SOLID STATE MODIFICATION BY CO-CRYSTALLIZATION OF SELECTED DRUG

PhD SYNOPSIS

Submitted to

GUJARAT TECHNOLOGICAL UNIVERSITY

For the degree of Doctor of Philosophy

in Pharmacy

by

Shah Priyal Kalpeshkumar

Enrolment No. 199999901528

Under Supervision of

Dr. Anuradha K. Gajjar

Professor and Head of the Department
Department of Pharmaceutical Chemistry & Quality Assurance
L. M. College of Pharmacy, Ahmedabad

Title: Solid State Modification by Co-Crystallization of Selected Drug

Abstract

A significant percentage of drugs, around 60-70 %, fall under BCS Class II, indicating their poor solubility. The cocrystal formation presents a promising solution to enhance drug solubility by modifying the crystal structure, thus potentially improving bioavailability. Fimasartan Potassium Trihydrate (FPT) is an antihypertensive molecule classified as BCS-II, presenting low solubility and high permeability. To address the solubility and bioavailability challenges associated with such compounds, cocrystal technology was employed in this study. A cocrystal of FPT with L-Proline (FPT-LP) was successfully obtained using the solvent evaporation method at a stoichiometric ratio of 1:2. The scalability of this technique was demonstrated through the Supercritical Fluid Extraction method for technology transfer and scale up. In silico studies revealed the binding mechanism of API and coformers to form cocrystal. This involves intermolecular hydrogen bonding (amino-nitro) and π-π stacking. The developed cocrystals were characterized comprehensively using various techniques like FTIR, SEM, TEM, DSC, PXRD, SCXRD, RP-HPLC, and U.V. visible spectrophotometer. In vivo studies were conducted on rats using the LC-MS/MS method that demonstrated a remarkable 88.88 % increase in bioavailability of FPT-LP compared to FPT. The developed cocrystals were successfully formulated into capsule dosage form, exhibiting drug release of 99.95 % within 60 minutes in phosphate buffer-6.8. Stability studies conducted via Dynamic Vapor Sorption and Accelerated stability studies confirmed the stability of the cocrystal. Additionally, In Vitro In Vivo correlation (IVIVC) analysis showed a direct point-to-point relationship between % Drug Release and Absorption Rate. The development of this cocrystal offers substantial benefits to society by enhancing drug bioavailability, also providing advantages to the industry through a facile and scalable manufacturing method. Moreover, the work is protected under patent, ensuring regulatory advantages.

Keywords: Fimasartan; L-Proline; co-crystallization; bioavailability; supercritical fluid extraction; IVIVC; cocrystal; capsule

Brief description on the state of the art of the research topic

Fimasartan blocks angiotensin II receptor type 1 (AT1 receptors), reducing pro-hypertensive actions of angiotensin II, such as systemic vasoconstriction and water retention by the kidneys.

The coformer selection is of great importance, as strong variations can occur depending on the nature of the selected coformer. A relevant choice in the coformer can either help to

improve the formulation stability, enhance solubility and increase bioavailability of fimasartan leading to lowering of dose and increase in safety and/or efficacy. The coformer was selected from Saccharine, Succinic Acid, Hydrochlorothiazide, L-Proline, L-Valine, L-Threonine, L-Cystine, L-Lysine, L-Glutamic acid and Glycine.

The cocrystals of fimasartan and coformer are prepared using solvent evaporation technique and Supercritical fluid extraction method. The process of preparing cocrystals of fimasartan by solvent evaporation technique comprises the steps of,

a) Taking molar ratio of fimasartan and coformer and dissolving in methanol: water (20:80 v/v);

b) Evaporating step (a) solution on a water bath at 80 °C;

c) The solid powder left was characterized for the confirmation of cocrystal formation.

The process of preparing cocrystals of fimasartan by Supercritical Fluid Extraction (SFE) method comprises the steps of,

a) Taking molar quantities of fimasartan and coformer;

b) Adding step (a) mixture in the sample vessel and covering with glass wool;

c) Supplying CO_2 under supercritical conditions, stable pressure (100 bar) and 80 °C temperature in step (b) mixture.

d) Pumping methanol in step (c) mixture;

e) Diffusing Supercritical solvent and modifier rapidly into the step (b) solid matrix and dissolving the material to be extracted;

f) Removing dissolved material (the developed cocrystal) of step (e) from the extraction cell into a separator at lower pressure, when the extracted material settled out;

g) Cooling and recycling supercritical CO_2;

h) Collecting liquid sample and drying at room temperature which led to formation of cocrystal named as FPT-LP.

The novel cocrystals of fimasartan were developed having greater solubility and bioavailability as compared to standard fimasartan and physical mixture of fimasartan and coformer.

Definition of the Problem

According to WHO, 42% of the population in the world suffer from hypertension. Out of the total, 20% and 40% are prescribed sartans in USA and India respectively. Fimasartan Potassium Trihydrate (FPT), approved by CDSCO in September 2019, is the latest generation of sartan. Being a BCS Class-II drug, it has a low solubility and bioavailability of 18.6%.

This leads to higher doses with the potential for greater side effects. The literature review suggested that there is no technique available for the formation of cocrystal of fimasartan; hence the literature review was conducted on the sartan class of drug. This helped in identifying the binding site and the tendency of cocrystal formation. It was a thought of interest to develop cocrystals, that increase the solubility and bioavailability, which in turn helps in reducing the dose and side effects of FPT.

Objectives and Scope of Work

Aim: To design, synthesize and evaluate pharmaceutical cocrystal of selected drug.

Objectives

- To investigate suitable co-formers and method of preparation for cocrystal.
- To characterize the developed cocrystals by: Fourier-transform infrared spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), Thermogravimetric analysis (TGA), Nuclear magnetic resonance (NMR), Powder X-ray Diffraction (PXRD), Dissolution Study, Solubility Study, Stability Study.
- To perform pharmacokinetic studies and calculate the % bioavailability.
- To prepare a suitable dosage form after preformulation studies and evaluation of the dosage form along with stability assessment.
- To establish an in-vitro-in-vivo correlation (IVIVC).

Scope of Work

The developed cocrystals can be used as an active tool to impact the physicochemical properties of Fimasartan. The coformer selection is of utmost importance, as strong variations can occur depending on the nature of the selected coformer. A relevant choice in the coformer can either help to improve the formulation stability, enhance the solubility and increase the bioavailability of the drug (FPT) leading to lowering of dose and increase in safety and/or efficacy.

Original contribution by the thesis

The entire work in this synopsis, as well as thesis is original. Extensive literature review was carried out on the fundamentals of cocrystals, cocrystal for the class of drug and analytical methods for the selection of coformer and techniques of preparation.

Benefit to the Society: There are 1.2 billion people suffering from hypertension and being treated with antihypertensive molecules. The advantages being offered by the prepared

cocrystal increases the bioavailability from 18% to 32% that is 88% increase which would lead to lowering of the dose and increase in safety with desired efficacy.

Benefit to the Industry: The cocrystals are prepared in pure, high-quality yield by Supercritical fluid extraction technique, an easily scalable technique. Comparison of profiles of the cocrystal and the drug leads to the beneficial changes with respect to dosing, process and/or cost to formulation.

According to USFDA, cocrystals of existing drugs can be patented as new cocrystal forms. The bonding combination of drug and coformer provides a platform for the establishment of inventive step and is already protected by patent filling (Application Number: IN 202221043126, Date of Filling: 13-Jul-2023).

Methodology of Research and Results

Computational work

3-D Structures of FPT and all coformers were downloaded from Cambridge Structural Database (with R-factor less than 5, to avoid any disorder in the structure). Material Studio was used for optimizing the geometry of the structure (crystal lattice, cell parameters). The optimized structures were imported in Mercury Software (MOPAC Version - 3.10) and the parameters were calculated for in silico cocrystal screening that also gave data for the crystal structure. It proved that the developed cocrystal was of monoclinic crystal system. Hirshfeld surface analysis and Surface electrostatic potential helped in identifying the hydrogen binding sites and the functional groups in FPT-LP.

Method of Preparation

Solvent Evaporation Method: FPT and L-Proline was weighed in a stoichiometric ratio of 1:2 (molar) and dissolved in methanol: water (20:80 v/v). The solution was heated at 70 ºC. The solid yield was dried and characterized for the formation of cocrystal.

Supercritical Fluid Extraction (SFE): *Principle*: SFE utilizes supercritical fluids above their critical temperature and pressure as solvents to selectively extract desired compounds from solids or liquids. By adjusting the pressure and temperature, the solvating power of the supercritical fluid can be optimized. CO_2 is the most commonly used supercritical fluid in SFE. It offers efficient extraction with a reduced need for organic solvents compared to traditional extraction methods. Hence, it is environmentally friendly and cost-effective option.

Method: FPT and L-proline were accurately weighed in a stoichiometric ratio of 1:2 (molar) and were mixed properly. The sample was placed in the sample compartment on a cotton wool. In the mobile phase section, methanol and water (5:95 v/v) were placed. The Supercritical CO_2 extraction processes were allowed to run at temperatures of 70 °C. The pressure was set at 80 MPa. The sample was extracted and collected in the collection tube. The solution from the collection tube was dried to obtain solid cocrystals.

Characterization of cocrystals

The developed cocrystals were characterized with various analytical techniques to confirm the formation of cocrystals and its hydrogen bonding.

SEM: Scanning Electron Microscope (SEM) is a type of electron microscope that produces images of a sample by scanning the surface with a focused beam of electrons. The electrons interact with atoms in the sample, producing various signals that contain information about the surface topography and composition of the sample. Inference: The SEM studies showed prismatic shape of FPT-LP. (Fig-1)

TEM: Transmission Electron Microscopy (TEM) is a microscopy technique in which a beam of electrons is transmitted through a sample to form an image. This allows capturing the intricate details of the sample and focusing into its impurities and state characterization, like amorphous or crystalline nature. Inference: The TEM studies proved that the developed cocrystal is crystalline and without any defects or impurities. (Fig-2)

FTIR: Fourier Transform Infrared Spectroscopy is used to identify and analyze the functional groups and chemical bonds present. Inference: Alterations in the characteristic pattern of absorption bands was observed in FPT-LP in comparison to FPT, L-Proline and Physical mixture that clearly indicated the formation of cocrystal as shown in Fig-3.

DSC: Differential Scanning Calorimetry (DSC) is a thermal analysis that measures the physical properties of a sample change, along with temperature against time. Inference: The DSC curve indicated an endothermic peak at 180 °C and 70 °C of FPT and L-Proline respectively, while FPT-LP showed an exothermic peak at 110 °C (Fig-4) which established the formation of a distinct entity.

RP-HPLC: The RP-HPLC method was developed with RP-C18, 250 mm × 4.6mm, 5µ as the stationary phase, Methanol : Water (90:10 v/v) as the mobile phase at 0.8 mL/min flowrate for 10 min at ambient column temperature. This method was developed for the cocrystal characterization and dissolution studies (Fig-5).

PXRD: Powder X-Ray Diffraction (PXRD) studies showed that FPT-LP showed two peaks of higher intensity, comprising one for FPT and another for L-Proline. It was also noted that the physical mixture (PM) did not show the same pattern and hence, this proved the formation of cocrystals as shown in Fig-6.

SC-XRD: Single Crystal X-ray Diffraction (SC-XRD) is a crystallographic method for the determination of structures at the atomic level. The SC-XRD preliminary studies were analyzed under an electron microscope to confirm the single crystal formation. (Fig-7) After the confirmation, the single crystal was placed on the sample holder of the instrument for further analysis. The crystallograph showed a distinct different peak for FPT-LP compared to FPT, L-Proline and PM (Fig-8).

Phase Transformation: The phase transformation studies refer to the investigation and analysis of changes that occur in the physical state of a material, such as transitions between solid, liquid, and gas phases. These studies aim to understand the stability and underlying mechanisms of the sample. The phase transformation studies of FPT-LP were conducted in aqueous medium. The solids obtained after the equilibrium time (48 hr) were dried and subjected to PXRD analysis. Inference: FPT-LP did not show any other extra peak that states that the developed cocrystal is stable and does not undergo any phase transformation (Fig-9).

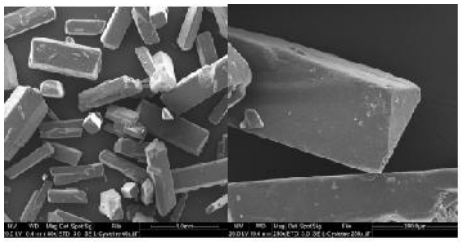

Figure-1: SEM Image

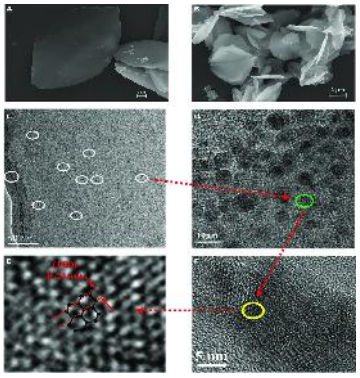

Figure-2: TEM Image

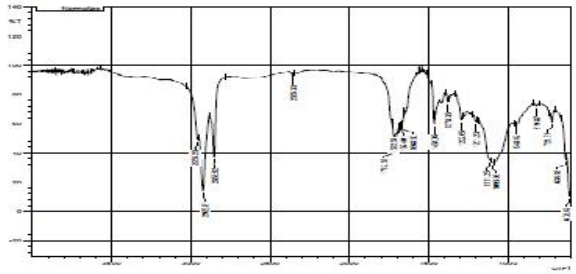

Figure-3: FTIR spectrum of FPT-LP

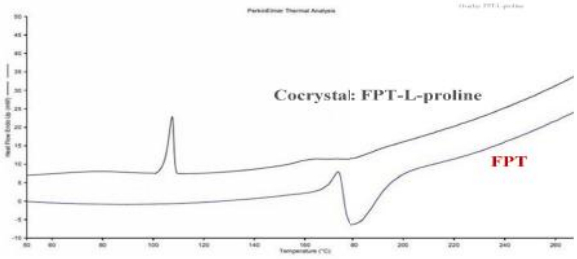

Figure-4: DSC Study Overlay of FPT and FPT-LP

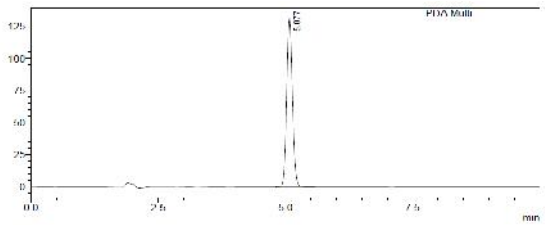

Figure-5: Chromatogram of FPT-LP

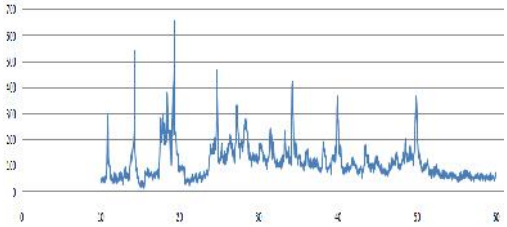

Figure-6: PXRD Study of FPT-LP

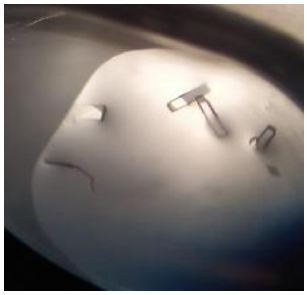

Figure-7: Microscopic Study

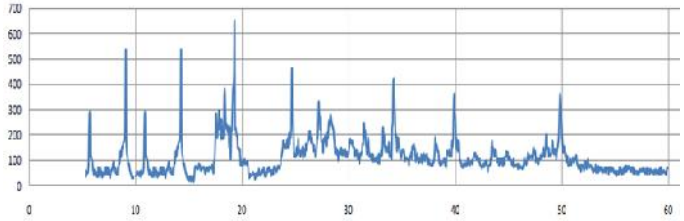

Figure-8: SC-XRD Study of FPT-LP

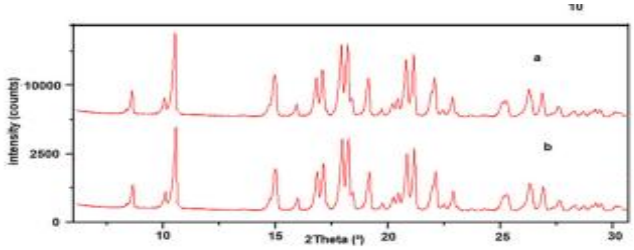

Figure-9: Phase Transformation Study of FPT-LP

Pharmacokinetic Studies

The pharmacokinetic studies were conducted by taking the approval of IAEC for 12 months (Proposal No: LMCP/IAEC/22/0024). The animal study protocol is described in Table-1 while Table-2 states the grouping of animals.

Table-1 Animal Study Protocol

Animal Specifications	Species and Strain: Sprauge-Dawley Rats of either sex Age: 8-10 weeks old; Weight: 250-300 g Total number of animals required: 12
Drugs/Chemicals	FPT (API) FPT-LP (Cocrystal)
Anesthesia	Isofluran
Blood collection route	Retro-orbital plexus

Table-2 Grouping of Animals

Sr. No.	Group	Treatment	No of animals
1	Standard Control	FPT API	06
2	Test Control	Developed cocrystals	06
Total no of animals			12

Experimental Design

FPT and FPT-LP was dissolved in water and administered orally to individual groups. The blood was withdrawn from the retro orbital vein, under light anaesthesia and the blood collection volume was less than 1 mL. The time points of blood withdrawal were 0, 1, 2, 2.5, 3, 3.5, 4, 8, 12, 24, 48 hours. The collected blood was mixed with 1% EDTA solution and then was centrifuged at 10,000 rpm for 10 min and plasma was collected. The plasma was analysed for the bioavailability of drug by LC-MS/MS and further comparision of the same was carried out for FPT and FPT-LP.

LC-MS/MS Method

The LC-MS/MS method was developed for the analysis of pharmacokinetic studies of FPT and FPT-LP. Table-3 shows chromatographic conditions while Table-4 indicates gradient mobile phase composition with respect to time.

Table-3 Chromatographic Conditions

Parameters	Conditions
Mobile Phase	A. 0.1% formic acid in water (v/v) B. ACN
Stationary Phase	Zorbax RP-C18, 100 mm × 3.0 mm, 1.8µ
Flow Rate	0.4 mL/min
Injection volume	1 µL
Column Temperature	30 °C
Run Time	10 min

Table-4 Mobile Phase Composition

Time (min)	Mobile Phase A (% v/v)	Mobile Phase B (% v/v)
0.00	60	40
2.00	50	50
5.00	20	80
6.00	20	80
10.00	60	40

Sample Preparation

50 µL of blood plasma was collected from rat and mixed with 50 µL Internal Standard - Losartan (100 ng/mL). The solution was mixed with 300 µL acetonitrile and centrifuged for 10 min at 15000 rpm and 4 ºC. The supernatant was collected and analyzed by LC-MS/MS.

Comparison of Pharmacokinetic Data: The comparative data for the pharmacokinetic studies is stated in Table-5. C_{max} data revealed that there in an increase in the concentration maxima from 240 to 320 ng/mL which showed that FPT-LP cocrystal is more bio-available then FPT (Figure-10). The pharmacokinetic data was calculated by PK solver 2.0.

Table-5 Comparative Pharmacokinetic Studies

Time (hr)	Concentration (ng/mL)	
	Cocrystal	FPT
0	0	0
1	150	150
2	180	180
2.5	260	200
3	320	240
3.5	270	230
4	230	220
5	210	210
6	180	170
7	160	150
8	150	80
12	80	60
24	50	50
36	0	0
48	0	0

Parameter	FPT-LP	FPT	% Change
$Lambda_z$	0.06	0.081	25.45
$t_{1/2}$	10.68	8.51	20.29
T_{max}	3	3	0.00
C_{max}	320	240	14.26
AUC_{0-t}	2682.50	2295	14.45
Cl_obs	0.01	0.02	18.64
Vss_obs	0.25	0.28	10.21

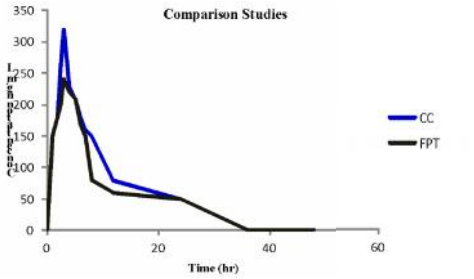

Figure-10: Pharmacokinetic Studies

Bioavailability Calculation: The calculated Absolute bioavailability and Relative bioavailability was 25% and 32% respectively for the developed cocrystal. The relative bioavailability of FPT was 18.6%. This showed the increase of 88.88 % in the bioavailability of FPT-LP in comparison to FPT.

Formulation Studies

Pre-formulation Studies

Various parameters were studied for the preformulation studies. Table-6 summarizes the preformulation studies conducted while Fig-11, 12 and 13 shows the % drug release and solubility of FPT-LP. It was observed that FPT-LP showed more % drug release and solubility in comparison to FPT and PM.

Table-6 Summary of Preformulation Studies

Sr. No	Parameters	Inference
1	Organoleptic Characteristics	Color: White Odor: Odorless
2	Melting point Determination	265-268 ^{0}C
3	Particle Size Determination	Dv (90) 14.4 µm
4	Powder Properties	Fine powder with Excellent flow (angle of repose)
5	Solubility Study	Solubility in water: 11.56 = 0.28 (mg/mL)
6	Intrinsic Dissolution Rate	% Drug release was highest for FPT-LP (20.48 mg/cm^2/min)
7	In-Vitro Dissolution	% Cum. Drug release (99.31% in 60 min)-highest for FPT-LP

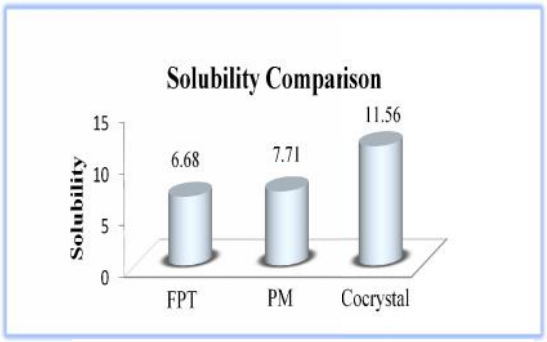

Figure-11: Solubility Study

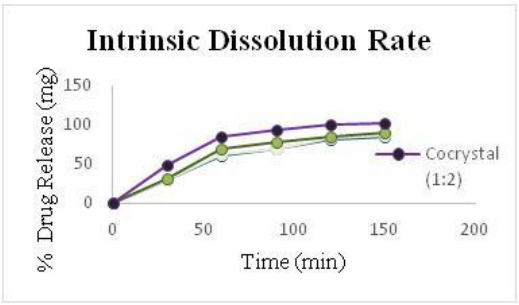

Figure-12: Intrinsic Dissolution Rate

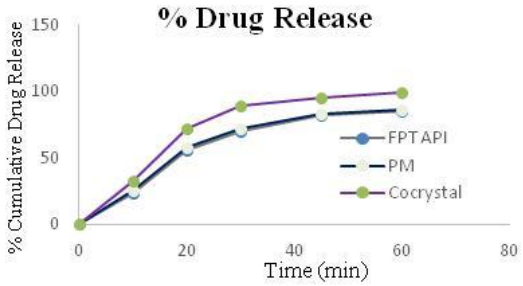

Figure-13: % Cumulative Drug Release

Dosage Form Preparation

The prepared dosage form was Capsule (Hard Gelatin Capsule - size 1). The interaction between the cocrystals and excipients was studied by FTIR and DSC, which showed there is no interaction. The Hygroscopicity study stated that the physical mixture of cocrystals and excipients was non-hygroscopic with a weight change of 0.03-0.9% w/w, while the assay study showed 99.98 % of FPT-LP.

Method of preparation: FPT-LP and excipients were weighed and passed through Sieve-80. FPT-LP was blended with all other excipients, except lubricant and glidant. Subsequently, lubricant and glidant were added to the blend of FPT-LP and excipient, and further blending was carried out. The formula is stated in Table-7.

Table-7: Formula for capsule preparation

Ingredients	Amount (mg)
Cocrystal (L-proline : FPT - 2:1)	87.50
Microcrystalline Cellulose	69.50
Sodium Starch Glycolate	16.00
Aerosil	2.00
Mg. Stearate (1%)	5.00
Total	180

Capsule Evaluation Parameters: For the evaluation of the capsule formulation various parameters were tested to check the amount of drug present- assay, % drug release and so on as described in Table-8.

Table-8: Capsule Evaluation Parameters

Parameter	FPT-LP Capsule
Weight variation (mg)	180.05 ±0.77
Assay (%)	99.31
Content uniformity (%)	99.1 ±0.4
Friability (%)	0.19
Disintegration Time (min)	1±2
Dissolution (30 min)(%)	89.68
Dissolution (60 min)(%)	99.46

Dissolution Medium Selection: After considering various media, phosphate buffer – 6.8 was selected for studying the dissolution profile of the formulation (Fig-14 and Table-9) as reported in the literature (Patent filled by EP which states that FPT shows lower solubility at pH 1.0 – 4.0 and decent solubility pattern under high pH such as purified water and pH 6.8.

Table-9: Dissolution Media Selection

Dissolution media	Solubility	
	mg per mL	mg per 900 mL
Water	0.63	567.0
0.1N HCl	0.25	225.9
P. Buffer -6.8	1.23	1110.6
P. Buffer -7.4	0.85	768.6

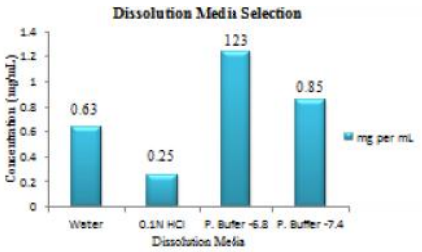

Figure-14: Dissolution Media Selection

Comparative Dissolution Studies: % Cumulative Drug Release was studied for FPT, PM, FPT-LP capsule and marketed formulation (Tablet with 60 mg strength). The studies determined that FPT-LP capsule showed maximum % drug release of 99.95% at 60 min in comparison to FPT (85.21 %), PM (83.57 %) and marketed formulation (88.26%) (Table-10 and Fig-15)

Table-10 % Cumulative Drug Release

Time (min)	% Cumulative Drug Release			
	FPT API (mg)	PM (mg)	Cocrystal (Capsule) (mg)	Marketed Formulation (Tablet) (mg)
0	0	0	0	0
10	23.2	21.1	40.6	32.5
20	49.56	43.13	72.05	51.3
30	67.43	65.17	91.3	68.7
45	79.01	78.15	99.76	81.32
60	85.21	83.57	99.95	88.26

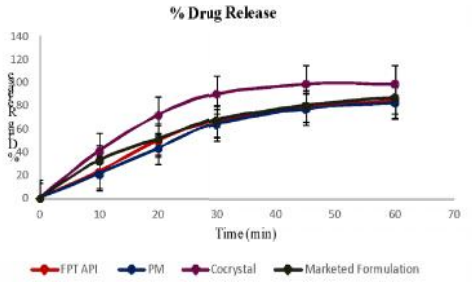

Figure-15: % Cumulative Drug Release

Stability Studies: Stability Studies were performed for the capsule formulation by Dynamic Vapor Sorption (DVS) Analysis and Accelerated Stability Studies. DVS studies proved that FPT-LP is non-hygroscopic (Fig-16). Accelerated stability studies were carried out for 3 months at 40 ± 5 °C/75 ± 5% RH which determined that FPT-LP cocrystal and the developed capsule formulation is stable. The predicted shelf life is of 2 years (Table-11).

Table-11 Accelerated Stability Studies

Sr. No.	Properties	Timeline (months)			
		0	1	2	3
1	Weight variation	192.05 ± 0.77	191.78 ± 0.52	191.23 ± 0.86	191.75 ± 0.74
2	Assay	99.31%	99.01%	99.17%	99.28%
3	Content uniformity	99.1 ± 0.4	99.7 ± 0.8	99.5 ± 0.3	99.6 ± 0.1
4	Friability	0.19	0.21	0.19	0.26
5	Disintegration Time (min)	1 ± 2	1 ± 2	1 ± 2	1 ± 2

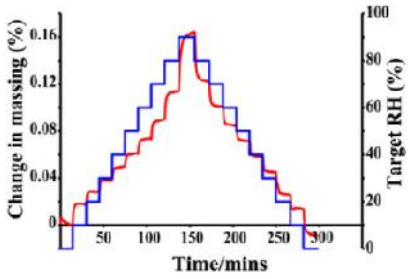

Figure-16: DVS Analysis

In Vitro In Vivo Correlation (IVIVC)

In Vivo Studies: The In vivo data was de-convoluted to get Absorption Rate vs Time (min) correlation as stated in Table-12 and Figure-17.

Table-12 In Vivo Studies

Time (min)	Concentration (mg/mL)	Absorption Rate
0	0	0
60	150	5.01
120	180	5.19
150	260	5.52
180	320	5.63

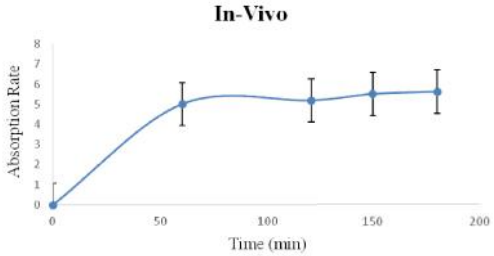

Figure-17: In Vivo Studies

In Vitro Studies: The In-Vitro Drug release pattern was studied upto 120 min (Table-13). The graph (Fig-18) showed Spring and Parachute effect which was typically seen during the drug release of cocrystal.

Table-13 In Vitro Studies

Time (min)	%Drug Release
0	0
10	28.2
15	40.6
20	61.82
30	72.05
45	82.13
60	91.3
90	99.76
120	99.95

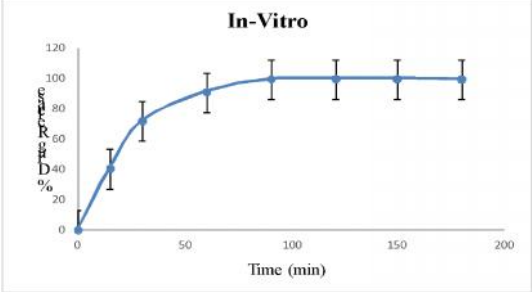

Figure-18: In Vitro Studies

IVIVC: The IVIVC study showed point to point relationship between % Drug Release and Absorption Rate. This means that the data followed Level-A correlation with % similarity of 99.77 % as coefficient of regression (Table-14, Figure-18 and 20).

Table-14 IVIVC Studies

In-Vitro		In-Vivo
%Drug Release	Time (min)	Absorption Rate
0	0	0
91.12	60	5.01
99.85	120	5.19
99.95	150	5.52
100.02	180	5.63

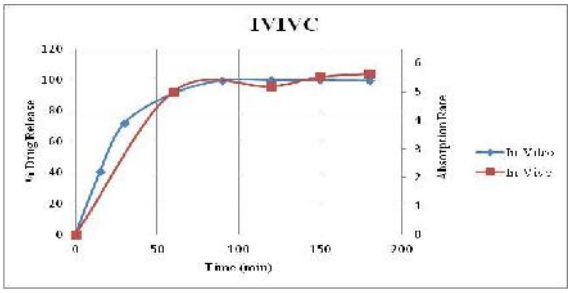

Figure-19: IVIVC Studies

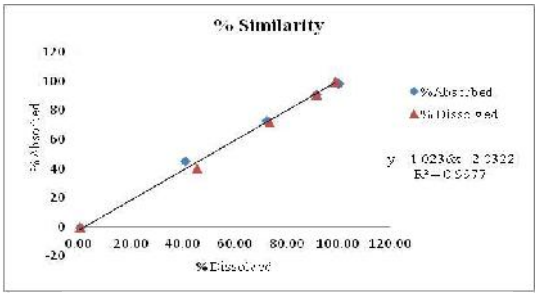

Figure-20: % Similarity

Achievements with respect to Objectives

- The selected coformer is L-proline with molar stoichiometric ratio as FPT: LP 1:2.
- The method of cocrystal formation is solvent evaporation technique and the scale up technique used is SFE.
- The analytical methods like SEM, TEM, RP-HPLC, FTIR, DSC, PXRD and SCXRD confirmed the formation and established the physicochemical characteristics of the cocrystal.
- The developed cocrystals showed increase of eight fold in the solubility of FPT.
- The FPT-LP cocrystals were formulated into capsule dosage form that showed the % cumulative drug release more in FPT-LP capsule (99.95 %) then FPT (85.21 %), Physical Mixture (83.57 %) and marketed tablet formulation (88.26 %) at 60 min.
- The formation of cocrystal leads to increase in the bioavailability by 88.88 %, where FPT and FPT-LP exhibited 18 % and 32 % bioavailability respectively.
- The IVIVC studies showed that there is a Level-A point to point correlation between the in vitro and in vivo data sets with % similarity of 99.77 % as coefficient of regression.

Conclusion

- The coformer chosen for creating the FPT cocrystal was L-Proline, an amino acid. Amino acids are natural compounds with low risk and chiral properties, facilitating easy hydrogen bonding with FPT. L-Proline is recognized as Generally Regarded as Safe (GRAS) and its pyrrole group contributes to enhanced dissolution rates, potentially leading to increased bioavailability of the cocrystal.
- FPT-LP cocrystals showed promising results when prepared by solvent evaporation technique and SFE with good yield in stoichiometric ratio of 1:2 for FPT and L-Proline respectively.
- The developed cocrystals were analyzed and the identity was established by FTIR, DSC, UV spectroscopy, RP-HPLC, PXRD, SEM, TEM, and SCXRD.
- The developed cocrystals showed increase of eight fold in the solubility of FPT.
- Computational studies determined the site of interaction and hydrogen bonding theoretically. It proved the presence of sandwich-like trimer upon addition of L-Proline.
- Pharmacokinetic studies proved that % bioavaibility of FPT and FPT-LP were 18 % and 32 % respectively resulting in increase in bioavailability of FPT to the extent of 88.88 %.
- The FPT-LP cocrystals were formulated into capsule dosage form that showed the % cumulative drug release more in FPT-LP capsule (99.95 %) then FPT (85.21 %), Physical Mixture (83.57 %) and marketed tablet formulation (88.26 %) at 60 min.
- The IVIVC studies showed that there is a Level-A point to point correlation between the in vitro and in vivo data sets with % similarity of 99.77 % as coefficient of regression.
- Stability Studies were performed by Dynamic Vapor Sorption (DVS) Analysis and Accelerated Stability Studies. DVS studies proved that FPT-LP is non-hygroscopic. Accelerated stability studies were carried out for 3 months according to ICH Q1A(R2) which determined that FPT-LP cocrystal and the developed capsule formulation is stable. The predicted shelf life is of 2 years.
- A complete patent has been filed for the work done to protect the invention. (Application Number: IN 202221043126, Date of Filling: 13-Jul-2023).

Publication

1. **Priyal Shah**, Anuradha Gajjar, “Development, Validation and Application of RP-HPLC Method for estimation of Fimasartan Potassium Trihydrate”, *International*

Journal of Research and Analytical Reviews, 2022, Vol:09, Issue:03, ISSN 2348-1269 (Accepted)

2. **Priyal Shah**, Anuradha Gajjar, "Development and Validation of Stability Indicating RP-HPLC Method for Efonidipine Hydrochloride ethanolate", *International Journal of Innovative Research in Technology*,2021, Vol:08, Issue:06, ISSN 2349-6002 (Accepted)
3. Jalpa Suthar**, Priyal Shah**, Krupali Patel, Pankti Pathak "A Study on Drug Utilization in Hypertension in Medical Care Hospital", *Indian Journal of Public Health Research and Development*,2020, Vol:11, Issue:03, ISSN 0976-5506 (Accepted)
4. Manan Patel, Romansha Beri **Priyal Shah**, "Nasal Drug Delivery System and it's Application", *International Journal of Research and Analytical Reviews*, 2021, Vol:08, Issue:02, ISSN 2348-1269 (Accepted)
5. Manan Patel, Nirav Shah, Dhruvi Dave, **Priyal Shah**, "A Review on Effectivity of Plant Based Vaccines in The Treatment of Viral Disease", *Journal of Drug Delivery and Therapeutics*, 2021, Vol:11, Issue:03, ISSN 2250-1177 (Accepted)

Communicated

1. Article: **Priyal Shah**, Anuradha Gajjar, "A promising approach for tailoring properties of API by Crystal Engineering" communicated to *Journal of Pharmaceutical Sciences*.
   Current Status- review is in process.
2. Book Chapter: "Theranostics Inorganic Nanohybrids: An Expanding Horizon" communicated to NK Jain.

Patents (if any): Yes, Complete Patent has been filled. Details are as below:

Patent No: IN 202221043126, Date of Filling: 13-Jul-2023, Title: Novel Cocrystals of Fimasartan and Process Thereof

References

1. Aitipamula SK, Banerjee RJ, Bansal AS, Biradha KT, Cheney MP, Choudhury AM, "Polymorphs, salts and co-crystals: What's in a name?" *Crystal Growth and Design* **2012,** 12, 2147-52.
2. USFDA guideline, "Co-crystal information", Oct-2019.

3. Thakuria RK, Sarma BM, “Drug-Drug and Drug-Nutraceutical Cocrystal/Salt as Alternative Medicine for Combination Therapy: A Crystal Engineering Approach.” *Crystals* **2018**, *8*(2), 101-107.
4. Vioglio MP,Chierotti MS,Gobetto R, “ Pharmaceutical aspects of salt and cocrystal forms of APIs and characterization challenges.” *Advanced Drug Delivery Reviews* **2017**, 117, 86-110.
5. Gadade DT, Pekamwar SA “Pharmaceutical Co-crystals: Regulatory and Strategic Aspects, Design and Development.” *Advanced Pharmaceutical Bulletin* **2016,** 6(4), 479-494.
6. Cheney ML “Coformer selection in pharmaceutical cocrystal development: a case study of a meloxicam aspirin cocrystal that exhibits enhanced solubility and pharmacokinetics.” *Journal of Pharmaceutical Sciences* **2011,** 100, 2172–2181.
7. Gadade DJ , Kulkarni DK, Rathi PS, Pekamwar SM, Joshi SH “Solubility Enhancement of Lornoxicam by Crystal Engineering.” *Indian Journal of Pharmaceutical Sciences* **2017**, 79(2), 277-286.
8. Newman AM, Edens SJ, Zografi GK “Coamorphous Active Pharmaceutical Ingrediente Small Molecule Mixtures: Considerations in the Choice of Co-formers for Enhancing Dissolution and Oral Bioavailability.” *Journal of Pharmaceutical Sciences* **2017,** 107 (18), 5-17.
9. Jafari MJ, Padrela LM, Walker GR, Croker DH “Creating Co-crystals: A Review of Pharmaceutical Cocrystal Preparation Routes and Applications.” *Crystal Growth and Design* **2018,** 18, 6370-6387.
10. Kumar SA, Nanda AK “ Pharmaceutical Co-crystals :An overview.” *Indian Journal of Pharmaceutical Sciences* **2017,** 79(6), 858-871.
11. Anti-Hypertensive Drug Classification Available: https://pharmabizz.wordpress.com/2020/05/20/antihypertensive-drugs-classification/ Accessed on: 19 November 2020.
12. Drugbank, “Fimasartan Potassium Trihydrate Drug Profile”, Available from: https://go.drugbank.com/salts/DBSALT001281Accessed on: 12 November 2020.
13. Pubmed, Fimasartan Potassium Trihydrate Drug Profile. Available here: https://pubchem.ncbi.nlm.nih.gov/compound/Fimasartan-Potassium-Trihydrate#section=Chemical-Gene-Co-Occurrences-in-Literature. Accessed on: 02 December 2020

14. Netmeds, Fimasartan brands. Available: https://www.netmeds.com/prescriptions/fimagen-60mg-tablet-10-s. Accessed on: 22 October 2019
15. Kimia Biosciences Ltd. Available: https://www.kimiabiosciences.com/products/fimasartan-trihydrate-potassium/ .Accessed on: 12 November 2020
16. Kumar SA, Nanda AB " Pharmaceutical Co-crystals :An overview." *Indian Journal of Pharmaceutical Sciences* **2017,** 79(6), 858-871.
17. Bolla GM, Nangia AK "Pharmaceutical co-crystals: walking the talk." *Chemical Communications* **2016**, 52(54), 8342-60.
18. Fukte SJ, Wagh MK, Rawat ST "Coformer Selection: An Important Tool In Co-crystal Formation.**"** *International Journal of Pharmacy and Pharmaceutical Sciences* **2014,** 6(7), 9-14.
19. Jafari ML, Padrela LS, Walker GK, Croker DJ "Creating Cocrystals: A Review of Pharmaceutical Cocrystal Preparation Routes and Applications." *Crystal Growth and Design* **2018,** 18, 6370-6387.
20. Saxena MJ, Kuchekar BM "Co-crystal Formulation, Characterization and Evaluation Study." *Indian Journal of Pharmaceutical Sciences* **2013,** 602-606.
21. Yamashita HJ, Hirakura YM, Yuda MN, Toshio TS "Detection of Co-crystal Formation Based on Binary Phase Diagrams Using Thermal Analysis." *Springer* **2013**, 30, 70–80.
22. Douroumis DM, Steven AK, Ross SV, Nokhodchi AH "Advance methodologies for co-crystal synthesis." *Elsevier* **2017,** 5(6)**,** 111- 117.
23. Gadade DM, Pekamwar SJ "Pharmaceutical Co-crystals: Regulatory and Strategic Aspects, Design and Development." *Advanced Pharmaceutical Bulletin* **2016,** 6(4), 479–494.
24. Chadha R, Bhandari S,Haneef J, Khullarb S,Mandal S;"Cocrystals of telmisartan: characterization, structure elucidation, in vivo and toxicity studies." *CrystEngComm* **2014**, 16, 8375-8389
25. Abdelquader M, Essa,E, Maghraby G;"Inhibition of Co-Crystallization of Olmesartan Medoxomil and Hydrochlorothiazide for Enhanced Dissolution Rate in Their Fixed Dose Combination." *PharmSciTech* **2019**, 20, 3.

26. Thenge R, Patel R, Kayande N, Mahajan N "Cocrystals of Valsartan preparation and characterization." *International Journal of Pharmacy and Biological Sciences;* **2019,**9 (4) 274-283.
27. Agrawal K, Gandhi L, Bhajipale L "UV Spectrophotometric Method Development and Validation of Fimasartan Drug and Its Tablet Formulation" Asian Journal of Pharmaceutical Research and Development 2019; 7(5): 26-30.
28. Whoog C, Shawmen T, Klefne ST, Manchow J,"Evaluation of stability and simultaneous determination of fimasartan and amlodipine by a HPLC method in combination tablets" Asian Journal of Pharmaceutical Sciences 9(3)2014, 123-128.
29. Pandya C, et al. "Validated Stability Indicating RP-HPLC Method for the determination of Fimasartan in presence of degradation products" *Indo American Journal Of Pharmaceutical Research***2017,**7(11)
30. Gadade DM, Pekamwar SK "Pharmaceutical Co-crystals: Regulatory and Strategic Aspects, Design and Development" *Advanced Pharmaceutical Bulletin* **2016,** 6(4), 479–494.