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Creating of CO- Crystal

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I INTRODUCTION

An important goal of solid state pharmaceutical development is to increase drug solubility while maintaing a stable form.Co-crystals are an emerging a solid state form to change physico-chemical and bio-pharmaceutical co-crystal drug properties.A pharmaceutical co-crystal is difined as multi-component molecular complex comprising of a solid API and co-former[which is safe for human consumption]that interact through non-covalent interactions in a definite stoichiometric ratio with-out compromising the structural intrgrity but improving the solubility.

Co-crystal former may be an excipient or another drug. Depending on the nature of the second component. Some of the co-crystals formed had higher and some lower melting points as compared to their pure components.

- Pharmaceutical co-crystals brought attraction to the pharmaceutical industry because they offer multiple opportunities to modify the chemical and\or physical properties of an API with out making or breaking covalent bonds formation of pharmaceutical co-crystal offers scope to transform an amorphous or hard to crystallise API into readled,stable crystalization would be better alternative toreplace other solid forms[meta stable.polymorphs,amorphous form,salt ect..]and thus offer greater stability and other desirable properties suitable for processing.

Advantages

1-stable crystalline form as compared to amorphous form.

2-Give increased solubility,thus increased bioavailability

3-Technique can be used for purification..

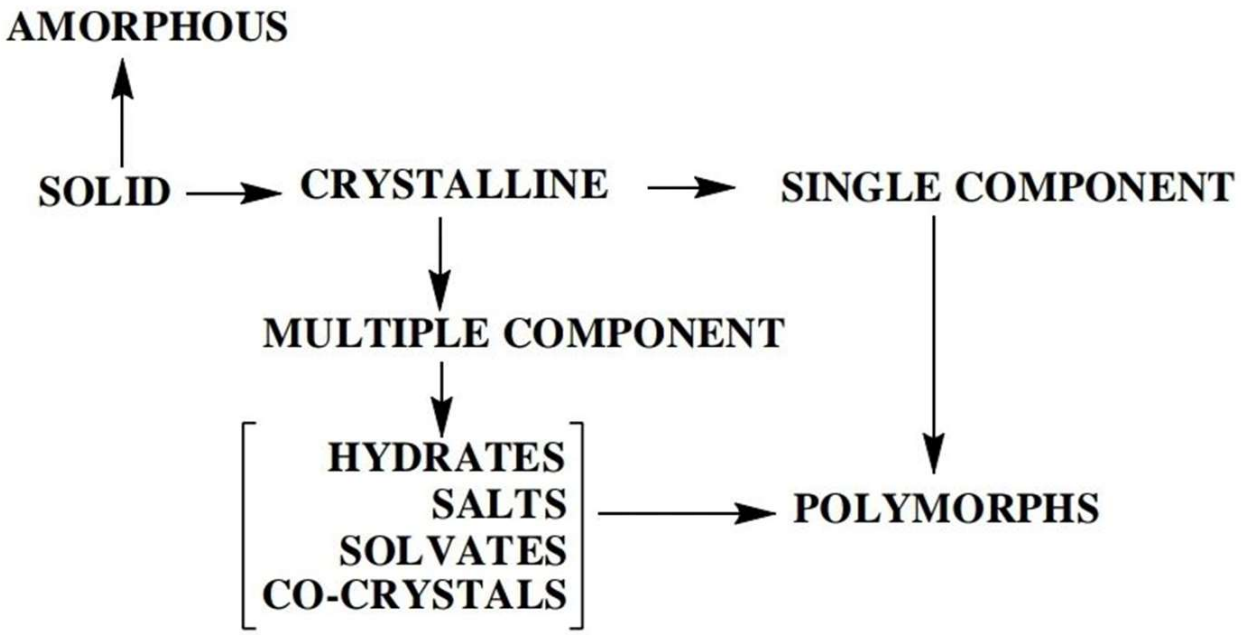
Disadvantages

Co-crystal screening is difficult to automate and labor intensive.

Multiple methods of synthesis , each one of them has advantages & disadvantages.

Additional developments in screening methodology is needed to elevate the profile of co-crystals on the pharmaceutical and intellectual property landscapes

FIGURE 1. API solid form classification based on structure and composition.



Components-

1-API

2-CO-crystal

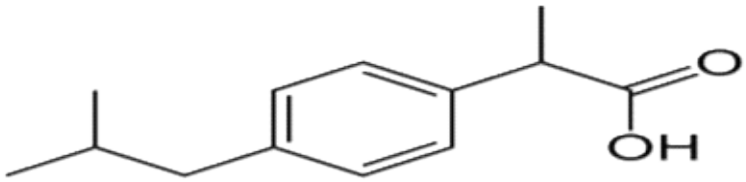
3-Solvent-

1.Ibuprofen [API]

(RS)-2-(4-(2-Methylpropyl)phenyl)propanoic acid

Formula C13H18O2

M.WT 206.29 g/mol g·mol−1



Physiochemical properties

Colorless, crystalline stable solid , has Characteristic odor with boiling point equal 157 °C & melting point of 75-77.5 °C.

Water Solubility 21 mg/L (at 25 °C).

Readily sol in most org solvents , very soluble in alcohol.

Soluble 1 in 1.5 of ethanol,1 in 1 of chloroform anf 1 in 2 of ether

Log P 3.97 , pKa= 5.2

According to biopharmaceutical classification,Ibuprofen has been classifed as a class 2 drug [low solubility and high permeability] therfore, drug dissolution may be rate limiting step in the drug absorption process.

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2.Coformers

Characterstic of co –formers

*1-*Most important for co-crystal formation.

2-Its structure dictate structure of co-crystal.

3-Also dictate solubility.

4-Differ from excipient.

---Example of coformers'

Acetamide,Saccarin,P-amino-benzoic acid, Nicotinamide,Isonicotinamide,Adenine,Cytosine,Fumaric acid ,Succinic acid,Oxalic acid, Adipic acid,Caffaien,Racemic mandelic acid Citric acid ,Tartaric acid, Aspirin

Difference between excipient and cocrystal coformer

Excipient	Cocrystal coformer
Supposed to be chemically inert.	Participate in thtermoleculare interaction
Do not become the part of the crystal structure.	Become part of –co-crystal structure.
Involved in the final dosage form.	They need further processing steps to be in final dosage form.

Characteristics of citric acid

Is an organic tricarboxylic acid which is an important metabolite in all animals and plants.

The Molecular formula of citric acid is C6H8O7 and its molar mass is 192.12 h\mol.

The citric acid is alpha-hydroxy acid with a three carbon skeleton,which has three carboxylic acid groups[COOH], and one hydroxy group[OH].

The citric acid is highly soluble in water to give an acidic,sour tasting solution.

The citric acid has three COOH groups that react with three base molecules .It commonly exists as anhydrous [water-free]f

3.Solvent

- 1-Also important comonent.
- 2-Cocrystal formation depended upon selection of solvent.
- 3-Solubility of drug-coformer is considered while selection of solvent.
- 4-Example,[ethanol,methanol,acetonitrile and others organic solvent.

Steps involved in preparation of cocrystalazation.

1-Selection of API.

2-Selection of co-former.

3-Empirical and theoretical guidance.

4-Cocrystal scanning.

5-Cocrystal characterization.

6-Cocrystal performance.

2 experimental work

2.1 Materials :

MaterilS	Manufacturer
ibuprofen	*Alfyhaa*
Citric acid (coformer)	*india*
ethanol	*iraq*
Distilled water	*iraq*

2.2 Instrument :

Insrument	Manufacture
Sonicater	Bandelin eletronic,Berlin\Germany
Electronic balance	Denver instument
UV-spectroscopy	Aquarius
PH meter	HANNA instrument
Conical flask [10,100,1000ml]	
Beaker 100ml	
Micro-filter 0.45	EMD Millipore
Pipettes	
Graduated cylindes[10,100,500ml]	
Morater and pestle	

2.3 Methods

2.3.1 Preparation of Buffer solution[13\3\2019]

1-Add 7.957g of K2HPO4

2-Add 7.393G KH2PO4

3-After that complet to 1L

4-Finally measure PH

2.3.2 Stock solution prepearation

By dissolve 10mg of Ibuprofen in 100ml of buffer

.

2.3..5 Determination scanning (λmax) of ibuprofen :

- prepare stock solution by dissolve 0.05g of ibuprofen in 100 ml of water
- Filteration
- Prepare five samples from stock solution with following concentration
- 500 ug/ml ..... V=10ml
- 400ug/ml .....V=8ml
- 300 ug/ml .....V=6ml
- 200 ug/ml ..... V=4 ml
- 100 ug /ml .....V=2 ml

- solutions of 500 µg/ml (stock solution) of ibuprofen was scanned by spectrophotometer from 200-400 nm, and then the λ_{max} of the drug was determined.

2-3-4Scanning of co-former citric acid[24\4\2019]

1-Prepare stock solution by dissolve 0.15g of citric acid in 1000ml of solvent[500ml D.W and 500ml of ethanol]

2-Filteration

3-Prepare five samples from stock sol. With following conc..

15 ug\ml

12 ug\ml

9 ug\ml

6 ug\ml

3 ug\ml

4-Take solution of 15 ug\ml [stock solution] of citric acid was scanned by specrtophotometer from 200-400nm, and then 0max of the drug was determined.

_2.3.5 Calibration Curve of co-crystal (ibuprofen and citric acid) :[7\5\2019][30\4\2019]

- Calibration curve of co-crystal prepare by mixing ibuprofen with citric acid In three molar ratio……
- Ratio molar 1 :1 (take 4.13g ibuprofen with 3.84 of citric acid)……
- Ratio molar 2 :1 (take 4.13g ibuprofen with 7.68g of citric acid) ……
- Ratio molar 1 :2 (take 4.13g ibuprofen with 1.92g of citric acid) ……
- Mixing done in mortar and pestle for five minutes with few drops of ethanol (about 5 drops)
- Take 20 mg of mixture of each ratio and dissolve it in 100ml of D.W at beaker 100ml

- Put the solution on magnetic sterrier at 5 rpm speed for five min (solution contain sterrier bars)
- By syringe take 3ml from solution and filterate it by using microfilter (0.45 pore size)
- Add to filtered solution ,equal amount of ethanol (3ml)
- The absorbance was then measured at the λ_{max} of ibuprofen.
- For each ratio ,should be take three reading and take average
- The measured absorbances were plotted against the respective

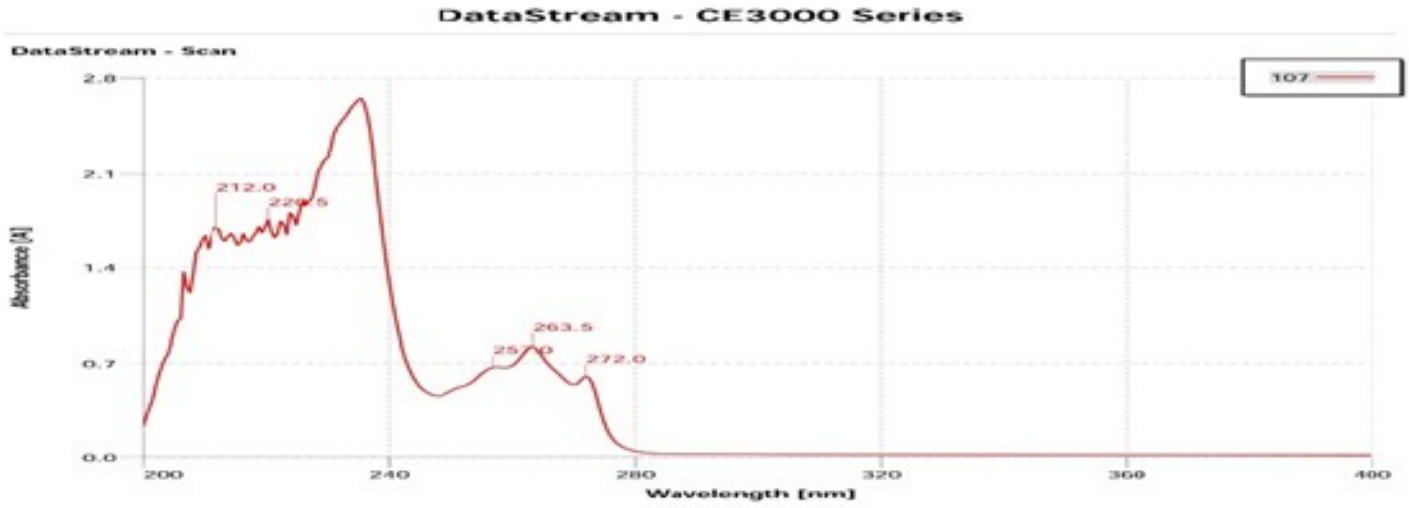
_2.3.6 detection solubility of ibuprofen in same condition of corystal :

- Take 20 mg of ibuprofen and dissolve it in 100ml of D.W at beaker 100ml
- Put the solution on magnetic sterrier five min (solution contain sterrier bars)
- By syringe take 3ml from solution and filterate it by using microfilter (0.45 pore size)
- Add to filtered solution ,equal amount of ethanol (3ml) . The absorbance was then measured at the λmax of ibuprofen.

3 Results and discussion

Scanning of ibuprofen

Sample	Conc.	Absorbance
1	100 ug/ml	0.131 nm
2	200 ug/ml	0.269 nm
3	300 ug/ml	0.417 nm
4	400 ug/ml	0.559 nm
5	500 ug/ml	0.723 nm



Figure(2) the λ¬max of ibuprofen is 263.5 nm

Calibration curve

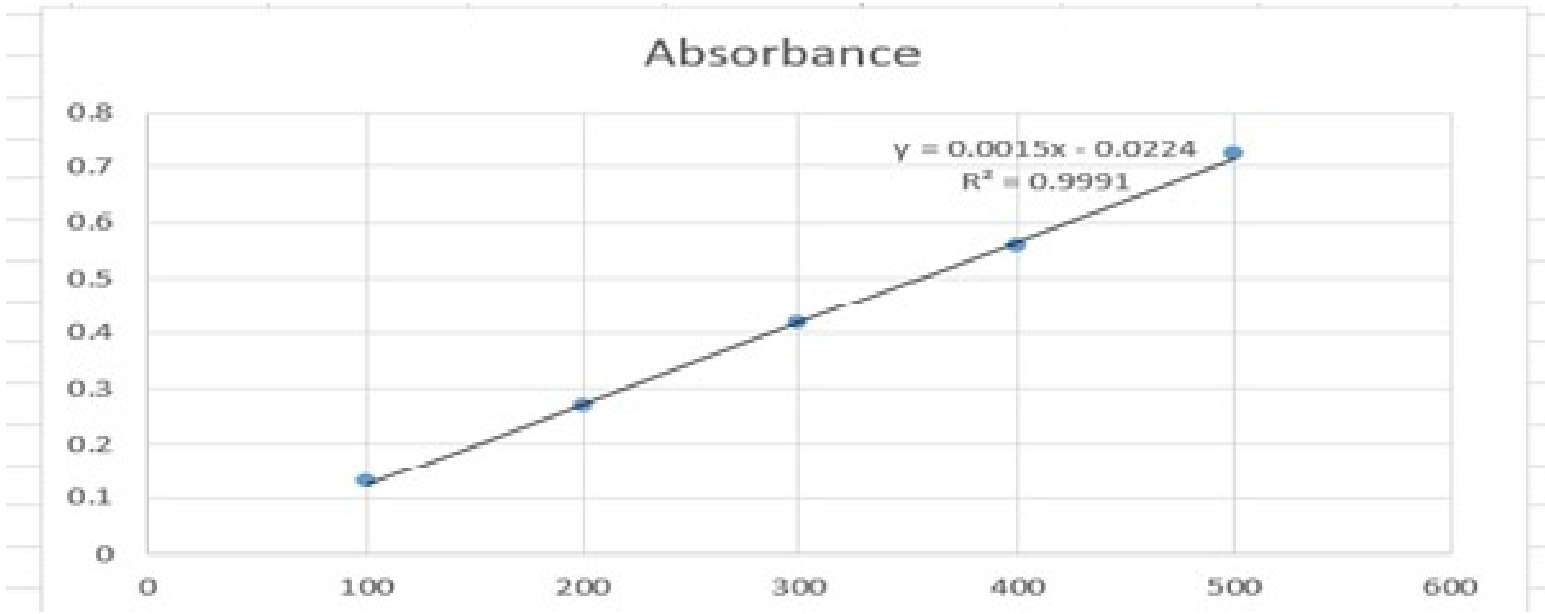


Figure (3) Calibration curve of Ibuprofen

Scanning of coformer results

Sample NO.	Concentration	Maximum wave	Absorbance
1	120mcg	220nm	----------
2	90mcg	220nm	----------
3	60mcg	220nm	----------
4	30mcg	220nm	----------
5	150mcg	220nm	0.715

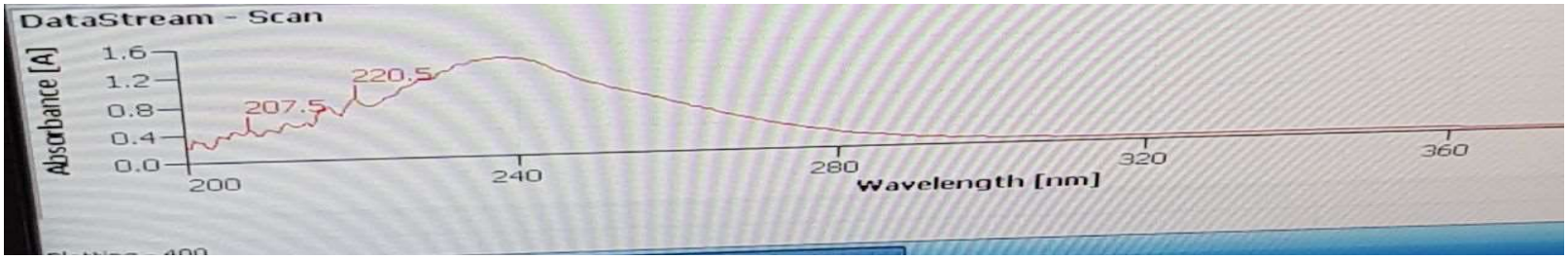


Figure (4) scanning of citric acid

- From result above see the citric acid not absorbance in 263nm [maximum wave length of ibuprofen], and the has maximum wave length 220nm and only has absorbance in high conc. Only in 150mcg equal to o.715 So this lead to the citric acid co-former is used only to increasing solubility of Ibuprofen,and not forming drug-drug interaction,or drug-co-former complexation.

detection enhancement of solubility of ibuprofen

-abs. of ibuprofen sample in same conditions of co-crystal is 0.226 nm

By using calibration curve equation y=0.0015x-0.0224

Conc. Of pure ibuprofen is 20mcg\100ml

Ratio	Wt. of ibuprofen [mcg	Conc.of ibuprofen[mcg \100ml]	Wt.of citric acid [mcg]	Conc.of citric acid [mcg\100ml]	Abs.
1;1	10360	103.6	9636	96.36	0.102
2;1	6994	69.94	63472	63.472	0.0773
1;2	13653	136.53	13226	132.26	0.127

Calibration curve of co-crystal[7\5\2019]

NO. of sample	Ratio	nm		nm	
1	1;1	220nm	0.590	263nm	0.112
2	1;2	220nm	0.519	263nm	0.215
3	2;1	220nm	0.573	263nm	0.135

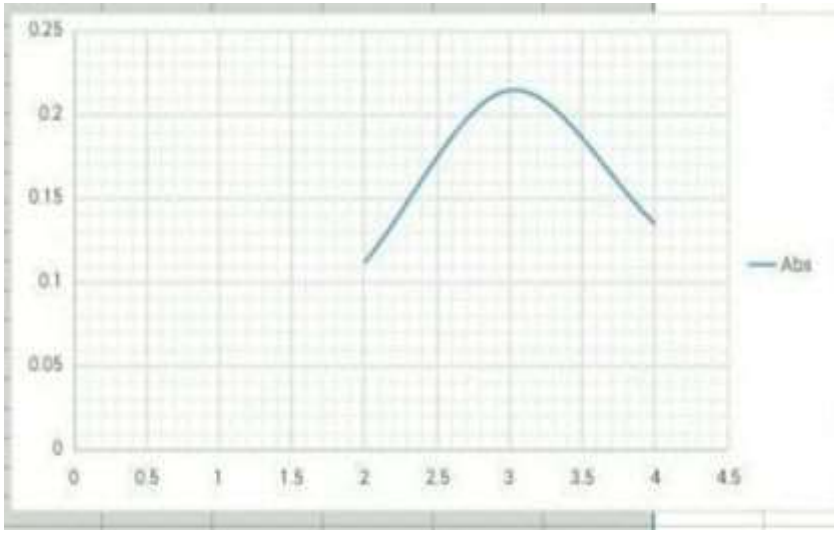


Figure (6) calibration curve of co-crystal at 263nm

- So from this calibration curve of ratio [Ibuprofen to citric acid]we see,
- Can not used citric acid as coformer with Ibuprofen in ratio 1;1 or 2;1 to increase it solubilty.
- And due to the abs.of abuprofen equal to 0.226,and abs.of cocrystal in ratio 1;2 equal to 0.215so,
- That may be improve in solubility by using ratio of coformer more than API,OR by using two coformer[after study prop.,scanning of them as depending on their relationship between coformer and API.

4-Concultion

Screening of ibuprofen in the beginning was to detect the equation between abs.(Y) and conc. (X) To determine the solubility enhancement in the end .

Screening of co-former (citric acid) was to ensure there was or not any interaction in absorbance between ibuprofen and CITRIC ACID so cocrystal absorbance at 263nm reflects only ibuprofen absorbance in the cocrystal .

Screening of ibuprofen in exactly same conditions of cocrystal to detect accurate enhancement of solubility

In ratio 1:1 and 1:2 the solubility decreased because of formation of complex , so this was expected and we were looking to detect the best ratio to enhance solubility which was 1:2 by increasing conformer to double amount the solubility of ibuprofen increased to about the double .

- *Solubility of the API and conformer in a solvent used for cocrystallization plays a significant role in determining the success of cocrystallization experiment*

- *Co-crystals are relatively new to pharmaceutical industry and pharmaceutical co-crystals have given a new direction to deal with problemsof poorly soluble drugs*

IN cocrystal development one of the approach of coformer selection is based on trial and error.

Factors determining cocrystallization

1-pka

2-Molecular recognition points

3-H-bonding donners and acceptors

4-Carbon-chain length of dicarboxylic acid coformers

5-Effect of solvent

6-PH

7-Temperature

- As cocrystallization is influenced widly by several imoprtant parameters,selecting a suitable confermer for cocrystallization requires an effective sreening process.
- Screening of a suitable confermer can be carried out expermentally or computationally.
- Experimental methods are exhaustive and time-consuming.ON the other hand, computational methods can serve as a rapid screening tools for initial assessment of coformers that suitable for cocrystallization

5.Reference

- 1-Brittain H-polymorphism in pharmaceutical solids .New York;Marcel Deker .INC. 1999.
- 2-European Medicines Agency[EMA]
- 3-Duggirala,NK,Perry,M,L.;Almarsson,O,,Zaworotoko,M.J.Pharmaceutical cocrystals;along the path to improved medicines.Chem.Commun.2016,52[4],640-655.
- 4-Davies,NM[February1998].Clinical pharmacokinetics of ibuprofen. The first 30 years".Clinical Pharmacokinetics.34[2];101-54.
- 5-Pharmaceutical cocrystals and their physicochemical properties.Cryyst.Growth and Design.9.2950-2967.
- 6-Zalte,A.,et.al 2014.Cocrystals;An Emerging Approach to modify Physicochemical properties of Drugs. Am.J. Pharm.Tech Res.4.179-189.
- 7-Alsenz,Jet.al.2012.The Impact of solubility and Dissolution Assessment on Formulation strategy and implications for oral drug disposition.Encyclopedia of Drug metabolism and interactions.1-53.
- 8-Aitipamula,S.,et.al2009.Polymorphs,salt and cocrystals;Whats in the name?. Cryst.Growth and Design,
- .12.2147-2152.
- 9-CAMEO Chemical Reactivity Classification
- 10-FDA Pharmacological Classification.
- 11—USP Pharmacopia
- 12-Sekhon BS.Pharmaceutical co-crystals-An update. Chem inform 2013;44;62.
- 13-Bolla G,Nangia A. pharmaceutical cocrystals; walking the talk. ChemCemmun 2016;42-60..
- 14- Zachary,B. FDA to Reclassify pharmaceutical co crystals
- 15-Reflection paper on the Use of cocrtsales and other solid state forms of Active substances in medicinal products.
- 16-Aitipamula, s, chow, ps, tan , R.B.H. polymorphism in cocrystals. A review and assessment of its significance. Crystal Eng comm2014,16,3451-3465.
- 17-Lee, k,kim ulrich,j. formation of salicylic acid\4,4 Dipyridyl cocrystals Bssed on the ternary phase Diagram .Chem Eng.Technol.2015,38,1073-1080.
- 18-Chadwick,K,Davey ,R;Cross,W.How does grinding produce cocrystala? Insights from the case of benzophenone and diphenylamine. CrystEngComm2007,9,732-734.

THANK TO YOU.