issue 30, 2017.	This research work demonstrates screening and characterization of drug:drug cocrystal of carbamazepine and para-aminosalicylic acid. Various molar ratios were screened and synthesized via liquid-assisted grinding, slurring and solution crystallization methods. The resultant 1:1 ratio cocrystal of both the API showed approximately a 1.5-fold increase in solubility and stability through
13	Marc P Maillard and Michel Burnier, "Is the fixed-dose combination of Telmisartan and hydrochlorothiazide a good approach to treat hypertension?", Vascular Health and Risk Management 2007:3(3) 265–278	This is a review article in which authors compiled data from different studies performed on Telmisartan and Hydrochlorothiazide. The authors also state that based on the studies, the combination of Telmisartan and low-dose hydrochlorothiazide lowers blood pressure more than Telmisartan or hydrochlorothiazide dosed individually. This review gives a good reason to pursue drug:drug cocrystal synthesis of these two drugs.
14	Alpana kulkarni, et al., "Novel	In this study, the author demonstrated

S. No	Title of the research/article	Key notes
	pharmaceutical cocrystal of telmisartan and hydrochlorothiazide", Asian J Pharm Clin Res, Vol 13, Issue 3, 2020, 104-112	cocrystal synthesis of telmisartan with the conformer hydrochlorothiazide. The study also captures improved solubility and dissolution rate of Telmisartan: hydrochlorothiazide co-crystal compared to the FDC tablets. Although this study does address the advantage of cocrystals that can help to improve the moisture sensitivity of tablets available commercially. To enhance the solubility of Telmisartan and Hydrochlorothiazide, FDC tablets are formulated with the usage of an alkalizer to provide an apt microenvironment to enhance solubility. That in turn increases the moisture sensitivity of the tablets. With the replacement of both the drug substances with drug:drug cocrystal, the moisture sensitivity issue of tablets can be addressed.
15	Micardis® HCT (Telmisartan and Hydrochlorothiazide) Patient Information Leaflet (PIL)	This information is captured from the leaflet of Micardis HCT tablets that are commercially available in the market. Micardis is a fixed-dose combination of Telmisartan and Hydrochlorothiazide. The clinical trials were conducted on the patient population of more than 2,500 patients, in which 1,017 patients received Telmisartan (20-160 mg) and hydrochlorothiazide (6.25-25 mg) simultaneously. These studies included a factorial study with the combination of Telmisartan (20, 40, 80, 160 mg or placebo) and hydrochlorothiazide

S. No	Title of the research/article	Key notes
		(6.25, 12.5, 25 mg and placebo). In four additional studies of his for at least 6 months, hydrochlorothiazide was administered to patients who were either poorly controlled on a randomized monotherapy dose or had an inadequate response after completion of Telmisartan titration.
16	Cocrystals of Telmisartan: characterization, structure elucidation, in vivo and toxicity studies	This research works provides information on the cocrystal of Telmisartan with saccharin as a coformer. In this work, the authors demonstrate improvement in the physiochemical properties of Telmisartan cocrystal. Additionally, pharmacokinetic studies were performed in rats indicating an increase in relative bioavailability and efficacy in terms of reduction in arterial blood pressure in rats. This work indicates the potential of Telmisartan drug substance that can be converted into cocrystal.
Manufacturing and characterization of co-crystals		
17	Vijaykumar K. Parma, et al., “Hydrochloride salt co-crystals: preparation, characterization and physicochemical studies”, Pharmaceutical Development and Technology, 2013; 18(2): 443–453	This work involved screening Fluoxetine hydrochloride for co-crystallization with a carboxylic acid as a coformer using the solvent evaporation technique. Cocrystals prepared were characterized using FTIR, melting point and crystal habit measurements were performed to characterize the products during screening. Co crystal properties obtained from FTIR analysis, thermal behavior from DSC analysis, and diffraction

S. No	Title of the research/article	Key notes
		pattern from PXRD analysis of Co crystals confirmed the formation of a new solid crystal form of fluoxetine hydrochloridehe melting point of the collection of fluoxetine hydrochloride-Co crystals is dependent on the coformer, according to melting point data. For instance, a lower melting co-former should be chosen if a higher melting co-crystal is needed, and vice versa. various co-crystals dissolve and dissolve at various speeds. Co-crystallization has been demonstrated in dissolution experiments to either raise or decrease an API's dissolution rate or essentially maintain it at the same level.
18	Cocrystal production method reducing deposition risk of undesired single component crystals in anti-solvent cocrystallization	The co-crystallization process carries the risk of isolating unwanted monocomponent crystals. Therefore, for a successful co-crystallization process, it is necessary to develop a selective production process that yields co-crystals with the desired stoichiometry.
19	Manish Kumar, et al., ‘”Dissolution Method Development and Validation for Tablet Dosage form of Telmisartan Using UV Spectrophotometric Method”, J. Chem. Pharm. Res., 2018, 10(5): 148-156.	In this article, the author developed and validated a method using UV spectroscopy of Telmisartan tablets. The method was validated in accordance with ICH guidelines. Based on work done, 0.1N HCl, USP apparatus type II, speed 100 rpm, 60 minutes for dissolution is suitable for dissolution testing of Telmisartan tablets. The developed validated methodology was also applied successfully for the quantification and quality control of

S. No	Title of the research/article	Key notes
		telmisartan tablet formulations.
20	A twist in Cocrystals of Salts: Changes in Packing and Chloride Coordination Lead to Opposite Trends in the Biopharmaceutical Performance of Fluoroquinolone Hydrochloride Cocrystals	The co-crystalline solids, CiHCl-4HBA and MoHCl-4HBA, can be obtained by various methods such as slurry conversion, solvent drop milling, crystallization by solvent evaporation, and reactive crystallization.
21	Xin Chen, et al., "Cocrystals of zileuton with enhanced physical stability", CrystEngComm, Issue 7, 2018.	This work demonstrates a successful synthesis of cocrystals of zileuton with Nicotinamide and isonicotinamide. Synthesized co-crystal forms, zileuton- nicotinamide and zileuton - isonicotinamide, displayed phase stability to moisture. Different analytical techniques like PXRD, Solid state NMR, DSC were used to characterize cocrystal forms, providing sufficient information about the solid state of this important drug substance.
22	Vijaykumar K. Parmar, et al., "Hydrochloride salt co-crystals: preparation, characterization and physicochemical studies", Pharmaceutical Development and Technology, 2013; 18(2): 443–453	In this research article, the author investigated the co-crystallization of Fluoxetine hydrochloride with different carboxylic acid coformers using solvent evaporation as a key technique. Cocrystals were characterized by PXRD, DSC and FTIR, methods. Additionally, the solubility of synthesized cocrystals was measured in a buffer solution of different pH and water. Intrinsic dissolution for co-crystals was measured to evaluate the improvement in dissolution rate. All the studies performed indicated improvement in the physicochemical properties of Fluoxetine hydrochloride.

S. No	Title of the research/article	Key notes
23	KarthikNagapudi, et al., “High-throughput screening and scale-up of cocrystals using resonant acoustic mixing”, International Journal of Pharmaceutics Volume 521, Issues 1–2, 15 April 2017, Pages 337-345	In this research article, the author demonstrated the application of resonate acoustic mixing to increase the success rate for cocrystal preparation of Carbamazepine, Theophylline and Caffeine. Key parameter identified which need to be optimized during this work was acceleration and mixing time. Through this work, resonate acoustic mixing was identified as a reliable and established technique for the scale-up.
24	Feng-Yuan Wang, et al., “Solid-state characterization and solubility enhancement of apremilast drug-drug cocrystals”, CrystEngComm, Issue 39, 2018.	This work demonstrated the synthesis of drug:drug cocrystal of Apremilast using Nicotinamide, Caffeine and acetylsalicylic acid. Different methods, including Thermogravimetric analysis, DSC, and PXRD, were used to characterise these cocrystals. Comparing the solubility and intrinsic dissolution rates to the drug ingredient alone, a significant improvement was seen, indicating improved pharmacokinetic qualities.
25	Skieneh, Jenna M., "Crystal Engineering of Active Pharmaceutical Ingredients with Low Aqueous Solubility and Bioavailability" (2017). Electronic Thesis and Dissertation Repository. 4708.	This work demonstrated efforts in the synthesis of co-crystals of Rufinamide using solution and milling techniques to screen and identify any other solid forms in addition to cocrystal form like co-amorphous, eutectic mixtures, solvates, etc. No other forms were formed during screening apart from the metastable form of Rufinamide, modification B. Computer-assisted co-crystal screening methodology was applied. Although no novel

S. No	Title of the research/article	Key notes
		cocrystal formation was made from suggested coformers, which questions the reliability of the Computer-assisted co-crystal screening methodology. Molecular synthon for screening of coformer is suggested to be a more reliable approach.
26	Yan Zhang, Zhao Yang, Shuaihua Zhang and Xingtong Zhou, "Synthesis, Crystal Structure, and Solubility Analysis of a Famotidine Cocrystal", Crystals 2019, 9, 360.	In this work, the author demonstrated the cocrystal formation of Famotidine and Malonic acid linked via an intermolecular hydrogen bond between the amide of Famotidine and the Carboxy of Malonic acid. Cocrystal manufacturing was characterized by single-crystal X-ray diffraction. The uniqueness of the formed cocrystal was established by analyzing thermal, spectral and PXRD properties which were found to be different from famotidine. An increase of 4.2-fold famotidine solubility was achieved without affecting stability.
27	Vijaykumar K. Parmar, et al., "Hydrochloride salt co-crystals: preparation, characterization and physicochemical studies", Pharmaceutical Development and Technology, 2013; 18(2): 443–453	In this research article, the author investigated the cocrystalization of Fluoxetine hydrochloride with different carboxylic acid coformers using solvent evaporation as a key technique. Cocrystals were characterized by PXRD, DSC and FTIR, methods. Additionally, the solubility of synthesized cocrystals was measured in a buffer solution of different pH and water. Intrinsic dissolution for co-crystals was measured to evaluate the improvement in dissolution rate. All the studies performed indicated improvement in

S. No	Title of the research/article	Key notes
		the physicochemical properties of Fluoxetine hydrochloride.
28	Wang, I.C., et al., "Anti-solvent co-crystallization of carbamazepine and saccharin", International Journal of Pharmaceutics (2013), ijpharm.2013.04.012	This work involves the synthesis of cocrystals using the anti-solvent methodology. The author emphasized on the selection of appropriate pair of solvents and anti-solvents during synthesis. For the study, Carbamazepine is considered as a drug substance along with saccharine as a coformer. Different solvents were screened for the anti-solvent methodology for cocrystal synthesis. Out of all the screened solvents, methanol was found to be an appropriate solvent in combination with water as an anti-solvent. Different ratio of the drug and coformer is also studied to observe its impact on yields and purity.
29	Michał Sowa, et al., "Cocrystals of fisetin, luteolin and genistein with pyridinecarboxamide coformers: crystal structures, analysis of intermolecular interactions, spectral and thermal characterization", CrystEngComm, Issue 38, 201.	This work mainly involves the application of Nicotinamide and Isonicotinamide as coformer for the synthesis of cocrystals with fisetin, luteolin and genistein which are natural polyphenolic compounds. For the synthesis of cocrystals, solvent drop grinding and solvent evaporation methods were applied. Cocrystals were obtained using the solvent evaporation method. Characterizations of these cocrystals were performed by XRPD, X-ray single-crystal diffraction, FT-Raman spectroscopy and thermal analysis.

S. No	Title of the research/article	Key notes
30	Arif Budiman, et al., "Virtual screening of coformers and solubility test for glibenclamide cocrystallization", National Journal of Physiology, Pharmacy and Pharmacology, 2018, Vol 8, Issue 1	In this article, the author illustrated the formation of a cocrystal of Glibenclamide with Oxalic acid, Bezoic acid and ascorbic acid. The coformers were selected based on te outcome of molecular docking. On the synthesized cocrystals solubility test was performed which showed 181.7% increased solubility of Glibenclamide oxalate cocrystal as compared to pure Glibenclamide. Also, same increase in dissolution rate for Glibenclamide oxalate cocrystal (77.3% at 60 minutes) compared to pure Glibenclamide (44.52% at 60 minutes) was demonstrated.
31	M. A. Elbagerma, et al., "Characterization of New Cocrystals by Raman Spectroscopy, Powder X-ray Diffraction, Differential Scanning Calorimetry, and Transmission Raman Spectroscopy, Crystal Growth & Design, Vol. 10, No. 5, 2010	In this research article, the author focused on cocrystal characterization techniques like Raman spectroscopy, Differential Scanning Calorimetry, Transmission Raman Spectroscopy and Powder X-ray Diffraction. Different aspects of analytical techniques and data interpretation are discussed. The cocrystals of salicylic acid with nicotinic acid and 3,4-dihydroxybenzoic acid with oxalic were synthesized using the solvent evaporation technique with ethanol as solvent. Characterization of cocrystal using Raman spectroscopy showed a broadening of the region of the carbonyl band which is indicative of the presence of co-crystals. Additionally, changes in the energy of the bands linked to the carbonyl vibration of the carboxyl group were observed. Through this

S. No	Title of the research/article	Key notes
		study, 1:1 molar ratio of co-crystal components was confirmed.

Table 2.2: Compilation of US patent in cocrystals

US Patent No.	Date of issue	Assignee	Compound(s)
US8097592	17-Jan-12	Astellas Pharma Inc., Kotobuki Pharmaceutical Co. Ltd.	SGLT-2 Inhibitor and l-proline cocrystal
US8124603	28-Feb-12	Thar Pharmaceutical	Meloxicam cocrystal with different carboxylic acids, including aliphatic and aromatic, as well as maltol and ethyl maltol.
US8163790	24-Apr-12	New Form Pharmaceuticals, Inc.	Metronidazole cocrystals with gentisic acid, gallic acid, a cocrystal of imipramine HCland (+)-camphoric acid, and particular x-ray reflections in each case.
US20170044176A1	16-Feb-17	Euticals Spa	Cocrystal of tiotropium bromide and lactose monohydrate
US20170224724A1	10-Aug-17	University Of South Florida	Co-crystal (ICC) of lithium with salicylic acid and 1-proline
US20170101433A1	13-Apr-17	Amri Sci. Llc.	Progesterone co-crystal with a co-former chosen from the list that includes vanillic acid, benzoic acid, salicylic acid, cinnamic acid, and vanillin.

Table 2.3: Compilation of EU patent in cocrystals

Patent no.	Date of issue	Assignee	Compounds
EP2334687B1	04-Jan-12	Pfizer Inc.	SGLT-2 inhibitors, l-proline and pyroglutamic acid cocrystals
EP2300472B1	18-Jan-12	Boehringer Ingelheim Intl. GmBH	Glucocorticoid analogs, phosphoric acid and acetic acid cocrystals
EP2114924B1	25-Jan-12	Vertex Pharmaceuticals Inc.	Cocrystals of telaprevir with 4-hydroxybenzoic acid; solvates
EP2288606B1	15-Feb-12	Bayer Pharma Ag	Rivaroxaban cocrystal with malonic acid
EP1608339B1	21-Mar-12	McNeil PPC	Celecoxib cocrystal with nicotinamide
EP3210975 A1	30-Aug-17	Enantia, S.L.	Cocrystals of Lorcaserin hydrochloride and an organic diacid
EP3240575 A1	08-Nov-17	Dr. Reddy's Laboratories Ltd.	Co-crystal of carfilzomib with maleic acid

Table 2.4: Compilation of commercially available products with drug modified into cocrystal

Drug combination	Therapeutic category
Entresto	A multi-drug co-crystal formulation of sacubitril and valsartan (brand name: Entresto, Novartis) was given USFDA approval on July 7, 2015, to lower the risk of cardiovascular disease and chronic heart failure.
Lexapro	Lexapro is a co-crystal formulation of escitalopram approved in 2009 for the treatment of major depression and anxiety disorders under the Lexapro brand name.
Steglatro	The USFDA has approved a co-crystal formulation of ertugliflozin (a co-crystal of ertugliflozin and his 5-oxoproline) under the brand name Steglatro™.
Suglat® (Ipragliflozin:	Iragliflozin is a sodium glucose cotransporter 2 (SGLT2) inhibitor. A co-crystal formulation has been approved and in Japan he is marketed under the

L-proline)	trade name Suglat®.
TAK-020 Gentisic acid Co-crystals	TAK-020 (Bruton's Tyrosine Kinase Inhibitor), a novel co-crystal-based formulation created by Takeda Pharmaceutical Company Limited, is intended to treat rheumatoid arthritis. Clinical trials for Co-Crystal's Phase I are finished.
Aripiprazole	Co-crystal aripiprazole is marketed under the trade name Abilify®. Aripiprazole and fumaric acid are combined to form the crystal Abilify.
Tramadol-Celecoxib (1:1) Cocrystal	Enantia and Esteve in Spanish R&D created and Laboratorios Del patented E-58425, a celecoxib plus tramadol (1:1) formulation. A multi-drug co-crystal like this one is one that is now undergoing clinical testing.

Material and Method

3. Material and Method

3.1. List of chemical and reagents used in the experiment

Table 3.1 List of materials used in present work

Name of material	Name of Manufacturer/supplier
Ranolazine (RAN)	Piramal Healthcare, Ahmedabad
Telmisartan (TEL)	Piramal Healthcare, Ahmedabad
Hydrochlorothiazide (HCT)	Piramal Healthcare, Ahmedabad
Nicotinamide (NIC)	Piramal Healthcare, Ahmedabad
Ethanol	Sigma-Aldrich, Merck, Mumbai (HPLC grade)
Methanol	Sigma-Aldrich, Merck, Mumbai (HPLC grade)
Microcrystalline cellulose	JRS Pharma,
Hypromellose	Jigchem universal, Mumbai, India
Starch	Auro chemicals, New Delhi, India
Lactose monohydrate FlocLac	DFE Pharma, Mumbai, India
Crospovidone	CDH Private Limited, New Delhi, India
Colloidal silicon dioxide	Sigma-Aldrich, Merck, Mumbai
Mannitol	Roquette, Mumbai
Lactose monohydrate	DFE Pharma, Mumbai
Povidone K25	BASF, Mumbai
Sodium stearyl fumarate	Angel Chemicals, Vadodara
Magnesium stearate	Vizag chemicals, Visakhapatnam
Sodium hydroxide	Sigma-Aldrich, Merck, Mumbai
Meglumine	Lexicare Pharma Pvt. Ltd
Ferric oxide red	Sigma-Aldrich, Merck, Mumbai
Cresar® H Tablets	Local Market

3.2. List of instruments used in experiments

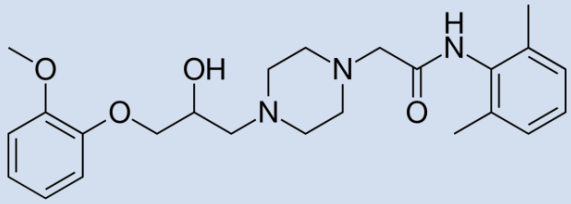
Table 3.2 List of equipments and instruments used in present work

Name of equipment/instrument	Make	Model
vacuum drier	Labsnova, China	DZF-6010
Spectrophotometer	Shimadzu	UV-1800
Differential scanning calorimeter	TA Instruments, USA	AQ20

Name of equipment/instrument	Make	Model
Melting point apparatus	Supertek®, India	MPA305
Turbula 3D shaker mixer	Willy A. Bachofen AG, Switzerland	TURBULA®
Compression machine	Korsch AG, Germany	XL 100
Rotavapor	Buchi, Switzerland	Rotavapor® R-100
Dissolution apparatus (paddle) USP type II	Electrolab	Inspire 8 Basic
Dynamic Vapor Sorption	Mettler Toledo	SPS23-100n

3.3. Profile of drug substances used in the study

Table 3.3 Profile of Ranolazine (pubchem)

Profile	Details
Name	Ranolazine
Category	Antiangina agent
IUPAC	N-(2,6-dimethylphenyl)-2-(4-(2-hydroxy-3-(2-methoxyphenoxy)propyl)piperazin-1-yl)acetamide
CAS	95635-55-5
Structural Formula	
Molecular Formula	$C_{24}H_{33}N_3O_4$
Molecular Weight	427.53 g/mol
BCS Class	II
Melting Point	120-124°C
Solubility	Soluble in dichloromethane, methanol; sparingly soluble in, ethanol, acetonitrile, acetone; very slightly soluble in water

pKa (Strongest Acidic)	2.2

Table 3.4 Profile of Telmisartan (pubchem)

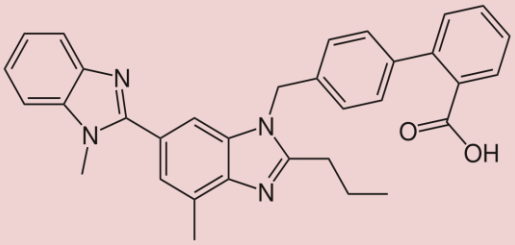
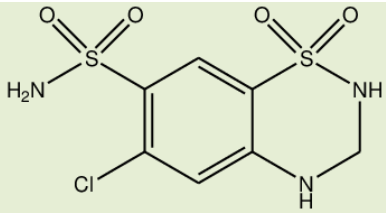
Profile	**Details**
Name	Telmisartan
Category	Angiotensin II receptor blocker
IUPAC	2-[4-[[4-methyl-6-(1-methylbenzimidazol-2-yl)-2-propylbenzimidazol-1 yl]methyl]phenyl]benzoic acid
CAS	144701-48-4
Structural Formula	
Molecular Formula	$C_{33}H_{30}N_4O_2$
Molecular Weight	514.63 g/mol
BCS Class	II
Melting Point	261-263 °C
Solubility	Insoluble in water and in the pH range of 3 to 7, sparingly soluble in strong acid
pKa (Strongest Acidic)	9.09
pKa (Strongest Basic)	- 2.7

Table 3.5 Profile of Hydrochlorothiazide (pubchem)

Profile	**Details**
Name	Hydrochlorothiazide
Category	Angiotensin II receptor blocker
IUPAC	6-chloro-1,1-dioxo-3,4-dihydro-2H-1λ6,2,4-benzothiadiazine-7-sulfonamide

CAS	58-93-5
Structural Formula	
Molecular Formula	$C_7H_8ClN_3O_4S$
Molecular Weight	297.74 g/mol
BCS Class	II
Melting Point	266-268 °C
Solubility	Slightly soluble in water, and freely soluble in sodium hydroxide solution.
pKa (Strongest Acidic)	9.08
pKa (Strongest Basic)	9.79

3.4. Synthesis of Ranolazine and Nicotinamide cocrystal

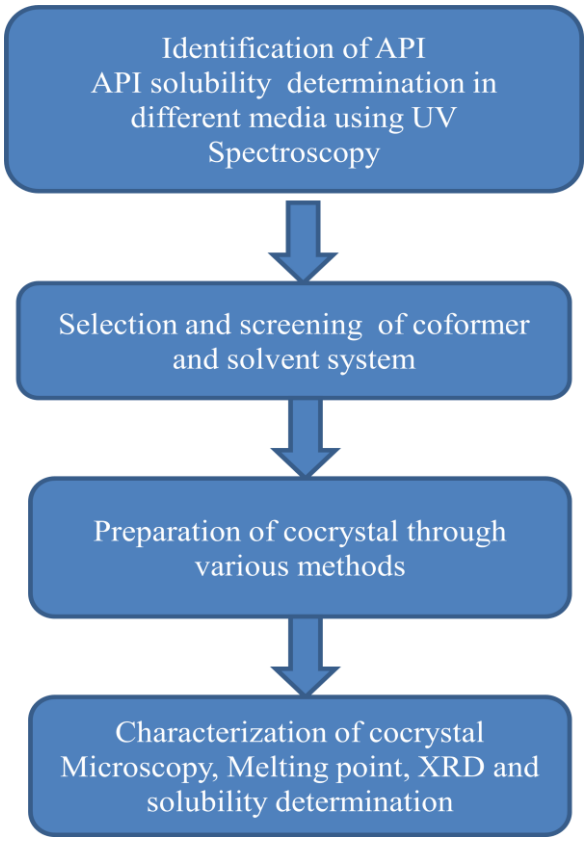


Figure 3.1 Flow chart depicting experimental plan for Ranolazine and Nicotinamide cocrystal

Cocrystals of Ranolazine-Nicotinamide (RAN-NIC) were fabricated using distinct ratios of two coformers utilizing different methodologies like solvent-assisted grinding, slurry preparation and solvent evaporation methods.

Table 3.6 Methodology applied for RAN:NIC cocrystal synthesis (Yadav et al.).

Sample	API	Coformer	Molar Ratio	Methodology
Sample 1	Ranolazine (25 mM- 100 mg in 10 mL methanol)	Nicotinamide (25 mM- 15 mg in 5 mL methanol)	1:1	Solvent evaporation method
Sample 2	Ranolazine (25 mM- 100 mg in 10 mL methanol)	Nicotinamide (25 mM- 15 mg in 5 mL methanol)	1:1	Slurry method
Sample 3	Ranolazine (25 mM- 100 mg in 10 mL methanol)	Nicotinamide (25 mM- 15 mg in 5 mL methanol)	1:1	Solvent assisted grinding

3.4.1. Synthesis via solvent evaporation

For the preparation of RAN-NIC cocrystals using the solvent evaporation method, equimolar quantities of Ranolazine (100 mg, 25 mmol) and Nicotinamide (15 mg, 25 mmol) were taken with 15 mL of methanol in a round bottom flask. The mixture was then stirred at 75 rpm and heated at 50℃ till the solvent evaporates completely. Additionally, the drying of the sample was performed in a vacuum drier at 50°C for 2 hrs to obtain dry powder (Yadav et al.).

3.4.2. Synthesis via slurry preparation

For the preparation of RAN-NIC cocrystals using the slurring method, equimolar quantities of Ranolazine (100 mg, 25 mmol) and Nicotinamide (15 mg, 25 mmol) were added to 15 mL of methanol in a beaker. The slurry was stirred using a magnetic stirrer at 75 rpm for 24 hrs. The slurry obtained was then filtered and the wet powder was dried in a vacuum dried at 50°C for 30 min to get dry powder (Yadav et al.).

3.4.3. Synthesis via assisted grinding

For the preparation of RAN-NIC cocrystals using the solvent-assisted grinding method, equimolar quantities of Ranolazine (100 mg, 25 mmol) and Nicotinamide (15 mg, 25 mmol) as a coformer were grounded in one direction using a mortar and pestle with intermittently dropwise addition of approximately 5 mL of methanol for 30 min. The grounded mixture was dried in a vacuum dried at 50°C for 30 min to get dry powder. The resultant dry powder was passed through sieve no. 40 and 60 and were collected in final product bottles (Yadav et al.).

3.4.4. RAN: NIC molar ratio screening

Different molar ratios of RAN and NIC were evaluated for cocrystal preparation using the solvent evaporation method. As solvent evaporation technique is faster and more reliable as compared to the solvent-assisted grinding and slurry method. RAN and NIC were taken in different molar ratios as mentioned along with 15 mL of methanol in a round bottom flask. The mixture was then stirred at 75 rpm and heated at 50°C till the solvent evaporates completely. Additionally, the drying of the sample was performed in a vacuum drier at 50°C for 2 hrs to obtain dry powder (Yadav et al.).

Table 3.7 Molar ratio screening for RAN:NIC cocrystal synthesis

Sample	API	Coformer	Molar Ratio
Sample 1	Ranolazine (25 mM- 106 mg in 10 mL methanol)	Nicotinamide (25 mM- 15 mg in 5 mL methanol)	1:1
Sample 2	Ranolazine (25 mM- 106 mg in 10 mL methanol)	Nicotinamide (50 mM- 30 mg in 5 mL methanol)	1:2
Sample 3	Ranolazine (25 mM- 106 mg in 10 mL methanol)	Nicotinamide (75 mM- 45 mg in 5 mL methanol)	1:3
Sample 4	Ranolazine (75 mM- 320 mg in 10 mL methanol)	Nicotinamide (25 mM- 15 mg in 5 mL methanol)	3:1
Sample 5	Ranolazine (50 mM- 213 mg in 10 mL methanol)	Nicotinamide (25 mM- 15 mg in 5 mL methanol)	2:1

3.5. Characterization of RAN:NIC cocrystal

The powder obtained after drying from three different methods was subjected to characterization using different techniques.

3.5.1. Physical Appearance

The physical appearance of fabricated cocrystals was performed using visual inspection to check the appearance and color of cocrystals.

3.5.2. Melting Point

The elting point of different samples was measured using the melting point apparatus model MPA305 from Labotec. Ranolazine, Nicotinamide, and different cocrystal prepared with different molar concentrations of RAN and NIC were recorded for characteristics sharp melting points (Vijaykumar K. Parma et al., 2013).

3.5.3. Differential scanning calorimetry

DSC was performed using DSC instrument model AQ20 from TA Instruments, USA. Samples (RAN: NIC with different ratios i.e. 1:3, 1:2, 2:1 and 3:1) of around 2 g were placed in aluminum pans and a heating rate of 10 °C/ min under a nitrogen atmosphere with a flow rate of 50 ml/min was supplied. DSC was performed in the range of 0 °C to 400 °C temperature. The data was collected by platinum advantage software (Xin Chen, et al., 2018).

3.5.4. X-ray Powder Diffraction

X-ray diffractometer from PANalytical X'Pert Pro powder system with CU anode, wavelength 0.154 nm, maximum 2.2 kW, 60 kV, long fine focus ceramic tube, type PW3373/00 was used. Illumination was done on the 15 mm sample size and analyzed from 5° and 40° in 2θ. X'Pert High Score software was used to refine captured pXRD patterns (Vijaykumar K. Parma, et al., 2013).

3.5.5. Saturation Solubility

Saturation solubility of the RAN: NIC cocrystals was performed by dissolving a surplus amount (approx 100 mg) of sample in 15mL each of different buffers (pH 1.2, pH 4.5 and pH 6.8) and water. Samples in different buffers and water were placed in a conical flask and shaking was carried out (Innova-2000 portable shaker) at 250 rpm for 24 h at room temperature. Resultant samples were filtered through a 0.45 µ membrane filter and quantitative analysis was done using a UV spectrophotometer (UV-1800 Shimadzu 1800).

3.5.6. Cocrystal Stability

Stability of RAN: NIC cocrystals were performed by keeping samples in a glass vial in long-term (25°C/60%RH) condition for 12 months and in accelerated (40°C/75%RH) condition for 6 months (ICH Q1A). Samples were tested for Assay and PXRD for any changes in the crystal lattice.

3.5.7. *In-vivo* pharmacokinetic study

The pharmacokinetic characteristics of new cocrystal formed were studied via an *In-vivo* study conducted on six albino rats weighing 190 ± 20 g. Rats were divided into 3 groups, The first group of animals was provided with pure RAN, the second group was provided with cocrystal of RAN:NIC, and the third group is treated as control. Samples were given at a dose of 55 mg/kg via a feeding tube (Mashayekhi-sardoo et.al., 2022). The blood samples were collected at 0, 30, 60, 90, 120, 180, and 240, minutes through the tail vein in a centrifuge tube (Mani et. al, 2019). To separate plasma from blood, collected blood samples were centrifuged at 4000 rpm for 10 minutes. Plasma samples were then analyzed for drug content using a spectrophotometer (UV-1800 Shimadzu 1800, Japan).

3.6. Tablet manufacturing using RAN:NIC cocrystal

Tablets were prepared using RAN:NIC 1:2 cocrystal and excipients suitable for the direct compression method. The composition of the tablet is provided in Table 3.8

Table 3.8 Composition of tablets manufactured using RAN:NIC cocrystals

S.No	Composition	Function	% w/w	mg/tab
1	RAN:NIC Co-crystal	Drug Substance	70.4	500.0
2	Microcrystalline cellulose	Bulking agent	7.0	50.0
3	Lactose monohydrate FloLac	Bulking agent	5.6	40.0
4	Maize Starch	Binder	2.8	20.0
5	Hypromellose	Binder	2.1	15.0
6	Crospovidone	Disintegrant	7.7	55.0
7	Colloidal silicon dioxide	Glidant	2.1	15.0
8	Magnesium Stearate	Lubricant	2.1	15.0
	Total		100.0	710.0

Procedure:

a. Drug substance (RAN:NIC cocrystal), Microcrystalline cellulose, Lactose monohydrate, Starch, Hypromellose and Crospovidone passed through #30 sieve.
b. Material sieved in the above step is blended in a Turbula blender for 10 min at 22 rpm.
c. Colloidal silicon dioxide and Magnesium stearate passed through #40 sieve and were added to the above material in Turbula blender for blending for 5 min at 22 rpm.
d. The final blend from the above step is compressed into a tablet using Korsch XL100 machine.

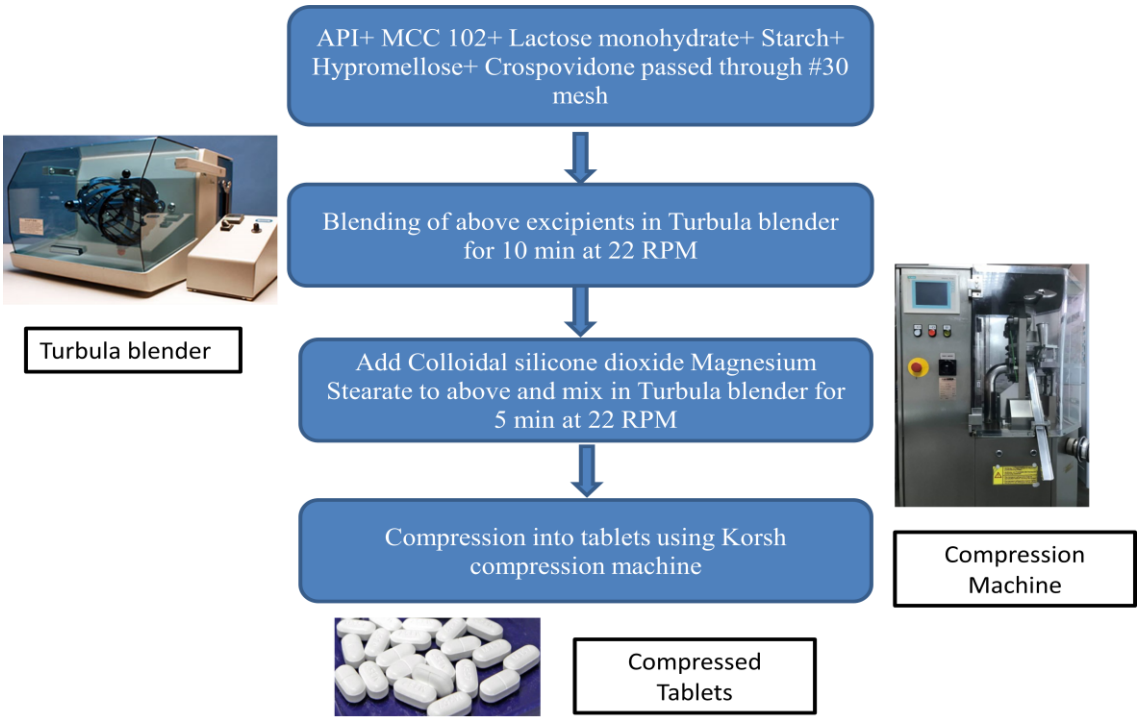


Figure 3.2 Flow diagram of tablet manufacturing process

3.6.1. Tablet characterization

3.6.1.1. Solubility study

Saturation solubility of the RAN: NIC cocrystals tablets and marketed Ranolazine tablets was performed by dissolving a surplus amount (approx 100 mg) of sample in 15mL each of different buffers (pH 1.2, pH 4.5 and pH 6.8) and water. Samples in different buffers and water were placed in a conical flask and shaking was carried out (Innova-2000 portable shaker) at 250 rpm for 24 h at room temperature. Resultant samples were filtered through a 0.45 µ membrane filter and quantitative analysis was done using a UV spectrophotometer (UV-1800 Shimadzu 1800).

3.6.1.2. Tablet assay and dissolution

Tablets prepared In-house and marketed tablets were subjected to dissolution using USP type II apparatus (paddle) in 0.1 N HCl (900 mL) at 37°C± 0.5°C using a paddle speed of 50 rpm. Samples were collected at 0, 10, 20, 30, 40, 50 and 60 min time points and analyzed using a UV spectrophotometer (Shimadzu UV 1800).

3.6.1.3. Stability study of tablets

Tablets of RAN:NIC were subjected to accelerated (40°C/75%RH) and long-term (25°C/60%RH) stability conditions as per ICH guidance for 6 months and 12 months

respectively. The samples were tested for XRPD and assay at initial, 6-month, and 12-month time points to check crystal lattice intactness after subjecting to stress conditions (ICH Q1A(R2).

3.7. Synthesis of Telmisartan:Hydrochlorthiazide Cocrystal (Drug: Drug Co-crystal)

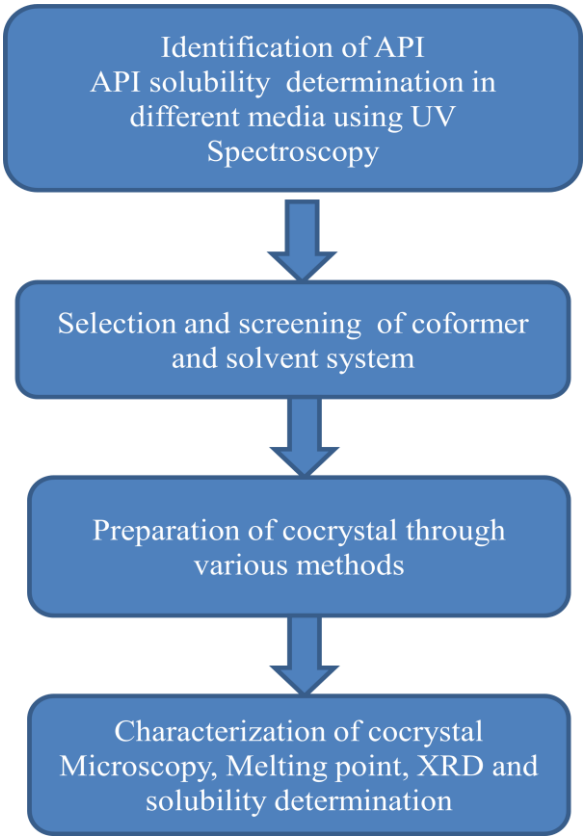


Figure 3.3 Flow chart depicting experimental plan for Telmisartan and Hydrochlorthiazide cocrystal

3.7.1. DoE method for cocrystal synthesis

Design of Experiment (DoE) has been applied as a systematic approach towards the synthesis of Telmisartan-Hydrochlorothiazide (TEL: HCT) cocrystal. A full factorial study using 3 factors at 2 levels was considered (Table 2.9). Molar ratios, synthesis methodologies and solvents used in synthesis were studied at two different levels to make out the most appropriate combination for cocrystal synthesis.

Table 3.9 Factors and levels for DoE trials

Factors	Level 1	Level 2
Molar ratio (TEL: HCT)	1:1	2:1
Method of synthesis	Solvent evaporation	Slurry Method
Solvent	Ethanol	Methanol

The experimental design was prepared using Minitab17 statistical software (Table 3.10). Eight randomized experiments were planned through the usage of software and executed as per run order.

Table 3.10 DoE trials as per standard order and run order

Std Order	Run Order	Molar ratio (TEL: HCT)	Method of synthesis	Solvent
2	1	2:1	Slurry method	Methanol
5	2	1:1	Solvent evaporation	Methanol
7	3	1:1	Solvent evaporation	Ethanol
4	4	2:1	Slurry method	Ethanol
3	5	1:1	Slurry method	Ethanol
8	6	2:1	Solvent evaporation	Ethanol
6	7	2:1	Solvent evaporation	Methanol
1	8	1:1	Slurry method	Methanol

3.7.1.1. Slurry method

Preparation of TEL-HCT cocrystals using the slurring method, for run 5 and 8 equimolar quantities of TEL (12 mg, 1 mM) and HCT (6 mg, 1 mM) and for run 1 and 4 molar ratio of 2:1, TEL (24 mg, 2 mM) and HCT (6 mg, 1 mM) were considered. For run 1 and 8, both the drug substances were added in 20 ml of Methanol and for run 4 and 5, 20 mL of Ethanol was used. The slurry was stirred using a magnetic stirrer at 200 rpm for 72 hrs. The slurry obtained was filtered and vacuum dried in an oven at 50°C for 30 min to get dry powder.

3.7.1.2. Solvent evaporation

Preparation of TEL-HCT cocrystals using solvent evaporation, for run 2 and 3 equimolar quantities of TEL (12 mg, 1 mM) and HCT (6 mg, 1 mM) and run 6 and 7 molar ratio of 2:1, TEL (24 mg, 2 mM) and HCT (6 mg, 1 mM) were considered. For run 2 and 7, both the drug substances were added in 20 ml of Methanol and for run 3 and 6, 20 mL of Ethanol was used. The mixture was heated at 50 °C in a rota evaporator till the complete solvent evaporates, followed by vacuum drying in an oven at 50°C for 30 min to get dry powder.

3.8. Characterization of TEL:HCT cocrystal

Powders obtained after drying from experiments were subjected to characterization using different techniques.

3.8.1. Melting Point

The melting point of the powder prepared from DoE experimentation was measured using the melting point apparatus (Labotec, MPA305). TEL, HCT, and cocrystal prepared with different molar concentrations of TEL and HCT were recorded for characteristic melting points. (Vijaykumar K. Parma, et al).

3.8.2. Differential scanning calorimeter (DSC)

Instrument model AQ20 from TA Instruments, USA has been used to perform DSC analysis. A sample of around 2 g was placed in an aluminum pan and a heating rate of 10 °C/ min, under a nitrogen atmosphere, was applied. DSC was performed in the range of 0 °C to 400 °C temperature. The data was processed by platinum advantage software (Xin Chen, et al., 2018).

3.8.3. X-ray Powder Diffraction (XRPD)

X-ray powder diffractometer (PANalytical, X'Pert Pro) system with CU anode, wavelength 0.154 nm, maximum 2.2 kW, 60 kV, long fine focus ceramic tube, type PW3373/00 was used. Illumination was done on the 15 mm sample size and analyzed from 5° and 40° in 2θ. X'Pert High Score software was used to refine captured PXRD patterns. (Vijaykumar K. Parma, et al, 2013).

3.9. Tablet manufacturing using RAN:NIC cocrystal

Tablets were prepared using identical excipients as per commercially available Cresar H tablets (Table 3.11), except alkalizing agents (Sodium hydroxide and Meglumin), used to enhance drug substance solubility. In-house tablets were prepared using the direct compression method.

Table 3.11 The qualitative composition of commercial tablets and In-house tablets

S. No.	Commercial Tablet Cresar H (40/12.5 mg)	In-House tablet composition (40 mg)	Functional Category	In-House Tablet % w/w
1	Telmesartan and Hydrochlorthaizide	TEL:HCT 1:1 co-crystal	Drug Substance	13.3
2	Mannitol	Mannitol SD 200	Bulking agent	45.0

3	Lactose monohydrate	Lactose monohydrate FloLac	Bulking agent	34.0
4	Povidone K25	Povidone K25	Binder	5.0
5	Sodium stearyl fumarate	Sodium stearyl fumarate	Lubricant	1.0
6	Magnesium stearate	Magnesium stearate	Lubricant	1.0
7	Sodium hydroxide	-	Solubility enhancer	-
8	Meglumine	-	Solubility enhancer	-
9	Ferric oxide red	Ferric oxide red	Colourant	0.7

Procedure

a. TEL: HCT 1:1 cocrystal along with bulking agents (Mannitol SD 200, Lactose monohydrate FLoLac), binder (Povidone K25) and Colorant (Ferric oxide red) were passed through #30 mesh (600 microns)
b. The above material is blended in a Turbula blender (Turbula®, T2F) at 22 RPM for 10 min.
c. The blend is then lubricated using Sodium stearyl fumarate and Magnesium Stearate in a Turbula blender at 22 RPM for 5 min.
d. The final lubricated blend is then compressed using a tablet compression machine (Korsch AG, XL 100).

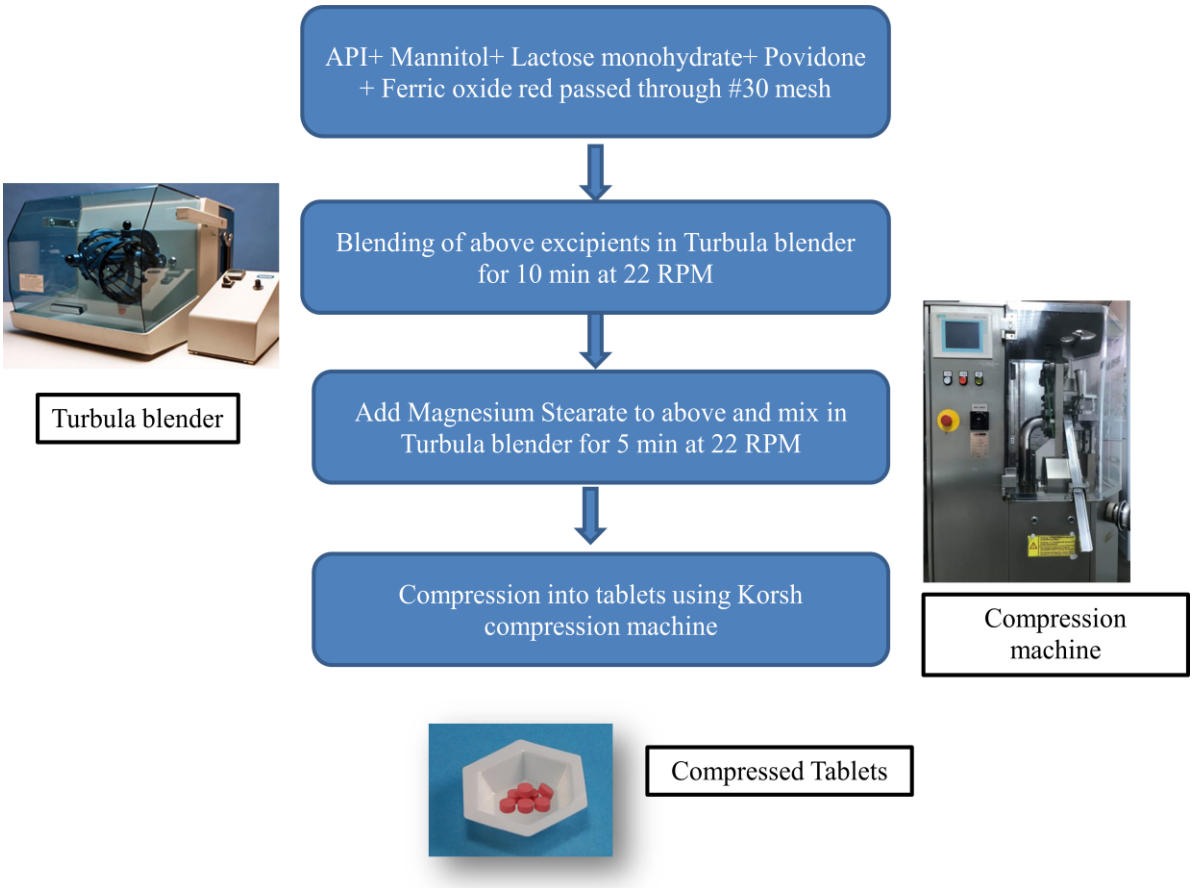


Figure 3.4 Flow diagram of tablet manufacturing process

3.9.1.Tablet characterization

3.9.1.1. Saturation solubility study

Saturation solubility of TEL, HCT, TEL: HCT 1:1 cocrystals, In-house tablets and commercially obtained (Marketed) tablets were performed by dissolving glut amount of sample in 20 mL each of different buffers (pH 1.2, pH 4.5 and pH 6.8) and water. Samples in different buffers and water were placed in a conical flask and shaking was carried out (Innova-2000 portable shaker) at 250 rpm for 24 h at room temperature. Resultant samples were filtered through a 0.45 µ membrane filter and the quantitative analysis was done using a UV spectrophotometer (UV-1800 Shimadzu 1800).

3.9.1.2. Assay and Dissolution testing

The assay of TEL and HCT was determined in a 1:1 ratio cocrystal sample. In-house tablets and marketed tablets were used in saturation solubility and dissolution testing using a UV spectrophotometer (UV-1800 Shimadzu 1800). The maximum absorbance value (λmax) for TEL and HCT was observed at 296.2 and 271.3 nm, respectively. In-house manufactured tablets, commercial Cresar H tablets, TEL:HCT 1:1 cocrystal, TEL, and HCT were subjected to dissolution using USP type II apparatus (paddle) in 0.1 N HCl 900 mL at 37°C± 0.5°C at a paddle speed of 50 rpm. Samples were collected at 0, 10, 20, 30, 40, 50, and 60 min time points and analyzed suitably using a UV spectrophotometer (Shimadzu UV 1800) (Sonali Rathod, et al.,2012).

3.9.1.3. Dynamic Vapor Sorption (DVS)

DVS study was performed on commercially available Cresar H tablets and In-house tablets using Intrinsic, Surface Measurement Systems, UK. The sample was stored on an equilibrium that was tared and allowed to first stabilise at 0% RH. The final weights were recorded after 15 mg of material had been weighed and had been re-equilibrated to 0% relative humidity. Standard DVS, Version 5.1.0.5, was the programme used to analyse the samples. The samples were run at 25°C with a 10% humidity interval, and the RH range was 0% to 90%. (Thorsten Muller, et al., 2015)

3.9.1.4. Cocrystal Stability

Stability of TEL:HCT 1:1 cocrystals were performed by keeping samples in a glass vial in long-term (25°C/60%RH) condition for 12 months and in accelerated (40°C/75%RH) condition for 6 months (ICH Q1A). Samples were tested for Assay and PXRD for any changes in the crystal lattice.

3.9.1.5. *In-vivo* pharmacokinetic study

The *In-vivo* assessment was conducted on albino rats weighing 190 ± 20 g. For the study, ten rats were taken and divided into five groups with two in each group. The first group of animals was administered with pure TEL, the second group was administered with pure HCT, the third group is administered with cocrystal of TEL:HCT 1:1, the fourth group is provided with tablet composition having DS in the form of TEL:HCT 1:1 cocrystal and the fifth group is treated as control. Samples were administered considering a dose of 1mg/kg via a feeding tube. The blood samples were collected at 0, 10, 15, 30, 60, 120, 240, 360, and 480 minutes

through the tail vein in a centrifuge tube (Mani et. al, 2019). To separate plasma from blood, collected blood samples were centrifuged at 4000 rpm for 10 minutes. Plasma samples were then analyzed for drug content using a spectrophotometer (UV-1800 Shimadzu 1800, Japan).

Results and Discussion

4. Results and Discussion

4.1. Results of RAN:NIC cocrystal

4.1.1. Physical Appearance

The fabricated appearance of cocrystals was prepared using distinct methods and resulted in white color and powder form.

4.1.2. Melting point analysis

Ranolazine exhibited a melting point in the range of 119-121 ºC, while and Nicotinamide was in the range of 126-128 °C. For RAN: NIC samples, sharp and distinct melting point was observed for samples processed using the solvent evaporation method and slurry method. However, for solvent assisted grinding method, no sharp melting point was observed. Melting of material started at 119 °C and continues till 127 °C, which indicates a physical mixture of Ranolazine and Nicotinamide.

Ranolazine and Nicotinamide show distinct melting points ranging 118-120°C and 126-128°C respectively. The equimolar ratio of RAN:NIC cocrystals prepared with different methods displayed multiple melting points, indicating the presence of two different crystalline structure. However, melting point ranging from 104°C to 109°C was also observed, which is different from the individual melting points of RAC and NIC. This different melting point indicates the presence of different crystalline lattices in the system. Furthermore, different ratios were screened using the solvent evaporation method, for RAN: NIC molar ratio of 1:2, a narrow melting point in the range of 106-109°C was observe. For all other ratios, multiple points were observed, indicating a mixture of multiple components rather than a single crystalline structure. In order to further confirm the formation of a new crystalline lattice, sensitive technique techniques like DSC and XRPD were applied.

Table 4.1 Melting point analysis of RAN, NIC and cocrystal samples

S. No	Samples	Molar ratio	Synthesis methodology	Melting points	Single/narrow melting point observed (Y/N)
1	Ranolazine	-	-	118-120 ºC	Y
2	Nicotinamide	-	-	126-128 ºC	Y
3	RAN:NIC	1:1	Solvent evaporation	104-106 °C, 116-117 °C	N

4	RAN:NIC	1:1	Slurry method	105-109 °C, 119-121°C	N
5	RAN:NIC	1:1	Solvent assisted grinding	107-108 °C, 117-119°C	N
7	RAN:NIC	1:2	Solvent evaporation	106-109 °C	Y
8	RAN:NIC	1:3	Solvent evaporation	105-107 °C, 124-127 °C	N
9	RAN:NIC	2:1	Solvent evaporation	104-106 °C, 117-119°C	N
10	RAN:NIC	3:1	Solvent evaporation	107-109 °C, 117-119°C	N

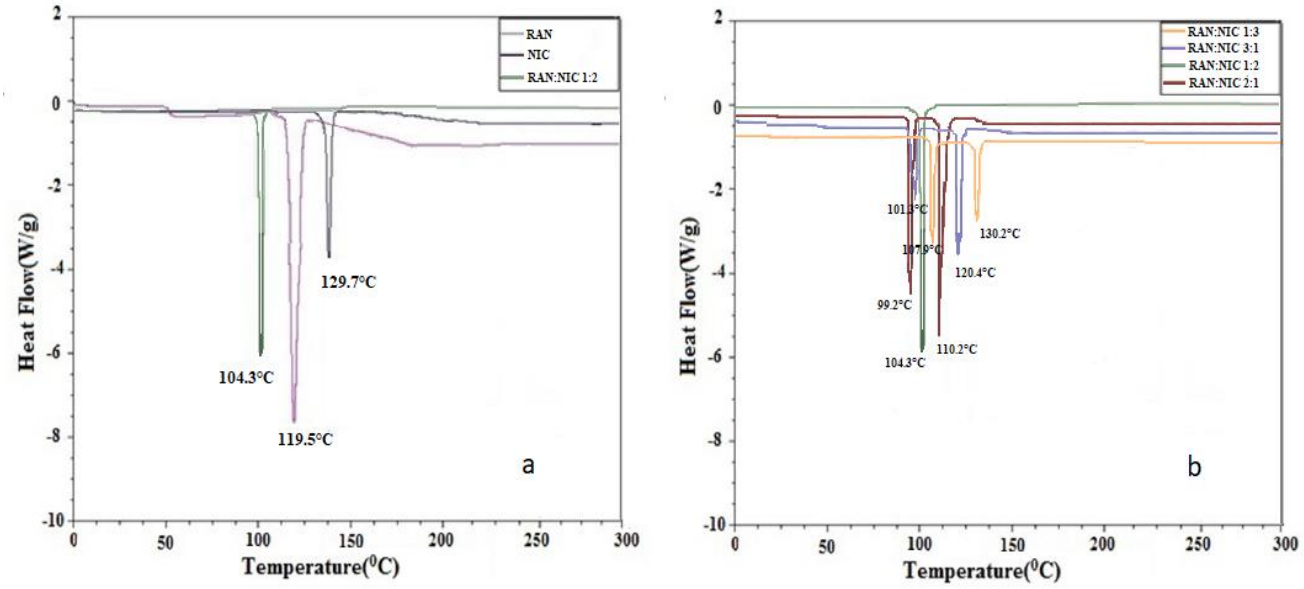


Figure 4.1 DSC endotherm peaks for **2a)** RAN, NIC, RAN:NIC 1:2 **2b)** RAN:NIC1:2, RAN:NIC1:3, RAN:NIC2:1, RAN:NIC3:1.

4.1.3. Differential scanning calorimeter

The cocrystals synthesized for RAN and NIC using the solvent evaporation method were tested for thermal properties of cocrystals which significantly help to determine the physicochemical properties of a drug such as a change in heat capacity, crystallization, melting point and purity. DSC technique is usually chosen to obtain comprehensive data on melting points (Gozali, 2016).

The cocrystals synthesized for RAN and NIC along with various molar ratios were tested for thermal behavior. RAN, NIC and RAN: NIC 1:2 molar ratio shown to have single endotherm at 119.5°C, 129.7°C and 104.3°C respectively (Figure 4.1). The pure NIC displayed a sharp endothermic peak at 129.7°C which was similar to the study performed by Shewale et al. in which the NIC displayed a sharp endothermic peak at 128°C which was in the acceptance range with insignificant difference therefore supporting our study (Sheetal et al., 2015). This single endotherm of RAN:NIC 1:2 molar ratio signifies the formation of a new crystal lattice. Additionally, this isotherm is distinct from RAN and NIC endotherm, indicating the absence of both the starting materials in the cocrystal. On the other hand, molar ratios 1:3, 2:1 and 3:1 exhibits two different endotherms indicating the presence of different crystal lattice in the sample. Furthermore, the thermograph of pure cocrystals displayed an endothermic peak; however none of the graphs displayed an exothermic recrystallization peak indicating an interaction of conformer and drug resulting in the prevention of the conversion of the drug to its most stable form (Anderson and Nawarskas, 2005). Further, pXRD studies were performed to further confirm the formation of the cocrystal.

Table 4.2 Endotherms observed for RAN, NIC and different cocrystals in DSC analysis

S.NO	Sample	Endotherm
1	RAN	119.5°C
2	NIC	129.7°C
3	RAN:NIC 1:2	104.3°C
4	RAN:NIC 1:3	107.9°C and 130.2°C
5	RAN:NIC 2:1	99.2°C and 110.2°C
6	RAN:NIC 3:1	101.3°C and 120.4°C

4.1.4. X-ray Powder Diffraction

pXRD study of RAN, NIC and equimolar ratios screened for cocrystal formation are provided in Figure 3 to determine the nature using an X-ray diffractometer to record diffractograms. pXRD pattern characterizes the structural arrangement of compounds to identify their nature in the form of an amorphous or crystalline form. From the different patterns observed, RAN:NIC 1:2 displayed a unique pattern, as new characteristic peaks were observed for RAN:NIC 1:2 at 11.2, 14.5, 18.0 and 28.9 which are absent in RAN, NIC and other equimolar ratios. The absence of a peak at 19.0 was observed which is present in the pattern of RAN and

different ratios. A unique pattern of RAN: NIC 1:2 confirms the formation of cocrystal. Additionally, the fabricated cocrystals displayed a reduction in the intensity of peaks as compared to their pure form at their characteristic specific angles which is owing to the formation of a new cocrystal form (Tomaszewska et al., 2013).

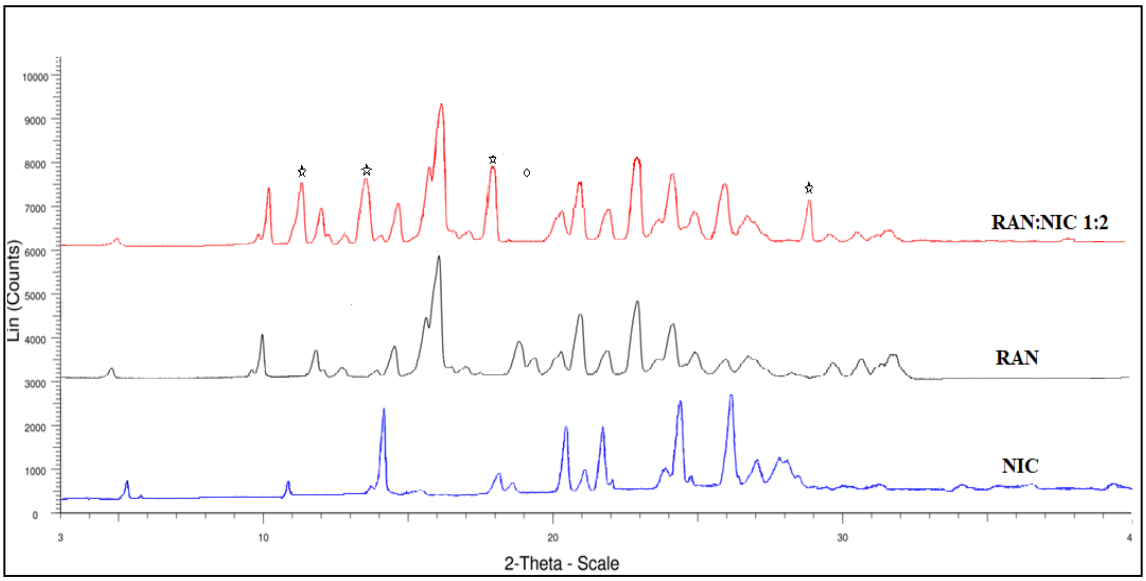


Figure 4.2 XRPD pattern for RAN, NIC and RAN:NIC 1:2

4.1.5. Saturation solubility study

Low aqueous solubility can frequently cause suboptimal drug delivery and absorption, resulting in ineffective drug efficacy and side effects. When the drug absorption process is limited by solubility, the rate of dissolution and bioavailability can be enhanced by using solubilization enhancement methods (Amidon et al., 1995). At present many formulation techniques such as size reduction (Khadka et al., 2014), surface modification (Jacob et al., 2018) complexation (Jacob et al., 2022), solid lipid nanoparticles (Samavini et al., 2018), and solid dispersion (Chaudhary et al., 2021) are adopted to improve the solubility of active pharmaceutical ingredients. Among these approaches, the cocrystallization technique is considered an excellent, low cost and feasible approach to improving drug solubility, which allows the drug to transform into an amorphous state and subsequent enhancement of solubility (Li et al., 2015).

The development of cocrystals has been shown to boost drug solubility by several orders of magnitude. The solubility of cocrystals in water has been reported to be 1,000 times that of pure-form drugs. A trend in cocrystal solubility advantage (SA=Scocrystal /Sdrug) has also

been found with coformer solubility over drug solubility (Scoformer /Sdrug). The cocrystal solubility advantage, or SA, is a dimensionless solubility number that describes a cocrystal's ability to change a drug's solubility at a certain pH, temperature, and concentration of the solubilizing agent, and so on. The solubilization media were chosen based on the administration of conventional dosage forms and the aqueous solubility of pure drugs (Dressman et al., 2007).

Saturation solubility of RAN: NIC cocrystals prepared in different ratios and RAN in 0.1 N HCl (pH 1.2), pH 4.5 acetate buffer, pH 6.8 phosphate buffer, and water were determined and reported in Table 3. The technique aids in evaluating the performance of cocrystals and the activity of the co-former in improving the drug's solubility properties. The saturation solubility study results demonstrated that as compared to the solubility of the pure form of the drug, the solubility of RAN: NIC (1:2) was found to be higher. However, both pure RAN and RAN: NIC (1:2) were employed for determining solubility in different media with different pH. The results indicated that both pure RAN (43.5 mg/ml) and RAN: NIC (1:2) (47.3 mg/ml) showed higher solubility in 0.1 N HCl (pH 1.2) media as compared to acetate buffer (pH 4.5) (pure form 21.7 mg/ml, cocrystal 24.2 mg/ml), phosphate buffer (6.8) (pure form 0.65 mg/ml, cocrystals 6.9 mg/ml) and water (pure form 0.31 mg/ml, cocrystals 5.2 mg/ml). Nevertheless, as compared to the pure form of the drug, their cocrystals displayed greater solubility as depicted in the figure. In the proceedings to the above-mentioned results, cocrystals displayed 1.08 folds enhancement in solubility as compared to their pure drug form. However, as compared to water, phosphate buffer (pH 6.8), and acetate buffer (pH 4.5), the 0.1 N HCl (pH 1.2) showed 9.09, 6.85- and 1.95-fold enhancement of solubility. Furthermore, the solubility of cocrystals in 0.1 N HCl (pH 1.2) was found to be 152.58 folds higher as compared to the solubility of the pure drug in water. Based on data, more than 10-fold from 0.69 mg/mL to 6.9 mg/mL increase in solubility in phosphate buffer and 17-fold from 0.31 mg/mL to 5.2 mg/mL increase in the water of RAN: NIC 1:2 can be observed as compared to RAN. Thus, it can be concluded that both the pure form of the drug and its cocrystal has solubility in an acidic medium and as the values shift towards a basic pH environment, the solubility decreases.

Table 4.3 Saturation solubility comparison of RAN and RAN:NIC cocrystal of different molar ratio

S. No.	Buffers	RAN Drug dissolved (mg/mL) Average (%RSD)	RAN:NIC 1:1 Drug dissolved (mg/mL) Average (%RSD)	RAN:NIC 1:2 Drug dissolved (mg/mL) Average (%RSD)	RAN:NIC-1:3 Drug dissolved (mg/mL) Average (%RSD)	RAN:NIC-3:1 Drug dissolved (mg/mL) Average (%RSD)	RAN:NIC-2:1 Drug dissolved (mg/mL) Average (%RSD)
1	0.1 N HCl (pH 1.2)	43.5 (1.5)	32.5 (1.8)	47.3 (0.6)	29.7 (1.3)	34.7 (1.8)	38.7 (2.3)
2	pH 4.5 Acetate Buffer	21.7 (3.3)	17.5 (1.5)	24.2 (1.2)	15.1 (1.5)	18.2 (1.1)	19.5 (1.5)
3	pH 6.8 Phosphate Buffer	0.69 (0.2)	4.8 (1.3)	6.9 (2.7)	6.6 (2.3)	4.2 (2.3)	4.4 (1.1)
4	Water	0.31 (0.3)	4.3 (1.0)	5.2 (1.9)	4.9 (2.2)	3.7 (3.2)	3.9 (1.7)

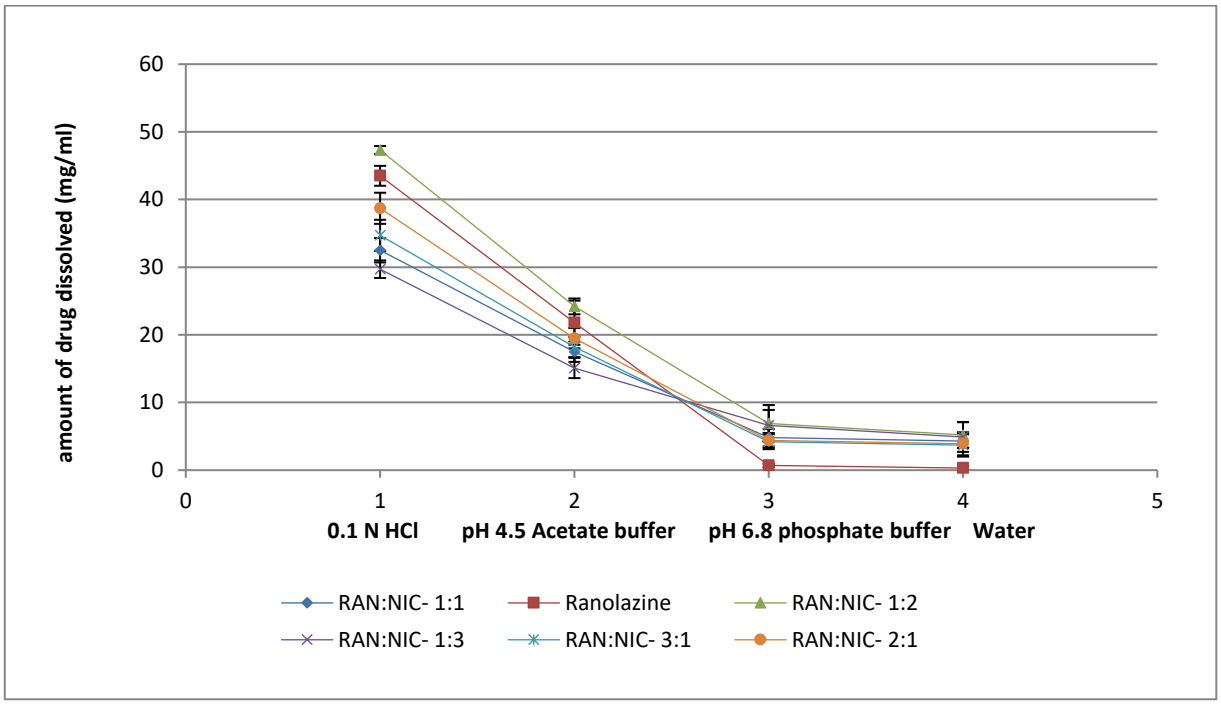


Figure 4.3 Saturation solubility graph for RAN and RAN:NIC cocrystal of different molar ratio

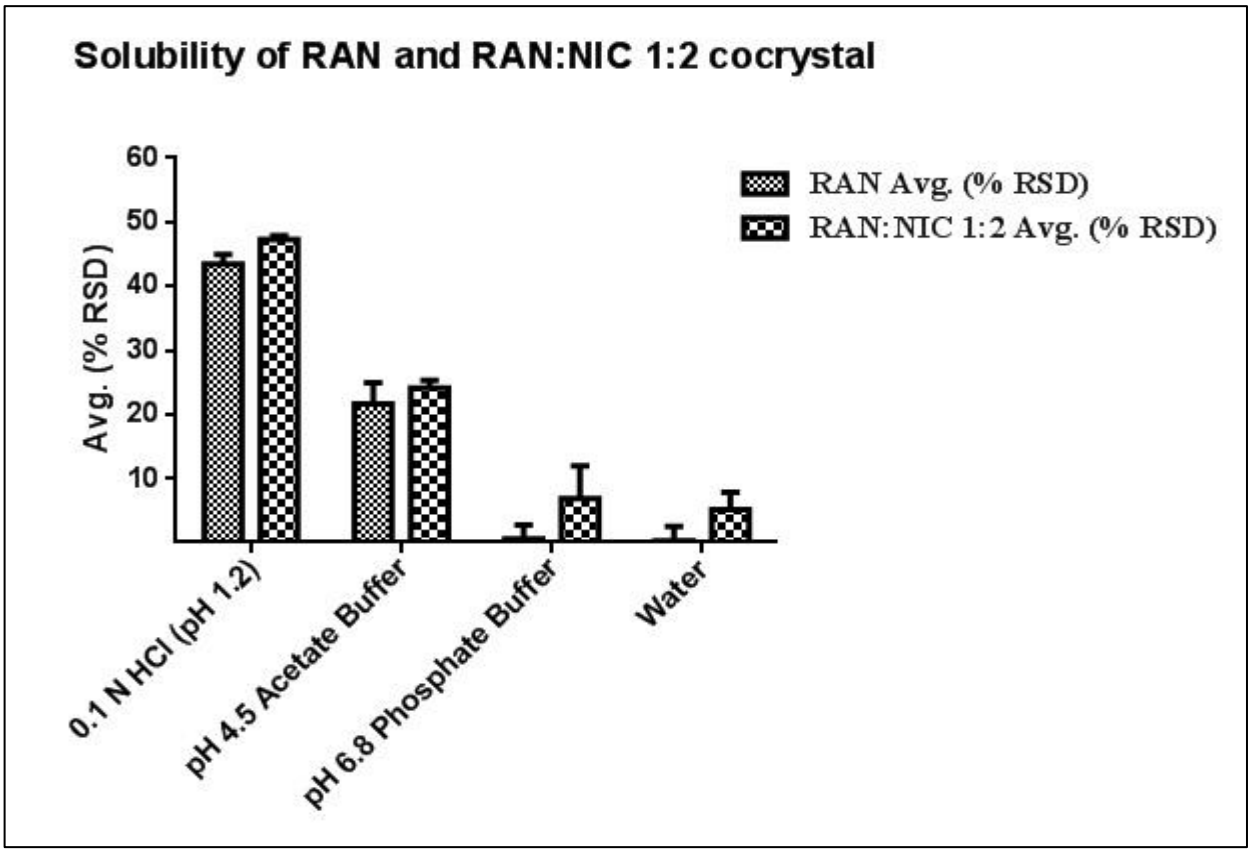


Figure 4.4 Graph showing saturation solubility of RAN and RAN: NIC 1:2

4.1.6. Cocrystal Stability

From the cocrystal stability study of RAN:NIC 1:2 cocrystal, based on PXRD scan results, no changes in crystal lattice were observed in accelerated and long-term stability conditions in 6 months and 12 months, respectively (Figure 4.5). Additionally, no significant change in assay values of the stability sample as compared to the assay of the initial sample (Table 4.4). These results indicate stable and robust cocrystal lattice formation.

Table 4.4 Assay of samples charged on stability for RAN:NIC 1:2 cocrystals

Stability Condition	Initial (T0)	3 month	6 month	12 month
25°C ± 2°C/60% RH ± 5% RH	99.0 %	98.9 %	99.1 %	99.5
40°C ± 2°C/75% RH ± 5% RH		98.8 %	98.9 %	-

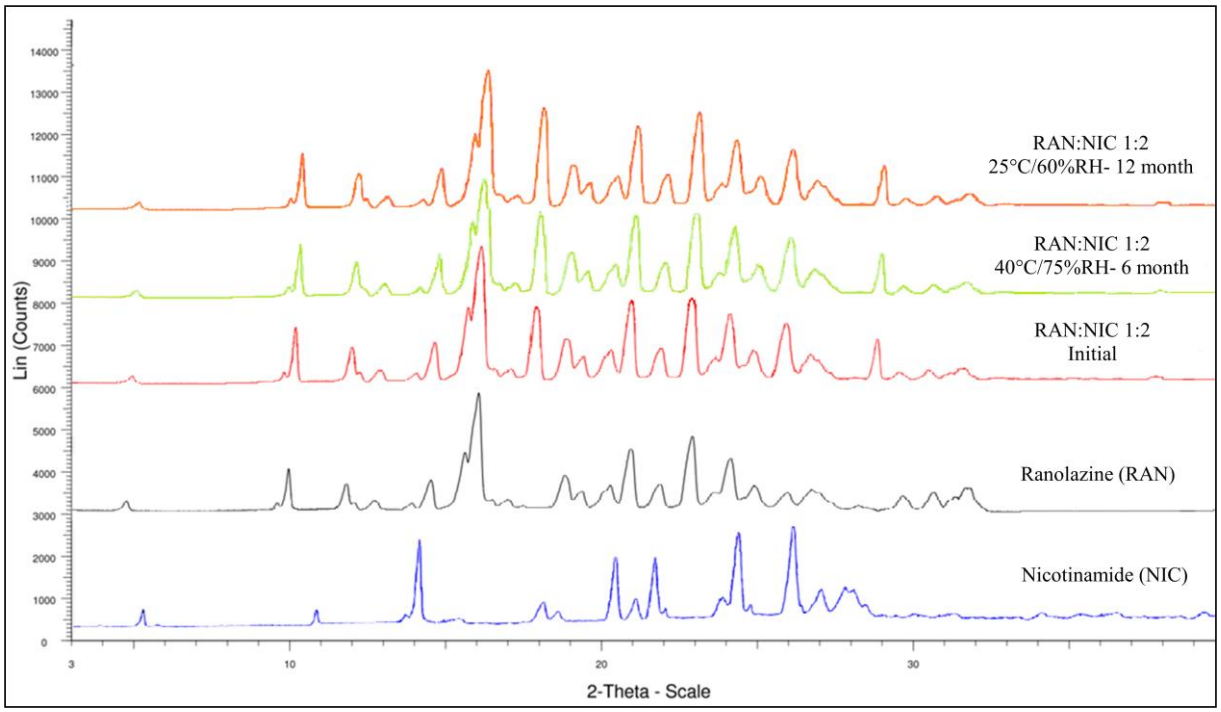


Figure 4.5 PXRD scans of samples kept at long-term and accelerated stability study as compared to the initial sample

4.1.7. In-vivo pharmacokinetic study

In-vivo pharmacokinetic parameters like peak plasma concentration (Cmax), area under plasma concentration-time curve (AUC), and relative bioavailability (%) of RAN and RAN:NIC as cocrystal are reported in **Table 4.5**. Results indicate an increase in drug plasma concentration (Cmax) of RAN alone (1.4 µg/mL) to RAN in cocrystal (2.5µg/mL). Similarly, an increase in AUC (µg.ml^{-1}.hr) and relative bioavailability (%) was observed for cocrystals in comparison to pure drugs.

Table 4.5 Pharmacokinetic parameters measured for from In-vivo study of RAN and RAN:NIC 1:2 cocrystals

S. No	Pharmacokinetics parameters	RAN	RAN:NIC 1:2 cocrystal
1	Cmax (µg/ml)	1.4	2.5
2	AUC (µg.ml^{-1}.hr)	91.5	181.5
3	Relative bioavailability (%)	-	198.3

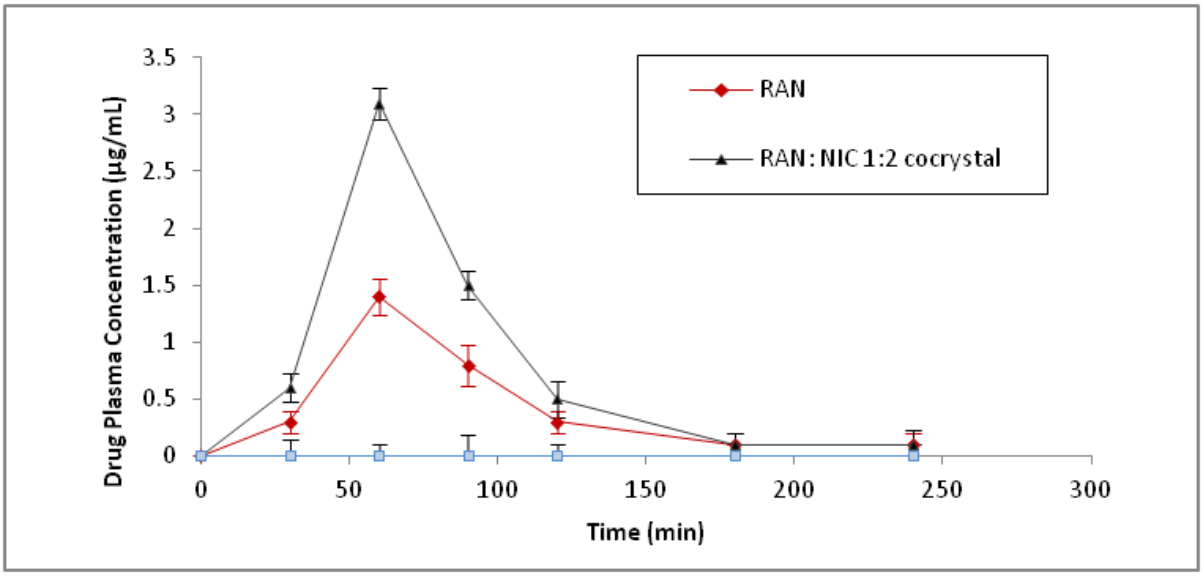


Figure 4.6: Comparative *In-vivo* study for RAN and RAN:NIC 1:2 cocrystal

These *In-vivo* results clearly indicate improved bioavailability of co-crystal of RAN:NIC compared to individual drugs. Increase in relative bioavailability by 98.3% for RAN.

4.2 Results of TEL:HCT cocrystal

The factorial design provides complete interaction and statistical evaluation for cocrystal formation. The experimental design was set up by considering molar ratio, synthesis method and solvent as independent factors while melting point provides a response. Measurement of melting point is considered a quick assessment of the formation of different forms of crystal structure. The brief knowledge of polymorphic phases was also understood by quantitative evaluations. The crystallization techniques were analyzed in the present context to measure the change in the crystalline behavior in the presence of an API co-former. Measurement of the melting point was considered a good capture during cocrystal formation. From the given design, 8 batches were predicted and enlisted in Table 4.5 to briefly account for considerable changes in the values independent factors. The response melting point summarizes the changes in the cocrystal formation. Crystallization is an important strategy to enhance drug characteristics (Kundu et al.).

4.2.1 Melting point analysis

The melting point determined for powder obtained after performing DoE trials along with TEL and HCT and captured in Table 4.6**.** Melting point analysis is considered an important tool during the synthesis and crystallization process. The melting point measurement provides a completed overview of crystal formation, physicochemical behavior and stability. The measurement of melting point is considered an easy and important tool to assure the changes during cocrystalization. The present design elucidates the variable synthesis protocol, molar ratios and solvent changes its characteristics feature by measurement of melting point.

Table 4.6 The melting point of TEL, HCT and DoE trials

Std Order	Run Order	Molar ratio (TEL: HCT)	Synthesis method	Solvent	Melting points (°C)
-	TEL	-	-	-	262
-	HCT	-	-	-	270
2	1	2:1	Slurry method	Methanol	262,266
5	2	1:1	Solvent evaporation	Methanol	263, 265
7	3	1:1	Solvent evaporation	Ethanol	235
4	4	2:1	Slurry method	Ethanol	236, 265
3	5	1:1	Slurry method	Ethanol	236, 264
8	6	2:1	Solvent	Ethanol	234, 264

			evaporation		
6	7	2:1	Solvent evaporation	Methanol	260, 266
1	8	1:1	Slurry method	Methanol	260, 267

Table 4.6 provides a complete response sheet and interaction mode on independent and dependent variables. From the melting point data, TEL and HCT shows a sharp melting point at 262 °C and 270 °C respectively. Table 4.5, illustrates the variable ratio of TEL and HCT showing two distinct melting points, suggest that extreme concentration may not form a unique crystalline structure and two individual cores may be separated after utilizing said methodology. The analysis suggests that the use of appropriate methods is also useful to recognize the formation of a single-core co-crystalline structure. Additionally, the effect of solvent also revolutionizes the cocrystal formation. The responses were statistically recognized and supported 95% confidence intervals. The comparison between the slurry method and the use of solvent may have a major impact on the formation of the cocrystal core while the molar ratio has less effect. The solvent evaporation method in the presence of ethanol as a solvent with a molar ratio of 1:1 produces a single measurement value for melting point (235 ^{0}C). The single measurement value indicates the formation of a new and unique crystal lattice structure considering two different molecular cores. The other run orders indicate the multiple values for melting point measurement. The process parameter and use of solvents may not form an appropriate cocrystal core and physically two components may be separable.

The variable molar ratio (2:1) also indicate multiple melting point measurement may be due to molecular interaction may be differentiated at higher concentration of TEL. The use of solvent methanol in the solvent evaporation method did not form a single cocrystal core that supports the methanol may be slightly ineffective during the interaction. In the case of the slurry method, all variable concentration shows very near melting point values may be due to more than 50% of API conforms to form a single core but molecular level interaction at the surface edge may separate the core.

From DoE trials, the sample exhibits multiple melting points except one sample prepared with solvent evaporation method using ethanol as solvent and drug substances in the molar ratio of 1:1 gives a sharp melting point at 235°C. This distinct melting point indicates the presence of a new crystalline lattice. On the other hand, for other samples, multiple melting points indicate the presence of a physical mixture of two components.

For simplification of response data melting point measurement was graded or rated on a point scale of 0 to 10. Based on the melting point measurement reading the quantitative assessment was recorded and input was provided for simplifying statistical investigation. The number rating system generates simple regression equations and reduces complexity during the prediction and processing of results. The optimization may be simplified by utilizing a coding strategy. The detailed modulated rating values were categorized and represented in Table 5. For samples observed with two melting points near the melting point of TEL or HCT is rated as 0, while the one with two melting points out of them one is different from TEL and HCT is rated as 5 and the one with a single melting point different from TEL and HCT melting point is rated as 10 (Table 4.7).

Table 4.7 DoE trials with melting point and rating to melting point as a response

Std Order	Run Order	Molar ratio (TEL: HCT)	Synthesis method	Solvent	Melting points (°C)	Rating of melting point
2	1	2:1	Slurry method	Methanol	262,266	0
5	2	1:1	Solvent evaporation	Methanol	263, 265	0
7	3	1:1	Solvent evaporation	Ethanol	235	10
4	4	2:1	Slurry method	Ethanol	236, 265	5
3	5	1:1	Slurry method	Ethanol	236, 264	5
8	6	2:1	Solvent evaporation	Ethanol	234, 264	5
6	7	2:1	Solvent evaporation	Methanol	260, 266	0
1	8	1:1	Slurry method	Methanol	260, 267	0

From the given rated values run order 3 represents 10 ratings due to a unique single melting point value. The data was used for analyzing statistical significance and evaluated by Analysis of variance (ANOVA) calculation.

Table 4.8 represents the degree of freedom (DF) for each independent variable with the interaction model. The DF signifies the importance of terms used in the design. The F-value and p-value suggest the level of significance after analyzing the factors statistically. The p-value predicted from the ANOVA calculation suggests that all the independent factors have 1 DF and the p-value less than 0.05 suggests the selected variables are significant with the respective response level. The molar ratio and method of synthesis mostly affect the formation

of a single crystal lattice and may deviate from the significance level. Additionally, the solvent has a major effect on the formation of cocrystals during the synthesis method. The p-value was found to be 0.007 suggesting an influencing role on cocrystal lattice formation. The method of synthesis statistically changes the crystal behavior and may also need to consider cofactors like reaction time, stirring or incubation time, saturation solubility, etc. All the terms used in the model are significant and linear increment was desirable as suggested in Table 4.8.

Table 4.8 ANOVA of different factors for the response of rating of melting point

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Model	3	84.375	28.125	9.00	0.030
Linear	3	84.375	28.125	9.00	0.030
Molar ratio	1	3.125	3.125	1.00	0.374
Solvent	1	78.125	78.125	25.00	0.007
Method of synthesis	1	3.125	3.125	1.00	0.374
Error	4	12.500	3.125		
Total	7	96.875			

The standardized effect of independent variables was analyzed via Pareto chart analysis. All the factors selected in the design show a confidence interval above 95%. The standardized effect of factors A, B and C represents molar ratio, solvent and method respectively, compared with response melting point as shown in figure 4.7. Factor A and C has minimal effect on the response melting point while factor B (molar ratio) suggests having a considerable impact. The bar diagram crosses the red dotted lines to provide a larger change in concentration ratio showing a major effect on melting point or shifts to higher values. As suggested from the melting point rated data, a ratio 2:1 segregates the formation into 2 separate cores and losses molecular interaction. The ratio gives melting point values at two extreme ends as their parent melting range. By considering the variable molar ratios, the melting point of the cocrystal can come closer in between to the melting range of individual components. In comparison to slurry, the method provides 0 rating as the melting range collapse on each other but distinctively segregates the two different crystalline cores.

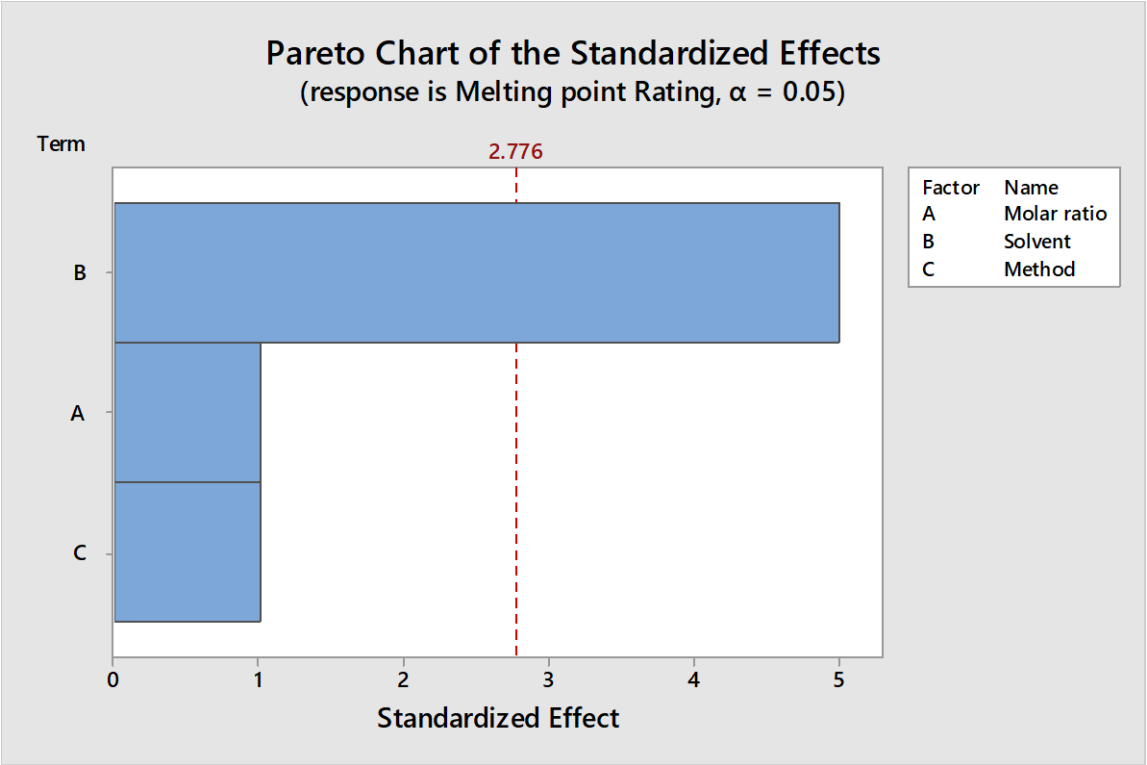


Figure 4.7 Pareto chart of standardized effects for the response in melting point rating

Figure 4.7 validates all the concern factors considered in the model terms the suggested 1:1 ratio was more productive in terms of the formation of a single core.

Figure 4.8 shows the main effects and interactions between independent and dependent variables. The main effect plot captures 3 independent variables with indicative response melting points represented. The molar ratio and synthesis method have an opposite effects on the melting point. The molar ratio at 1:1 decreases the effect by using the slurry synthesis protocol while the 2:1 ratio with the slurry method has similar responses. The 2:1 molar ratio also shows the opposite response with the synthesis method solvent evaporation deviates the melting point to the highest values. The effect of solvent in the formation of cocrystals has a major and wider effect. The use of methanol decreases cocrystallization ability may be due to less interaction with surface functional groups. The presence of ethanol promotes hydrogen bonded interaction between both API and channelize towards success. Figure 4.8 indicates the significant impact of Ethanol in cocrystal formation as compared to Methanol. Additionally, the 1:1 molar ratio and solvent evaporation as a method of synthesis show more impact than the 2:1 molar ratio and slurry method.

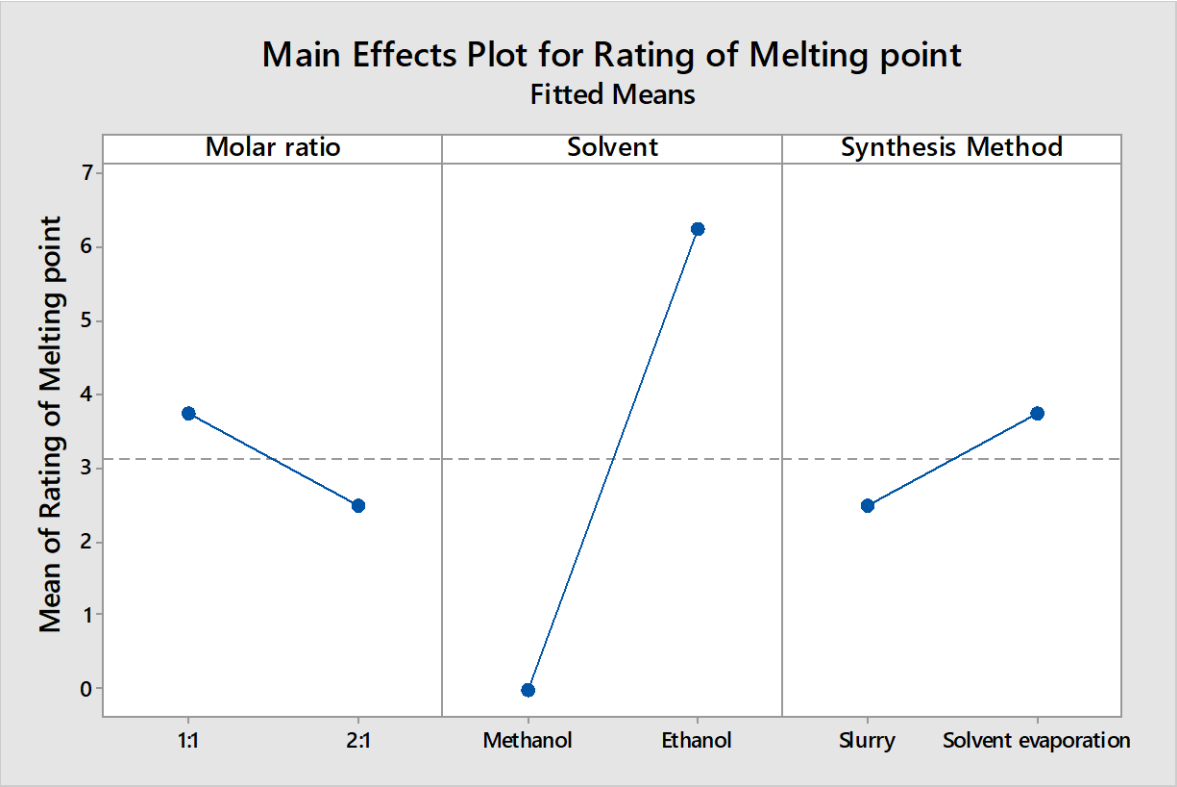


Figure 4.8. Main effects for the response in melting point rating

The multiple response predictor was set to analyze the optimum levels of factors to achieve desirable productive yield. From the given set of analyses, the multiple response predictor suggests the standard values for the optimum concentration of factors. The multiple response predictors suggest a molar ratio (1:1), a solvent evaporation method and ethanol as a solvent for the formation of a cocrystal lattice of combination APIs.

4.2.2 Differential scanning calorimeter (DSC)

The thermal analysis of drug crystals and cocrystals was analyzed by differential scanning calorimetry and is considered to be an important technique for verification. The laboratory melting point apparatus method may provide range but DSC provides an accurate endpoint of melting of the drug. Also rectifies the degradation temperature or impurities associated. Figure 4.9 shows the thermogram of pure TEL, HCT, and physical mixture containing TEL: HCT (1:1) and optimized run 3 TEL: HCT (1:1). The DSC thermogram of TEL depicted in Figure 4.9 suggests a single endothermic sharp peak at 263.8 ^{0}C (Chadha et al.). The melting temperature of TEL was similar to standard melting range values. The pure form of HCT was analyzed by observing melting temperature at 274.3 ^{0}C with a sharp endothermic peak (Gioumouxouzis et al.). The pure TEL and HCT suggest that the drug sample supplied by the

manufacturer was pure and did not contain any impurities. The physical mixture of TEL: HCT was taken in a 1:1 ratio to understand any chemical interaction. The DSC thermogram suggests the two sharp endothermic peaks observed at 263.1^{0}C and 274.5 ^{0}C were distinctly similar to the melting temperature of pure forms (Chadha et al., Gioumouxouzis et al.). Detailed endotherms of all samples were depicted in Table 4.8.

After the cocrystallization process, the co-formers help to reduce the crystallinity and form a single-core crystal lattice structure. The co-crystalline product containing TEL: HCT (1:1) shows a sharp endothermic peak at 240.5^{0}C suggesting the conversion and submerging of two crystalline cores into the single lattice. No other peaks were observed in the thermogram of TEL: HCT suggesting that the cocrystals are devoid of their earlier pure components. The melting temperature was shifted to a slightly lower value compared to parent pure forms of active drugs. The decrease in melting temperature suggests the amorphization of the drug with simultaneous single cocrystal lattice formation. The single endothermic peak precludes the formation of a single core structure. The DSC thermogram did not show any solvent peak after preparation suggest that the complete removal of solvent takes place. The change in crystalline behavior was analyzed from PXRD data.

The cocrystals synthesized for TEL, HCT, and TEL:HCT cocrystals prepared from DoE trials were tested for thermal behavior and endotherm as reported in Table 4.8.

TEL, HCT, and TEL:HCT 1:1 (Run 3) molar ratio was shown to have separate endotherms at 278.8°C, 285.3°C, and 240.5°C, respectively (Figure 4.9). A single endotherm exhibited for TEL:HCT at a 1:1 molar ratio indicates the formation of a new crystal lattice. This endotherm is distinct from the TEL and HCT endotherms, indicating the absence of both the starting materials in the cocrystal. Furthermore, samples from other DoE runs were also measured for DSC and found to have two endotherms, indicating the presence of two different crystal lattices in the same sample.

Table 4.9 Endotherms observed for TEL, HCT and TEL: HCT1:1

S.NO	Sample	Endotherm
1	TEL	278.8°C
2	HCT	285.3°C
3	TEL:HCT 2:1 (Run 1)	259.7°C and 265.3°C

4	TEL:HCT 1:1 (Run 2)	258.2°C and 266.8°C
5	TEL:HCT 1:1 (Run 3)	240.5°C
6	TEL:HCT 2:1 (Run 4)	238.1°C and 269.3°C
7	TEL:HCT 1:1 (Run 5)	236.2°C and 269.1°C
8	TEL:HCT 2:1 (Run 6)	237.5°C and 269.7°C
9	TEL:HCT 2:1 (Run 7)	267.7°C and 269.5°C
10	TEL:HCT 1:1 (Run 8)	266.9°C and 268.9°C

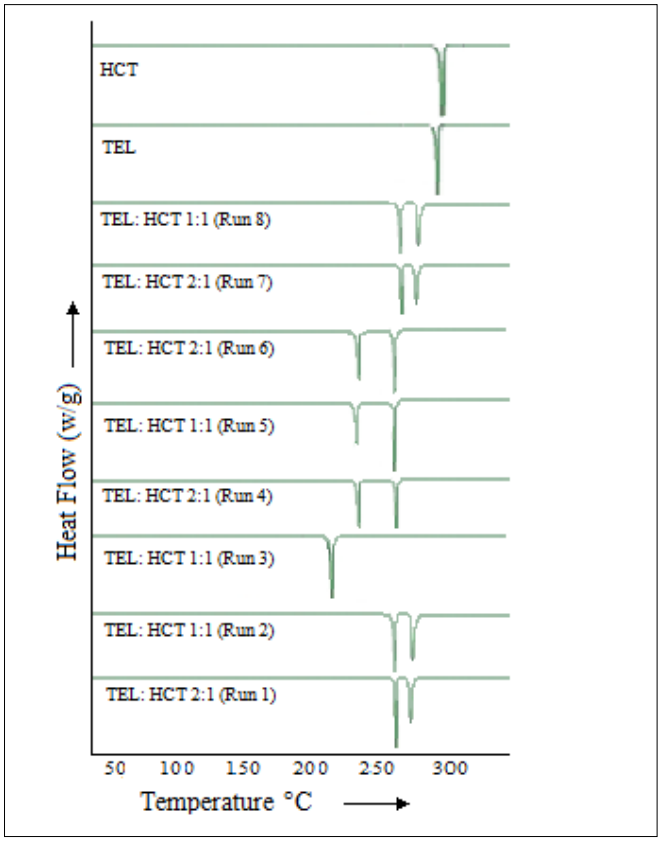


Figure 4.9 TEL, HCT and TEL+ HCT mixture and TEL: HCT 1:1 cocrystal DSC endotherms

4.2.3 X-ray powder diffraction (XRPD)

X-ray powder diffraction analysis suggests the formation and structural conformation of the crystalline core. The XRPD was a very important technique in the analysis of solid components, especially pharmaceutical solids. The XRPD patterns screen for crystallite size and crystalline behavior. The modification in the crystal core structure was also highlighted.

Figure 4.9 shows XRPD data of TEL, HCT, TEL: HCT (Physical Mixture) and TEL: HCT (optimized cocrystal). The single crystalline TEL shows multiple crystalline peaks with a stable polymorphic structure. A characteristic intense peak of TEL was shown at 7.2^0, 9.8^0, 13.7^0, 15.2^0, 17.9^0, 20.2^0, 23.1^0, 26.7^0 revealing the raw crystalline form (Shrimal et al.). Similarly, HCT shows a highly crystalline structure as represented in Figure 4.9. The sharp distinct crystalline peak of HCT was observed at 10.1^0, 16.2^0, 18.9^0, 21.5^0, 24.1^0, 28.7^0, 2θ values. The sharp and intense peak indicates the HCT was highly crystalline in nature (Giri et al.).

The physical mixture containing TEL: HCT shows distinct multiple peaks suggesting the individual crystalline characteristics of pure forms. The peak intensity slightly decreased due to the overlap of the crystalline plain of TEL and HCT. The optimized TEL: HCT XRD pattern is depicted in Figure 4.10. Suggest the decrease in crystallinity in the presence of a co-former. After conversion into co-crystals, the few crystalline peaks disappeared may be due to the formation of a single crystal structure. The 2 theta peak positions at 7.2, 9.8, 14.4, and 15.1 were disappeared in the XRD pattern of an optimized batch of TEL: HCT. The formation of new characteristics peaks at 13.3 and 18.0 suggesting the formation of cocrystalline phases.

From the different patterns, the TEL:HCT 1:1 molar ratio (Run 3) displayed a unique pattern, as new characteristic peaks were observed for TEL:HCT 1:1 at 13.3 and 18.0, while many of the peaks like those at 7.2, 9.8, 14.4, and 15.1 that were originally present in TEL or HCT disappeared. Similar differences in diffraction peaks were observed when Run 3 was compared to other DoE run samples (Figure 4.10). A unique diffraction pattern observed for TEL:HCT 1:1 (Run 3) confirms the formation of the cocrystal.

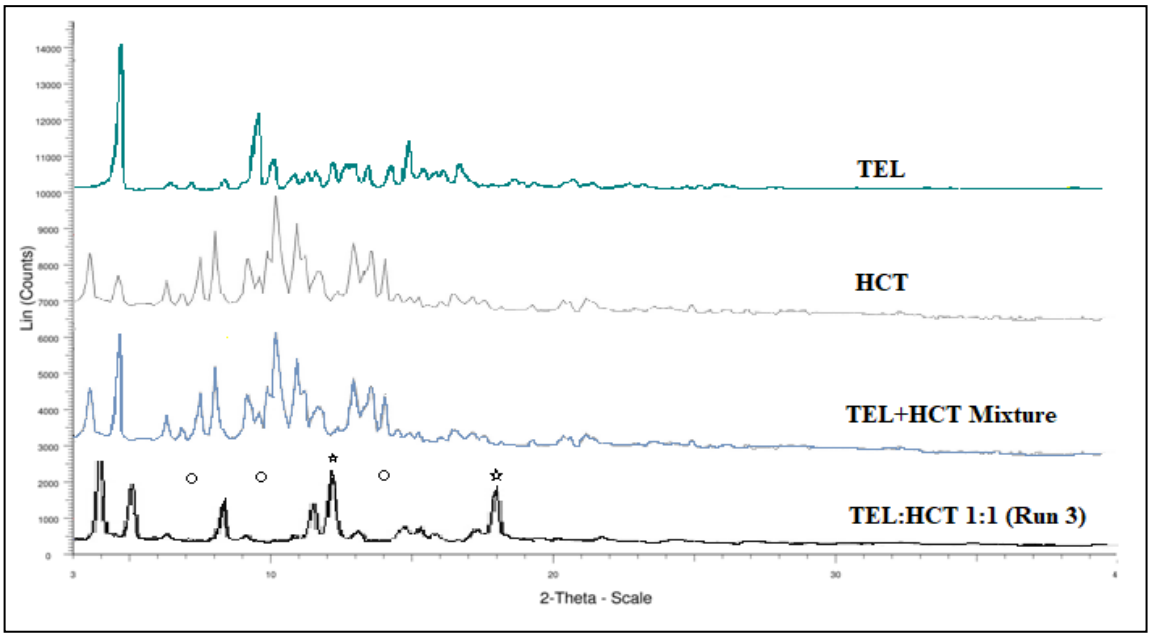


Figure 4.10 XRPD patterns for TEL, HCT and TEL+ HCT mixture and TEL: HCT 1:1 cocrystal

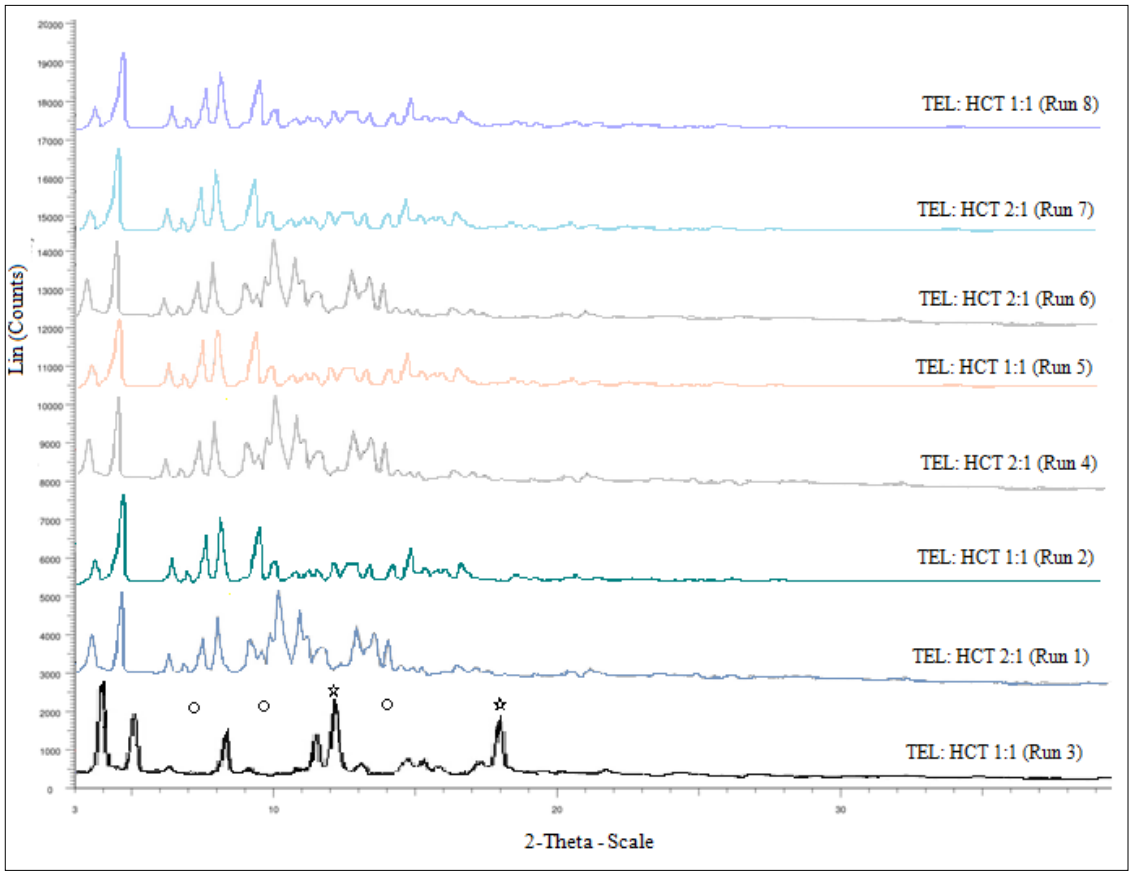


Figure 4.11 XRPD patterns for TEL:HCT 1:1 cocrystal (Run3) and other DoE runs

4.2.4 Saturation solubility study

Saturation solubility of TEL, HCT and optimized batch containing TEL: HCT (1:1) was performed in different solubilization media given in Figure 4.12. The solubilization media was selected according to the delivery of conventional dosage form and solubilization of pure drugs in an aqueous environment. The solubility analysis was performed in 0.1 N HCl (pH 1.2), pH 4.5 acetate buffer, pH 6.8 phosphate buffer, and water to assess the amount of drug that goes into the solution before and after the formation of cocrystals. The technique helps to evaluate the performance of cocrystals and the activity of co-former in enhancing the solubility characteristics of the drug. The parent drug TEL and HCT has limited solubility in an acidic and aqueous environment, while drugs are slightly soluble in basic pH (pH 6.8). The drugs are mostly suitable for delivery in the intestine but poor soluble nature may also limit the absorption characteristics. Cardiovascular diseases require continuous control over plasma concentrations and require desirable solubilization characteristics possessed by the formulation.

Figure 4.12 shows enhancing the solubilization characteristics of a cocrystal of TEL: HCT in all dissolution media. The multifold increment in solubility suggests the optimum utilization of the technique in FDC. The cocrystal structure suggests the co-formers help achieve a more than 20-fold increase in the solubilization of behavior of TEL and HCT in comparison to pure form. In acidic pH, both TEL and HCT show limited solubility with less than 2.1 mcg/mL but cocrystals increase solubility by about 25.4 mcg/mL. The aqueous solubility of the cocrystal was also improved and found to be 43.2 mcg/mL. Saturation solubility of TEL:HCT 1:1 cocrystal, TEL, HCT, In-house tablets, and marketed tablets (Cresar® H) in 0.1 N HCl (pH 1.2), acetate buffer (pH 4.5), phosphate buffer (pH 6.8) and water were determined and reported in Table 4.10.

A comparison of the saturation solubility of different samples is provided in Figure 4.13. The saturation solubility of TEL:HCT 1:1 showed similar solubility across different pH, which was found to be multifold higher as compared to TEL and HCT alone. Marketed tablets show better solubility as compared to TEL and HCT but are not as good as cocrystal and In-house tablets.

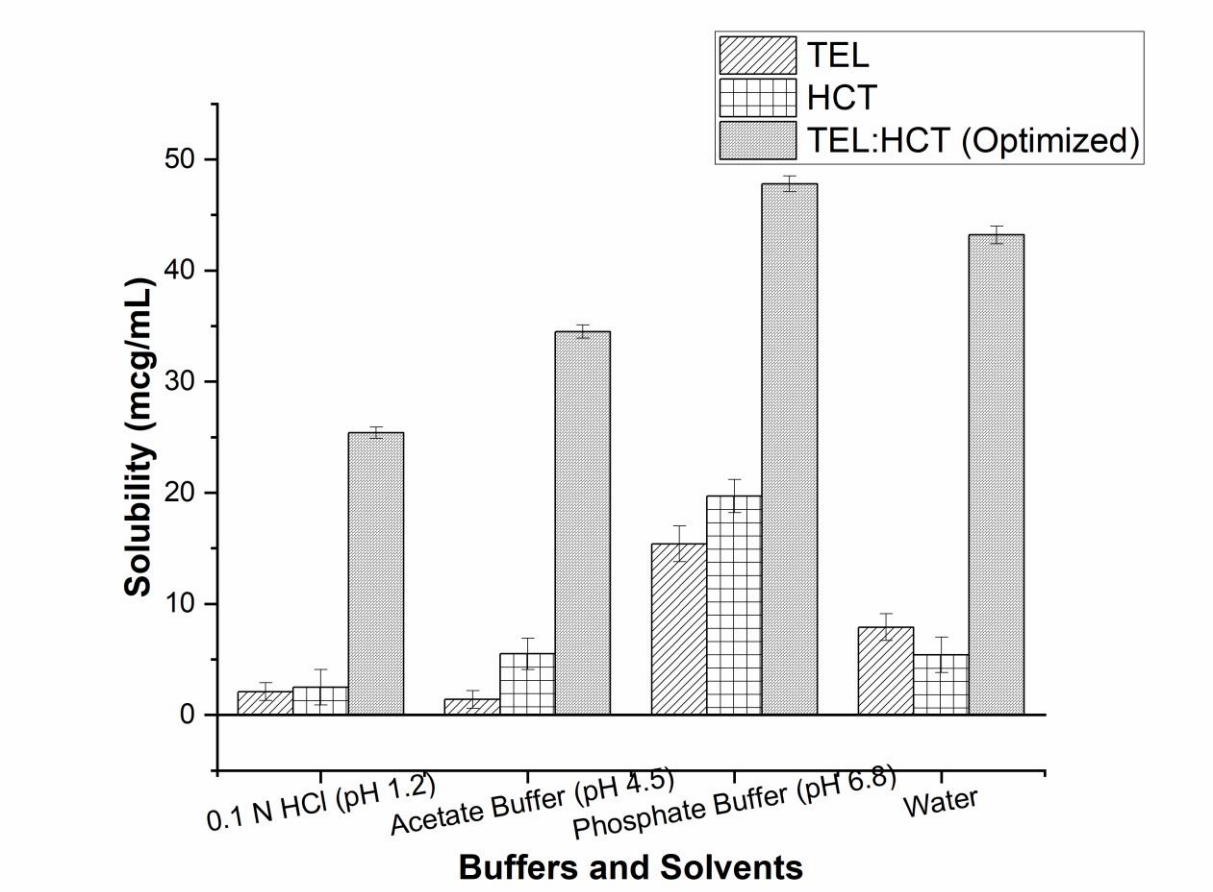


Fig. 4.12 Graph showing solubility of TEL, HCT and TEL: HCT 1:1 cocrystal at different pH

Table 4.10 Saturation solubility comparison of TEL:HCT 1:1 cocrystal, TEL, HCT, In-house tablets, and Cresar® H tablets

S. No.	**Buffers**	**TEL Avg (%RSD) (n=2)**	**HCT Avg (%RSD) (n=2)**	**TEL:HCT 1:1 Avg (%RSD) (n=2)**	**In-House Tablets (n=2)**	**Marketed tablets - Cresar® H (40/12.5 mg) (n=2)**
1	0.1 N HCl (pH 1.2)	2.1 (6.73)	2.52 (10.40)	25.35 (0.84)	24.9 (1.14)	10.4 (1.70)
2	Acetate Buffer (pH 4.5)	1.4 (10.10)	5.5 (1.30)	34.5 (0.62)	35.2 (0.60)	12.5 (1.98)
3	Phosphate Buffer (pH 6.8)	15.4 (3.22)	19.7 (1.44)	47.8 (0.15)	48.9 (0.58)	29.8 (1.19)
4	Water	7.9 (3.58)	5.4 (9.25)	43.2 (0.49)	45.5 (1.71)	15.2 (1.86)

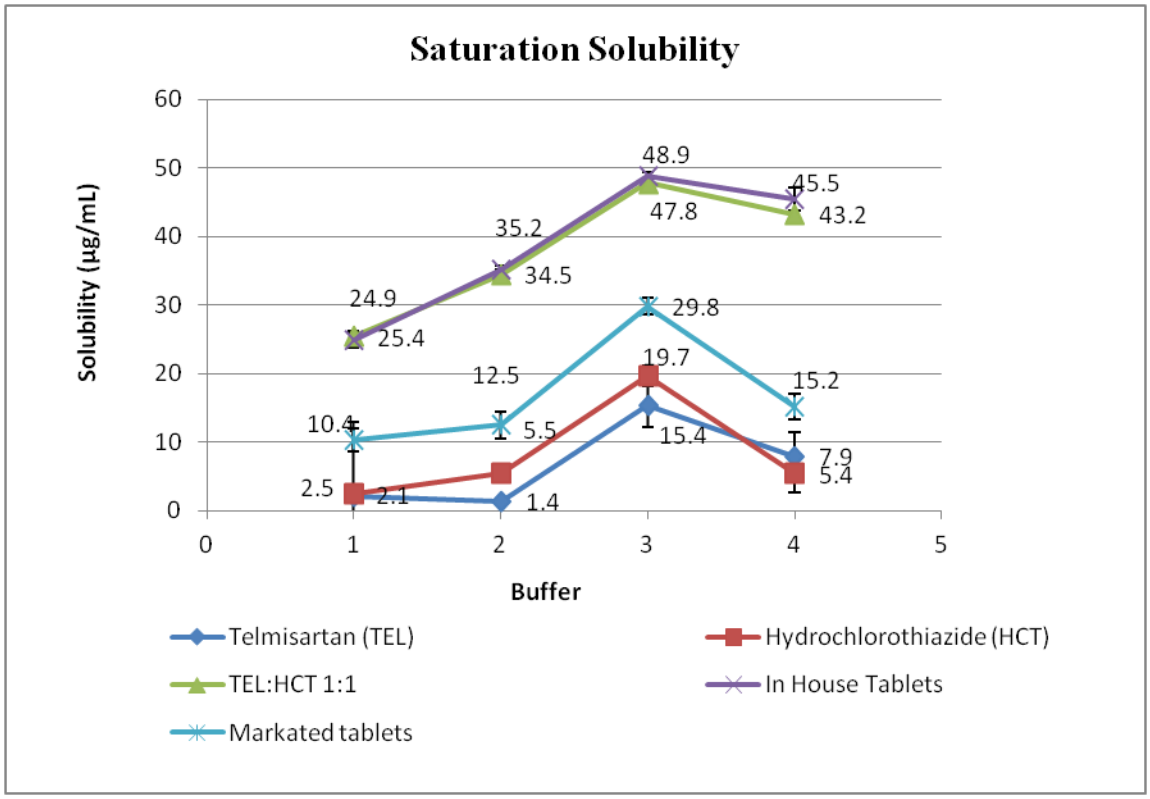


Figure 4.13. Graph showing saturation solubility of TEL, HCT, and TEL:HCT 1:1, In-house tablets, commercial

4.2.5 Assay and dissolution testing

Individual drug assays in TEL:HCT 1:1 cocrystal were performed, and TEL content was found to be 99.7% and HCT content was found to be 99.4%, as shown in Table 4.11.

From the dissolution data generated for In-house tablets, Cresar H tablets, TEL:HCT 1:1, TEL and HCT tablets in 0.1 N HCl, a faster dissolution rate for In-house tablets and TEL:HCT 1:1 cocrystal as compared to TEL, HCT and Cresar tablets were observed. This higher dissolution rate indicates an improvement in the solubility of drug substances in 0.1 N HCl (Table 4.13 and Figure 4.14). The dissolution profile demonstrated by both In-house tablets and Cresar® H tablets even complies with the dissolution acceptance criteria recommended by Food and Drug Administration (FDA) guidance document for immediate release solid dosage form drug products containing high solubility drug substances (FDA, 1997) (Jacob and Nair, 2018).

Table 4.11 Average assay of TEL and HCT in TEL:HCT 1:1 cocrystal

Samples	Assay of individual drugs (Number of samples=2)			
	Avg. TEL (%)	Std. Dev.	Avg. HCT (%)	Std. Dev.
TEL:HCT 1:1	99.7	2.1	99.4	1.5
In-house Tablets	98.7	1.2	98.4	2.1
Cresar® H Tablets	99.9	1.3	100.7	1.8

Table 4.12 Dissolution of In-house tablets, Cresar® H tablets, Tel:HCT 1:1, TEL, and HCT in 0.1N HCl

Time (min)	% Cumulative drug release (n=6) in 0.1 N HCl									
	In-house Tablets		Cresar H Tablets		TEL:HCT 1:1		TEL		HCT	
	% drug release	Std. Dev.	% drug release	Std. Dev.	% drug release	Std. Dev.	% drug release	Std. Dev.	% drug release	Std. Dev.
0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
5	35	2.3	25	2.9	31	3.3	10	2.9	12	3.0
10	60	2.1	40	3.5	54	2.5	21	3.4	26	2.7
15	78	1.9	55	2.9	74	3.1	33	3.1	37	2.0
20	89	1.1	70	1.5	88	1.7	42	2.2	45	1.9
30	98	0.5	85	1.0	98	1.5	51	2.5	55	2.0
60	98	0.2	99	0.4	98	1.0	65	0.9	69	1.5

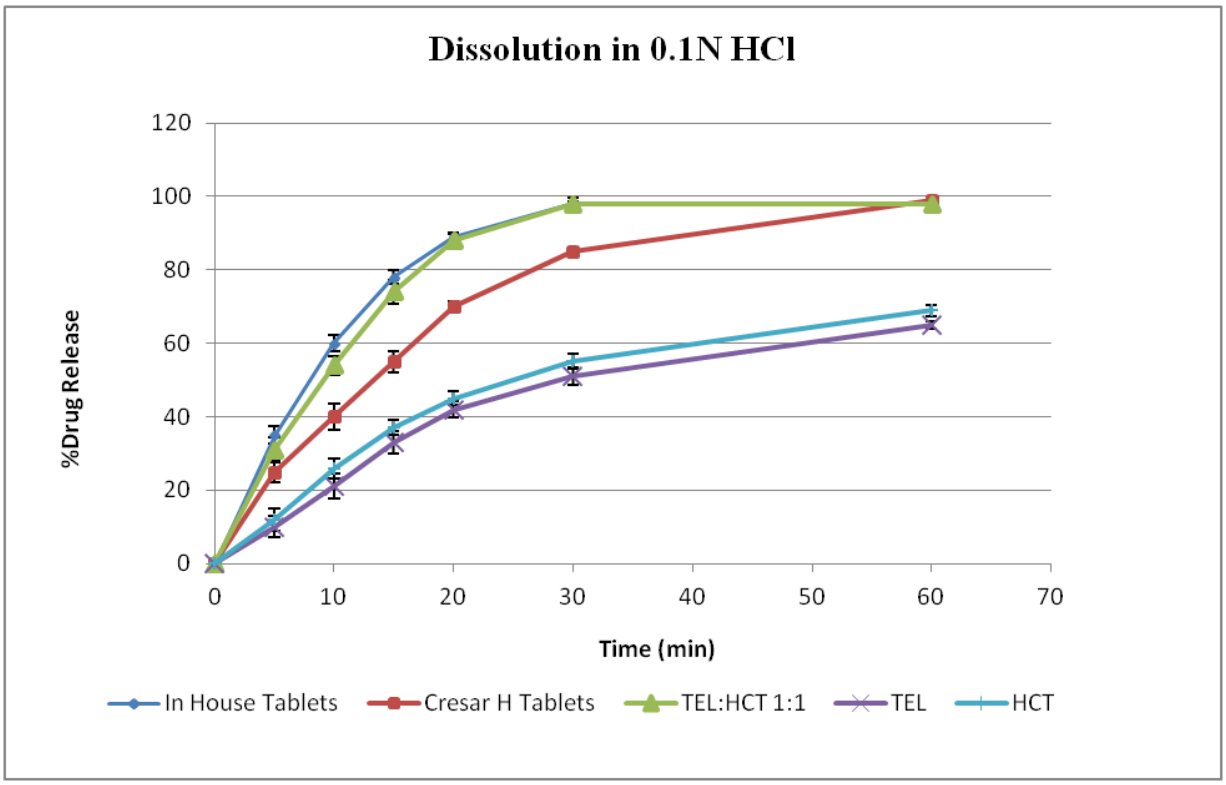


Figure 4.14. Dissolution graph of In-house tablets and Cresar H tablets in 0.1N HCl

4.2.6 Dynamic Vapor Sorption (DVS)

During the sorption cycle of the DVS study, it can be observed that there is a 20% increase in the mass of the Cresar H tablets (Figure 4.15), as compared to 5% for the in-house tablets, as RH reaches 90%. At the end of the desorp cycle, Cresar H tablets had a permanent mass gain of up to 2.5% (Figure 4.15), whereas In-house tablets had a change in mass (%) of close to 0% (Figure 4.16).

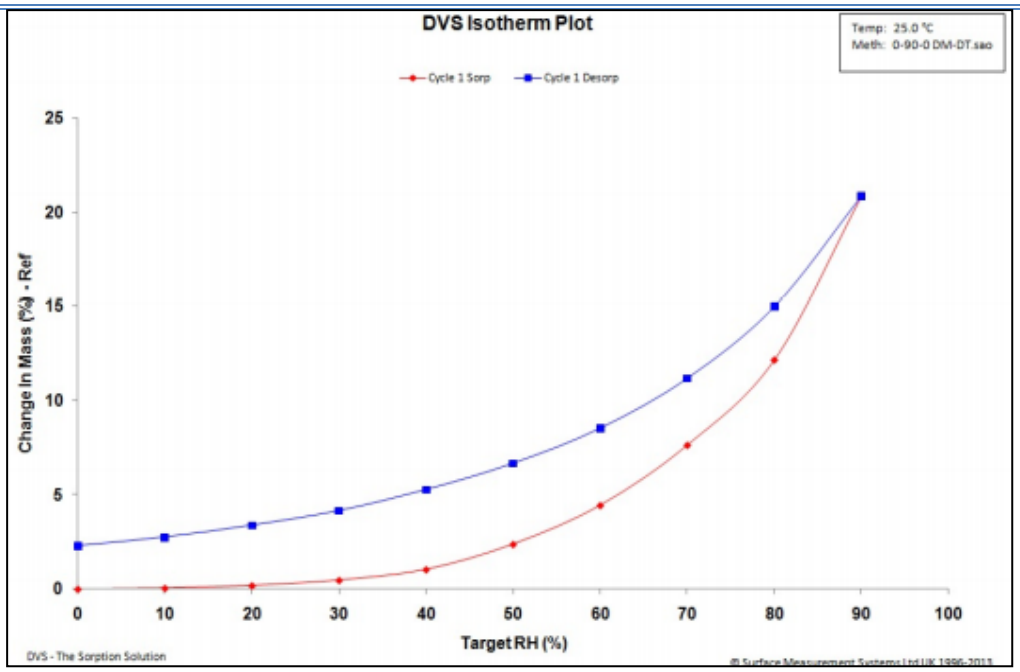


Figure 4.15 DVS isotherm of Cresar H tablets

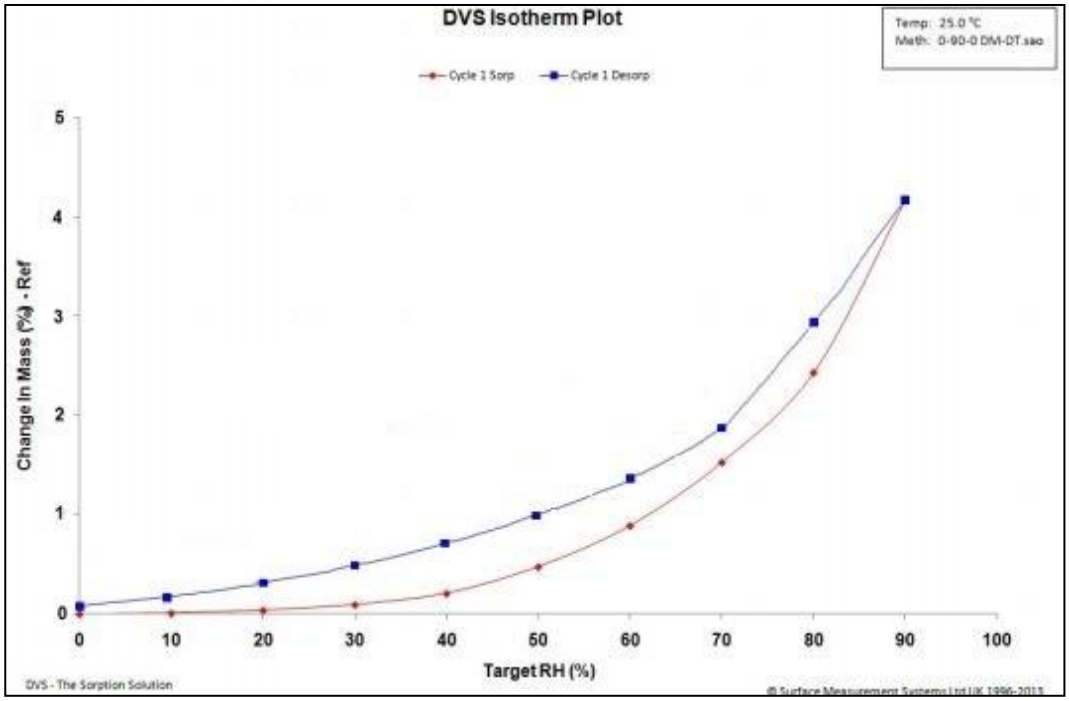


Figure 4.16 DVS isotherm of In-house tablets

4.2.7 Cocrystal Stability

From the drug:drug cocrystal stability study of TEL:HCT 1:1 cocrystal, based on PXRD scan results, no changes in crystal lattice were observed in accelerated and long-term stability conditions in 6 months and 12 months, respectively (Figure 4.17). Additionally, no significant change in assay values of the stability sample as compared to the assay of the initial sample. These results indicate stable and robust cocrystal lattice formation.

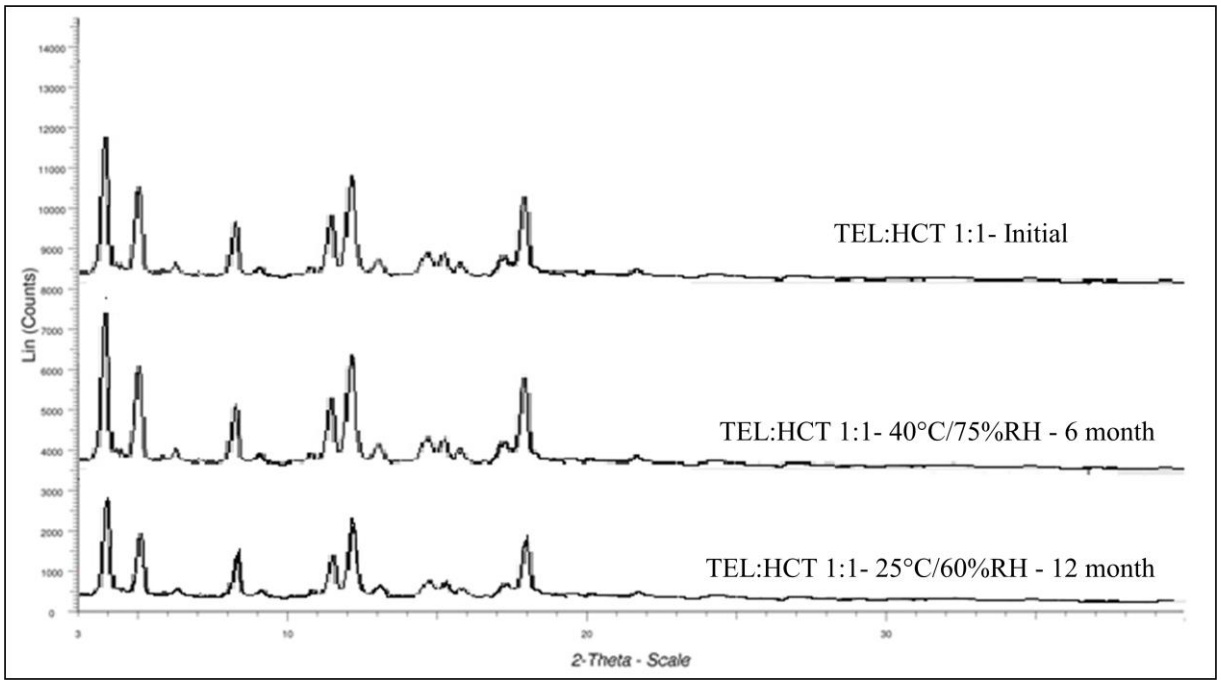


Figure 4.17 PXRD scans of samples kept at long-term and accelerated stability study as compared to the initial sample

Table 4.13. Assay of samples charged on stability for TEL:HCT 1:1 cocrystals

Stability Condition	Initial (T0)	3 month	6 month	12 month
25°C ± 2°C/60% RH ± 5% RH	99.5 %	99.4 %	98.9%	99.5%
40°C ± 2°C/75% RH ± 5% RH		99.2 %	99.7%	-

4.2.8 *In-vivo* pharmacokinetic study

Pharmacokinetic parameters like peak plasma concentration (Cmax), area under plasma concentration –time curve (AUC), and relative bioavailability (%) of TEL, HCT, TEL and HCT as cocrystal, and cocrystal in the tablet are reported in Table 4.14, Figure 4.18 and 4.19. Results indicate an increase in drug plasma concentration (Cmax) of TEL alone (1.5 µg/mL) to TEL in cocrystal (2.5µg/mL) and HCT alone (2.2 µg/mL) to HCT in cocrystal (3.1 µg/mL). Similarly, an increase in AUC (µg.ml^{-1}.hr) and relative bioavailability (%) was observed for cocrystals in comparison to pure drugs. Comparable results were observed for cocrystal and cocrystal in tablet composition for all the pharmacokinetic parameters.

Table 4.14. Pharmacokinetic parameters measured for TEL, HCT and TEL:HCT cocrystal from *In-vivo* study

S. No	**Pharmacokinetics parameters**	**TEL**	**TEL from TEL:HCT cocrystal**	**TEL from TEL:HCT cocrystal (Tablet composition)**	**HCT**	**HCT from TEL:HCT cocrystal**	**HCT from TEL:HCT cocrystal (Tablet composition)**
1	Cmax (µg/ml)	1.5	2.5	2.6	2.2	3.1	3.2
2	AUC (µg.ml^{-1}.hr)	59.3	94.0	93.5	410.0	581.5	597.0
3	Relative bioavailability (%)	-	158.65	157.81	-	141.8	145.6

These *In-vivo* results clearly indicate improved bioavailability of co-crystal of TEL:HCT and co-crystal in tablet compared to individual drugs. Increase in relative bioavailability by 58% to 59% for HCT and 42% to 46% for HCT.

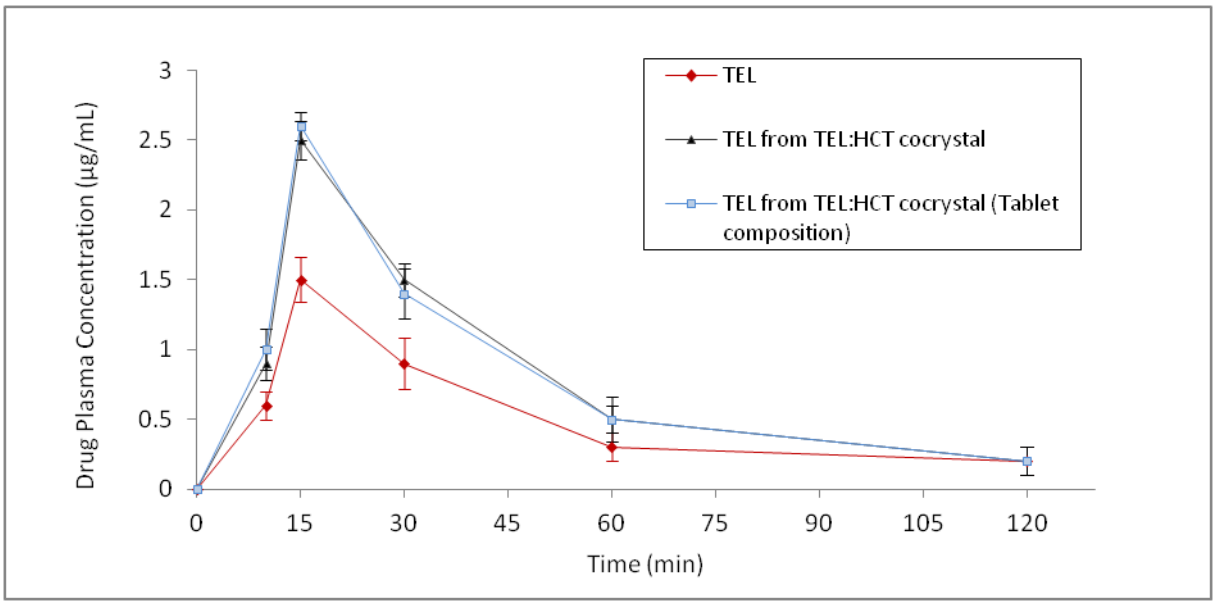


Figure 4.18: Comparative In-vivo study for TEL, TEL from TEL:HCT cocrystal and TEL from TEL:HCT cocrystal (Tablet composition)

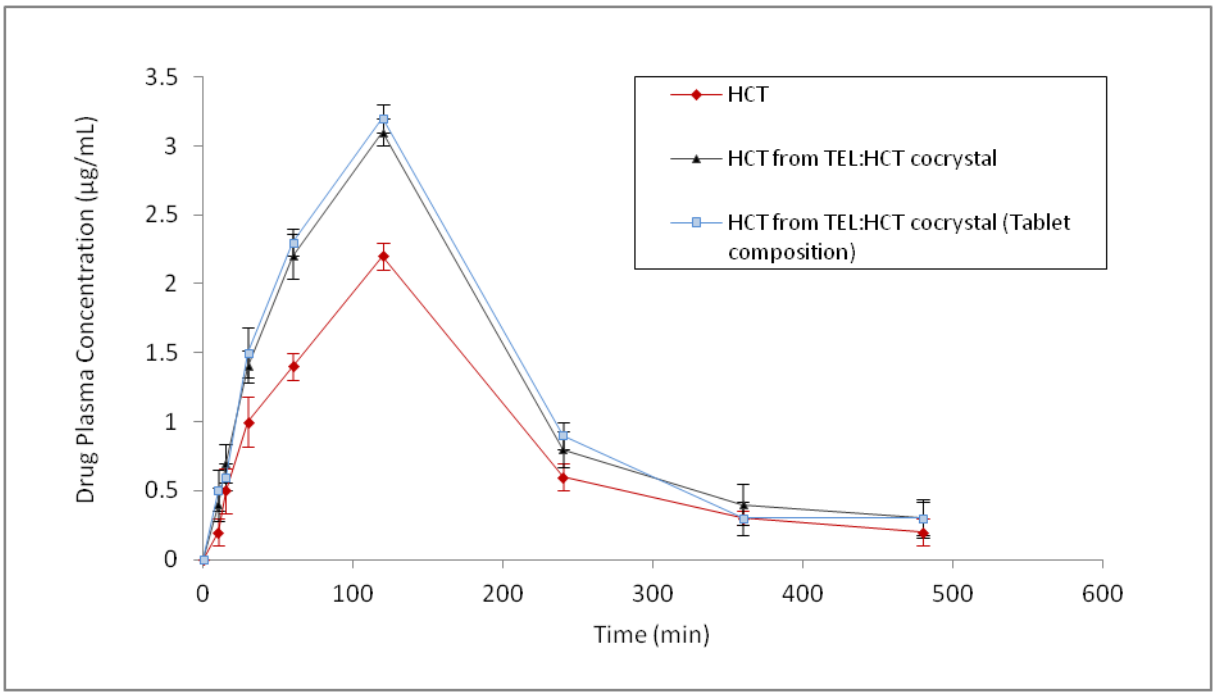


Figure 4.19: Comparative In-vivo study for HCT, HCT from TEL:HCT cocrystal and HCT from TEL:HCT cocrystal (Tablet composition)

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Conclusion

5. Conclusion

An attempt has been made to develop a cocrystal of Ranolazine using Nicotinamide as a coformer. Different molar ratios Ranolazina and Nicotinamide (1:1, 1:2, 1:3, 2:1 and 3:1) were evaluated to find the most apt ratio for cocrystal formation. Different methods were evaluated for cocrystal synthesis, out of which solvent evaporation was found to be a better and more convenient approach for synthesis as compared to solvent assisted-grinding and slurry preparation. The characterization using melting point analysis, DSC and XRPD was performed on crystalline phases obtained after synthesis. Based on the characterization, RAN: NIC in the molar ratio of 1:2 was found to be the most appropriate to achieve the most suitable crystalline arrangement. In order to evaluate the desired outcome in terms of solubility enhancement, a saturated solubility study of RAN and RAN:NIC 1:2 cocrystals was performed. From the solubility study, an increase in solubility was observed for cocrystals in all the buffers and water. An increase in solubility by more than 10 folds in pH 6.8 phosphate buffers and 17-fold increase in water solubility has been observed. Results obtained clearly demonstrate that the cocrystalization of Ranolazine using Nicotinamide as a coformer helped in improving solubility in basic pH.

Ranolazine (RAN) exhibits pH-dependent solubility, with high solubility in acidic pH and lower in basic pH. Cocrystal formation of Ranolazine (RAN) with Nicotinamide (NIC) has been synthesized and evaluated for different molar ratios (1:1, 1:2, 1:3 2:1 and 3:1). Various techniques like liquid-assisted grinding, slurry preparation and solvent evaporation were implemented to synthesize cocrystals. Conformational and characterization analysis has been performed using techniques like melting point analysis, powder X-ray diffraction and TGA. Saturation solubility of RAN alone along with cocrystals prepared in different molar ratios in buffers of different pH (1.2, 4.5 and 6.8) and in water has been studied to establish enhancement in solubility. RAN cocrystals with NIC were shown to have enhanced solubility in basic pH. Utmost improvement in solubility has been observed for RAN: NIC molar ratio of 1:2.

Telmisartan (TEL) and Hydrochlorothiazide (HCT) fixed-dose combination is a known and effective combination for the treatment of hypertension. Both drugs are known for their low solubility and work has been done to get better solubility through cocrystallization of standalone moieties. The currently commercially available Fixed-Dose Combination (FDC) of TEL and HCT, the usage of alkalizers in tablet formulation to uphold the micro pH

environment of drug substance to augment solubility in a physiological environment, which makes tablet formulation prone to gain moisture during storage. Drug-Drug cocrystal synthesis of TEL and HCT has been demonstrated by implementing the design of experiment (DoE). Molar ratios, different synthesis techniques and various solvents used for synthesis were evaluated in an orderly manner by applying the DoE concept. Prepared cocrystals were evaluated for melting point, differential scanning calorimeter, X-ray powder diffraction, dynamic vapor sorption and saturation solubility. From the various techniques applied for characterization, it has been established that a new crystal lattice of TEL: HCT cocrystal was formed. This new drug-drug cocrystal has been used in the manufacturing of tablet dosage form which demonstrates enhanced solubility, dissolution and no sensitivity towards moisture uptake compared to commercially accessible tablets.

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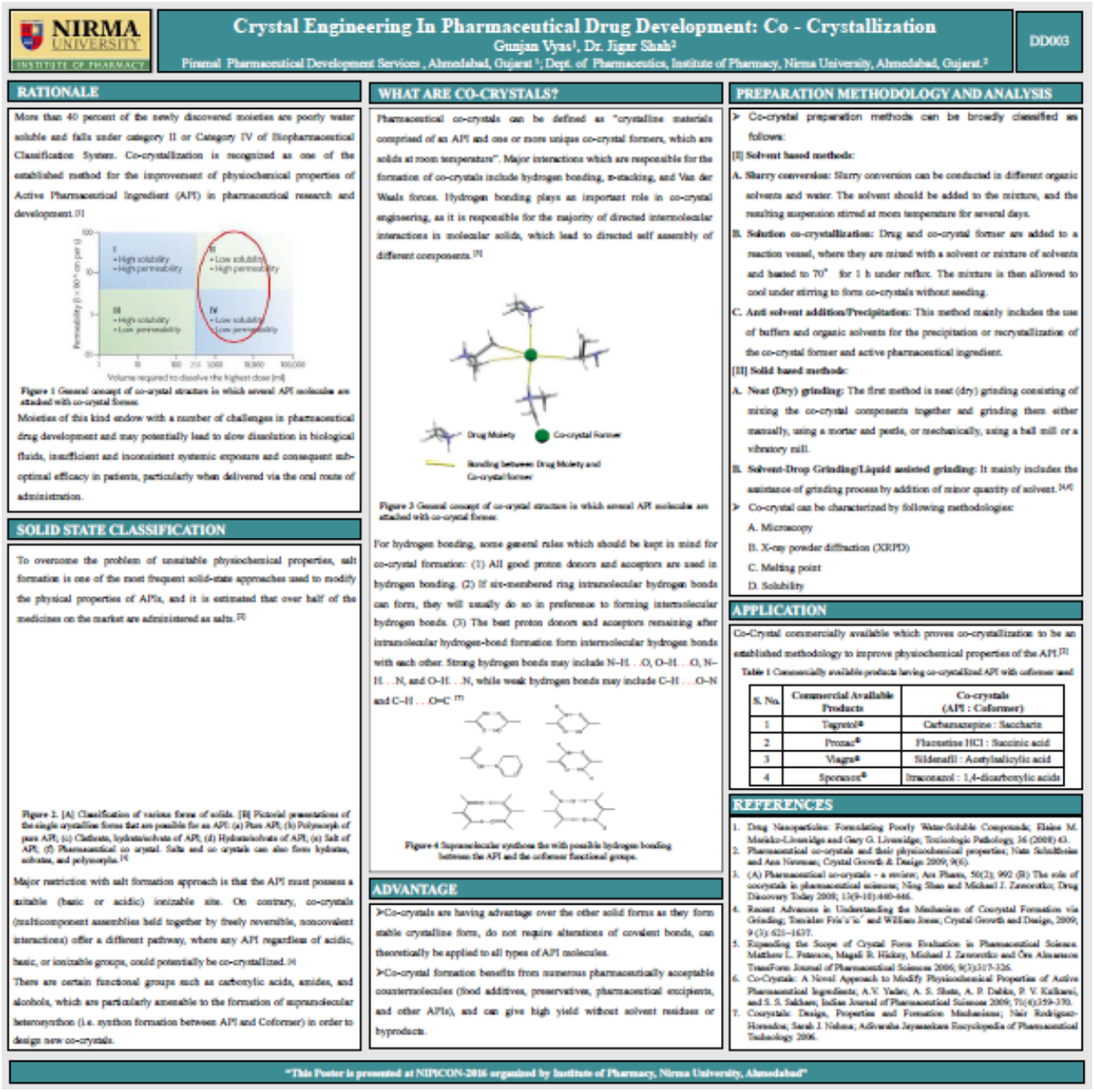
Publications and Presentation

6. Publications and Presentations

Poster presentation in NIPICON 2016



NIRMA UNIVERSITY
INSTITUTE OF PHARMACY

Crystal Engineering In Pharmaceutical Drug Development: Co - Crystallization

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DD003

RATIONALE

More than 40 percent of the newly discovered moieties are poorly water soluble and falls under category II or Category IV of Biopharmaceutical Classification System. Co-crystallization is recognized as one of the established method for the improvement of physiochemical properties of Active Pharmaceutical Ingredient (API) in pharmaceutical research and development.[1]

Figure 1 General concept of co-crystal structure in which several API molecules are studied with co-crystal former.

Moieties of this kind endow with a number of challenges in pharmaceutical drug development and may potentially lead to slow dissolution in biological fluids, insufficient and inconsistent systemic exposure and consequent sub-optimal efficacy in patients, particularly when delivered via the oral route of administration.

SOLID STATE CLASSIFICATION

To overcome the problem of unsuitable physiochemical properties, salt formation is one of the most frequent solid-state approaches used to modify the physical properties of APIs, and it is estimated that over half of the medicines on the market are administered as salts.[2]

Figure 2. [A] Classification of various forms of solids. [B] Pictorial presentations of the single crystalline forms that are possible for an API: (a) Pure API; (b) Polymorph of pure API; (c) Clathrate, hydrate/solvate of API; (d) Hydrate/solvate of API; (e) Salt of API; (f) Pharmaceutical co crystal. Salts and co crystals can also form hydrates, solvates, and polymorphs.[3]

Major restriction with salt formation approach is that the API must possess a suitable (basic or acidic) ionizable site. On contrary, co-crystals (multicomponent assemblies held together by freely reversible, noncovalent interactions) offer a different pathway, where any API regardless of acidic, basic, or ionizable groups, could potentially be co-crystallized.[4]

There are certain functional groups such as carboxylic acids, amides, and alcohols, which are particularly amenable to the formation of supramolecular heterosynthon (i.e. synthon formation between API and Coformer) in order to design new co-crystals.

WHAT ARE CO-CRYSTALS?

Pharmaceutical co-crystals can be defined as "crystalline materials comprised of an API and one or more unique co-crystal formers, which are solids at room temperature". Major interactions which are responsible for the formation of co-crystals include hydrogen bonding, π-stacking, and Van der Waals forces. Hydrogen bonding plays an important role in co-crystal engineering, as it is responsible for the majority of directed intermolecular interactions in molecular solids, which lead to directed self assembly of different components.[5]

Figure 3 General concept of co-crystal structure in which several API molecules are studied with co-crystal former.

For hydrogen bonding, some general rules which should be kept in mind for co-crystal formation: (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 with each other. Strong hydrogen bonds may include N–H . . .O, O–H . . .O, N–H . . .N, and O–H . . .N, while weak hydrogen bonds may include C–H . . .O–N and C–H . . .O=C.[7]

Figure 4 Supramolecular synthons the with possible hydrogen bonding between the API and the coformer functional groups.

ADVANTAGE

➢Co-crystals are having advantage over the other solid forms as they form stable crystalline form, do not require alterations of covalent bonds, can theoretically be applied to all types of API molecules.

➢Co-crystal formation benefits from numerous pharmaceutically acceptable counter molecules (food additives, preservatives, pharmaceutical excipients, and other APIs), and can give high yield without solvent residues or byproducts.

PREPARATION METHODOLOGY AND ANALYSIS

➢ Co-crystal preparation methods can be broadly classified as follows:

[I] Solvent based methods:

A. Slurry conversion: Slurry conversion can be conducted in different organic solvents and water. The solvent should be added to the mixture, and the resulting suspension stirred at room temperature for several days.

B. Solution co-crystallization: Drug and co-crystal former are added to a reaction vessel, where they are mixed with a solvent or mixture of solvents and heated to 70° for 1 h under reflux. The mixture is then allowed to cool under stirring to form co-crystals without seeding.

C. Anti solvent addition/Precipitation: This method mainly includes the use of buffers and organic solvents for the precipitation or recrystallization of the co-crystal former and active pharmaceutical ingredient.

[II] Solid based methods:

A. Neat (Dry) grinding: The first method is neat (dry) grinding consisting of mixing the co-crystal components together and grinding them either manually, using a mortar and pestle, or mechanically, using a ball mill or a vibratory mill.

B. Solvent-Drop Grinding/Liquid assisted grinding: It mainly includes the assistance of grinding process by addition of minor quantity of solvent.[8,9]

➢ Co-crystal can be characterized by following methodologies:

A. Microscopy

B. X-ray powder diffraction (XRPD)

C. Melting point

D. Solubility

APPLICATION

Co-Crystal commercially available which proves co-crystallization to be an established methodology to improve physiochemical properties of the API.[3]

Table 1 Commercially available products having co-crystallized API with coformer used

S. No.	Commercial Available Products	Co-crystals (API : Coformer)
1	Tegretol®	Carbamazepine : Saccharin
2	Prozac®	Fluoxetine HCl : Succinic acid
3	Viagra®	Sildenafil : Acetylsalicylic acid
4	Sporanox®	Itraconazol : 1,4-dicarboxylic acids

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Research Paper: Acceptance letters

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OSP Health

February 22, 2023

Dear Jigar Shah

I am pleased to inform you that your manuscript titled "DoE implementation for Telmisartan and Hydrochlorothiazide drug-drug cocrystal synthesis to enhance physicochemical and pharmacokinetic properties" (Manuscript Number: JAPS-2022-12-1203) is provisionally accepted for publication in the Journal of Applied Pharmaceutical Science. You will receive further updates shortly.

Please note that this acceptance is subject to the EIC's approval and the journal can refuse to publish the article if we detect any violation of publication ethics and malpractice guidelines which includes plagiarism, duplicate submissions, etc.

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Paper Title: Enhancement of physicochemical and pharmacokinetic characteristics of Ranolazine drug substance using cocrystalization technique

Acceptance of Manuscript

With reference to your article titled **'Enhancement of physicochemical and pharmacokinetic characteristics of Ranolazine drug substance using cocrystalization technique'** Author by **Gunjan Vyas, Jigar Shah, Shery Jacob**. We wish to bring to your kind notice the following:

- We acknowledge the receipt of the above mentioned article.
- The above mentioned article has been sent to the reviewer of expert comments.
- The above mentioned article have been accepted for publication in 2024 Volume-17, Issue-7 of the journal.

Thanking you for submission of manuscript.

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