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Organic Acid Coformer Selection for Lopinavir by Cosmo-Rs Screening Approach Using Solvent Evaporation Method and Characterization Thereof

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ABSTRACT
LPV is a poorly water-soluble drug (7µg/ml) with reduced bioavailability due to extensive metabolism by CYP3A4. Coformer selection is an essential part of cocrystal formation, which can be accomplished through virtual screening approaches such as COSMO-RS. Organic acids, such as oxalic acid, salicylic acid, glutaric acid, caffeine and nicotinamide, were found to have high negative H^E values and were selected as coformers. Batches were prepared using slow solvent evaporation, and the resulting product was characterized. The study found that the solubility of LPV with coformers enhanced. However, FTIR, DSC and PXRD studies showed that there was no cocrystallization with LPV, suggesting that the enhancement of solubility was due to the presence of the coformers there could be change in lattice energy of LPV after solvent evaporation. Therefore, it is suggested that different coformers, such as amino acids, be investigated for cocrystal formation with LPV for further enhancement of solubility and dissolution.

KEY WORDS: Cocrystals; Lopinavir; Organic acids; Slow solvent evaporation

I. INTRODUCTION

Enhancing the solubility of poorly water-soluble drugs is one of the pharmaceutical industry's ongoing concerns.[1]Because newly manufactured drugs are larger and more lipophilic molecules, they are less water-soluble. According to official figures, 40 % of currently available drugs and 70–90 % of drugs in development are poorly soluble. Thus, increasing the solubility of these drugs when delivered orally is necessary to achieve optimal bioavailability.[2]

Particle size reduction, amorphization, cyclodextrin complexation, solid dispersion, nanoparticles, and other approaches are routine to overcome solubility problems.[2]Multicomponent systems are a practical and widely used method for increasing a crystalline API's solubility profile.[3]Conventional design of crystalline forms of APIs within a multicomponent system involves, but is not limited to, the use of salts, solvates, and hydrates.Among all solubility enhancement approaches, cocrystals have the most advantages, such as the ability to produce cocrystals with any molecule and the lack of bond breaking or formation.[4][5]

Pharmaceutical cocrystals are "crystalline materials formed of two or more distinct molecules/ingredients API and co-formers with specified stoichiometric ratio within the same crystal lattice linked by non-ionic and noncovalent bonds," [2][6]

Recent advancements in cocrystal engineering have ignited interest in developing next-generation formulations for improved drug delivery. The potential of cocrystals is reported via different researchers in fine-tuning physicochemical features of problematic medications, such as solubility, dissolution performance, hygroscopicity, and compressibility.[7]

A cocrystal is a new chemical entity of a drug substance synthesized by weak forces (noncovalent and non-ionic bonds) such as hydrogen bonds, π bonds, and van der Waals bonds

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in a unique crystal lattice under ambient conditions.[8][2]

Finding an appropriate co-former for successful cocrystal development a is a very difficult task.co-former interacts with API non ionically in crystal lattice it should not -toxic and, no side effects and non-volatile. The screening of co-former is time-consuming and costly so alternative techniques are used to find appropriate co-former for API.[6][9]

Another significant component of co-crystallization is finding a suitable solvent, which has an impact on the shape and size of the forming crystals, polymorphism, and overall yield. The solvent is generally selected based on solubility measurements, that emphasizing the importance of knowledge an API's solubility in a certain solvent.[9]

Solution crystallisation, mechanical grinding, and melt crystallisation are all options for producing a co-crystal. Solution crystallisation is the primary method for producing co-crystals in the pharmaceutical industry due to its simplicity and high productivity.[9][10]

Therefore, in this work, lopinavir (LPV)[11], a drug molecule classified into BCS class IV with low aqueous solubility and low permeability was subjected to co-crystallization for improvement in its solubility and dissolution. LPV ((2S)-N-[(2S,4S,5S)-5-[[2-(2,6-dimethylphenoxy) acetyl] amino]-4-hydroxy-1,6-diphenylhexan-2-yl]-3-methyl-2- (2-oxo-1,3-diazinan-1-yl) butanamide) is protease inhibitor and classified into anti-retroviral agent, under brand name keletra with combination of ritonavir. Available dosage form of LPV with combination of ritonavir are oral suspensions and soft gel capsules. LPV is white amorphous powder, practically insoluble in water and soluble in methanol, ethanol and acetonitrile. LPV neutral drug pKa 2.88[11] and LogP value of LPV 1.7 that reflects its poor drug solubility in water.Many approaches for enhancement of solubility of LPV reported include use of solid dispersion, nanoparticles, microspheres, self-nano emulsified drug delivery, cyclodextrin complexation, liposomes etc.[11]

The aim of study was to formulate LPV cocrystals and to perform comprehensive characterization of prepared cocrystals. Objective of work was to check possibility of achieving solubilityand dissolution enhancement characteristics using organic acids screened through COSMO-RS using slow solvent evaporation method.

II. EXPERIMENTAL SECTION

2.1 Materials

Lopinavir (LPV) was supplied from Bharat ParenteralsPvt. Ltd (Vadodara, India). Salicylic acid, Oxalic acid, Caffeine, Nicotinamide and Glutaric acid were purchased from ChemdyesCorporation (Rajkot, India). Methanol of analytical grade was purchased from Krishna scientific traders (Rajkot, India).

2.2 Method

2.2.1 Screening of cocrystals of coformers

COSMO-RS (AMS COSMO-RS 2021.102) allows users to quickly screen for co-formers that could form a cocrystal with a certain API. COSMO-RS quickly performs three calculations to obtain Hex: one for each of the pure component's A and B, and one-mixture calculation for A and B in the subcooled liquid containing the mixture of A and B with the provided stoichiometry. The results are sorted by excess enthalpies; the compounds with the highest propensity to co-crystallize are at the top of the list.[6][9]Here LPV was screened with different organic acid for preliminary batches coformer selection.

2.2.2 Preparation of LPV cocrystals

Solvent evaporation method[15], where drug and co-former solubilize in suitable solvent or solvent mixture and then stirring at 600 RPM on magnetic stirrer for 45 min, is carried out initially. Pour liquidmixture into petri-plate, cover with funnel, and allow solvent to evaporate and collect the dried product. There was a patch formation after evaporation of solvent.

Hence, slow solvent evaporation[12]method was used for further batches preparation, in that drug and co-former solubilize in solvent or solvent mixture and stirring at 600 RPM on magnetic stirrer for 45min.Solvent is allowed to slowly evaporate to obtain completely dry product that further used for cocrystal characterization.

2.3 Characterization of cocrystals

2.3.1 Microscopic evaluation

A microscope was used to undertake a microscopic examination of the pure drug and the produced cocrystal for preliminary examination. In 10x, pure drug and prepared batches were observed, and morphological changes were compared to pure drug microscopic features.[9]

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2.3.2 Fourier Transform Infra-Red Spectroscopy (FT-IR) study

A Fourier Transform Infrared Spectrometer was used to record the FTIR spectra of the pure drug, co-former, and formulation. The fingerprint measurement ranged from 400 to 4000 cm^{-1}. The amount of 99 mg KBr crystal and 1 mg sample were mixed and compressed to be a disc using a hydraulic presser. The pellet was mounted on the holder, and the infrared spectral measurements were carried out. The technique involved subjecting a sample to a KBr press and compressing the disc in a hydraulic press at a pressure of 5t for 5 minutes. The nature and intensity of solvent interaction with cocrystals can be determined using infrared (IR) spectroscopy of crystalline samples, which offers a fingerprint pattern of the unique crystalline materials. [13][14]

2.3.3 Differential scanning colorimetry

Differential scanning colorimetry was used to construct the DSC thermogram. Internal standards of indium (156 ^{0}C), tin (232^{0}C), and zinc (419.5^{0}C) are used to calibrate the device. 4-10 mg of sample were placed in an aluminium pan and sealed. The probes were heated at a rate of 10^{0}C/min from 30 to 300 ^{o}C using nitrogen as a purge gas. It is one of the most common ways to confirm cocrystal formation. The melting point, endothermic peak and exothermic peak was noticed in the thermogram. It is also used for determination of degree of crystallinity. Data were processed and overlay of drug, co-former and product was generated by using TA60 software. [9][13]

2.3.4 Powder X-ray diffraction

The most common method for characterizing cocrystals is PXRD. PXRD was used to analyse pure drug, co-former and cocrystals. The powder diffraction pattern was collected from 2θ = 5^0 to 40^0 at ambient temperature at the step and scan speeds of 0.01◦ and 3◦ min^{-1}, respectively, using a Cu-Kα source at 45 kV and 200 mA. [9][13]

2.3.5 Saturation solubility study

In 10 ml 0.1 N hydrochloric acid, add an excess of LPV and crystal, separately. Shake the samples for 48 hours at 37°C and 150 RPM in a rotary shaker. After 48 hours, filter the solution through syringe filter and dilute using 0.1 N hydrochloric acid, and spectrophotometrically measure at 260 nm against 0.1N hydrochloric acid as a blank. Repeat three times and note down the concentration**.** [15]

III. RESULT AND DISCUSSION

3.1 Screening of co-formers using COSMO-RS modeling suite

Here, co-formers were screened by COSMO-RS software based on their H^E values.As per graph nicotinamide, gallic acid, benzoic acid, urea, glutaric acid, succinic acid, malic acid and stearic acid were showing higher negative enthalpy value that suggest more chances of cocrystal formation. AMS gives the idea based on H^E value of co-former based on their stoichiometric ratio but it was not confirmative for co-crystallization. **(Error! Reference source not found.)**[6][9] Based on the data LPV was formulated preliminarily with screened coformers. It is not possible to date to predict and develop computational model with complexities involved in nucleation and crystal growth and there comes the role of COSMO-RS. It computes the excess enthalpy of stoichiometric mixtures created after reaction between drug and coformer.

The batches were prepared by solvent evaporation method as discussed above in experimental section and FTIR, DSC and PXRD performed their characterization. First, the below combinations were prepared by solvent evaporation method that yielded a patch in petriplate. After repetitive experimentation and careful observation, it was concluded that initially LPV and coformer, salicylic acid and oxalic acid, starts crystalizing out individually as was observed under microscope. Soon after exposure to ambient conditions, LPV starts absorbing moisture and finally patch as sticky mass was obtained.Therefore, slow solvent evaporation method used thereafter and B1 to B8 were prepared we yielded crystalline product that subjected to characterization. **(**

Table *1)*In order to decrease the rate of evaporation beaker was covered with aluminum foil having 1 cm diameter opening during 45 min stirring and then when remains were transferred to

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the petri plate it was covered with inverted funnel untilcompletely dry product was obtained.

Table 1 Preliminary batches prepared based on COSMO-RS screening

Sr.no	Drug (LPV) (mg)	Coformer (mg)	Molar ratio	Solvent
B1	125.7	Salicylic acid (27.6 mg)	1:1	Methanol (5 ml)
B2	125.7	Oxalic acid (15 mg)	1:1	Methanol (5 ml)
B3	125.7	Oxalic acid (30 mg)	1:2	Methanol (5 ml)
B4	125.7	Oxalic acid (45 mg)	1:3	Methanol (5 ml)
B5	125.7	Caffeine (38.2 mg)	1:1	Methanol (5 ml)
B6	125.7	Caffeine (155.2 mg)	1:4	Methanol (5 ml)
B7	125.7	Nicotinamide (12 mg)	1:0.5	Methanol (5 ml)
B8	125.7	Glutaric acid (26.42 mg)	1:1	Methanol (5 ml)

3.2 Microscopic characterization of prepared batches

The microscopic characterization was performed for prepared batches and the results compared with LPV microscopic features. Microcopy gives the initial confirmation as to whether the particles have changed form and morphology or not.[9]Microscopy of prepared batches clearly indicated some degree crystalline structure of product as compared to drug. **(Figure 1)**Further analyze batches using FTIR spectra.

3.3 Interpretation of FTIR spectra

For cocrystals, the FTIR investigation is an initial assessment to detect whether there is any hydrogen bonding taking place or not between reactive functional groups. The simultaneous analysis of the spectra of the individual components of cocrystals is known as Fourier-transform IR (FTIR). Due to the presence of hydrogen bonding, the spectra of the cocrystal differ from that of the component mixture.[9]

FTIR do have its limitations though as due to the intense absorption of excipients or other sample components sometimes, quantifying cocrystals by IR becomes problematic, since most excipients form bonds with a large dipole moment, and multiple absorptions occur that are difficult to separate and assign to each component.

Here,LPV showed characteristics picks at 3373 cm^{-1}, 3287 cm^{-1} and 1662 cm^{-1} corresponding to the stretching vibration of -OH, -CH_2 and amide C=O. Salicylic acid showed characteristics peaks at 3226cm^{-1} and 2991-2848 cm^{-1}corresponding to -OH and -CH stretching. The prepared formulation had similar spectra to LPV and salicylic acid, which suggests there was no interaction between LPV and salicylic acid. **(Figure 2)**

Oxalic acid showed characteristics picks at 3412 cm^{-1}, 1641 cm^{-1} and 1222 cm^{-1} corresponding to stretching vibration of -OH, -C=O and -C-O. The FTIR spectra of prepared batch showed similarity with LPV that suggests there is no interaction between LPV and oxalic acid, no hydrogen bonding between drug and co-former. **(Figure 3)**

Caffeine showed characteristics picks at 3100-3000 cm^{-1}, 3347 cm^{-1}, 1690 cm^{-1} and 1356cm^{-1} corresponding to stretching vibration of nitrogen heterocyclic aromatic compound, primary aliphatic amine, -C=O and -C-N stretch. The prepared batch had similar spectra to LPV, which suggests there was no interaction between LPV and caffeine. **(Figure 4)**

In the batch of LPV:nicotinamide,nicotinamide showed characteristic peak at 3350 cm^{-1}, 1593 $cm^{-1}$and 3062 cm^{-1} corresponding to the -N-H stretching, -C=N stretching and C-H ring stretching. The prepared batch had similar spectra to LPV, which suggests there is no interaction between LPV and nicotinamide. **(Figure 5)**

Glutaric acid showed characteristics peaks at 3032 cm^{-1}, 1679cm^{-1} and 2898cm^{-1} corresponding to the stretching vibration of -OH, -C=O and -CH stretching. The prepared batch had similar spectra to LPV, which suggests there is no interaction between LPV and glutaric acid. **(Figure 6)**

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3.4 Saturation solubility study of prepared batches

Table 2 Saturation solubility data of prepared batches based on COSMO-RS

Batch no.	Batch	Conc. (µg/ml)
	LPV Pure	20.67±2.57
B2	LPV: OXA (1:1)	30.24±1.83
B3	LPV: OXA (1:2)	32.15±0.98
B4	LPV: OXA (1:3)	39.15±2.21
B5	LPV: CAF (1:1)	21.20±1.75
B6	LPV: CAF (1:4)	36.52±1.20
B7	LPV: GLU (1:1)	28.43±1.32
B8	LPV: NIC (1:0.5)	31.41±0.42

Saturation solubility of LPV and prepared batches was carried out in 0.1 N HCl. Three times the procedure was carried out and results obtained were as reported in **(Table 2)**. LPV showed saturation solubility of 20.67 µg/ml after 48 hrs. Compare to that B2 to B8 batches shows improved solubility. Highest solubility amongst prepared batches was found to be in B4 containing LPV:OXA ratio 1:3 while B5 having LPV: CAF showed slight change in saturation solubility with difference of only 0.53 µg/ml in average solubility value. Batches were further investigated using DSC and PXRD studies.

3.5 DSC study

One of the most used methods for confirming cocrystal formation is DSC. The thermogram reveals the melting point, endothermic peak, and exothermic peak. It is used to figure out how much crystallinity is there. If there is no peak shifting or generation between the exothermic peaks of the drug and the co-former, but the peak energy is lower in comparison to the drug and the co-former, co-crystallization is expected.[9][13]

The thermogram of LPV, salicylic acid, LPV: salicylic acid (1:1) showed **(Figure 7A)** endothermic peak at 97.84^{o}C, 160.04^{o}C and 158.42^{o}C, respectively. There was only2^{o}C change in peak with reference to salicylic acid and no distinguishable peak of LPV observed. There was reduction in peak intensity as well but at the same time peak of LPV vanished completely. No conclusion was possible on cocrystallization from DSC data of LPV: salicylic acid.Thermogram of LPV, oxalic acid, LPV: oxalic acid (1:1) showed no shifting of peaks or reduction of heart energy so no co-crystallization **(Figure 7B)**.

The thermogram of LPV and caffeine showed endothermic peaks at 97.84^{o}C and 268.19^{o}C. LPV: caffeine (1:1) showed two different peaks that have lower values as compare to LPV and caffeine (Fig.8C). This warrants further investigation by PXRD study.The thermogram of LPV, caffeine, LPV: caffeine (1:1) showed endothermic peak at 97.84^{o}C, 268.19^{o}C and 228.38^{o}C, respectively**(Figure 7C)**. The thermogram of LPV, caffeine, LPV: caffeine (1:4) showed endothermic peak at 97.84^{o}C, 268.19^{o}C and 101.07^{o}C, respectively**(Figure 7D)**.The single peak of formulation between values of LPV and caffeine may suggest interaction between LPV and caffeine. This requires detailed investigation of interaction.

The thermogram **(Figure 7E)** of LPV and nicotinamide, showed endothermic peak at 97.84^{o}C and 131.20^{o}C. LPV: nicotinamide (1:0.5) peak at 92.41^{o}C suggests interaction leading to a lower value peak compared to LPV and nicotinamide both. First peak of glutaric acid was near 74^{o}C due to change of β form of glutaric acid (low temperature) to α form (high temperature). Second peak was the known melting point of high temperature (α) form of glutaric acid. In case ofLPV: glutaric acid (1:1) (Fig.8F)peaks were nowhere to see. This may be due to conversion of crystalline form to amorphous form,

Based on literature review, there were many cases with no significant change in FTIR and DSC butcocrystals (4% cases as per CDS data) were observed.The PXRD study is of great help in determining cocrystal formation with accuracy.[9]Therefore, further study was carried out to confirm the cocrystallization occurred or not that evaluated by PXRD study of prepared batches.

3.6 PXRD study

PXRD is most reliable confirmative data analysis for cocrystals. The prepared batches PXRD data**(**

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Table *3*) suggests there is no significant change or generation of any new peak other than drug and coformer that suggests there is no cocrystallization in these coformers.[13]

Peaks	LPV	LPV: OXA (1:1)	LPV: OXA (1:2)	LPV: OXA (1:3)	LPV: CAF (1:1)
a	10.49^0	10.38^0	10.58^0	10.68^0	10.19^0
b	15.38^0	15.28^0	15.58^0	15.38^0	15.28^0
c	18.8^0	18.47^0	18.8^0	19.47^0	19.17^0
d	22.6^0	22.36^0	22.56^0	22.96^0	22.86^0

Table 3Crystallographic data of LPV, LPV: OXA and LPV: CAF

The crystallographic data of batches prepared with COSMO-RS software screening showed no significant change in PXRD peaks**(Figure 8)** that proves no cocrystallization was occurred between organic acid and LPV along with different stoichiometric ratio.

Here the enhancement of saturation solubility is due to presence of coformer and that interfere with abs of that batches may chances that coformer/s absorption maxima interfere with drug absorption maxima that leads to higher abs and higher fold enhancement to solubility. As the study of crystallographic behaviour of prepared batches showed no change in PXRD that conclude no cocrystallization was occurred.

Cocrystallization of poorly water-soluble drugs is one of the novel approaches to improve their aqueous solubility or dissolution characteristics. Many researches synthesized cocrystal of BCS class II & IV drugs with appropriate coformer. In above reported work, cocrystal of LPV (BCS class IV drug) were prepared with different coformers with the help of virtual screening program COSMO-RS. The results obtained by formulating cocrystals of LPV with organic acid coformer by using slow solvent evaporation method. The yielded dry product subjected to characterization that showed negative results. So, we concluded that the virtual screening method COSMO-RS and slow solvent evaporation method is not suitable for formulating LPV cocrystals. That open the window for researcher to formulate cocrystals of LPV by using appropriate method for screening of coformer and then prepare cocrystals with suitable method. Numerous coformer screening methods are available like ΔpKa method, Hansen solubility parameter method, supramolecular synthon method etc. and various preparation methods for cocrystals synthesis were reported like solvent assisted grinding, solvent evaporation, neat grinding, spray drying etc. Now a days the area of coformer/s were shifted to amino acid due to its less toxic, improved physicochemical properties of API and supporting green method for cocrystallization of API.

IV. CONCLUSION

In the present research work, we tried to prepare cocrystals of LPV by comprehensive screening of coformer/s with the use of COSMO-RS software. The prepared batches with screened coformer/s showed negative results in FTIR. DSC, PXRD and saturation solubility. The FTIR analysis showed no change in peaks appearance and wavenumbers that suggested no hydrogen bonding between LPV and coformer/s. DSC thermograms observation showed no shifting of peaks or reduction of specific heat energy based on that we concluded that there is no cocrystallization was occurred. After that negative data of DSC and FTIR final confirmative data PXRD also showed negative results.Therefore, organic acids are not suitable coformer/s for cocrystallization of LPV using slow solvent evaporation.

V. FUTURE OUTLOOK

Cocrystallization of poorly water-soluble drugs is one of the novel approaches to improve their aqueous solubility or dissolution characteristics. Lots of researches are focused on synthesizing cocrystal of BCS class II & IV drugs with appropriate coformer. In above reported work cocrystal of lopinavir (BCS class IV drug) were prepared with different coformers with the help of virtual screening program COSMO-RS. The results obtained by formulating cocrystals of lopinavir with organic acid coformer by using slow solvent evaporation method. The yielded dry product subjected to characterization that showed negative results. So, we concluded that the virtual screening method COSMO-RS and slow solvent evaporation method is not suitable for formulating lopinavir cocrystals. That open the window for researcher to formulate cocrystals of lopinavir by using appropriate method for screening of coformer and then prepare cocrystals with suitable method. There

were numerous coformer screening methods were available in that ΔpKa method, Hansen solubility parameter method, supramolecular synthon method etc. and various preparation methods for cocrystals synthesis were reported like solvent assisted grinding, solvent evaporation, neat grinding, spray drying etc. Now a days the area of coformer/s were shifted to amino acid due to its less toxic, improved physicochemical properties of API and supporting green method for cocrystallization of API.

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Figures

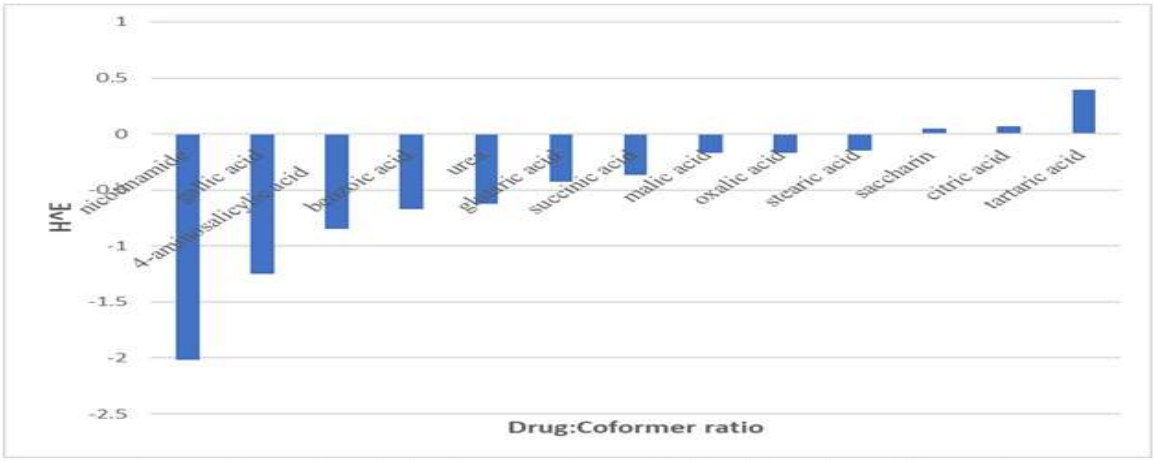

Figure 1 Screening of Co-former using AMS COSMO-RS modeling suite

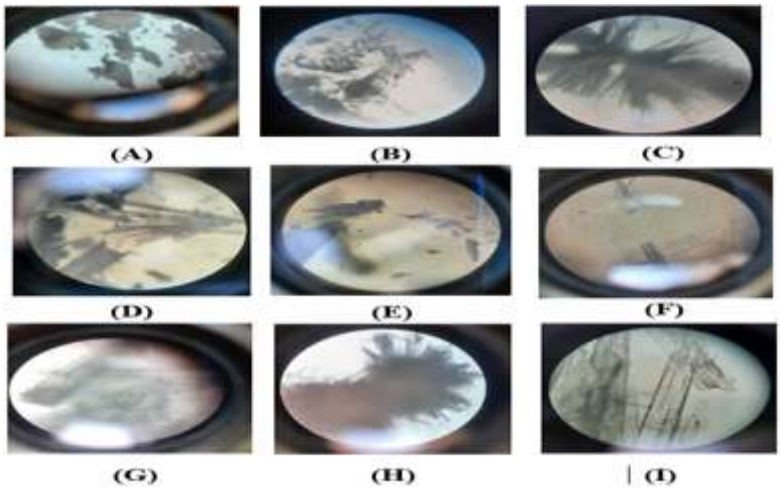

Figure 1 Microscopical Characterization of Prepared batches (COSMO-RS)
(A) Pure drug **(B)** LPV: SLA (1:1) **(C)** LPV: OXA (1:1) **(D)** LPV: OXA (1:2) **(E)** LPV: OXA (1:3) **(F)** LPV: CAF (1:1) **(G)** LPV: CAF (1:4) **(H)** LPV; NIC (1:0.5) **(I)** LPV: GLA (1:1)

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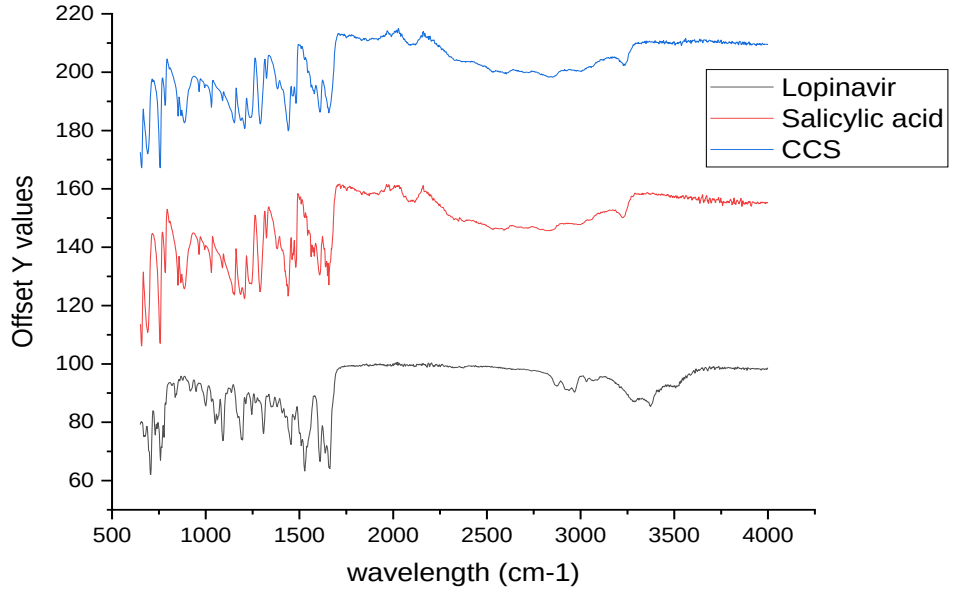

Figure 2 FTIR study of LPV: SLA (1:1)

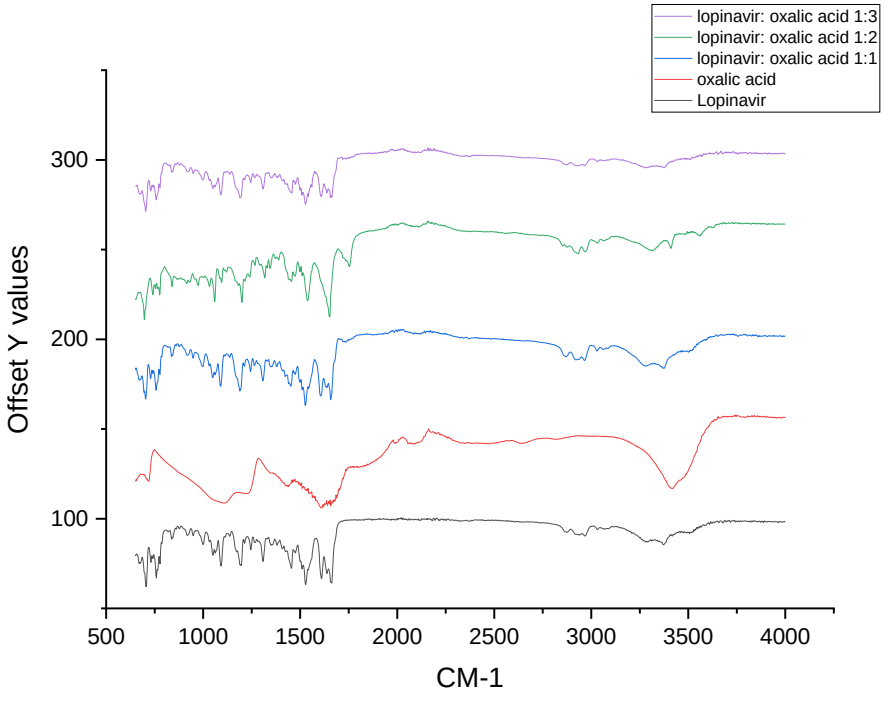

Figure 3 FTIR study of LPV: OXA with different stochiometric ratio

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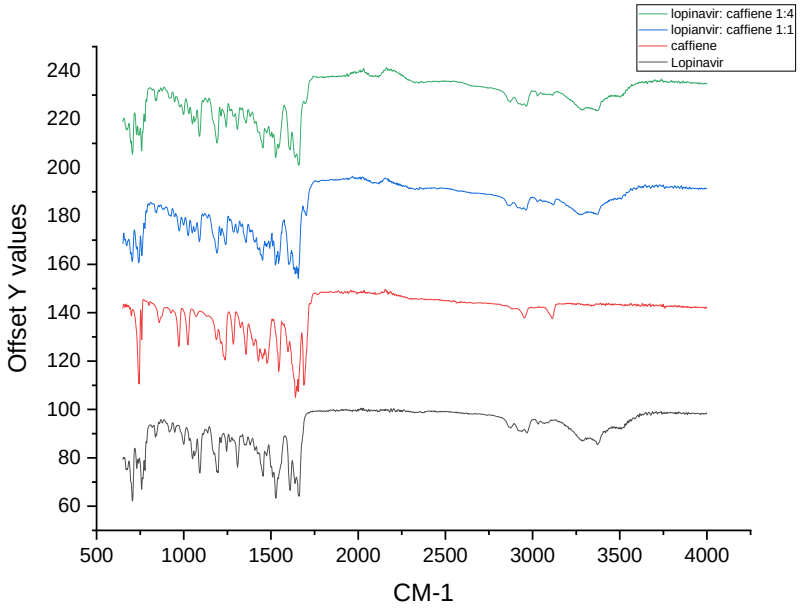

Figure 4 FTIR study of LPV: CAF with different stochiometric ratio

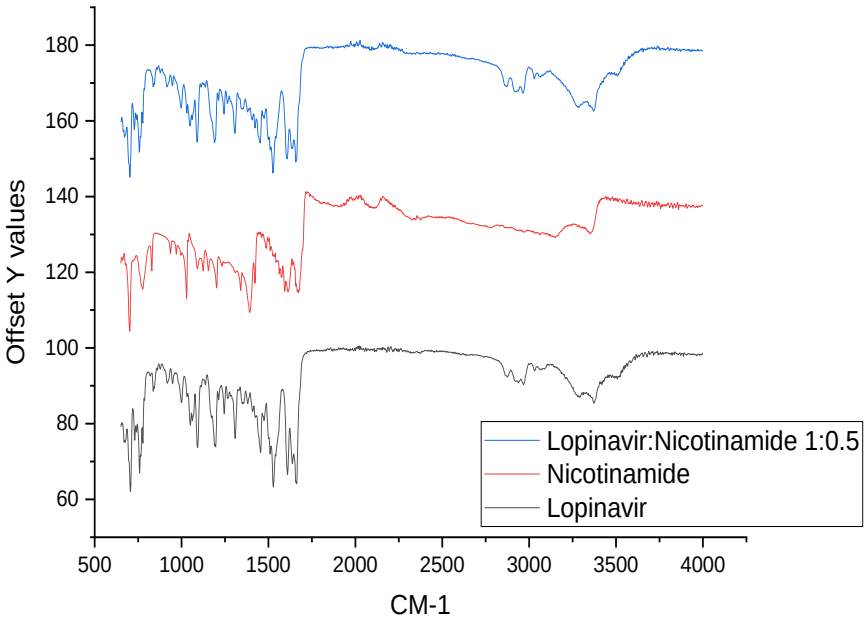

Figure 5 FTIR study of LPV: NIC (1:0.5)

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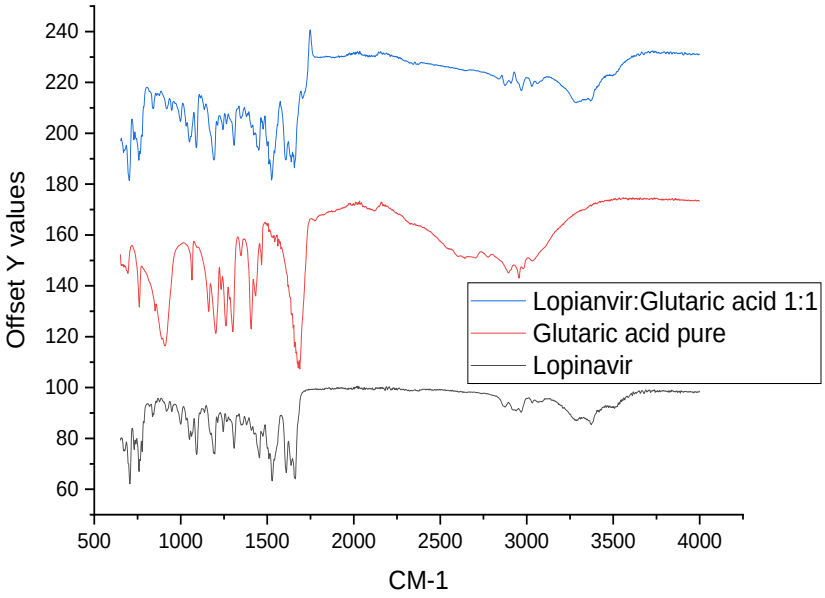

Figure 6 FTIR study of LPV: GLA (1:1)

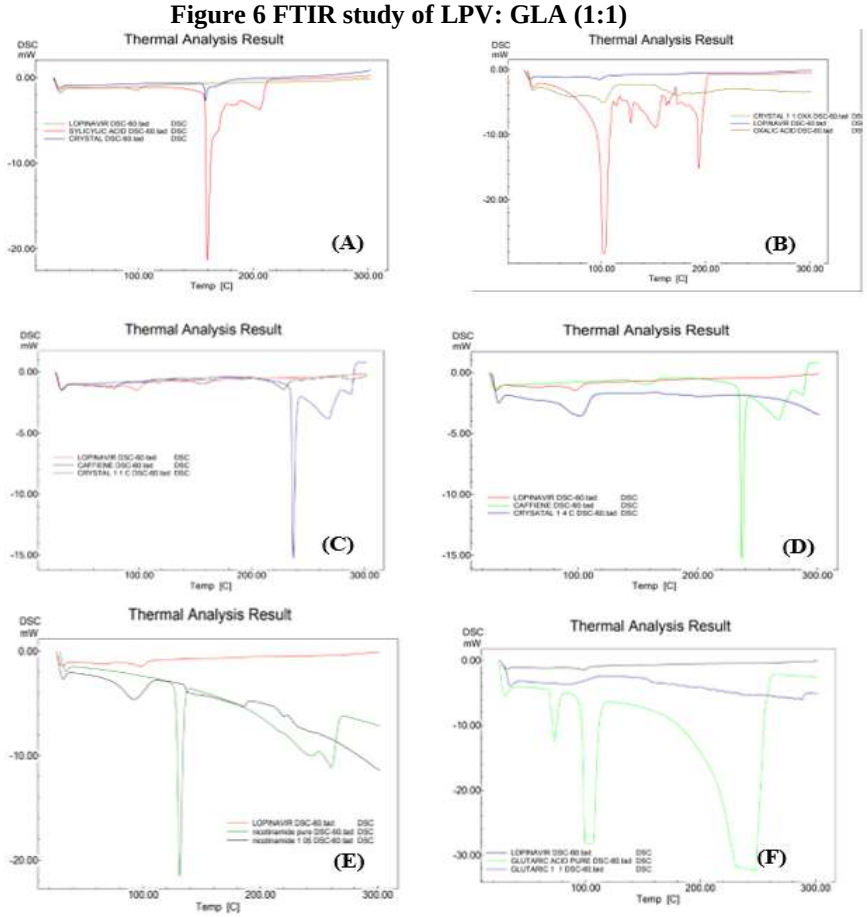

Figure 7 DSC study of prepared batches based on COSMO- RS screening
(A) LPV: SLA (1:1) (B) LPV: OXA (1:1) (C) LPV: OXA (1:2) (D) LPV: CAF (1:1) (E) LPV: CAF (1:4) (F) LPV; NIC (1:0.5) (G) LPV: GLA (1:1)

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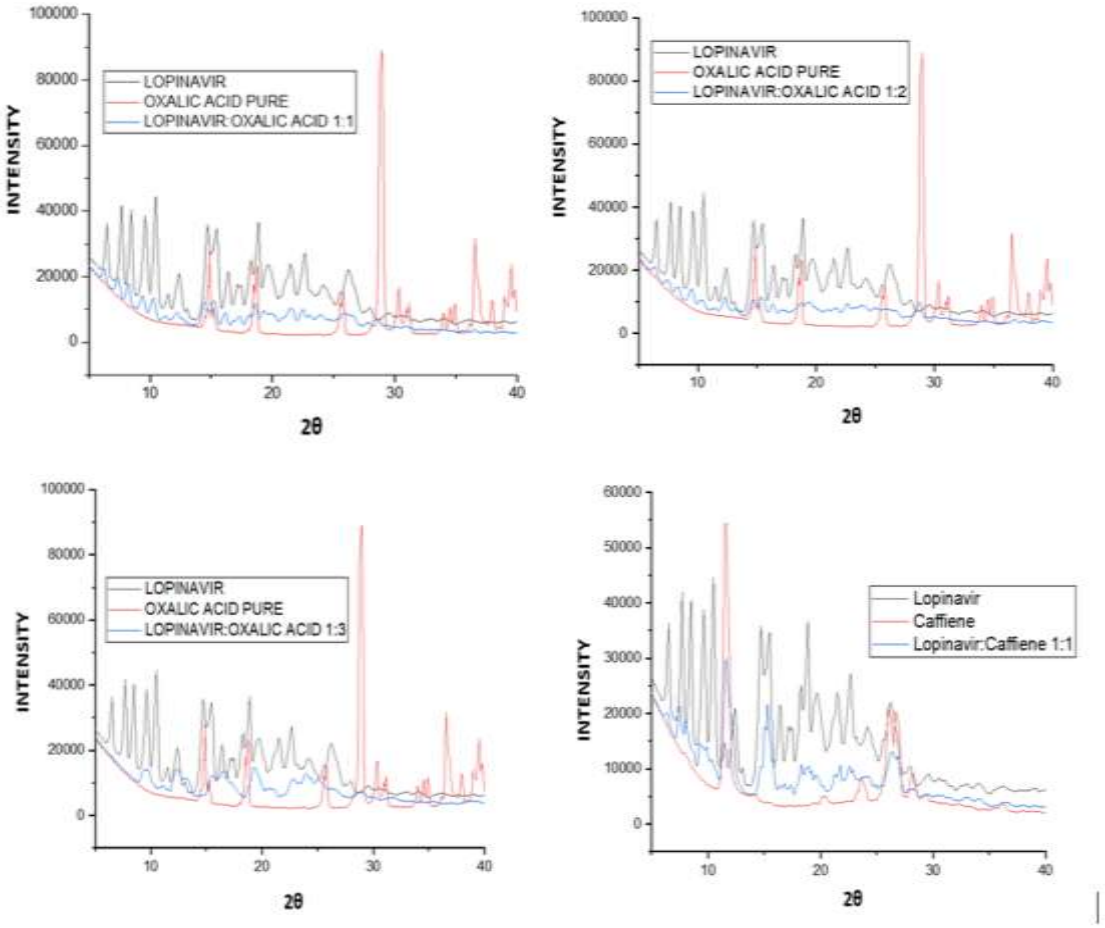

Figure 8 Experimental Powder X-ray diffraction of LPV, OXA, CAF, LPV: OXA cocrystals and LPV: CAF cocrystals based on COSMO-RS screening